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Navigating Intricacies of Human Gut Microbiota: A Comprehensive Review

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ABSTRACT

Gut microbiota is a very intricate ecosystem that shelter an abundant and multifarious community of microbes that evolve in a human host in a reciprocal relationship. At the same time, gut microbiome sums up all genomic characteristics of gut microbes that are closely linked with the health status of the host. Moreover, as the human gastrointestinal tract is a generous environment comprising over 100 trillion microbes, this aspect makes the microbiome the great "virtual organ" of the body, which consequently influences and modulates the host's fitness, phenotype, and health.[1] Dysbiosis, which is known as disequilibrium in this complex ecosystem, is responsible for a variety of human illnesses that may manifest at every physiological system level.[2] Even though the notion of "dysbiosis" is a broad term used lately as a mental shortcut, intestinal dysbiosis is more and more associated with unwholesome microbiota and pathogenesis of both gut-related and extra-intestinal affections.[3] At the same time, the complex nature of the gut microbiota is also particular to every individual organism and is extremely responsible for both well state of an individual, and unhealthy outcomes when pathogenic microbes known as pathobionts are expended.[4] Moreover , metabolic and nutritional homeostasis, immune system functioning, intestinal barrier integrity, and cerebral activity are all influenced and modulated by the gut microbiota, which directly impacts the crucial physiological functions of the host.[5]Alterations in the microbiota can result from exposure to various environmental factors, including diet, toxins, drugs, and pathogens. Of these, enteric pathogens have the greatest potential to cause microbial dysbiosis as seen in experimental animal models, where foodborne viral pathogens can trigger both local and systemic inflammation altering the composition of the microbiota and barrier functions, as a mechanism for developing auto immunity, as in type 1 diabetes and T-cell mediated destruction of insulin-producing pancreatic beta-cells.[6]

I. GUT MICROBIOTA

Fig 1.1.1 GUT MICROBIOTA

The human gut harbours a complex community of microorganisms known as the gut microbiota, which plays a significant role in maintaining the host's physiology [7]. The gut microbiota contributes to the development of the immune system through different mechanisms, including the maintenance of the intestinal barrier and the maturation and regulation of immune cells through the production of short-chain fatty acids (SCFAs). SCFA- producing bacteria have the ability to regulate immune cell differentiation and the development of regulatory T cells (Tregs), which are critical for maintaining immune homeostasis and controlling immune responses [8].

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Gut microbiota can also regulate other organs remotely by its signals and metabolites. An example of this is the remote control of gut microbial metabolites on the permeability of blood–brain barrier and the development of neuroinflammation in patients with Multiple Sclerosis. However, relying only on the taxonomy of bacterial communities is insufficient to understand the complex role of gut micro biota dysbiosis in ADs. Recent findings have highlighted the importance of studying microbial metabolites and their interactions with humans using multi-omics methods. Multi-omics approaches offer detailed insight into the gut microbiota-host crosstalk and its impact on ADs. For instance, metabolomic profiling has revealed distinct microbial patterns in RA and MS compared to healthy controls.[9]

Fig 1.2.1 Ilya Ilyich Metchnikoff

1.1 THE DISCOVERY OF HUMAN GUT MICROBIOTA

The main scientific step was in 1907, by Ilya Ilyich Metchnikoff, in his study titled "The Prolongation of Life" that he promoted the Lactobacillus acidophilus and the main metabolite of the fermentation of sugars, the lactic acid. Metchnikoff was the first who discovery the importance of lactobacilli in human health and longevity, thus their reduction was the responsible agent for the weakening of the intestinal system and aging.[10] The Human gastrointestinal microecology consists of 3 million species or over

100 trillion microorganisms, thus 400 species and 1014 bacterial cells. In the gastrointestinal tract there are mainly 2 of the 55 Phyla known today (Firmicutes and Bacteroides) and about 15% of the more than 900 known species. The mouth and the all intestine contain the widest population of bacterial species and the stomach the least one (small intestine 104 -106 Lactobacilli, Gram + cocci and Colon 1012/g of Bacteroides, Bifidobacter, Peptostreptococci, Fusobacteria, Lactobacilli, Enterobacteria, Enterococci, and Clostridia).[11,12]

1.2 COMPOSITION AND STRUCTURE OF HUMAN GI MICROBIOTA

Around a decade ago, most knowledge about the adult human gut microbiota stemmed from labour intensive culture-based methods. [13] Recently, our ability to survey the breadth of the gut microbiota has greatly improved due to the advent of culture-independent approaches such as high-throughput and low-cost sequencing methods. Recently, the focus of 16S rRNA sequencing has shifted to analysing shorter subregions of the gene in greater depth; however, the utilisation of shorter read lengths can introduce errors. Targeting of the bacterial 16S ribosomal RNA (rRNA) gene is a popular approach. [14] since this gene is present in all bacteria and archaea and contains nine highly variable regions (V1–V9), which allows species to be easily distinguished. Former techniques concentrated on sequencing the entire 16S rRNA gene. In an early study using this method, the extreme insensitivity and bias of culturing methods were highlighted, since 76% of the rRNA sequences obtained from an adult male faecal sample belonged to novel and uncharacterised species. The study identified the presence of country- specific microbial signatures, suggesting that gut microbiota composition is shaped by environmental factors, such as diet, and possibly also by host genetics. More reliable estimates of microbiota composition and diversity may be provided by whole-genome shotgun metagenomics due to the higher resolution and sensitivity of these techniques. However, it should also be noted that microbiotas that differ in terms of composition may share some degree of functional redundancy, yielding similar protein or metabolite profiles.[15]

1.3 GUARDIAN MICROBIOTA

The protective functions of gut microbiota occur at several levels through mucosal adhesion and the 'crowding out' of potential pathogens, through the elaboration and secretion of anti-microbial peptides (such as bacteriocins), as well as through interactions with various components of the intestinal barrier [16] and immune response. Gut microbiota can also have trophic functions – modulating and influencing gut epithelial cell differentiation and proliferation, affecting neuroendocrine pathways, and impacting on

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homeostatic regulation of the immune system. Extensive cross-talk between the gut bacteria and the immune system, contributes to the development of a healthy immune system. Gut commensals can also induce regulatory T cells, allowing the host to tolerate the massive burden of antigens presented to the gut, ensuring that innocuous antigens do not trigger inflammation; the phenomenon known as tolerance. [17]

1.4 BIOGEOGRAPHY OF THE HUMAN GUT MICROBIOTA IN THE GI TRACT

In contrast with the differing microbiota composition between varying GI organs, the microbiota of different colorectal mucosal regions within the same individual is spatially conserved in terms of both composition and diversity. This feature is apparent even during periods of localised inflammation. On the other hand, the faecal/luminal and mucosal compositions are significantly different. [18] For example, the abundance of Bacteroidetes appears to be higher in faecal/luminal samples than in the mucosa. In contrast, Firmicutes, specifically Clostridium cluster XIVa, are enriched in the mucus layer compared with the lumen. Interestingly, recent experiments in mice colonised with a diverse specific pathogen- free microbiota showed that the outer mucus of the large intestine forms a unique microbial niche and that bacterial species present in the mucus show differential proliferation and resource utilisation compared with the same species in the intestinal lumen. [19]

1.5 INTEGRITY OF THE GUT BARRIER AND STRUCTURE OF THE GITS

Currently there is a convincing body of evidence that supports the role of the gut microbiota in maintaining the structure and function of the gastrointestinal tract. Bacteroides thetaiotaomicron is reported to induce expression of the small proline-rich protein 2A (sprr2A), which is required for maintenance of desmosomes at the epithelial villus. Another mechanism that maintains the tight junctions is by TLR2 mediated signalling that is stimulated by the microbial cell wall peptidoglycan. Furthermore, the Lactobacillus rhamnosus GG strain produces two soluble proteins namely p40 and p75 that can prevent cytokine induced apoptosis of the intestinal epithelial cells in an epithelial growth factor receptor (EGFR) and protein kinase C (PKC) pathway dependent manner. The endocannabinoid system is yet another entity that regulates gut microbiota mediated maintenance of the gut barrier function. E.g., the gramnegative bacteria Akkermansia muciniphilia can increase the levels of endocannabinoids that control gut barrier functions by decreasing metabolic endotoxemia. [20] The gut microbiota contributes to structural development of the gut mucosa by inducing the transcription factor angiogenin-3, which has been implicated in the development of intestinal microvasculature.[21] This is also supported by a significant reduction of villus capillary network in germ-free (GF) mice, which in turn can impair nutrient digestion and absorption. Other evidence that support role of gut microbiota in maintaining structure and function is obtained from GF mice that have a lower intestinal surface area thin villi (secondary to lower regeneration) increase cell cycle time and impaired peristalsis. The gut microbiota can also modulate mucosal glycosylation patterns that are microbial attachment sites both at the cell surface and subcellular levels. For example, a signalling molecule secreted by the organism Bacteroides thetaiotaomicron can stimulate expression of the carbohydrate moiety fucose on the cell surface glycoconjugates. [22]

1.6 GUT MICROBIOTA AND DISEASES

- CARDIOVASCULAR DISEASE AND GUTMICROBIOTA

Cardiovascular disease (CVD) remains the leading cause of death in both the United States and industrialized societies, with growing incidence in developing countries. Factors contributing to CVD arise from genetic sources, environmental sources, or a combination of genetic and environmental sources. Despite extensive investigations in search of causal genetic variants, such as large-scale GWAS, less than one-fifth of attributable cardiovascular risk has been accounted for from genetic determinants. [23] Our largest environmental exposure is what we eat. Technically speaking, food is a foreign object that we take into our bodies in kilogram quantities every day. From the latest National Health and Nutrition Examination Survey (NHANES, 2009 2010), the majority of individuals sampled achieved an intermediate or poor Healthy Eating Index. [24] However, dietary composition is often difficult to assess, and even precise quantification of dietary intake may not necessarily reveal the many known and unknown factors that may influence the contributions of specific dietary nutrients to disease susceptibility. There has also been an overwhelming lack of appreciation at the bedside regarding the intricate and complicated processes that transform ingested food into the myriad metabolites that enter the circulation and fulfil or adversely affect various functional and

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metabolic processes in the body. Over the past decade we have increasingly begun to appreciate the ecological diversity of microbes living symbiotically within us, a large proportion of which reside within our intestines. We now know that the human gut harbours more than 100 trillion microbial cells, far outnumbering the human host cells of the body. [25] Indeed, a sobering fact is that Homo sapiens DNA is estimated to represent less than 10% of the total DNA within our bodies, due to the staggeringly large numbers of microbes that reside in and on us, primarily within our gut. Our microbial symbiont guests have coevolved with us and affect a wide range of physio logic and metabolic processes of the body. The major taxa present in gut microbiota consist primarily of 2 major bacterial phyla, Firmicutes and Bacteroidetes, whose proportions appear to remain remarkably stable over time within individuals and their family members. [26]

- GUTMICROBIOTA AND ALZHIEMERS

There are billions of colonized microbes in the human gut. Increasing evidence suggests that there is a bidirectional association between the human gut microbiota and the brain, which is known as Microbiota–Gut–Brain Axis (MGBA). [27] Gut dysbiosis has been associated with a variety of diseases, especially neurological conditions such as neurodegenerative diseases. In this regard, experimental studies have revealed that gut flora is involved in the regulation of brain functions such as memory and learning. More importantly, the function and composition of intestinal flora affect the pathophysiology of age-related cognitive impairment and dementia, suggesting its crucial role in the onset and progression of AD. [28]

