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The role of gut microbiota in human metabolism and inflammatory diseases: a focus on elderly individuals

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Abstract

Background The gut microbiota plays a crucial role in regulating the host's immune responses during aging, which was characterized by a different abundance of bacteria in several age groups.

Main body Gut microbiota dysbiosis is associated with aging, antibiotic exposure, underlying diseases, infections, hormonal variations, circadian rhythm, and malnutrition, either singularly or in combination. The appropriate use of prebiotics and probiotics may be able to prevent or reduce this disruption.

Conclusion The current review focuses on the gut microbiota composition across the life cycle, factors affecting gut microbiota changes with aging, and interventions to modulate gut microbiota.

Keywords Gut microbiota, Aging, Inflammatory disease, Metabolism, Probiotic

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Introduction

Estimated to be 10 times more common than human host cells, commensal bacteria are found in billions in the human gastrointestinal system (Ramakrishna 2007). Known as "microbiota" the human body contains a wide variety of bacterial species and, to a lesser extent, viral and eukaryotic microorganisms. Since most microorganisms are found in the human gut, it can be referred to as an "organ of the microbiome." The "gut microbiota" is the term used to refer to all gut bacteria together, whereas the "gut microbiome" refers to the genes that they are connected with (Sender et al. 2016). When one or more elements of the microbiota disappear, the microbiota profile is characterized by low diversity (Jeffery et al. 2016). Gut bacteria may mainly colonize hosts vertically, acquired from parents early in life and persisting after that. Alternatively, bacteria can also persist due to repeated recolonization of the host; persistence is possible through repeated reintroduction. Thus, dispersal strategies, bacterial transfer, and colonization of new environments may all contribute to persistence (Hildebrand et al. 2021).

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The population of microbes known as the microbiota is not uniform. Instead, it is made up of a complex spectrum of microbial communities that interact with the host and one another in ways that have an impact on the health of the host (Clemente et al. 2012). The two primary phyla of bacteria are Bacteroidetes and Firmicutes, with several smaller subphyla, including Fusobacteria, Cyanobacteria, Proteobacteria, Verrucomicrobia, and Actinobacteria (Vemuri et al. 2018). The gut microbiota, which is regarded as an endocrine organ involved in preserving energy balance and host immunity, has recently been discovered to play a crucial role in the development of metabolic diseases (Clarke et al. 2014a, b). The gut microbiota mainly steady throughout adulthood, but as we age, disruptions emerge due to endogenous variables like cellular stress and external factors, including antibiotic consumption (Kohl et al. 2012). Major physiological changes brought on by aging include altered immune function, metabolism, and gut microbial composition (dysbiosis), which can result in a variety of gastrointestinal inflammatory diseases and autoimmune illnesses. Due to the disruption of gut homeostasis, there is immunosuppression and a low-grade inflammatory response (Franceschi 2007; Magrone and Jirillo 2013; Ostan et al. 2008).

A large variety of physiological, genetic, metabolic, and immunological systems are impacted by the complicated process of aging. This involves a weakened capacity to maintain a healthy, effective metabolic function as well as an immunological response. According to Alarcón and Rojo (2020), this illness is characterized by a gradual deterioration of cellular physiological functioning that impacts the immune system, causes inflammation, and metabolic problems, all of which are risk factors for developing other chronic diseases (Alarcón and Rojo 2020). Having access to health care for a longer period of time does not always imply living longer (WHO 2019). Frailty, which is described as "a condition of greater sensitivity to an inadequate resolution of homeostasis after a stressful event, which raises the likelihood of unfavorable consequences, including falls, delirium, and disability," unfortunately frequently presents itself negatively as people age (Clegg et al. 2013). For elderly persons, in particular, the potential effects of gut microbiota on health are significant. This is due to the possibility that age-related alterations in innate immunity, sarcopenia, and cognitive function—all of which contribute to frailty—may be tempered by the microbiota. Independent investigations and cell culture-based research both demonstrate that the gut microbiota of older individuals varies from that of younger individuals. There is no age or time limit at which the profile of the microbiota abruptly changes. Changes happen instead gradually and over time. More senior citizens desire or want the ability to live independently. Weakness is the main barrier to independent existence. Frailty does not result from chronological aging but from the accumulation of illnesses. The human gut microbiota is one "organ" that cannot be anticipated to follow a typical course of physiological decline. Although gut bacterial cells do not age on their own, aging may bring on disorders linked to the stomach and gut bacteria (O'Toole and Jeffery 2015). Centenarians have a microbiota that differs from that of the elderly (Biagi et al. 2010), consistent with the general trend of age-related microbiota. Lifestyle, especially diet, plays an important role, as aging is often associated with a decrease in the amount and variety of fiber-rich foods, and there is often a risk of malnutrition (Claesson et al. 2012). The homeostasis of numerous genetic, metabolic, and immunological systems may be preserved in order to slow down the aging process, according to recent research that has made significant strides in this area. Disturbances in the composition and function of the gut microbiome are intimately tied to several clinical concerns, including exposure to numerous medications and antibiotics, dietary changes, and constipation, which is frequently associated with age (Ivanov et al. 2008; Odamaki et al. 2016).

Gut microbiota composition across the life cycle

Maintaining the integrity of this superorganism is crucial for optimum health since 10^{13} human cells and 10^{14} common bacteria make up the physiological sequence of the gut microbiota throughout the human life cycle. Humans gradually develop a stable gut microbiota throughout an age-related physiological sequence that is impacted by both the host's internal characteristics and outside stressors (Kim et al. 2011). The gut microbiota in people changes throughout time (Mateos et al. 2018). The process through which the microbiota changes over time due to host or ecological changes is known as "physiological succession" (Hamady et al. 2008). This dynamic gut microbial community expands quickly at birth (primary exposure), undergoes fast change before the age of three, notably during the weaning period (transition phase), stabilizes (stable phase), and then changes with aging (regression) occur (Ling et al. 2022). Understanding the precise pattern of gut microbiota growth throughout a person's life provides insight into the function and processes of bacteria in host health and illness (Fig. 1).

Initial exposure

Long before the infant develops its unique microbiota, the gut is initially colonized. The primary determinant of the first microbial implantation is the maternal microbiome. Growing data supports the idea that during
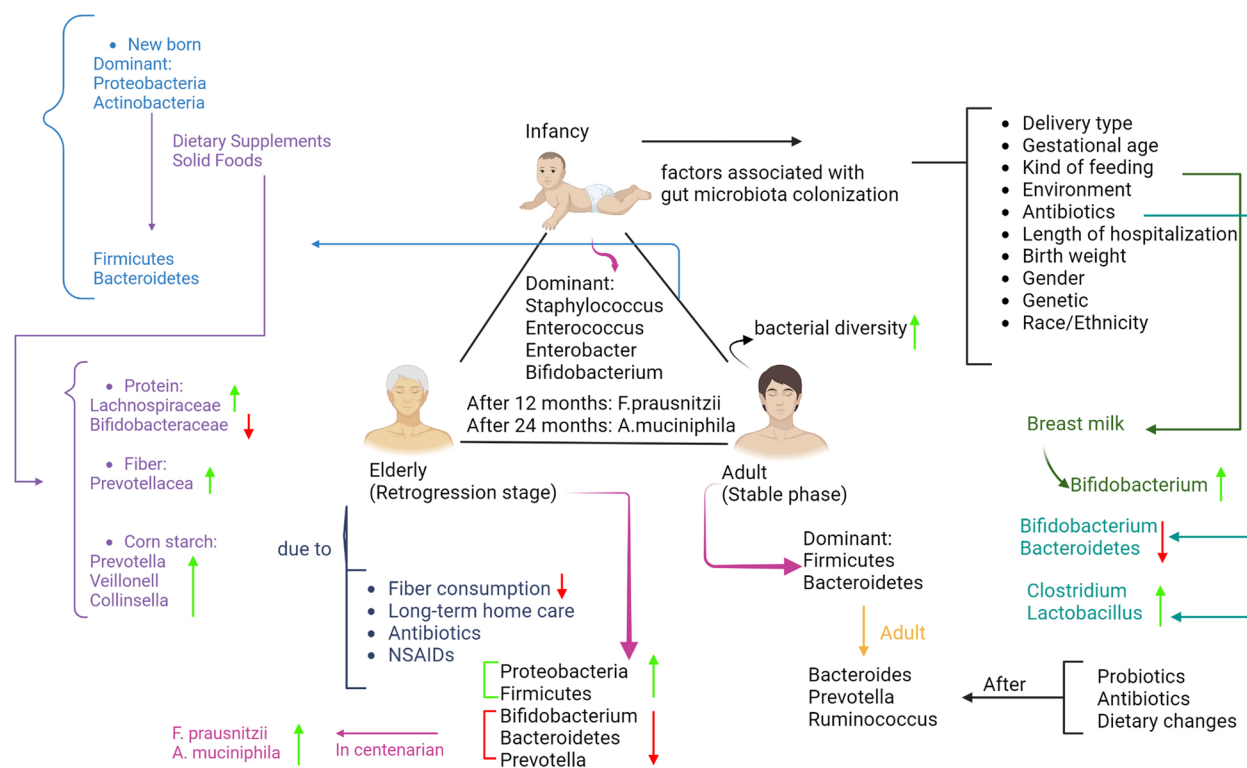
Fig. 1 Overview of the development of gut microbiota

pregnancy, the mother's microbiota is transferred to the fetus (Selma-Royo et al. 2021). Bacterial transmission across the placenta occurs naturally throughout development, and microbes present in the uterus may cause colonization in the growing fetus. These microbes interact well with the healthy maternal immune system, causing immunological tolerance and avoiding fetal rejection (Escobar et al. 2020). Along with intrauterine exposure, factors including the way a baby is born, the gestational age, the kind of feeding, the use of antibiotics, and the surroundings all have an impact on how the gut microbiota develops early (Ganal-Vonarburg et al. 2020; Vandenplas et al. 2020). It is acknowledged that one of the critical determinants of early colonization is the method of delivery. While the gut microbiota of babies delivered by cesarean delivery resembles the mother's skin microbiota, that of normally born infants is comparable to their mothers' vaginal and intestinal microbiota (Dominguez-Bello et al. 2010; Liu et al. 2019). In infants born through cesarean section, the development of the gut microbiota is postponed during the postpartum period, which in turn delays immune system maturation (Magne et al. 2017; Olszak et al. 2012). One of the most significant influences on the composition of the gut microbiota after delivery is the fetal age (C. J. Hill et al. 2017). Compared to their peers, preterm babies (those born at fewer than 37 weeks

