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Review Article

Gut Microbiota Dysbiosis: The Impact on Carcinogenic Processes and the Influence of Helminths

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Abstract

Carcinogenic diseases are a worrying and challenging matter in the Modern world since these are such fast-growing and impactive diseases to the human body. Emerging data have been linking the gut microbiota with both health and disease. This way, a healthy individual is associated with a balance in the microorganisms harbouring our gut and when the normal balance is disrupted - dysbiosis- the immune system becomes susceptible to pathogenic invasions. Internal and external factors, as well as different lifestyles and pathogenic microorganisms, due to the potential of modulating the gut microbiota, have been immensely studied in attempting to prevent and avoid cancer progression.

Although helminthic parasites have co-habited our intestines, they are associated with a diversity of immunomodulatory mechanisms that affect the host's immune response, in order to ensure their persistence within the body. Moreover, these parasites can also modify the microbiota structure which can, possibly, lead to a state of dysbiosis, making the host more vulnerable to inflammatory, autoimmune, and malignant disorders.

The gut microbiota has been known to have a major potential when it comes to preventing diseases and their development, showing evidence of being a very promising and effective therapeutic target. Several established methods can alter gut microbiota, such as Faecal Microbiota Transplantation (FMT), prebiotics, probiotics and targeting the tumour microbiota itself. These, when used as anti-cancer therapies, help restore the gut previously damaged or, in some cases, even protect the host from developing these deadly and incapacitating diseases.

Keywords: *Gut Microbiota; Modulating Factors; Dysbiosis; Helminths; Cancer*

Abbreviations

AHR: Aryl Hydrocarbon Receptor; BC: Breast Cancer; BE: Barret's Oesophagus; CRC: Colorectal Cancer; FAO: Food and Agriculture Organization; FDA: Food and Drug Administration; FMT: Faecal Microbiota Transplantation; GIC: Gastrointestinal Cancer; HER2: Human Epidermal Growth Factor Receptor Type-2; HGM: Human Gut Microbiota; IL-22: Interleukin-22; IMT: Intestinal Microbiota Transplantation; OEC: Oesophagus Cancer; PC: Pancreatic Cancer; PDAC: Pancreatic Ductal Adenocarcinoma; ROS: Reactive Oxygen Species; STH: Soil-Transmitted Helminths; TLR: Toll-like receptors; TNF: Tumour Necrosis Factor; WHO: World Health Organization

Introduction

Humans are known to be colonized by a wide range of non-pathogenic bacteria, viruses, fungi and eukaryotic parasites which exchange mutual interactions between them, and also with the host themselves [1,2]. The Human gut has been a challenge to the scientific community mainly due to its complexity and multifaceted networks established in the body [3]. Although Humans are harboured by a diversity of microorganisms, only some individuals suffer from cancers [3]. Cancer is one of the main health problems worldwide, being the third leading cause of death in the world [4]. Therefore, external factors such as diet, antibiotics usage, type of infant delivery, feeding method, age, host genotype and many other risk-driving aspects are believed to be responsible for the process and development of carcinogenesis, since they can modulate the microbiota and how well our immune system will react.

A healthy individual's gut microbiota is acknowledged to provide several benefits to the host, such as immune modulation, pathogen protection, nutrition, and metabolism regulation, among others and is mostly dominated by *Bacteroidetes* and *Firmicutes* [5]. However, when the normal balance is disrupted - Dysbiosis- the immune system is susceptible, increasing the host's susceptibility to certain diseases. This way, the host microbiota is more vulnerable to attacks by pathogenic microorganisms, possibly leading to negative outcomes [4,6].

Since the beginning of time, both helminths and bacteria have co-habited our intestines, establishing relationships and impacting with, and on each other. Although helminths currently infect around 2 billion people, nearly one-third of the World's population, only a few species are prevalent in Humans [7]. Among all the species of helminths inhabiting the gut, most mammals are often colonized by soil-transmitted helminths (STH). These parasites are known for their demarked immunoregulatory activity, having the ability to easily modify the gut microbiota structure, colonizing this organ and persevering among different populations of microorganisms [2,8].

During the past few years, the gut microbiome has also been strictly correlated with either, health or disease, particularly cancer diseases, due to microorganisms' involvement in carcinogenesis [9]. Furthermore, evidence also suggests that dysbiosis not only increases the risk of gastrointestinal tract malignancies but in other organs too, being breast cancer as one of the main examples [4].

In this review, I aim to particularly focus this discussion on the impacts gut microbiota dysbiosis can have on our health, directing to an important current concern, cancer diseases and their processes, as well as efficient therapies directed to modulate gut microbiota.

Gut microbiota: The human fingerprint

It is often said "We are what we eat" and this sentence was never more accurate than these days, as our health and even, maybe our mood and behaviour depend not only on what we eat but, also on what we host [1]. Back in the fourth century BC Hippocrates, named the father of medicine, stated "All the disease begins in the gut" and little did they know how right and how important that finding came to be [6].

Microbiome and microbiota are two terms often used interchangeably and usually confused. However, they do not mean the same as microbiota refers to all microorganisms found in an organ environment, including bacteria, viruses, and fungi. On the other hand, the microbiome refers to the group of microorganisms and their genome within each environment or organ [10].

Early findings came to prove the previous establishments that healthy humans remarkably differ in the types and respective amounts of the microbes they colonize in different habitats, such as the gut, oral cavity, vagina, respiratory tract, and skin, among many others. Among them, the gastrointestinal tract retains the biggest amount and more diverse number of microorganisms, with, at least, 10^{14} bacteria, making a total of one kilogram. Although there are many bacterial species shared by most humans, developed technology has shown "large interindividual microbial diversity" [5]. Being said this, the human microbiome is frequently referred to as the "second human genome" [1].

What is it and how is it composed?

For many years, thanks to faecal and metagenomic studies, it has been established that Humans are colonized by a wide range of non-pathogenic bacteria, viruses, fungi and eukaryotic parasites which exchange mutual interactions between them, and also with the host themselves [1,2]. This way, all these microorganisms represent our microbiota, differing in composition, according to the body organ [4]. Among all the many microbes (over 100 trillion microbial cells [5]) that live in our body, authors say the major phyla, out of the 5 that colonize our body, with more than 1000 different species of bacteria (some of them described in table 1), are *Bacteroidetes* (Gram-negative bacteria). Right after comes the *Firmicutes* (Gram- positive), *Actinobacteria* (genera *Bifidobacterium* as one of the examples), *Proteobacteria* (with the genera *Escherichia* and *Enterobacter*) and, to a lesser extent, *Verrucomicrobia*, combining a total of several million genes living in our body. A substantial number of fungi also inhabit the gut microbiome, making a total of 66 fungal genera and 184 fungal species [1,6,11]. The structure and composition of the microbiota are key factors for the host immunity, when facing certain environmental factors, such as attacks by pathogenic microorganisms [2].