- GUTMICROBIOTA AND PARKINSON DISEASE

The discovery of a bidirectional communication between the brain and the gut, the so-called gut-brain axis, has revolutionized our current understanding of the physiology of the central nervous system (CNS) and the pathophysiology of several neurological conditions, including Parkinson disease (PD).[29] Patients with PD are severely affected by gastrointestinal (GI) disorders throughout their lifetime and can present with GI symptoms (e.g., constipation) up to two decades before the onset of motor disturbances. Pathological hallmarks of PD such as accumulation of abnormal α-synuclein are detected in the enteric nervous system of PD patients before disease development and in individuals at high risk of developing PD such as those suffering from idiopathic REM (rapid eye movement) sleep behaviour disorder. [30]

1.7 GUT MICROBIOTA AND BRAIN FUNCTION

The association between the gut flora and the Central nervous system (CNS) is due to the interaction between the intestine and the brain with each other via the nervous system or chemicals which cross the blood-brain barrier (BBB). The gut flora produces chemical substances (i.e., amino acids and monoamines) that reach the neurons of CNS via the vascular and lymphatic system and can affect their activity, with probable influences on behaviour. On the other hand, the gut microbiota is affected by the messages as neurotransmitters sent by the brain.[31] Several communication pathways between the brain and gut have been investigated. The Vagus nerve plays a central role in the connection between the gut and the autonomic nervous system. This nerve ends to the brain stem nuclei, which give efferent fibers and receive afferent fibers. In this pathway, stem nuclei may regulate many gut activities and send signals to the other regions of the brain, such as the cortical areas and thalamus. Additionally, the enteric nervous system can send and receive signals from the CNS via the gut flora. Also, blood circulation is involved in the exchange between the gut and brain [32]. Intestinal mucosa and BBB allow the passage of endocrine and immune molecules, the most important of which are hormones and cytokines, which can affect the function of both the gut and brain. On the other hand, the other possibility for MGBA regulation by gut bacteria is that these microorganisms produce substances that are toxic to the brain, such as ammonia and D-lactic acid. In addition, during several inflammatory processes, the gut microbiota produces and releases other toxic proteins to the brain, such as host innate immune activators. Alterations in the mentioned processes, especially immunological processes, can contribute to anxiety, memory impairment, and other cognitive alterations.[33]

II. METHODS OF DEVELOPMENT OF GUT MICROBIOTA

The development of the microbiota is generally believed to begin from birth, although this dogma is challenged by a limited number of studies in which microbes were detected in womb tissues, such as the placenta. After birth, the GI

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tract is rapidly colonised, with life events such as illness, antibiotic treatment and changes in diet causing chaotic shifts in the microbiota. The mode of delivery also appears to affect the microbiota composition, with vaginally delivered infants' microbiota containing a high abundance of lactobacilli during the first few days, a reflection of the high load of lactobacilli in the vaginal flora.[34]

The first 1000 days of a child represent a critical window for the maturation of the immune system and the establishment of gut microbiota.[35] This simultaneous development has caught the attention of immunology researchers, making it an area of study that is both intriguing and captivating. The human being lives in harmony with microbiota, which is made up of not only bacteria but also viruses and fungi. These microorganisms are present throughout the human body in different sites such as the skin, mouth, nasopharynx, and intestine. Identifying the bacterial composition of the prenatal meconium has been challenging due to the potential of microbiological contamination. It is widely documented that the process of microbial colonization starts quickly after birth, as evidenced by numerous studies.[36] This group of bifidobacteria includes Bifidobacterium bifidum, Bifidobacterium breve, and Bifidobacterium longum spp. The microbiome undergoes significant transformations during two crucial developmental phases early in life: from birth until weaning, and then during the transition from weaning into early adulthood. These modifications are driven by the diversification of the diet, resulting in considerable changes to the microbial composition.[37]

2.1 DEVELOPMENT OF GUT MICROBIOTA IN INFANTS

- MODE OF DELIVERY

The Finnish Birth Cohort study compared asthma rates in children at 7 years of age and found vaginally delivered children had lower rates of asthma compared with those delivered by Caesarean section (366/8826 (4.25%) vs. 1684/51 039 (3.3%], odds ratio 1.27 (1.13–1.42), P < 0.001). Association between mode of delivery and type I diabetes was examined in a meta-analysis of observational studies, and an increased risk of 20% was detected among those delivered by Caesarean section.In a study of 25 overweight children and 24 normal-weight controls aged 7 years, matched for all possible confounding factors (such as gestational age, birth body mass index (BMI), mode of delivery, breastfeeding, use of antibiotics and probiotics), an examination was made of their overall colonisation patterns from birth onwards. The study found that those later becoming overweight had lower counts of bifidobacteria at the ages of both 6 and 12 months than normal-weight controls, as well as lower levels of total Bifidobacterium genus pool, and specifically of B. longum and B. breve.[38]

- BREAST FEEDING

The next step in colonisation in the first months of life is breast feeding. There is considerable debate about the importance of the duration of breastfeeding. However, it is important to consider the 'quality' of breastfeeding. What is breast milk? It is a very interesting mixture, containing a number of anti-inflammatory compounds that modify the feeding child's immunity development (fatty acids, antioxidants, nucleotides, glutamine, lactoferrin and immunoglobulin A(IgA)). Breast milk is clearly not sterile. It contains a range of bifidobacteria and lactobacilli strains, and in particular B. longum and B. lactis, which, importantly, are not typical strains found in an adult, but are typically infantile bifidobacteria.[39] Bifidobacteria numbers in breast milk are directly affected by the mother's immunological status. Babies at 1 month, solely breastfed by their allergic and skin prick test-positive mothers, had lower levels of bifidobacteria. Bifidobacterium counts were lower in women with excessive weight gain during pregnancy compared to those with lower weight gain, with similar findings in the breast milk of such mothers, along with higher levels of TGF-b2 and soluble CD14 (which enhances immune recognition) in normal-weight mothers. Further, TGF-b levels in breast milk have been pro moted by providing probiotics to the pregnant and lactating mother.[40]

2.2 CULTURE TECHNIQUES

Until the 1990s, knowledge of the gut microbiota was limited to culture-based techniques, an approach that has been used since the early 20th century. Since then, advances have been made in the phenotyping of isolates on the basis of their fermentation profiles and in vitro growth requirements. Although bacterial identification by culture is fairly cheap, it is labour intensive and culture alone gives a limited view of the diversity of the gut microbiota because <30% of gut microbiota members have been cultured to date. [41] In parallel with the development of culture-independent techniques, culture techniques have

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become more sophisticated through the use of, for example, gel microdroplets and microbial culture chips ('micro petri dishes').[42]

- 16S rRNA

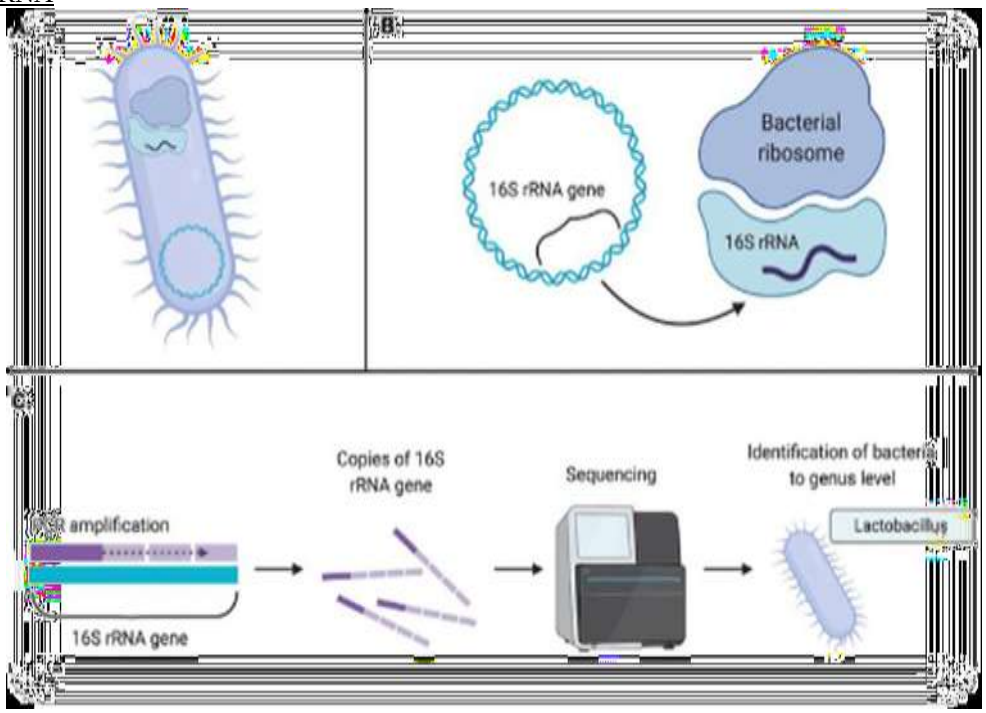

Fig 2.2.1: 16S rRNA sequencing

70S ribosomes are dispersed throughout the cytoplasm of a bacterial cell. They are made up of two subunits: 30S and 50S. The 50S subunit contains two RNA molecules: 5S and 23S. The 30S subunit (or small subunit) contains one RNA molecule: 16S ribosomal rRNA (16S rRNA). One of the functions of 16S rRNA is the initiation and extension of protein synthesis. As rRNA (5S, 16S and 23S) is highly conserved between bacterial species, yet contains variable regions that yield a phylogenetic signal, it is a useful target for phylogenetic identification (bacterial identification). Of the three bacterial rRNA genes, the 16S rRNA gene provides the most tractable combination of conserved sites for PCR primers and variable regions that act as evolutionary chronometers, and it is, therefore, usually used in preference to 5S or 23S rRNA genes for phylogenetic identification.[43]

- PCR

Although PCR has been a huge technical advance across the medical field, it has limitations; each physical, chemical, and biological step—from retrieving a sample to the resulting 16S rRNA amplicons—represents a potential source of bias.For example, differential lysis of microbial cells can affect the final apparent microbiota composition; Gram-positive organisms typically require rigorous conditions to lyse the bacterial cell wall (which is thicker than in Gram-negative bacteria), while these same conditions may cause excessive fragmentation of Gram negative chromosomal DNA[44]

Fluorescence in situ hybridization:- The sample is denatured and 'fixed' in a hybridization solution—fixation is a crucial step to ensure optimal results. This step is performed using cross-linking agents (for example, aldehydes) or precipitating agents (for example, methanol or ethanol) or a mixture of both fluorescently labelled oligonucleotide probes are added and incubated overnight in a hybridization solution at high temperatures (typically 65–75 °C). When hybridization occurs, fluorescence can be enumerated using flow cytometry, with resulting identification of the target species [45] (fig 4).