of gestation) have a distinct microbiota composition. According to Hesla et al. (2014) research, preterm newborns exhibited significantly more Proteobacteria in their gut microbiota than infants of normal gestational age did in the first week (Hesla et al. 2014). According to Korpela et al. (2018), the microbiota develops after birth in four phases, with Staphylococcus, Enterococcus, Enterobacter, and ultimately Bifidobacterium dominating each stage. However, the Enterococcus phase was only seen in extremely preterm children and seems to be a rare occurrence. It appears that it postpones the succession of microorganisms. The sterile atmosphere of the neonatal intensive care unit, cesarean birth, mother and baby antibiotic exposure, and other difficulties specific to preterm newborns may affect the gut microbiota's normal pattern of absorption (Ling et al. 2022). Mother-to-infant microbial transmission is restricted when mothers are exposed to antibiotics close to the time of delivery because this decreases the variety and richness of the maternal gut microbiota (M. Gibson et al. 2016). Greater than fetal age is the impact of antibiotic usage on the microbiome (Zhou et al. 2020). Compared to babies whose mothers got antibiotics, Arboleya et al. (2016) discovered that babies who did not get antibiotics had greater Firmicutes levels and lower Proteobacteria levels. The administration of perinatal antibiotics was hypothesized to be the cause

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of the lower levels of Bifidobacterium and Bacteroidetes and the abundance of Clostridium and Lactobacillus in newborns delivered via cesarean section (Rutayisire et al. 2016), which is connected to the concurrent changes in the level of Short-chain fatty acid (SCFAs) (Arboleya et al. 2016). The influence of nutrition on gut colonization is another significant element. Due to its high concentration of special oligosaccharides, breast milk aids in the formation of a healthy microbiome in babies. The oligosaccharides and glycoproteins included in human milk can encourage the development of good microbes and inhibit harmful germs (Cong et al. 2016). Breast milk microbiome is the primary source of bacteria like Bifidobacterium, which has health advantages beyond nutrition (Benítez-Páez et al. 2020). These microbiota components may be vertically passed from mother to newborn during nursing. The bacterial makeup of breast milk is impacted by the stage of lactation, gestational age, birth method, mother food, and antibiotic exposure (Rogier et al. 2014). In addition to the aforementioned elements, the first colonization of the gut microbiota is also influenced by the surrounding environment, the length of hospitalization, birth weight, gender, genetic variables, race/ethnicity, maternal education, and maternal illnesses (Xu et al. 2020).

Transitional phase

Weaning causes the gut microbiota's composition to shift in a significant way. For newborns, the progressive switch from a diet high in milk to one that also contains other foods is a special and important event, but it may also be difficult on the host gut's physiology (Lallès et al. 2007). When solid food is introduced, the gut microbiota enters a new stage of growth marked by a sharp rise in bacterial population and evolution toward a makeup more resembling that of the adult microbiota (Subramanian et al. 2014). Proteobacteria and Actinobacteria are replaced as the main members of the newborn microbiota by Firmicutes and Bacteroidetes phyla due to the addition of dietary supplements and new nutrients during weaning (Fallani et al. 2011; Koenig et al. 2011). Consuming foods high in protein and fiber, such as meat, cheese, and Danish rye bread, is particularly linked to increased alpha diversity. Consuming more protein enriched the Lachnospiraceae family and decreased saccharolytic bacteria like those in the Bifidobacteraceae family, whereas increasing Prevotellacea numbers was associated with higher fiber intake (Laursen et al. 2016). *Faecalibacterium prausnitzii* and *Akkermansia muciniphila* are absent or present in early infancy and reach adult levels by 12 months and 24 months, respectively (Yassour et al. 2016). In addition to having an impact on the variety and composition of the gut microbiota, the timing of supplemental feeding

(3 and 12 months) also has an impact on the concentration of SCFAs throughout the first year of life (Differding et al. 2020). The weaned group's fecal microbial population undergoes considerable alterations as a result of the consumption of an amylose corn starch diet, with Prevotella, Veillonella, and Collinsella levels linked with propionate synthesis significantly rising (Wang et al. 2019). The "weaning response," as it was dubbed by Nabhani et al. was discovered to be a potent immunological reaction brought on by the increasing microbiota at weaning. Inhibition of weaning causes pathological imprinting for increased susceptibility to colitis, allergic inflammation, and cancer later in life (Al Nabhani et al. 2019).

Stable phase

The human gut microbiota changes into adult composition 3 years after birth (Caporaso et al. 2011; Rajilić-Stojanović et al. 2009; Wu et al. 2011). Firmicutes and Bacteroidetes predominate in the stable, mature microbiota, characterized by increased bacterial diversity (Ho et al. 2018). In contrast to the first two phases, where Bifidobacterium predominated, the adult intestinal microbiota is dominated by Bacteroides and Eubacterium, which are referred to as the major microbiome. Although these genera may be a normal component of the intestinal bacterial community, Veillonella has been linked to various infections, and an abundance of intestinal bacteroids is linked to a higher body mass index in young children (Brook 1996; Lagier et al. 2012; Schwiertz et al. 2000; Vael et al. 2011). The adult-type gut microbiota may be categorized into three groups, or enterotypes, according to the primary microbiome: Bacteroides, Prevotella, and Ruminococcus (Costea et al. 2018; Manimozhiyan et al. 2011). Each of these three enterotypes, which are typically flexible, represents several stable states in the human gut microbiota. The gut microbiota can be disturbed by several diseases, including those brought on by probiotics, antibiotics, and dietary changes. A healthy microbiota must be maintained by homeostatic equilibrium among microbial communities and between microbes and the host gut interface. Our resistance to diseases linked to dysbiosis is facilitated by a robust microbiome (Ling et al. 2022). Beyond the capacity of the gut microbiota, the change from a main steady state to an alternate steady state can put the host in a pre-disease state and predispose them to chronic illnesses (Goyal et al. 2018). It implies that a critical factor in both health and disease is the flexibility of gut microbes (Sommer et al. 2017). By contrasting gut microbiomes and how they interact with tolerant and vulnerable hosts, omics research might find indicators of resilience. Increased gut microbiome flexibility can result in new disease prevention techniques by neutralizing or suppressing illness triggers, as well as

by finding and encouraging species and activities that are beneficial to health (Rosier et al. 2018). According to earlier studies, dietary interventions with significant compositional alterations can impact and modify the enterotype within 4 days (Kovatcheva-Datchary et al. 2015; Wu et al. 2011). Enterotypes, however, seem stable after around 10 days (Wu et al. 2011). According to Morrison et al. lowering soluble fiber can have an impact on the production of microbial metabolites that are crucial for controlling outcomes in the areas of metabolism, immunity, behavior, and neurobiology (Morrison et al. 2020).

Retrogression

The gut microbiota's makeup and activity are significantly influenced by aging. Less fiber consumption, ongoing home care, the use of antibiotics, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) may all be risk factors for these alterations (O'Toole and Jeffery 2015). As people get older, the microbiota in their intestines undergoes several changes, including a reduction in the variety of species present, an increase in the variation between people, an increase in the prevalence of proteobacteria, and a decrease in the prevalence of probiotic bacteria like Bifidobacterium. The breakdown of the intestinal mucosal barrier and a greater vulnerability to pathogen infection may be related to these alterations (Claesson et al. 2012; Lahtinen et al. 2009). The proportions of Firmicutes and Bacteroidetes have changed, one of the most significant microbiota traits in older adults. Younger persons have greater proportions of Firmicutes, whereas older adults have greater amounts of Bacteroidetes. As a result, one sign of aging is a decline in the Firmicutes/Bacteroidetes ratio (Mariat et al. 2009). Once someone enters long-term care, species linked with variety, such as Prevotella and allied taxa, see a dramatic drop in abundance (Claesson et al. 2012). Furthermore, recent studies have shown that aging is accompanied by changes in the dynamic network and an increase in the number of dominating species (Biagi et al. 2016; Rampelli et al. 2020). Elderly persons in excellent health have higher abundances or richer populations of some health-related groups in their gut microbiota, such as Christensenellaceae, Bifidobacterium, and Akkermansia (Biagi et al. 2016). Since they have achieved the pinnacles of life by avoiding, eliminating, or postponing chronic illnesses, centenarians serve as examples of healthy aging (Biagi et al. 2010). Chinese researchers (Luan et al. 2020) found that *Faecalibacterium prausnitzii*, a species with anti-inflammatory properties, was much more prevalent in centenarians' gut microbiota throughout the transition from health to death. In contrast to *Eubacterium limosum*'s more than tenfold growth, the microbiota of centenarians showed a considerable decline (Biagi et al.

2010). When compared to other age groups, centennial gut communities had much higher levels of *Akkermansia muciniphila*, a bacterium that is frequently used as an indication of a healthy gut community (Biagi et al. 2010). Two strains of Bacteroides, one strain of Ruminococcaceae, and one strain of Desulfovibrio were found to be associated with age and residency in healthy elderly Birmingham residents by a team of Chinese scientists (Zhao et al. 2011).

Gut microbiota and human metabolism

To provide energy for biological functions and growth, intestinal microbiota consumes food components (carbohydrates, proteins, and lipids) and host-derived components, such as expelled epithelial cells and mucus. These mechanisms produce metabolites that have an impact on human health and metabolism. SCFAs are produced as a result of carbohydrate fermentation and are used by the host (Ramakrishna and Roediger 1990). Protein fermentation generates phenolic compounds that might harm the host (Windey et al. 2012). These metabolites can be detoxified by the liver and the gut (Ramakrishna et al. 1989). Additionally, the gut bacteria produce several chemicals, including vitamin K and vitamin B compounds. It is doubtful that the host will be able to directly access vitamin B12, which is created by the gut flora. Because of the way vitamin B12 is metabolized, it must attach to factor R in the stomach, move to the intrinsic factor in the small intestine, and then be absorbed (Ramakrishna et al. 1989).