Bacteria	Role in Human Body
Bacteroides spp.	Involved in immunity by activating CD4+ and T cells. These can include both non- pathogenic and opportunistic human pathogens.
Bifidobacterium spp.	Some species are used as probiotics due to their gut mucosal barrier improvement, production of short-chain fatty acids and decrease of lipopolysaccharide levels
Enterobacteriaceae	This family includes symbionts and pathogens such as *Salmonella, Yersinia pestis* and *Shigella*
Escherichia coli	It can activate Toll-like receptors (TLR)
Helicobacter pylori	Known by causing peptic ulcer disease and gastric cancer
Lactobacillus spp.	Some species are used as probiotics, and it produces short-chain fatty acids. Moreover, it plays a role in anti-cancer and anti-inflammatory processes.
Prevotella spp.	This species may cause anaerobic infections of the respiratory tract
Staphylococcus spp.	These bacteria reside normally on the skin and mucous membranes in humans are responsible for several common infections
Streptococcus spp.	Some of these can cause scarlet fever, heart disease and pneumococcal pneumonia

Table 1: *Roles of certain human gut bacteria (Adapted from 6).*

Homeostasis - The importance of a healthy gut

The Human Gut Microbiota (HGM) of a healthy individual is acknowledged to provide several benefits to the host, such as immune modulation, pathogen protection, nutrition and metabolism regulation, among others [5]. This way, when the gut is balanced, *Bacteroidetes* and *Firmicutes* dominate. However, a disturbance will lead to a decrease in these bacterial communities, as well as an increase in some others [4]. It is crucial that the structure of the microbiota remains unaltered since it is a vital factor for the host immunity [2].

Being such an important metabolic "organ" in our body, the intestinal microbiome has established strict relations with the host and, when an alteration happens, major consequences, either beneficial or harmful can affect the host [5]. Disrupting the normal microbiota balance may impact the immune system, increasing the host's susceptibility to certain diseases. Consequently, it may lead to a negative outcome when facing an intestinal pathogen. At this point, an imbalance in the gut microbiota structure is instituted - Dysbiosis [2].

Influence and modulating factors

Although the habitants of HGM remain, more or else, stable over the years, some factors may alter this balance and, consequently, the host becomes more vulnerable to negative outcomes. As said before, the microbes that harbour our intestine are quite different, either in terms of species or also in number, from the ones who live in other parts of our body, for instance, the colon has more than 10^{14} microbes whereas there are only 10^4 in the small intestine [1]. Some key factors, for instance, age, sex, type of infant feeding, delivery method, ethnicity, usage of antibiotics and other pharmaceuticals, can easily modulate and influence our gut microbiome and how well our immune system will react [6]. This way, colonization and persistence of pathogenic microorganisms are facilitated, generating toxic products known to be part of a diversity of chronic and degenerative disorders [2].

Age and host genotype

The intestinal gut is extremely diverse and changes over the years, between individuals and even in each intestine area [2]. Over time, the infant's gut tends to stabilize and, by the end of its first year, it starts to look like the adult gut, becoming even more complex and developed around the age of seven [6,12]. A study using germ-free animals suggests that ageing is usually associated with a "shift in microbiota profile", leading to low levels of *Firmicutes* bacteria and increasing bacteria in the phylum *Proteobacteria*. This loss was associated with fragility intensification in the ageing population [1]. Furthermore, some factors such as usage of pharmaceuticals, swallowing difficulties and digestive problems, may also affect the gut microbiota, when combined with the ageing process. Also, elderly microbiota gradually becomes less diverse, characterized by chronic low-grade inflammation - "inflammageing" [5]- which can lead to an easier pathogenic invasion due to the reduced amount of bacterial species [6,13].

The genetics of each individual is also known to have a significant impact on the composition of the microbiome, which will lead to a unique microbiota phenotype. Interconnecting these two factors, age and genetics, gut microbiota in older people seems to differ with the individual's nationality, for instance, *Bacteroides* are increased in German, Austrian and Finnish while Italian seniors do not share the same data [6]. Mutations in certain genes may also influence how our gut is expressed, possibly increasing the risk of some diseases. However, some studies claim that environmental factors might have a higher impact than genetics when it comes to shaping the microbiota profile [6,13].

Infant delivery and feeding method

New-born babies have, according to some authors, a sterile gut or, at most, containing a very low level of microbes which is immediately colonized after birth [5]. At this point in life, the number and diversity of microorganisms existing in the gut are much different from the adult ones. Within the first year, the microbiota remains fairly stable and then it is rapidly dominated by anaerobic *Firmicutes* and *Bacteroidetes* [1], replacing bacteria from the phyla *Actinobacteria* and *Proteobacteria*. Aspects such as delivery mode, formula-feeding vs breastfeeding, antibiotic treatment, hygiene, geography, genetics, and dietary habits, among others, may affect the composition and diversity of the microbiota, having an impact on the definite HGM and, therefore, on how well the body will react when facing future disorders [1]. On one hand, when it comes to vaginal delivery, the new-borns microbiota is formed within 20 minutes of birth, through the maternal vagina or faecal microbiota. Saying this, the most abundant bacteria in the infant's gut will be *Lactobacillus, Prevotella* and *Sneathia* [12]. In addition, *Lactobacillus* is known to be a catabolic agent of the amino acid tryptophan into its metabolite, a ligand to the aryl hydrocarbon receptor (AHR). This last one is expressed by innate lymphoid cells and, when activated can induce the expression of interleukin-22 (IL-22). Furthermore, IL-22 activates antifungal resistance, protecting the host's intestinal mucosa from inflammation [4].

On the other hand, a caesarean delivery will provide the newborns with a similar microbiota to the hand skin, touching them after birth [14]. In this case, the bacteria with the most abundance are *Staphylococcus, Corynebacterium*, and *Propionibacterium*, suffering a shift and being dominated by *Proteobacteria* and *Actinobacteria* [1,6,12,15].

When the progenitress chooses to breastfeed the newborn, the right microbes will be established in the gut, helping to set a correct microbiota maturity due to the production of sialylated milk oligosaccharides, able to ease the microorganisms to colonize the gut and supplying the new-born with defences for life [1]. After that, the inclusion of solid foods, after the first year of life, will result in a more complex and stable gut microbiota, similar to the adult one [6,16].

Treatments with antibiotics

These substances usually act by inhibiting the death of microorganisms when a bacterial disease is affecting our body. However, it is not possible for them to differentiate the pathogenic microbes from the ones that are extremely needed for our immune defence. Thus, antibiotics may cause depletion of the gut microbiota, leaving it susceptible to new infections and even more dangerous consequences, especially when it has been verified an increase in antibiotic therapy [6]. Animal studies came to prove, after antibiotics usage that gut microbiota may take a while to come back to its regular profile. Adding to this, a prolonged treatment is relatively capable of dysregulating the normal form and it may not the microbiota to return to its normal [1]. A five-day antibiotic treatment may lead to four weeks of recovery to restore the normal gut microbiota, while some taxa may need six months to have the levels back to normal, seriously reducing the diversity and/or abundance and influencing the gut's composition [6].