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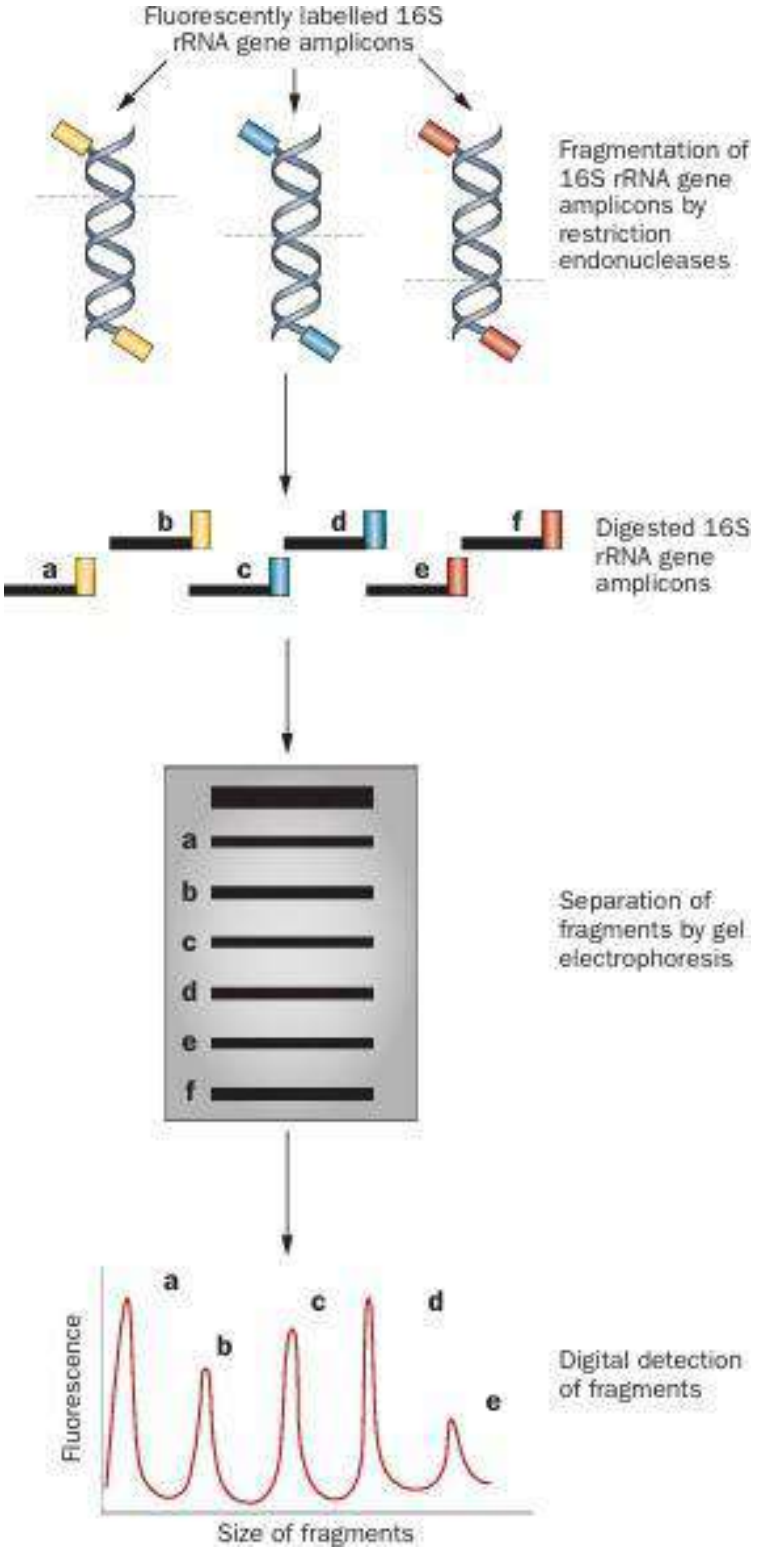

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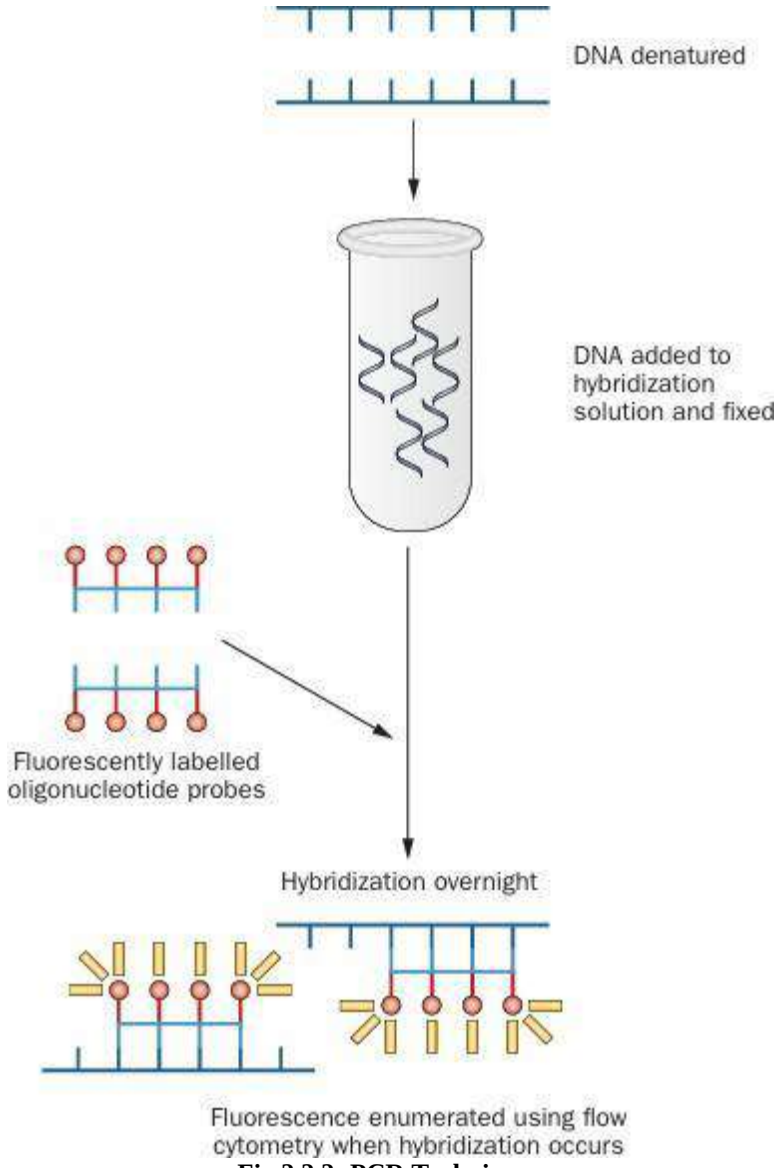

Fig 2.2.2: PCR Techniques

- FINGERPRINTING

DNA fingerprinting is a community analysis tool that allows comparison of DNA fragments in a sample. DGGE separates complex mixtures of 16S rRNA gene amplicons (for example, those derived from a stool sample), which are the same length but have different DNA sequences.[46] This technique (along with TGGE, T-RFLP and FISH) is sometimes regarded quantitative because it gives visual impressions of band and/or species intensity and abundance. However, strictly speaking, these techniques are semi-quantitative at best, because varying amplification dynamics make precise quantitative comparison inadvisable. Disadvantages include PCR bias and the absence of direct phylogenetic identification unless sequencing or probe hybridization is performed. TGGE has also been used in the study of the gut microbiota and it works in a similar manner to DGGE, but a linear temperature gradient is used instead of a denaturing gradient gel. [47]

- DATA PROCESSING

Sequencing reads were analysed using the Quantitative Insights into Microbial Ecology (QIIME) version 1.9.0 package' following the recommended pipeline for the combination of multiple 454 FLX datasets. Denoising was performed using denoise_wrapper.py, and the data

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sets integrated. Chimera removal was performed with Chimera Slayer [and singletons removed. An average of 1657 sequencing reads was obtained per sample. Sequences were clustered at 97% sequence identity using the UCLUST algorithm into operational taxonomic units (OTU) and aligned to the SILVA rRNA database version 119 [48]. Rarefaction to 664 reads per sample was performed, removing heterogeneity of sequencing reads per sample whilst still retaining an accurate representation of diversity. Diversity calculations were performed in the R statistical package using vegan.

- STATISTICAL ANALYSIS

Statistical analyses were performed with the R statistical package.Alpha diversity measures (Shannon Index, Shannon's Equitability, the Inverse Simpson Index and Faith's Phylogenetic Diversity) and Beta diversity measures (the Jaccard index, Bray-Curtis dis similarity, unweighted unifrac and weighted unifrac) were calculated using QIIME . Beta diversity distances between sample groups were compared using the Mann–Whitney U test (testing distances within groups to between groups) and the Wilcoxon signed rank test (testing matched sets of distances at different time points). Alpha diversity was compared using the Wilcoxon signed-rank test. Canonical ordination analysis (CCA) was performed in R with the vegan statistical package.[49]

III. APPLICATION OF GUT MICROBIOTA

3.1 IN IMMUNE SYSTEM

Gut microbiota symbiosis plays a multifaceted role in shaping the immune responses of the human host. This complicated crosstalk allows for the normal functioning of immune tolerance and immune surveillance, which recognizes and eliminates opportunistic bacteria to prevent potential infection. The critical role of the gut microbiota in the formation of a fully functional immune system was identified in GF animals.As a go-to animal model for bacteria- host interactions, GF animals display distinct features in the gut, including an immature mucus system, unformed gut-associated lymphoid tissues, and a reduced number of immune cells Interactions between immune cells and gut microbiota Immune cell types Crosstalk with the gut microbiota.[50]