The gut microbiota and obesity

Studies in germ-free mice, who are typically thin, showed that the gut flora of normal mice increased body weight by more than 50% when they were given the transplanted flora (Bäckhed et al. 2004), demonstrating the importance of gut microbiota in the control of body weight. This is linked to an increase in the expression of genes from microorganisms that produce the enzymes necessary for the metabolism of SCFAs and the enzymatic breakdown of complex carbohydrates and sugars. Obese mice's intestinal microbiota exhibited a decline in bifidobacteria compared to wild-type mice's microbiota, along with the presence of Halomonas and Sphingomonas in the cecum, which likely plays a role in storing energy from carbohydrates that are not digested in the small intestine (Turnbaugh et al. 2006). Studies of human relationships worldwide show that obese persons have altered gut microbiotas compared to lean people, but the specific microbial communities affected by these alterations vary (Turnbaugh et al. 2009). There have been several attempts to clarify the nature of the connection between obesity and gut microbiota (Zsálig et al. 2023). Many

microbial genes have been discovered to be shared by co-twins in studies of twin pairs matched for body mass index, indicating the existence of a core microbiome. Obese twins had bacteria and actinobacteria, but there were no appreciable alterations in the phylum Firmicutes, decreased microbial diversity, or alterations in the genes regulating metabolic pathways (Brand et al. 2021). Several microbial communities that are a part of the phylum Firmicutes are significant fermenters of carbohydrates and may aid in preserving energy from carbs. Microbial fermentation products influence energy metabolism and salvage through a number of neuroendocrine processes in addition to directly supplying energy in the form of SCFA (Canfora et al. 2017). By enhancing the oxidation of fatty acids in skeletal muscles and decreasing glycogen storage in the liver, this enzyme's activation may be necessary for germ-free mice to maintain their leanness (Li et al. 2022). In conclusion, the data we currently have pointed to the gut microbiota as being a significant factor in the emergence and maintenance of obesity. Their function might be influenced by how they interact with the genetic components of the host. Their enhanced ability to absorb energy from the large intestine by fermenting unabsorbed carbohydrates is one of the methods by which they cause obesity. Increased fatty acid uptake into fat cells and reduced fatty acid oxidation in skeletal muscle are the results of soluble substances released by the small intestine as a result of hormonal changes caused by SCFA nuclear receptors (Amorim et al. 2020). Additionally, increased intestinal permeability causes low-grade systemic inflammation in various organs, contributing to insulin resistance and its ensuing metabolic consequences (Ramakrishna 2013).

Gut microbiota and energy malnutrition

Intestinal mucosal inflammation may be linked to a lean body habit (Ramakrishna et al. 2006). In cases with tropical enteropathy, a subclinical inflammatory disease of the intestinal mucosa marked by lymphoplasmacytic inflammatory cell infiltration of the intestinal lamina propria, a lean body habitus may be present (Venkatraman et al. 2003). In animal models of overt colitis, changing the gut microbiota (by giving the animals certain microbial communities) reduces intestinal inflammation and increases body weight (Nanda Kumar et al. 2008). Studies on the gut microbiota and malnutrition are still in their infancy, and it is unclear how the two are related or whether changes in the gut microbiome are what cause malnutrition. Weight loss and a reduction in amino acid and carbohydrate metabolism were observed in gnotobiotic mice fed a Malawian diet and subsequently transplanted with the gut microbiota of Kwashiorkor children (Smith et al. 2013). That the gut microbiota has a role in the onset of malnutrition follows logically.

Gut microbiota and mineral absorption

Lactobacilli are substantially underrepresented in the gut microbiota of individuals with iron deficiency anemia, according to studies on patients with the condition. Lactobacilli need iron for significant development, thus those with low levels of iron may have less of it in their stomach (Scholz-Ahrens and Schrezenmeir 2002; Scholz-Ahrens and Schrezenmeir, 2007). Although the right colon and cecum also express enterocyte transporters involved in iron transport, the duodenum is still the predominant source of iron absorption (Levrat et al. 1991). A reasonable explanation for the connection between lactobacilli depletion and iron deficiency anemia is provided by the fact that lactobacilli are involved in the conversion of lactate to propionate in fermentation systems (Ramakrishna 2013).

Gut microbiota and glucose metabolism

There has been speculation regarding the significance of gut bacteria in the development of type 2 diabetes (T2D). Impairment of insulin signaling is caused by changes in the phosphorylation of the insulin receptor, insulin receptor substrate (IRS), and Akt, as well as alterations in the serine phosphorylation of the inhibitory IRS-1. It is connected to a notable rise in Firmicutes and a slight rise in Bacteroides (Munukka et al. 2012). Women with metabolic syndrome, a population linked to metabolic illness, have been found to have an increased frequency of *E. rectale*/*C. cocci* belonging to the Firmicutes group (Caricilli et al. 2011). In an intriguing randomized study, male recipients received intestinal injections of microbiota from lean donors (or the patient's microbiota as a control). Insulin sensitivity (glucose clearance rate) in receivers who received microbiota from lean donors dramatically enhanced 6 weeks after microbiota injection in patients with metabolic syndrome. This was linked to an increase in the number of butyrate-producing bacteria in feces (Tremaroli and Bäckhed 2012). However, it is still unknown exactly how the gut microbiota contributes to the development of diabetes and what mechanisms they may use to do so (Vrieze et al. 2012).

By having a nutritional impact and stimulating the production of GLP-2, butyrate fuels enterocytes and improves intestinal barrier performance (Cani et al. 2009). By encouraging preadipocyte and macrophage proliferation, upregulating ILC3, and boosting B and T lymphocyte infiltration, bacterial components in mouse metabolic tissue exacerbate inflammation. Proinflammatory cytokines associated with diabetes can aggravate

its consequences by reducing insulin signaling (Sanders et al. 2021).

Gut microbiota and lipid metabolism

The synthesis of bile salt hydrolases by some intestinal microbiota, particularly lactobacilli, allows them to hydrolyze bile salts. This disrupts the hepatic cycle of bile salt reabsorption, causing an increase in fecal bile salt loss and a subsequent drop in serum cholesterol as a result of diverting cholesterol synthesis to bile acid production (Favier et al. 1995; Levrat et al. 1994). Another way that the gut microbiota and dyslipidemia are related is through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A synthase by propionic acid, a substance that is produced by the gut bacteria. Reduced cholesterol synthesis is caused by liver activity (Y. Lin et al. 1995).

Reabsorbing fat and promoting lipid metabolism are benefits of the gut microbiota, which inhibits the inhibitory expression of lipoprotein lipase in adipose tissue cells. Sterol response element binding protein 1 (SREBP1), carbohydrate response element binding protein (ChREBP), and acetyl-CoA carboxylase 1 (ACC1) are among the genes that have increased in relation to the microbiota through lipid metabolism (Ilhan 2018) (Fig. 2).

Bacteroides thetaiotaomicron increases lipid hydrolysis by regulating the expression of cholesterol esterase (de Punder and Pruimboom 2015). Lipopolysaccharide

(LPS), the main component of Gram-negative bacteria's cell wall, is elevated in plasma levels, and mucus integrity is weakened by high-fat diets. TLR-4 is involved in a process that transmits increased levels of LPS via intestinal capillaries. Impaired intestinal permeability raises blood levels of TNF-α, IL-1, IL-6, and plasminogen-1 activating inhibitor (PAI-1) and causes systemic inflammation with a significant accumulation of adipose in the liver. When short-chain fatty acids (SCFAs) produced by the microbiota activate AMPK, they reduce the production of fasting-induced adipose factor (FIAF), which increases the activity of LPS and inhibits the activity of PGC-1α, the proximal proliferator-activated receptor co-activator. Most often, PPARα is recognized as a metabolic regulator involved in energy storage that is expressed in the liver and brown adipose tissue. Lipogenesis improves control of beta-oxidation and fatty acid metabolism (Duszka et al. 2020) (Fig. 3).

The progression of metabolic disorders, such as diabetes and obesity, is subsequently accelerated by PPARa suppression (Fluitman et al. 2017).

Propionate binds to both GPR41 and GPR43, butyrate to GPR41, and acetate to GPR43, among other SCFAs. Within the intestinal epithelium, GPR41 and GPR43 receptors are expressed (Sivaprakasam et al. 2016). PPARs are crucial mediators of adipogenesis, and SCFAs boost their expression. SCFAs induce adipose cells to produce leptin by attaching to GPR41. It is believed that
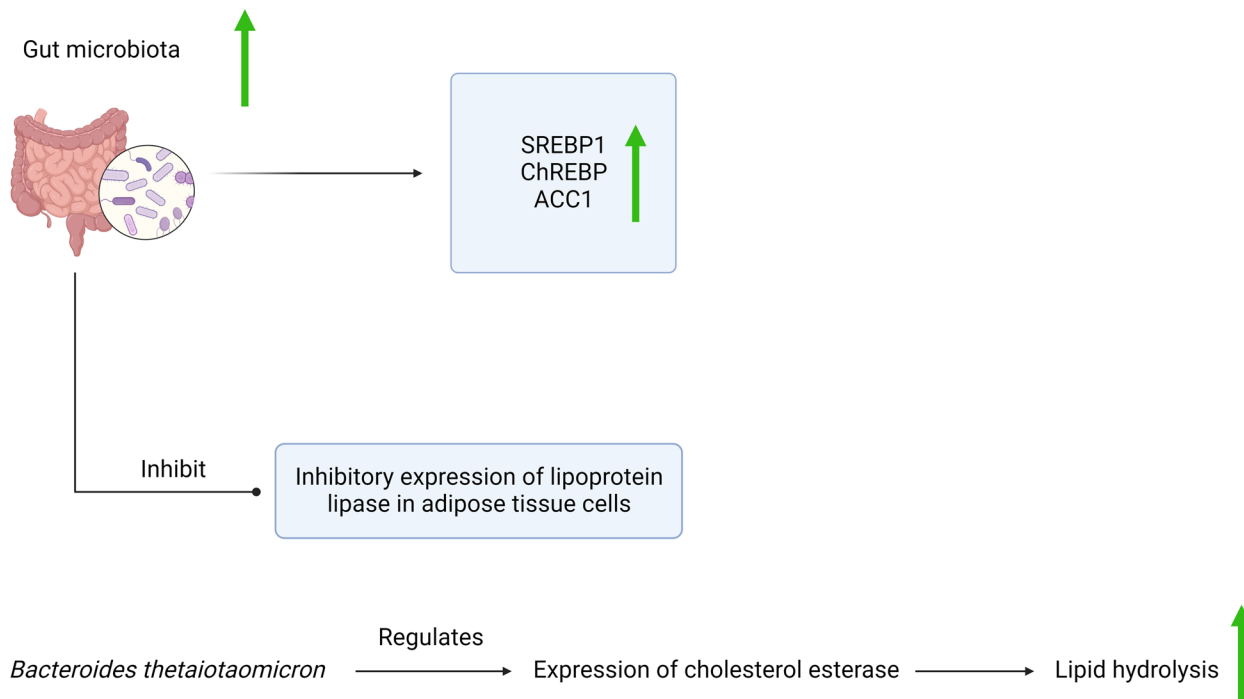