Diet

It is claimed that diet is the factor with the highest impact on the composition and diversity of the HGM. It is also sustained by the fact that the microbiota in malnourished humans substantially differs from a well-nourished one. As stated back in 431 BC, by Hippocrates, "Let food be the medicine and the medicine be the food", food was already known to affect our life. Several microbial communities play a significant role in every step of human digestion processes, as well as nutrient extraction, making the gut microbiota a key component of our normal function. A healthy diet, with increased consumption of plant foods and limited intake of meat, will help set up a healthy gut microbiota. This way, the nutrients provided are altered by the microbes harbouring our gut, releasing numerous other nutrients that the human body is incapable of digesting [9].

Furthermore, diet significantly influences the host immune system and, therefore, the response to a possible attack of pathogenic microorganisms. Recent data based on epidemiological and experimental studies point out that alterations in the dietary regime, microbiome and immunity are also connected to the increased number of adversities, especially in obesity and chronic inflammatory conditions such as type 2 diabetes, atherosclerosis and cardiovascular diseases [1].

The gut microbiome of vegetarian-based diets has been observed to have some differences from the omnivores, indicating the association between the gut composition and the dietary type chosen by the host. On one hand, not only this type of diet affects the HGM, but also people who consume high protein and animal fats are mostly inhabited by *Bacteroides* while, on the other hand, high carbohydrate diets and simple sugars show a bigger amount of *Prevotella* in the gut. Furthermore, *Firmicutes* and *Proteobacteria* have higher expression in the gut of overweight and obese people, while the levels of *Bifidobacterium* are decreased. Therefore, it has been scientifically proved that our gut microbiome profile can easily be changed by unhealthy food consumption if left with no attention and for long periods of time, leading to an increased susceptibility to some diseases.

Dietary choices, such as a vegetarian or vegan diet and even the Mediterranean diet, rich in fruits, grains and vegetables, have been found to influence the composition of the gut microbiota, altering the amount and species of bacteria harbouring our gut [6]. The "Western diet" approach, low in dietary fibre but, rich in animal protein as well as saturated fatty acids, is known, not only, to result in the loss or increase of several types of bacterial, but also to decrease the stability and diversity, indicating a possible unhealthy gut microbiota [6].

Roles in our body

Our gut microbiota, a "complex bacterial community", plays a very important and remarkable part in digestive processes, metabolism, vitamin synthesis and an intimate connection to the host's immunity, being able to reach the entire host organism [2,4]. Likewise, HGM has a very well-known role in the development and education of the immune system, as well as being part of neurological disorders, host perception, behaviour and emotional response, according to some recent evidence [1,11]. However, some studies have been showing that gut microbiota may also lead to autoinflammatory disorders and gastrointestinal conditions, such as obesity and inflammatory bowel disease [5] when the normal balance is disturbed [17].

It is estimated that HGM is colonized by 10^{13} - 10^{14} microorganisms/mL of luminal content, with a total estimated weight of 1.5 kg [6]. There is no surprise these microbes have the power to supply the host with a significant metabolic impact and that the microbiota is also capable of modulating "tissue integrity and immune defence". These factors will lead to a healthy and balanced ecosystem - symbiosis- which is not in favour of pathogenic invaders [1].

Due to the wide range of roles played by the gut, when facing a dysbiosis situation, essential compounds for stronger human health, such as vitamins, amino acids and even neurotransmitters and neuropeptides, are crucial for a vigorous protective function, may put our future defences at risk, leaving the host more vulnerable to diseases [4,6].

Interactions between the host and microbiota

A new finding was able to connect the influence of the microbiota on neurological pathologies, affecting brain behaviours via gut-brain axis or through "metabolic-by products" and bioactive mediators or "hormone-like neurochemicals". This discovery is not completely accepted by the scientific community as scientists are sceptical to accept the possibility microbes and gut microorganisms can have a significant impact on our minds and behaviours [1]. Emerging research state a possible impact of the microbiota on several human diseases, claiming to exist some achievable "microbiota-based strategies", capable of improving these health conditions. Nevertheless, it is not confirmed the unbalanced gut microbiome is fully capable of leading to some health disorders since there is not enough data on these facts, especially in humans [1]. Moreover, recent data linked Human health with microbiota diversity, while some disease states derive from a less diverse bacterial community [5,11].

On one hand, HGM is a crucial feature in our health and immune defence, on the other hand, it may have a significant effect on metabolic and autoimmune diseases, pathologies affecting the nervous system and, more seriously, it can impact the development and progression of cancer disease. The link between metabolic, as well as psychiatric diseases, with gut dysbiosis, is well-known by the scientific community, whereas a lot of studies are still needed to fully understand the correlation with cancer processes [6].

Helminth infections - How do they affect the gut?

Since the beginning of time, both helminths and bacteria have cohabited our intestinal microbiota [17], establishing relationships and impacting with, and on each other. Although a lot of advances have been made in this field, the impact of helminths in this interaction is still unexplored. It has been proved the association between intestinal helminths and their immune- modulation behaviour, nonetheless, it is less known whether this activity demands interaction with intestinal bacteria [11]. Even though the regulation of host immune responses by helminths is subtle, it can be powerful and harmful to the host, since some pathways of immune activation are suppressed such as dendritic cells antigen presentation and B-cell antibody production [7].

It is essential to highlight that scientists are starting to look at the gut as a complex community, where there's an indistinctive interaction between the host, microbiome and helminths [11].

Although these parasites currently infect around 2 billion people, nearly one-third of the World's population, only a few species are prevalent in human subjects. Even though helminths tend to localize themselves in a range of tissue and intestinal areas, they usually do not multiply once inside the host. However, they can still produce eggs or larvae to infect new hosts [7].

Helminth parasites, due to their demarked immunoregulatory activity, just like some intestinal bacteria, can easily modify the gut microbiota structure, colonizing this organ and persevering among the different populations of microorganisms [2,8]. However, some species inhabiting the gut may be able to deactivate the helminth colonization [18]. Besides, certain bacterial compositions existing in the microbiota are capable of blocking helminth colonization or, in some cases, preventing their persistence in case of colonization [2].

Recent trials using stool and blood samples, some of them after a three-month albendazole treatment and comparing groups of people, both infected and uninfected with helminths, suggest substantial differences in the relationship between the intestinal microbiome and its respective immune response [17]. It has been indicated that intestinal helminths might be able to modulate and influence the host's immune responses, working along with the gut microbiota [17]. Nevertheless, these findings still need more information to sustain, remaining, so far, as just a hypothesis.