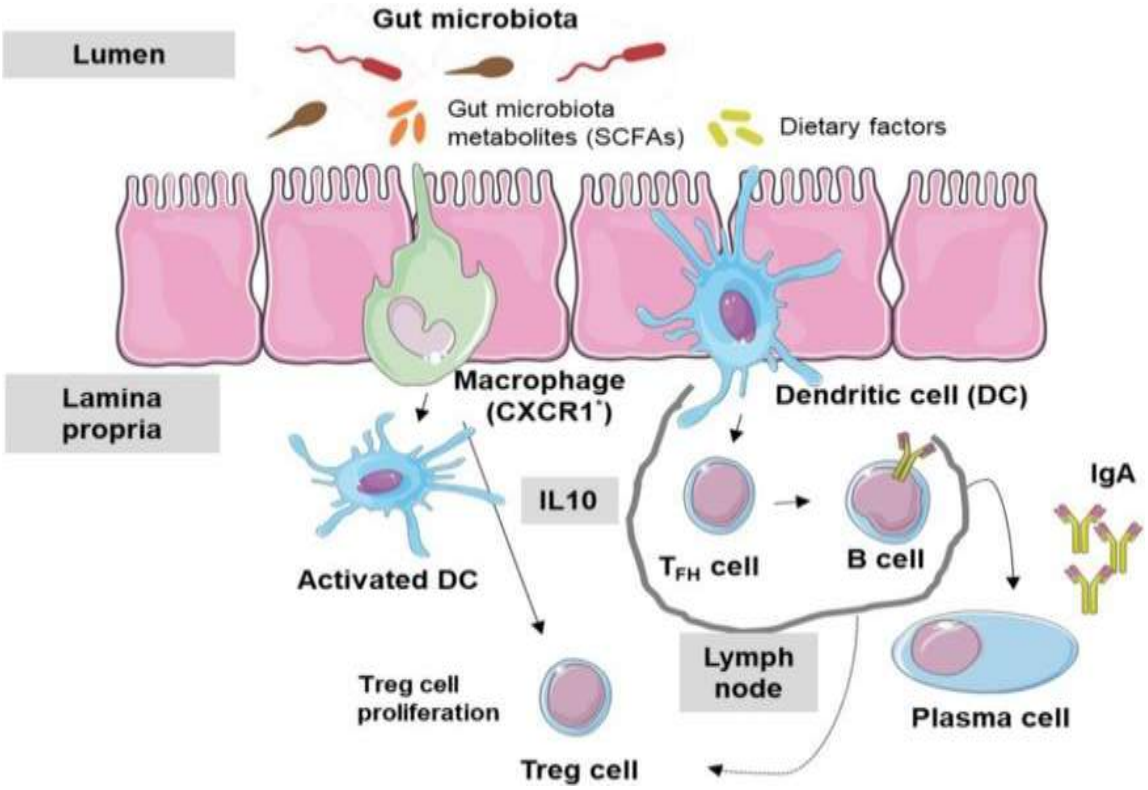

Fig 3.1.1: Activity of gut microbiota in immune system

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3.2 IN IMMUNOMODULATION

The GI microbiota is also important for the development of both the intestinal mucosal and systemic immune system as demonstrated by the deficiency in several immune cell types and lymphoid structures exhibited by germ-free animals. A major immune deficiency exhibited by germ-free animals is the lack of expansion of CD4+ T-cell populations. This deficiency can be completely reversed by the treatment of GF mice with poly saccharide A from the capsule of B. fragilis. This process is mainly performed via the pattern recognition receptors (PRRs) of epithelial cells, such as Toll-like or Nod-like receptors, which are able to recognise the molecular effectors that are produced by intestinal microbes. These effectors mediate processes that can ameli orate certain inflammatory gut disorders, discriminate between beneficial and pathogenic bacteria or increase the number of immune cells or PRRs. SFB, a class of anaerobic and clostridia-related spore-forming commensals present in the mammalian GI tract, actively interact with the immune system. [51]

3.3 MICROBIAL METABOLITES IN CANCER IMMUNOTHERAPY

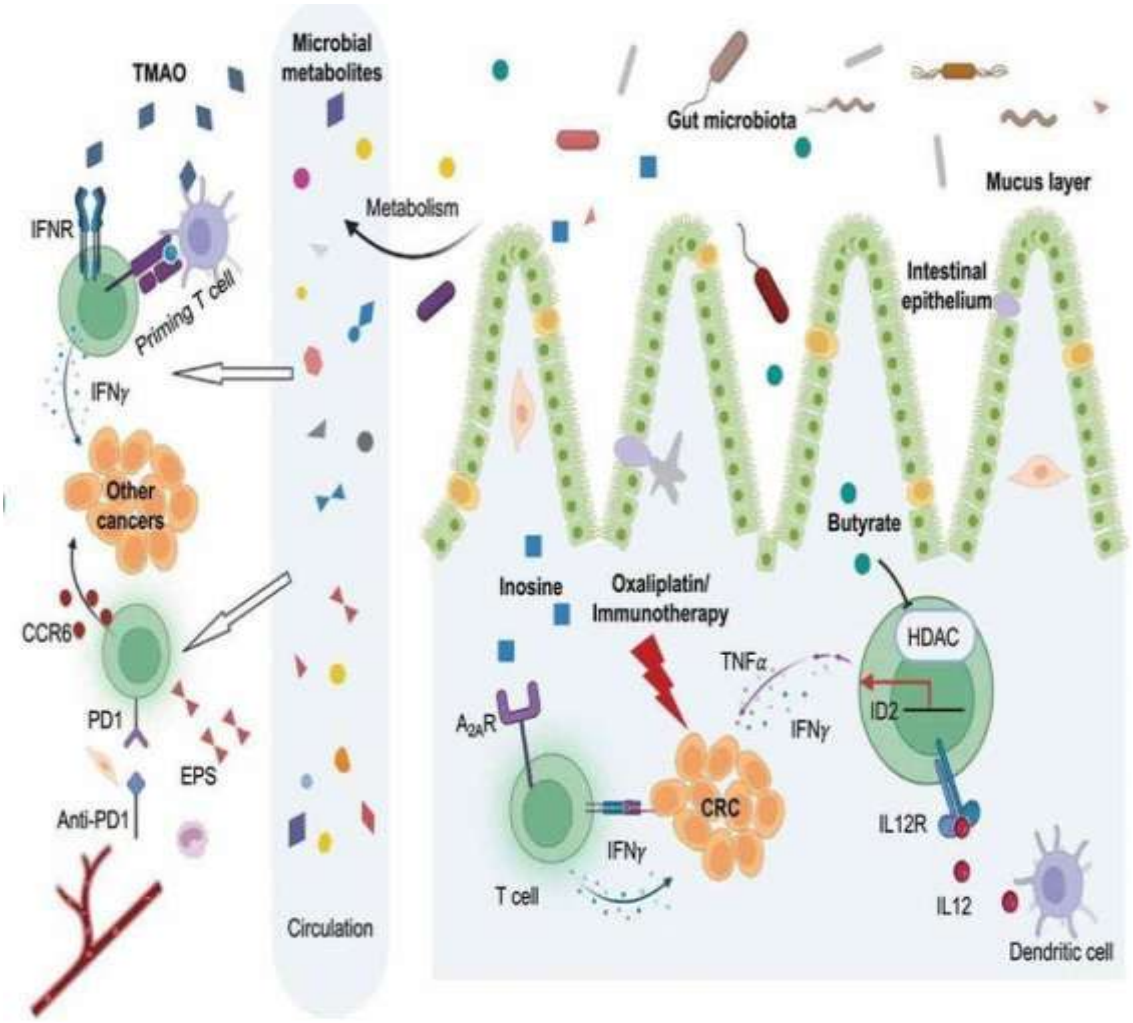

Fig 3.3.1: Derivation of metabolites and action on cancer therapy

Metabolites derived from the gut microbiota have been identified as important regulators of the development and function of immune cells.[52]

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3.4 IN CARDIOMETABOLIC DISEASES

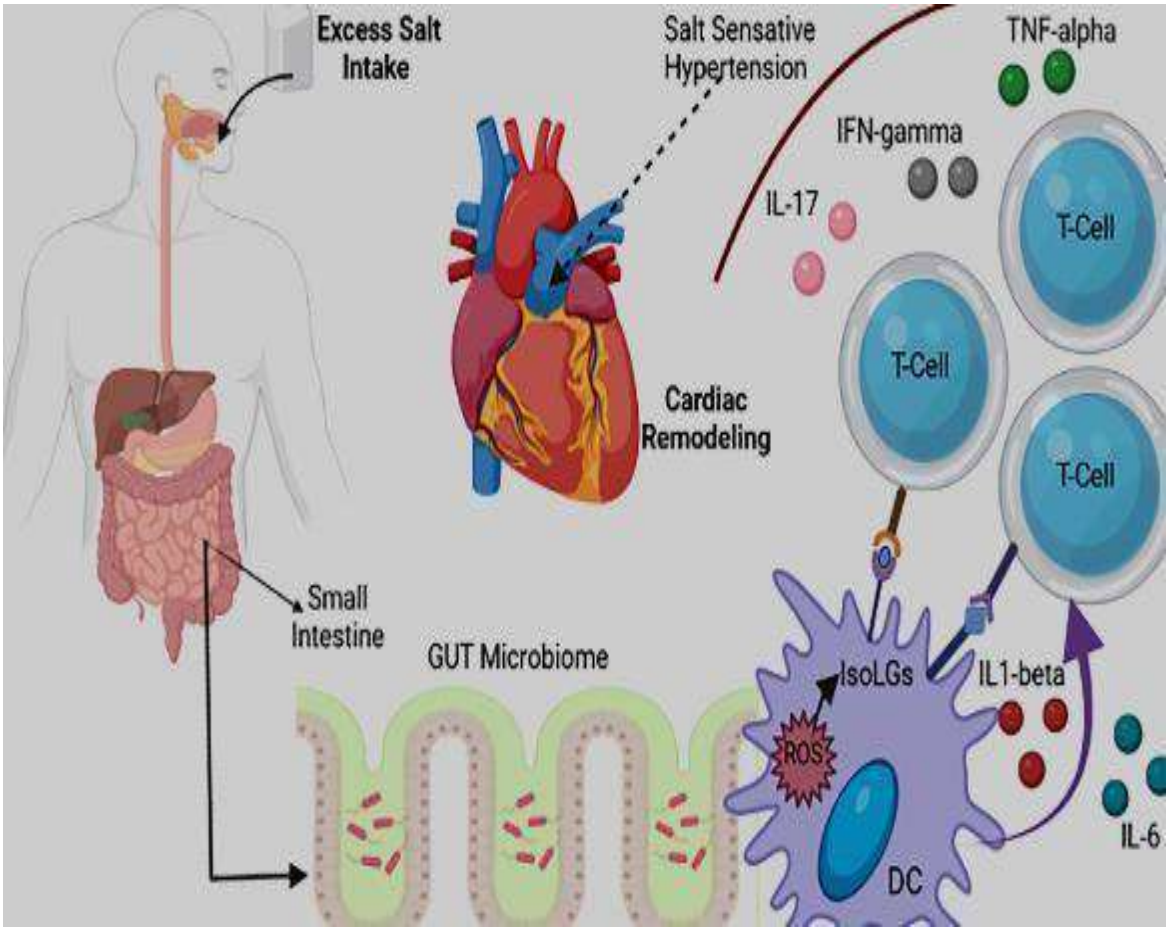

Fig 3.4.1: Action of gut microbiota in cardiovascular disease

An imbalance in the gut microbiome is called dysbiosis. The correlation between gut microbiota dysbiosis and many diseases/phenotypes has been a hot topic in the past decade. Identifying specific microbiomes associated with disease susceptibility is a fascinating research. Most gut microbial communities are composed of Bacteroides, Proteobacteria, Actinobacteria, Firmicutes, and Cerrucomicrobia, with Bacteroides and Firmicutes as the main phylum, and the ratio of Bacteroides to Firmicutes is also considered to be associated with the health.[53] However, there are differences among different individuals, different diseases, and different intestinal sites. The change of bacterial diversity is also associated with host genome and environmental Fig. 7 The changes of gut microbiota and its metabolites lead to CMD in the host. SCFA, short-chain fatty acid; TMAO, trimethylamine oxide; BA, bile acids; AAA, aromatic amino acids; Phen, phenylacetylglutamine; CMD, cardiometabolic disease factors. However, with the rapid development of sequencing technology, these microorganisms can be identified and characterized. Common diseases in which gut microbiota and their metabolites lead to CMD in the host through different pathways are shown in (Fig 3.4.2).

