New Developments in Microbiology

Editor
Suna KIZILYILDIRIM

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Contents

CHAPTER I

Neutrophıls And Theır Role In Acute Inflammatıon

Dilek VURAL KELEŞ[1]

The human body's response to infections is the most important function of the immune system. Immunity consists of innate immunity, which forms the first protective response against infections, and then adaptive immunity, which provides a more specific and effective defense against infections with the memory formed in the immune system (Abul et al., 2014). Neutrophils, which have a central role in innate immunity, are short-lived cells that constitute the majority of circulating white blood cells (Borregaard et al., 2007). Neutrophils are vital in host defense against bacteria and fungi and play a role as the main defense cell in acute inflammation. In acute inflammation, five main external symptoms occur: rubor, calor, tumor, dolor, and functio laesa. These symptoms

[1] Asst. Prof. Kırklareli University Faculty of Health Sciences

occur due to edema and changes in blood vessels in the infected area. In acute inflammation, neutrophils migrate from the blood into the tissue to eliminate the agent causing inflammation by phagocytosis (Antonelli & Kushner, 2017). The general characteristics and life cycles of neutrophils before their role in acute inflammation are described below.

Neutrophils have a diameter of 12–15 μm and constitute 60–70% of white blood cells (Patrick et al., 2010). The nucleus of the neutrophil has 2–5 lobes, which have heterochromatic and euchromatic areas and are connected to each other by thin extensions. In women, the X chromosome has a drumstick shape and is attached to the nuclear lobes, and is called a Barr body. They are called polymorphous leukocytes due to their multi-lobed nuclei (Miknienė & Ivanauskaitė, 2018). This cell, which is poor in organelles, has an undeveloped granular endoplasmic reticulum, and the Golgi apparatus is centrally located. These cells, which have a small number of mitochondria, meet their energy needs through glycolysis (Mescher, 2018). Neutrophils have numerous primary, or ausorophilic, and secondary, or specific, granules in their cytoplasm. Primary granules are also called peroxidase-positive granules and contain antibacterial proteins such as defensins, myeloperoxidase, bactericidal/permeability-increasing protein, lysozyme, and proteases such as cathepsin G, proteinase 3, and elastase. Secondary granules are also called peroxidase-negative granules and contain antibacterial proteins such as hCAP18, NGAL, B12BP, lactoferrin, haptoglobin, lysozyme, and pentraxin 3, as well as proteases such as collagenase, gelatinase, uPA, cystatin C, and cystatin C. (Borregaard et al., 2007). Neutrophils are produced in the bone marrow and released into the circulation. Their half-life in circulation is 6 hours, and they are eliminated by phagocytosis by macrophages after living in the tissue they migrated to for 6-7 hours (Kierszenbaum, 2006). In healthy individuals, its amount in the blood is between 4000 and 10000 per ml, but in cases of infection, neutrophil production from hematopoietic stem cells in the bone marrow increases with the effect of cytokines and chemokines, and their number in the blood

reaches 20,000 per ml. (Abul et al., 2014; Furze & Rankin, 2008). The production of neutrophils from the bone marrow occurs through a process called granulopoiesis. In the process of granulopoiesis, a series of cells are observed until the mature neutrophil is formed from the hematopoietic stem cell. These are, respectively:

1- **Multipotent hematopoietic stem cell** that can generate other hematopoietic cells and itself.

2- **Oligopotent common myeloid progenitor cell** that forms the myeloid series.

3- **Oligopotent granulocyte-monocyte progenitor cell**, which is the first cell line in the myeloid series.

4- **Unipotent myeloblast** that forms granulocytes.

5- **Promyelocyte** is the largest cell of the myeloid series and has many aurophilic granules.

6- **Myelocyte** is the first cell in which specific granules are observed.

7- **Metamyelocyte** with indented nucleus.

8- **Band cell** with a convoluted nucleus.

9- **Neutrophil** with a 2–5 lobed nucleus.

The granulopoiesis process occurs under the influence of various colony-stimulating factors such as SCF and GM-CSF, and cytokines such as IL-1, IL3 and IL-6. (Cowland & Borregaard 2016 ; . Lawrence et al., 2018).

In healthy individuals, circulating neutrophils are in a non-reactive state called the 'dormant state'. The first host response due to infection is acute inflammation, which starts within minutes and ends within a few days, and neutrophils play a role as the main defense cell in this process. The onset of acute inflammation is triggered by the release of pro-inflammatory mediators and chemokines by various cells, such as macrophages, dendritic cells, mast cells, and stromal cells in the infected tissue (Witko-Sarsat et

al., 2000). The release of these chemical mediators causes changes in postcapillary venules and causes neutrophils to migrate into the tissue. Migration of neutrophils occurs in four stages, as follows:

a) **Capturing (or tethering):** Capturing neutrophils with L-selectin on the vascular endothelium. (Eriksson et al., 2001).

b) Rolling: After capturing, neutrophils roll along the endothelium surface by binding to P and E selectins on endothelial cells with glycoprotein ligand 1 and sialyl lewis x receptor on their surface. (Cappenberg et al., 2022).

c) **Adhesion:** After rolling, neutrophils adhere to the endothelium surface by binding to ICAM-1 and VCAM-1 adhesion molecules on endothelial cells with leukocyte function antigen 1 (LFA1) and very late antigen 4 (VLA4) on their surface. (Xing et al., 2012).

d) Diapedes: After adhesion, neutrophils pass into the tissue by opening the gap between the endothelial cells with their extensions (Xing et al., 2012).

Neutrophils entering the tissue move to the area of inflammation, that is, the area where pathogens are located, under the influence of chemotactic agents such as interleukin 8 (IL-8), leukotriene B4, complement fraction C5a, platelet-activating factor, and the bacterial chemotactic peptide N-formyl-methionyl-leucyl-phenylalanine.(Ley et al., 2007). Neutrophils arriving at the infected area recognize bacteria with various surface receptors. Neutrophils bind to pathogen-associated molecular patterns (PAMPs) such as glycolipid, lipopolysaccharide, triacyl lipopeptide, peptidoglycan, and diacyl lipopeptide in the bacterial wall with their pattern recognition receptors (PRP) and take them into the cell by forming phagosomes. Additionally, neutrophils recognize bacteria opsonized with IgG antibodies and C3b opsonized with Fc and complement receptors on their surfaces and take them into the cell by forming a phagosome (Michael and Wojciech, 2014). Phagosome formation causes neutrophils to be activated. In activated neutrophils,

glycolysis increases, and NADPH production from glucose via the pentose monophosphate pathway increases. NADPH oxidase, located in the membrane of the phagosome inside the bacterium, uses NAPDH to produce superoxide radicals from molecular oxygen (Leto et al., 2009). The phagosome, filled with superoxide radicals that are toxic to bacteria, fuses with neutrophil granules. Bacteria within the phagosome are killed either enzymatically or by more toxic reactive oxygen species generated from superoxide radicals. The superoxide radical inside the phagosome turns into hydrogen peroxide, an unstable compound, via the SOD enzyme (Dahlgren & Karlsson, 1999). Increased hydrogen peroxide turns into hypochlorous acid, which is more toxic to bacteria, via the myoloperoxidase enzyme and halide ions, and into toxic hydroxyl radicals via the Fenton reaction. These free radicals, which increase in the phagosome, damage the membrane and other components of bacteria and cause their death (Uslu et al., 2015). Moreover, as a result of the fusion of phagosomes with primary and secondary granules, bacteria can be killed independently of oxygen by antibacterial proteins such as defensins, bactericidal/permeability-increasing protein, lysozyme, hCAP18, NGAL, B12BP, lactoferrin, haptoglobin, and pentraxin 3 within the granules. (Borregaard et al., 2007).

Activated neutrophils release metalloproteinases such as gelatinase and collagenase and some antimicrobial agents in their granules into the tissue by exocytosis. Metalloproteinases facilitate the amoeboid movements of neutrophils by enzymatically breaking down connective tissue components. Antimicrobial agents released into the tissue contribute to the killing of bacteria and other pathogens (Murphy et al., 1980; Faurschou & Borregaard, 2003). Apart from the mechanisms by which neutrophils kill bacteria by phagocytosis and the antimicrobial agents they secrete into the tissue, a new bacterial death mechanism mediated by neutrophil extracellular traps (NETs) has been identified. Neutrophil extracellular traps are defined as extracellular strands composed mainly of DNA strands that contain various antimicrobial agents.

Neutrophil extracellular traps play a role in both capturing and killing bacteria. (Papayannopoulos, 2018) In neutrophil phagosomes, digested bacterial particles are stored as residual bodies or released by exocytosis. The dead bacterial particles, neutrophils that die in this process, and the increased tissue fluid form the thick exudate called pus. This exudate is later eliminated by macrophages, and the tissue is cleared. (Michael & Wojciech, 2014).

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CHAPTER II

West Nıle Vırus

Dilek VURAL KELEŞ[1]

West Nile virus (WNV) is a neurotropic pathogen that causes encephalitis and was first isolated from a human in the West Nile region of Uganda in 1937. This virus, which spreads throughout the world, was first detected in Türkiye in 1977 in the Southeastern Anatolia region using the hemagglutination inhibition method (Meco, 1977). A spread was observed in the Aegean region with the diagnosis of infected individuals in 1980. (Serter, 1980). WNV seropositivity was detected in the seroepidemiological study conducted throughout Turkey in 2005, covering the provinces of Adana, Antalya, Ankara, Bursa Hatay, Izmir, Muğla, and Şanlıurfa. (Ozkul et al., 2006). In 2010, in the official statement by the Ministry of Health of the Republic of Türkiye, encephalitis cases and deaths due to this virus were officially announced for the first time and reported to the World Health Organization (Kalaycıoğlu, 2010). An

[1] Asst. Prof. Kırklareli University Faculty of Health Sciences

increase in WNV case reports has been observed in Türkiye since 2010.

The purpose of this book chapter is to present and summarize recent discoveries regarding the taxonomy, genome and structure of WNV, its life cycle, and pathogenesis in humans.

1. Taxonomy of West Nile Virus.

The West Nile virus is an arbovirus taxonomically belonging to the Flaviviridae family. (Hayes et al., 2005). The Flaviviridae family contains four genera, including flaviviruses, pesitiviruses, pegiviruses, and hepaciviruses, and 89 species. (Wang, 2022). West Nile Virus belongs to the Flavivirus genus from the Flaviviridae family (Bakonyi et al., 2005). At the meeting held by the International Committee on Taxonomy of Viruses (ICTV) in 2022, the Flavivirus genus name was changed to Orthoflavivirus, and the new name of the West Nile virus was defined as Orthoflavivirus nilense (Postler et al., 2023). WNV is one of the Japanese encephalitis antigenic serocomplex viruses, and this group also includes St. Louis Encephalitis Virus, Japanese Encephalitis Virus, Cacipacore Virus, Koutango Virus, Yaounde Virus, Alfuy Virus, Usutu Virus., and Murray Valley Encephalitis Virus. (Bakonyi et al., 2005).

2. Genome and Structure of West Nile Virus.

WNV is a spherical, small-enveloped virus approximately 50 nm in diameter. The outermost viral envelope contains a lipid bilayer and 90 anti-parallel homodimers of glycoprotein E and small membrane protein M. The E protein is located on the surface of the flaviviral envelope and enables it to recognize and bind to the receptor on the host cell (Zhang et al., 2003). The viral capsid is approximately 30 nm in diameter and consists of capsomer units composed of C-protein dimers. The WNV genome is a linear, positive-sense, 11-kb single-stranded RNA located in an icosahedral capsid. (Brinton, 2002). The RNA genome begins with a short non-coding region of approximately 100 nucleotides and ends with a non-

coding region of 400–700 nucleotides. (Campbell et al., 2002). The 5' end of the genome has a nucleotide cap that is methylated for canonical cellular transcription, and the 3' terminus has a loop structure that does not contain the Poly-A tail. The genome consists of a 10 kb protein that encodes 3 structural proteins: capsid (C), premembrane (prM), and envelope (E), and 7 non-structural proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. It contains a single open reading frame (ORF) (Brinton, 2002). The process of producing structural and nonstructural proteins of WNV begins with the binding of the E glycoprotein to the host cell surface receptor, clathrin-mediated endocytosis, fusion with the endosomal membrane, and delivery of the RNA genome to the cytoplasm. (Martin & Nisole, 2020). Positive-sense single-stranded viral RNA works like mRNA and synthesizes a single polyprotein in ribosomes. This polyprotein is converted into 10 viral proteins (3 structural and 7 non-structural proteins) by the viral serine protease complex (NS2B-NS3) and various cellular proteases during and after translation. (Brinton, 2002). Negative-sense single-stranded RNA is created by the viral RNA polymerase (NS5) enzyme from genomic RNA and serves as a template for the transcription of new genomic RNAs. After the production of the genome and structural proteins is completed, the structural formation of the virion is completed in the rough endoplasmic reticulum and Golgi apparatus, and the newly formed virion is released from the cell by exocytosis (Saiz et al., 2021).

3. Life Cycle and Transmission Routes of West Nile Virus.

The primary host of WNV, a zoonotic virus, in nature is wild birds, and although they have high viremia, they do not show symptoms. WNV has been detected in more than 300 bird species, and especially the Corvidae and Passeridae families have been shown to be more effective in replicating and transmitting the virus than other birds (Vidaña et al., 2020). The life cycle of WNV in nature is between birds and mosquitoes. Major female Culex mosquito species serve as the main vectors and become infected with

WNV while feeding on infected viremic birds. WNV replicates in the midgut epithelial cells of the mosquito and spreads to the salivary glands via hemolymph. (Girard et al., 2004). After an incubation period ranging from 10 days to 2 weeks in mosquitoes, WNV can infect either the primary host, birds, or the final host, other humans and other mammals. (Dauphin et al., 2004). Humans and other mammals are considered the final hosts because they exhibit low viremia despite being infected with the virus (Gyure, 2009; Murray et al., 2010). Vector mosquito species involved in the WNV life cycle are generally the genus Culex and rarely the genera Anopheles and Aedes. (Tosun, 2012). However, WNV has been isolated from different species of Culex in different regions of the world. While Culex modestus and Culex pipiens species are the main vectors on the European continent, Culex vishnui, Culex tritaeniohynchus, and Culex quinquefasciatus species are the main vectors in Asia (Shocket et al., 2020). While Culex annulirostris is the main vector on the Australian continent, Culex univitattus is the main vector in Africa and the Middle East. (McIntosh et al., 1976 ; Shocket et al., 2020) While the main vectors in the north of the American continent are Culex pipiens and Culex restuans, Culex quinquefasciatus has been reported as the main vector in the south of the American continent. (Shocket et al., 2020). Culex pipiens in the eastern United States and Culex tarsalis in the west have been identified as the main vectors for WNV. (Kilpatrick et al., 2005).

There are limited studies on mosquitoes that are vectors for WNV in Turkey, and in these studies, WNV was detected in Culex pipiens, Culex martinii species, and Aedes mosquitoes. (Muslu et al., 2011; Akıner et al., 2019).

While transmission of the virus to humans occurs mainly through the bite of an infected mosquito, transmission of the virus from humans to humans, from birds to humans, and from other mammals to humans has not been detected. (Sampathkumar, 2003). It is known that other identified transmission routes of WNV include dialysis, blood transfusion, organ transplantation, breast milk, and transplacental transmission. (Robinson & Enriquez, 2019).

4. Pathogenesis of West Nile Virus.

People infected with WNB generally exhibit low viremia and are clinically asymptomatic. 20% of infected people develop West Nile fever with mild flu-like symptoms, and 1% of infected people develop West Nile neuroinvasive disease. (Barzon et al., 2015). West Nile neuroinvasive disease occurs especially in elderly patients, and disruption of the blood-brain barrier is the main factor in the inoculation of the virus into the central nervous system. (Maximova & Pletnev, 2018). The mortality rate in West Nile neuroinvasive disease is 10–30%, and sequelae are observed in the majority of recovered patients. (Barzon et al., 2015).