Fig. 2 Effect of the gut microbial community on fat metabolism and fat reabsorption
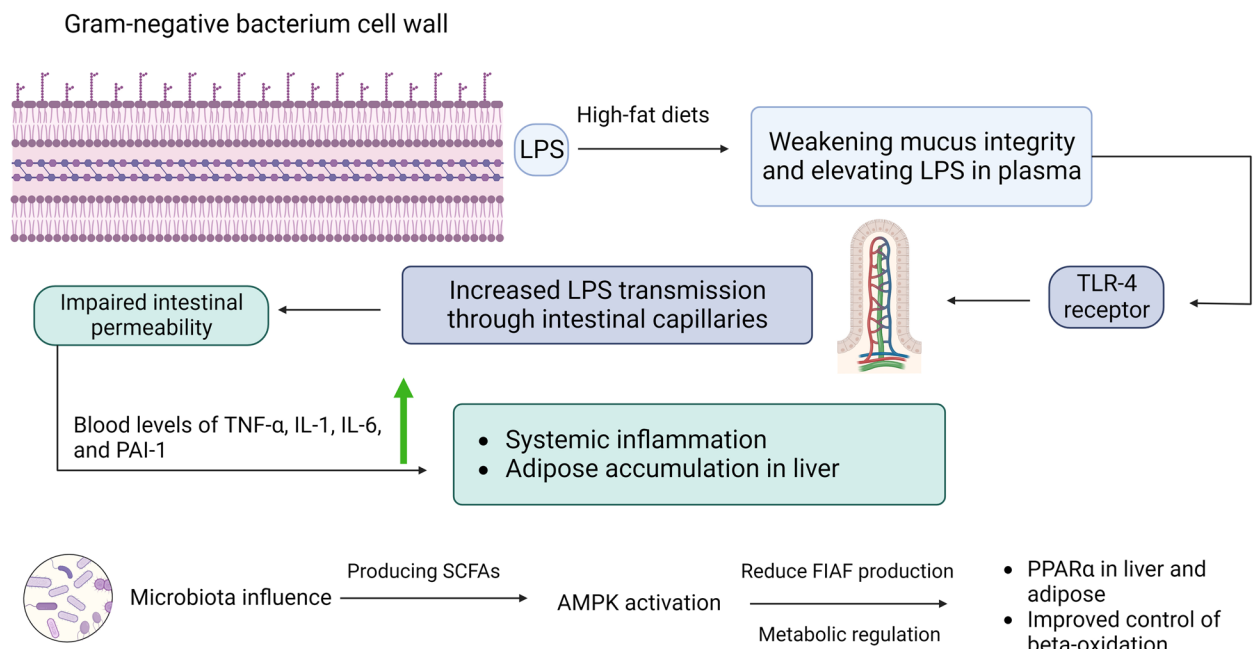
Gram-negative bacterium cell wall

Fig. 3 Overview of the development of gut microbiota bacteroides thetaiotaomicron and its role in lipid metabolism and metabolic disorders

binding to GPR43 promotes adipogenesis. As a result, the fatty acid profile that results may be linked to the onset of obesity (Gomes et al. 2018). However, further research is required to validate these results in people.

Gut microbiota and protein metabolism
In a healthy state, nonabsorbable protein generated from the host is most likely the protein that travels to the large intestine and is subjected to microbial processing. Branch-chain amino acids, as well as a number of phenolic and other metabolites that may be hazardous to the host, are produced as a result of protein fermentation. These are mostly detoxified by the liver and intestinal wall. By supplying fermentable carbohydrates like lactulose to modify the fermentation profile to metabolites that do not influence cognition in the context of liver illness, where hepatic encephalopathy is mainly related to microbial metabolites of protein, this can be decreased. Recent research indicates that the makeup of the gut microbiome is related to cognition in people with liver disease (Davila et al. 2013; Nyangale et al. 2012). Compared to those without encephalopathy, cirrhotic patients with hepatic encephalopathy had higher levels of Veillonellaceae. A change in pathogenic microbiota in the stomach, or an increase in Alcaligenaceae and Porphyromonadaceae, was linked to cognitive impairments (Bajaj et al. 2012). Increased blood saturated and unsaturated microbial fatty acids and unsaturated microorganisms were the results of giving

rifaximin to cirrhotics with little hepatic encephalopathy (Bajaj et al. 2013). The gut microbiota undoubtedly supports the metabolic diseases linked to liver dysfunction, but their major involvement in the genesis of these instances is less plausible, while it is recognized, and will be the subject of research in the near future.

PPARs are crucial mediators of adipogenesis, and short-chain fatty acids (SCFAs) boost their expression. SCFAs induce adipose cells to produce leptin by attaching to GPR41. It is believed that binding to GPR43 promotes adipogenesis. As a result, the fatty acid profile that results may be linked to the onset of obesity (Davila et al. 2013). These bacterial metabolites impact epithelial physiology by regulating the signaling pathways of epithelial cells and modifying the host immune system (Blachier et al. 2007). Additionally, by modifying the expression of bacterial genes, these bacteria produce enzymes involved in the metabolism of amino acids (Bron et al. 2004). Numerous metabolites produced by the anaerobic breakdown of endogenous or undigested proteins in the colon are known to have hazardous qualities. It is commonly accepted that the presence of these metabolites, particularly from a high-protein diet, is linked to a range of inflammatory and chronic illnesses, including atherosclerosis, inflammatory bowel disease (IBD), and colon cancer, due to their detrimental effects on the host's health (Windey et al. 2012). Laboratory experiments using isolated colonocytes or cell types have demonstrated that protein

fermentation byproducts such as NH3 and H2S can be hazardous to health (Leschelle et al. 2002).

The relationship between gut aging and inflammatory/autoimmune diseases

Numerous processes that could impact human function and the immune system may explain the link between gut microbiota imbalance and autoimmune disorders. For example, altering the host immune response and stimulating antigen-presenting cells (APCs), such as dendritic cells (DCs), can lead to the presentation of antigens and the release of cytokines, which in turn can affect T cell development and functionality. Additionally, this can diminish the action of T-regulating cells (Tregs) and Th17 cells, which are crucial for maintaining homeostasis. Antigen mimicry may cause exogenous and endogenous antigens to resemble each other, heightening autoimmunity through the activation of autoimmune T and B cells produced by pathogens. Moreover, variations in the intestinal mucosa's permeability due to the modulation of tight junction protein expression have been observed. Research suggests that in individuals with autoimmune illnesses, the gut microbiota may play a role in both the onset and aggravation of the condition (H. Xu et al. 2019). Among the potential mechanisms are antigenic mimicry, microbiota-induced host immune response, impact on intestinal mucosal permeability, and molecular mimicry (Cusick et al. 2012; English et al. 2023; Wildner 2023). Autoimmune illnesses have been related to changes in the populations of microbes in the gut. A possible contributing factor to autoimmune illnesses is the gut microbiota's ability to influence or impede the immune system's ability to distinguish between intrinsic and non-intrinsic stimuli. The immune system may become exposed to gut commensal bacteria in patients with autoimmune disorders, who often exhibit evidence of compromised gut barriers. In addition, immunological responses linked to the gut microbiota become aberrant and pathogenic when mucous immunity is not tolerated, which exacerbates the illness. There is growing scientific and clinical evidence that autoimmune illnesses may be more severe due to a persistent inflammatory response brought on by gut microbiome dysbiosis. Overall, in genetically predisposed people, the microbiota may either induce or prevent autoimmunity (H. Xu et al. 2019).

According to research using microbeless mice, TLR-2 impairment (TLR activation is dependent on the mice's microbiota state) causes a reduction in Treg-suppressing activity and Foxp3 expression, which in turn causes arthritis. TLR4 was also discovered to have a role in severe arthritis by regulating Th17 cell proliferation and IL-17 synthesis (Jiao et al. 2020). Additionally, Th17 growth and the synthesis of IL-1ß and IL-6 are aided by

the presence of segmented filamentous bacteria (SFB) in the gut. Thus, preserving homeostasis and averting RA and some other autoimmune disorders depends on a healthy balance in the TLR-mediated microbial differentiation of the gut. In mice lacking IL-1RA, arthritis developed on its own. Reduced IL-17 and IL-1ß secretion and increased TLR-2 and TLR-4 activation were seen in IL-1RA/GF mice, and these observations were linked to a weakening of RA (Abdollahi-Roodsaz et al. 2008; Rogier et al. 2015). After observing an increase in Th17 cells in the colon and the onset of severe arthritis, Maeda and colleagues transferred the intestinal microbiota from rheumatoid arthritis patients to SKG mice that were susceptible to arthritis but did not have germs. The researchers also noted an increase in IL-17 release when they cultured SKG dendritic cells with Prevotella copri in the presence of RA autoantigens. These findings suggest that the gut microbiota from RA causes autoreactive cells in the gut and increased joint inflammation (Maeda et al. 2016). Two autoantigens supporting the molecular mimicry process in RA include N-acetylglucosamine-6-sulfatase and filamine A, which have sequence homology with epiphones of gut microorganisms such as Prevotella spp (Bradley et al. 2017; Maeda and Takeda 2019) (Fig. 4).

