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THEME

Bibliographic summary on intestinal flora and their relationship with human health

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اليك يامن دفعتني الى المواصلة في طريق العلم والمعرفة رغم توعدي كل يوم بالتوقف وانهاء مشواري الدراسي

الى امي العزيزة انا بدونك لا شيء

اليك اهدي هذا العمل المتواضع

الي والدي الكريم اهدي هذا العمل ثمرة تضحياتك و تحملك مشاقنا اليومية وتقصيرنا سعيا منك لوصولنا الى الافضل.

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TAKIA

Abstract

Abstract

The intestinal flora is defined as all the microorganisms that live in the digestive tract. This complex ecosystem consists mainly of bacteria, with the presence of viruses, yeasts and protozoa, and occupies an important and recognized place in human health. Its composition is generally stable over time for the same individual. Some intestinal flora can metabolize drugs, toxins, and other xenobiotics, which may affect their effectiveness or toxicity. The intestinal flora plays an essential role in all aspects of the body. It is the largest immune organ in the human body and is essential for the development of the innate and adaptive immune system of the intestinal mucosa, as well as its response to pathogens. However, there are certain factors that can cause changes in the intestinal flora and lead to an imbalance, which can be observed in many diseases (intestinal, allergic, neurological...) that affect a large number of the world's population.

Résume

La flore intestinale est définie comme l'ensemble des micro-organismes qui vivent dans le tube digestif. Cet écosystème complexe est constitué principalement de bactéries, avec la présence de virus, de levures et de protozoaires, et occupe une place importante et reconnue dans la santé humaine. Sa composition est généralement stable dans le temps pour un même individu. Certaines flores intestinales peuvent métaboliser des médicaments, des toxines et d'autres xénobiotiques, ce qui peut affecter leur efficacité ou leur toxicité. La flore intestinale joue un rôle essentiel dans tous les aspects de l'organisme. C'est le plus grand organe immunitaire du corps humain et il est essentiel au développement du système immunitaire inné et adaptatif de la muqueuse intestinale, ainsi qu'à sa réponse aux agents pathogènes. Cependant, certains facteurs peuvent provoquer des modifications de la flore intestinale et conduire à un déséquilibre, que l'on peut observer dans de nombreuses maladies (intestinales, allergiques, neurologiques...) qui touchent une grande partie de la population mondiale.

Abstract

الملخص

تُعرف النباتات المعوية بأنها جميع الكائنات الحية الدقيقة التي تعيش في الجهاز الهضمي .يتكون هذا النظام البيئي المعقد بشكل رئيسي من البكتيريا، مع وجود الفيروسات والخمائر والأوالي، ويحتل مكانة مهمة ومعترف بها في صحة الإنسان .ويكون تكوينه مستقرًا بشكل عام مع مرور الوقت بالنسبة لنفس الفرد .يمكن لبعض النباتات المعوية استقلاب الأدوية والسموم وغيرها من المواد الغريبة الحيوية، مما قد يؤثر على فعاليتها أو سميتها .تلعب النباتات المعوية دورًا أساسيًا في جميع جوانب الجسم .وهو أكبر عضو مناعي في جسم الإنسان وهو ضروري لتطوير الجهاز المناعي الفطري والتكيفي للغشاء المخاطي المعوي، وكذلك استجابته لمسببات الأمراض .ومع ذلك، هناك عوامل معينة يمكن أن تسبب تغيرات في الفلورا المعوية وتؤدي إلى خلل في التوازن، وهو ما يمكن ملاحظته في العديد من الأمراض (المعدية، التحسسية، العصبية...) التي تصيب عدداً كبيراً من سكان العالم.

AA metabolism	Amino acid metabolism
ACVD	Atherosclerotic cardiovascular disease
ADN	Acidedésoxyribonucléique
Ag	Antigène
AhR	Aryl hydrocarbon receptor
AMPs	Anti microbial peptides
ARNr	Acideribonucléiqueribosomique
ASD	Autism Spectrum Disorder
B fragilis	Bacteroides fragilis
BBB	Blood brain barrier
CD	Crohn's disease
CD103	Dendritic cells
CNS	Central Nervous System
CRC	Colorectal Cancer
EC	Epithelial cells
ENS	Enteric nervous system
FA oxidation	Fatty acid oxidation
FA synthesis	Fatty acid synthesis
FAO	Food and Agriculture Organization,
FISH	Fluorescence in situ hybridization
FoxP3	Forkhead box P3
FXR	farnesyl X receptor
GABA	Gamma aminobutyric acid.
GIT	Gastrointestinal tract
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GPCRs	G protein-coupled receptors
GSH	Glutathione
HPA	Hypothalamus–pituitary–adrenal
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IBS-C	Irritable bowel syndrome and constipation
IBS-D	Irritable bowel syndrome and diarrhea

IFN	Interferon
IgA	Immunoglobulines A
IL-22	Interleukine 22
ILC	Innate lymphoid cells
IR	Insulin resistance
LPS	Lipopolysaccharide
ET	Effectors T cells
LT	lymphocytes T
LT reg	lymphocytes T régulateur
LTh	Lymphocyte T helper
MAMPs	Microbial-associated molecular patterns
MDD	Major depressive disorder
Naïve TL	Naive T cell
NLRs	NOD-like receptors.
PAMP	Pathogen-Associated Molecular Pattern
PPP	Pentose phosphate pathway
PRR	Pattern Recognition Receptor
qPCR	Quantitative real-time polymerase chain reaction
RA	rheumatoid arthritis
RORyt	Related orphan receptor gamma
rRNA 16S	Acide ribonucléique ribosomique de la sous-unité 16
SCFA	Short chain fatty acid
T2DM	type 2 diabetes
TCA	Tricarboxylic acid cycle
TeNT	Tetanus neurotoxin
Tfh	T follicular helper
TGF	Transforming growth factor
Th17	T helper
TLR	Toll like receptors
TLR4	Toll-like receptor 4
TMA	Trimethylamine-N
TMAO	trimethylamine-N-oxide
TNF	Tumor necrosis factor

Treg	Regulatory T cells
UC	ulcerative colitis

Introduction

The human intestinal flora is a set of microorganisms living inside the digestive tract. It is complex and is part of a dynamic intestinal ecosystem in permanent interaction with different functions of the body. Intestinal flora are key regulators of digestion along the gastrointestinal tract **(Rinninella *et al.*, 2019**). Intestinal microorganism is an important bridge between diet and human health and plays a vital role in maintaining the homeostasis of the human body **(Song *et al.*, 2021)**.To maintain a balance with its host. Its place is essential in intestinal physiology and in human health for which it is increasingly evoked and studied. A balanced and diversified intestinal flora is, in this sense, indicative of a good state of health. intestinal flora is a living world of one hundred thousand billion bacteria, i.e. 10 times more microorganisms than the whole body has cells **(Goulet., 2019)**.

Its qualitative and quantitative composition changes over time. It is dependent on environmental factors, eating habits, lifestyles or taking antibiotic treatments. It is therefore fragile and an imbalance in its composition is responsible for disturbances intervening in the triggering and/or maintenance of pathologies (**Marie., 2020)**. Intestinal flora possesses enzymes that humans lack, allowing them to break down complex carbohydrates. Certain intestinal flora can metabolize drugs, toxins, and other xenobiotics, potentially affecting their efficacy or toxicity.

The intestinal flora of human beings plays a major role in the proper functioning of the body **(Yun Xin *et al.*, 2022)**.

The intestinal flora plays an essential role in all aspects of the body, and the intestinal flora is the largest immune organ in the human body **(Yun Xin *et al.*, 2022)**. Metabolic, immune, cognitive and psychiatric diseases could be the consequence of an alteration of this flora and its functions (**Marie., 2020)**. Intestinal flora has a crucial immune function against pathogenic bacteria colonization inhibiting their growth, intestinal flora also prevents bacteria invasion by maintaining the intestinal epithelium integrity **(Rinninella *et al.*, 2019**).The microbiome plays a key role in the development of the host's innate and adaptive system, while the immune system orchestrates the maintenance of host-microbe symbiosis **(Wang *et al.*, 2022)**. In short, the intestinal flora affects the development of disease by affecting the intestinal immunity. Further, by reshaping the intestinal microenvironment, the microflora improves the function of the regional immune system, resulting in disease relief and treatment **(Bolun *et al.*, 2020)**.

The intestinal flora plays a significant role in both health and disease **(Hayes et Sahu, 2020)**. Increasing evidence suggests that intestinal flora dysbiosis would lead to a number of diseases, including gastrointestinal disorders, obesity, cardiovascular diseases and CNS-

related diseases, which affect a large population in the world. Besides, mood and behavior are also susceptible to alterations in the intestinal flora. Experimental and clinical trials for treatment of these diseases based on modulating intestinal flora composition have shown promises as a therapeutic strategy of intestinal flora on human diseases (**Hao *et al.*, 2018)**.

This work focuses on this particular and complex community that is the intestinal flora, as many researchers made reviews about intestinal flora , such as **Pengqing *et al.*, (2019)** on flora intestinal interventions in human health and diseases, **Zongxin *et al.*, (2022)** on intestinal flora The Cornerstone of Life and Health, **Mehra *et al.*, (2022)** on intestinal flora and Autism Spectrum Disorder, **khalid *et al* (2022)** worked on flora intestinal Disruption in COVID-19 or Post-COVID Illness .

In light of current knowledge, we have made a bibliographical synthesis to take stock of the relationship between intestinal flora and human health. This study is divided into four chapters :

1. General information on intestinal flora.
2. Mechanisms of action of the intestinal flora.
3. Relation between flora intestinal and immune system.
4. Relationship of intestinal flora with human health.

Chapter I

This chapter aims to consider general information on the intestinal flora, which will mainly target their composition and the importance of flora balance in the human intestine. This part is considered as an overview to the other chapters.

I.1 History on the intestinal flora

We can summarize the most important actions that describe the findings of the intestinal flora in the points below:

- Louis Pasteur (1981), the brilliant French bacteriologist, discovered anaerobic intestinal bacteria(**Sebastián et Sánchez, 2018)**.
- In the mid of 1880,microorganisms are part of the human system, when Theodor Escherich, an Austrian pediatrician, observed *Escherichia coli* in the intestinal flora of healthy children and children with diarrheal disease**.**
- Throughout the 20th century, microorganisms continued to be isolated from nasal passages, oral cavities, skin, the gastrointestinal tract, and the urogenital tract and characterized as part of the human microbiota **(Hayes et Sahu, 2020)**.
- The word ‘microbiome’ was coined in 2001 when Lederberg and Mc Cray published their monumental paper. They defined the human "microbiome" as "the ecological community of commensal, symbiotic, and pthogenic microorganisms that literally share our body space".
- Around the same time, Relman and Falkow published their "second human genome project" that "would entail a comprehensive inventory of microbial genes and genomes at the four major sites of microbial colonization in the human body: mouth, intestinal, vagina, and skin".
- A year later Relman advocated that would be argued that a ‘‘study of host genome-wide expression analysis,’’ would lead to important “‘insights into the role of the endogenous flora in health and disease**(Hayes et Sahu, 2020)**.
- In recent years, biomedical research has led to advances in our knowledge of the intestenal flora (referred to as intestinal flora until 2014). However, there is still a great deal to learn, much more than what we have already learnt during the last three centuries(**Sebastián et Sánchez, 2018)**.

I.2 Generality of intestinal flora

Semantically, the term microbiota evokes more living microorganisms (bios) than a plant world suggested by the word "flora". The Microbiota is the set of genes of the intestinal flora ecosystem **(Goulet, 2019)**. The intestinal flora, also called intestinal flora, is defined as a

complex set of microorganisms, living inside the human digestive tract and more precisely at the level of the intestine.

The flora is implanted throughout the digestive tract according to an oro-anal gradient but it predominates in the colon, in particular the right colon **(Michaudel et Sokol, 2020)**.

This the human intestinal flora is composed of trillions of microorganisms considered non-pathogenic **(Simon *et al.*,2015)**. Covers the surface of the intestinal mucosa. It is made up of fungi, viruses, yeasts, archaea and especially bacteria with a density of up to 10^{14} bacterial cells, 100 times more than the cells of the human body organism **(Anne, 2020)**.

Intestinal flora plays an important role in the function and integrity of the gastrointestinal tract, maintenance of immune homeostasis and host energy metabolism. flora refers to the entire population of microorganisms that colonizes a particular location **(Jandhyala *et al.*, 2015)**. We live in symbiosis with our intestinal flora.

The intestinal flora is a major biotope, essential for the maturation of digestive functions. It exerts numerous effects, in particular on angiogenesis, intestinal trophicity (thickness of the mucous membrane, size of the villi), the production of mucus, or on the enteric neuromuscular system. It therefore participates in the development and maturation of non-specific defence systems of the intestinal axis **(Goulet, 2019)**.

I.3 Composition of intestinal flora

The dominant intestinal microbiota phyla are *Firmicutes*, *Bacteroidetes, Actinobacteria*, *Proteobacteria*, *Fusobacteria* and *Verrucomicrobia*, with the two phyla *Firmicutes* and *Bacteroidetes* representing 90% of intestinal flora. Taxonomically, bacteria are classified according to phyla, classes, orders, families, genera, and species (**Rinninella *et al.*, 2019)**. Some examples of taxonomic intestinal flora composition are illustrated in (figure 01)

- The *Firmicutes* phylum is composed of more than 200 different *genera* such as *Lactobacillus*, *Bacillus*, *Clostridium*, *Enterococcus* and *Ruminicoccus*. *Clostridium* genera represent 95% of the *Firmicutes* phyla.
- The *Bacteroidetes* consists of predominant genera such as *Bacteroides* and *Prevotella.*
- The *Actinobacteria* phylum is proportionally less abundant and mainly represented by the *Bifidobacterium* genus (**Rinninella *et al.*, 2019)**.

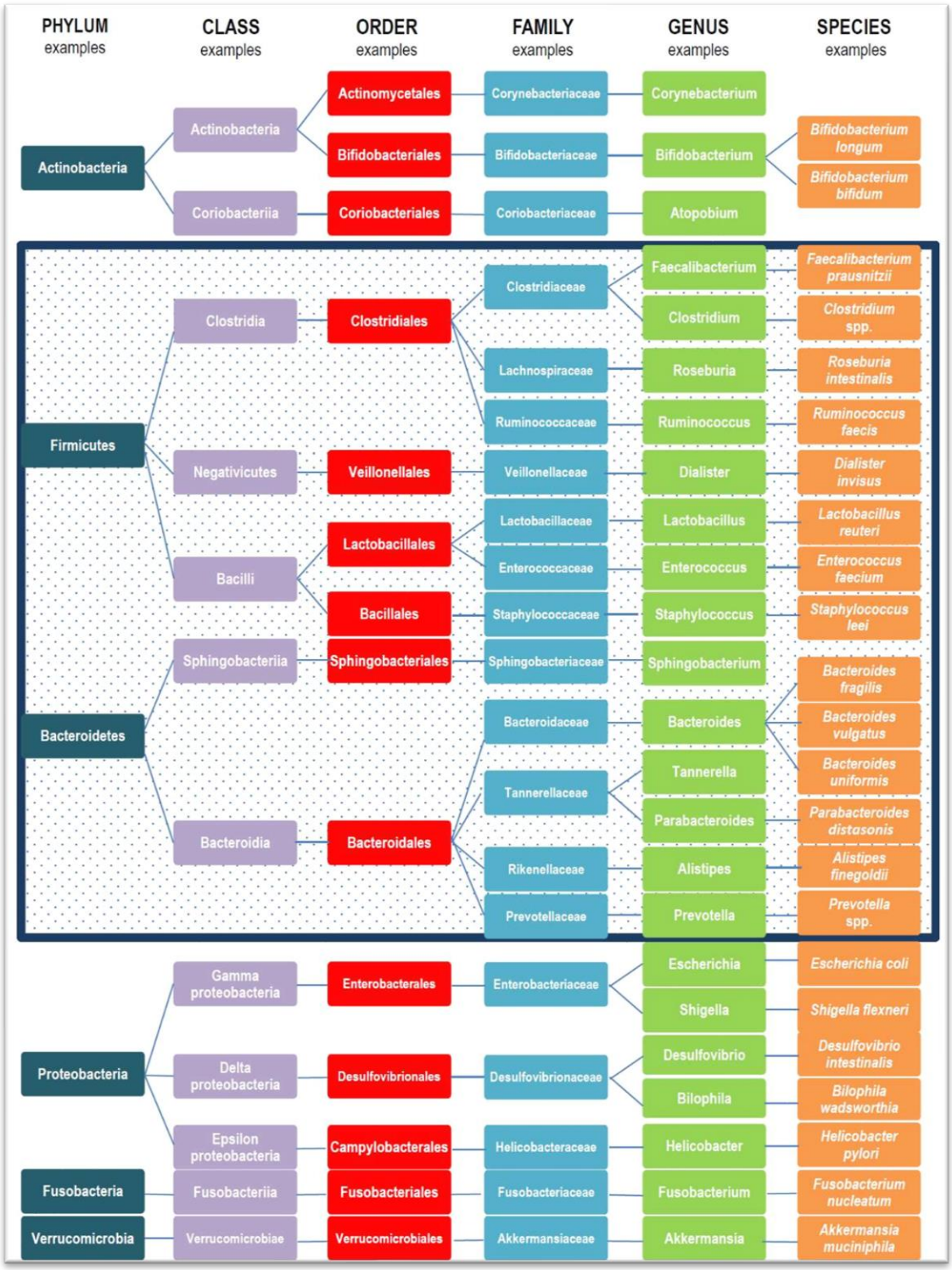

Figure 01: Intestinal flora composition **(Rinninella *et al.*, 2019)**.