The pathogenesis of the infection begins when the mosquito bites human skin and inoculates the skin with the virus in the salivary glands. WNV infects the Langerhans cells in both the epidermis and dermis and the keratinocytes in the epidermis (Lim et al., 2011). Infected Langerhans cells acquire a dendritic cell phenotype and migrate to the lymph nodes. Virus replication in Langerhans cells migrating to the lymph nodes occurs in the skin, during migration, and in the lymph nodes. (Byrne et al., 2001). Viral replication increases in Langerhans cells migrating to the lymph nodes, and primary viremia occurs. The WNV virus spreads from the blood to internal organs such as the spleen, liver, heart, lung, and kidney. (Samuel & Diamond, 2006). In some cases, penetration of neurotrophic WNV into the central nervous system is observed after secondary viremia. Although it is not known how the virus crosses the blood-brain barrier, it has been suggested that WNV spreads to the central nervous system through various mechanisms, such as the virus infecting endothelial cells, disruption of vascular integrity with cytokines, and the mediation of infected leukocytes. (Morrey et al., 2008 ; Paul et al., 2017). Due to the spread of WNV to the central nervous system, West Nile neuroinvasive disease develops, in which meningitis, encephalitis, and meningoencephalitis cases are observed together or separately. (Sampathkumar, 2003). In neuroradiological examinations of the central nervous system with MRI in people infected with WNV, there are abnormal findings such

as lesions in the basal ganglia, cerebellum, and mesencephalon in the brain and cervical myelitis, and cauda equina arachnoiditis in the spinal cord (Qian et al., 2014). Individuals with West Nile neuroinvasive disease may experience symptoms such as high fever, headache, disorientation, dizziness, convulsions, neck stiffness, tremors, convulsions, muscle weakness, paralysis, and coma. (Sejvar et al., 2003). In West Nile fever patients, whom WNV does not infect the central nervous system, the main symptoms are fever, headache, fatigue, body aches, skin rash, swollen lymph nodes, loss of appetite, nausea and vomiting, and may be rarely observed hepatitis and myocarditis due to infection of other organs by the virus. (Waleed et al., 2021 ; Petersen et al., 2013)

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CHAPTER III

Effectıveness Of Propolıs And Nıgella Satıva Agaınst The Effects Of Antımıcrobıal Resıstance

Gokcenur SANİOGLU GOLEN
Kadir AKAR

1. INTRODUCTION

Microorganisms are known as the oldest living creatures on earth due to their ability to adapt to changing conditions quickly. This ability prevents them from being affected by the new antibiotic. In this case, we face the problem of antibiotic resistance, which is the most challenging problem in combating infections. The event that gave rise to great hopes regarding antibiotics was obtaining pure penicillin in the 20th century. However, about a year later, Abraham and Chain's discovery of penicillin shattered their hopes. Today, antibiotic resistance observed in many gram-negative, gram-positive and acid-resistant microorganisms has made it difficult to treat infections (Demirtürk & Demiral, 2004).

Microorganisms can quickly adapt to any conditions. They are known as the oldest living creatures because they can quickly

adapt to situations. Among these microorganisms, there are apathogenic ones, as well as pathogenic ones. Pathogenic microorganisms pose a danger to both human and animal health. For this reason, antibiotics were invented to combat microorganisms. Due to excessive and unconscious use of antibiotics and improper use, microorganisms compatible with antibiotics have become resistant. The introduction of antibiotics, their mechanism of action, antimicrobial resistance and what needs to be done to prevent resistance were examined.

2. HISTORY

Belief in the power of plants to cure diseases has existed since humankind's earliest times. Throughout human history, various botanical forms have been used for boiling or eating (Erdoğan and Everest, 2013). We encounter abundant historical evidence of the use of plants on all continents of the world. Neanderthals who lived 60,000 years ago were even discovered to have used the "hollyhock" plant found in modern-day Iraq (Şengün & Öztürk, 2018). There are clay tablets written in cuneiform script dating from 2600 BC. At the end of the 5th century BC. Hippocrates' book mentions 300,000 different medicinal plants, and Dioscorides' De Materia Medica in the 1st century AD are the oldest writings that form the basis of modern pharmacology. To this day, these plants and their new species are still used in traditional treatments. It is believed that all herbs are used in traditional medicine worldwide. Scientific curiosity about the plants used in conventional therapies, their extracts, their compositions and their effects on the world has led to the emergence of the ethnographic field. Millions of magical resources have now begun to be replaced by technology databases. For example, it provides a catalogue of over 27,000 known varieties with more than 300 diseases and symptoms created from scientific studies of ethnographically valuable plants. When you look around the world, about half of all deaths in tropical countries are due to infections. In East Africa, 300,000 children die annually from infections caused by microorganisms of the Enterobacteriaceae species. Although this situation is not surprising considering the socio-economic situation

of the countries, infectious diseases and deaths are increasing day by day in developed countries. For example, according to research conducted in the United States, while death from infection ranked 5th in 1981, it rose to 3rd place in 1992. This situation has made it necessary to develop new strategies for preventing and treating infectious diseases. Therefore, it is natural that pharmacologists, especially microbiologists, turn to plants to search for antimicrobial agents. Over time, microorganisms become resistant to drugs and transmit them to new members. This limits the drug's shelf life and makes the need for antibiotics permanent. Therefore, plants continue to support clinical microbiologists in their search for new antimicrobial agents. In addition, by benefiting from botanical experience throughout history, information is obtained about the contents and uses of plants studied scientifically in laboratories. Therefore, disclosing the plants' effects on microorganisms will prevent abuse by the public (Navarre & Schneewind, 2010).

3. DEFINITION

The word antibiotic is derived from the Greek words "anti (against)" and "bios (life)". Antibiotics are defined as 'Inhibiting the growth or metabolic activities of bacteria and other microorganisms with a chemical substance of microbial origin'. According to the Dictionary of Veterinary Medicine Terms of the Turkish Language Association, antibiotics are drugs produced by some types of fungi, actinomycetes and bacteria or synthetically and that prevent the reproduction or development of microorganisms or have a lethal effect (TDK, 2009). Antibiotics are substances that prevent the growth and proliferation of bacteria in a way that does not harm the host or causes minimal harm to the damage caused by harmful living microorganisms inside or outside the living body (Akkan & Karaca, 2003; Küçükbüğrü & Acargöz, 2020; Topal & et al., 2015).

Realising that anthrax bacilli, which can grow well in sterile urine, cannot grow in contaminated urine and die, Pasteur and Joubert wanted to reveal the reasons for their observations experimentally. These experimental events constituted the first steps

in the field of treating infections with antibiotics (Küçükbüğrü & Acargöz, 2020; Topal & et al., 2015).

The increasing use of antibiotics in recent years manifests itself in every aspect of our lives. Antibiotics are used extensively, especially for human and animal health, food preservation in the food industry, health and development of aquatic creatures such as fish, and scientific research activities in hospitals and the pharmaceutical industry. However, as a result of unconscious and unnecessary use of antibiotics, health problems occur in living things, especially humans, through both environmental issues and the food chain. Antibiotics are among the most used drugs all over the world. Antibiotics are misused and overused in developing countries (Hart, 1998). Antibiotics can be sold without a prescription in pharmacies or markets (Saltoğlu, 2005). In Europe, two-thirds of antibiotic drugs are used in human medicine, and one-third are used for veterinary purposes (FEDESA, 2001).

4. MECHANISM OF ACTION

The multiplication of bacteria consists of three stages. These are slow development, rapid development and rest. Antibiotics cannot act during the resting period of bacteria. Therefore, the antibiotic must either stop the development and reproduction of the bacteria or kill it. Substances such as penicillins, aminoglycosides, cephalosporins, vancomycin, fluoroquinolones and bacitracin kill bacteria, while tetracyclines, macrolides and sulfonamides inhibit the development and reproduction of bacteria (Akkan & Karaca, 2003). Antibiotics are classified into two groups according to their spectrum of action: narrow and broad spectrum. They are divided into five groups according to their mechanism of action: antibiotics that disrupt bacterial cell wall synthesis and activate lytic enzymes, antibiotics that disrupt cytoplasm membrane permeability, antibiotics that disrupt protein synthesis in ribosomes, antibiotics that act on bacterial genetic material, and bacterial antimetabolites (Akkan & Karaca, 2003; Topal & et al., 2015). Antibiotics that disrupt bacterial cell wall synthesis and activate lytic enzymes: beta-

lactams (penicillins, cephalosporins, monobactams, carbapenems), cyclosarin, ristocetin, bacitracin, teicoplanin and vancomycin. Antibiotics that disrupt cytoplasm membrane permeability are also known as those that have a detergent effect. These: polymyxins, gramicidin, nystatin, amphotericin B, candycein, ketoconasal and other antifungal imidazoles, fluconazole and other antifungal trizoles, hexachlorophene and cationic detergents. Antibiotics that disrupt protein synthesis in ribosomes can be classified as tetracyclines, aminoglycosides, macrolides, amphenicols, lincosamides and fusidic acid. Antibiotics that act on bacterial genetic material can also be defined as disrupting DNA and RNA synthesis. Antibiotics that work on bacterial genetic material: fluoroquinolones, rifamycins, nalidixic acid, metronidazole, actinomycetes, mitomycins, bleomycin, acyclovir, doxorubicin, daunorubicin and methotrexate. Bacterial antimetabolites are sulfonamides, sulfones, Para aminosalicylic acid (PAS), isoniazid, ethambutol and trimethoprim (Akkan, 1997).

5. ANTIBIOTIC RESISTANCE

The ability of a microorganism to resist the effect that can eliminate it and to continue its existence against this is called resistance. This resistance may be natural or acquired. The fact that bacteria and other microorganisms are not affected by chemotherapeutic drugs is called resistance. There is also the situation that bacteria are naturally resistant to some antibacterial medicines. This is called natural resistance. This makes it resistant to other antibiotics with similar chemical structure and mode of action. This is also called cross-resistance. If the structure and effect are resistant to different antibiotics, this situation is called “multidrug resistance”. If a mutation occurs in the chromosome of the microorganism or if the resistance gene of a resistant microorganism is transferred to a sensitive microorganism, it is called acquired antibiotic resistance (Akkan & Karaca, 2003; Daş & Atmaca, 2015; Demirtürk & Demiral, 2004; Fındık, 2011; Kayiş, 2019).

Application of inappropriate doses of antibiotics without an antibiogram, use of low-quality antibiotics, and deficiencies in treatment and control strategies in human and veterinary medicine may lead to antibiotic resistance. In addition, it has been reported that antibiotic resistance can occur due to deficiencies and wrong practices, such as inadequacies in antibacterial drug residue screening and monitoring programs, international and national legal regulations, and weaknesses in research and development in drug production. Antibiotics have been used for therapeutic and preventive purposes and to accelerate animal development. However, antibiotics used as feed additives for development in the half of the 20th century influenced the emergence of resistant strains in bacteria. Nowadays, reasons such as the increased consumption of antibiotics, the impaired immune systems of most patients, the increase in intensive care units, and the unconscious use of antibiotics, especially in the food industry, have led to the rise in antibiotic resistance (Akkan & Karaca, 2003; Demirtürk & Demiral, 2004; Yarsan, 2018).

It is recommended that antibiotic combinations be used when necessary, in addition to giving drugs at appropriate doses and time intervals for short periods. If these are not followed, streptomycin and penicillin-type resistance may occur. Streptomycin type resistance: It is a single-stage mutation and can be defined as rapid and advanced resistance with one or more contacts with the drug. Penicillin-type resistance, on the other hand, occurs through multi-stage mutation and can occur slowly but with increasing severity. There is also an increase in resistant bacteria due to excessive use of antibiotics, known as positive selection. In other words, when antibiotics are used excessively, sensitive bacteria die while resistant bacteria increase (Akkan & Karaca, 2003; Fındık, 2011).

6. EFFECTS OF ANTIBIOTIC RESISTANCE

It is a health problem that connects humans, animals and the environment and affects the whole world. But the most important thing is that sometimes resistant bacteria pose a danger to humans

even though they do not harm animals. If antibiotics lose their effectiveness, performing many medical procedures can become dangerous. Antimicrobial resistance (AMD) causes hundreds of thousands of deaths annually, and especially multiple antimicrobial resistance causes food poisoning. It has been determined that if urgent measures are not taken against this situation, deaths and such poisoning situations will increase (Fındık, 2011; İrkin & et al., 2019).

Diseases can have adverse effects on health and well-being if left untreated. For example, resistance in animals kept as companions or for sports can lead to negative social consequences and economic losses for their owners in case of disease. In cases of infectious diseases in animals fed for food production, if treatment is not done, there may be negativities regarding the amount of productivity the affected enterprises should receive and the economic return they should obtain. Apart from this, if the way of using antibiotics is not changed, especially if the unconscious use of antibiotics and the use of antibiotics more or less than the recommended days are continued, these new antibiotics will either be less effective in the following treatment process or will suffer the same fate as those on the market and become ineffective. New drugs are generally more expensive because of new methods and methods to obtain them. After all, the old ones do not work. If the mechanism of action or chemical properties of the new antibiotic is the same as the old one, resistance to the new antibiotic will have already developed. Industrial problems arise when using the drug because most patients (in human medicine) or patient owners do not know the effect of antibiotics on beneficial microorganisms or harmful microorganisms, which is also essential. Most importantly, the antibiotics used in farm animals recently have a broader spectrum of action than in the past, creating a more general selective pressure. Reservoirs of resistant bacteria are undesirable in animals raised for food production. Because foods are offered for human consumption, despite this, these drugs are still used in many treatments (Fındık, 2011; İrkin & et al., 2019).

7. SPREAD OF RESISTANT BACTERIA IN THE ENVIRONMENT

The spread of resistant bacteria into the environment poses a risk for both animal and public health. After resistant bacteria spread from the environment to other living things, they cause disease and survive in the host. Because it is resistant, it causes both social and economic losses. Resistant bacteria: They can spread to the environment through animal products, animal waste, contaminated water or soil, contaminated surfaces, or flies and insects from scientific evaluation facilities (Yarsan, 2018).

8. PREVENTION OF ANTIBIOTIC RESISTANCE

Veterinarians, pharmaceutical companies, pharmaceutical warehouses, livestock business owners, and farmers must act responsibly to prevent antibiotic resistance and residue problems. The antibiotic's dosage regimen and treatment duration should be known. Pharmacokinetic (PK) and pharmacodynamic (PD) information is used in developing antibiotic resistance and new antibiotics, as well as in determining the appropriate antibiotic preparation, determining its dose, and accurately determining the plasma or tissue concentrations required to remove bacteria. PK and PD are essential in eliminating harmful microorganisms while not damaging beneficial bacteria. Because antibiotics that are not used in the appropriate dose and regimen harm beneficial bacteria and cause resistance. In addition, reducing antibiotic resistance can be possible by knowing the antibiotics used in treatment and the spectrum of effects they will create when used together. If antibiotic resistance is desired to be reduced, attention should be paid to the dose, dose intervals and duration of drug administration. Herd treatment should also be taken into consideration in reducing antibiotic resistance. Because poultry and fish are generally treated collectively with antibiotics added to their feed or water. After antibiotics are given collectively, sick animals in the herd are treated, and those who are not ill are protected. If microorganisms cannot be sterilised entirely after using antibiotics, bacteria that have mutated

and become resistant to the environment will increase and become dominant. Of course, since the main issue is human and animal health, antibiotics should be avoided as much as possible, and if used, they should be used under supervision and in a limited manner. If innovations or improvements are made in terms of human and animal health other than antibiotics, these should be done in more organic ways (Akalın, 2011; Daş and Atmaca, 2015; Fındık, 2011).

The physician performing the treatment must be knowledgeable in theory and practice. In addition to clinical experience, the patient must be able to use laboratory diagnostic tools. Likewise, the physician who continues the fight against resistant bacteria should establish authority in individuals, agriculture, industry, and health and continue the struggle in connection with these (Daş & Atmaca, 2015; Yarsan, 2018).

The correct antibiotic must be chosen. The priority in choosing antibiotics is the effectiveness of the drug in treatment. In other words, the antibiotic must be effective in the selected animal species. The sensitivity of the causative microorganism to the drug must be known. In addition, whether it has side effects and harm to the environment and the person applying it should be known. It must be diagnosed correctly. The drug's effectiveness must be demonstrated by field testing (Daş & Atmaca, 2015).

If the patient's condition is severe and the morbidity and mortality rate is high, the patient is first diagnosed clinically, and treatment is started taking this into account. The antibiotic to be used initially should be used in the starting dose. Then, microbiological examination and antibiogram tests are performed. Based on the data obtained from these tests, if the diagnosis is correct or antibiotic resistance is low, a narrow-spectrum antibiotic is used. If there is no response to the treatment after starting, that is, if the treatment is unsuccessful, the test is performed again after a week. Suppose the disease agent is unknown and the disease is severe and acute. In that case, a combination of antibiotics should be made without waiting for the antibiogram test results, paying attention to antagonist

interactions, taking precautions against the possibility of more severe side effects than usual, and paying attention to cross-resistance. Apart from combination, if the agent is known, antibiotics should be used in a programmed manner, i.e. rotation, to prevent the development of resistance. In cases where bacterial detection will take a long time, treatment should be started with broad-spectrum antibiotics. In the case of bacterial detection, treatment should be continued with narrow-spectrum antibiotics. If the patient's general condition returns to normal, antibiotics should be used for at least two more days after that day (Akalın, 2011; Akkan & Karaca, 2003; Yarsan, 2018).

It is necessary to have information about the patient's immune system. With this information, the use of appropriate spectrum antibiotics is decided. It is also essential to know the pharmacokinetic profile and distribution of the drug to be used later in the body. Knowing antibiotic combinations is also critical for correct treatment and shaping resistance. Immune status is vital for a healthy upbringing and sustainable farming. The patient's immune system is supported without medication by minimising or eliminating stress factors. If the immune system is insufficient or suppressed, antibiotics that kill bacteria should be used first because antibiotics that prevent the growth and development of bacteria are inadequate. This is also related to the fact that the antibiotic is effective when we use it in vitro but may not be effective when we use it in vivo. In some enterprises, the milk given to strengthen immunity is not clean but antibiotic-containing. This must also be prevented (Akkan & Karaca, 2003; Daş & Atmaca, 2015).

Pet animals show affection towards humans. People can infect others directly by licking or physical injuries or indirectly by contaminating the environment at home. Therefore, broad-spectrum or potentiated antibiotics should be used for pets. Although this is not the case in other farm animals, the correct antibiotics should be used in line with the necessary tests, except in exceptional cases. More importantly, precautions should be taken against the possibility that substances with food value, such as meat and milk,

and non-food substances, such as faeces, but used in other sectors, may carry resistant bacteria (Daş & Atmaca, 2015; Yarsan, 2018).