On the other hand, Dysbiosis can be caused by both environmental changes and host genetic vulnerability (Harmsen and de Goffau 2016; Lee and Mazmanian 2010). A dysbiotic condition can cause changes in the relative abundance of particular microbial species, which can affect the integrity of the intestinal barrier and host immunological responses. Th1, Th2, and Th17 cells are frequently upregulated while Tregs and IgA are downregulated during dysregulated mucosal immune responses (Belkaid and Hand 2014; DeGruttola et al. 2016).

Inflammatory bowel disease (IBD)

IBD is a catch-all name for various intricate, long-term, inflammatory gastrointestinal illnesses (Mulder et al. 2014). IBD is connected to alterations in the gut microbiota and frequently manifests as Crohn's disease (CD) and ulcerative colitis (UC). However, it is uncertain if inflammation brought on by the disease or its etiology is to blame for these alterations. In contrast to healthy people, IBD patients have smaller microbiotas with less functional variety and stability. *Desulfovibrio desulfuricans*, *E. coli*, and Firmicutes from the *Clostridium leptum* group, especially *F. prausnitzii*, have been reported to be more common in the microbiome of IBD patients (Gevers et al. 2014; Martinez-Medina et al. 2009; Pascal et al. 2017). IBD patients often have 25% fewer microbial genes in their bodies than healthy individuals (Qin et al. 2010). Gut microbiome changes in inflammatory bowel disease patients
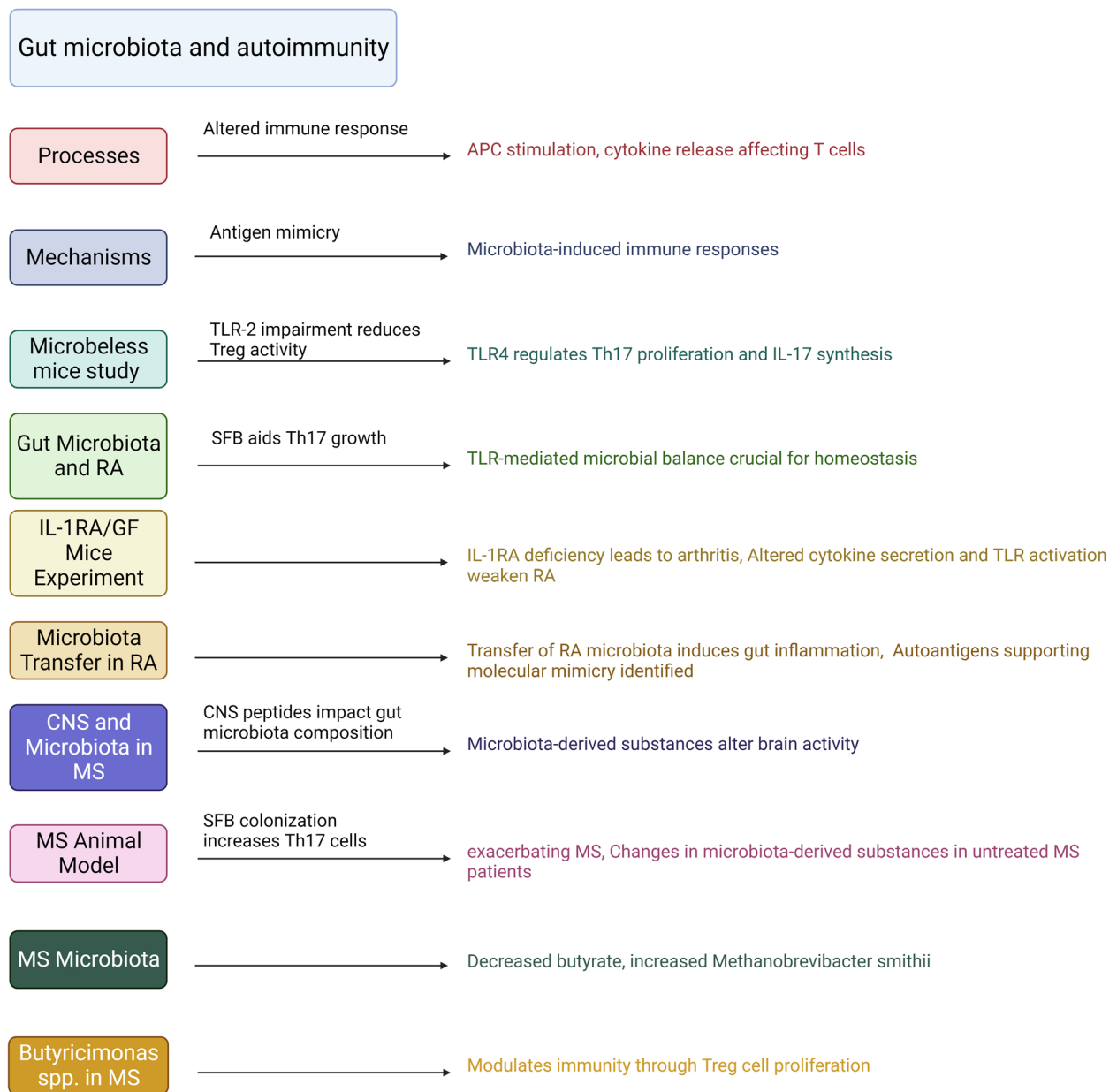
Gut microbiota and autoimmunity

| Processes | Altered immune response → | APC stimulation, cytokine release affecting T cells |

| Mechanisms | Antigen mimicry → | Microbiota-induced immune responses |

| Microbeless mice study | TLR-2 impairment reduces Treg activity → | TLR4 regulates Th17 proliferation and IL-17 synthesis |

| Gut Microbiota and RA | SFB aids Th17 growth → | TLR-mediated microbial balance crucial for homeostasis |

| IL-1RA/GF Mice Experiment | → | IL-1RA deficiency leads to arthritis, Altered cytokine secretion and TLR activation weaken RA |

| Microbiota Transfer in RA | → | Transfer of RA microbiota induces gut inflammation, Autoantigens supporting molecular mimicry identified |

| CNS and Microbiota in MS | CNS peptides impact gut microbiota composition → | Microbiota-derived substances alter brain activity |

| MS Animal Model | SFB colonization increases Th17 cells → | exacerbating MS, Changes in microbiota-derived substances in untreated MS patients |

| MS Microbiota | → | Decreased butyrate, increased Methanobrevibacter smithii |

| Butyricimonas spp. in MS | → | Modulates immunity through Treg cell proliferation |

Fig. 4 The role of gut microbiota imbalance in autoimmune disorders: mechanisms and implications

are linked to shifts in the populations of bacteria that have a role in either dampening or increasing inflammation. Low levels of *F. prausnitzii*, a SCFA-producing bacterium that promotes gut health by increasing Tregs and anti-inflammatory cytokines, are found in people with CD (Sokol et al. 2008; Willing et al. 2009). Having less *F. prausnitzii* bacteria in the body is linked to a higher risk of CD relapse after surgery in people (Sokol et al. 2008). Increased generation of hydrogen sulfate has also been linked to an increase in the prevalence of

sulfate-reducing bacteria such desulfuricans in people with IBD, which can damage IECs and lead to mucosal inflammation (Jia et al. 2012; Loubinoux et al. 2002). CD patients have been shown in multiple human investigations to have elevated levels of *E. coli* that live in the mucosa (Darfeuille-Michaud et al. 2004; Martinez-Medina et al. 2009), causing the gut lining to become more permeable and inflammatory (Palmela et al. 2018). Reduced tryptophan levels have been linked to IBD in humans and mice (Lamas et al. 2016; Nikolaus et al. 2017). Disease severity and IL-22 production are

inversely associated with serum tryptophan levels in inflammatory bowel disease patients (Nikolaus et al. 2017).

IBD patients frequently have stronger T cell and antibody responses to microbial antigens (Britton et al. 2020; Moayyedi et al. 2015) The coexistence of gut microbiota and T-cell differentiation subgroups in the immune response may influence the development of inflammatory bowel disease (IBD) (Qiu et al. 2022). Though Th cell-driven inflammation defends the body against dangerous infections, intestinal inflammation is linked to an overabundance of Th cell activation. The prevailing consensus is that Th1 cells and Th17 cell activation play a major role in Crohn's disease (CD) occurrence, whereas the interaction between Th1 and Th2 cells results in ulcerative colitis (UC) occurrence (Lopetuso et al. 2018). Further research has revealed a stronger correlation between Th17 cell activity and the incidence of inflammatory bowel disease (IBD). IL-17 and IL-22, the two primary cytokines released by Th17 cells, are essential mediators of immunological damage and autoimmune disorders. In cases of acute colitis, IL-22 is thought to have a protective effect. However, research has also revealed that IL-22 and IL17A work together to mediate pathogenicity in chronic colitis (Powell et al. 2020).

Th17 cells are generated by necrotic intestinal mucosal cells, which stimulate macrophages to produce IL-6 and TGF-β via the activity of STAT3 and retinoid-related orphan receptor gamma (RORγt) (Owaga et al. 2015). Effective T cells have the ability to cause an exaggerated immune response in the gut, which might ultimately result in harm to the intestinal mucosa due to the immunosuppressive control of Treg cells (Sun et al. 2017). In a typical setting, Th17 and Tregs are in balance. The Th17/Tregs balance is upset when there is an overabundance of Th17 and a reduction in Treg cells. The gut mucosa may sustain harm as a result of this imbalance. T cells can be stimulated to develop into Th17 cells by IL-6 and modest doses of TGF-β. Excessive TGF-β can promote the growth of Treg cells while suppressing the generation of Th17 cells. Additionally, Th17 cells can inhibit Treg cell multiplication. In peripheral blood, patients with inflammatory bowel disease (IBD) exhibited lower Treg counts and higher Th17 counts, suggesting a major role for the Th17/Treg imbalance in the onset and maintenance of IBD. Furthermore, Th17 and Treg phenotypes in T cells can be induced by the gut microbiota through changes in the intestinal environment. Colonized segmented filamentous bacteria (SFB) in the small intestine of mice can cause inflammation in the gut by stimulating Th17 cells in the intestinal lamina propria to produce IL-17 and IL-22 (L. Lin and Zhang 2017). On the other hand, Treg cells, which have anti-inflammatory properties, can also

be increased by gut bacteria. In inflammatory bowel disease (IBD), Bacteroides thetaiotaomicron summarizes the impact of gut microbiota and compels Tregs to modify the immune system (Hoffmann et al. 2016).