The composition of the intestinal flora is determined and influenced by a number of endogenous and exogenous factors, such as geographic origin, age, genetics, diet and the use of prebiotics and antibiotics**(Rinninella *et al.*, 2019)**.

I.4 Balance and imbalance intestinal flora

The intestinal flora lives in symbiosis with the human body and therefore interacts with many functions of the body such as protective, structural, immune or even metabolic and neuromodulation functions. All these functions allow the intestinal flora when it is stable, to ensure intestinal homeostasis, that is to say a state of balance with the intestinal organism **(Anne, 2020)**.

The flora can therefore no longer exercise its functions in a physiological way, leading to a breakdown in the symbiosis with the host. The elements which can disturb the balance of the intestinal flora are in particular drugs and especially antibiotics, viral, bacterial or parasitic infections, an immune deficiency, various pathologies, a sudden change in diet and/or environment or still the stress whether it is psychic or physical, the tobacco, the alcohol and the extreme temperatures**(Anne, 2020)**. From here, we will learn more about variation of the flora intestinal over time from birth to equilibrium.

Beginning the fetus is sterile in the uterus and bacterial colonization only begins at birth from the flora of its mother (vaginal and fecal) and the environment **(Emilie, 2018)**. And the balance of the intestinal flora is reached between the second and the third year of life, depending on the type of diet as well as the date and methods of its diversification. As soon as the diet becomes, in its diversity, close to that of the adult, the flora has a composition similar to that of healthy adults.

If the intestinal flora suffers from an imbalance, then we speak of dysbiosis, it is defined as a state of "imbalance in the intestinal flora resulting from changes in its composition and which may be associated with certain diseases" **(Anne, 2020).**

where dysbiosis is a disturbance of the homeostasis of the intestinal flora due to an imbalance of the flora itself, changes in its functional composition and metabolic activities, or changes in its local distribution, also the imbalance of the intestinal flora or dysbiosis, is characterized by a decrease in biodiversity and the development of potentially pathogenic bacteria at the expense of other **(figure 02)**(**Gruttola, 2016**).

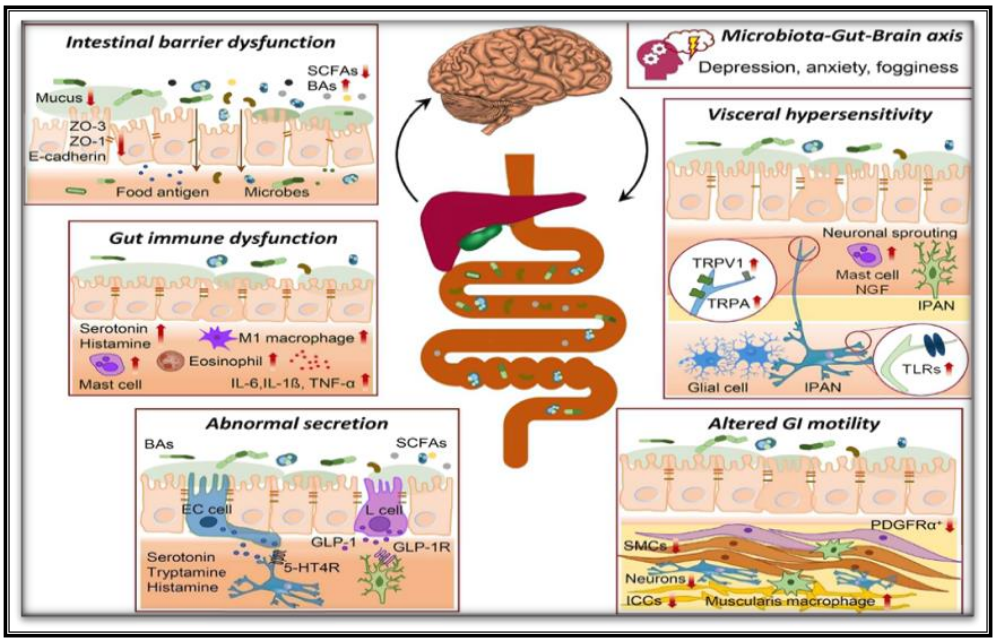

Figure 02: Imbalance intestinal flora affect on body humain **(Joseph *et al.*, 2021)**.

I.5 Characteristics of the flora intestinal

The acidic environment, bile acid and oxygen levels, and anti-microbials present in the small intestine contribute to its lack of overall flora diversity. Therefore, facultative anaerobes that can withstand these conditions dominate this region of the intestinal (**Iara *et al.*, 2019)**. Although fewer in number, may elicit significant changes in host physiology. Abundant phyla of the small intestine include *Firmicutes* and *Proteobacteria* **(Martinez *et al.*, 2018)**.

The large intestine houses most microbes found in the body due to its large surface area and more conducive conditions for bacterial growth. While *Firmicutes* and *Bacteroidetes* dominate, the large intestine consists of an array of anaerobes that utilize undigested carbohydrates and resources for continuous colonization.

A high level of inter-individual variability exists in intestinal microbiota composition and can influence the level of microbial metabolites that are generated given the presence of particular substrates. While each individual's microbiome is vastly unique. This conservation of bacteria suggests that bacteria perform necessary functional processes critical for host survival. These include protection against pathogens, bile acid conjugation, short chain fatty acid (SCFA) production via metabolism of indigestible carbohydrates, nutrient digestion and absorption, promotion of epithelial integrity and immune function (**Iara *et al.*, 2019)**.

I.6 Techniques for studying the composition and function of the intestinal flora

The composition of the intestinal flora could be analyzed by techniques of high throughput DNA sequencing. These methods have made it possible to identify and characterize the different bacterial species within a community of microorganisms such as those present in the intestinal flora organism **(Anne, 2020)**.

Most of the techniques used to profile the diversity of the intestinal flora are based on the 16S ribosomal RNA (rRNA) gene, which is present in all organisms with both conserved and variable domains, and thus the 16S rRNA gene is the most widely used molecular chronometer **(Nie *et al.*, 2019)**.

I.6.1 16S rRNA gene-based techniques

Fingerprinting techniques, the variable region of the 16S rRNA sequence is amplified and examined on a denaturing gradient polyacrylamide gel. The fluorescently tagged genetic segments are detectable by capillary electrophoresis. Quantitative real-time polymerase chain reaction (qPCR) and fluorescence in situ hybridization (FISH) aim to validate the composition and abundance of specific microorganism groups.

(qPCR) is frequently used in conjunction with sequencing to investigate alterations to the intestinal flora in many human diseases **(Nie *et al.*, 2019)**.

I.6.2 Function-focused analysis

Metagenomics based on shotgun sequencing enables the profiling of the full genome of a community. Metagenomics analysis has been applied to explore functional gene information, such as antibiotic resistance genes and disease-associated markers. Several groups have applied this method to assess gene expression of the human intestinal flora and comparison with metagenomics has revealed more variation among transcriptomes than among genomes **(Nie *et al.*, 2019)**.

After studying the metagenome of the intestinal flora, they highlighted 3 types of microbiotas which differ according to the type of bacteria that compose them, their abundance and the functions expressed by the microorganisms. They are called "enterotypes" and allow all individuals to be divided into 3 groups regardless of the factors influencing the constitution of the intestinal flora organism **(Anne, 2020)**.

I.6.3 Emerging techniques

Single-cell genome analysis relies on microfluidics, flow cytometry, and other methods to isolate single microbe cells followed by DNA extraction, amplification, and de novo sequencing. The main applications of this method in microbial community studies are for

exploring rare species and revealing the functions of specific microbes. At present, the application of single-cell genomics to the intestinal flora is rare, though the potential of this technique is clear.

The combination of gene-sequencing technology and flow cytometry enables quantitative profiling of flora communities**(figure 03) (Nie *et al.*, 2019)**.

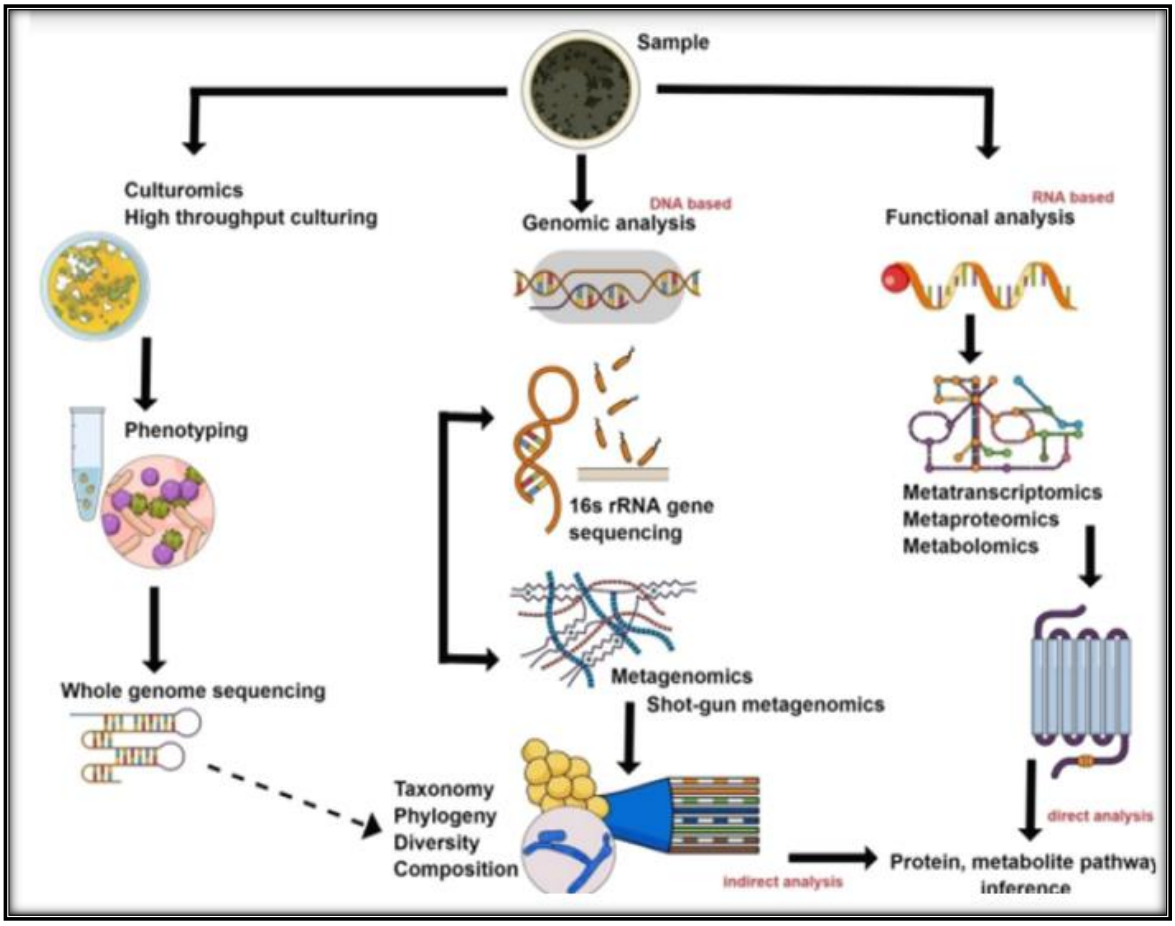

Figure 03: Methods used to profile the structure of the flora intestinal **(Philips *et al.*, 2020)**.

Chapter II

The intestinal flora of human beings plays a major role of the body. The activity of intestinal microorganisms is beneficial in a variety of ways. In this chapter, we explain how the intestinal flora works and its effective roles in maintaining the safety and health of humans.

II.1 Structure of the intestinal flora

The intestinal barrier is no static structure while permeability varies between proximal and distal regions, as well as between crypts and villi, molecular mechanisms regulating the passage of substances through the epithelium are similar along the bowel and include intercellular protein interactions, the actin cytoskeleton, endocytosis and intracellular signaling. On the other hand, enteric neurons play a role in the management of paracellular permeability and epithelial cell proliferation **(Eloisa *et al.*, 2015)**.

The intestinal barrier is regarded as the first defense against pathogenic agents acids, It provides a complex multilayer defense system capable of separating the intestinal contents from host tissues, modulating the absorption of nutrients, allowing the interaction between the intestinal flora and the mucosal immune system, promotes host metabolic balance and serves as a biological defense against infectious agents. **(Xiaoxi *et al.*, 2022)**. The intestinal flora is critical for the formation of the mucous layer (**Nie *et al.*, 2019)**. These mainly include the outer mucus layer with the commensal flora intestinal. **(Maaike *et* Séverine, 2017)**. The intestinal flora contributes to the maintenance of the intestinal barrier function by supporting the structural development of the intestinal mucus layer, desmosomes and tight junctions (**liying *et al.*, 2022)**. Most pathogens are restricted to the intestinal lumen and the dense and firm structure of the inner mucus layer blocks bacterial contact with intestinal epithelial cells (EC) in a mucus mucin dependent manner by goblet cells. Separation from the intestinal epithelium is also an important strategy for commensals to avoid removal by the immune system **(figure 04) (Nie *et al.*, 2019)**.

