The Intrinsic Relation between Bacteria and Cancer - A review.

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Abstract. Over the last decades studies have shown the importance of the microbiome in the development of some diseases, including cancer, anxiety, obesity, and some neurological diseases. Understanding the genesis of a pathology such as cancer is the reason for several studies over the last decades and one of the most emerging explanations is the fact that our microbiome is an important biomarker for carcinogenesis development. The mechanisms which a disruption of homeostasis by bacterial infection lead to cancer are promising for a better understanding of the origin and future therapies. Yet a deeper comprehension of the intercommunication host-microbiome is still necessary for a better conception about the pathogenicity of the species that could lead to cancer progression. In contrast, some types of bacteria have been used in innovative treatments that facilitate drug delivery, helping to prevent cases and treat people with less toxicity and side effects.

Keywords. Dysbiosis, microbiome, carcinogenesis, bacteriotherapy.

1. Introduction

Human microbiome is composed of bacteria, viruses, eukaryotic fungi, and protozoa [1]. Gut microbiota is the name given to the heterogeneous population of commensal microorganisms, mainly bacteria, but also fungi, archaea and viruses, populating the intestinal tract. [2].

The importance of studying the microbiota is becoming even more evident after studies have demonstrated that the gut microbiota perform an essential role in maintaining healthy homeostasis [3]. That means that dysbiosis can lead to obesity, diabetes, liver illnesses, cancer and neurological diseases [3].

Carcinogenesis, that means the process by which normal cells are transformed into cancer cells [11], can be induced by factors such as mutation during DNA replication, dysregulation of signalling pathways and also environment exposure and lifestyle habits [16].

Other significant risk factors are: genetic susceptibility, hormones and chemical carcinogens and the colonisation of some microorganisms in the gastrointestinal tract can be a crucial environmental factor [5].

Nowadays, with the advance of techniques of DNA sequence and the arising of the Human Microbiome Project, the role played by bacteria in tumorigenesis is an extensively studied topic and even so there are some mechanisms that are not fully understood.

In this review, it will be described the relation between the human microbiome and cancer, some mechanisms and treatments in which bacteria can be used in a positive way to provide a better response to regular therapy and also as a pioneering drug delivery system.

2. Gut microbiome and cancer

It is estimated that there are ~10^{12} microbial species on earth and just a small number are identified as direct human carcinogens, known as the "oncomicrobes" [9]. Regardless of that, these oncomicrobes are estimated to cause millions of cases of cancer per year.

As some bacteria influence dysbiosis and therefore carcinogenesis by a chronic and pro-inflammatory immune response (immunosuppression) [10], the gut microbiota has been recognized as an important element of studies.

It is known that bacteria can cause cancer by mechanisms which include the production of bacterial components, such as toxins and metabolites, as well as bacterial-induced chronic inflammation [4]. There is a high association between the infection with *Helicobacter pylori* and gastric cancer, but also there are associations between the infection with *Escherichia coli*, *Fusobacterium nucleatum*, and *Bacteroides fragilis* and colon cancer. [4].

The link between local microbes and cancer development has been established at three primary mechanisms that demonstrated potential modes of action: direct facilitation of tumorigenesis via increasing mutagenesis, regulation of oncogenes or oncogenic pathways and reduction or enhancement of tumour progression via modulation of host immune system [10].

One of the main reasons bacteria could lead to cancer is the chronic inflammation, which intensifies malignant transformation, tumour growth, invasion and metastasis [5]. Moreover, growth inhibition is inactivated in inflammation conditions with a legit escape from apoptosis [5]. These factors elevate the potential to enhance angiogenesis [5].

The inflammation process is a natural immune response to protect the host cells. Phagocytes secrete pro-inflamatory cytokines such as TNF-α (tumour necrosis factor-alpha), IL-23 and IL-1 [5]. These responses are a trigger to uncontrolled cell proliferation [5]. Besides, the recruited immune cells increase reactive oxygen species (ROS) and nitrogen oxide species (NOS), which further will kill pathogens, can also lead to damaged proteins, DNA and cell membranes because of its free radicals and derived metabolic products like HNO2, N2O3 and peroxynitrite [5].

The damage caused in proteins and DNA usher to another alteration which can explain carcinogenesis. Genomic stability protects cells from DNA replication error, oxidative stress, exogenous carcinogenic agents that cause DNA damage, etc [5].

The bacterial genotoxins like cytolethal distending toxins produced by certain gram-negative bacteria like *Helicobacter pylori* induce DNA damage, leaning to genomic instability and oncogenic transformation [5]. The DNA damage response enhances the mitogen-activated protein kinase (MAPK) by activating the neuroepithelial cell-transforming gene 1 protein (NET1), resulting in malignant mutation in infected cells [5].