As mentioned before, a complex and interconnected community, between the intestinal parasites and the bacteria harbouring the environment, is formed. Any slight changes in this balance will impact the host's immune response. This happens as their function is to metabolize substrates and generate products that affect one another. Moreover, helminths keep secret molecules able to change the structure and, as a consequence, disturb the healthy gut microbiota [2].

Soil-transmitted helminths (STH)

Among the thousands of species of helminths inhabiting our gut, most mammals are often colonized by STH, which live, as adults form, for prolonged periods (1 - 2 years). STH, although rarely kill, can easily affect human health, due to malnutrition, culminating in "growth retardation, vitamin deficiencies and poor cognitive function". Some helminths can even lead to anaemia situations [19], as well as adverse physical and cognitive developments in childhood [20]. Not only STH but most helminth species can establish long chronic infections, lasting up to 20 years. This way, several functions of the immune system are modified and dysregulated, facing a state of "immune hypo responsiveness" or, in other words, immunologic tolerance [7].

Besides, according to several studies, STH are known to "suppress host immunity", establishing chronic infections and, as a consequence, impacting future responses to other microorganisms [11]. Under the STH classification, the intestinal parasites included are *Ascaris lumbricoides, Trichuris trichiura* and the hookworm species, *Ancylostoma duodenale* and *Necator americanus* [20]. Although STH may have a heterogeneous distribution, they are highly prevalent in "low-income countries" due to a lack of access to clean water and hygiene [20]. STH's eggs are excreted through the faeces of infected hosts when it's not used a decent sewer system (for example when people defecate in gardens or fields), depositing the eggs on soil [20]. These intestinal parasites don't require third parts or vectors, which make the eggs able to be transmitted directly through food preparation when sufficient hygiene conditions are not verified. It's recommended that possible contaminated vegetables by dirt are carefully washed, peeled and cooked to prevent ingestion of infectious eggs of Ascaris and Trichuris and keeping the host safe from infection or even reinfection [20]. Although these parasites share similar features in their life cycle, their behaviour outside the host may differ significantly [20]. Initially, the eggs suffer a period of maturation, 2 - 3 weeks, becoming infectious after that. Moreover, *Ascaris* and *Trichuris* eggs can remain active in the soil for several months, whereas hookworm eggs will hatch into larvae form, being able to survive for weeks, without a host (Figure 1) [20].

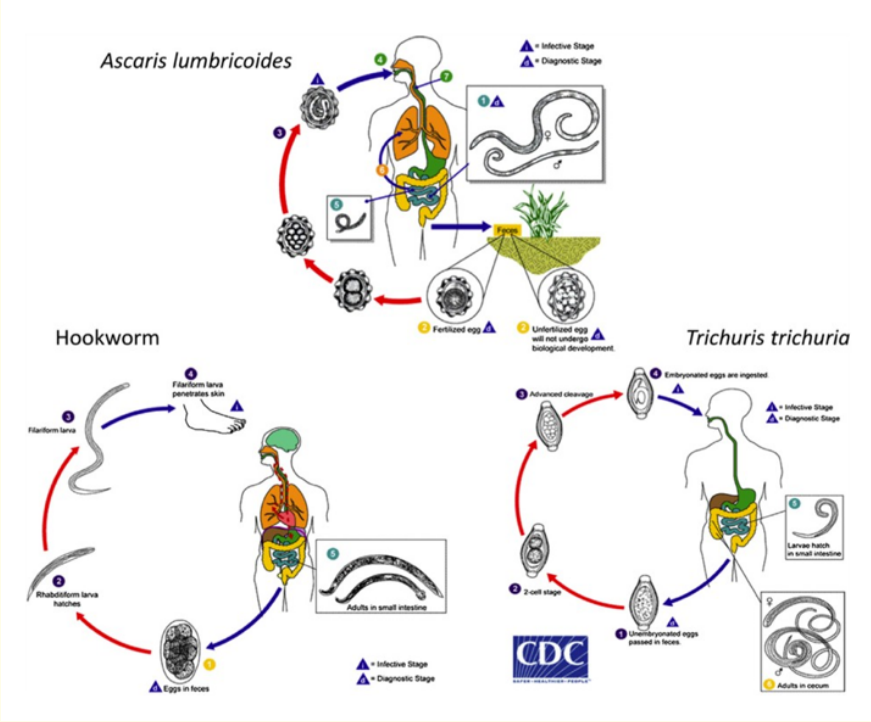

Figure 1: *Schematic life cycles of Ascaris lumbricoides, Trichuris trichuria and Hookworm (Adapted 20).*

Gut dysbiosis and cancer development

Researchers have been linking cancer development with gut microbiota since carcinogenic processes are strongly related to immune response. A disturbance in the species that harbour our gut, is suggested able to increase the risk of inflammatory, autoimmune, and malignant disorders [4]. Being said this, when the gut microbiota is intact and unaltered, studies have been showing evidence that microbiota-driven innate immunity activation, via regulation of CD4+, CD8+ and T-cells, acts as a sensor and inducer of reactions, much needed to defend the host, both locally and systemically. On the opposite side, when facing a dysbiosis scenario, the imbalanced gut microbiota gives rise to self-reactive T-cells, capable of potentially inducing inflammatory processes and carcinogenic effects [4]. Bacteria were detected in human tumours more than 100 years ago. However, the tumour microbiome characterization is not yet completely developed, being even a challenge for researchers, due to its low biomass [21].

During the past few years, the gut microbiota has also been strictly correlated with either, health or disease and the same situation is true for cancer diseases, due to microorganisms' involvement in carcinogenesis and "cellular dysplasia". It has been proved that a dysbiosis of the gut microbiota is the genesis and contribution of carcinogenic processes [9].

However, the mechanisms through which dysbiosis may affect the tumour growth or even its microbiota - adenoma or cancer-associated microbiota - are not yet fully understood, it is only known that the adenoma is significantly different from the surrounding microbiota. Additionally, evidence has been proving that microorganisms, like helminth parasites, confer susceptibility to certain cancers, either directly by harbouring the tumour environment or via systemic impact through the gut microbiota [9].

Evidence also suggests that dysbiosis not only increases the risk of gastrointestinal tract malignancies but in other organs too, such as breast cancer, lung cancer and adult T-cell leukaemia [4]. A shift in the normal inhabitants of the intestinal gut will allow "unwanted" ones to take advantage, leading to pathogenic reactions. These can induce different forms of cancer processes in numerous organs, according to 3 different pathways and classes of action [4]:

- Class A: Bacteria stimulate chronic inflammation in immunologic tissues and, the inflammatory mediators produced instigate cell proliferation, mutagenesis, angiogenesis and oncogene activation [4,22].
- Class B: It's required direct microbial interactions with parenchymal cells that activate cell proliferation and pro-inflammatory situations, leading to carcinogenic pathways [4,22].
- Class C: Implicates distant effects from local gut microbiota interactions, due to substances produced by microorganisms, like hormonal intermediates and metabolites, possibly acting in a carcinogenic manner [4,22].