Finally, the more straightforward and economical thing we can do under the name of protection is record all treatments given to animals, prescriptions written, and medications used. The e-prescription system has been officially introduced to record the drugs used from 2017 to 2018. However, as mentioned before, antibiotic resistance is essential for human and animal health and should be addressed within the 'One Health Approach' due to its connection with agriculture and industry. Coordination centres should be established, and this problem should be combated with determined work with the necessary coordination (Daş & Atmaca, 2015; Yarsan, 2018).

9. NIGELLA SATIVA BIOACTIVE PROPERTIES AND AREAS OF USE

Nigella sativa (black cumin) appears to have antioxidant, anti-tumour, anti-inflammatory, anti-bacterial and stimulating effects on the immune system (Randhawa and AlGhamdi, 2002). Additionally, the biologically active compounds of black cumin include dithymoquinone, thymoquinone and thymohydroquinone. It is accepted that the primary active nutraceutical substance is thymoquinone. According to Hippocrates, the discoverer of today's modern medicine, it was used to strengthen the liver and eliminate problems in the digestive system. However, it is mentioned that Hippocrates used black cumin seeds for poisonous snake and scorpion stings, old tumours, wound treatment and skin rash, head area inflammations and flu infections. Penedius Dioscorides is the founder of modern herbal medicine, using black cumin oil to soothe headaches and toothaches, relieve nasal congestion, and eliminate parasites and intestinal infections. In its famous work called De Materia Medica (Medical Substances), she reported the areas of herbal production and their benefits. Additionally, black cumin seeds have been mentioned to treat menstrual irregularities, increase milk production and have diuretic properties. Studies have shown that

thymoquinone in black cumin has anti-cancer effects. It has been observed that it has healing and preventive properties against stomach cancer. The last prophet of Islam is Hz. Muhammad (S.A.V.) generally recommends using black cumin in his medicine. The words "Use this black cumin (nigella sativa); it will cure everything except death" have significantly affected the consumption of black cumin seeds in religion and society. Arab/Greek doctors use black cumin seeds and oil in medicine to relieve high fever, cold, headache, rheumatism and various microbial infectious diseases and destroy intestinal parasites. In Ibn Sina's work "The Law", which is considered an essential work in the history of medicine, he mentions the effects of black cumin, which stimulates metabolism and reduces fatigue. In addition, black cumin heals the lungs, helps digestion and eliminates toxins, is helpful against high fever, relieves colds, headaches and toothaches, treats skin diseases, heals cuts and parasites, and is therapeutic against intestinal tract, reptile and insect bites. In addition, while black cumin has rich nutritional and energy values, it is mentioned that black cumin oil regulates body temperature. Since the antihypertensive/lowering effects of black cumin seeds are well known, they are effective in controlling blood lipids due to their impact on blood pressure and fat metabolism. Low metabolic rate is believed to be the cause of many diseases. In addition, black cumin, rich in vitamins and minerals, is a source of vitamins A, C, H, B1, B2 and B6, folic acid and niacin. In addition, natural essential oils and oils obtained from the leaves, fruits, bark or non-woody root parts of trees are called "essential oils" and "ethylene oils" due to their smell. The compositions and concentrations of black fennel essential oils are presented in Table 1. These oils, generally liquid, are transparent or slightly yellow. These volatile extracts are immiscible in water and have a strong odour and explosive properties (Vijay, 2013).

Table 1. Essential oil components obtained from the black cumin plant (Wagh, 2013).

Critical oil names	Concentration (%)
Timokinon	23.25
Dihidrotimokinon	3.84
p-Simen	32.02
Timol	2.32
α-Thujen	2.4
Karvakrol	10.8
α-Pinen	1.48
t-Anethol	2.10
β-Pinen	1.72
Minor Components	23.81

These oils are essential antioxidants that are directly involved in reducing the effects of oxidation and peroxidation in foods and preventing and repairing oxidative cell damage. Studies have shown that it is helpful against peroxidation caused by free radicals in human and animal foods and against the trichomonas parasite, whose treatment is problematic. The antibacterial, antifungal, anti-inflammatory, anti-cancer, anti-diabetic and antioxidant properties of black cumin seed oil have been scientifically determined. In addition to its pleasant scent in pasta, bread, cakes, and other bakery products, cheese and pickles, its medicinal plant protection and support is also increasing. It is also used in cosmetics, dietary supplements, coffee, tea, and salads. Its chemical composition provides properties that indicate its use in foods. Percentage in chemical composition: The harvest time of the tree may vary depending on factors such as tree species, production region, and climate (Table 2) (Bankova & et al., 1995).

Table 2. *Chemical components of black cumin (Nigella sativa) plant*

Components	Concentrations %
dietary fibre	16.0
crude fibre	5.4
water	7.0
protein	23.0
oil	39.0
starch	15.0
ash	4.3

Antioxidant phytochemicals preserve food quality and extend food safety and shelf life by protecting foods against natural oxidation and peroxidation processes, as long as raw materials are used, production techniques, packaging, appropriate storage methods, high quality and diversity and reliable quantities. Studies have reported that black cumin oil has a higher antioxidant effect than saturated oil due to its polyunsaturated fatty acids. It has been determined that black cumin oil contains carotenoids and tocopherols, and its seed contains thymoquinone. The results show that the extraction method directly affects the composition and quality of black cumin oil and that oils produced by the cold press technique should be preferred, as oxidation of the oil from the dill is preferred. Black cumin oil is generally obtained by cold pressing rather than extraction (Vijay, 2013).

10. SOURCE, CONTENT AND AREAS OF USE OF PROPOLIS

Propolis is a substance obtained from the enzymatic secretion of plant secretions such as mucilage, gum, and resin by honey bees and from the leaves of various tree species such as date palm, pine, alder, poplar, oak and birch (Bankova & et al., 1995). Propolis, also known as propolis, is used to protect the hive against external factors

and invaders such as wind and water, fills the gaps in the hive, prevents the reproduction of microorganisms that may occur in bee larvae, honeycombs and hives, and keeps the hives alive. The composition of propolis, which has a characteristic odour and taste, varies according to the conditions of the harvest area, harvest time and type of production, regional conditions and climate characteristics. For example, in China, the plant source of propolis is predominantly poplar, while in Brazil, it is Baccaris. Due to these differences, the main components of Chinese propolis are flavonoid aglycones, phenolic acids, and phenolic acid esters; Brazilian propolis is rich in fumaric acid, which is the precursor of acetophenone, diterpenes and flavonoids. Although propolis generally consists of P resin and herbal balsam, it contains beeswax, 5% pollen, aromatic essential oil and more than 20 components. The main components of propolis consist of aromatic acids (cinnamic acid, caffeic acid, ferulic acid), aromatic esters (ethyl esters of cinnamic acid and caffeic acid), volatile compounds (geraniol, nerol, farnesol, βeudesmol), aromatic compounds (vanillin), hydrocarbons (Eicosan, triclosan, pentosan), steroids (cholesterol, fucosterol, stigmasterol), enzymes (αamylase, βamylase), flavonoids (pinocembrin, chrysin, galangin, apigenin, kaempferol), acids (palmitic acid, acid melisic, cerotic acid), minerals (calcium, potassium, magnesium, sodium, zinc, chlorine, iron), vitamins (Thiamine, riboflavin, pyridoxine, vitamins C and E) and essential oils (Monoterpenes and sesquiterpenes) (Kubiliene & et al., 2015). Before application, raw propolis is extracted by solvents such as ethanol, methanol, chloroform, ether, acetone, and water. Although propolis extract as a nutritional supplement in the pharmaceutical field has recently gained popularity, it is also used in dental products, creams, antiseptics and cosmetic products (Bankova et al., 1995). In addition to its widespread use, propolis has the potential to be used as a natural preservative in foods with its functional components (Vijay, 2013).

People in British Columbia have used propolis for a variety of medicinal purposes. It is known that it has been used for 300 years.

It is generally accepted that propolis positively affects human health with its antibacterial, antioxidant, antifungal, anti-inflammatory, antiviral, anaesthetic, antitumor and antiprotozoal, anticancer, antihypertensive and antitoxic activities. In addition, propolis has therapeutic effects on livestock growth performance and productivity. Propolis can act as a biocide and exhibits antibacterial activity by stopping bacterial division and protein synthesis, destroying the bacterial cell wall and cytoplasm. Studies in the literature report that propolis has activities such as scavenging and quenching free radicals and preventing lipid peroxidation due to its high antioxidant composition. In addition, various studies have shown that more than 26 components in the structure of propolis, especially components such as flavonoids, 3acetyl pinobanksin, pinobaxin, pinocembrin, fumaric acid and caffeic acid, have antimicrobial activity. Although the composition of propolis varies depending on various factors, propolis samples collected from different regions have been reported to be highly bioactive (Beyaz, 2014).

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CHAPTER IV

Role of Gut Microbiota in Neurodegenerative Diseases

Pınar Ellergezen[1]

The fields of neurology and microbiology have historically developed on separate paths with minimal intersections, excluding instances of central nervous system (CNS) infections (bacterial or viral), Guillain-Barré syndrome, and some encephalopathies. Nevertheless, in the last twenty years, a transformative innovation has taken place in biomedicine, bringing about the realization that the gut microbiota, comprising countless microorganisms inhabiting the gut, and the microbiome, encompassing the genetic material of these microorganisms, play a crucial function in preserving homeostasis and orchestrating nearly every primary physiological system, comprising the CNS. Investigations on animals have played a pivotal role in demonstrating the essential significance of the microbiota in

[1] Dr. Pınar Ellergezen, Bursa Uludag University, Faculty of Medicine, Department of Medical Pharmacology

fundamental facets of neurodevelopment, neuroinflammation, and behavior. Extensive research has concentrated on uncovering the bidirectional communication routes connecting gut bacteria with the CNS, often called the microbiota-gut-brain axis (MGBA). Over the past five years, there has been an increasing acknowledgment of the role played by dysregulation in the MGBA in the development of neurological disorders, encompassing conditions such as Alzheimer's disease (AD), autism spectrum disorder (ASD), multiple sclerosis (MS), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and schizophrenia. This review presents a refreshed analysis of the relationship between microbiota and brain function within the framework of neurological disorders.

Microbiota–Gut-Brain Axis (MGBA)

The physiological link between the gut and the brain is pivotal in attaining gastrointestinal balance and upholding cognitive and limbic operations. This interwoven correlation involving the CNS, autonomic nervous system (ANS), enteric nervous system (ENS), and hypothalamic-pituitary-adrenal (HPA) axis is widely referred to as the gut-brain axis (Mayer, 2011). The interaction contains direct and indirect pathways that link the cognitive and emotional hubs of the brain with peripheral digestive activities. The autonomic nervous system's sympathetic and parasympathetic divisions are within the gut-brain axis. These divisions transmit sensory and motor neural signals that establish connections within the gut-brain axis. Experimental findings demonstrate gut microbiota's prominent effect on the modulation of the gut-brain axis (Cryan & O'Mahony, 2011; Collins & Bercik, 2013). An imbalance in the gut microbiome can play a role in the onset of immunological, neurological, and psychiatric conditions. Furthermore, disruptions in gut microbiota composition are associated with gastrointestinal disorders (Foster & McVey Neufeld, 2013).

The Arrangement of Gut Microbiota Contributes to the Regulation of Nervous System Functions

Studies conducted on animals without microorganisms have demonstrated that populating gut microbiota is crucial for developing the CNS and the ENS. Insufficient establishment of the microbiota induces changes in gene expression and the production of neurotransmitters and disturbances in the sensory-motor functions of the gut (Rao & Gershon, 2016). Similarly, the nutrients within the gastrointestinal (GI) tract initiate a sequence of neural and hormonal reactions, transforming information to the brain regarding ongoing changes in nutrition. Sensory nerve fibers transmit data from the GI tract to both subcortical and cortical regions of the brain, while motor fibers transport signals to the smooth muscles within the GI tract (Rinaman, 2007). Hormones from the gut, secreted by intestinal cells, usually get information to the brain by directly engaging with the CNS via sensory fibers. Certain gut hormones are directly discharged into the bloodstream, and their impacts are typically observed upon entering the brain (Scarlett & Schwartz, 2015). Activating the parasympathetic branch of the ANS via the vagus nerve is crucial for the gut microbiota to impact neurophysiological function (Forsythe et al., 2010). A study involving mice that had undergone vagotomy revealed that behavioral traits showed no noticeable improvement after treatment with the probiotic *Lactobacillus rhamnosus.* This discovery underscores the vital importance of stimulating the vagus nerve and transmitting signals through it to induce shifts in behavior. The signal transmission from the intestine to the brainstem occurs via the activated vagus nerve, utilizing nuclei and ganglion nodes as intermediary points in establishing the link between the gut-brain axis (Latorre et al., 2015). Peptide hormones released by enteroendocrine cells stimulate the vagus nerve, transforming crucial information to the brain (Lihua & Liddle, 2017). The deliberate positioning of enteroendocrine cells close to the gut lumen and the presence of gut microbiota facilitates interactions with gut microbes via the metabolites they generate. This interplay contributes to the regulation of targeted peptide

hormone secretion. Moreover, the metabolites generated by the microbiota are commonly taken up into the bloodstream. In the meantime, metabolites resembling sugars and vitamins in the structure are conveyed via dedicated transporters (Furness, 2016). Upon breach of the epithelium, metabolites can traverse the membrane, permitting other microbes to bypass the barrier. This can result in microbial imbalance or dysbiosis, frequently followed by inflammation. Thus, the circulatory system assumes a crucial role in regulating signal transmission to the brain and facilitating the transport of metabolites.

Molecules like lipopolysaccharides (LPSs) and peptidoglycans, released by the gut microbiota, initiate the immune response. In specific scenarios, gram-negative bacteria that produce LPS can travel from the gut to the circulatory system, sparking immune reactions in peripheral tissues. Research has indicated that such peripheral immune activation can contribute to the emergence of behavioral disruptions, including depression (Leonard, 2010). Studies conducted on mice without any microorganisms demonstrate a connection between gut microbes and the subsequent immune reaction, implying the potential impact of the microbiota on neural functions via immune responses (Wu & Eric, 2012). Moreover, the gut microbiome can establish connections with the brain by producing and synthesizing a range of neurotransmitters, such as serotonin, GABA, melatonin, histamine, and acetylcholine, along with neurotrophic factors like brain-derived neurotrophic factor (BDNF). Subsequently, these interactions impact the enteric nervous system's (ENS) functioning (Chen, Xu & Chen, 2021).

The CNS Plays A Pivotal Role in Regulating Gastrointestinal Functions

The brain holds a significant role in overseeing a range of gut functions, encompassing motility, releasing of acids, mucosal immune response, and the adequate upkeep of the mucus layer and biofilm. Additionally, the brain can impact the composition and operation of the microbiota by inducing differentiation in intestinal

permeability (Sittipo et al., 2022). Research suggested that acute stress could result in structural modifications in the epithelial barrier of the colon, coupled with diminished mRNA expression of the tight junction protein ZO-2. Consequently, gut microorganisms could potentially breach the barrier (Kelly et al., 2015). Furthermore, the brain impacts immune functions via the autonomic nervous system (ANS). CNS also has the potential to influence mast cell activity, and the discharge of mast cell mediators could play a role in gastrointestinal dysfunction. Based on a study, stress can regulate mast cell activity and induce histamine and tryptase release (Kempuraj et al., 2017). Products from mast cells, such as corticotropin-releasing factor, can elevate epithelial permeability, making it easier for bacteria to reach immune cells in the lamina propria. Mild stress induced by neonatal maternal separation in adult rats has been linked to the emergence of colonic barrier dysfunction, predominantly driven by corticotropin-releasing hormone receptors (S¨oderholm et al., 2002). Experiments conducted on mice in laboratory settings have shown that bilateral olfactory bulbectomy results in the initiation of depression, marked by heightened expression of central corticotropin-releasing hormone and elevated serotonin levels. These alterations were associated with a changed gut microbiota composition (Becker, Pinhasov & Ornoy, 2021). Furthermore, the release of norepinephrine during periods of stress induces the expression of *Pseudomonas aeruginosa* virulence factors, potentially leading to gut sepsis (Carabotti et al., 2015). As a result, stress could trigger the activation of virulence factors in particular gut microorganisms within the suitable host. Additionally, norepinephrine prompts the expansion of different types of enteric microbes, which could lead to heightened growth of pathogenic and nonpathogenic *Escherichia coli* strains (Sasikiran et al., 2014). Indications propose that gut microbiota enables two-way communication between the gastrointestinal and nervous systems. The correlation between the gut microbiota and the CNS has been related to anxiety, stress, and memory capabilities. On the other

hand, the CNS can also impact microbial composition by disturbing the mucosal environment.

The gut microbial community has a profound impact on the human brain and, in turn, the entire body, given that the brain governs the functioning of the human body. Consequently, a substantial disturbance in the gut microbiota can impair overall body function, potentially leading to the development or exacerbation of specific diseases. Because of its direct interaction with the brain, the impact on neurological function is more notable than other complications arising from CNS disruptions caused by microbiome community changes (Figure 1).