Human blood and colon mucosa have been shown to include circulating T cells CD4 and CD8α (DP8α), as well as Faecalibacterium prausnitzii, which have characteristics similar to Treg cells (Godefroy et al. 2018). Inadequate colonization of *Klebsiella pneumoniae* in the gut shows a distinct method for generating colitis but does not enhance the generation of regulatory T cells or anti-inflammatory T cells. Instead, it preferentially enhances Th1 induction (Atarashi et al. 2017). IBD is primarily caused by gut microbiota dysbiosis, cytokine imbalances, and mucosal barrier deterioration, which all work together to induce mucosal inflammation.

Rheumatoid arthritis (RA)

Approximately 0.5–1 percent of people worldwide suffer from RA, a systemic autoimmune condition that causes joint damage (Silman and Pearson 2002). Reduced gut microbial diversity is seen in RA patients, and their guts have dysbiosis, which is marked by an excess of Prevotella, Lactobacilli, and Collinsella (Chen et al. 2016; Liu et al. 2013; Maeda et al. 2016). Inducing a Th17 response, which in turn causes B-cell differentiation, the creation of autoantibodies, and an increase in intestinal permeability, is what Prevotella and Collinsella can do in mouse models, according to those studies (Chen et al. 2016). The inflammation associated with RA is believed to be caused by these autoantibodies, which attack the joints.

Multiple sclerosis (MS)

The CNS and microbiota are interdependent in MS (Mahajan et al. 2021). Because the CNS contains peptides that can modify food absorption and physiological processes governing nutrient absorption, such as neuropeptide Y and the peptide linked with the melanocortin antagonist agouti-related peptide, it has an impact on the composition of the gut microbiota. The gut microbiota secretes LPS, polysaccharide A, and SCFAs that can alter brain activity (Wang and Kasper 2014). The animal model of autoimmune encephalomyelitis for multiple sclerosis has shown that colonization of segmented filamentous bacteria (SFB) increases the number of Th17 cells in the propria and CNS layers, thereby exacerbating the severity of the disease (Ochoa-Repáraz and Kasper 2014). The production of microbiota-derived butyrate by Firmicutes and Butyricimonas decreased, but Methanobrevibacter smithii was more prevalent in untreated MS patients (Jhangi et al. 2014). Because they cause Treg cells to proliferate in the gut, Butyricimonas spp., a type of bacterium that produces butyrate, modulates immunity.

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Patients with active MS frequently have decreased species richness, greater abundance of Anaerostipae, Faecalibacteria, and Pseudomonas, as well as lower concentrations of Bacteroides, Prevotella, Parabacteroides, and Adlercreutzia. However, a typical MS microbiome phenotype has not yet been discovered (Cantarel et al. 2015; Chen et al. 2016). Reduced levels of IL-17 in the gut and central nervous system, as well as an increase in peripheral Tregs, were seen in a GF mouse model of autoimmune encephalomyelitis (EAE), which is also a model for MS (Lee et al. 2011). Additionally, decreased submucosa thickness, altered tight junctions expression in IEC, and altered intestinal permeability are strongly associated with disease severity in EAE models (Nouri et al. 2014; Secher et al. 2017).

Factors affecting gut microbiota changes with aging

Following a study of the relevant academic research, it can be assumed that some of the most important variables that can influence the composition and general health of the human gut microbiota include genetics, geographic environment, food, exercise, illness, and concurrent medicines. In the following subsections, these aspects are thoroughly evaluated regarding their impact and mode of operation.

Genetic background and environmental factors

The crucial role of genetics in modulation was discovered based on prior research on twins and first-degree relatives, as well as the observation that family members share a microbiota that is more similar than that of unrelated people (Turnbaugh et al. 2009; Yatsunenko et al. 2012). However, Rothschild et al. reported that environmental factors like diet, lifestyle, and drug interactions have a greater impact on our microbiome composition than host genetics, which only have a minor effect (Rothschild et al. 2018). The composition of our gut microbiota and our quality of life may both be significantly impacted by our living environment (Mueller et al. 2006).

Dietary habits, physical activity and the gut microbiota

The diet is one of the primary determinants of the composition, diversity, and function of the gut microbiota community, as shown by the most recent scientific research (Cotillard et al. 2013; Gibson et al. 2004; Sonnenburg and Bäckhed 2016; Zmora et al. 2018). Thus, lifelong dietary practices may contribute to inter-individual heterogeneity in the relative number of gut microbes and enterotype distribution (Cordain et al. 2005; Wu et al. 2011). A study that compared the fecal microbiota of Western European and African children from a community in Burkina Faso 10 years ago amply illustrated the impact of intergenerational dietary practices on gut microbiota composition (De Filippo et al. 2010). The study's findings suggest that nutrition, more so than other significant factors like ethnicity, health, cleanliness, location, and climate, has a significant impact on how gut microbiota develops. Our gut microbiota's diversity and function have been significantly altered as a result of significant changes in diet and living conditions, particularly those brought about by industrial developments (such as processed foods, antibiotics, and clean environments), with significant implications for current outbreaks (Cordain et al. 2005; Sonnenburg and Sonnenburg, 2019; Sonnenburg and Sonnenburg, 2019). In addition to gastrointestinal issues, a number of other conditions may make it more difficult for older persons to meet their ideal nutritional needs (Nagpal et al. 2018; Saffrey 2014). For instance, a diminished desire and capacity to eat solid foods is one way that poor dental health might adversely influence nutritional status (Razak et al. 2014). For decades, regular physical activity and exercise have been linked to improved health and quality of life (Penedo and Dahn 2005). Additionally, it was shown that exercise promotes the generation of SCFA, improves intestinal mucosal immunity, and modifies the Firmicutes/Bacteroidetes ratio in the gut microbiota (Clarke et al. 2014a, b; Mach and Fuster-Botella 2017; Mailing et al. 2019; Monda et al. 2017). There is little information on the possible effects of exercise on gut microbiota in elderly individuals; however, several instances have recently been reported (Taniguchi et al. 2018; Zhu et al. 2020).

Concomitant disease and medication

Chronic sickness and disability are often more common as people age (Vos et al. 2017). Multiple drugs are frequently needed to treat various disorders, and long-term usage of these medications is frequently linked to an increased risk of adverse health effects (Maher et al. 2014). The interaction of various medications with the microbiota in the gut impacts both the therapeutic effect of the treatment as well as the composition and metabolic operation of the microbial ecology. Numerous prescription medications have been proven to be metabolized in part by our gut flora, which might help to explain some of the interindividual variation in reactions (efficacy and safety) (Zimmermann et al. 2019).

Medication exposure causing dysbiosis (antibiotics and proton pump inhibitors)
Antibiotics
In both medical settings and agriculture (Chang et al. 2015), the widespread (and usually excessive) use of broad-spectrum antibiotics raises two fundamental problems (Organization 2018). In contrast to rural, more

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traditional cultures (Martínez et al. 2015; O'Keefe et al. 2015; Pasolli et al. 2019), it has led to the emergence of antibiotic (Davies and Davies 2010; Laxminarayan et al. 2013) resistance and a decrease in the variety of microbial species in our "industrial" microbiome (Blaser and Falkow 2009; Sonnenburg and Sonnenburg, 2019). Colonization resistance is one characteristic of a healthy microbiota (Nagpal et al. 2018; Sullivan et al. 2001), which protects against opportunistic strains and infections, and a microbiota that has been impacted by antibiotics, which may have fewer numbers and species, which can favor the establishment of opportunistic species like *Enterococcus faecalis* (Bartosch et al. 2004) and even increase the risk of *C. difficile* (Kwok et al. 2012). SCFA synthesis is also reduced by antibiotic treatment (Woodmansey et al. 2004), which are vital biological regulators of immunological responses and modulators of inflammation in older adults, and are produced as key metabolites during bacterial fermentation (Chambers et al. 2018; Ríos-Covián et al. 2016; Sanna et al. 2019).

Proton-pump inhibitors

Peptic ulcers and gastroesophageal reflux disease are two gastrointestinal conditions frequently treated with proton pump inhibitors (Olbe et al. 2003). Because they are considered low-risk, they are among the most often used drugs. Yet, new research has connected this to an increased risk of intestinal infections, notably *C. difficile* (Kwok et al. 2012; McDonald et al. 2015). Proton pump inhibitor usage over an extended period of time has been linked in more extensive studies to changes in the gut flora (Imhann et al. 2016; Jackson et al. 2016).

Chronic constipation, laxatives and dysbiosis

Chronic constipation is a common gastrointestinal illness that affects both the general population and the elderly in particular, with prevalence rates of around 20% in people over the age of 65 and 30% in persons over the age of 84 (women are more likely to experience chronic constipation than males) (Gallegos-Orozco et al. 2012). Laxatives are frequently used to relieve constipation symptoms (Ford and Suares 2011). However, certain laxatives can affect the gut flora long after being used for a short period of time (Tropini et al. 2018). A Dutch cohort study examining how various medications affected the composition and metabolic activity of the gut microbiota found that laxatives had one of the strongest connections with the microbiome (Vich Vila et al. 2020).

Obesity and dysbiosis

Even among older age groups, obesity and the issues it brings about are on the rise (Han et al. 2011; Mathus-Vliegen et al. 2012). Obesity alters the metabolism and activities of the gut microbiome, as well as the relative abundance of the two major bacterial phyla, Bacteroidetes and Firmicutes, at the phylum level. It also reduces bacterial diversity and gene expression. The transplantation of microbiota in mice may also pass these features on (Ridaura et al. 2013; Turnbaugh et al. 2009). Alterations in the gut microbiota can therefore result in an increase in gut permeability and have an impact on insulin sensitivity, inflammation, and metabolic endotoxemia (Cani et al. 2007; Cani et al. 2009). Additionally, diabetes, cardiovascular disease, and several malignancies are significantly influenced by this low-grade inflammation (Cani and Jordan 2018).