The connections established between helminths and bacteria seem to have exerted a "strong selective pressure" on the progression and development of our metabolic and immune systems [11]. However, since the 90s, industrialized countries with the help of the World Health Organization (WHO) have extensively eradicated helminths through mass drug administration [2,20]. This led to a shift in intestinal balance, maybe even being the genesis of the increase of chronic inflammatory diseases. Although the eradication happens within the Western population, people living in rural areas keep suffering from infections with these microorganisms. Therefore, well-established helminth-bacteria interactions might be an essential key to a healthy homeostasis [11].

Many correlations have been made between parasite infections, in this case, helminth infections, with intestinal microbiota impact [11]. Consequently, the host's immune responses will be affected disadvantageously, and, as a result, increase the risk of tumour progression. There are numerous mechanisms through which parasites increase. Among them, are:

- Low-grade chronic inflammation responses when there was no parasite ejection. *Schistosoma haematobium* deposits eggs in the bladder wall, which is highly linked with the appearance of bladder cancer. The eggs will trigger an inflammatory event, predisposing the host to a higher chance of tumorigenesis [7];
- Suppression of the immune surveillance is, so far, the least studied mechanism, allowing the mutated host cells to escape, instead of being eliminated by the immune system [7];
- Secretion of carcinogenic factors, for instance, *Opisthorchis viverrini* inhabits the bile duct, secreting a granulin-like growth factor (Ov-GRN-1). This factor can stimulate the proliferation of the cells and, when conjugated with factors like dietary carcinogens, the bile duct is transformed and cholangiocarcinoma emerges [7].

Although the mechanisms through which dysbiosis and, therefore, the impact of helminths, may affect the tumour growth or even its microbiota are not yet fully understood it has been proved that dysbiosis of the gut microbiota is in the genesis of carcinogenic processes. This way, some cancers not only gastrointestinal ones but also in other organs, have been associated with microbiota changes. This review will specifically focus on some of these cancers.

Colorectal cancer (CRC)

CRC, commonly diagnosed in the elderly [23], has been ranked the third most common as well as one of the deadliest worldwide [6,24]. Recent publications have shown a close correspondence between the gut microbiome and the emergence of CRC, due to the matter that diet is a well-known and important factor associated with both the development and progression of this disease [3,6,9]. The composi-

tion of the gut has also been linked with carcinogenesis, since it was discovered an increased amount of *Firmicutes, Bacteroidetes* and *Prevotella* in CRC patients when compared to healthy controls [6,23]. Thus, several explanations have been proposed for the role of gut microbial dysbiosis in the development of CRC. One of them is believed to be that microbiota may have an epigenetic influence on the host DNA (Deoxyribonucleic Acid) expression, promoting carcinogenesis [6].

Although it has not been found a specific organism in the genesis of this cancer, in a study where fluorescent in situ hybridization was used, *Fusobacterium* spp. was linked to CRC and colon adenomas [9] when compared to control groups, due to the higher levels found in these patients [6]. Therefore, it is suggested that *Fusobacterium* spp. plays a significant part in tumorigenesis through inflammatory mechanisms (a risk factor for carcinogenesis), reducing the number of bacteria from *Firmicutes* and *Bacteroidetes* [3,5]. *F. nucleatum*, with the gene FadA and the protein Adhesin A, a complex FadAc is formed, activating a signalling pathway (Wnt/β- catenin) and, as a consequence, it results in transcriptional changes [9]. This way, using *in vitro* cancer models, it was observed how *F. nucleatum* stimulates CRC cells, making FadA a potential biomarker for the diagnosis and therapy of CRC [3]. Additionally, other bacterial species also affect how the tumour is developed. For instance, studies using both human and mouse models show that toxins produced by *Bacteroides fragilis*, an enterotoxigenic bacteria responsible for causing diarrhoea and gastrointestinal inflammation [6], can stimulate an inflammatory state and increase the production of reactive oxygen species (ROS), leading to a scenario of carcinogenesis [9]. Moreover, higher levels of *Escherichia coli* have also been observed in patients with CRC, while this was not registered in healthy subjects [6,25].

Gastrointestinal cancer (GIC)

GIC is considered to be associated with inflammation, known to promote tumour progression, and metastasis while accelerating the invasion [3]. In this cancer, the expression of TLR, receptors capable of recognizing different patterns, seemed to be related to different progressive stages of this disease, being homogeneously spread in tumour cells, whereas this is not verified in healthy cells [26]. Although this disorder is associated with different etiologies, it is believed that *Helicobacter pylori* is the most well-established risk factor for its development, being observed in 1 - 3% of patients with GIC [6]. Furthermore, due to the gastric acidic environment, only *H. pylori* is capable of colonizing the human stomach, provoking chronic inflammation, believed to be the first step of GIC. A comparison between *H. pylori*-positive and *H. pylori*-negative showed evidence of significant increased bacterial richness in these last patients, particularly in bacteria from the phyla *Firmicutes, Bacteroidetes* and *Actinobacteria*, as well as a bigger amount of *Streptococcus* spp [3,6]. This way, a dysbiotic state can influence the development and/or progression of GIC. Nevertheless, it has been suggested that *H. pylori* eradication may be an effective therapy in order to prevent GIC [6].

Oesophageal cancer (OEC)

OEC is known to be one of the deadliest cancers, primarily because of its reflux esophagitis, making it the sixth most common cause of cancer-related death [6]. Recent evidence has shown that OEC might be a result of factors like diet and lifestyle (smoking as a huge risk) and antibiotics treatment, linking the microbiome's role to health and disease conditions and, in this case, to the emergence of OEC [26]. Although there is evidence proving the relationship between the microbiome and OEC, there is still a need to better clarify this association [6].

The oesophagus is recognized to be "microbe-free", with very limited microbes coming from swallowing and gastroesophageal reflux. However, some distinct microbial communities were found to inhabit the oesophageal mucosa of individuals with carcinogenic diseases in this organ, when compared to a healthy oesophagus [3].

Differences between the microbiome of a normal oesophagus and one with oesophagitis or even Barret's oesophagus (BE-considered a precancerous of OEC, consist in the presence of goblet cells and involve a columnar epithelium instead of the normal stratified squamous

epithelium [27]) were shown in biopsies, where a healthy host was dominated by *Streptococcus* (gram-positive), while the esophagitis was mostly inhabited by gram-negative anaerobic species, most prevalent *Prevotella* and *Neisseria*, among many others [4,26,28]. Another study showed evidence of the appearance of *E. coli* in BE and oesophageal adenocarcinoma patients, being inexistent in people with tumour-adjacent normal epithelium, highlighting the need of *E. coli* presence in BE development [4].