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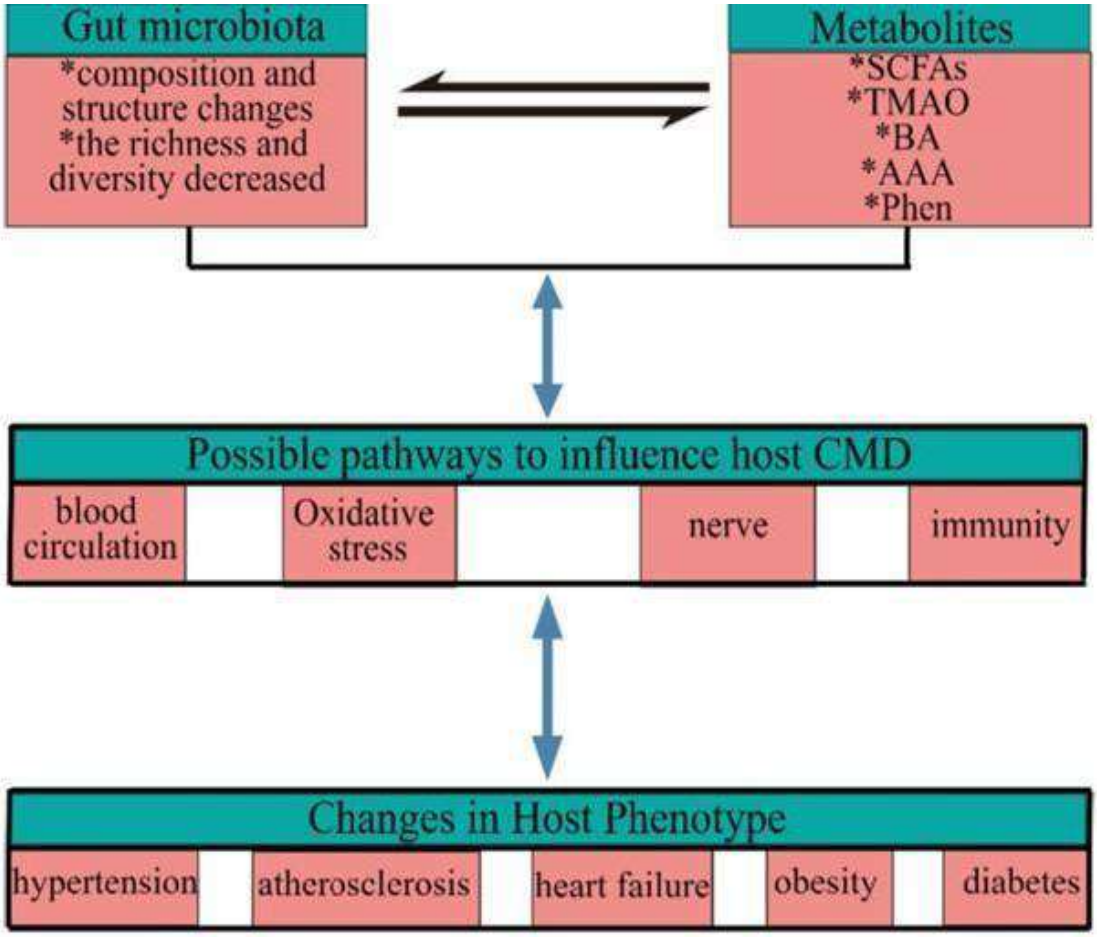

Fig 3.4.2: Gut microbiota and CVD

- HYPERTENSION

Hypertension is a risk factor on cardiovascular disease [54]. The research in the experimental animal model showed that the regulation of gut flora was helpful to prevent hypertension. Most studies have found that the gut microbiota of patients with hypertension was identified a reduced alpha diversity. A large population cohort study analyzed the relationship between gut microbiota and blood pressure (BP) in 6953 Finns aged 25 to 74. There was a negative correlation between 19 different lactobacilli and BP index.[55]

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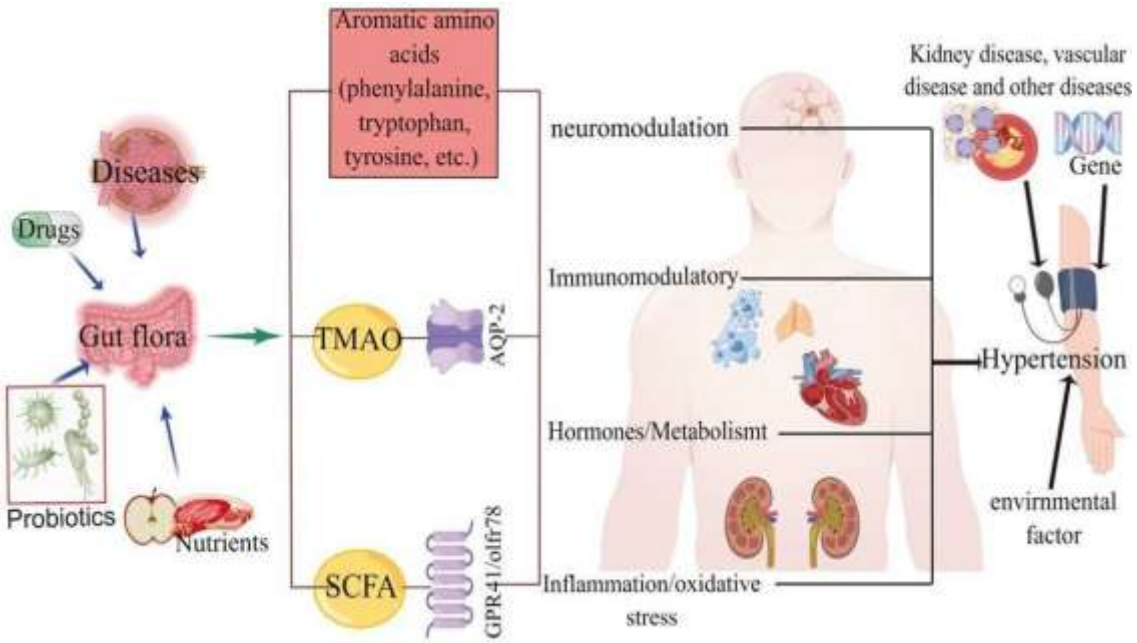

Fig 3.4.3: Gut microbiota in hypertension

- ATHEROSCLEROSIS

Patients with atherosclerosis have the accumulation of low density lipoprotein plaque buildup and vascular cell dysfunction in their blood vessels. Chronic inflammation is a potential driving factor for atherosclerosis. The three factors affecting atherosclerosis by gut flora, including harmful inflammatory reaction, metabolism of cholesterol and lipids by gut flora, and dietary and specific components of gut flora metabolism. An accumulating amount of research demonstrated that atherosclerosis is associated with specific bacterial groups, but its specific causal mechanism and downstream molecular pathways need to be further explored. Probiotics and prebiotics can regulate gut flora to improve cardiovascular metabolic diseases. [57]

- HEART FAILURE

Heart failure (HF) is a disease in which the heart's ability to pump blood decreases. HF could lead to splanchnic circulation congestion and impaired intestinal barrier function, thus increasing the bacterial products in the blood circulation of the system and heightening the inflammatory state. The diversity of gut microbiota was significantly decreased in HF patients, and the key intestinal bacteria were reduced. Another study also showed that the gut flora richness of chronic HF was low, and butyrate-producing bacteria were significantly reduced.[58]

- OBESITY AND TYPE-2 DIABETICS MELLITUS

An increasing body of evidence suggests that gut flora is associated with the development of obesity and associated metabolic diseases. Gut flora is closely associated to host food digestion, nutrient absorption, energy metabolism, and central appetite, which are all associated with obesity. Bifidobacterium longum and Para bacteroides goldsteinii have been reported to reduce body weight and regulate gut flora in HFD-fed mice, and also reducing fat accumulation, reducing insulin resistance, and increasing glucose tolerance. In addition, obesity may also be associated with the Firmitutes /Bacteroidetes ratio, Akkermania, Bifi dobasteria, and Enteractor. [59]

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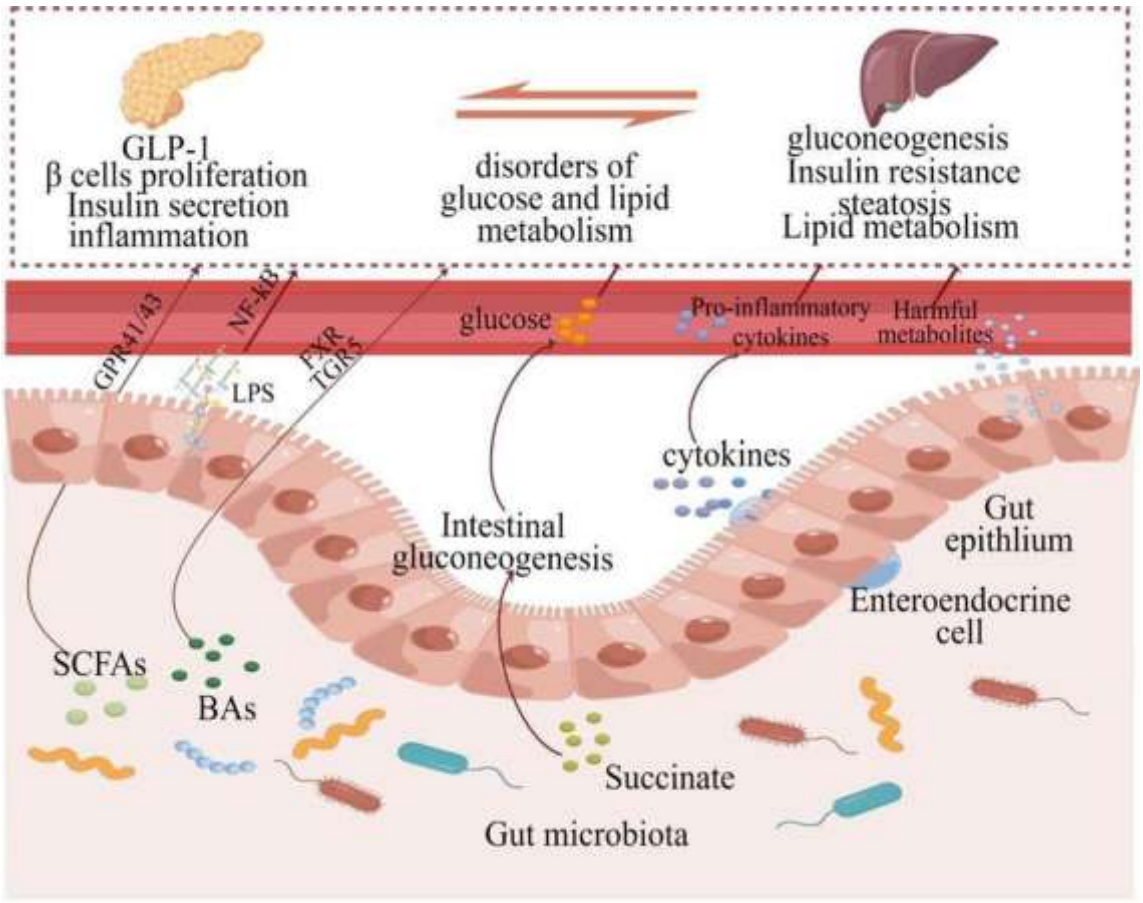

Fig 3.4.4: Gut microbiota in obesity and DM

3.5 IN GENERATION OF SCFAs METABOLITES

Colonic bacteria express carbohydrate-active enzymes, which endow them with the ability to ferment complex carbohydrates generating metabolites such as SCFAs.[60] Three predominant SCFAs, propionate, butyrate and acetate, are typically found in a proportion of 1:1:3 in the GI tract. These SCFAs are rapidly absorbed by epithelial cells in the GI tract where they are involved in the regulation of cellular processes such as gene expression, chemotaxis, differentiation, proliferation and apoptosis. Acetate is produced by most gut anaerobes, whereas propionate and butyrate are produced by different subsets of gut bacteria following dis tinct molecular pathways. Butyrate is produced from carbohydrates via glycolysis and aceto-acetyl-CoA, whereas two pathways, the succinate or propanediol pathway, are known for the formation of propionate, depending on the nature of the sugar. In the human gut, propionate is mainly produced by Bacteroidetes, whereas the production of butyrate is dominated by Firmicutes.[61]