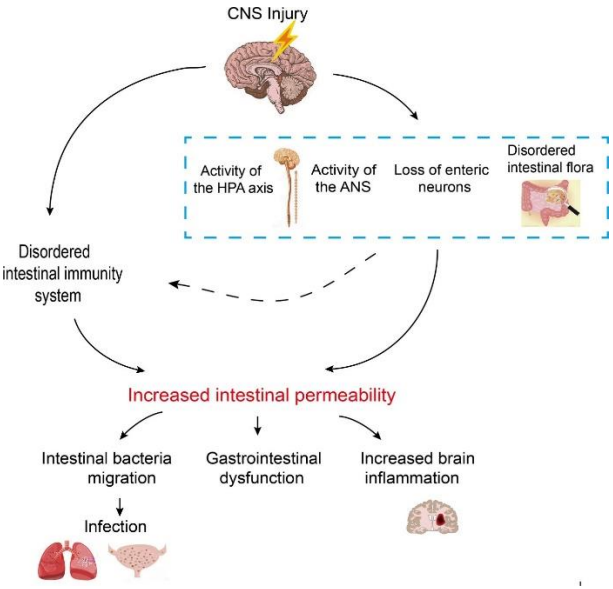

Figure 1. Overstimulation of the hypothalamus-pituitary-adrenal axis and the autonomic nervous system, coupled with the partial depletion of intestinal neurons and a disruption in the balance of the intestinal flora following central nervous system injury, alter the internal milieu. This alteration contributes to heightened intestinal permeability, potentially resulting in adverse effects such as intestinal bacteria's translocation, gastrointestinal system

dysfunction, and brain injury exacerbation. Additionally, nervous dysfunction and imbalances in the intestinal flora contribute to immune imbalances in the intestines, further escalating intestinal permeability and negatively impacting patient outcomes.

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Microbiota and Neuroinflammatory Conditions

Autism Spectrum Disorder (ASD)

ASD is a neuropsychiatric condition identified by repetitive behaviors, cognitive difficulties, and challenges in social interactions (Hodges, Fealko & Soares, 2020). The condition usually becomes apparent before age three and impacts around one in 68 children, with a prevalence four times higher in males than females (Lord et al., 2018). Furthermore, the disorder's heterogeneity is accompanied by an unclear understanding of its pathophysiology and the etiological mechanisms linked to disrupted gut microbiota. These processes could encompass glutamate excitotoxicity, oxidative stress, and neuroinflammation. Physiological elements that highlight the impact of the gut microbiota on autism might include autoimmune responses, dietary sensitivities, upper gastrointestinal conditions, atypical stool patterns, enterocolitis linked to autism, increased gut permeability, elevated inflammation, disrupted glutathione levels, and irregularities in metal or mineral concentrations (Ristori et al., 2019). Among children with autism, heightened intestinal permeability can result in a permeable gut, enabling the passage of neurotoxic compounds via an inflamed gut lining. This process may play a role in the emergence of neurological diseases. Following the onset of a permeable gut, which permits the entry of molecules into the bloodstream, a sequence of events, including immune activation, tissue impairment, and potential damage to brain tissue, may ensue progressively (Dargenio et al., 2023). Furthermore, opioid peptides generated from specific diets could potentially influence behaviors resembling autism, resulting in

decreased social interaction, altered pain perception, atypical language, and the manifestation of self-injurious or repetitive conduct through their interaction with neurotransmitter activity. Nevertheless, a direct connection between these dietary preferences and ASD has not been conclusively established. Studies have also noted that children with ASD commonly prefer starchy foods, snacks, and processed items, frequently displaying an aversion to fruits, vegetables, and proteins (Esposito et al., 2023). While disruption in the gut microbiota can potentially result in gut dysbiosis, certain pathogenic bacteria might trigger neurological disorders significantly when the immune system is compromised. Toxins produced by these bacteria can accumulate in the bloodstream, giving rise to symptoms such as confusion, delirium, and, in severe cases, even coma (Yoo et al., 2020). The connection between the gut microbiota and autism was additionally reinforced when the transplantation of gut microbiota from individuals with autism into germ-free mice led to the manifestation of autistic behaviors in a rodent model (Sharon et al., 2019). Williams et al. proposed a hypothesis stating that children with ASD might have a deficiency of Bacteroidetes, which have significant assignments in polysaccharide digestion. As a result, individuals with ASD might demonstrate compromised carbohydrate digestion capabilities and encounter mucosal dysbiosis (Williams et al., 2011). Subsequently, a metagenomic analysis showed that ASD patients exhibited reduced Bacteroidetes, an elevated Firmicutes to Bacteroidetes ratio, and increased Betaproteobacteria (Oh & Cheon, 2020). Furthermore, an analysis of fecal microflora using pyrosequencing unveiled noteworthy disparities within the Actinobacteria and Proteobacterium phyla compared to healthy individuals' microflora (Plaza-Díaz et al., 2015). The pyrosequencing investigation and three supplementary studies disclosed an increased prevalence of Desulfovibrio species and *Bacteroides vulgatus* in the fecal samples of individuals with ASD. Desulfovibrio species are also associated with elevated propionic acid production, which could potentially play a role in the development of ASD (Fattorusso et al., 2019).

Additionally, the decreased presence of Akkermansia, which are bacteria responsible for breaking down mucin, in children with ASD indicated a potentially thinner gastrointestinal mucosal barrier compared to the control group. This could lead to compromised gut permeability in children with ASD (Agarwala, Naik & Ramachandra, 2021). In a separate investigation, fluorescent in situ hybridization exhibited elevated quantities of *Clostridium hystolyticum* in children diagnosed with ASD compared to their healthy counterparts. Clostridia, acknowledged for their role in propionate production, have been postulated as potential triggers of autism, attributing to their participation in the neurological changes identified in rat models (Solgi et al., 2020). In an independent study examining the occurrence of four strains of beneficial bacteria- Bifidobacterium, *Lactobacillus spp., E. coli*, and Enterococcus- it was revealed that children diagnosed with ASD exhibited notably diminished quantities of Bifidobacterium, slightly decreased levels of Enterococcus, and markedly elevated levels of Lactobacillus. Moreover, they showed more *Bacillus spp*. and fewer *Klebsiella oxytoca* than other subjects. In the same investigation, it was also observed that children with ASD exhibited decreased levels of SCFAs, potentially stemming from a diminished saccharolytic fermentation process carried out by beneficial bacteria. This observation further strengthens the association between the gut microbiome and autism. Considering that metabolites generated by bacteria can directly impact neural functions, it was noted that individuals with ASD displayed heightened urinary excretion of an anomalous phenylalanine metabolite known as HPHPA, which is produced by Clostridia species. Clostridia species influence autism symptoms in experimental animals, encompassing stereotyped behaviors, hyperactivity, and hyper-reactivity through the depletion of catecholamines (Argou-Cardozo & Zeidán-Chuliá, 2018).

Apart from a leaky gut and the inclusion of specific foods in an individual's diet, metabolites produced by gut microorganisms can potentially influence symptoms resembling ASD in individuals. Furthermore, the excessive or diminished presence of particular

microorganisms in the gut is acknowledged as a potential element contributing to neurological disorders such as ASD, a notion reinforced by multiple hypotheses.

Multiple Sclerosis (MS)

MS is a persistent neurodegenerative condition marked by inflammation and demyelination, impacting the CNS and giving rise to distinctive brain and spinal cord lesions (Ghasemi, Razavi, & Nikzad, 2017). MS can lead to various symptoms, encompassing fatigue, numbness, impaired coordination, vertigo, visual impairment, dizziness, discomfort, bladder and bowel function disruptions, and even depressive states. It affects around 2.3 million people worldwide (Joshua et al., 2022). Furthermore, MS triggers a rise in autoreactive immune cells that target the CNS. Considering the gut microbiota's function in educating the immune system and its significant involvement in various autoimmune and metabolic disorders, it is plausible to establish a connection between gut commensal flora and susceptibility to MS (Ochoa-Repáraz, Kirby & Kasper, 2018). A study by Rumah et al. showed that a patient experiencing her first MS relapse exhibited human gut colonization by *Clostridium perfringens* type B. This pathogen released epsilon toxin, which resulted in microangiopathy. Further investigations indicated that this toxin could lead to BBB disruption, causing damage to neurons and oligodendrocytes. Upon comparison between MS patients and controls, MS patients exhibited a higher prevalence of antibodies against epsilon toxin in their sera (Rumah et al., 2013). Additionally, Jangi et al. demonstrated an elevated concentration of the archaea Methanobrevibacter in MS patients. When comparing MS patients to control subjects, a notable reduction was observed in the levels of Butyricimonas, Lachnospiraceae, and Faecalibacterium. The diminished prevalence of Faecalibacterium was similarly noted within the microbiome of individuals afflicted with inflammatory bowel disease. The bacteria *Faecalibacterium prausnitzii* plays a role in producing butyrate, contributing to T_{reg} cell proliferation. This correlation implies a potential link between alterations in gut microbiota and the onset of MS (Jangi et al., 2016).

Additionally, it was discovered that heightened levels of Shigella, Escherichia, and Clostridium were linked to infection and inflammation, as well as diminished levels of *Eubacterium rectale* and Corynebacterium when investigating pediatric MS patients (Forbes, Domselaar & Bernstein, 2016). In a study by Baranzini et al., 71 MS patients and 71 healthy controls were analyzed using 16S rRNA gene sequencing. The findings indicated that individuals with MS exhibited elevated levels of *Akkermansia muciniphila* and *Acinetobacter calcoaceticus*, alongside reduced levels of *Parabacteroides distasonis* within the gut, in contrast to the healthy control group (Tremlett & Waubant, 2018). Subsequently, upon transplanting gut bacteria from a mouse model of autoimmune encephalomyelitis, the researchers observed that the MS-associated microbiota worsened the condition of encephalomyelitis (Berer et al., 2017). Multiple studies have demonstrated that MS patients may exhibit alterations in specific gut microorganisms compared to healthy controls, with some microorganisms showing decreased abundance while others showing increased levels. Additionally, heightened concentrations of particular antibodies, generated as a response to toxins released by microorganisms, have been detected in individuals with MS (Schepici et al., 2019). Considering the crucial role of the gut microbiota in immune system development and maturation, it is logical to associate the microbiota with the pathogenesis of multiple sclerosis, an immune-mediated neurological disorder. Cross-sectional investigations have primarily shown that among children with MS within the initial two years of disease onset, distinct alterations in the taxonomic composition of the gut microbiota are evident, rather than significant variations in α-diversity or β-diversity. These changes are contrasted with those observed in healthy children without autoimmune disorders, spanning up to the age of 18 years (Tremlett et al., 2016). In two distinct investigations, microbiota obtained from individuals with multiple sclerosis was introduced into experimental autoimmune encephalomyelitis models, a well-established animal model frequently used for studying multiple sclerosis. These studies

underscored the importance of IL10-producing CD4 T cells in the immunomodulatory impacts of the gut microbiota (Perez-Muñoz et al., 2021). Preliminary examinations in germ-free mice showcased their increased resilience against developing experimental autoimmune encephalomyelitis. Subsequently, this resistance was counteracted by the transplantation of fecal microbiota from healthy mice into germ-free mice. Moreover, the presence of particular Gram-positive segmented filamentous bacteria in the gastrointestinal tract, responsible for activating Th17 cells, substantially impacted the severity of experimental autoimmune encephalomyelitis (Li et al., 2020).

Converging evidence from studies involving germ-free mice and antibiotic-based preclinical research has pointed to the involvement of the microbiota in regulating myelin production in the prefrontal cortex of mice. This underscores the importance of MS as a demyelinating disorder (McMurran et al., 2019). Research conducted on germ-free mice has connected the disruption of the blood-brain barrier, a characteristic feature of multiple sclerosis, to the microbiota. Additionally, oral supplementation of short-chain fatty acids or bacterial strains producing such fatty acids has shown potential in reversing the loss of blood-brain barrier integrity. Changes in microbiota composition caused by dietary factors have been associated with the onset of experimental autoimmune encephalomyelitis (Silva, Bernardi & Frozza, 2020).

Mounting evidence indicates that the microbiota plays a substantial role in governing neuroinflammation. However, more research is required to fully comprehend the implications of this relationship in the pathophysiology of MS. By integrating findings from human and animal investigations, it becomes clear that the microbiota might notably influence various aspects of MS pathology. The task involves identifying practical approaches for targeting the microbiota as an intervention strategy to mitigate relapses and alleviate patient symptoms. In an initial inquiry, a combination probiotic containing Lactobacillus, Bifidobacterium, and Streptococcus species was administered twice daily over two

months. This intervention reversed alterations in the microbiota and exhibited potential anti-inflammatory effects. These findings indicate the potential value of a microbiota-targeted approach, but larger-scale trials are required to validate these results conclusively (Tankou et al., 2018).

Alzheimer's Disease (AD)

AD is an advancing neurodegenerative disorder marked by cognitive decline and abnormal accumulation of amyloid beta (Aβ) protein in the interstitial spaces of brain tissues, leading to memory impairment (Knopman et al., 2021). Approximately 44 million individuals globally are diagnosed with AD, with a higher likelihood of occurrence in individuals aged over 65 years (Monfared et al., 2022). AD symptoms tend to worsen gradually, causing challenges in language, disorientation, mood fluctuations, diminished motivation, and difficulties with self-care. The microbiota of the gastrointestinal tract holds a noteworthy responsibility in upholding the host's regular physiology and operations. Any alterations in the gut microbiota can consequently affect brain function, leading to alterations in the host's conduct. The precise origin of AD remains elusive and is believed to arise from an intricate interplay of genetic and environmental elements.

As per Appleton's research, the human gut's commensal microbiota can impact brain function and behavior via the microbiota-gut-brain axis, indicating a potential involvement in AD mechanisms. (Appleton, 2018). Additional examinations utilizing germ-free animals and subjects exposed to pathogenic microbial infections, antibiotics, probiotics, and fecal microbiota transplantation have furnished insights into the influence of gut microbiota on host cognition and the development of AD pathology. Dysbiosis of the microbiota can result in heightened gut permeability and affect the blood-brain barrier (BBB), influencing the pathogenesis of AD and other neurodegenerative conditions (Wu et al., 2021). Furthermore, specific bacteria in the gut microbiota can secrete amyloids and LPSs, potentially impacting signaling

pathways and stimulating the generation of proinflammatory cytokines, thereby potentially contributing to AD (Megur et al., 2021). Moreover, recent studies involving rodents have suggested a potential link between alterations in the gut microbiome and the accumulation of amyloid deposits (Vogt et al., 2017). On the other hand, human studies have yet to entirely characterize the specific microorganisms associated with AD. DNA was extracted from fecal samples to compare the gut microbiome composition in participants with and without AD-related dementia. The study employed bacterial 16S rRNA gene sequencing on the isolated DNA and found that AD patients had decreased microbial diversity and a distinct composition compared to age- and sex-matched individuals without AD (Chen et al., 2022).

Aging represents a significant risk factor for AD and can induce excessive innate and adaptive immune system stimulation, resulting in inflammation. Such inflammation can result in heightened gut permeability and the translocation of bacteria (58). In the elderly population, the makeup of the gut microbiota changes, including a reduction in specific beneficial bacteria like Bacteroidetes, Lactobacillus, and Bifidobacterium. Bifidobacterium, Lactobacillus, and Faecalibacterium have the potential to modulate inflammation at the gut epithelium level (Guo et al., 2022). Age-related compromise of the BBB affects the clearance of Aβ from the brain. It impacts the secretome and receptor-mediated signaling involved in the neuroinflammation seen in AD (Marques et al., 2013). Consequently, alterations in the gut microbiota that occur with age could potentially contribute to inflammatory processes, thereby intensifying the neuroinflammatory effects seen in AD.

Bacteria residing in the gut release significant quantities of LPSs and amyloids, potentially adding to the pathogenesis of AD due to the heightened permeability of the gastrointestinal tract epithelium and BBB associated with aging (Sochocka et al., 2019). Lipopolysaccharides (LPSs), crucial constituents of the outer membrane in gram-negative bacteria, have demonstrated the ability to induce the inflammatory and pathological characteristics seen in

AD when introduced into the fourth ventricle of experimental rat models (Batista et al., 2019). Furthermore, an in vitro study indicated that bacterial LPSs enhance the fibrillogenesis of Aβ peptides (Kowalski & Mulak, 2019). In a separate study, mice receiving numerous intraperitoneal injections of LPSs exhibited increased levels of Aβ in the hippocampus and cognitive impairments (Kahn et al., 2012). As indicated by Jaeger et al., intraperitoneal injections of LPSs in mice led to an augmentation in blood-to-brain influx and a reduction in brain-to-blood efflux, ultimately culminating in the accumulation of Aβ (Jaeger et al., 2009). Furthermore, in a study investigating Bacteroides fragilis, the exposure of LPSs to human primary brain cells revealed their potent role as inducers of a proinflammatory transcription factor, contributing to the initiation of inflammatory neurodegeneration in AD (Lukiw, 2016). Moreover, numerous bacterial strains, such as *E. coli*, *Bacillus subtilis*, *Salmonella typhimurium*, *Salmonella enterica*, *Mycobacterium tuberculosis, and Staphylococcus aureus*, can produce a substantial amount of functional amyloid along with LPSs. This functional amyloid might play a role in AD pathology by fostering the buildup of misfolded proteinaceous Aβ oligomers and fibrils (Gerven et al., 2018). A hypothesis suggests bacterial amyloids could escape from the gastrointestinal tract, potentially adding to the systemic and central nervous system amyloid load. These amyloids might stimulate proinflammatory cytokines, which could cross the gastrointestinal tract and blood-brain barrier, leading to immune reactions and signaling processes contributing to neurodegeneration (Miller et al., 2021).