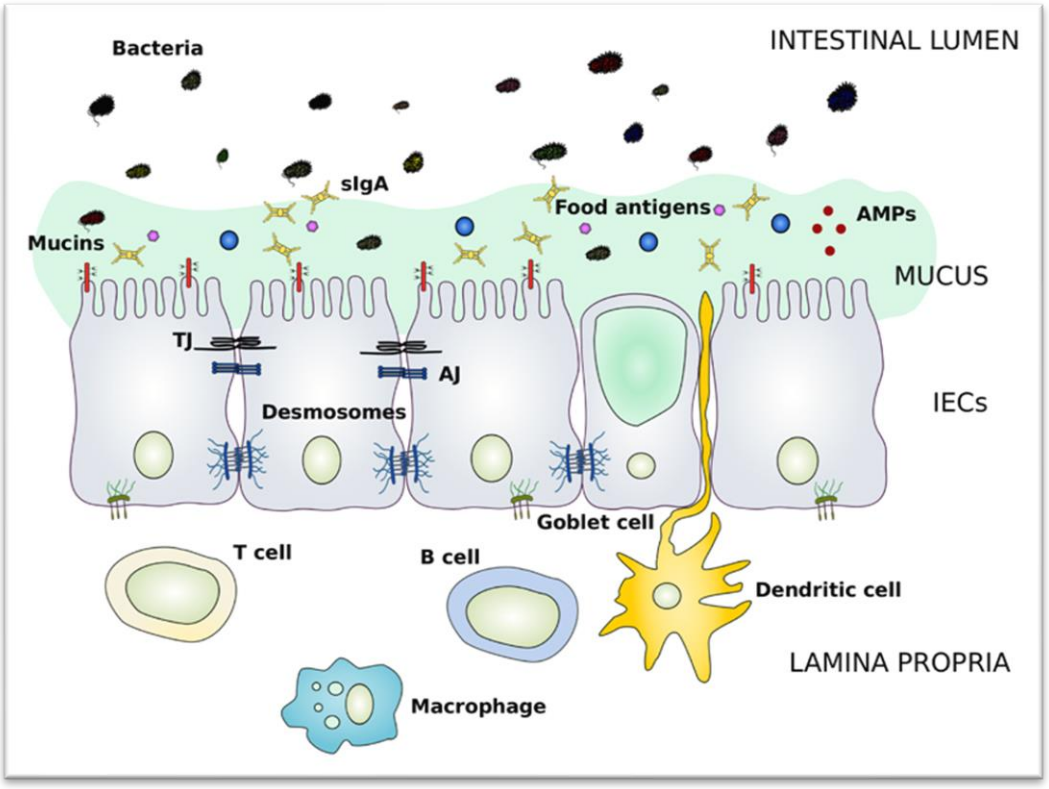

Figure 04: Structure of the intestinal barrier **(Maaike et Séverine, 2018)**.

II.2 Mechanism d'action of intestinal flora

The primary agency for entrance intestinal flora into the body is food. They will take up permanent residence and when they multiply, they will colonize the intestine and form that organ's flora. Intestinal flora has a distinctive method of reproducing quickly. The body loses a portion of its intestinal flora on a daily basis, but it is constantly being replaced by new bacteria produced by this same flora. The human body gains a huge advantage from the bacteria of the intestinal flora, and they in turn are beneficiaries of the body. Every day the intestines provide nourishing food residue and a warm, moist environment that is essential for their survival (**Healing, 2021)**.

Food components that are not digested in the small intestine travel to the colon. These nondigestible elements are substrates for fermentation by the intestinal flora. **(Merlin, 2017)**. The presence of the bacterial flora in the intestinal favors the absorption of ions and the production of vitamins **(Laura, 2020)**.

Not only the intestinal flora itself but also the metabolites of the intestinal flora participate in the regulation of body activities and metabolism. The metabolites of the intestinal flora consist mainly of short chain fatty acids (SCFAs), indole derivatives, polyamines, organic acids, and vitamins. SCFAs are the most common metabolites of the

flora intestinal (**Xueyang *et al.*, 2020**). The intestinal flora affect the host's regional immunity by digesting dietary fiber into SCFAs. Some SCFAs are then used as energy sources for cells, upon passive and active absorption by the intestinal epithelial cells. However, others are used as signals activating the immune system and are recognized by G protein-coupled receptors (GPCRs) on the surface of intestinal epithelial cells and spontaneous inflammation **(figure 05) (Zhou B *et al.*, 2020)**.

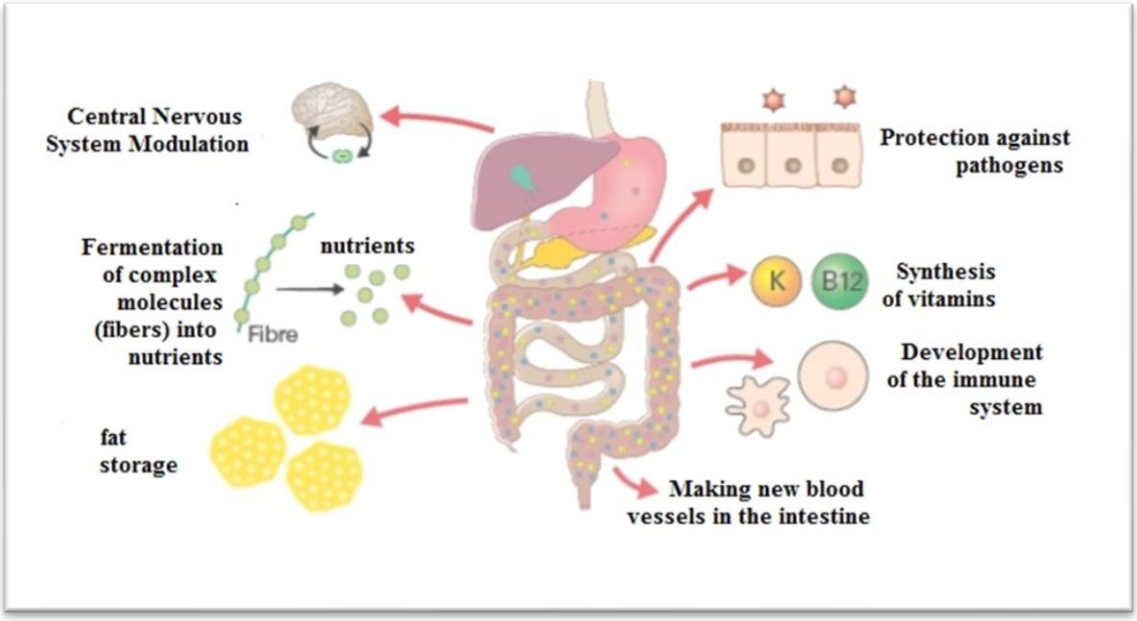

Figure 05: Mechanism d'action of intestinal flora **(https://www.google.com/ =https www.annabac.com)**.

II.2.1 Relationship of the intestinal flora mechanism of action with digestion

The intestinal flora carries out the transformations that are still necessary. They produce enzymes that break down the fibers and framework of the tissues and reduce the volume of the large particles. Nutrients that are still highly useful will be released by this process: amino acids, carbohydrates, vitamins, and so forth **(Healing, 2021)**. The intestinal flora is involved in lipid metabolism since it participates in its storage regulates lipogenesis fatty acid oxidation and regulates its absorption, since it is capable of suppressing lipoprotein lipase inhibition which promotes lipid metabolism the intestinal flora has a direct participation in the metabolism of bile acids from dietary cholesterol **(Passos, 2017)**.

The intestinal flora participates in the degradation carbohydrates ingested by the individual by transforming the polysaccharides into fermentation metabolites through several steps fibrolytic bacteria synthesize enzymes which ensure the hydrolysis of carbohydrate polymers contained in plant fibers into small fragments (oses and oligosides) as a first step

which cannot be carried out by human cells Secondly, glycolytic bacteria transform carbohydrates into pyruvate by glycolysis then, the latter will be transformed into short chain fatty acids which serves as an energy source for the epithelial cells of the colon by promoting their rapid renewal and by stimulating the exchange of water and minerals **(Descoins, 2017)**.

II.2.2 Relation of the intestinal flora mechanism of action with detoxification

Tiny as they are, they are still living beings that can be injured or destroyed by the action of certain poisons. They are not, however, defenseless. Like all living things, they can fight back against the attack. They do this primarily with the help of enzymes they manufacture themselves. These enzymes will neutralize the poisons by rendering them inoperative or breaking them down into simpler elements that have no dangerous properties. These elements are then either eliminated in this state or reabsorbed into the bloodstream to be used by the body.

The microorganisms of the intestine are very vulnerable to poisoning. The foods we eat today often carry toxic substances (herbicides, pesticides, food additives, poisons created by pollution and so forth) with them into the body. The bacteria that live in our intestines are therefore the first to confront them. In addition, these bacteria share a limited living space with trillions of other individual microorganisms, each of which produces wastes that are partially toxic. In order to survive, the intestinal microorganisms must be capable of neutralizing these poisons.

When intestinal flora neutralizes toxic substances, it is self-protection, rather than an effort to rescue the human being, but we benefit from their efforts. By protecting them selves against these attacks, they are also helping us since the poisons (or at least a portion of them) that would otherwise be able to make us sick are neutralized before they have a chance to attack us. Due to their large numbers, intestinal microorganisms perform an enormous amount of detoxification work. This work is estimated to be on a par with that of the liver, which is known to be the most powerful organ in the body when it comes to detoxification. Intestinal flora, therefore, offer the body “a second liver” so that it can clean and purify itself (**Healing, 2021**).

II.3 Factors that influence the mechanism

The different factors which influence the mechanism of action of the intestinal flora are shown schematically in (figure 06).

II.3.1 Medications

Increasing evidence suggests that many nonantibiotic drugs have an impact on the intestinal flora **(Devkota, 2016)**. Likewise, the intestinal flora also affects the efficacy of

drugs antibiotics also have a profound effect on the normal intestinal flora. The effect is rapid and sometimes persistent. Broad spectrum antibiotics reduce bacterial diversity while increasing the abundance of some bacteria that can be used by opportunistic pathogens and decreasing the number of beneficial bacteria. Early antibiotic exposure in neonates can lead to microbial dysbiosis, which may be a predisposing factor to inflammatory bowel disease. There also appears to be an interaction between antibiotic administration and diet **(Wen *et al.*, 2017)**.

II.3.2 Diet

Increasing evidence suggests that the link between diet and obesity lies in the intestinal flora. Understanding that diet is an important contributing factor to the composition of the intestinal flora makes it the most logical target to manipulate. Interventional studies show that dietary changes result in substantial and rapid changes in the make-up of the intestinal flora. A fiber-rich diet has been shown to be beneficial to health because it modulates the intestinal flora, also the results showed that a high-fat diet can alter intestinal flora and lead to dysbiosis and ultimately disease **(Wen *et al.*, 2017)**.

II.3.3 Age and delivery pattern

Intestinal flora colonization process begins in utero by microbiota in the amniotic fluid and placenta**.** Birth, the mode of delivery affects the early life development of the intestinal flora**.** Newborns delivered vaginally have primary intestinal flora dominated by *Lactobacillus* and *Prevotella* derived from the mother's vaginal flora, while those born via cesarean delivery derive their intestinal flora from the skin, leading to dominance of *Streptococcus, Corynebacterium,* and *Propionibacterium*. These primary floras evolve over time to become more diverse and relatively stable. At the age 3 years, they become similar to an adult's intestinal flora **(Hasan et Yang, 2019)**.

II.3.4 Geographical location

To further evaluate the geographical effects, the intestinal flora composition in different origin populations was measured based on diversity analysis and showed that Europeans were significantly different from Indians **(Rehman *et al.*, 2016**). Even for people who live in geographically adjacent places, their intestinal flora shares a common diversity index and similar diversity (the diversity within single sample), as evidenced by that the observed number of operational taxonomic units is dramatically higher in the rural Bassa, infants than urban infants and adults (**Ayeni *et al*., 2018**). Therefore, geographical location as an influencing factor should be taken into account in the evaluation of the composition and diversity of the intestinal flora **(Jing *et al*., 2021)**.

II.3.5 Physical exercise

It is well known that physical exercise promotes the metabolism and immunity ability of the human body though it might also adversely affect intestinal permeability (**Jing *et al.*, 2021)**. Physical exercise affects the health of the intestinal flora by altering the composition of the intestinal flora with an increased proportion of microorganisms that contribute to intestinal health. This kind of bacteria contribute to metabolize muscle-derived lactic acid (entering into the colon through the epithelial barrier) to produce the SCFA propionic acid, which improves endurance performance**(figure06)** (**Scheiman *et al.*, 2019)**.

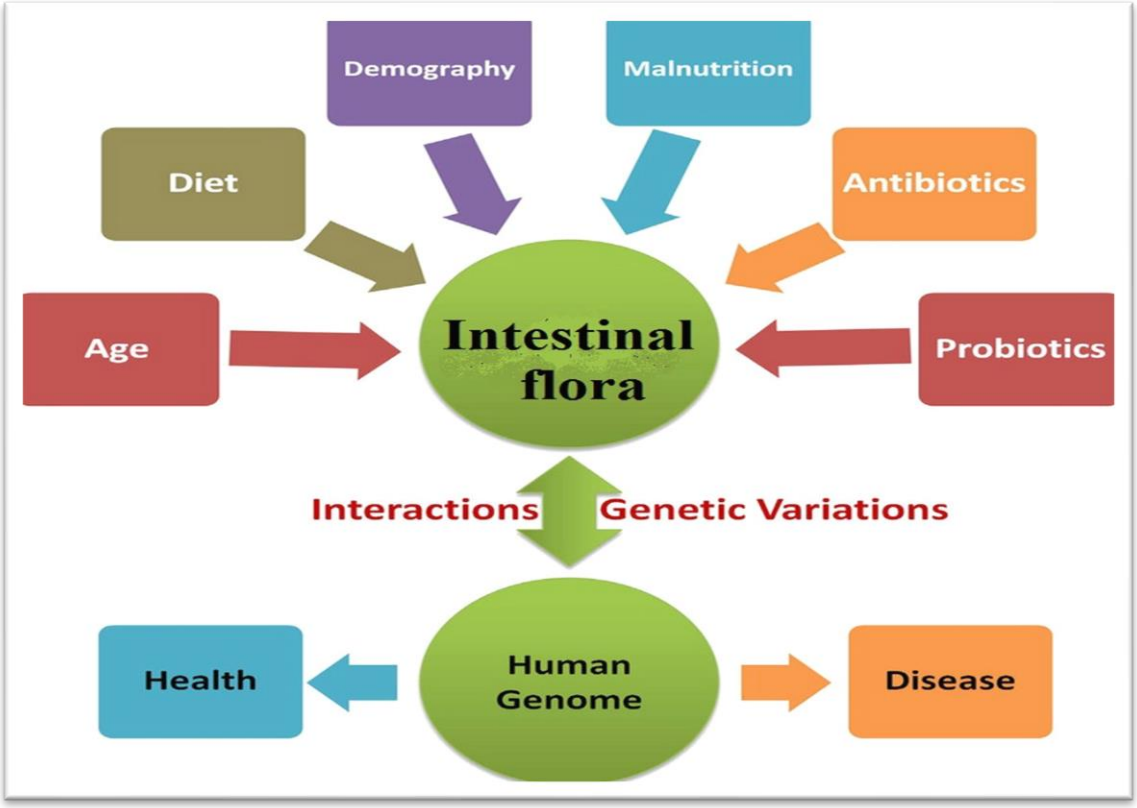

Figure06: Factors that influence the mechanism of intestinal flora **(https://www.researchgate.net/figure/Complex-interplay-of-the-human-gut-microbiome)**.

Chapter III

In the current review, we provide an overview of the role played by intestinal flora within the regional intestinal immune system. Accordingly, we focus on the mutual impact between intestinal flora and intestinal area immunity, as well as the relationship between intestinal flora and the different diseases.

III.1 Generality on intestinal flora and immune system

The human intestinal tract has evolved unique regional immune characteristics maintained by the mature intestinal mucosal immune system. This intricate system involves intestinal epithelial cells, and intestinal lymphoid tissue of the neuroendocrine system. Additionally, the microenvironment created by the intestinal flora and its products are important factors affecting the immunity of the intestinal region. In early life, appropriate intestinal colonization by specific microflora stimulates maturation of the intestinal mucosa-associated lymphoid tissue **(Zhou *et al.,* 2020)**.

Intestinal flora promotesthe maturation and regulation of mucosal and systemic immune systems through innate and adaptive immune cells. For example, the activation of intestinal cells, macrophages, pattern recognition receptors, and highly specific receptors on the surface of T cells and B cells in the mucosa is highly regulated by intestinal microorganisms **(Ren*et al.*,2021)**.

The intestinal flora is essential for the development of the innate and adaptive immune system of the intestinal mucosa, as well as its response to pathogens. The innate immune system provides immediate, but not long-lasting defense against infectious agents.Conversely, the adaptive immune system concedes a later but more lasting response. The commensal intestinal flora plays a direct role in the functions as well as the number of lymphocytes belonging to the adaptive immune system. Intestinal bacterial colonization is directly involved in the immune development of the host. Indeed, although the cells of the innate immune system express ligands for toll like receptors (TLR), their response to the flora differs from that found in adults **(Tirelle, 2020)**.