Pancreatic cancer (PC)

Pancreatic ductal adenocarcinoma (PDAC) or PC has been recognised as one of the most lethal cancers with an overall 5-year survival rate between 7% and 9%, mostly due to the tumour surrounding biological complexity, leading to hypovascularity, hypoxia, poor drug delivery and ineffective therapies [10]. Some risk factors such as age, cigarette smoking, obesity, diabetes and chronic pancreatitis have been linked to PC [3].

Once again, a shift in the normal balance of gut microbiota causes a disease state, promoting inflammatory conditions and cancer aetiology, being PDAC one of the perturbations. This happens because of the impact microbes have on carcinogenesis, since they induce inflammatory responses, avoid immune destruction and some of their metabolites are capable of deregulating host genome balance, resulting in cancer development.

Some potential associations have been made between PDAC and gut microbiome such as the risk of gastric cancer and *H. pylori* and their role in promoting carcinogenic processes. However, more information is still needed to confirm or deny these factors since studies have not found any relationship so far [10]. Another link has been made regarding hepatitis B and C viruses, hepatotropic viruses that mainly affect the liver but can be detected in extrahepatic tissues like the pancreas, increasing the chances of developing PDAC [10]. Moreover, studies have also connected the presence of gram-negative such as *Pseudomonas* spp. and *E. coli* in the bile, with inflammatory status, being linked with a higher risk of PDAC [10,29].

A comprehensive analysis of seven different tumour microbiomes, from different cancers, including PDAC, found that those were mostly dominated by *Proteobacteria*, maybe reflecting a "retrograde bacterial migration" from the duodenum to the pancreatic duct. Moreover, species from *Proteobacteria* and *Firmicutes* were the most commonly found in all cancer types, varying the ratio between each tumour [21].

Breast cancer (BC)

Contrarily to many beliefs, gut dysbiosis is not only capable of originating gastrointestinal cancers but also in other organs like the breast There are 3 types of BC, according to its aetiology and how receptive the cells are to HER2 (Human Epidermal growth factor receptor type-2), estrogen and progesterone. This way, BC can be classified as HER2 positive, HER2 negative and estrogen/progesterone positive and Triple-negative, where hormone therapy is not a treatment option [30]. It is important to highlight evidence proving that, even though each tumour has a distinct microbiome composition, BC appears to be the one with the richest and more diverse one [21].

Authors define "estrobolome" as the complex of enteric bacterial genes, that can metabolize estrogens, connecting these two terms: gut microbiota and BC [31]. The estrobolome is enriched in hydrolytic enzymes that favour estrogen degradation, reabsorbing free estrogens (non-protein-bounded) and, therefore, increasing estrogen levels [31]. However, estrogen is one of the many factors for the development of some BC types, playing a negative role in promoting carcinogenesis and neoplastic growth [4]. This way, there is plenty of evidence that links systemic estrogens being modulated by gut microbiota, when dysbiosis is witnessed, due to an over presence of bacteria encoding hydrolytic enzymes.

Moreover, it is believed that microbial dysbiosis may also play a role in the development of BC, since higher levels of *Bacillus, Staphylococcus* and other non-commensal species, were found in the breast tissue of women with either being or cancerous tumours, when

compared to women without this condition [6]. In addition, benign and invasive BC seem to have similar microbiomes, with *Firmicutes* and *Bacteroidetes* dominating and just differing in the increase of certain genera, including *Fusobacterium* and *Lactobacillus* [6].

It is also curious to observe that most, if not all, the developments made in this field of microbiota treatments are mainly been made to modulate the gut microbiota, rather than in the local microbiota population of the affected organ [4]. As mentioned before, this is due to the gut microbiota's role as a central regulator for other organ populations, through immune response modulation and cellular gene expression patterns.

Gut microbiota in anti-cancer therapy

The microbiota not only has an impact on making the host more prospective to certain outcomes, but it may also modulate the host's response to cancer therapies, from the most conventional ones to the most recent and developed treatments, in order to fight this deadly and incapacitant disease. Although the literature on anti-cancer therapy is extremely rich, it lacks evidence about the importance of gut microbiota as a potential therapeutical target.

Murine models used to evaluate the microbe's mechanisms, as well as helminths, to develop diseases showed that the gut microbiota can modulate how efficient the anti-cancer therapy will be, affecting the host's immune response. This way, it is possible to decrease the amount of tumour necrosis factor (TNF) expressed, reduce the production of ROS, as well as inhibit the tumour progression, giving the host a higher chance of survival [26].

All things considered, gut microbiota dysbiosis is prospective to develop carcinogenic effects, being extremely important to maintain an intact and normal microbiota, in order to prevent such events. A dysbiotic state will induce pro-inflammatory cytokines, activate mutagenic cells, as well as alter metabolite production [4]. This way, cancer growth and progression are enhanced, making the gut microbiota a very promising therapeutical target [4]. Thus, there is no doubt how relevant it is to modulate or reverse an unbalanced microbiota population (Figure 2). Since different microbiota compositions may be favourable or unfavourable for parasite colonization, using microbiota modulation can be a potential therapeutical target. This way, it is possible to avoid inadequate immune response against the microbes, suppressing immunological disorders [2]. There are several established methods able to alter gut microbiota, such as Faecal Microbiota Transplantation (FMT), prebiotics and probiotics and targeting the tumour microbiota itself, among others.

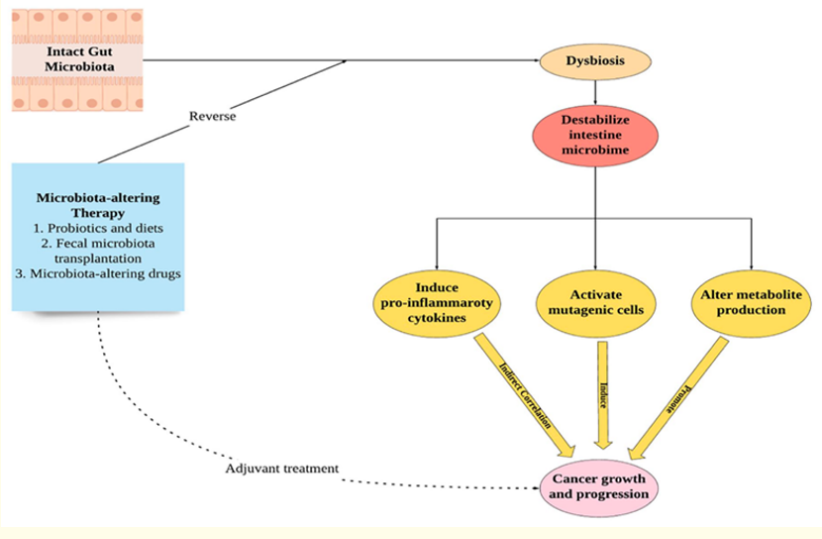

Figure 2: *Schematic correlation between gut microbiota, dysbiosis, cancer and microbiota altering therapies (Adapted from 4).*

Faecal microbiota transplantation (FMT)

The Faecal Microbiota Transplantation (FMT) method, also known as Intestinal microbiota transplantation (IMT) [6] consists of liquefying and filtering stools from a healthy donor and transplanting them to recipients during various procedures like colonoscopy and enema administration [4]. It is believed that FMT started to be applied roughly 2000 years ago by the Chinese ancients by administrating a slurry of stool from a healthy host, known as "yellow soup", to cure severe diarrhoea, being successfully used since those days [6,9]. The aim is to restore the normal microbiota balance, transplanting it from a healthy donor.