Parkinson's Disease (PD)

Despite the several defining cellular and molecular features of PD, specific experts propose that PD might originate from intestinal pathologies and that the intestinal microbiota has a crucial function in initiating and propagating the disease (Huang et al., 2021). PD patients frequently exhibit intestinal microbial overgrowth, characterized by a substantial increase in coliform bacteria, as a common occurrence (Yemula et al., 2021). The

significant rise of almost two-fold in urinary indican concentrations, an indicator of microbial dysbiosis, among PD patients suggests the pivotal role of intestinal microbiota in PD development. The community of microbes found in the fecal matter of individuals with PD can exhibit notable differences compared to those without the condition (Yang et al., 2019). Research outcomes demonstrated that a reduction in the usually beneficial and inflammation-reducing bacteria that produce butyrate, such as Blautia, Coprococcus, and Roseburia, was observed in the fecal samples of individuals with PD compared to healthy controls (Singh et al., 2022). In contrast, the intestinal mucosa of individuals with PD exhibited a higher prevalence of pro-inflammatory gram-negative bacteria belonging to the Ralstonia genus compared to the intestinal mucosa of healthy individuals (Hashish & Salama, 2023). Moreover, a direct association was identified between increased Unified Parkinson's Disease Rating Scale (UPDRS) scores in individuals with PD, indicating a more severe stage of the disease, and higher levels of *Eubacterium eligens, Eubacterium rectale*, and *Eubacterium hallii* within their system (Gerhardt & Mohajeri, 2018). Several studies have confirmed that PD patients commonly exhibit a reduced quantity of *Prevotella spp.* and an increased abundance of Enterobacteriaceae family bacteria (Gerhardt & Mohajeri, 2018; Jin et al., 2019).

Prevotella bacteria are regarded as advantageous due to their involvement in converting plant polysaccharides and vitamins into valuable bioactive compounds through metabolic processes. They also produce neuroactive short-chain fatty acids (SCFAs) like GABA, positively affecting the nervous system (Salim et al., 2023). Diminished mucin production has been linked to reduced levels of *Prevotella spp.* Mucin proteins, characterized by their substantial molecular weight and O-linked glycoprotein structure, form a lining on mucosal surfaces, playing a vital role in upholding the integrity of the epithelial barrier. The formation of mucin is connected to heightened intestinal permeability, a clinical characteristic linked to microbial imbalance and PD (Suriano et al., 2022). However, there

is some disagreement among experts regarding the connection between microbial dysbiosis and PD, particularly concerning the weakened integrity of the intestinal mucosa (Berthouzoz et al., 2023). The BBB disruption is commonly observed in PD patients. It could contribute to the targeted escalation of dopaminergic neuron loss in the substantia nigra (SN). The reduced integrity of the intestinal barrier and the BBB may create a scenario where enhanced indirect communication occurs between gut microbiota and CNS cells (Gwak & Chang, 2021). In mice, administering LPS through peripheral injections has been employed as a model to replicate PD, as it triggers a PD-like phenotype characterized by selective neurotoxicity in the SN (Deng et al., 2020). The marked diversity in microglia activation corresponded with an observable distinction in motor capabilities between the two sets of mice. SPF mice administered SCFAs from wild-type mice exhibited a notable enhancement of two to three times in performance across a range of murine motor skills assessments compared to their counterparts. These discoveries illustrate the potential advantages of healthy mice-derived microbial metabolites for brain well-being, while metabolites from PD mice may promote neuroinflammation (Bihan et al., 2022). A longitudinal investigation uncovered that constipation correlated with an elevated risk of developing PD, ranging from 3 to 11-fold higher, contingent upon the severity of the symptoms. This finding confirms that constipation is one of the non-motor manifestations of PD (Yu et al., 2018). Gut bacteria can significantly impact intestinal operations, encompassing gastric emptying and constipation. Specific investigations have proposed a potential connection between constipation in PD patients exhibiting symptoms resembling irritable bowel syndrome (IBS) and reduced levels of Prevotella bacteria, distinguishing them from PD patients who do not experience pronounced gastrointestinal symptoms. The studies mentioned above reveal alterations in microbiota composition among individuals with PD, but causation remains uncertain (Mancabelli et al., 2017; Mertsalmi et al., 2017). Human research has shown a higher prevalence of *Helicobacter pylori*

infections in individuals with PD compared to the general population (Nyholm & Hellström, 2021). A double-blind clinical trial was conducted to investigate the role of *H. pylori* in PD pathology. The findings demonstrated that eliminating *H. pylori* infection among PD patients led to notable enhancements in disease symptoms, including augmented stride length and diminished rigidity, regardless of the administration of PD medications (Hashim et al., 2014). Preceding the motor symptoms of PD, specific gastrointestinal problems and instances like constipation have been noted to be impacted by the intestinal microbiota composition (Rodger, 2018). Further substantiation of PD as a disease associated with gut microbiota is apparent in research, pointing to the presence of PD's pathological traits, like α-synuclein protein aggregates, within neurons of the peripheral nervous system, including those situated in the enteric neurons of the gut (Scheperjans et al., 2015). A study using adult wild-type Sprague Dawley rats noted that when α-synuclein protein lysates obtained from human PD patients were introduced into the intestinal wall of rats, they gradually migrated towards the dorsal motor nucleus through the vagus nerve. By the twelve-hour mark following injection, α-synuclein was mainly identified within the intestinal wall, showing limited presence in the vagus nerve. However, within two days, α-synuclein began to be observable in the vagus nerve, and by the sixth day after injection, its presence was apparent in the rats' brainstem. This sequence underscores the transport of α-synuclein from the peripheral nervous system to the CNS. Given the ability of the intestinal microbiota to interact with the CNS via the vagus nerve and impact intestinal absorption, the notion arises that gut microbes could potentially contribute to the conveyance of α-synuclein from the gut to the CNS. The mounting body of evidence implies that PD could emerge from gut-related factors or, at minimum, that gut microbiota can exert substantial influence over PD's progression, notably through neuroinflammatory pathways (Yang et al., 2023).

Amyotrophic Lateral Sclerosis (ALS)

While primarily characterized by diminished neural function and weakened muscles, ALS is associated with gastrointestinal manifestations like delayed gastric emptying and reduced colonic transit times. These aspects underscore its classification as a multi-system disorder (Martin, Battistini & Sun, 2022).

In a recent clinical investigation, a limited cohort of ALS patients underwent evaluation, revealing that gastrointestinal symptoms manifested before neurological symptoms in this group. Moreover, the study demonstrated that all individuals with ALS displayed a diminished variety in their gut microbiome compared to those in good health. The observed gastrointestinal abnormalities in individuals with ALS might be connected to the identified rise in intestinal permeability in these patients (Zhang et al., 2009). Research has consistently shown that ALS patients encounter heightened gut permeability, resulting in roughly a twofold increase in circulating LPS levels compared to those in good health. Elevated activation of monocytes accompanies this escalation in LPS levels. In ALS patients, there is a reduction in the integrity of the blood-spinal cord barrier (BSCB) and the BBB. In contrast to healthy individuals, ALS patients exhibit a notable decrease of around 25% in the expression of ZO-1 at the BSCB. Follow-up investigations have corroborated and broadened this finding, unveiling a reduction in brain ZO-1 expression by up to 2.7-fold, a twofold decrease in occludin expression, a threefold decline in claudin-5 expression, a decrease in junction adhesion molecule (JAM)-1 expression by 2.5-fold, and a reduction in vascular endothelial (VE)-cadherin expression by 1.8-fold along both the BBB and BSCB within the brains of ALS patients. The notable changes in tight junction protein expression noted among ALS patients were linked to a roughly 3.5-fold increase in BBB permeability. This heightened leakage of the BBB corresponded with elevated markers of immune cell infiltration and intensified inflammation within the CNS (Mirian et al., 2022). For example, investigations indicated that the compromised integrity of the BBB in individuals with ALS led to increased macrophages

and mast cells infiltration into the brain and spinal cord. Furthermore, there was an elevation in COX-2 levels within these affected regions (Garbuzova-Davis & Sanberg, 2014). In mouse models of ALS, there is a significant alteration in gut microbial colonization, characterized by a decreased relative abundance of fecal *E. coli*, *Firmicutes peptostreptococcus*, and *Butyrivibrio fibrisolvens*. Each bacterial type exhibits a reduced presence of around 50% compared to wild-type mice. The variations in gut microbiota correspond to a 50% decline in colonic expression of ZO-1 and a 25% decrease in E-cadherin in ALS mice when contrasted with wild-type mice, leading to an almost four-fold rise in gut permeability. Moreover, ALS mice display an increase in systemic inflammation overall, as evidenced by an approximately 1.5-fold rise in intestinal IL-17 and a 1.6-fold elevation in serum IL-17. Furthermore, the G29A mouse models of ALS transform their intestinal microbiota before exhibiting ALS-like symptoms. These discoveries indicate that ALS pathology could be influenced, to some extent, by shifts in the intestinal microbiota. This change in microbiota contributes to widespread inflammation and undermines the integrity of intestinal and central nervous system barriers (Martin, Battistini & Sun, 2022). Specific elements originating from the impaired intestinal microbiota may contribute to the neuroimmune-driven progression of ALS.

Schizophrenia

Schizophrenia is a complex and debilitating neurological condition marked by various behavioral anomalies, including hallucinations, delusions, apathy, recurrent episodes of psychosis, and profound disturbances in thinking. Schizophrenia impacts around 21 million individuals worldwide and leads to considerable social and physical morbidity (Patel et al., 2014). The interplay of environmental and genetic factors contributes to the development of schizophrenia (Wahbeh & Avramopoulos, 2021). Symptoms typically emerge between the ages of 16 and 30, with a higher prevalence among males (Li et al., 2016). A study conducted by Li et al. established a correlation between schizophrenia and

disturbances in the gut microbiome (Li et al., 2021). Additionally, Schwarz et al. noted that individuals undergoing their initial episode of psychosis exhibited higher levels of the Lactobacillaceae, Halothiobacillaceae, Brucellaceae, and Micrococcineae families (Schwarz et al., 2018). In contrast, the Veillonellaceae family was found to be less abundant in comparison to nonpsychiatric individuals (Singh et al., 2022).

The gut microbiota governs neurotransmission, immune balance, and brain maturation (Sittipo et al., 2022). Disruption in the microbiome can trigger immune activation and disturbances in the gut-brain axis, potentially contributing to schizophrenia. Changes in the gut microbiota can diminish protective elements while elevating neurotoxins and inflammatory agents, potentially causing harm to neurons and synapses, thereby potentially initiating the development of schizophrenia (Dash, Syed & Khan, 2022). *Clostridium sporogenes* plays a role in generating the metabolite indole propionic acid through the breakdown of tryptophan. This metabolite is crucial for upholding the integrity of the intestinal barrier and ensuring the equilibrium of monocytes/macrophages and T cells (Li, 2023). Conversely, the bacterial endotoxin LPS can damage the integrity of the intestinal mucosal barrier and trigger immune system responses, leading to mild endotoxemia (Manilla et al., 2023). Moreover, SCFAs are vital constituents supporting intestinal and central immunity through microglia, aiding in preserving immune balance (Yao et al., 2022). Disturbances in either can impact the other, and both can contribute to the emergence of schizophrenia. Furthermore, schizophrenia has been associated with heightened levels of IL-6, IL-8, and TNF-α, alongside diminished levels of the anti-inflammatory IL-10 (Reale, Costantini & Greig, 2021). Individuals diagnosed with schizophrenia have exhibited heightened antibody production as a reaction to *Saccharomyces cerevisiae*, indicating intestinal inflammation and raised bacterial translocation marker sCD14 levels (Szeligowski et al., 2020).

The gut microbiome additionally has a role in governing the permeability of the BBB. As a result, imbalances in the gut may give

rise to infection and inflammation in the CNS, potentially playing a role in the development of the disorder (Tang et al., 2020). Furthermore, the lack of gut microbes has been linked to decreased levels of central BDNF, which hampers the production of N-methyl-D-aspartate receptors (NMDARs). This reduction in NMDAR influence on GABA inhibitory interneurons subsequently impacts glutamatergic signaling, leading to atypical synaptic functioning and cognitive impairments. Considering the link between NMDAR and the onset of schizophrenia and other neurological disorders, changes in the gut microbiome composition might provide insight into the disease's development (Maqsood & Stone, 2016). In a separate study investigating the link between gut microbes and schizophrenia, scientists performed a transfer of gut microbe samples from individuals with schizophrenia into the gut microbiomes of a cohort of healthy control mice. Remarkably, this transplantation of gut bacteria from individuals with schizophrenia led to the development of distinct symptoms resembling murine schizophrenia in the recipient mice, including glutamatergic hypofunction. The mouse models also exhibited reduced glutamate levels and elevated glutamine and GABA levels within the brain's hippocampus. These observations supported the specific link between alterations in gut microbiota composition and schizophrenia, further connected to the severity of the disease's symptoms (Patrono, Svoboda & Stuchlík, 2021).

Imbalances in the microbiome have the potential to initiate immune activation and disrupt neuronal function, both of which are regarded as potential contributors to the emergence of schizophrenia. Furthermore, research suggests that decreased protective factors coupled with increased neurotoxins could play a role in the evident neuronal and synaptic impairments observed in individuals with schizophrenia.

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CHAPTER V

The Importance Of The Anti-Quorum Sensing Effect of Probiotics on Intestinal Health

Esin KIRAY[1]

Introduction

Quorum sensing (QS) is one of the mechanisms that occurs after the number of bacterial cells reaches a certain level and provides communication both between and within species. This communication is achieved through molecules called autoinducer (AI) molecules produced by cells. Bacterial cells that reach a certain concentration threshold produce these molecules, bind to a detector protein, and thus initiate the QS transduction pathway. Through the QS pathway, genes responsible for the virulence effects of bacteria and biofilm formation begin to be expressed. (Garg et al., 2014).

There are three common systems that bacteria use to regulate gene expression through the QS mechanism. The first of these is the luxRI type, which is mostly used by Gram-negative bacteria. Acyl

[1] Kırşehir Ahi Evran University Health Services Vocational School, Kirsehir, Turkey.

homoserinelactone (AHL) molecules synthesized as AIs are involved in the activation of this system. AHL molecules then bind to the LuxR type protein, which initiates gene expression. They enable the formation of the AHL-LuxR complex. These are then encoded by the luxR gene (Deep et al., 2011). The second most used QS system is a system used mostly by Gram-positive bacteria. This QS system is called the accessory gene regulator (Agr) or Agr-like QS system (Bourret, 1995). The third QS system used is AI-2/LuxShomolog, which is a system used by both Gram-negative and Gram-positive bacteria. After AI-2 is synthesized by the luxS gene, it binds to the AI-2 receptor, which varies depending on the bacterial species.

The QS mechanism, which is communicated by bacteria, is very important for the protection of intestinal microflora and plays an active role in maintaining intestinal health (Deng et al., 2020). In intestinal health, it ensures intestinal homeostasis and regulation of inflammation, and also ensures the survival of pathogenic bacteria that form biofilms by enabling communication with bacteria (Deng et al., 2020). In addition to ensuring the survival of QS pathogenic bacteria, probiotics that provide QS inhibition have also been shown to balance and modulate the intestinal microbiome by mediating mechanisms that prevent the survival of pathogenic bacteria and reduce their harmful effects on intestinal health. Since QS plays a dual role in improving food quality and gut health, disrupting QS can improve food quality and promote gut health. In this sense, the use of probiotics as QS inhibitors (QSI) can also be considered as an alternative treatment method in combating resistance against infections caused by pathogenic bacteria (Zhao et al., 2020).

For this reason, the number of studies conducted by researchers on the role of QS in preventing the formation of biofilms formed by pathogenic bacteria and regulating their pathogenesis is increasing day by day. This review aims to provide information about the potential use of probiotics in improving intestinal health and the effect of the anti-QS mechanism of probiotics on this relationship.

Mechanism of QS Inhibition

As a result of studies conducted in recent years, the anti-QS activity of probiotics and the mechanisms they use on pathogenic bacteria have been further clarified. In this context, especially lactic acid bacteria (LAB) are one of the most researched microorganism groups and are seen as a promising source of QSI in the fight against pathogenic bacteria. The mechanism of QS degradation is discussed in detail below.