Someauthors suggest that the immunological responses triggered by the intestinal flora can strengthen the intestinal **(Passos et Moraes, 2017**). From recent studies, suggest that the intestinal flora and the immune system establish a constant interaction of mutualism with the host, in which both are benefited. This inters relationship results in several immunological responses, such as immunoglobulin A secretion and the release of antimicrobial peptides, which allow the maintenance of a dynamic equilibrium with the commensal microorganisms

intestinal **(Passos et Moraes, 2017**). Intestinal flora can also stimulate the differentiation of T cells and monocytes to activate the innate and adaptive immune system **(Zhou *et al.*, 2020)**.

III.2 The intestinal flora on innate immunity

Innate lymphoid cells (ILC) usually develop in the absence of intestinal flora, but their maturation seems to depend on bacterial signals (**Artis et Spits, 2015)**. The family of ILCs are divided into cytotoxic ILCs (Natural killer, NK cells) and non-cytotoxic ILCs. These ILCs present a lymphocytic phenotype but do not have specific antigen receptors compared to B and T lymphocytes. Non-cytotoxic ILCs are divided into 3 groups depending on the expression of surface molecules, transcription factors and their secretory profile; ILC1, ILC2 and ILC3.Many studies show a link between ILC3 and the flora. Depending on the stimulus, ILC3 can produce IL-17A, IL-17F, IL-22, granulocyte-macrophage colony-stimulating factor (GM-CSF) or TNF. It has several functions such as anti-bacterial immunity, chronic inflammation or tissue -repair (**Artis et Spits, 2015)**.

The absence of ILC3 leads to a systemic passage of commensal bacteria associated with systemic inflammation prevented by the supply of IL-22 The presentation of bacterial Ag by ILC3 limits the specific T response to a commensal bacterium. As mentioned above, ILCs also play a role in the production of IgA. Flagellate bacteria recognized by antigen presenting cells expressing +CD103 secrete IL-23 necessary for the production of IL-22 by ILC3 IL-22 allows both a reinforcement of the intestinal barrier and production of antimicrobial peptides by intestinal epithelial cells **(figure 07)(Clelia, 2017)**.

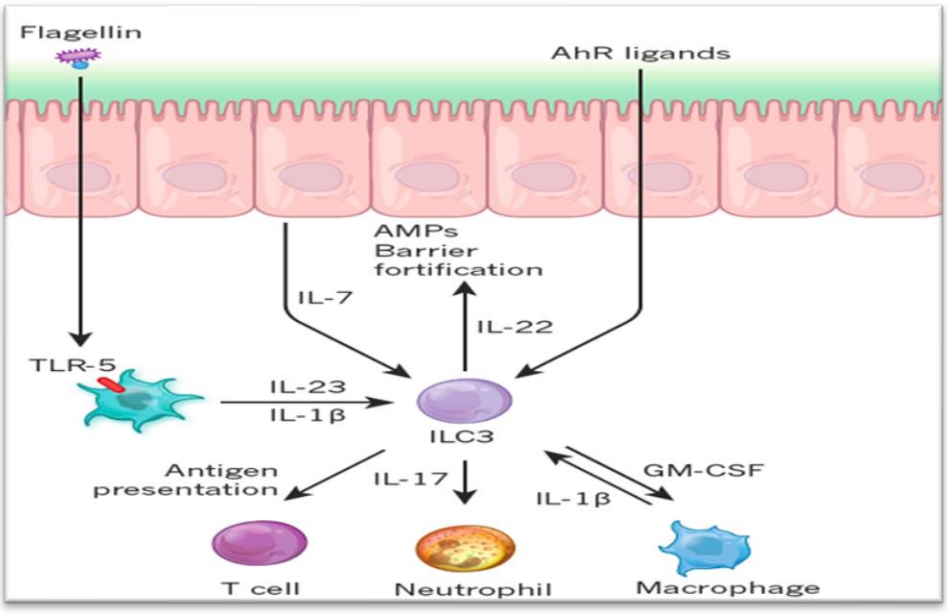

Figure 07: ILC3 and intestinal flora **(Thaiss*et al.*, 2016)**.

ILCs communicate with the intestinal flora via cytokines, microbial associated molecular patterns (MAMPs) and anti microbial peptides (AMPs). ILC3s interact with innate and adaptive immune cells. They secrete IL-22 which induces anti microbial peptides (AMPs) and reinforces the intestinal barrier. They recruit neutrophils and macrophages via the secretion of IL-17 and GM-CSF respectively **(Thaiss*et al.*, 2016)**.

III.3 The intestinal flora on adaptive immunity

We will be interested in T lymphocytes, in particular Th17 and Treg. Differentiation of Th17 cells is characterized by expression of the transcription factor RORyt and requires TGF and either IL-6 or IL-21 to differentiate into Th17 from naïve TL, and of IL-23 for their maturation and survival their cytokine signature includes IL-17A, IL-17F and IL-22 which stimulate the production of antimicrobial peptides by intestinal epithelial cells and the formation of tight junctions Th17 also have a major role in inflammation in particular during stimulation by IL-23), where Th17 also secrete interferon (IFN) and granulocyte macrophage colony stimulating factor (GM- CSF) increasing inflammation. These Th1/Th17 cells are called pathogenic Th17 and are involved in autoimmunity also promoting the differentiation of Th17 cells in the colonic lamina propria **(figure 08)** (**Clelia, 2017)**.

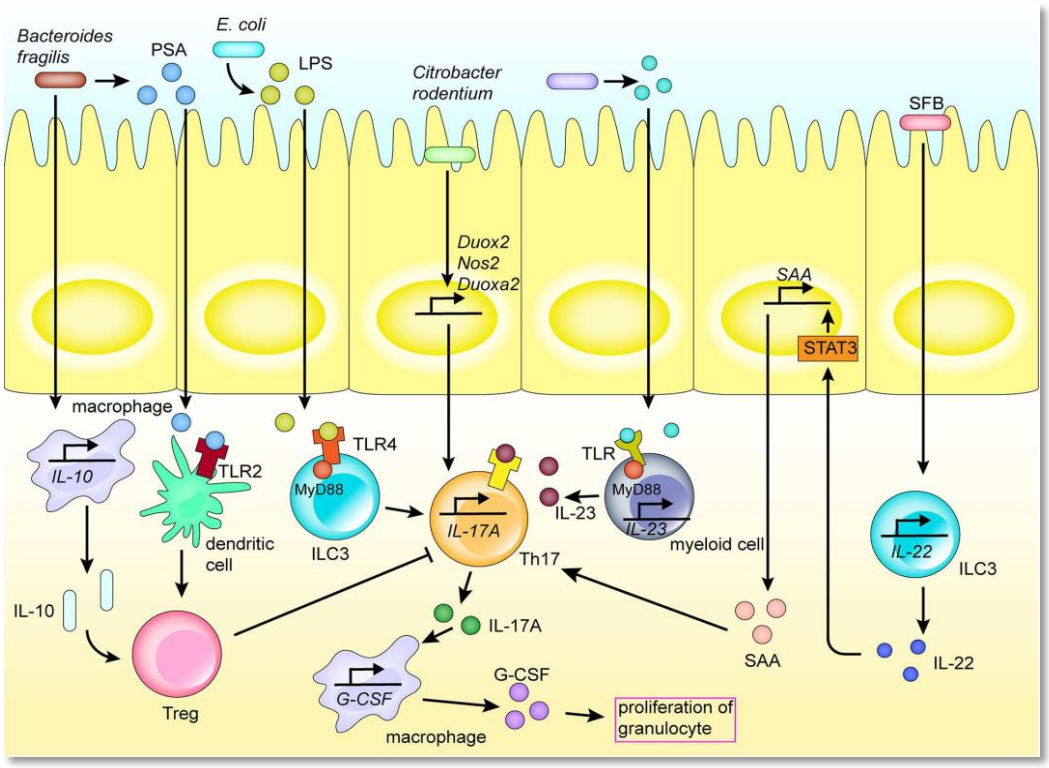

Figure 08: Mechanism of Th17 activation of the regional immune system in the intestinal tract **(Zhou B *et al.*, 2020)**.

T regs expressing the transcription factor FoxP3 are found in large proportions in the lamina propria of the intestine and play a role in maintaining tolerance to the intestinal flora. They also have a suppressive function preventing excessive inflammatory responses mediated by LT effectors. The intestine contains both thymic or natural T regs developing under the influence of selection pressure, and peripheral ones from, in particular, naive CD4+ T lymphocytes. Peripheral T regs secrete IL-10, which is a major immunoregulatory cytokine that helps maintain immune tolerance at the digestive level. IL-10 secreted by Tregs is essential for the suppression of pro-inflammatory responses induced by myeloid cells, LT and Th17 pathogens **(figure 09) (Clelia, 2017)**.

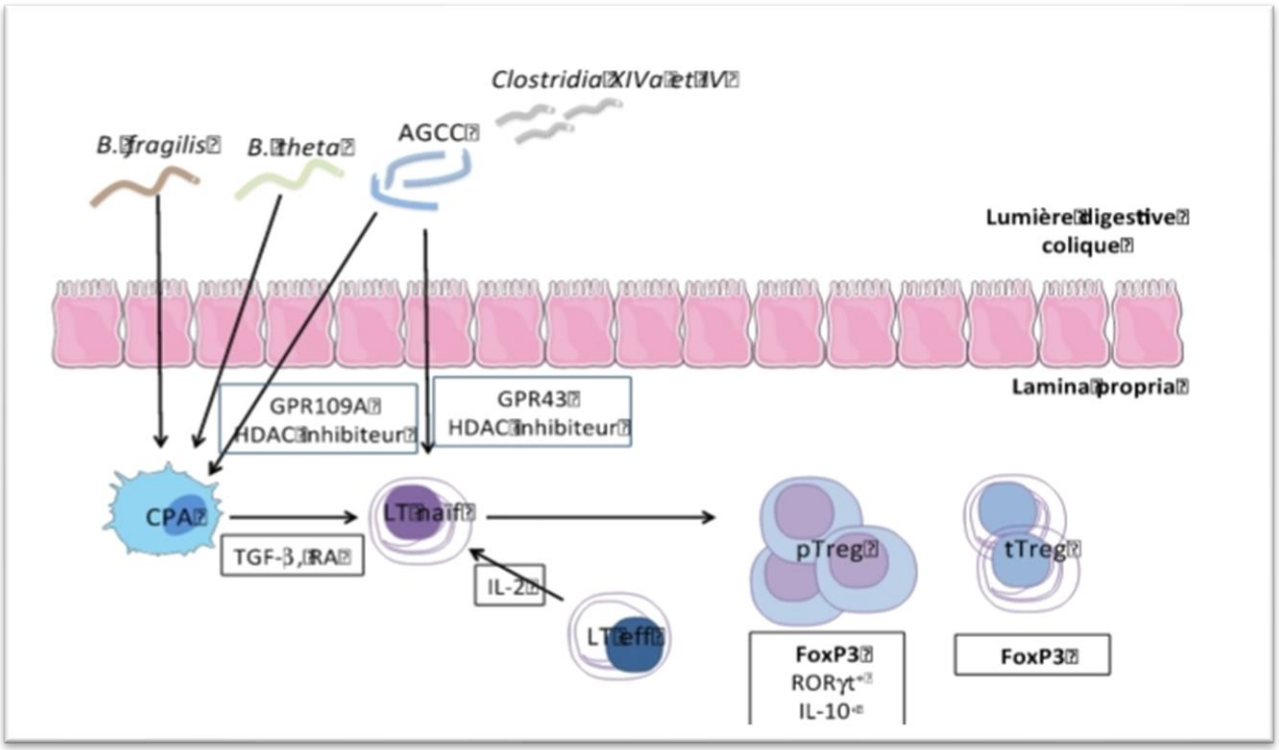

Figure 09: Influence of intestinal flora on T regs **(Honda et Littman, 2016)**.

III.4 Interplay ofthe intestinal flora and host immunity

The immune system is not fully developed before birth, and appropriate flora stimulation in early life has an irreplaceable effect on the maturation of the immune system**(Nie*et al.*, 2019)**. The actions of the intestinal flora on host immunity can be characterized by three effects: "activation" of the immune system, "modulation" of immune responses and, finally, "regulation" of responses allowing short- and long-term good adequacy of these to the different antigenic stimuli. The postnatal period seems crucial in the

establishment of some of these regulatory mechanisms, especially those involved in atopic diseases flora **(Jean, 2004)**.

Collectively, the host immune system development depends on the contact and interaction of microorganisms with the intestine in early life. In the absence of such interaction, development of the host's immune system is affected **(Zhou *et al.*, 2020)**. In humans, both cesarean-born and formula-fed infants without a genetic predisposition have a greater chance for immune disorders in early life compared with those born naturally and breastfed (**Kristensen et Henriksen, 2016)**.The same situation applies to infants treated with antibiotics **(Francino, 2015)**.

Moreover, systematic and longitudinal descriptions of immune cells and proteins in newborns show stereotypes of immune system development and its adaptation to intricate environmental exposure, among which perturbation of the intestinal flora leads to increased activated T cells in the blood **(Olin *et al.*, 2018)**.

For most commensals, induced T cell-independent IgA responses avoid bacterial contact with antigen-presenting cells, thus preventing T-cell activation **(Donaldson *et al.*, 2018)**. The diverse metabolites produced by flora intestinal affect the immune response and disease progression through interacting with cells in the intestinal tract of the host **(figure 10)(Rooks et Garrett, 2016)**.

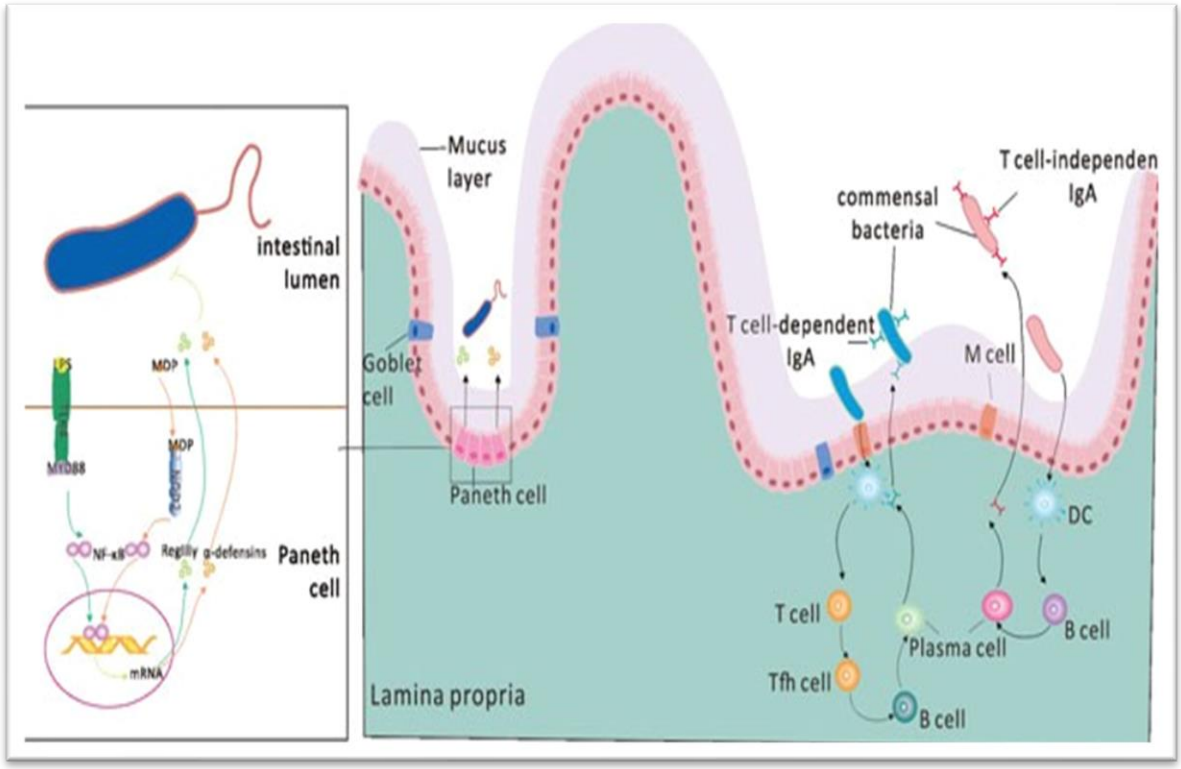

Figure 10 : A brief diagram of a cross-section of the intestine **(Nie *et al*., 2019).**

III.5 Relation between bacterial colonization flora and the establishment of the intestinal immune system

There is a formal link between the bacterial flora, the intestinal mucosa and the immune system, in particular via the innate immune system of which the toll-like receptors (TLR) are the main players. The intestinal mucosa, with a surface of more than 300 m is permanently exposed to a very large quantity of antigens, whether of food or bacterial origin.