The risk of *H. pylori*-induced gastric diseases is associated with the heterogeneity of host genetics and *H. pylori* strain virulence factors [12]. One of the most important virulence factors is CagA (cytotoxin-associated gene A), a protein that can interact with intercellular proteins and activated tyrosine phosphorylation, [12] that regulates the functions of the proteins [13].

The same happens with the infection by *Salmonella spp.* Some examples of virulence factors are mobility, biofilm formation and T3SS1 and T3SS2 (type III of secretion systems) which will affect the effectiveness of the invasion of the host cells [14]. In the intestinal epithelium flagellin (TLR5) can inhibit apoptosis when translocated to the basolateral side of the epithelial cells [14].

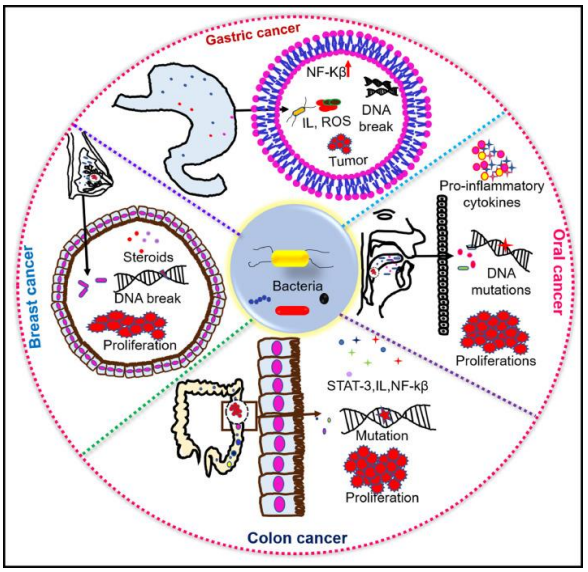

Fig. 1 - Chronic inflammation caused by bacterial infection of the immune host cells leading to cancer. Adapted from [5].

Breast cancer, one of the most common types of cancer worldwide (2.3 million diagnoses only in 2020 [6]), could be initiated by bacterial infection [5]. Species like *Bacillus*, *Enterobacteriaceae*, and *Staphylococcus* were largely found in breast cancer tissues, once these bacterias cause DNA double-stranded breaks in HeLa cells [5].

To emphasise the role played by microbiota in cancer development, it has been observed an association of the steroid hormone oestrogen (risk factor in breast cancer) [5]. Gut microbiome encode oestrogen deconjugating enzymes (β-glucuronidase and hydroxysteroid dehydrogenase) that activate oestrogen metabolism, take them into hepatic

circulation, guiding to hormonal imbalance [5].

3. Bacteriotherapy

Despite the fact that bacterial infection increases the chances of cancer development, over the last few years bacteria has been being used as a therapy. Bacteriotherapy can be used together with other usual therapies such as chemotherapy, radiotherapy and immunotherapy but also can be a stand-alone therapy [5].

The use of probiotics, that are "live microorganisms that are intended to have health benefits when consumed or applied to the body" [15] to modulate gut microbiome can contribute to the effectiveness of cancer treatment, by increasing intestinal permeability which allows bacterial translocation resulting in the maturation of T helper 17 cells (TH17) within the lamina propria and effector lymph nodes, easing a systemic antitumor effect [7].

In addition to this, another aspect is that chemotherapy and the antibiotics prescribed during the treatment and radiotherapy cause massive dysbiosis. This way, probiotics could be a way to minimise this negative impact.

Bacteria like *Escherichia coli* and *Salmonella typhimurium* are used as a vector in a drug delivery system (DDS) because of its spores [8]. These spores germinate, multiply, replicate and become lively in certain parts of the tumour where there is a lack of oxygen and anticancer drugs are grouped with these spores for a therapeutic result that require a lower dose, leading to minimum adverse effects and less toxicity [8].

What's more, another strategy is the combination of microbial cells with non-living materials like microparticles, nanoparticles and microbots that helps bacteria to travel directly to the target, making therapeutic agents penetrate in the cells more easily [8]. Materials like polyethylene glycol (PEG) are widely researched as an inert material to be used as a carrier [8].

4. Methodology

The literature review was guided by three databases: Google Scholar, PubMed, and ScienceDirect. The terms "cancer", "bacteria", "treatment" and "therapy" were used with the boolean AND in between the words.

5. Conclusion

The microbiota is becoming the key to understanding the progression of several diseases. In cancer, knowing the tumor microenvironment is essential for the progression and prognosis.

Although a lot of studies are being carried out throughout the last decades, there are some aspects that are not fully described and extended research should be undertaken, once the mechanisms and the relation between our microbiome and their host can be complex and be influenced by numerous factors.

Furthermore, it is important to mention the potential of the bacterias in new cancer treatments, like drug delivery combined with the regular treatment can become a promising system of therapy for many diseases, not only cancer.

For all that, bacteria are essential for the human body, being part of the immune system and maintaining the digestive system physiology.

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