Tablo 1. Probiotics that play a role in inhibiting the QS mechanisms of some pathogenic bacteria

Microorganism	**QSI**	**Target**	**Type of Study**	**Mechanism**	**Reference**
L. rhamnosus GG	CFS	*P. aeruginosa*	In vitro	Inhibition of AHL synthesis.	[Devi et al., 2022]
L. casei PTCC 1608	Lyophilizedpostbiotics	*P. aeruginosa*	In vitro	Repression of QS genescontrollingbiofilmformationandvirulence (*rhlI*, *rhlR*, and *pelf*), potentiallyduetoorganicacidcontent.	[Azami et al.,2022]
B. subtilis KATMIRA1933	Subtilisin	*L. monocytogenes* biofilm formation *E. coli* biofilm formation	In vitro	Inhibition of proton motive for cesandeffluxpumps.	[Algburi et al., 2017]

B. subtilis	Fengycin	*S. aureus*	Cross-section alanalysis (Thaip opulation)	Fengycin competes with AIP for binding to *agrC*.	[Jiang et al., 2019]
L. plantarum KCTC10887BP	LPA	*S. aureus*	In vitro	Biofilmformationwasinhibited. LPA induced AI-2 release in *S.. aureus*, whichrepressedbiofilm-relatedgenes.	[Ahn et al., 2018]
L. rhamnosus GG microcapsules	N/A	*E. coli*	In vitro	Repression of *lsrK* and *luxS* genes	[Deng et al., 2020]
L. acidophilus A4	EPS	*E. coli* O157:H7	In vitro	Repression levels of curligenes (*crl*, *csgA*, and *csgB*) and chemotaxis (*cheY*) related to biofilm formation.	[Kim and Kim, 2009]
L. casei CRL431 *L. acidophilus* CRL 730	DKPs	*P. aeruginosa*	In vitro	DKPs compete with AI for binding QS receptors.	[Díaz et al., 2020]

As can be seen in Table 1, various types of LAB were used in the studies. *E. coli*, *P. aeruginosa*, *S. aureus* exhibited anti-QS activity. *S. aureus* and *E. coli* (Ahn et al., 2018; Deng et al., 2020), has been observed to act through inhibition of AI-2 production or downregulation of biofilm-related genes without affecting AI-2 synthesis. One of the deficiencies in the literature is that anti-QS

compounds have not been fully identified as a result of the studies (Díaz et al., 2020; Kim and Kim, 2009).

S. aureus is one of the microorganisms that cause serious diseases and deaths worldwide in terms of foodborne pathogenesis and especially nosocomial infections. In general, cases of bacteremia caused by *S. aureus* have a mortality rate of 10% to 30% [Van et al., 2012]. Inhibition of QS in *S. aureus* may be one of the treatment methods that can be used as an alternative to antibiotics that can be used to control the virulence factors of *S. aureus* and the treatment of the infection it causes (Li et al., 2011).

Other compounds with anti-QS effects are biosurfactants synthesized by LAB. Biosurfactants produced by *B. subtilis*, *P. aeruginosa*, *S. aureus* from *Helveticus* and *Pediococcus pentosaceus* have been shown to reduce biofilm formation (Jiang et al., 2019).

Bacteriocins, secreted by many LABs, are antimicrobial peptides that have an inhibitory or lethal effect on other microorganisms. In recent studies, bacteriocins have been associated with the QS mechanism (Rizzello et al., 2014) and that the *L. plantarum* C2 bacterial strain plays a role in plantaris production, and in a different study, the synthesis products of reuterin and lactosine produced by *L. reuteri* LR 21 s and *L. curvatus* CRL1579 strains, respectively. QSI has been reported to be effective (Xu et al., 2022, Melian et al., 2019).

Generally speaking, probiotics can show preventive effects on QS by producing and secreting different QSIs. These QSI substances include lipopeptides, lipoproteins (biosurfactants), organic compounds, cyclic peptides, lipoteichoic acid, exopolysaccharides, bacteriocins and AHL-lytic enzymes. However, although some studies demonstrate anti-QS activity, there is a gap in identifying QSI compounds or elaborating the mechanism of QS inhibition.

QS, Biofilm Formation and Intestinal Health

A biofilm is a community of microbial cells attached to a surface and encapsulated in an extracellular polymeric substance (EPS) matrix. Biofilm formation is one of the important mechanisms for bacterial resistance and is of great importance in combating bacterial infections (Zhou et al., 2020).

Probiotics, which provide induction or inhibition of the QS signal among pathogenic bacteria for intestinal health, suppress the expression of biofilm-related genes. Studies conducted in this field are summarized in Table 1.

The stability of the gut microbiota depends on QS (Thompsonet al., 2016). All bacterial QS systems consist of signaling molecules, sensing molecules, and downstream regulatory proteins. When the number of bacteria reaches a certain threshold, AIs bind to the corresponding QS receptors on the bacterial surface at high density.

QS is found in both Gram-positive and Gram-negative bacteria. AI species in bacterial QS include autoinducer peptides (AIPs), acylated homoserin lactone (AHL), pseudomonas cinolone signaling (PQS), autoinducers-2 (AI-2), autoinducers-3 (AI-3). *E. coli* in the intestine is regulated by at least three QS signaling molecules. One of the signaling molecules is AHL, which is mainly found in Gram-negative bacteria (Pereira et al., 2013). The last one is AI-3, which produces a series of amplification reactions similar to epinephrine; this suggests that AI-3 may be structurally similar to adrenergic/norepinephrine. QS systems AinS/AinR, LuxI/LuxR, and LuxS/LuxPQ found in *V. cholerae* regulate bacterial colonization and subsequent biofilm formation (Jung et al., 2015).

The signaling molecule of the AHL system in gram-negative bacteria is AHL. The AHL-mediated QS system was first found in *Vibrio fischeri* (Nealson and Hastings, 1979). The AHL system is present in Gram negative bacteria, and the signaling molecules used in this system are N -acyl homoserinlactones. The AIPs and is found

only in Gram-positive bacteria. Today, there are many studies on these two systems (Zhou et al., 2020). In gram-negative bacteria, the AHL signal, N-(3-oxohexanoyl)-L-homoserinlactone (OHHL), is biosynthesized by AI synthase LuxI, and the resulting OHHL diffuses outside the bacterial cell. When the OHHL concentration reaches a critical threshold with increasing cell density, OHHL activates the expression of genes associated with biofilm formation by binding to LuxR, which is not only an OHHL receptor but also a DNA binding transcriptional activator (Engebrecht et al., 1983); Engebrecht and Silverman, 1984). Currently, it is well known that this regulatory process is a typical model for the regulation of biofilm formation by AHL systems in most Gram-negative bacteria.

Evaluation

QS is a mechanism that varies depending on the number and behavior of bacteria and is affected by various stress and environmental conditions. This makes QS the focus of recent research aimed at both protecting food safety and quality and determining its effects on intestinal health. Probiotic microorganisms that are active in the intestine act as QSI by interfering with the QS activity of target bacteria by synthesizing and secreting various metabolites. In this context, microencapsulation of probiotics is a promising strategy to increase the anti-QS activity of probiotics and needs to be developed. However, most of the studies in the literature on the anti-QS activity of probiotics are in vitro studies and more in vivo studies are needed. Probiotics have a positive effect on the intestinal microbiota by creating and changing the pro-inflammatory response in the immune system with their anti-QS activity and play a potential role in intestinal health.

According to the investigations, the potential effects of the QS and anti-QS activities of probiotics on intestinal health can be better understood if future research focuses on the following issues: (1) investigating the potential of species with probiotic characteristics in terms of anti-QS activity and identifying anti-QS compounds; (2) the effects of the identified compounds on intestinal

health and their mechanisms against bacteria that cause disruption of the intestinal microflora; (3) effect of microencapsulation method on the anti-QS activity of probiotics; and (4) to investigate the potential effect of probiotic microorganisms on the inflammatory response of QS and changes in the intestinal flora in in vitro studies as well as in vivo studies.

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CHAPTER VI

The Effect of Malnutrition at Early Age on Intestinal Microbiota and Host-Microbe Relationship

Tutku TUNÇ[1]
Hakan ÇELENK[2]

Introduction

Childhood malnutrition is an important global health problem. In 2020, the World Health Organization (WHO) published a study stating that approximately 45% of child deaths under 5 years of age are due to malnutrition (WHO, 2020). Nutritional deficiencies at an early age predispose to poor health outcomes (Guerrant, et al., 2013) and reduced cognitive functioning (Bourke, et al., 2016), as in the case of 146 million children with growth retardation.

Growth retardation is usually evident at birth and in many conditions, such as weight-for-age and height-for-age Z-scores (standard deviation changes from normal). These symptoms regress

[1] Assistant Professor, Sivas Cumhuriyet University
[2] Pharmacist, Sivas Cumhuriyet University

during the first 2 years of life, with little improvement thereafter (Victora, et al., 2008). Stunted children are shorter than healthy reference populations and this is quantified by a height-for-age Z score of less than 2. Contrary to popular belief, early stunting does not show any clinical signs resulting in immunodeficiency, metabolic imbalance, and cognitive impairment (Dewey, et al., 2011).

In contrast, severe acute malnutrition (SAM), measured by a Z score of less than 3, affects approximately 52 million children. Of these, children with AIB show more clinical symptoms than those who are stunted (Kerac M, et al., 2014).

EIB is also characterized by the loss of fat and muscle, especially in the body, referred to as wasting. It is particularly evident in the thighs, upper arms, and ribs, and in some cases children lose all of their abdominal muscles, resulting in protruding abdomens (Collins, 2006). A disease called Kwashiorkor, also known as "edematous malnutrition", is clinically diagnosed in children with EIB, with symmetrical edema and the presence of a fatty liver (Collins, 2007). Protein, micronutrient, and energy-dense foods are used to mitigate the effects of AYB, but in many cases, these children are still at high risk of death due to impaired organ function, co-infections, and refusal of refeeding treatments (Mengesha, et al., 2016).

While undernutrition is often a consequence of inadequate food intake, the etiology of childhood undernutrition cannot simply be explained by limited access to macro- and micronutrients, but instead may be due to a complex interplay between factors such as food insecurity, impaired absorption due to recurrent infections, reduced immune function, host genotype, and alteration in intestinal microbial structure and function (Kau, et al., 2011).

This review aims to highlight the impact of early-life malnutrition (protein, fat, carbohydrate, iron, vitamin D, and vitamin B12, etc.) on host-microbe interactions through changes in the intestinal microbiota and its potentially harmful effects later in life.

Human Microbiota

The human body is known to contain ten times more microbial cells than human cells. These microorganisms colonize almost every surface of the human body exposed to the external environment, including the skin, oral cavity, respiratory, urogenital, and gastrointestinal tract. Among these body sites, the gastrointestinal (GI) tract is by far the most heavily colonized organ. The complex community of microorganisms residing in or passing through the GI tract is referred to as the intestinal microbiota (Gerritsen, et al., 2011).

Following pioneering experiments in clinical and animal models more than a century ago, researchers have produced a variety of tools, including animal models devoid of microorganisms (germ-free/axenic models) that provide information on host processes regulated by the presence and/or composition of the intestinal microbiota in health and disease. Depending on their interactions with the host, members of the microbiota are broadly classified as beneficial/commensal species or pathogenic species, including pathobionts such as Helicobacter pylori and opportunistic pathogens (Parker, et al., 2018).

The microbial communities harbored by the human intestinal constitute a new, fascinating, and promising field for understanding the development of intestinal function and some health disorders and diseases, as well as their treatment and prevention. Bacterial communities within the intestinal have undergone thousands of years of coevolution with humans to achieve a symbiotic relationship leading to physiological homeostasis (Arrieta, et al., 2014).

Although the terms "microbiota" and "microbiome" are often used interchangeably, microbiota refers to the organisms that make up the microbial community, while microbiome refers to the collective genomes of microbes, including bacteria, bacteriophages, fungi, protozoa, and viruses living in and on the human body. The microbiota is now recognized as a human organ with its functions, namely modulating the expression of genes involved in mucosal

barrier reinforcement, angiogenesis, and postnatal intestinal maturation (Dave M, et al., 2012).

From birth, the normal intestinal microbiota has co-evolved with its host, adapting optimally to the intestinal environment of the respective host. Therefore, it is not surprising that the microbial community living in the digestive tract influences host physiology in many ways, mainly by interacting with the host immune system and expanding the metabolic potential of the host. However, it should be kept in mind that although this microbial community often lives in harmony with the host, intestinal bacteria are not altruistic, but only benefit from the constant temperature and the wide variety of substrates present in the digestive tract. (Woting A, et al., 2016)

In turn, thanks to its enormous metabolic potential, the intestinal microbiota makes otherwise unavailable nutrients available to the host. For example, indigestible carbohydrates, also called dietary fiber, are fermented into short-chain fatty acids (SCFA) that can be used by the host. However, under certain conditions, the harmonious relationship between the host and its microbiota is lost. Possible causes include medications, disease state, and/or unhealthy diet. Interestingly, various diseases are often accompanied by changes in the intestinal microbiota, often referred to as dysbiosis (Woting A., et al., 2016).

The infant intestinal microbial community is characterized by low diversity with high instability and is susceptible to modification by exogenous factors such as antimicrobial drugs and/or diet. Disturbances during microbiota formation and development, for example by antibiotic use (both breastfeeding and postpartum), can have long-lasting effects on microbial composition by selecting resistant species (Mathew, 2004).

The diversity of the intestinal microbiota has been revealed by the application of high-throughput sequencing of microbial ribosomal RNA or DNA (metagenome). This clearly showed that the microbiota is represented by more than 1500 microbial species (Goulet, 2015).

Metagenomic studies have shown that despite strong variability in the microbiota between individuals, there is a microbiota with shared characteristics in the microbiome (Turnbaugh PJ, 2009). This shared microbiota, referred to as the "core microbiota", is found in all humans worldwide and accounts for approximately 50% of the intestinal microbiota. The remaining microbiota varies according to environmental factors such as genetic characteristics, living environment, cultural characteristics, diet, antibiotic use, and exposure to food additives (Gevers, et al., 2012).

When the diversity of the microbiota was examined by phylogenetic studies; four main strains: *Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria* are the dominant strains in the microbiota; species from *Verrucomicrobia, Synergistetes, Planctomycetes, Tenericutes, and Deinococcus-Thermus phyla* were also shown to be common (Rajilic-Stojanovic, et al., 2014).

Intestinal microbiota metabolism and its effects on human health

Despite growing evidence linking microbiota to health and disease, their causal contribution is not fully understood. Microbes are niche-specific, i.e. adapted to a particular lifestyle or ecological niche (Dutta, et al., 2012). The microbial signature, reflecting the presence and activity of microbes, changes in response to a variety of exogenous factors, including diet, disease, antibiotic use, and host genetics (Kho, et al., 2018).

There is a symbiotic relationship between intestinal flora and human health. While the host provides a suitable environment and food for the bacteria, the microbiota has benefits on the health of the host, such as energy production and storage, fermentation of indigestible carbohydrates, enhancement of immune functions, and synthesis of certain vitamins (Gill, et al., 2006).

Commensal bacteria do not only contribute to the production of B group vitamins such as vitamin K, folic acid, biotin, and vitamin B2 for the host. Commensal bacteria are also involved in the

transformation of some plant compounds such as flavonoids and affect host metabolism systemically by modulating the metabolic profile of organs such as the human microbiota, liver, and kidney (Claus, et al., 2008).

Although microbial signatures have been associated with disease, it is not clear whether they are causally linked or a consequence of altered intestinal ecology due to metabolic and immunological changes occurring in the diseased host. Even though microbial contributions may be secondary to the causative agent of the disease, research on environmental intestinal dysfunction (EDD) has strongly suggested that their presence is essential for disease pathogenesis and demonstrated that microbes play a key role (Forgie, et al., 2020)

Developmentally, a direct dietary intervention directed at the microbiota has been shown to enhance biomarkers and mediators of growth, bone formation, neurodevelopment, and immune function compared to a healthy phenotype (Gehrig, et al., 2019). Kau et al. were able to show that a higher proportion of Enterobacteriaceae members relative to *Akkermansia munciphila* and *Clostridium scindens* in malnourished Malawian children was indicative of a pathogenic community associated with malnutrition (Kau, et al., 2015).

The 1000-Day Critical Window in the Development of the Intestinal Microbiota

The developmental origins of the health and disease hypothesis propose that an early life window exists in which environmental exposures, including mode of birth, nutrition, breastfeeding, infection, and antibiotics, lead to programming effects that can affect long-term health. (Stiemsma, et al., 2018). Even temporary disturbances in microbial communities ("dysbiosis") during this critical developmental window have been associated with immune-mediated, metabolic, and neurodevelopmental disorders (Arrieta, et al., 2015).

It is theorized that the critical developmental window begins in the preconception period, which lasts from conception to the first 1000 days of life (Robertson, et al., 2019). It is considered the period during development characterized by the greatest phenotypic plasticity and during which exogenous factors such as diet, antibiotics, mode of birth, and pollutants can lead to long-term physiological and immunological programming (Bokulich, et al., 2016).

The "fetal programming hypothesis" proposes that maternal nutrition and exogenous factors have long-term metabolic, immune, cardiovascular, and central nervous system effects on offspring (Zheng, et al., 2017). Additionally, the "missing germ hypothesis" that has emerged over generations is believed to increase disease susceptibility due to inadequate host-microbe-mediated immune development. For example, the adoption of a low-fiber diet is considered a key player responsible for the transgenerational extinction of microbes that may increase intestinal stability and resilience (Martínez, et al., 2015).

Exogenous factors that alter the early colonization and succession of microbes in the intestine may delay intestinal maturation and development. Disruptions in microbial networks during this critical developmental window are associated with asthma, allergies, diabetes, inflammatory bowel disease, and obesity (Bokulich, et al., 2016). During this time, the host is thought to establish a mutualistic or immune-tolerant relationship with the microbes, altering disease susceptibility (Figure 2.1).