The intestinal flora plays essential roles in the intestinal and peripheral immune systems: role of activation, role of modulation of specific responses, for example at the intestinal level on the vaccine response or on the anti-rotavirus IgA protective response. Finally, the flora plays a regulatory role in the immune system. This is immature and characterized by an unbalanced response of T helper 2 (Th2) lymphocytes greater than that of Th1 as well as an insufficiency of regulatory T cells. The progressive bacterial colonization of the digestive tract is, in this respect, essential to establish a balance between Th2 and the other types of lymphocytes (Th1 and Th3). The intestinal flora therefore plays a role in the acquisition of tolerance and therefore in the prevention of allergy **(figure 11) (Goulet, 2009)**.

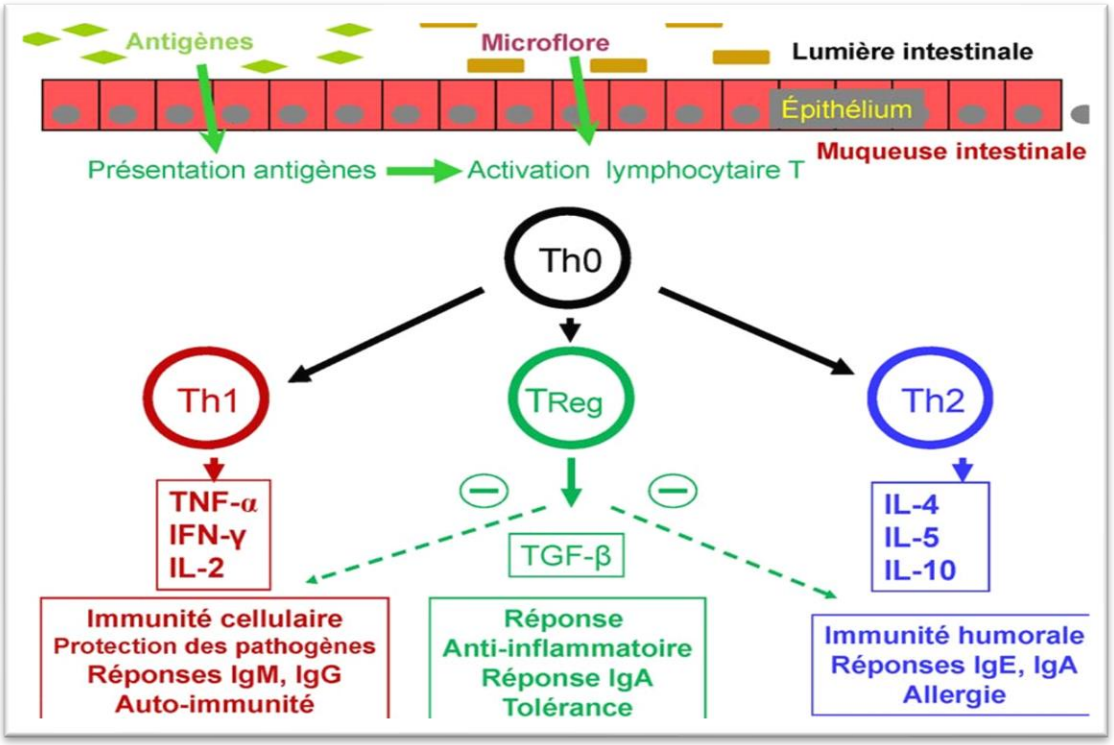

Figure 11: Interactions between microflora and the immune system and orientations of the immune response **(Goulet, 2009)**.

III.6 Intestinal flora activates and promotes the development the intestinal immune system

Many myeloid cells in the intestine, such as macrophages and dendritic cells, are activated by the intestinal flora to initiate innate and adaptive immunity, and inflammatory reactions **(Gorjifard et Goldszmid, 2016**). In addition, intestinal epithelial cells, as the first barrier of innate regional immunity, play an important role in activating the immune system and protecting the host from pathogens **(Zhou *et al.*, 2020)**.

Development of the immune system exists in every stage of life. However, the influence exerted by the internal and external environment on shaping the early immune system is particularly important, especially before and immediately after birth. In the early life stages of life, appropriate colonization by intestinal flora results in PAMP stimulation of PRRs expressed on the intestinal mucosal epithelial cells or immune cells. This stimulation subsequently induces maturation of the intestinal mucosa-associated lymphoid tissue **(Zhou *et al.*, 2020)**.

The intestinal epithelium, and numerous natural immune cells, express a series of PRRs, such as TLRs and NOD-like receptors (NLRs). These receptors enable direct sensing of

carbohydrates and lipid-based bacterial cell wall components, thereby activating the immune system**.** For example, lipoproteins and LPS secreted by certain bacteria are recognized by TLR-1, 2, 4, 6, and 10 on the surface of myeloid cells, mucosal epithelial cells and other immunocytes (**Wang *et al.*, 2019)**.

Activation of the intestinal immune system has both positive and negative effects on maintenance of human health. As one of the primary factors activating intestinal immunity, intestinal flora plays an important role in protecting the body from pathogens and promoting formation of intestinal inflammatory response **(figure 12)(Zhou *et al.*, 2020)**.

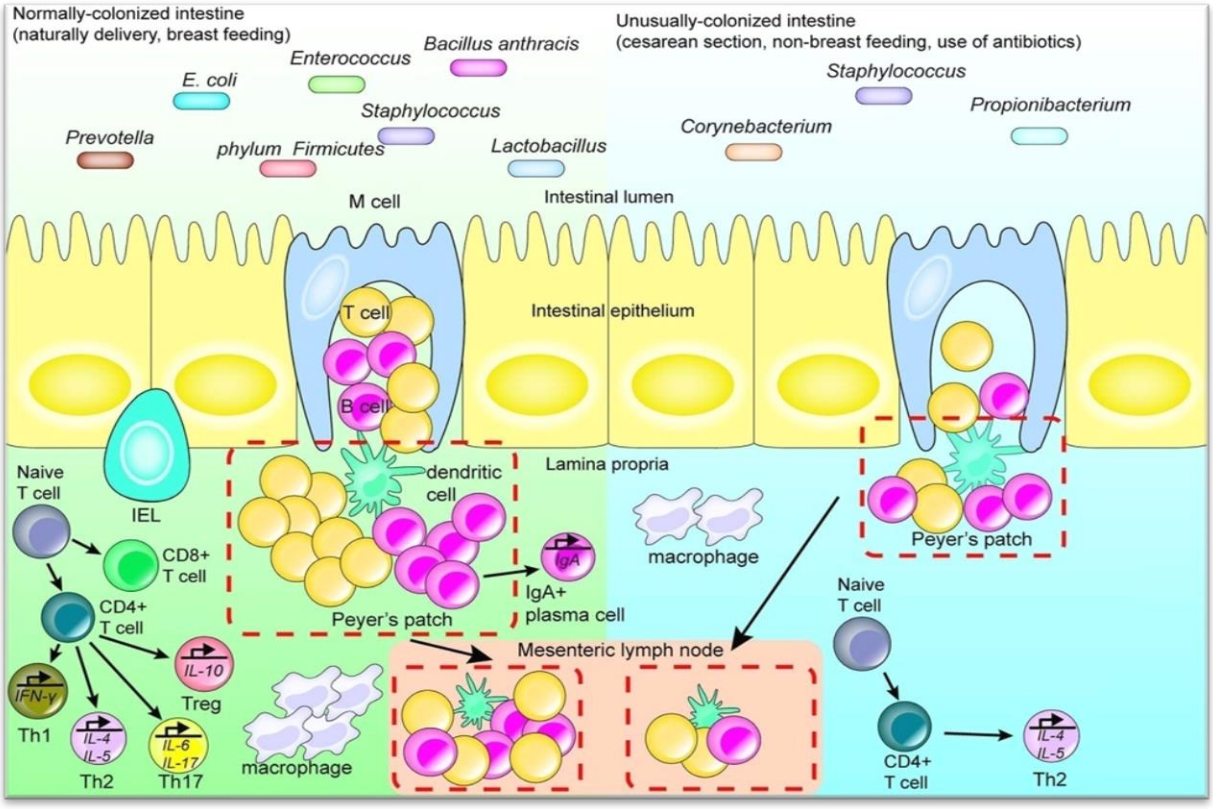

Figure 12: Intestinal flora affects the development of the regional immune system **(Zhou *et al.*, 2020).**

III.7 Relationship between intestinal flora, regional immune regulation, and regional immune tolerance

The intestinal flora acquires a tolerance to the presence of commensal bacteria in our digestive tract cytokines**(Anne, 2020**). WhereImmune tolerance prevents the body's immune system from eliciting an immune response to the intestinal flora that dwells symbiotically within the body, while inhibiting progression of inflammatory response **(Chang *et al.*, 2017)**.

In return, it is able to trigger an immune response to pathogenic bacteria that come into contact with it. It thus plays an important role in maintaining the balance between activation and inhibition of immune reactions to commensal bacteria, foods and pathogenic microorganisms. In addition, it provides anti-inflammatory activity thanks to the presence of bacteria that produce anti-inflammatory cytokines **(Anne, 2020).** Also, T regs play an important role in immune regulation and immune tolerance. For instance, Bacteroides fragilis contains capsular polysaccharide A, which can activate FoxP3 + + CD4 T regs in the lamina propria by up-regulating the inhibitory cytokine, IL-10; which subsequently activates the TLR2 signaling pathway. Further, B fragilis may alter the Treg/Th17 balance by counteracting the inflammatory response induced by LPS, thereby exerting an immunomodulatory effect **(figure 13)(Chang *et al.*, 2017)**.

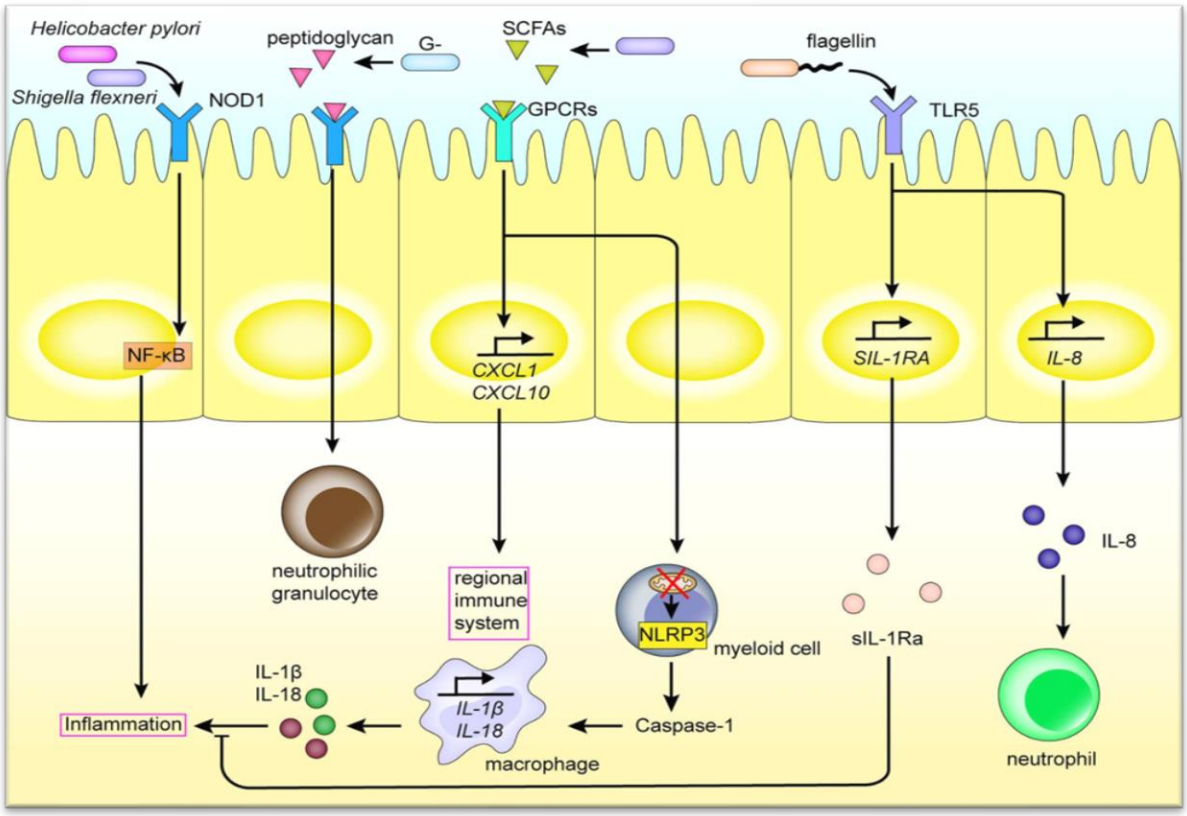

Figure 13: Intestinal flora and metabolites interact with the regional immune system in the intestinal tract **(Zhou *et al.*, 2020)**.

III.8 Immunometabolism of flora intestinal

The intestinal flora ensures the metabolism of lipids, proteins, carbohydrates and gases and its main source of energy comes in particular from carbohydrates and proteins. All this also contributes for the host to a regulation of its energy metabolism **(Anne, 2020)**.

Immune cells use the same pathways as other cell types to generate energy and ensure their effective functioning. The main metabolic pathways involved in immunometabolism are glycolysis, the tricarboxylic acid (TCA) cycle, the pentose phosphate pathway (PPP), FA oxidation (FAO), FA synthesis, and AA metabolism. Among the flora intestinal metabolism pathways impacting; the metabolism of the immune cells**(Michaudel*et al.*, 2020)**.

Where the intestinal flora contributes directly to the metabolization of nutrients and vitamins essential for host viability collaborating to obtain energy from food. This energy is acquired especially through the fermentation of non-absorbable carbohydrates, in a reaction that induces the production of short chain fatty acids (SCFAs), hydrogen and carbon dioxide **(Passos et Moraes, 2017)**.

In conclusion immune metabolism at steady state promotes homeostasis. However, the energy requirement of immune cells during inflammatory and infectious diseases is much higher, and their whole metabolism is altered. These processes are involved in both the pathogenesis of nonseptic inflammatory disorders and in the resolution of infection **(Zmora *et al,* 2017)**. The intestinal flora modulates immunometabolism and thus can have positive or negative effects on these pathological events **(figure 14)(Michaudelet Sokol, 2020)**.