Role and association between aging and physiological

Environmental elements, including diet, illness, and stress, combine with cellular, organ, and integrated system aging processes to create a complex interplay that determines how an organism ages. It's never ideal to fully recover from insults that set off a pathological response. One of the true indicators of aging is the progressive variety in "physiology," which includes the steady reduction of potential function (Young and Maguire 2019).

Age-related neurological loss, diminished neurotransmitter function, and reduced neurogenesis are the main causes of cognitive function decline. Delirium risk increases due to these alterations, which also cause slower mental processing and more perceptual impairment (Manor and Lipsitz 2013). Aging also throws off physiological rhythms, which include sleep cycles and the endocrine system. Deterioration of sensory organs, such as eyesight or hearing, can also lead to cognitive decline (Young and Maguire 2019).

There are lung structural changes that include reduced pulmonary rubber retreat, increased chest wall stiffness, and reduced respiratory muscle force generation capacity. These changes result in reduced mandatory critical capacity, forcible expiration volume in 1 second (FEV1) and critical capacity, and increased functional residual capacity (FRC). Changes in lung volume in the elderly are given in Fig. 1 (Young and Maguire 2019).

The aorta and carotid arteries are two examples of the major rubber arteries that constrict with age. The predecomposition and retreat of arterial waves are increased by a 50% rise in pulse wave velocity and a prolonged ejection, which also increases systolic and pulse pressure, cardiac effort, and oxygen demand (Mitchell 2008). Renal impairment and cerebrovascular events are caused by left ventricular hypertrophy, which is tissue damage resulting from increased pulse flow, particularly in high-flow organs. Furthermore, as people age, their b-adrenoceptor sensitivity declines, and their responsiveness to

B-agonists is diminished. This multifactorial decline in baroreflex includes diminished responsiveness of terminal organs, inadequate transmission of stretch signals, changed central neuronal processing, and altered autonomous baseline currents (Young and Maguire 2019).

After the age of 70–60, there is a rapid drop in physiological functional capacity (PFC) due to a decrease in maximal oxygen consumption (VO2 max) and a decrease in the pace of training on the lactate threshold. Numerous physiological markers, including PFC, VO2 max, aerobic capacity, vascular adaptability, and endothelium-dependent expansion, are all improved by regular aerobic exercise. Additionally, the oxyradical collecting capacity decreases the thickness of the intima-media wall, restores the endothelium (maintains the number of endothelial precursor cells), and boosts the fibrinolytic capacity (maintenance of endothelial tpa level) (Young and Maguire 2019).

Twenty percent less energy and physical activity are required to maintain the same level of basal metabolic rate. Other beneficial effects include lowering ATP-ASE NA activity, fat oxidation, gluconeogenesis, and altering the permeability of the mitochondrial membrane proton. Age-related anorexia is brought on by reduced ghrelin levels and increased cholecystokinin, which cause earlier satiety, quicker anthral filling, and impaired taste and smell. Several anorexic cytokines, including ciliary nerve agent tnf-alpha, IL-1, IL-2, and IL-6, are implicated20% less energy and physical activity are required to maintain the same level of basal metabolic rate. Other beneficial effects include lowering ATP-ASE NA activity, fat oxidation, gluconeogenesis, and altering the permeability of the mitochondrial membrane proton. Age-related anorexia is brought on by reduced ghrelin levels and increased cholecystokinin, which cause earlier satiety, quicker anthral filling, and impaired taste and smell. Several anorexic cytokines, including ciliary nerve agent tnf-alpha, IL-1, IL-2, and IL-6, are implicated (Wilson and Morley 2003).

Role and association between aging and genetic

It may seem that aging and cancer are opposite processes: aging is marked by a loss of fitness, whereas cancer arises from an unnatural increase in cellular fitness. But perhaps there is a deeper connection between aging and cancer. It is generally accepted that the buildup of time-dependent cell damage is the primary cause of aging (Faggioli et al. 2012; Gems and Partridge 2013; Kirkwood 2005).

Both internal hazards, such as spontaneous hydrolytic processes, reactive oxygen species (ROS), mistakes in DNA replication, and external physical, chemical, and biological forces continuously threaten the integrity and stability of DNA (Hoeijmakers 2009). The range of genetic lesions resulting from external or intrinsic insults is extensive and includes point mutations, transposons, chromosomal gain and loss, telomere shortening, and gene impairment due to virus or transposon mergers. In order to mitigate this damage, organisms have developed an intricate system of DNA repair mechanisms that, when combined, are capable of repairing the majority of nuclear DNA damage (Lord and Ashworth 2012). Moreover, direct DNA lesions in nuclear architectural deficiencies such as laminopathy might result in genomic instability and premature aging disorders (Worman 2012).

Older humans' and model creatures' cells accumulate somatic mutations (Moskalev et al. 2013). Aging is also linked to other types of DNA damage, including chromosomal anopleoids and variations in copy number (Faggioli et al. 2012; Forsberg et al. 2012). Pigmentosome subderma trichotidestrophy, cocaine syndrome, Werner syndrome, Bloom syndrome, Sekel syndrome, and other human progeroid syndromes are caused by a lack of DNA repair pathways, which also accelerates aging in animals (Gregg et al. 2012; Hoeijmakers 2009; Murga et al. 2009). Aging may also be influenced by aging-related mtDNA mutations and deletions (Park and Larsson 2011). The idea that mtDNA damage may be important for aging and age-related disorders was originally raised by the finding of multi-system human illnesses brought on by mtDNA mutations that partially phenocopy aging (Wallace 2005). Research on mice lacking the enzyme mitochondrial DNA polymerase provides more proof. The mtDNA mutation accumulation and random point deletions in these mutant mice cause them to age more quickly and live shorter lives (Kujoth et al. 2005; Trifunovic et al. 2004). Genome instability can also result from mtDNA abnormalities in the nuclear layer or genomic damage that affects the nucleus (Dechat et al. 2008). Nuclear laminate changes and the production of an abnormal preclamine isoform called progerin have also been identified during normal human aging (Ragnauth et al. 2010). In addition to these age-related changes in Type A laminas, Lamin B1 levels decrease during cellular aging, pointing to its application as a biomarker of this process (Freund et al. 2012; Shimi et al. 2011).

Role and association between aging and metabolic

Aging is a natural process associated with important metabolic changes in the body. At the cellular level, the function of the mitochondria responsible for generating energy in cells decreases. This means reducing cells' ability to produce energy and making more unstable use of metabolic fuels, such as glucose and fats. These mitochondrial changes may lead to a decrease in physical

strength and endurance in older people (López-Otín et al. 2013).

In addition, aging can have effects on internal balance and hormonal regulation of the body. In aging, the balance of hormones in the body may break down, which can lead to metabolic disorders such as diabetes and obesity. These hormonal changes may cause changes in body scale and fat distribution in the body (Kalyani and Egan 2013).

The inflammatory process also increases with aging. This means an increase in the level of inflammation in the body, which can lead to the destruction of tissues and disruption of the functioning of metabolic systems, including the immune system, cardiovascular system, and nervous system. Chronic inflammation over time can lead to damage and destruction of tissues, causing unwanted side effects (Franceschi et al. 2018).

Role and association between aging and immunological

Significant immune system alterations occur with aging. There are several aspects of aging that affect both the innate and adaptive immune systems. These include variations in the amount of dendritic and monocytic cells in the blood, a decrease in neutrophil phagocytic activity, restricted variation in B/T cell sets, T cell exhaustion or swelling, and the long-term production of inflammatory cytokines, or inflammation. Immunizations against infectious illnesses are less effective in older adults because their immune systems are not able to mount a strong enough resistance (Chan et al. 2019).

Figure 1 lists the cellular and molecular features of aging that have previously been reported, including immune system failure, sarcopenia, telomere erosion, epigenetic modifications, cellular aging, and mitochondrial dysfunction. Together with these features, chronic inflammation is thought to be the primary cause of aging and age-related disorders (López-Otín et al. 2013).

There are notable alterations in the innate and adaptive immune systems associated with aging. Aging may cause both quantitative and qualitative changes in innate immunity, such as a reduction in the quantity of circulating monocytic and dendritic cells (dcs), a downturn in the phagocytic activity of migrating macrophages or neutrophils, and an interference with the capacity of dcs to deliver AG. Because of the thymic complexity of maturity and the buildup of old, worn-out T cells that are either sleepy or functionally inefficient, aging can cause a reduction in the TCR complex in T cells. Age-related immune system disruption can result from a number of factors, such as persistent viral infection and the production of damage-associated molecular patterns (DAMPs)

(Gibson et al. 2016; Goronzy and Weyand 2013; Goronzy et al. 2001).

Multiple viruses cause persistent infections as host immune system escape mechanisms evolve. Certain viruses can be triggered to produce debilitating symptoms due to a lack of appropriate immunity, as well as delays at low viral replication levels. Elderly people who have infections, particularly respiratory tract infections, may experience consequences that increase their risk of illness and fatality (Chan et al. 2019).

Interventions to modulate gut microbiota in the elderly

Because dysbiosis, or an imbalance in the gut microbiota, has been linked to numerous health problems in humans (from metabolic to neurological disorders) (Cryan and Dinan 2012; Round and Mazmanian 2009; Sarkar et al. 2020; Zmora et al. 2019), Attempts to improve certain health outcomes by restoring a healthy microbiome have been the subject of extensive studies. Animal studies have been modified to include the human microbiome (Arrieta et al. 2016) to demonstrate causal relationships in people (Cryan and Dinan 2012; Round and Mazmanian 2009; Sarkar et al. 2020; Zmora et al. 2019).

Probiotics, prebiotics, and synbiotics

The bulk of health therapies over the past 20 years have included adding probiotics, substrates to encourage the growth of these beneficial bacteria (prebiotics), or a combination of both (synbiotics) to the human diet (Coman and Vodnar 2020).