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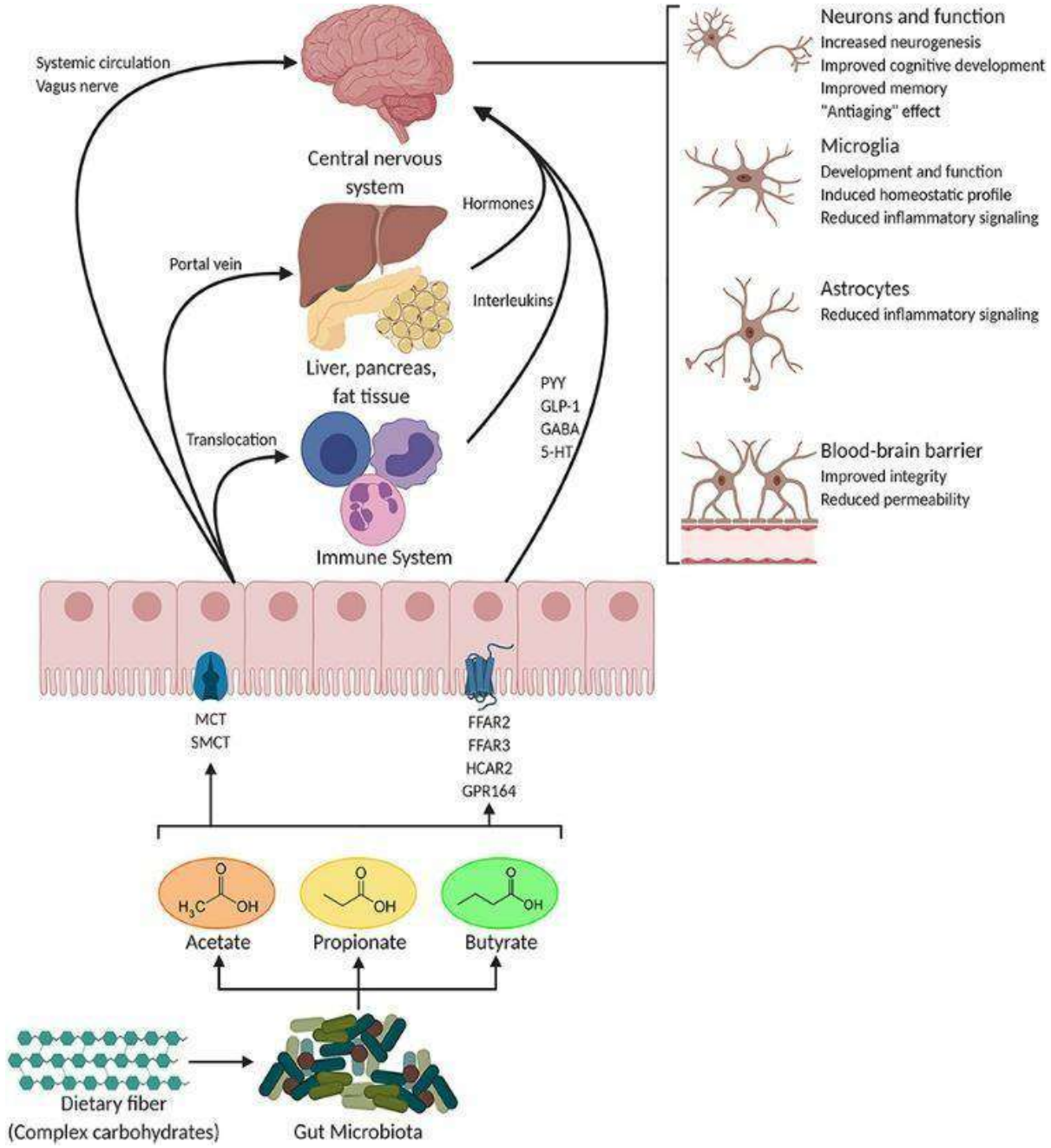

Fig 3.5.1: Gut microbiota in generation of SCFAs metabolites

3.6 IN DENOVO SYNTHESIS

The GI microbiota is also crucial to the de novo synthesis of essential vitamins which the host is incapable of producing. Lactic acid bacteria are key organisms in the production of vitamin B12, which cannot be synthesised by either animals, plants or fungi.[62] Bifidobacteria are main producers of folate, a vitamin involved in vital host metabolic processes including DNA synthesis and repair. Further vitamins, which gut microbiota have been shown to synthesise in humans, include vitamin K, riboflavin, biotin, nicotinic acid, panthotenic acid, pyridoxine and thiamine. Colonic bacteria can also metabolise bile acids that are not reabsorbed for biotransformation to secondary bile acids. All of these factors will influence host health. For example, an alteration of the co-metabolism of bile acids, branched fatty acids, choline, vitamins (i.e. niacin), purines and phenolic compounds has been associated with the

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development of metabolic diseases such as obesity and type 2 diabetes.[63]

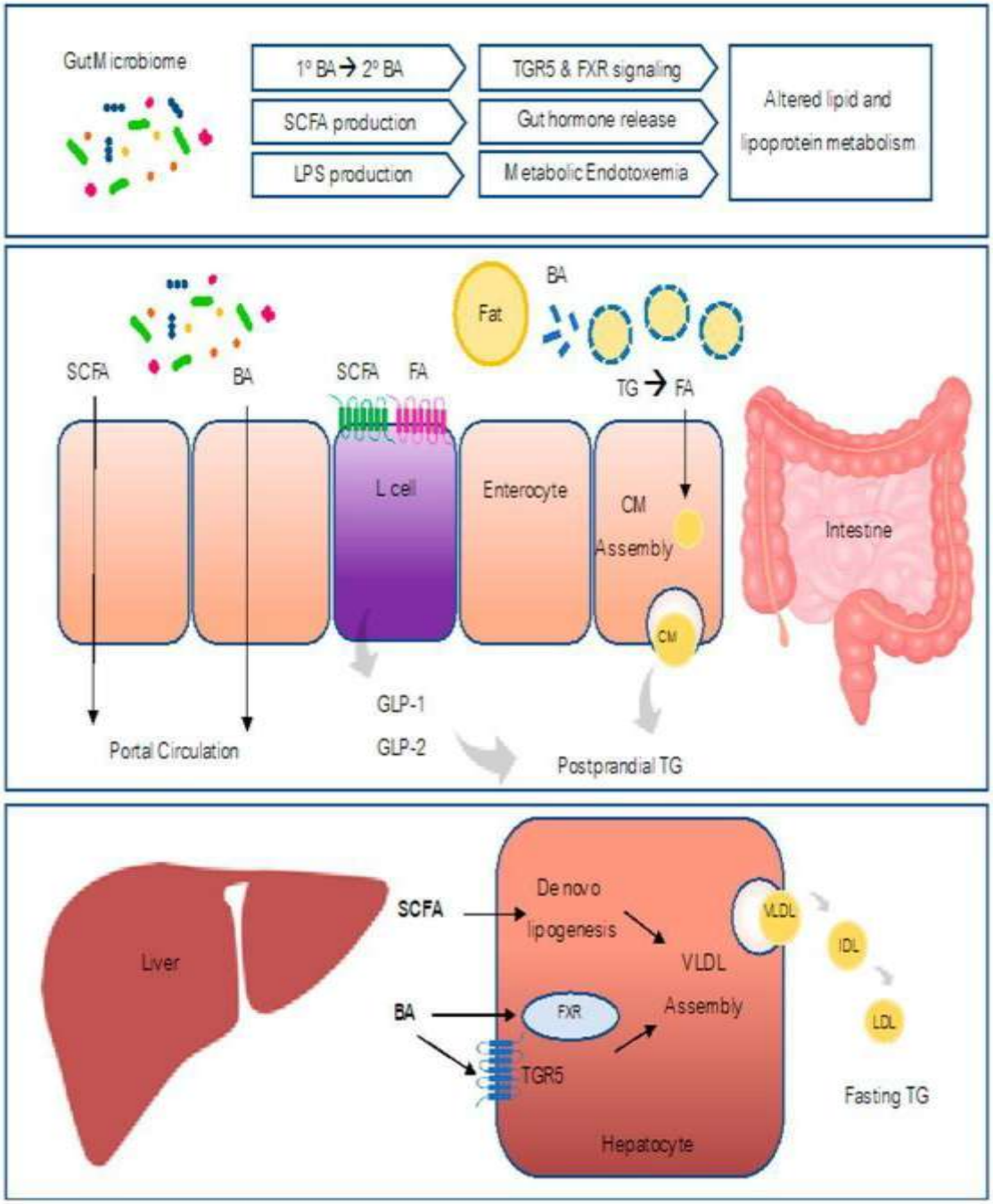

Fig 3.6.1: Denovo synthesis

IV. CURRENT THERAPIES USING GUT MICROBIOTA

4.1 PROBIOTICS

Numerous organisms meet the criteria established by the World Health Organization to define probiotics: "A live organism which provides a benefit to the host when provided in adequate quantities." The gram negative Escherichia coli strain Nissle 1917, various lactic acid producing Lactobacillus strains, and a number of bifidobacteria represent the primary microorganisms classified as probiotic agents.

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Probably the most effective strategy to select probiotic species is based on production of beneficial clinical outcomes in humans. The beneficial effects of probiotics may be related to their capacity to produce vitamins, antioxidants, and defence against pathogenic competitors.[64] Probiotics are also characterized by their production of SCFAs and absence of toxins. Probiotic bacteria may also inhibit the growth of pathogens through various mechanisms. Many beneficial probiotics such as bifidobacteria and lactobacilli are Gram-positive bacteria, which are devoid of LPS. Such bacteria may reduce the risk of infection by competing with pathogens for dietary nutrients or receptors on the gut wall. Other bacterial genera that include bacteriodes, enterococci, eubacteria, and streptococci are potentially beneficial or harmful to the host, depending on the particular bacterial species under study. Moreover, the butyrate producer Roseburia and the mucin-degrading bacterium Akkermansia muciniphila have also been reported as potential probiotics. The use of Bifidobacterium longum and Bifidobacterium breve for prevention and treatment of acute diarrhea in newborns and infants has gained interest.[65]

4.2 PREBIOTICS

Nutrients that restore a healthy gut microbiota by modulating its composition are being developed as new therapeutic approaches to treat inflammatory diseases. Since the gut microbiota plays a major role in maintaining physiological reactions in the host, new dietary treatments based on the use of dietary supplements (organic selenium and Lithothamnium muelleri algae) and probiotics (Saccharomyces boulardii UFMG 905 and Bifidobacterium) have been developed to modulate the gut immune response and restore intestinal homeostasis.[64] In addition, changes in the diet of the host could be used to modulate the gut microbiota and restore homeostasis. Accordingly, the faecal microbiota of children from Europe or rural Africa showed major differences that might be attributed at least in part to different dietary habits. Currently, protein and animal fat consumption appears to be more closely linked with disease than the intake of carbohydrates. Prebiotics stimulate the growth or activities of specific microbial genera and species in the gut microbiota in order to confer health benefits to the host. In general, prebiotics favour the growth of bifidobacteria and lactobacilli over potentially harmful proteolytic and putrefactive bacteria. Prebiotics have been classified mainly into two groups, the inulin-type fructans (ITF) and the galacto-oligosaccharides (GOS), based on their chemical structures. [66]