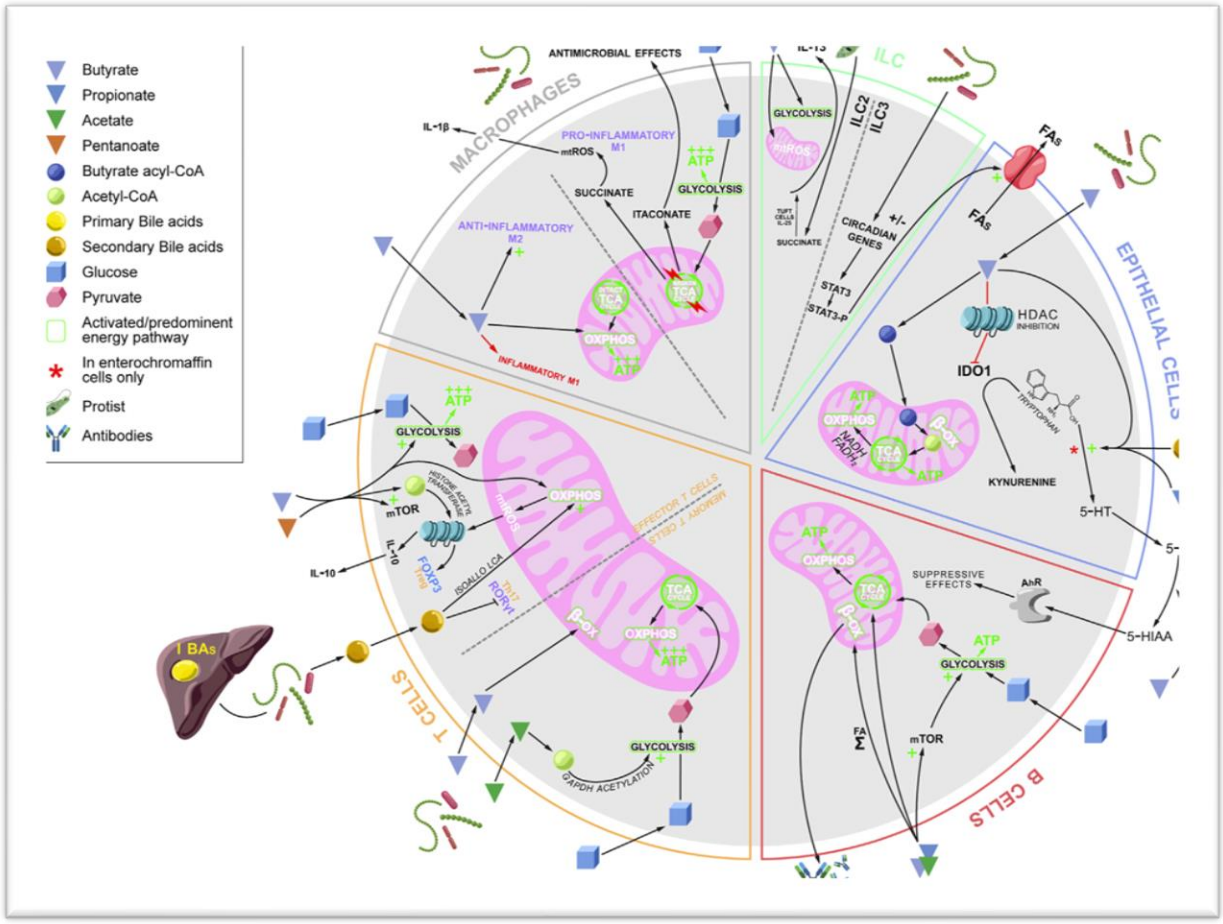

Figure 14: Influence of the intestinal flora on Immunometabolism**(Michaudel et Sokol, 2020)**.

Chapter IV

That permanent alteration in the composition or function of the flora (dysbiosis) can alter visceral sensitivity, bowel motility, and permeability, as well as alter the immune response, such changes, especially in the immune and metabolic functions of the host, can arise or contribute to the emergence of many diseases. Recent studies have also shown the participation of microbes in causing many diseases. In this chapter, we will learn about some of them.The relationship between intestinal flora and human health is illustrated in **(figure 15)**.

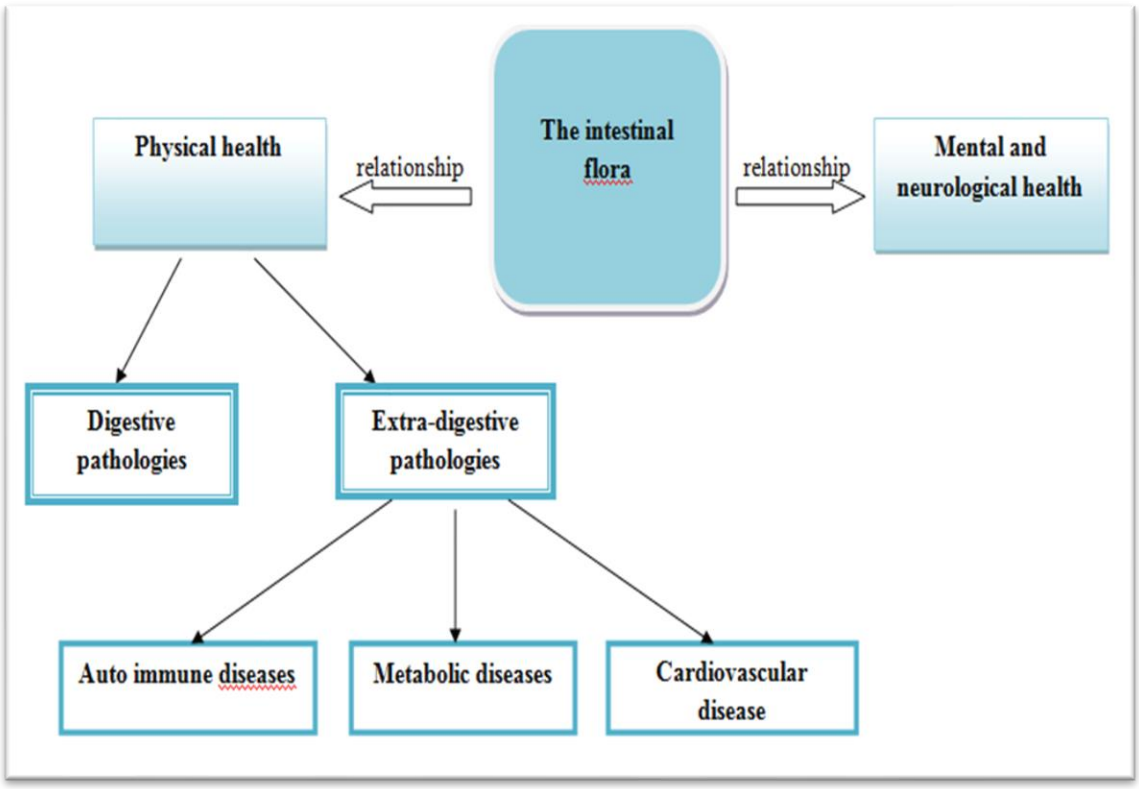

Figure 15: The relationship between intestinal flora and human health.

IV.1. Physical health

The intestinal flora plays critical roles in maintaining human health, affects the development and function of the immune system. intestinal flora dysbiosis may lead to a number of physical health diseases, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), colorectal cancers, type 2 diabetes(T2DM), rheumatoid arthritis (RA), obesity andcardiovascular disease.

IV.1.1. Digestive pathologies

IV.1.1.1. Inflammatory bowel diseases (IBDs)

Inflammatory bowel diseases (IBD) is a chronic inflammatory disease caused by abnormal immune response to intestinal florain genetically susceptible populations. The

distribution characteristics of intestinal flora in IBD patients were different, and the richness and diversity of intestinal flora are different from normal people in various degrees. The intestinal flora of IBD patients not only species richness and diversity declined, but stability and mucus layer structure were destroyed **(Song *et al.*, 2021)**.

Crohn's disease (CD) and ulcerative colitis (UC), which are known as infammatory bowel diseases (IBD), are chronic and relapsing infammatory disorders of the gastrointestinal tract **(Nishida *et al.*, 2018)**.Environmental factors, genetic factors and immune responses have been considered as the major etiology of IBD (Crohn's Disease and Ulcerative Colitis) which have a diversified pathogenesis **(Passos et Moraes, 2017)**.

Dysbioses associated with IBD have been described. They are characterized by a deficiency in certain bacteria, such as *Faecalibacteriumprausnitzii* or other species of the *Clostridium* group, as well as by an increase in the population of other pro-inflammatory bacteria such as *enterobacteriaceae* or bacteria of the genus *Fusobacterium*. It is believed that these imbalances are both a cause and a consequence of the disease: dysbiosis appears under the influence of genetic and environmental factors, but itself plays a role in the onset, maintenance or severity of the disease. inflammation, creating a vicious circle. The role of bacterialmetabolites in these mechanisms is also suspected**.**

IV.1.1.2. Irritable bowel syndrome

Although the etiopathogenesis of irritable bowel syndrome (IBS) is not fully understood, several pathophysiological changes have been described (altered intestinal motility, visceral hypersensitivity, immune activation, dysregulation of the brain-bowel axis), thus constituting a multifactorial syndrome. In recent years, important etiopathogenic contributions have been described, with the demonstration that some patients with IBS also have an alteration in the flora and changes in the intestinal mucosa (dysbiosis).

Initial studies of the intestinal flora in patients with IBS demonstrated a decrease in the proportion of *Bifdobacterium* and *Lactobacillus* and an increase in *Enterobacter*. A greater reduction of Lactobacillus was detected in patients with IBS and diarrhea (IBS-D) than in those with IBS and constipation (IBS-C). A lower amount of Bifdobacteria was also observed in IBS-D and a greater amount of *Veillonella* in IBS-C. On the other hand, there are higher levels of intestinal bacteria and lower levels of *Faecalibacteriumprausnitzii*in patients with IBS-D. Using DNA sequencing techniques, the stool of patients with IBS was analyzed, indicating a reduction in *Lactobacillus* and *Bifidobacteria.* Another study noted a two-fold increase in the *Firmicutes/Bacteroidetes* ratio in patients with IBS, as well as an association between abdominal pain and lower amounts of *Bifdobacteria.*

Research on experimental animals have demonstrated that behavioral changes, such as stress, can change the composition of the intestinal flora, making it more vulnerable to the inflammatory and immunological stimuli of the gastrointestinal tract. It is worth mentioning that the great heterogeneity of the results is justifed, at least in part, by the multiple methods used to determine the flora and the different inclusion criteria used for patients with IBS **(Passos et Moraes, 2017)**.

IV.1.1.3 . Colorectal cancers

Colorectal cancers of somatic origin are characterized by mutations in tumor suppressor genes such as APC, Catenin β1, TP53 or KRAS and often by microsatellite instability due to inactivation of the mismatch repair systems of the DNA. Although it is not debatable that these mutations have a decisive role in the transformation of healthy mucosa into adenoma and then into cancer, it has recently appeared that upstream a certain number of environmental and behavioral factors could be decisive. In particular, dysregulation of the immune response to the host flora is a key event in the occurrence of inflammatory bowel diseases, themselves representing a significant risk factor for colorectal cancer **(Debré et Jean, 2014)**.

Initially, it was demonstrated that certain species of the genus *Fusobacterium* and in particular *Fusobacteriumnucleatum*, played a role in the appearance of colorectal cancer in humans due to their abundant quantity.In addition, an increase in other species such as *Bacterioidesfragilis* or *Escherichia coli* is found as well as an overall decrease in bacteria from the *Bacterioidetes* and *Firmicutes phylum*, with the latter in particular a bacterium with anti-inflammatory properties, *Faecalibacteriumprausnitzii***(figure 16) (table01) (Marie, 2020)**.

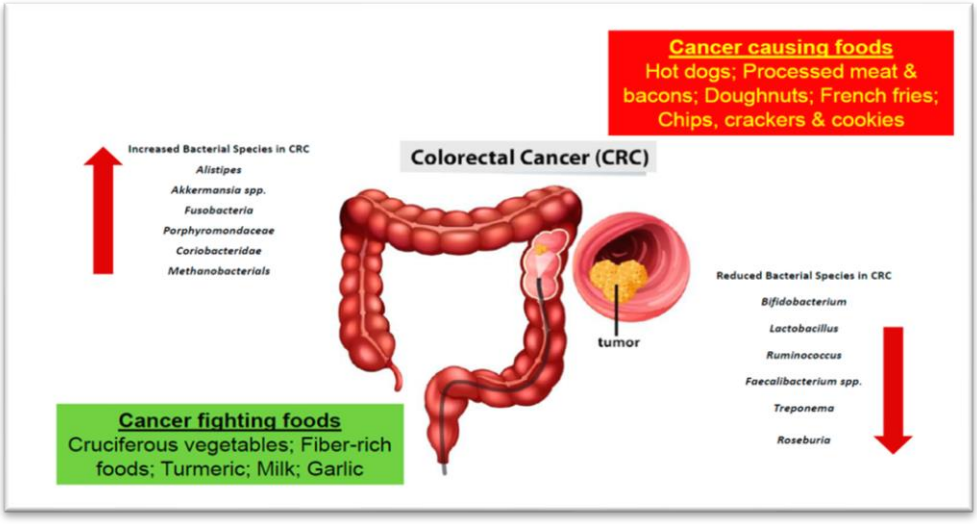

Figure 16: Changes bacterial species in colorectal cancer **(Siddiqui *et al.*, 2022)**.

In patients diagnosed with CRC the bacteria families found to have increased in number include *Alistipes, Akkermansia spp., Fusobacteria, Porphyromondaceae, Coriobacteridae*and *Methanobacterials.* Whereas the bacteria species belonging to *Bifidobacterium, Lactobacillus, Ruminococcus, Faecalibacteriumspp, Treponema* and *Roseburia* are decreased in number **(table01) (Siddiqui *et al.*, 2022)**.

Table01: Bacterial Species Increase or Decrease in Colorectal Cancer (CRC) Patients **(Siddiqui *et al.*, 2022)**.

Bacterial Species	Increase or Decrease in Colorectal Cancer (CRC) Patients
Alistipes *Akkermansia spp* *Fusobacteria* *Porphyromondaceae* *Coriobacteridae* *Methanobacterials*	Increase
Bifidobacterium *Lactobacillus* *Ruminococcus* *Faecalibacterium* spp *Treponema* *Roseburia*	Decrease

The pathogenic bacterial species mentioned above are involved in colon carcinogenesis through the toxins they produce. They play a role in inflammatory phenomena and the activation of signaling pathways that target DNA. These relate to angiogenesis, inflammation and cell proliferation, which can promote the initiation and development of tumors and therefore cancer **(Marie, 2020)**.

IV.1.2. Extra-digestive pathologies

IV.1.2.1. Autoimmunediseases

IV.1.2.1.A. Type 2 Diabete

Type 2 diabetes mellitus (T2DM) is a clinically chronic metabolic disease characterized by insulin resistance that is prevalent throughout the world, especially in western developed countries **(Song *et al.*, 2021)**. In recent years, numerous studies have pointed out that the intestinal flora participate in the process of energy metabolism, which is closely related to the occurrence and development of T2DM.It is generally believed that the occurrence of T2DM is

one of the results of the intestinal flora disorders caused by the over nutrition diet, such as excessive ingestion of salt, sugar and fat, etc.

Over nutrition diet has devastating effect to the diversity and stability of microflora, and it is characterized by the decrease of beneficial microflora and/or the increase of conditional pathogenic microflora, which induces chronic low-grade inflammation in the intestine, thus leading to the occurrence of insulin resistance (IR) and T2DM **(Quantao *et al.*, 2019)**.

There are several mechanisms for the induction of T2DM caused by intestinal flora imbalance **(figure17)** and **(figure18)**. First, the abnormalities in SCFAs levels are important factors in causing T2DM **(Song *et al.*, 2021)**.Short-chain fatty acids (SCFAs) are organic carboxylic acids with1˜6 carbon atoms, including acetic acid, propionic acid, butyric acid, lactic acid, isobutyric acid, isovaleric acid, isohexanoic acid and so on.

Table 02: Changes of intestinal flora in patients with T2DM **(Quantao *et al.*, 2019)**.