The transplant can occur through several methods, depending on the disease we are facing [6]. Although the many routes FMT can be administered to the host, a trial with *Clostridium difficile*, a known human pathogen, showed evidence of the highest response rate when the route chosen was colonoscopy or enema, followed by nasogastric tube and oral encapsulated FMT. However, to date, it has been demonstrated that the clinical efficacy between colonoscopy and oral encapsulated method is not significant [9]. The method used to treat *C. difficile* led to decreased levels of *Bacteroidetes* and *Firmicutes*, being the host dominated by *Bacteroides* spp., after 14 days of the procedure [6].

FMT can also be considered an effective option when conjugated with probiotics administration, in order to change the microbiota and, as a consequence, other local microbiota populations [4]. However, this method is not usually well accepted and tolerated by the patients [6].

Probiotics

Probiotics were first defined in 1964 [32], only coming to a definite concept in 1998 as being "live bacteria, or a combination of them, able to confer health to the host when consumed in adequate amounts", being treated as dietary supplements [6,33]. Nowadays, an entire industry focuses on this matter as it has been both a lucrative business and also beneficial for our health, due to its proven effect on gut microbiota modulation [9]. Probiotics are also fairly involved in metabolic functions, protection against diseases and anti-tumorigenic effects. Some even believe probiotics can normalize brain functions [6].

As an example, the parasite *Trichuris muris* is capable of causing anxiety-like behaviour but, when probiotics such as *Bifidobacterium longum* and *Lacticaseibacillus rhamnosus* are administered in animal trials, the anxiety caused by the parasite is normalized [6,34].

It is generally agreed that the consumption of probiotics, as well as fibre-rich food, might be the most well-known and established method to modulate the gut microbiota, so as to treat and prevent several health conditions [4]. Nevertheless, probiotics can differ in the classification where they are inserted. On one side, when used for therapeutics, they fall under Food and Drug Administration (FDA) regulations. On the other side, some are classified as dietary supplements, these being the majority, have not been through a rigorous FDA review process before being available to the public. This way, the probiotics content may vary from what is advertised, since there's a lack of compositional studies. Moreover, there is some uncertainty about the impact on the gut microbiota and the overall effect on the host's health may be limited. The positive effects of probiotics can be argued since both recent data and trials have been showing great positive effects for instance on CRC, as well as uncovered effects that led to tumour multiplicity, also verified in other studies [9]. When probiotics are administered to patients with CRC, the gut microbiota is altered, and the abundance of butyrate-producing microbes both in mucosal and faecal samples is increased. These microbes interact closely with colon cells, working as an energy source and modulating signalling pathways. They also play a very important role in CRC by inhibiting cell proliferation, reducing inflammation and promoting cell apoptosis, as well as tumour suppressor gene expression [35].

Not only the effect of probiotics on cancer development and response to treatment has been studied, but clinical trials are also being focused on the impact probiotics have on treatment-related toxicity. One successful case is the administration of *Lactobacillus rhamnosus* which led to decreased diarrhoea, in patients with CRC receiving 5-fluorouracil, as well as improvement of oral mucositis in patients suffering from head and neck cancer being treated with chemotherapy [9].

All in all, studies and reports suggest that these compositional changes in the gut microbiota or even in the tumour environment, can affect and modulate patient outcomes and, probiotics can also enhance conventional anti-cancer treatment efficacy when administered in combination [26].

Diet and prebiotics

These two factors, diet and prebiotics, are mainly used due to their effect on modulating the gut microbiota. Firstly, diet can influence how the gut microbiota is composed in terms of, not only bacteria, but also fungi, viruses, protozoa, and bacteriophages. It also affects their transcriptomic and metabolomic profiles [9]. Furthermore, different types of diet have different outcomes on our gut microbiota composition, as previously mentioned, leading to changes in the inhabitants and, therefore, may affect our propensity to develop particular diseases [9].

Secondly, prebiotics, are characterized by promoting the growth of a specific group of bacteria and, consequently, a diverse and "healthy" microbiota and they also are able to modulate our gut microbiota composition [9]. The concept, introduced in 1995, describes prebiotics as a "non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria, and thus improves health" [24]. Moreover, the WHO and Food and Agriculture Organization (FAO) define prebiotics as a "non-viable food component that confers health benefit(s) on the host associated with modulation of the microbiota" [36].

These products consist of a group of nutrients which are fermented by the microbes, mostly bacteria, living in the gut since they are not hydrolysed by the gut enzymes [6]. Due to the degradation products, short-chain fatty acids, released into blood circulation, will have an effect, not only in the gastrointestinal tract but also in other organs, by modulating the composition and function of the microorganisms that normally harbour our gut. For instance, the use of these substances can also have a decrease in the risk of atopic dermatitis, while reducing the erythema and increasing water retention as well as collagen formation (Figure 3) [24]. This way, the gut's environment is also susceptible to modification, since most products resultant from prebiotic fermentation are acids, a decrease in the gut pH (6.5 to 5.5) is observed, being able to change the bacterial population to acid-sensitive species, for example, *Bacteroides*, and promote butyrate formation by *Firmicutes*- "Butyrogenic effect" [24].

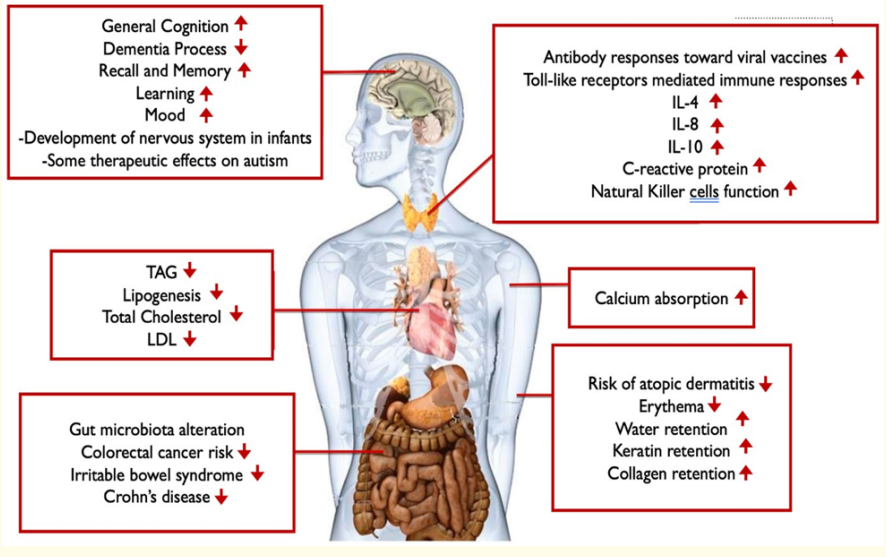

Figure 3: *Prebiotics effect in several organs. These substances affect not only the gastrointestinal tract but also other organs and systems, such as the central nervous system, immune system, cardiovascular system (Adapted from 24).*