4.3 POSTBIOTICS

Post-biotics include cell wall components, such as protein molecules and lipopolysaccharides, extracellular polysaccharides, and microbial metabolites of carbohydrate fermentation or protein degradation, such as SCFA and branched chain fatty acids. Several studies have found that post-biotics can exert positive biological functions to the host.[67] Post- biotics could modulate host immunity by improving gastrointestinal barrier function and inhibiting pathogen translocation. In one study, CFS from L. plantarum fermentation could regulate barrier integrity and function in lambs through increasing levels of tight junction protein, occludin, claudin-1, and CLDN-4. Post-biotics may affect the innate and adaptive immune system through the interaction of many cell types along the mucosa, such as B cells, T cells, monocytes, macrophages, NK cells, and dendritic cells (DCs). Cell wall components, including peptidoglycan, have been shown could bind to receptors on the surface of monocytes and macrophages, consequently stimulating immune cells to produce cytokines indirectly. Tryptophan metabolites can inhibit inflammation by acting on T cell aromatics receptors and stimulating DCs to induce Treg activation through retinoic acid.[68]

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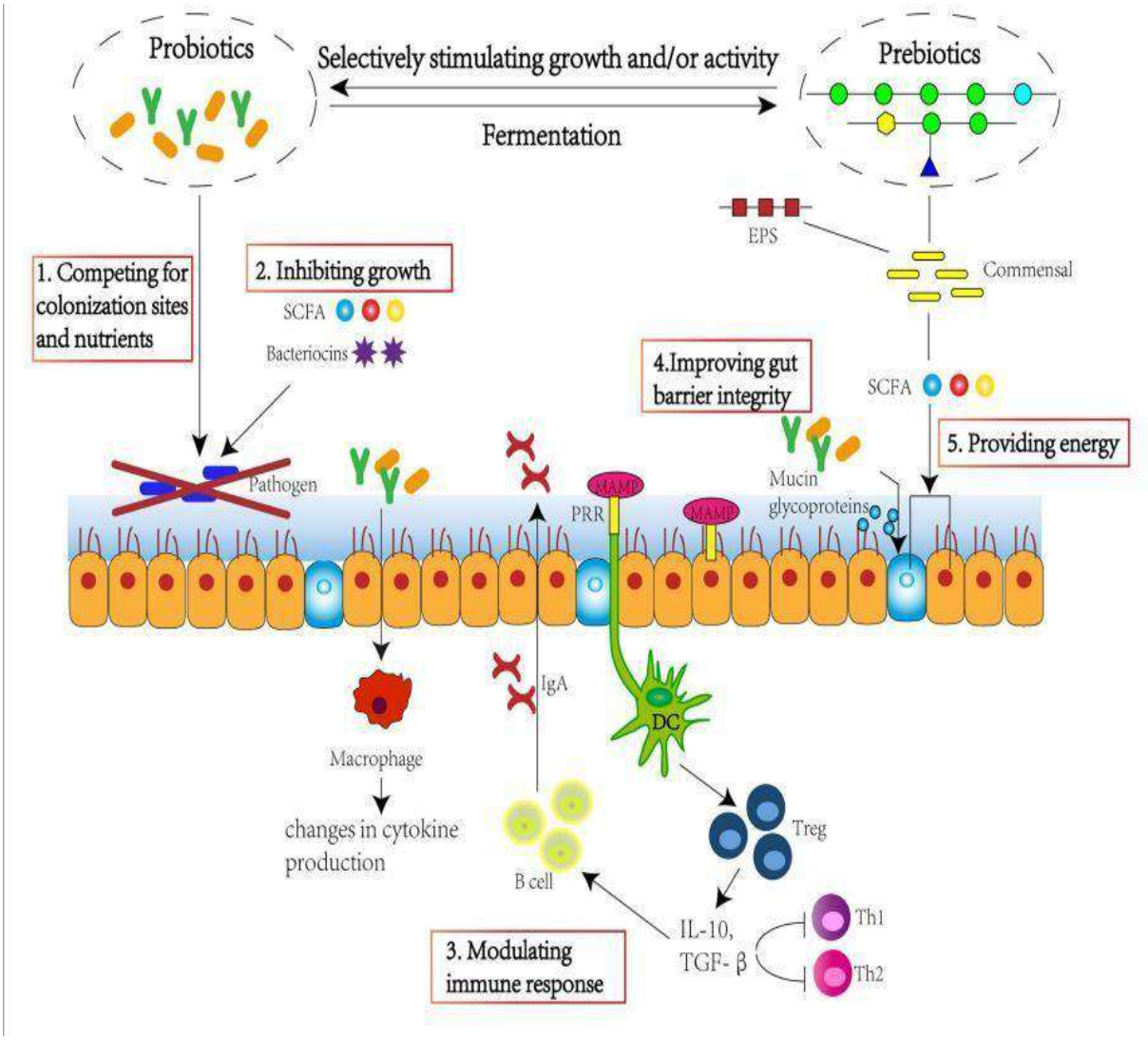

Fig 4.3.1: Prebiotics, probiotics and postbiotics

4.4 FAECAL TRANSPLANTATION

Faecal transplantation represents a potential therapy that is effective against many diseases, including anorexia nervosa, autoimmunity, infections, inflammatory bowel disease, obesity, and multiple sclerosis [69]

In a recent randomized clinical trial, researchers found that recurrent diarrhea caused by Clostridium difficile could be treated by duodenal transfer of faeces from healthy individuals. Notably, the researchers showed that faeces transfer restored normal bacterial diversity in the recipients. Cultured strain mix has been proposed as a potential alternative for treatment of C. difficile infections. Faecal microbiota transplantation from lean donors to patients with metabolic syndrome has also been reported to induce changes in intestinal microbiota composition and improve insulin resistance. [70]

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4.5 RESPIRATORY HEALTH

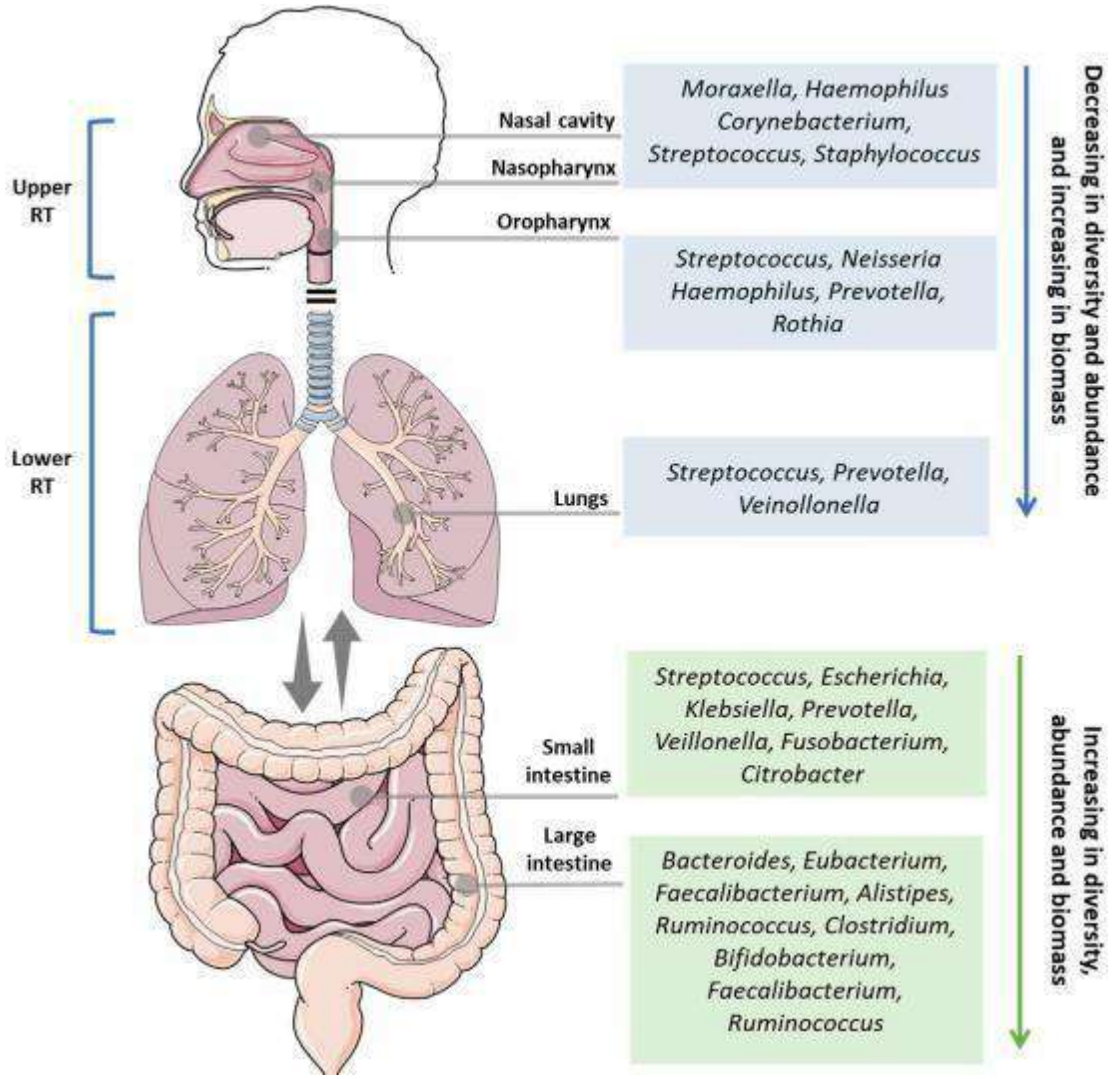

Fig 4.5.1: Gut microbiota and respiratory health

The immune responses in the gut-lung axis depend on the balance of microbiota composition, particularly in the gut. The regulated interaction between the metabolites and antigens of symbiotic microbiota with the host is crucial for the activation of pattern recognition receptors (PRRs) and metabolic sensor receptors such as G-protein-coupled receptors (GPCRs), and the production of inflammatory mediators, which are necessary for the migration, activation, and proliferation of innate and adaptive immune cells responsible for the production of pro-and anti-inflammatory cytokines, immunoglobulins, and antimicrobial peptides. These cells and molecules can move bidirectionally between the lungs and the gut through the bloodstream and lymphatic system and regulate immune and inflammatory responses [71].

The URT comprises the nostrils, nasal passages, paranasal sinuses, nasopharynx, and oropharynx, while the lower respiratory tract comprises the trachea, bronchi, bronchioles, and alveoli. These organs make up one of the largest surface areas in the human body, that from the nostrils to the lungs, is colonized by a symbiotic and diverse community of microorganisms (Fig 4.5.1)

4.6 PRECISION DIAGNOSIS AND PERSONALIZED TREATMENT

Various evidence suggests that dysregulation of microbiota-host interaction is correlated with different diseases such as IBD, diabetes, cirrhosis and colorectal cancer . Recently, studies have been conducted concerning the

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reactions between bacteria and cancer treatment drugs and the findings suggest that interactions of the bacteria mediated with the immune system, are necessary for drug efficacy, although little information is available on the effects of human microbiome combinations, and treatment outcomes in cancer patients [72]. Many studies have shown that the patients in accordance with gut microbiome combinations have the potential to respond to or not respond to immunotherapy, and this can be considered in the evaluation of drug interactions. Moreover, the emergence of the role of gut microbiome as a biomarker for disease phenotype, prognosis and response to treatment, is well described in relation to the alteration of microbial population structure in various diseases [73].