Prebiotics

Three non-digestible oligosaccharides are effective in this field for prebiotic interventions, which are defined as "a selectively fermented substance that enables specific changes, both in composition and/or activity, in the gastrointestinal microflora that confer benefits on the health and well-being of the host" (Gibson et al. 2004). These are xylo-oligosaccharides (XOS) (Chung et al. 2007), galacto-oligosaccharides (GOS) (Vulevic et al. 2015), and fructo-oligosaccharides (FOS) (Scheid et al. 2014). According to Vazquez et al. (2000), xylose subunits, which make up XOS, have great prebiotic potential and crucial food-related uses (Vazquez et al. 2000). According to studies, GOS are significant prebiotic components of functional foods and are made up of -linked galactose subunits (Sangwan et al. 2011; Torres et al. 2010). Due to their prebiotic properties, FOS, which are made up of linear chains of fructose connected by (2-1) connections, are frequently utilized in food (Sabater-Molina et al. 2009; Sangeetha et al. 2005). The quantity of fecal bifidobacteria is dramatically increased by XOS use. According to

Pokusaeva et al. bifidobacteria can identify different oligos and saccharides in the human gut (Pokusaeva et al. 2011) and have a positive impact on health (O'Callaghan and Van Sinderen 2016). During the course of the trial, no negative impacts on blood counts, nutritional intake, or gastrointestinal (GI) health were seen (Chung et al. 2007). The ingestion of GOS has a bifidogenic impact, which may also be detected immunologically by an increase in IL-10 production and a notable rise in NK cell activity (lymphocytes with the main role against viral infections and some malignancies) (Shaw et al. 2010). In contrast to a placebo (maltodextrin), the intervention of FOS supplementation on blood pharmaceuticals (glucose and lipids) and intestinal transit was shown to minimize the effect of medicines on serum glucose, but no effect of FOS on serum lipids or intestinal transmission was detected. Nothing unfavorable happened, such as gas or discomfort in the abdomen (Scheid et al. 2014).

Probiotics

Live bacteria that provide health advantages when taken in appropriate concentrations are known as probiotics (Hill et al. 2014). Probiotics have been demonstrated to be helpful in the treatment and management of gastrointestinal disorders and immunological responses to respiratory viruses generally in adult populations by longitudinal meta-analyses of RCTs (Ritchie and Romanuk 2012). Diet and lifestyle, age, comorbidities, exposure to biotic risks, and the make-up and function of the basal microbiota are examples of host variables that may affect the effectiveness of an intervention (Suez et al. 2020).

Probiotics aid the intestines by strengthening the immune system and balancing out inflammation brought on by an invading foreign body (Ashaolu 2020). Along with dendritic and epithelial cells, they also cooperate with monocytes and lymphocytes, which are crucial for both innate and adaptive immunity. Probiotics can enhance mucosal immune responses by decreasing the expression of pro-inflammatory cytokines like TNF and IFN-γ, thereby inducing anti-inflammatory cytokines like IL-10 and TGF-β (Corr et al. 2007; Di Giacinto et al. 2005). Furthermore, certain probiotic microbes employ cellular surface features, including fimbrias and capsules, as mechanical stimulation for immune-boosting processes (Sanders et al. 2019).

Cloning resistance is a notion that most likely results from the coordinated action of several immune-boosting processes brought forth by probiotics. This phenomenon is defined as the intestinal intrinsic microbiota occupying host tissue with the aim of eliminating potentially harmful pathogens (Chiu et al. 2017).

The production of antimicrobial compounds is one of the efficacious processes via which probiotics benefit the host by strengthening human immunity and protecting against gastrointestinal infections. Competitive eradication for food sources and binding sites enhanced immune system regulation, and gut barrier are some of the mechanisms through which probiotics exert their beneficial effects (Wan et al. 2019). Probiotics generate a variety of compounds, including bacteriocins, hydrogen peroxide, and organic acids, as a result of their antimicrobial activity (Fig. 5).

These compounds have the ability to kill both gram-positive and gram-negative bacteria. Bacteriocins are produced by many Lactobacillus strains. The mechanism of action involves blocking the creation of cell walls or
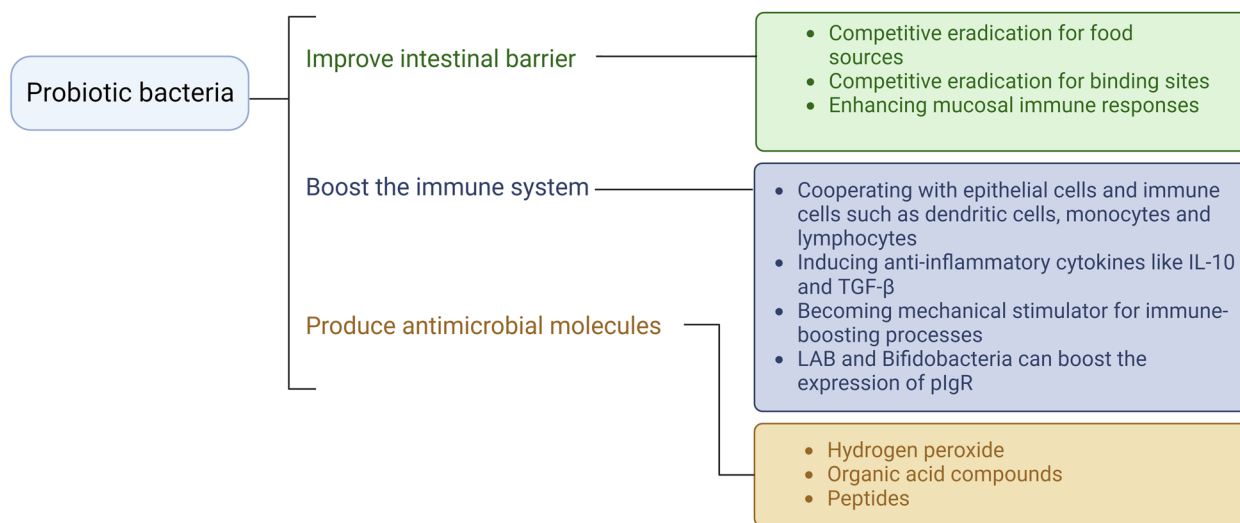
Fig. 5 The immunomodulatory effects of probiotics: enhancing immunity and protecting against inflammation and infections

creating pores, which kills the target pathogenic cells. Additionally, the release of antimicrobial compounds, such as acetic and lactic acids, acidifies the environment to prevent the growth of pathogens like Salmonella. This acidification inhibits nutrient transport, leading to bactericidal consequences (De Keersmaecker et al. 2006; Russell and Diez-Gonzalez 1997). Furthermore, microcin is secreted by probiotic bacteria and works by binding to iron-siderophore receptors to either enter the cell or cause the production of hazardous compounds once inside. These mechanisms result in the suppression of intracellular enzymes, including RNA polymerase, DNA gyrase, and ATP synthase, as well as their activities, such as mRNA translation, ultimately leading to the death of pathogenic cells. The competitive elimination process involves binding locations and nutritional rivalry between pathogenic and probiotic organisms. Probiotics can halt the development of pathogens by employing surface protein structures like mucins or using antimicrobial secretions like organic acids to create an inhospitable environment for infections. Certain research indicates that the expression of tight junction signaling-related genes increases when probiotics are consumed, thereby maintaining the integrity of the intestinal barrier intact (Wan et al. 2019).

Probiotics like Lactobacillus acidophilus (LAB) and Bifidobacteria can boost the expression of polymeric immunoglobulin receptors (pIgR), which may help prevent invasion of the mucous barrier. It is important to note that LAB can influence intestinal dendritic cells and epithelial cells (Kikuchi et al. 2014; Sakai et al. 2014). Certain components of LAB have the ability to trigger dendritic cell production of TGF-β or IL-6 via TLR2 (47). Moreover, lactic acid bacteria use polysaccharides to promote NK activity, which in turn boosts host defense by stimulating the synthesis of IL-12 (Hachimura et al. 2018).

Synbiotics

Synbiotics: Using probiotics and prebiotics together is another option for managing the microbiota (Caso et al. 2013). Probiotics, or live microbial additions, can be used in combination with certain prebiotic substrates (such as lactitol and Lactobacillus organisms or fructoligosaccharide and bifidobacterial strains) to promote development. Due to the compound's easily accessible specialized substrate for fermentation and the advantages that a live prebiotic bacterium provides for the host, it can increase the probiotic organism's chances of survival (Palmer and Jensen 2022).

In the realm of vaccination, it has been extensively studied how geriatric immune system function is affected. It revealed an increase in monocyte and granulocyte phagocytic activity (the main mechanism in clearing pathogens). Consuming synbiotics also led to changes in the microbiota's composition (a rise in Bifidobacteria, Firmicutes, and Actinobacteria vs a decline in Proteobacteria), as well as an increase in butyrate synthesis (Maneerat et al. 2013). Finally, the use of synbiotics demonstrated a considerable reduction in various cardiovascular risk variables and indications of insulin resistance (Cicero et al. 2021; Costabile et al. 2017).

Fecal microbiota transplantation

For patients who have experienced several recurrences of *C. difficile* infection and have not responded to proper antibiotic treatment, current clinical recommendations from the United States advise FMT (L. C. McDonald et al. 2018). This advice is supported by multiple RCTs that show fecal microbiota transplantation (FMT) to be a successful alternative treatment for *C. difficile* infection (Cammarota et al. 2015; Kelly et al. 2016; Lee et al. 2016; Van Nood et al. 2013; Youngster et al. 2014). Elderly persons are disproportionately impacted by *C. difficile* infection, according to research (Keller and Surawicz 2014; Smits et al. 2016). This is mostly due to worries about safety, greater exposure in hospital settings, and regular use of antibiotics and proton pump inhibitors (Loo et al. 2011).

Conclusion

Along with its role in metabolism and immune system control, the gut's microbial diversity declines as we become older. This presents a window of opportunity for opportunistic microorganisms to enter and inflame the gut, resulting in a range of illnesses from low-grade chronic sickness to hospitalizations and even death. There has been a lot of study on the gut microbiota, but it has not yet been possible to pinpoint the best method for treating or preventing dysbiosis in the elderly. Over the course of a person's life, diet may influence the gut microbiota, and older persons may benefit the most from this. It is almost likely that using broad-spectrum antibiotics harms the gut flora. The diversity of the gut microbiota can be restored, and probiotic supplementation has a strong potential to do both.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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