Classification	Species of bacteria	Contentchange
Beneficial bacteria	Lactobacillus	down
	Clostridium	down
	Bifidobacterium	down
	B.vulgatus	down
	Rothia	down
	Fecalibacterium Prausnitzii	down
Harmful bacteria	Escherichia coli	up
	Enterococcus	up
Conditional pathogenic bacteria	Bacteroides	up
	Clostridiumramosum	up
	Desulfovibrio	up

SCFAs are mainly produced by the fermentation of oligosaccharides, polysaccharides, peptides, proteins and glycoproteins by bacteria in the intestine. Acetic acid, propionic acid and butyric acid are relatively abundant. Common SCFAs producing bacteria include *Bacteroides, Clostridium, Bifidobacterium, Eubacterium, Streptococcus, Peptostreptococcus* and so forth **(Quantao *et al.*, 2019)**.

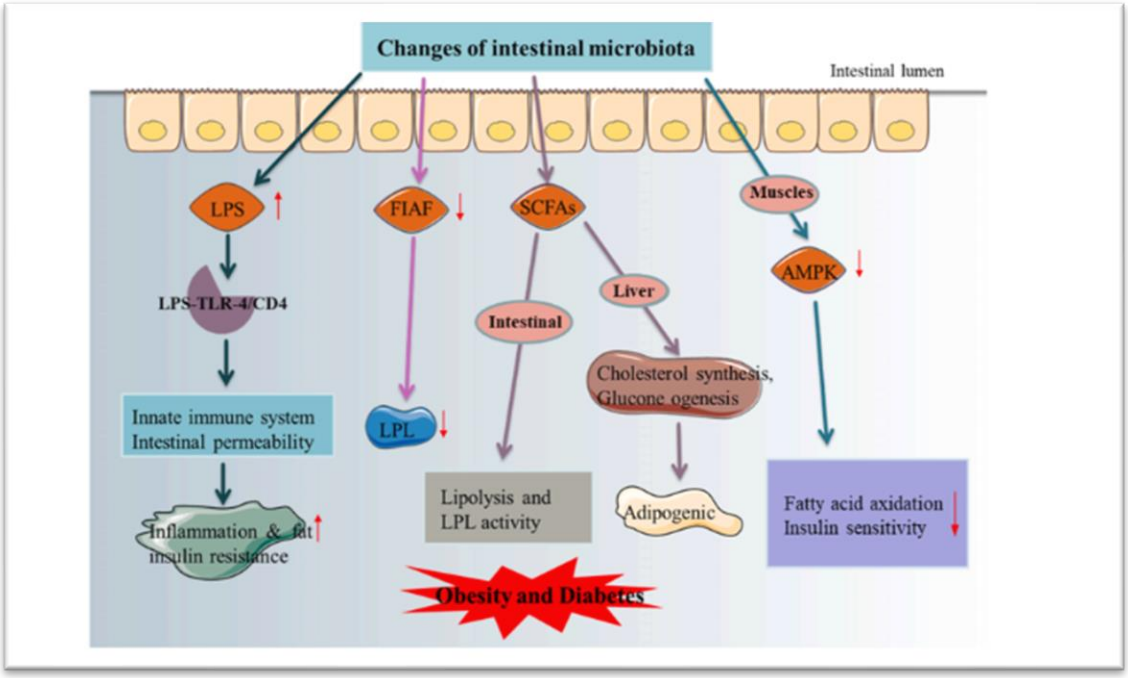

Figure 17: The main mechanisms of obesity and type 2 diabetes **(Song *et al.*, 2021)**.

Defciency of these intestinal flora can cause abnormalities in SCFAs**,** and the low levels of SCFAs**,** can promote the release of inflammatory factors by affecting the signaling pathways associated with macrophages and T cells, then leading to the intestinal inflammation, thus cause impaired islet cell function and insulin resistance.

The imbalance of intestinal flora leads to an increase in the proportion of G− bacteria, and LPS can bind to the CD14/Toll-like receptor 4 complex (CD14/TLR4), which causing a series of inflammatory reactions. The alteration of intestinal permeability, promotes the LPS into the bloodstream, causes low levels of chronic inflammation, and renders insuffcient insulin secretion.

Intestinal flora also affects the development of diabetes through bile acids. The intestinal flora acts as a regulator of bile acids and has an effect on bile acid production and metabolism. As signaling molecule, bile acids involve in the regulation of energy metabolism and inhibit the excessive proliferation of intestinal flora.

Intestinal flora converts primary bile acids into secondary bile acids, promotes activation of G protein coupled receptor 5 (TGR5) and farnesyl X receptor (FXR), and is of great importance in bile acid reabsorption and energy metabolism. Intestinal microbiota disorders cause bile acid formation and activation of its receptors to be blocked and triggers the development of T2DM **(figure 18) (Song *et al.*, 2021)**.

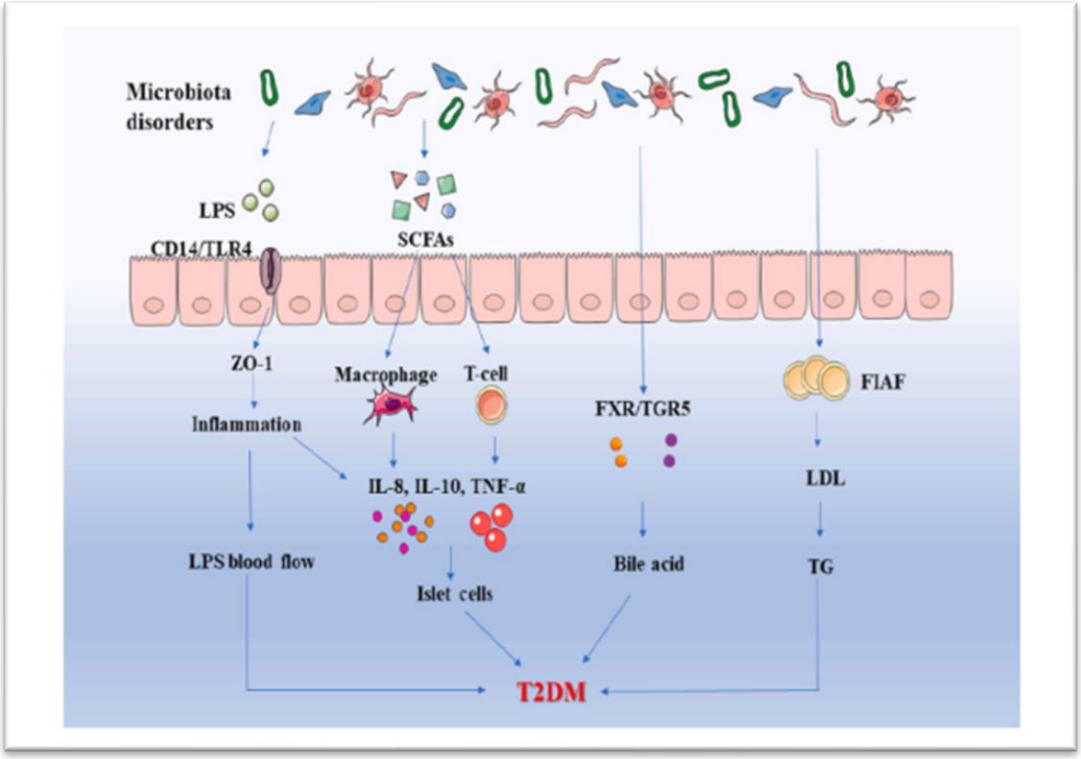

Figure 18:The mechanisms of type 2 diabetes due to flora disorders **(Song *et al.*, 2021)**.

IV.1.2.1.B. Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints which results in bone and cartilage damage, and even disability. However, much of its aetiology remains unknown and the gut microbiome has been suggested to play a role in its pathogenesis. Gut and oral microbiome dysbiosis were observed in RA patients and the alterations in microbiome were able to distinguish RA patients from healthy individuals.

Haemophillusspp were found in lowered abundance and were negatively correlated with serum autoantibodies level in RA patients. On the other hand, abundance of Lactobacillus salivarius was found to be elevated.

It has been shown that changes to the gut microbiome precedes the development of arthritis, and that it is possible to attenuate arthritis development via total elimination of the gut microbiome using antibiotics.

Abundance of intestinal Th17 immune cells is also highly associated with severity of arthritis, but is greatly reduced when the intestinal flora is eliminated, suggesting that the intestinal flora propagate inflammatory signals to promote arthritis development, possibly mediated by Th17 T cell immune response **(Ding *et al.*, 2019)**.

IV.1.2.2. Metabolic diseases

IV.1.2.2. A. Obesity

Obesity is tightly associated with specific diets and life styles, both of which can influence the composition of the intestinal flora. Thus, an association between changes in the intestinal flora and the development of obesity has been proposed **(Hao *et al.*, 2018)**.The flora diversity of obese individuals is signifcantly reduced among the obese and lean twins, and this difference of intestinal flora is closely related to the occurrence of obesity **(Turnbaugh *et al.*, 2009)**.

Transplanting human faecal microbiota from obese and lean twins to germ-free mice provided direct evidence that the gut microbiota modulates host metabolism to regulate body weight. The mice that received faecal flora from the obese twins had increased total and fat mass and showed obesity-associated metabolic phenotypes, something not observed in the mice receiving faecal flora from the lean twins **(Hao *et al.*, 2018)**.

The proportion of Gram-positive (G+) bacteria to Gram-negative (G−) bacteria is related to obesity, the obese individuals have an increased proportion of G+ bacteria and a decrease in the proportion of G− bacteria. Among them, the ratio of the *Firmicutes* and the *Bacteroidete*s is the most signifcant. The mice fed with high-fat diet are characterized by an increase in the proportion of the *Firmicutes/Bacteroidetes* (F/B). Correspondingly, the higher proportion of F/B in obese individual has also been observed in human study.

However, have found that the ratio of F/B in phylum was not directly related to obesity, but the proportion of *Bifdobacteria* was found to decrease after a diet that reduced carbohydrates.

In addition, the correlation of intestinal flora with obesity at the species level is more signifcant than that of the phylum. It has been found that the levels of Lactobacillus in the obese people changed signifcantly. Although the specifc relationship between flora and human obesity is inconclusive but there are indeed inextricably linked relationship between obesity and intestinal flora **(Song *et al.*, 2021)**.

IV.1.2.3. Cardiovascular disease

Regarding the cardiovascular complications associated with these metabolic disorders, intestinal florapromote the appearance of atherosclerotic plaques as well as their rupture **(Marie, 2020)**.In a metabolomic study of specific indole and phenyl-derived metabolites originating solely or partly from intestinal flora, it was concluded that specific microbe-derived metabolic signatures are associated with advanced human atherosclerosis and postoperative cardiac complications.

In particular, indole and indole-derived metabolites are associated with advanced atherosclerosis, whereas the kyn/trp ratio and the phenyl derivative hippuric acid are associated with post-operative major cardiac events and with major adverse cardiac events. These findings suggest the potential role of these metabolites as new biomarkers for atherosclerotic disease and highlights the imperative need for a better understanding of the mechanisms by which the intestinal flora and its derived metabolites contribute to the development of atherosclerosis.

The intestinal flora has also been shown to be associated with atherosclerotic cardiovascular disease (ACVD), characterized by an increase in abundance of *Enterobacteriaceae* and *Streptococcus spp*.

In addition, it was also observed that there was an association between thecopies of bacterial genes coding for trimethylamine-N (TMA) lyase and ACVD. TMA lyase is responsible for the generation of trimethylamine-N-oxide (TMAO), a gut microbiome-derived metabolite that has been shown to play a causal role in the development of ACVD in animal models and is highly associated in human studies, highlighting the key role TMAO may play in the pathogenesis of ACVD **(Ding *et al*., 2019)**.

IV.2. Mental and neurological health

Alink between the intestinal flora and the neuropsychiatric sphere has been mentioned in the appearance of many disorders. Indeed, interaction pathways exist between the brain and the intestine from metabolites produced at the intestinal level by commensal bacteria.

The flora also plays a role in the permeability of the blood-brain barrier preventing certain substances from passing through this level. An intestinal dysbiosis will therefore be at the origin of a dysfunction of the communication pathways between the intestine and the brain, of a possible accumulation of metabolites produced by the bacteria becoming toxic for the neuronal functioning and therefore of disorders at the level of the nervous system **(figure 19) (Marie, 2020)**.

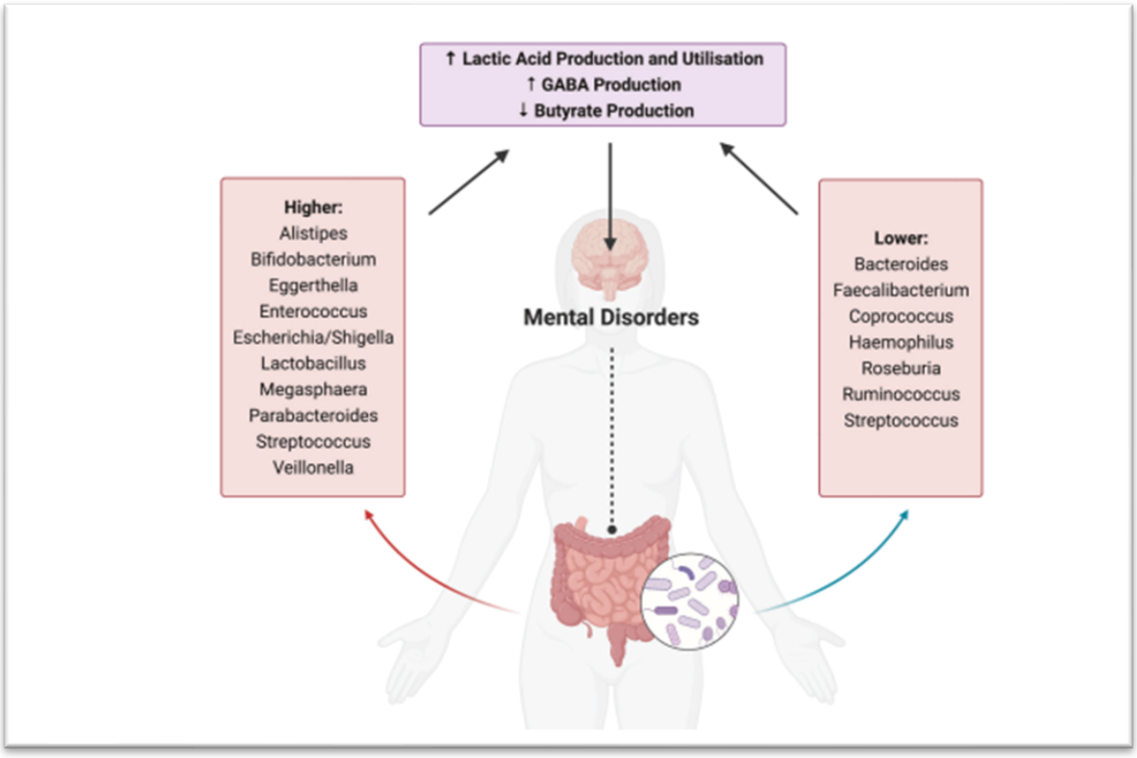

Figure19 : Potential functional implications of bacterial genera implicated as different in mental disorders **(McGuinness *et al*., 2022)**.

IV.2.1.Depression

According to the world health organization, depression causes major mental illness, affecting more than 300 million people globally (2017–2020). Depression, especially major depressive disorder (MDD), is the second leading cause of disability and the most commonly affective disorder diagnosed in millions of adolescents and adults worldwide within the age bracket of 15–44 years old**.**

Several clinical and pre-clinical studies have reported a causal link between depression and gut dysbiosis directly, which alters brain activities via GBA. The neural transmission (both the hypothalamus–pituitary–adrenal (HPA) axis and afferent fibers of the vagal nerve) was reported to be disrupted by gut dysbiosis directly associated with gut leakiness and local inflammation, which are in turn connected to anxiety and depression.

O'Mahony *et al*(2009) suggested that anxiety causes an HPA axis imbalance, leading to systemic immune responses and intestinal dysbiosisdirectly. Gut dysbiosis directly aggravates anxiety or depressive behavior and also causes cognitive impairment **(Sonali *et al*., 2022)**.