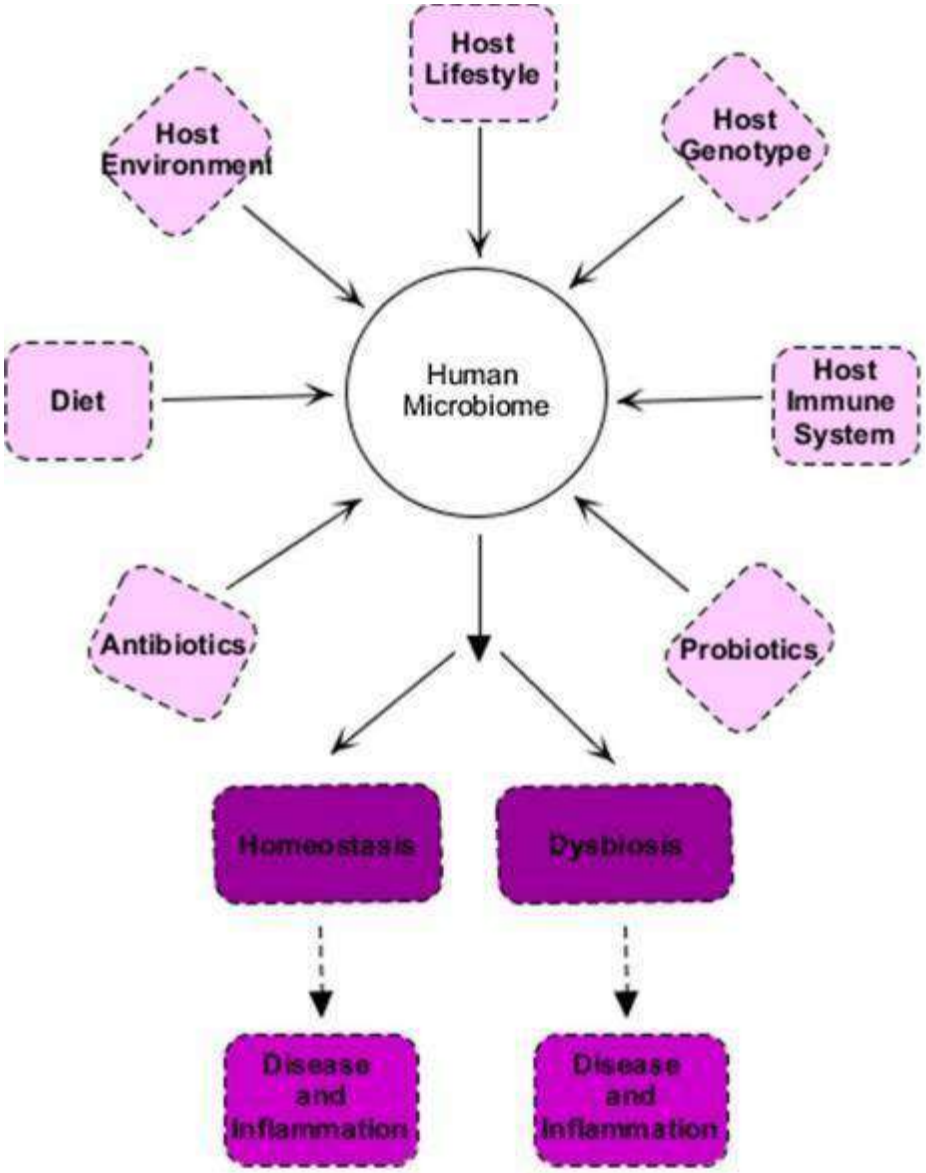

Fig 4.6.1: Gut microbiota and diagnosis

4.7 PHAGE THERAPY

Among the perspectives on therapeutic modulation, the use of phage to manipulate bacterial population of the microbiota is highly interesting [74]. Phage therapy is applied either for rebalancing the microbiota in chronic diseases or for compassionate therapies in acute cases. In both cases the advantage of phage therapies with cocktails to reduce the risk of resistance is well

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recognized. Two strategies are used to enrich phage cocktails:

i. training the phage with a selection of local bacteria
ii. tailoring the phage cocktail selecting the ones "trained" to infect the resistant bacteria as shown in intensive care patients.

The use of lytic phage has been proven efficient to reduce the number of pathogenic bacteria. Although such strategy implies that pathogenic bacteria are identified as major contributors of chronic diseases like Helicobacter pylori in the stomach or Clostridium difficile in secondary infection. To overcome this problem, a cocktail of six different phage has been set up by a Russian laboratory. These phage cocktails were analyzed and tested for adverse effects and toxicity but no negative effects have been reported [75].

4.8 CANCER THERAPY

Multiple studies demonstrate that the therapeutic efficacy was diminished in the absence of the gut microbiota, suggesting that, through different mechanisms, commensal microbes modulate the anticancer immune responses induced by the therapies. Cyclophosphamide (CTX), an approved chemotherapeutic drug, has been shown to alter the composition of intestinal microbiota in mice and promote the translocation of specific Gram- positive bacteria into secondary lymphoid organs, stimulating the production of 'pathogenic' Th17 cells, which share hallmarks of T helper 1 (Th1) cells and Th17 cells. Removal of the gut microbiota in germ-free mice or mice that have been treated with antibiotics leads to drug resistance to CTX.[76] On the other hand, genetic models consisting of Escherichia coli and Caenorhabditis elegans were used to elucidate the complex interactions among the host, bacteria and fluoropyrimidines, antimetabolite drugs commonly used to treat cancer.[77] Mechanism used by gut microbiota to modulate anticancer drug efficacy (fig 15)

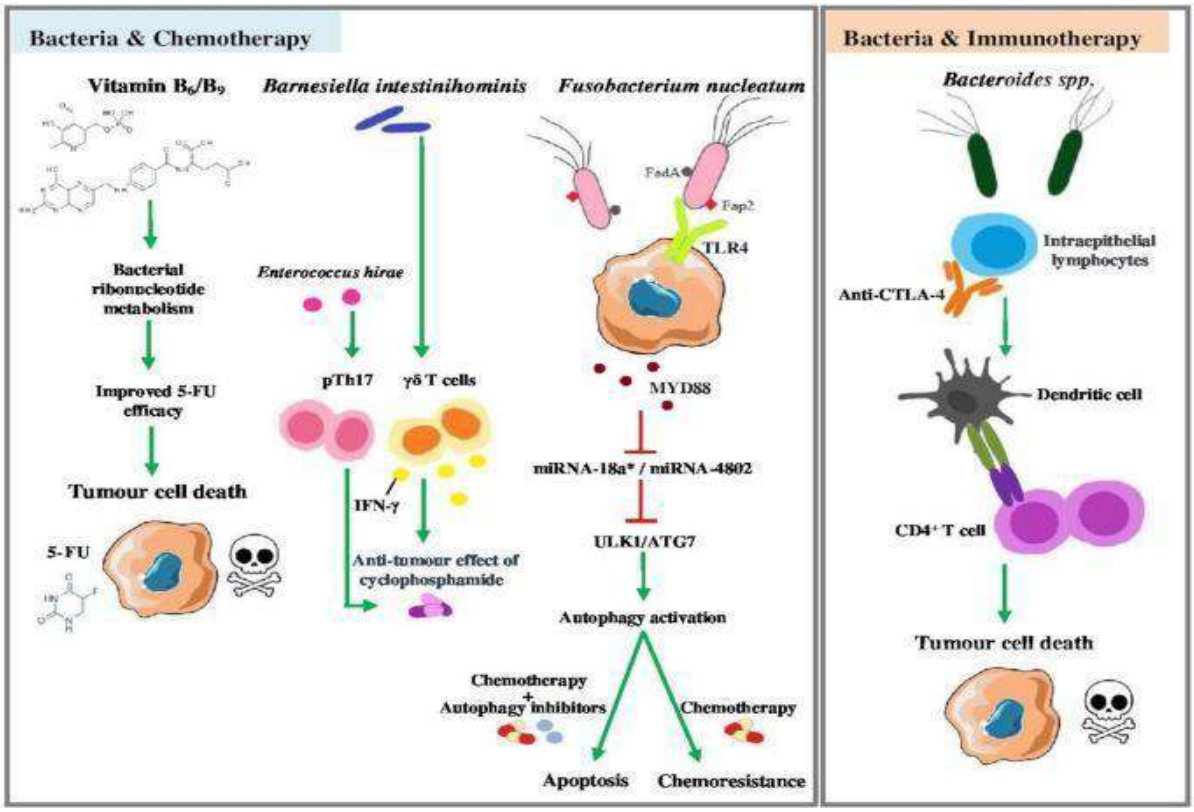

Fig 4.8.1: Gut microbiota in cancer therapy

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V. SUMMARY AND CONCLUSION

The human gut microbiota consists of a diverse community of microorganisms that play a crucial role in various physiological processes, including digestion, immune function, and metabolic regulation. This complex ecosystem begins developing at birth and is influenced by factors such as mode of delivery, diet, environment, and antibiotic exposure.

Development of Gut Microbiota:

- Early Colonization: The colonization process starts at birth, where infants acquire microbes from their mothers and environment. The mode of delivery (vaginal birth vs. cesarean section) significantly affects the initial microbial composition.
- Infancy to Adulthood: Breastfeeding contributes beneficial bacteria, such as Bifidobacterium, that support healthy gut development. As diet diversifies, the microbiota becomes more complex, stabilizing into a unique composition in adulthood.
- Factors Influencing Development: Diet, lifestyle, antibiotics, and other environmental factors can shape the microbiota's composition and diversity throughout life.

Therapeutic Potential:

- Probiotics
- Prebiotics
- Postbiotics
- Faecal Microbiota Transplantation (FMT)
- Phage Therapy

The study of gut microbiota continues to reveal its critical role in human health, highlighting its potential for novel therapeutic strategies and personalized medicine. Understanding the development and functions of this microbial community is essential for advancing treatments for various diseases and promoting overall health.

Conclusion

The human gut microbiota, a complex and dynamic community of microorganisms, plays an integral role in maintaining health and influencing disease processes. Its development begins at birth and is shaped by numerous factors, including genetics, diet, environment, and lifestyle choices. The diverse functions of gut microbiota, ranging from metabolic and digestive processes to immune modulation, underscore its critical role in overall well-being.

As research advances, the therapeutic potential of manipulating the gut microbiota through probiotics, prebiotics, postbiotics, and innovative approaches like fecal microbiota transplantation (FMT) and phage therapy becomes increasingly evident. These interventions offer promising avenues for treating a wide range of conditions, from infectious diseases to metabolic and autoimmune disorders.

In conclusion, understanding the intricate interactions within the gut microbiota and their impact on human health is crucial for developing targeted therapies and preventive strategies. As we continue to unravel the complexities of this microbial ecosystem, we open new frontiers in personalized medicine and public health, paving the way for innovative treatments and enhanced quality of life. The future of gut microbiota research holds great promise for transforming our approach to health and disease management.

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