Prebiotics naturally exist in food products such as asparagus, sugar beet, garlic, onion, honey, banana and even human's and cow's milk, among others. However, since the concentration in these products is fairly low, prebiotics started to be manufactured at an industrial level [24]. Clinical trials have been demonstrating the effect of prebiotics in CRC in a matter that fermentation products, like butyrate, can have a protective effect by inducing apoptosis, preventing the risk of developing CRC and its progression. It has also been demonstrated the correlation between the increase of protective microorganisms as well as a decrease of harmful bacteria, through prebiotics consumption, and immunity function improvement [9,24].

Targeting the tumour microbiota

In the past few years, efforts have been made to understand how the tumour microbiota can be a target in order to prevent cancer progression, as well as improve reactions to cancer therapy. In addition to the therapies above mentioned, many drugs are known to change the microbiota population. Although antibiotics are probably the main example, there are several other drug classes such as statins, which might be related to the changes in lipid and glucose metabolism induced by these substances [4]. However, even with the well-known dysbiotic effect of antibiotics, capable of shifting the microbiota population towards the "unwanted" ones, these substances can still have a beneficial effect on the host.

Interestingly enough, studies referencing antibiotic usage were associated with enhanced responses to chemotherapy, as well as immune checkpoint blockade, due to bacterial depletion. Nowadays, despite the major complexity beyond this process, since systemic antibiotic administration needs to be taken into account, emerging data has been focusing on the trials to target this bacteria, while combining it with conventional cancer therapy [9]. All things considered, the use of microbiota-altering drugs is a promising strategy, mostly due to its increased efficacy in comparison with probiotics or dietary changes alone [4].

Future Directions

Altering the gut microbiota composition, even though it seems to be a very effective and reliable therapy, is not the only option. Not many studies have been made in the field of altering gut microbiota for cancer prevention however, it is becoming a promising therapeutical target. A recent study observing long-term effects in lung cancer showed evidence that by altering dietary consumption, such as adding yoghurt (probiotic source) and fibre consumption (main source of prebiotics), the gut microbiota will mainly be composed of the normal bacterial population [37]. As mentioned, these bacteria play a very important role in maintaining immune responses, while suppressing inflammatory responses and in producing metabolic products [4]. Nevertheless, these preventive effects have also been studied in oral cancer [38] and hepatocellular carcinoma [39], using probiotics in order to lower gastrointestinal inflammation, showing effective reduction of the growth in a mice model [39]. These examples show evidence of the role of microbiota composition in preventing carcinogenesis, not only in gastrointestinal cancers but also in other organs.

The usage of microbiota-altering drugs, mainly antibiotics, is also looking very interesting for many researchers due to their bacterial depletion effects within the microbiota [4,9]. Although these substances have been known to shift microbiota's normal bacterial population, inducing dysbiosis and consequently negative pathological outcomes, this method's efficacy can potentially be much more superior when compared to probiotics or dietary changes alone [4], showing promising evidence of improved responses to chemotherapy [9].

Moreover, when it comes to trying to eject the parasitic helminth out of the host, some setbacks are faced. Due to the complexity of these methods, vaccines against helminth infections have been attempted to be developed [7]. Nonetheless, this is an even bigger challenge since a relevant risk exists to the host. Additionally, the risk of anaphylaxis in infected populations is also a problem, adding to the lack of defined "immunodominant" antigens [7].

There are also several treatment opportunities when combining conventional anti-cancer therapies with emerging ones, such as vaccines designed through synthetic biology, in order to reduce cancer incidence, taking into consideration that our microbiome is largely known by the scientific community [26].

The HGM field is far from being fully understood and there are still many unanswered questions, especially when it comes to the mechanisms of actions of these events, as well as the exact microorganisms that mediate tumour and antitumoral effects. There are still lots of research opportunities, from basic research to clinical trials and epidemiological studies, in order to understand this complex ecosystem and, hopefully, be able to discover an efficient treatment for cancer [9].

Conclusion/Final Considerations

For many years, it has been established that Humans are colonized by a wide range of non-pathogenic microbes which exchange mutual interactions between them and, also, with the host themselves, representing our microbiota [1,2]. In a healthy host, the gut microbiota is in a symbiosis state and when facing an imbalance in the normal commensal microbes that harbour our gut, a dysbiotic microbiota will dominate. Undoubtedly, dysbiosis will affect the human host, leading to a disease state, and modulating the immune response [2]. Even though the microbiota remains, more or else, stable over the years, some factors including age, genotype, treatment with antibiotics and diet, may alter this balance and, consequently, the host becomes more vulnerable to negative outcomes.

Helminth parasites currently infect nearly one-third of the World's population [7] and have a demarked immunoregulatory activity, easily modifying the gut microbiota structure [8]. Most found are the STH, known to suppress host immunity, establishing chronic infections and, therefore, impacting future responses [11]. Although the mechanisms through which dysbiosis may affect the tumour growth or even its microbiota are not yet fully understood, it has been proved that dysbiosis of the gut microbiota is in the genesis of cancer diseases [9].

With cancer being such a fast-growing and extremely impactful disease to the human body, it is highly important to stop its development, as well as improve people's chance of survival, as well as health and well-being. Furthermore, oncological problems also entail socioeconomic problems and psychological disturbances. Likewise, there is an emergent and valuable need to eradicate this disease. Each day, improved treatments are beginning to become available to cancer patients, either to treat them or to try to prevent this uncontrollable disease.

The most conventional cancer therapies and treatments, like chemotherapy, can cause drastic side effects from gastrointestinal mucositis with diarrhoea, and constipation to an increased risk of gastrointestinal infections. Research demonstrated the potential of gut microbiota use to both prevent and avoid cancer progression, instead of using commonly used invasive approaches. The microbiome represents numerous opportunities for therapeutic targets for cancer. Modulating the gut microbiota may enhance treatment efficacy, lighten treatment toxicities and, possibly, prevent carcinogenesis.

Prebiotics and Probiotics, two recent anti-cancer strategies, can restore our healthy gut microbiota, previously lost by either internal or external factors as discussed in this review, preventing some effects of toxic therapies, and helping the host to have a better life quality and prosperity. Although not yet unanimous, it is generally agreed that good health is associated with a high degree of microbial diversity and richness, and this is one of the action fields where emerging strategies are trying to have an impact [1].

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