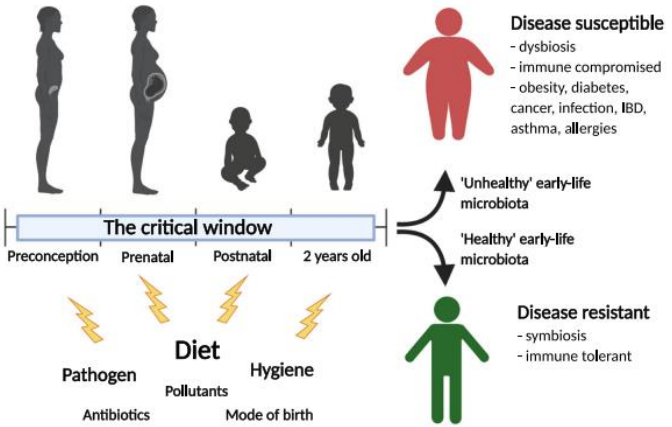

Figure 1. *The perinatal period represents a time in development when exogenous factors affecting the microbiome, such as antibiotics, diet, hygiene, pathogens, mode of delivery, and pollutants, can alter immune and physiological programming. The effects of programming early in life can lead to increased susceptibility to disease later in life.*

Intestinal Microbiota and Immunity

Intestinal microbiota has an essential role in the development of the intestinal mucosa and the host's immune system by competing with foreign pathogens, acting as a physical barrier against these pathogens, and ensuring the production of antimicrobial substances (Bouskra D, et al., 2008). Bacteria colonized in the intestines take part in the immune system by stimulating the humoral and cellular mucosal immune system (Cebra, 1999).

Microbiota-derived stimuli, together with various features of the immune system, protect the organism against opportunistic pathogens by creating an intestinal barrier. This protective effect prevents commensal bacteria from being inactivated. Barrier system; Mucus secretion and secretory IgA are antimicrobial peptides produced from intestinal epithelial cells and neutralize pathogenic microorganisms. IgA, stimulated in response to colonization by

specific commensal bacteria, plays a fundamental role in mucosal immunity by protecting mucosal surfaces and contributing to host-microbe mutualism. In addition to the survival, proliferation, and differentiation of the intestinal microbiota, it also has important functions such as epithelial permeability (barrier function) and cytokine production. (Akansel, 2021)

Disruption of the barrier causes chronic inflammation and impairment of immune functions, causing some diseases (Berbers, et al., 2017). As a result of this disruption, commensal microorganisms, pathogenic microorganisms, and nutrients that pass into the intestinal lumen encounter the enteric immune system and play a role in the initiation of immunological functions. Therefore, the intestinal microbiota plays a critical role in the host's immune development and response and also determines the host's tolerance to foreign antigens. (Grigg, et al., 2017)

The Effect of Intestinal Microbiota on Brain Functions

The intestinal microbiota is also important for brain function: there is a direct, bidirectional communication channel between the gut and the brain called the gut-brain axis, which includes a connection between the enteric and central nervous systems (Carabotti, et al., 2015). Gut microbes, their metabolites (De Vadder, et al., 2014), hormones, and immune factors (Tracey, 2002) have been shown to influence gut and brain functions through this axis in humans and animals (Carabotti, et al., 2015). Because microbes and the metabolites they produce can activate the host's immune, metabolic, and stress pathways after leaving the intestinal environment, an important part of the gut-microbe-host relationship is the distinction between intestinal tissue, the intestinal ecosystem, and the rest of the host. (Srugo, et al., 2019)

This separation is mediated by the intestinal epithelial barrier, which lies at the interface between exogenous host factors and the internal intestinal microenvironment and helps regulate microbe-host interactions. During periods of optimal nutrition and host health, two key cell types are recruited to support and maintain this

intestinal barrier: Paneth cells and enteric glial cells (EGHs). Paneth cells are found in the epithelium of the small intestine, maintain intestinal integrity prevent microbial translocation through the production of tight junction proteins and produce antimicrobial peptides that regulate the host-microbe relationship (Ayabe, et al., 2000). Furthermore, due to their proximity to crypt stem cells, Paneth cells may influence intestinal epithelial cell differentiation and intestinal maturation (Bry, et al., 1994) (Sato, et al., 2011). Toll-like receptors, Paneth, which activate the innate immune response when bacterial components are recognized in the intestinal environment, are claimed to play an important role in inducing antimicrobial peptide production (Said, 2011).

In addition, EGHs are part of the enteric nervous system and the gut-brain axis and respond to and control intestinal inflammation (Rühl, et al., 2001). EGHs also affect intestinal integrity and permeability through their long cytoplasmic processes that directly contact the barrier (Savidge, et al., 2007). Other enteric cells, such as goblet cells, maintain intestinal barrier integrity by producing mucus (Pearce, et al., 2018). Importantly, Paneth cells and EGHs are established in early development, suggesting that they are key to early and lifelong gut and brain health. (Bry, et al., 1994)

Yet, few studies have described the effects of malnutrition on Paneth cell and EGH development and function (none to our knowledge have examined EGHs during malnutrition) or described how any of these cells are affected and/or maintained by intestinal dysfunction. Additionally, although Paneth cells and EGHs are known to be regulated and functional early in life, little is known about how early life adversities, including malnutrition or gut microbes, may affect their development and function. (Srugo, et al., 2019)

Effects of Malnutrition on Microbiota and Host-Microbe Relationship

With rates of malnutrition, underweight, overnutrition, and obesity increasing worldwide and an impaired gut barrier leading to both immune-related and chronic diseases, it is important to understand the effects of malnutrition on the gut-host relationship.

Most nutrients are absorbed in the intestinal tract and it is the largest human interface with the external environment, making it central to normal functioning to resist disease caused by malnutrition. In addition to dietary intake, studies of malnourished individuals emphasize that environmental exposures from poor care and hygiene early in life are associated with stunting and malnutrition rates worldwide (Humphrey, 2009).

The integrity of the intestinal barrier and the composition and function of the gut microbiome can be greatly influenced by the host diet (Subramanian, et al., 2014), as indigestible polysaccharides in the host diet become gut bacterial substrates and nutrients (Tremaroli, et al., 2012). Indeed, adaptations to gut bacterial metabolism and transcription occur within days of dietary changes in humans (David, et al., 2014). In response to both over (Araújo, et al., 2017) and undernutrition (Genton, et al., 2015), collectively known as malnutrition, gut barrier function and integrity can become dysregulated, leading to gut microbial dysbiosis, altered gut function, and a leaky gut barrier.

During pregnancy, the gut epithelial barrier and the microbes present in the gut are doubly important as they protect both the mother and, by extension, the fetus from harmful bacteria and xenobiotics (Ruiter-Ligeti, et al., 2018) and produce nutrients essential for pregnancy health and absorb nutrients into the bloodstream that are vital for fetal development (Wikoff, et al., 2009).

Sebastian A. Srugo et al. have shown that maternal malnutrition affects the maternal gut microbiome and is associated with increased

levels of inflammation in the maternal gut and peripheral circulation (Connor, et al., 2018). In offspring, a mature intestinal epithelial barrier provides a healthy and homeostatic gut environment that allows the offspring to respond appropriately to infections, absorb and produce nutrients, and possibly establish optimal communication with the brain and other organs (Carabotti, et al., 2015). Yet, little is known about how malnutrition affects the maternal epithelial barrier during pregnancy, whether it is a 'stress test' in itself or whether maternal malnutrition negatively programs fetal gut development and function.

Malnutrition may be associated with malabsorption due to intestinal damage and/or microbial disruption, particularly in the context of enteric infections. Malabsorption of model carbohydrates has been frequently reported in malnourished children (Kvissberg MA, et al., 2016). Peripheral intestinal dysfunction (or peripheral enteric dysfunction) is generally considered to be an important cause of malnutrition in children and is associated with poor sanitation and frequent GI infections (Ahmed, et al., 2014). Peripheral intestinal dysfunction is a subclinical inflammation of the small intestine and is further characterized by histological abnormalities and increased intestinal permeability, contributing to malabsorption and reducing growth and cognitive development (Crane RJ, et al., 2015).

The 'maturation' of the microbiome parallels the host development of the GI tract and central nervous system (Borre YE, et al., 2014). An altered microbiota composition and activity has been reported in malnourished children compared to well-nourished children, which can be characterized as a less 'mature' microbiota. In mice, protein malnutrition resulted in overall reduced richness and diversity and a microbiota less capable of deriving energy from indigestible dietary compounds (Preidis GA, et al., 2015).

Brown and colleagues show in a mouse model that specific bacteria are essential for the development of CD (Brown EM, et al., 2015). The researchers were able to recreate all the effects of human MDD by probing mice fed a protein-deficient diet (7% of the diet)

with a mixture of a specific Bacteroidales species and Escherichia coli. However, when given an isocaloric protein-sufficient diet (20% of the diet), mice colonized with the same bacterial mixture did not develop symptoms of MDD. This suggests that both diet and microbes are required to induce CD. The observations in mouse models mirror those observed in clinical studies where symptoms of ESRD are associated with both a malnourished diet and specific microbial signatures (Smith MI, et al., 2013).

Metabolomic and proteomic analysis of blood plasma combined with metagenomic analyses of stool samples revealed different microbe and host functions between healthy children and children with severe acute malnutrition when consuming the same therapeutic diet. As children transitioned from severe to moderate acute malnutrition, their proteomic profiles became more similar to those of healthy children (Gehrig JL, et al., 2019). A direct dietary intervention targeting the microbiota in these children had a greater impact than conventional therapy on restoring microbiota structure and health (Raman et al., 2019).

In a cross-sectional study of Bangladeshi children, malnutrition, defined by a lower number of OTUs in the malnourished microbiota characterized by higher Proteobacteria and lower Bacteroidetes compared to healthy controls, was linked to a less diverse microbiota. Furthermore, higher proportions of *Klebsiella and Escherichia* were found in the intestinal microbiota of malnourished children (Monira S, et al., 2011).

The Kwashiorkor microbiota is associated with a lower b diversity and a lower anaerobic diversity, including a depletion in *Methanobrevibacter smithii* in particular. Furthermore, the kwashiorkor microbiota is enriched with potentially pathogenic *Proteobacteria, Fusobacteria, and Streptococcus gallolyticus* (Tidjani Alou M, et al., 2017). In contrast, a cross-sectional study of Ugandan children found no significant difference in biodiversity and abundance of specific genera in terms of edema in the EIB. However, a-diversity was found to be lower in the gut microbiota of children

hospitalized with non-edematous EIB compared to children with edematous EIB (Kristensen KH, et al. 2016).

In a cross-sectional study of Indian children with different nutritional status, the abundance of *Escherichia, Streptococcus, Shigella, Enterobacter, and Veillonella* genera increases with worsening nutritional status. In addition, microbial genes related to energy production and conversion, amino acid and carbohydrate transport, and metabolism were positively linked to nutritional index (WHZ, WAZ, and height-for-age Z-score calculated). This may indicate better nutrient utilization in healthy children compared to malnourished children (Ghosh TS, et al., 2014).

Time series from Malawian twin pairs discordant for kwashiorkor revealed a reduction in the relative abundance of Actinobacteria in children with kwashiorkor after 2 weeks of ready-to-use therapeutic food treatment, but not in their healthy twins. Microbiota transfer from discordant twins to gnotobiotic mice showed 37 species that differed between gnotobiotic mice harboring kwashiorkor compared to healthy microbiota (Smith MI, et al., 2013). Two twin cohorts (Malawi and Bangladesh) linked chronic malnutrition to a lower a-diversity. Stunting was associated with the depletion of *Prevotella, Bacteroides, Eubacterium, and Blautia* genera in the Malawi cohort and *Lactobacillus, Olsenella, Dorea, and Blautia* genera in the Bangladesh cohort. In addition, the relative abundance of *Acidaminococcus* sp. is linked to lower future linear growth (Gough EK, et al., 2015).

A longitudinal birth cohort study of low birth weight Indian children showed that stunting was associated with enrichment in the genera Prevotella stercorea, Prevotella copri, Desulfovibrio and Catenibacterium, and the order Campylobacterales, which have inflammatory properties. In contrast to the Malawi and Bangladesh cohort, no differences were found in a-diversity indices or rates of increase with age between low birth weight and persistent stunting and healthy controls (Dinh, et al., 2016). It is thought that the conflicting results may be due to different sorting methods and

platforms, geographical location, variation in antibiotic use, breastfeeding, and weaning practices.

A meta-analysis of 5 studies involving children from Niger, Senegal, Malawi, Bangladesh, and India revealed a dramatic depletion of obligate anaerobes in malnutrition regardless of age and gender. Undernutrition is associated with the depletion of several species from the families Bacteroidaceae, Eubacteriaceae, Lachnospiraceae and Ruminococceae and the enrichment of several aerotolerant species with potential pathogenic effects, such as *Escherichia coli, Enterococcus faecalis and Staphylococcus aureus* (Million, et al., 2016). Both cross-sectional and longitudinal studies show that childhood undernutrition is associated with intestinal microbiota immaturity, altered diversity, enrichment in potentially pathogenic and inflammogenic species, depletion in obligate anaerobes, and less efficient nutrient utilization.

Effect on Mucosal and Skin Barrier Functions

The integrity of the gastrointestinal mucosa is often compromised in malnutrition, leading to increased susceptibility to certain pathogens with reduced gastric acid secretion (Peterson, et al., 2014). High rates of cell proliferation and DNA replication in the intestinal epithelium make this tissue particularly vulnerable to the effects of a diet lacking protein, zinc, vitamin A, or folate. Furthermore, many children living in areas with inadequate sanitation are affected by CD, a disease of the small intestine characterized by villous atrophy, moderate to severe crypt hyperplasia, chronic inflammatory cell infiltration, and increased permeability (Prendergast, et al., 2012). The mechanisms driving CD are unclear, but exposure to high amounts of intestinal pathogens and disruption of the normal gut microbiota (dysbiosis) have important roles. Dietary deficiencies in zinc, vitamin A, vitamin D, and protein may also play a role by altering intestinal epithelial barrier function and inflammation (Assa, et al., 2014).

Several studies have found a strong association between markers of ESRD and childhood malnutrition (Hossain, et al., 2010).

A pig model with severe stunting (pigs fed only corn meal) showed that malnutrition leads to atrophy of the small intestinal mucosa (Lykke, et al., 2013). Rats subjected to a low-protein diet suffered from impaired gastric epithelial cell proliferation (Kasai, et al.,2012).

Disruption of the intestinal epithelial barrier is associated with loss of lymphoid tissue and altered gut microbiota (see below), both of which affect the risk of enteric infection. Disruption of the epithelial gut barrier with increased levels of markers of intestinal inflammation (e.g. fecal calprotectin, neopterin, and myeloper oxidase) and microbial translocation (serum soluble CD14 and antiendotoxin antibody) is associated with CD. Similarly, chronic malnutrition (stunting) is mediated, at least in part, by chronic translocation of bacteria or bacterial products leading to chronic inflammation and suppression of the growth hormone-insulin-like growth factor-1 axis.

Chronic inflammation in malnourished hosts may also contribute to the high frequency of anemia, not all of which can be explained by iron deficiency. Recently, intestinal and systemic inflammation has been associated with mortality in children with complicated severe acute malnutrition (Ibrahim, et al., 2017). In a model of recently weaned mice, malnutrition (low levels of dietary protein and fat) combined with repeated exposure to certain enteric bacteria (several common Bacteroidales species and Escherichia coli cocktail) resulted in bacterial overgrowth, inflammation, villous blunting, and increased bacterial overgrowth, all characteristic of CD (Brown, et al., 2015).

Effects on Immunity and Metabolism

In terms of both obesity and malnutrition, evidence is accumulating that diet-induced effects on body physiology can be transmitted through epigenetic reprogramming of maternal and paternal DNA. Furthermore, there is a critical early period in a child's life when environmental exposures (including diet and microbes) can shift immune-metabolism-microbiota interactions

into pathophysiologic states, which can ultimately lead to changes in host growth rates, metabolism, and immunity, resulting in obesity and malnutrition-related diseases (such as type 2 diabetes and ESRD, respectively). A recent study has suggested that the impact of dietary and environmental change stresses on the host can be passed from mother to children through epigenetic modulation of DNA through methylation (Dominguez-Salas, et al., 2014).

Apart from nutritional intake early in life, many children are exposed to antibiotics throughout their childhood. Sub-therapeutic doses of several classes of antibiotics have been widely used for decades in the agricultural industry as growth promoters. study showing that these sub-therapeutic doses are sufficient to alter the intestinal microbiota has shown that enrichment of key microbial genes responsible for carbohydrate metabolism to form SCFAs, as well as systemic changes in hepatic lipid and cholesterol metabolism, lead to many changes in young mice, such as increased adiposity (Cho, et al., 2012).

Thus, low-dose use or exposure to antibiotics can cause subtle shifts in the microbial ecosystem for a more favorable environment for weight gain and energy harvesting. Epidemiologic studies show that antibiotic use early in life and obesity are associated. The states with the highest obesity rates in the US also have the highest rates of antibiotic use (Riley, et al., 2013).

Numerous studies have shown that the presence/absence of certain microbes can modulate and program lifelong changes in immunity (Hooper, 2012). Future studies should assess in more detail how these influence changes in metabolic disease progression. The early-life microbiota is less stable less resilient, and more susceptible to differences in immunity or metabolism that may lead to programmed lifelong changes. This leads to an increased risk of obesity and related diseases (Yatsunenko, et al., 2012).