In human studies, evidence of changes in microflora composition explains depression. Patients diagnosed with mental conditions, including depression, have demonstrated gut

microbiome dysbiosis. The lack of bacterial microflora in germ-free (GF) mice reduced the immobile period in the forced swimming test compared to the healthy mice. The composition and diversity of bacteria between healthy and depressed patients showed significant disparity with the depressed group showing mostly *Firmicutes, Bacteroides*, and Actinobacteria in the intestinal. This supports how the gut bacterial content's dysbiosis changes the behavior of the host.

In recent years, neurobiological modifications have been related to the development of depression. Inflammation is one of the connections that leads to the modification process. It showed high levels of concentration of neurotransmitters in inflammation, and increasing psychological processes are noted **(Limbana *et al.*, 2020)**. the production of several neurotransmitters such as 5-HT, norepinephrine, GABA, and dopamine are directly regulated by intestinal flora.

The gastrointestinal tract contains high concentrations of 5-HT (and melatonin). Kim and Camilleri found that 90% of 5-HT is secreted by epithelial ECCs, with the remaining 10% from the ENS. Several microorganisms produce neurotransmitters, such as acetylcholine (e.g., *Lactobacillus plantarum*), dopamine (e.g., *Proteus vulgaris, Bacillus,* and Serratia marcescens), GABA (e.g., *Lactobacillus and Bifidobacterium)*, histamine (e.g., *Citrobacter and Enterobacter*), norepinephrine (e.g., *Saccharomyces, Bacillus*, and *Escherichia coli*), and 5-HT (e.g., *Escherichia coli, Enterococcus,Candida*, and *Streptococcus*).

Gut dysbiosis directly affects the synthesis of neurotransmitters such as 5-HT, dopamine, glutamate, noradrenaline, and GABA in the intestinal lumen, while vice versa alterations in these neurotransmitters affect the flora composition and abundance. The pathological mechanisms underlying intestenal dysbiosis-induced depressive symptoms include: altered intestinal flora composition, abundance, and metabolites, breakdown of the intestinal barrier integrity (reduced expression of tight junctions proteins such as claudin-5 and occluding inthe gastrointestinaltract), loss of goblet cells (resulting in reduced mucus secretion and thinning of the mucus layer), and translocation of pathobionts and toxic metabolites into the blood circulation, leading to chronic local and systemic inflammatory responses.

Intestinal dysbiosis can represent microbe-associated molecular patterns (MAMPs) that constitute bacterial products, including flagellin and LPS. MAMPs in turn stimulate NLRP3 inflammasome and NF-kB, which are recognized by pattern recognition receptors of the innate immune system, leading to the increased production of pro-inflammatory cytokines (e.g., interleukin (IL)-18, IL-1, IL-6, and TNF-α) and peptidoglycan metabolites.

LPS activates the toll-like receptor (TLR)-4 and peptidoglycan stimulates nucleotide-binding oligomerization domain-containing protein-1 and/or nucleotide-binding oligomerization domain-containing protein-2, which is linked to depressive behavior.

Further, LPS translocates from the gut to the brain via the leaky mucosal barrier and negatively affects brain functions by disrupting the blood–brain barrier with decreased levels of tight junctions and anchoring junction proteins in the frontal cortex, hippocampus, and striatum. These data indicate that gut dysbiosis affects neurochemical signaling and initiates the cascade of pro-inflammatory pathways, which are positively linked with depressive behaviour **(figure20) (Sonali *et al*., 2022)**.

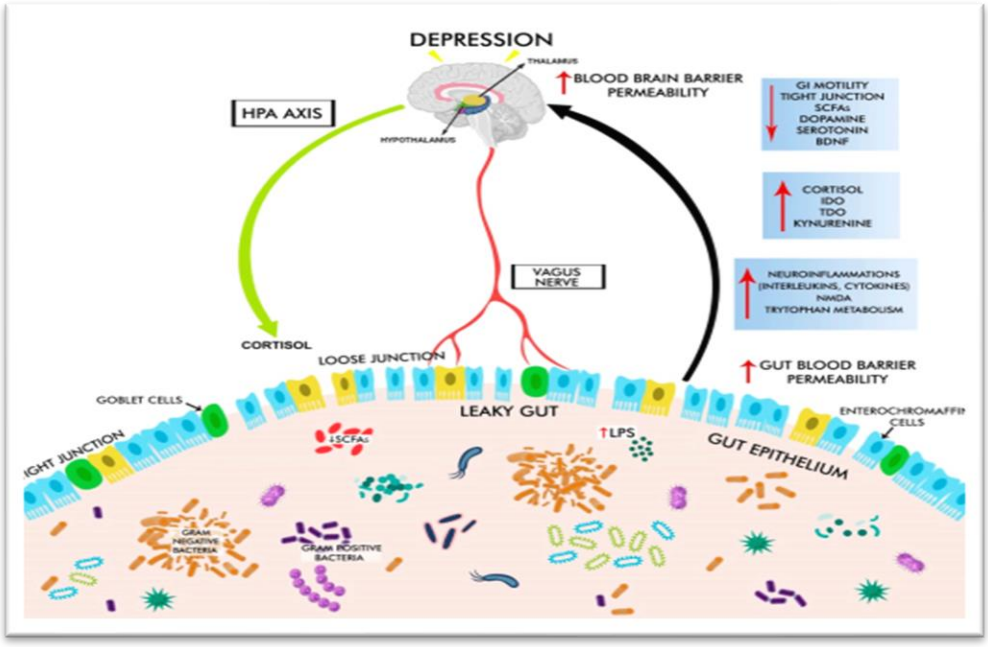

Figure20: The gut–brain axis and depressive disorder **(Sonali *et al*., 2022)**.

IV.2.2. Autism spectrum disorder (ASD)

Autism is a neurodevelopmental abnormality characterized by shortfalls in social communication, reiterative and obstinate behavior which leads to consequential loss in quality of life **(Mehra *et al*., 2022)**. Genetic and environmental factors play a role in the pathogenesis of ASD.

Although singlegene polymorphisms are effective in autism, autism does not occur without environmental factors**(Ekmekçi et Erbas, 2020)** .Therefore, in addition to genetic factors (combination of autism related genes), specific environmental factors (maternal infections, dietary factors, gut dysbiosis, exposure to pesticides, stress, medications, antibiotic consumption during pregnancy) might act as risk factors that can trigger the development of autism **(Mehra *et al*., 2022)**.

The recent finding of the microbiota–gut–brain axis indicates the bidirectional connection between our intestenal and brain **(Taniya *et al*., 2022)**.thus, any alteration in composition can inturn perturb the coordination between gastrointestinal microflora and brain **(Mehra *et al*., 2022)**.

Autism is seen in children who cannot cope with environmental problems due to their genetic tendencies, as a result of a series of mechanisms. Therefore, these environmental factors in autism, the intestinal flora (microbiota) is differentiated. Differentiated microbiota led to gastrointestinal symptoms in individuals with autism **(Ekmekçi et Erbas, 2020)**.Most autistic patients suffer from gastrointestinal (GI) symptoms, like constipation, abdominal pain, diarrhea, and vomiting **(Taniya *et al*., 2022)**.

In addition, almost all children with autism do not have a normal intestinal flora **(table03) (Ekmekçi et Erbas, 2020)**.

Table 03: Effect of different microbes in autistic patients **(Mehra *et al*., 2022)**.

Name of microbes	**Microbial level in autistic patients**	**Effect in autistic patients**
Proteobacteria	Increases	It caused host inflammation and reduction in levels of GSH. It also led to the production of LPS which is the majorcause of immune dysregulation in autism.
Bacteroides	Increases	It produces short chain fatty acids and their metabolites especially propionic acid which may influence autism behavior by gut brain axis.
Clostridium	Increases	It produces endotoxins and propionate that may be associated with severity of ASD symptoms.
Faecalibacterium prausnitzii	Increases	It produces anti-inflammatory butyrate which is regarded as commensal or even beneficial in children withautism.
Candida albicans	Increases	It results in absorption of carbohydrates and releases ammonia which leads to excess of GABA production that can

		lead to the appearance of autistic behavior.
Bifidobacterium	Decreases	Bifidobacterium synthesize GABA, as its level decreases in autism so children with autism have low levels of GABA.
Blautia	Decreases	This bacterium has role in synthesis of Tryptophan and bile acid that acts as a precursor of Serotonin. Hence, its lower levels leads to less serotonin in brain and can be correlated to autistic behavior.
Prevotella	Decreases	Involved in metabolism of saccharides due to which autistic patients are thought to have impaired Carbohydrate metabolism.

The gut-brain-axis is regarded as the biochemical bidirectional signaling that takes place between the gut and the brain acting through the neuroendocrine system, neuroimmune system, hypothalamic pituitary-adrenal (HPA) axis, sympathetic and parasympathetic nervous system, the enteric nervous system (ENS) and vagusnerve **(Mehra *et al.*, 2022)**.And toxin production of the flora **(Ekmekçi et Erbas, 2020)**. Stool samples that obtained from children with ASD revealed higher levels of Clostridium histolyticum compared to samples from healthy unrelated children **(Ekmekçi et Erbas, 2020)**.

This specific strain of bacteria produces tetanus neurotoxin (TeNT), which passes through the vagus nerve to the Central Nervous System (CNS) and blocks neurotransmitters by the proteolytic cleavage of synaptobrevin, a synaptic vesicle membrane protein, and precipitates a whole range of behavioraldeficits **(Taniya *et al.*, 2022)**.In addition, intestinal dysbiosis has occurred in children with autism **(Ekmekçi et Erbas, 2020)**.

The main factor underlying the relationship between ASD and the intestine is the increased permeability of the intestinal tract of individuals with ASD, and this is referred to as leaky gut According to the leaky gut hypothesis, the permeability of the mucosal barrier increased with reduced tight-junction activity. Since the function of intestinal cells is impaired, vitamins, minerals and other nutrients related to carrier proteins cannot pass into the blood sufficiently **(Ekmekçi et Erbas, 2020)**.

Moreover, literature showed that flora intestenal exerts its action on the brain through its influence on production and expression of neurotransmitters like serotonin, gamma-Aminobutyric acid (GABA) and sensory afferents, production of various bacterial metabolites and mucosal immune regulation.

On the other hand, theCNS exerts its action on intestinal through metamorphosis in mucous and biofilm production, modulation in the motility of gastrointestinal tract (GIT), alteration in the equilibrium of intestinal permeability and reorganization in immune functions **(Mehra *et al*., 2022)**.

The intestenal-brain-flora axis plays a major role in the pathogenesis of autism in different ways. Primarily and most prominently by contributing to the maintenance of intestinal permeability and the formation of leaky intestenal in autism due to alteredflora.

Secondly, microorganisms play a role in the maturation of the immune system and dysregulation in autism leading to dysregulation of the immune system. The activated immune system releases chemicals and cytokines such as interleukin-1b (IL-1b), interleukin-6 (IL-6), interferon-g (INF-g), tumor necrosis factor-a (TNF-a) that cross the blood brain barrier (BBB). These mediators bind to endothelial cells of the brain and stimulate immune responses in the brain.

Ashwood *et al* (2011) have found a significant increase in plasma cytokine levels in children with autism spectrum disorder. Reports indicate that autistic patients had an elevated abundance of *Proteobacteria, Lactobacillus, Bacteroides, Desulfovibrio,* and *Clostridium,* while their levels of *Bifidobacterium, Blautia, Dialister, Prevotella, Veillonella*, and *Turicibacter* were consistently lower. *Proteobacteria* that are abundant in the gut of autistic patients are associated with host inflammation.

Studies have indicated that *proteobacteria* produce LPS which can reduce the level of glutathione (GSH) in the brain, an antioxidant. Another important flora intestinal is *Bacteroides* which are the main producers of propionates in the intestenal and the abundance of propionate in the stool correlates strongly with the abundance of *Bacteroides* in patients with autism **(figure 21) (Mehra *et al*., 2022)**.

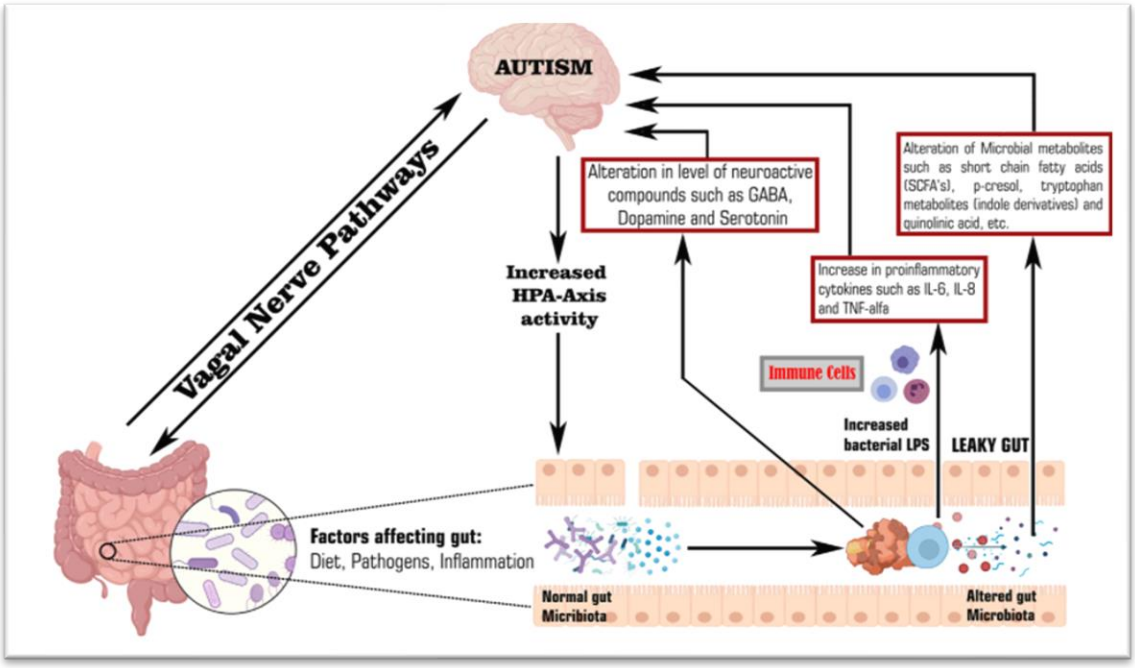

Figure21 : Potential relationship between intestinal dysbiosis, its metabolites and autism**(Mehra *et al*., 2022)**.

Conclusion

The human intestinal flora is a set of microorganisms living inside the digestive tract intestinal flora play a fundamental role in the maintenance of the body consisting mainly of bacteria, to which is added the presence of viruses, yeasts and protozoa, this complex ecosystem occupies an important and recognized place in human health. Its composition is generally stable over time for the same individual. However, certain factors can induce

The primary agency for entrance intestinal flora into the body is food. They will take up permanent residence and when they multiply, they will colonize the intestine and form that organ's flora. The activity of intestinal microorganisms is beneficial to the body in a variety of ways. Due to their large numbers, intestinal microorganisms perform an enormous amount of detoxification work. This work is estimated to be on a par with that of the liver, which is known to be the most powerful organ in the body when it comes to detoxification. Intestinal flora, therefore, offer the body "a second liver" so that it can clean and purify itself.

Intestinal microbiota is the largest immune organ in the human body. Metabolic, immune, cognitive and psychiatric diseases could be the consequence of an alteration of this flora and its functions. the interaction between the intestinal flora and the mucosal immune system, promotes host metabolic balance and serves as a biological defense against infectious agents.Intestinal flora promotesthe maturation and regulation of mucosal and systemic immune systems through innate and adaptive

immune cells. The intestinal flora is essential for the development of the innate and adaptive immune system of the intestinal mucosa, as well as its response to pathogens. The innate immune system provides immediate, but not long-lasting defense against infectious agents.

The intestinal flora plays a significant role in both health and disease. Increasing evidence suggests that intestinal flora dysbiosis would lead to a number of diseases, including gastrointestinal disorders, obesity, cardiovascular diseases , and CNS-related diseases , which affect a large population in the world.

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