By understanding the metabolic capabilities and differential energy harvesting of each child's microbiota, we may be able to create microbiota-based interventions to reverse the predisposition

to obesity early in life. Two studies have shown that treatment of obese mice with *Akkermansia muciniphila* improved fat mass gain, metabolic endotoxemia, symptoms of high-fat diet-induced metabolic disorders, inflammation, and insulin resistance (Shin, et al., 2014). Colonization with *A. Muciniphila* controls inflammation by increasing intestinal endocannabinoid levels and also increasing the thickness of the inner mucus layer (Everard, 2013). These studies and future efforts keep alive the hope that susceptibility to obesity can be controlled through the microbiota in early life and that obesity-related diseases can be corrected with probiotics.

Similar to obesity, the composition of the gut microbiota also plays a role in the etiology and symptoms of malnutrition (Tilg, et al., 2013), and this relationship is bidirectional (Kane, et al., 2015). Children who are malnourished during the first two years of life have been shown to have an immature development of their gut microbiota compared to healthy, case-control children (Subramanian, et al., 2014). A comprehensive study across multiple geographic regions concluded that children in lower socioeconomic regions of the world consistently have significantly more diverse early-life microbiota (Yatsunenko, et al., 2012).

The function and composition of the intestinal microbiota also play a role in the development and severity of malnutrition. Using a similar strategy, Smith and colleagues demonstrated a direct role for the microbiota in mediating malnutrition symptoms when fecal samples from Malawian twins were transferred into germ-free mice, resulting in severe maladaptive protein deficiency (Smith MI, et al., 2013). Furthermore, the rapid weight loss of germ-free mice fed the Malawian diet and the failure of this effect to be completely reversed after feeding a therapeutic diet demonstrated that changes in the microbiota can permanently alter host immunity and metabolism. Which microbes drive this effect was discovered with IgA-SEQ, an IgA sorting and sequencing method used to compare microbe sequences targeted by IgA with non-targeted sequences. Using this method, approximately 13 Bacteroidetes and Proteobacteria strains

were found to be highly targeted by IgA and may have a growth-inhibiting effect on its own (Kau, et al., 2015).

IgA targeting means that the host recognizes these bacterial species, and research shows that they will target beneficial microbes such as Akkermansia and Lactobacillus during homeostasis, dysbiosis, and inflammation (Palm, et al., 2014). These studies suggest that microbes may play a role in causing malnutrition, but the role of microbes in exacerbating malnutrition is complex and multifaceted and is only just beginning to be understood. Studies conducted on humans shed light on the possibility that early-life microbiota enzyme functions may be altered in ways that may lead to malnutrition.

Breast milk provides an important source of nutrition for children during the first six months. It is also an important nutritional factor that promotes the growth and development of healthy species in the microbiota (Walker, et al., 2015). Breast milk contains many complex glycosylated proteins and many members of the gut bacteria that have enzymes that unlock and release these sugars for use by both the bacteria and the host (Zivkovic, et al., 2011). For example, instead of producing sialic acid in the first three months of life, humans obtain it from dietary sources such as breast milk via the microbiota. Recent research shows that malnourished mothers have less sialylated breast milk, which contributes to conditions such as growth retardation and susceptibility to pathogens that cause developmental problems for their children (Charbonneau, et al., 2016a).

The goal is to move forward to reverse malnutrition by leveraging the knowledge that dysbiotic microbiota thrives with poor dietary intake. Signs of malnutrition can be reversed early in life using a probiotic approach. Studies in mice have shown that Clostridium scindens and Lactobacillus plantarum only promote growth when given during this “critical window” early in life (Brown, 2013).

The success of these studies relies on carefully controlled mice that are genetically identical in terms of diet and environmental exposures. Translating this success to malnourished people will be difficult, as field studies have shown that microbial-based treatments based on a single microbial strain fail (Galpin, et al., 2005). Individualized or regionalized strategies to address malnutrition likely need to be established and dietary therapy combined with any probiotics to provide the best chance for colonization of the microbe. Diet in early life is a powerful driver of a person's gut microbial composition. (David, et al., 2014). In contrast, diet-induced alteration of the gut microbiota may have different consequences on host metabolism and immunity depending on the composition and metabolic potential of the colonizing microbes (Sommer, et al., 2013).

Microbial Ecology in the Malnourished Gut

Microbiota composition

Numerous studies have shown that malnutrition is associated with dysbiosis of the gut microbiota and support the proposed relationship between fecal-oral contamination and growth retardation. One of the most consistent findings is the increased abundance of Proteobacteria species in malnourished children, particularly pathogens such as *Campylobacter, Klebsiella*, and entero-adhesive *E. coli*. Helminths, parasites, and enteroviruses, as well as other bacterial pathogens such as enterotoxin-producing *Bacteroides fragilis,* are also common in the fecal microbiome of stunted children. This abundance of pathogens is accompanied by a shortage of strictly anaerobic bacteria, especially the Firmicutes phylum. This lack of Firmicutes and abundance of proteobacteria has been conceptualized as “immaturity” of the gut microbiota because it reflects the natural composition of the microbiome in infancy and early life; This bacterial signature is also a hallmark of intestinal inflammatory dysbiosis in multiple diseases in children and adults (Huus, 2020).

Undernourished mice infected or coinfected with pathogens such as enteroaggregative E. coli, Giardia, and enterotoxin-producing B. fragilis experience exacerbated inflammation and stunting (Wagner, et al., 2017). The combination of Bacteroidetes, Enterobacteriaceae, and Enterococcus from children with severe acute malnutrition has been independently shown to induce enteropathy in malnourished gnotobiotic mice (Kau, et al., 2015). These studies provide proof of the principle that certain microorganisms, including those not traditionally considered pathogens, can induce MCD traits during malnutrition. These findings point to a microbial etiology in MCD, leading to inflammation and damage in the gut in the context of a complex community of multiple pathobionts (Huus, 2020).

Metabolic function

The assembly, maintenance, and functional output of microbial communities depend on metabolic exchanges between microbes. In the mammalian gut, bacteria compete for nutritional niches; integrate symbiotic cross-feeding; and alter gene expression and metabolism in response to microbial, host, and dietary cues. Microbial metabolism and resulting metabolites together contribute to the synthesis, digestion, and absorption of nutrients, influence host inflammation and immunity, and influence the virulence of enteric pathogens (Huus, 2020).

Metabolic interactions between bacteria help determine ecosystem stability, including the susceptibility of the microbial community to probiotic “blooms” or invasion of new pathogens. Changes in host diet and disease can further perturb this ecosystem and affect its functionality (Lee, et al., 2014).

Under nutrient-limited conditions, competition for limited energy resources occurs between the host and its gut microbiome and among members of that microbiome. When deprived of dietary alternatives, bacteria hoard food sources to fuel their metabolism. For example, bacterial foraging of the mucus layer is increased in mice lacking dietary fiber, and this disruption of the host mucus layer

increases susceptibility to intestinal pathogens (Desai, 2016). Bacterial N-linked glycan metabolism is also altered in malnourished neonatal mice, indicating changes in microbial metabolism of mucus and other polysaccharides (Preidis, et al., 2015).

One study found that malnourished children showed signs of increased microbial proteolysis, another possible sign of a bacterial starvation response. Supporting the existence of altered microbial metabolism in malnutrition and MDD, numerous studies have identified differences in bile acidity (host cholesterol derivatives that are extensively metabolized by members of the microbiota) in these populations (Brown, et al., 2015).

Mucosal inflammation may also affect microbiota metabolism. The intestinal mucosa leads to infection and inflammation by increasing the production of reactive oxygen species, nitric oxide species, and oxidized sugars such as galactarate and glucarate, as well as increasing mucus shedding. These responses may paradoxically make growth substrates more suitable for pathogens adapted to exploit them.

Pathogens may also be better adapted to exploit growth substrates released by the commensal microbiota during inflammatory dysbiosis. The inflamed bowel is typically a more oxygenated environment associated with a bloom of facultative anaerobic Proteobacteria at the expense of strictly anaerobic bacteria. These facultative anaerobes carry a different metabolic repertoire that is generally less beneficial to the host compared to members of the anaerobic microbiota. As previously mentioned, Proteobacteria are more abundant in the stunted microbiota, which is a potential indicator of this inflammatory oxidation of the intestinal environment and suggests its reduced metabolic functionality.

Mortality in children with severe acute malnutrition in Malawi has been associated with low circulating butyrate, a short-chain fatty acid produced by strict anaerobes in the intestine. Thus, not only the

composition of the microbiota but also its metabolic output changes during malnutrition and MCD. This may have important consequences for the host's health (Huus, 2020).

Nutrition management for malnourished children

WHO/United Nations Children's Emergency Fund recommends exclusive breastfeeding for the first 6 months of life and exclusive breastfeeding for up to 24 months. The benefits of breastfeeding in reducing morbidity and mortality from respiratory and gastrointestinal infections are discussed. However, in resource-limited populations, rates of early breastfeeding cessation and early introduction of complementary foods are high, which increases the risk of malnutrition (WHO, 2016). Children with severe acute malnutrition are treated according to WHO guidelines (WHO, 2013). In the presence of clinical complications such as mental status change, serious infection, hypothermia, hypoglycemia, severe anemia, or anorexia, children are hospitalized and 3-stage nutritional rehabilitation is applied.

In the first intensive phase, patients with EED are treated with liquid therapeutic “milk” called F75, specifically formulated to meet calorie (100 kcal/kg/day) and micronutrient requirements and avoid protein and sodium overload. Once the child stabilizes and his appetite returns, he moves into the transition and maintenance phases; At this stage, F75 is gradually replaced by either F100, a more concentrated milk formula, or ready-to-use supplementary food (KHEG) for a minimum caloric intake of ∼175 kcal/kg (Ibrahim, et al., 2017).

Current protocols recommend discontinuation of therapeutic feeding when WHZ-2 or MUAC is greater than 125 mm, although a longer treatment duration will likely reduce the risk of relapse. Children with EED but without clinical complications can be effectively treated with CHEG from the outset, provided they pass an appetite test and can consume the recommended amount (WHO, 2013). KHEG is a high-energy, high-lipid, high-protein ready-made food supplement fortified with vitamins and trace elements

(Hendricks, 2010). It has several advantages over F100 infant formula in that it is not water-based (most KHEG formulations are peanut butter-based), so it does not need to be reconstituted with potentially contaminated water, does not require field or home preparation, does not need refrigeration, is resistant to microbial colonization, is highly palatable, and can be used on a mass scale It is easily distributed. A recent review of data from studies involving more than 20,000 malnourished children determined that therapeutic dietary intervention with KHEG led to improved growth in approximately 80% of children (Bhutta, et al., 2008).

Treatment of moderate acute malnutrition is less defined. Current WHO guidelines include nutritional counseling, diagnosis and treatment of underlying infections, and, where possible, the provision of supplementary food to ensure a caloric intake of at least 75 kcal/kg/day, half of what is needed to catch up with growth. While fortified spreads are becoming increasingly common, various types of supplements are used. Brief intervention with KHEG led to improvement of growth indicators in children with moderate acute malnutrition. Short-term preventive interventions in at-risk populations may also have short- and long-term growth benefits. A recent large trial of corn-soy blend flour fortified with oil and dry skim milk showed improvement (height-weight z score ≥ -2) in 85% of children within an average of 4 weeks after the start of KHEG (Ibrahim, et al., 2017).

Various interventions are effective in preventing or reducing the prevalence of stunting (Bhutta, et al., 2013). However, there is no consensus for treatment, largely because the pathophysiology of this condition is complex and poorly understood.

Results

Reversing global trends in childhood stunting and malnutrition is a priority. According to UNICEF, the main causes of childhood malnutrition can be divided into three main underlying factors; household food insecurity, inadequate care and unhealthy home

environment, and lack of health services (UNICEF, 2019). These are affected by income, poverty, employment, housing, assets, remittances, pensions, and transfers, which are determined by socio-economic and political factors. Interventions to prevent malnutrition should target these underlying causes.

WHO recommends CHEG feeding as the main intervention for malnourished children. So far, clinical trials have shown that currently available therapeutic food interventions, such as KHEG, fail to fully improve health in more than half of malnourished children (Bhutta, et al., 2008). The reason why it is not 100% is that the effectiveness of nutritional interventions for malnutrition is not yet fully understood.

However, one study has shown that antibiotic treatment before nutritional intervention is important in improving health disorders caused by malnutrition. This demonstrates the importance of understanding microbial-induced disease pathologies in the gut and underlying malnutrition-induced defects in the gut (Trehan, et al., 2013).

It is worth noting that mothers of malnourished children reported the delivery room as the main setting for nutritional advice, whereas mothers of well-nourished children reported child health registries as the main source of nutritional advice. One study found that mothers of well-nourished children were more likely to deworm their children every 6 months. Regular deworming in children has been reported to be a useful intervention to prevent malnutrition in some settings (Bhutta, et al., 2013) and this appears to be one of them (Bhutta, et al., 2008).

Additionally, most mothers reported receiving nutritional counseling or advice from the health service, one of the interventions expected in a national plan. The delivery room is an important environment for counseling mothers about early initiation of

breastfeeding. Pregnant women should be encouraged to access prenatal care and mothers should be included in health care. Vitamin A supplementation is not associated with malnutrition even in univariate analysis. Growth arrest occurred in both groups; however, after multivariate analysis, it was found to be significantly more common in malnourished children. (Edem, et al., 2015)

Malnutrition has also been associated with absence or inadequate prenatal care, failure to regularly deworm children, low birth weight, previous episodes of diarrhea, and developmental delay. Although the last three conditions can be consequences of malnutrition, they can also aggravate malnutrition due to lack of health care. Therefore, preventing these conditions and ensuring adequate follow-up of patients with diarrhea will be important steps in preventing malnutrition in this population.

Maternal gene transfer causing children to be more susceptible to obesity and malnutrition has also been documented (Victora, et al., 2008). For example, population-based obesity studies show that prior dietary practices and exposure to a social “meta-community” of microbes within social groups can influence responses to dietary interventions and obesity rates (Griffin, et al., 2017). Maternal diet and microbial exposure are crucial for the development of the microbiota at an early age, as children may inherit genes with different potential for susceptibility to malnutrition or obesity depending on their mother's diet.

Maternal health for malnutrition is of particular importance for early seeding of the gut microbiome and immune development through breast milk (Gordon, et al., 2012A). Future studies should therefore focus not only on therapeutic interventions at an early age to promote improved gut health to combat obesity and malnutrition but also on maternal health to achieve a holistic approach to suppress the impact of malnutrition and obesity on society today.

Interventions to reduce malnutrition should therefore begin before birth. Reproductive Health Services can provide the environment for policy strategies that can reduce low birth weight (Bhutta, et al., 2013) by increasing birth spacing and reducing teenage pregnancy (Lartey, 2008). Maternal malnutrition during pregnancy medical conditions such as low weight gain, weight loss due to illness, malaria during pregnancy, hypertension, smoking, and drug and alcohol use increase the risk of low birth weight (Forero-Ramirez, et al., 2014). Therefore, low birth weight may be a measure of success in preventing malnutrition during pregnancy through prenatal care. Promotion of breastfeeding, appropriate complementary feeding, vitamin A supplementation, and malnutrition case management are most effective in preventing malnutrition or its effects (Bhutta et al., 2008, Bhutta et al., 2013).

Interestingly, the approach to using social determinants of health requires some sort of multisectoral, multidisciplinary approach. Therefore, it requires leadership that can mobilize stakeholders, mediate, and manage relationships between multiple sectors while using resources to achieve a common goal (HPP, 2014). Most articles recommend some form of multisectoral approach to addressing malnutrition. Using a multisectoral approach promotes the optimization of resources as duplication will be avoided (Salunke, 2017). Leveraging the expertise and resources of different stakeholders can be very efficient and cost-effective. Although power inequalities, different institutional cultures, and incompatible foci make multisectoral approaches difficult, they have been used successfully to improve health program outcomes in other health areas (Efevbera, et al., 2020).

Care of adolescents to prevent malnutrition should include contraception to delay pregnancy, nutrition education, inculcation of hygiene habits, and continuing formal education to improve future employment opportunities. Researchers agree that mothers who

exclusively breastfeed for the first 6 months successfully overcome barriers to breastfeeding and indirectly prevent malnutrition. Barriers can be attributed to the mother or baby, the healthcare system, family pressures, and mothers' work/schooling status. Inadequate breastfeeding and inappropriate complementary feeding can lead to malnutrition, especially if there is poor adherence to personal and environmental hygiene at the individual and/or household level as the likelihood of infection and disease increases. Breastfeeding education, family support, the healthcare system, and the supportive legal environment are considered factors that enable breastfeeding, especially if mothers know the benefits of breastfeeding and are committed to breastfeeding (Nyarko, et al., 2023).

Malnourished microbiota is associated with gut microbiota immaturity, altered diversity, enrichment in potentially pathogenic and inflammatory species, depletion in obligate anaerobes, and less efficient nutrient utilization. Early colonization, antibiotic exposure, and diet appear to contribute to weight gain in later childhood. Effects on the gut and brain axis, microbial disruption, and energy metabolism are among the possible mechanisms. However, it is not currently possible to draw a clear conclusion from human studies as to whether changing SCFA levels leads to the modulation of appetite-regulating hormones and affects nutritional status through this mechanism. Dietary modulation of the gut microbiota may be a strategy for the prevention and treatment of childhood malnutrition. However, more randomized clinical trials are needed to test the effectiveness of probiotics, prebiotics, and synbiotics, while stratifying by type of malnutrition, geographical region, pubertal stage, and basic composition of the microbiota.

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