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Bacteria and cancer: Advances, perspectives and applications

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Abstract

A bacterium has all the essential information for life in a single molecule of circular, double-stranded deoxyribonucleic acid. Such knowledge has been used on a large scale by genetic engineering, which with in vitro techniques alter the genetic material in the laboratory and can insert this modified material in the original organism or some other. Today, it is known that the microbiota modulates responses to cancer treatment and susceptibility to toxic side effects. In the present work, a bibliographical review of scientific articles in the science direct database was carried out, with combinations of keywords covering publications from the period between 2015 to 2017. As a criterion of choice we chose to select papers that deal with the role of bacteria in carcinogenesis, since pro-and anticarcinogenic functions have been attributed to microorganisms, and it has been found that there is still no consolidated research on the therapeutic potential, and it is necessary to invest in this line to effectively apply of them.

Introduction

The bacterium has all the essential information for life in a single molecule of double-stranded and circular deoxyribonucleic acid. Some bacteria have circular extrachromosomal DNA called plasmid DNA, not essential to bacterial cell survival, but it confers selective/adaptive advantages, although they may be lost under situations of cellular stress. The bacterial chromosome is large (500 to 10,000 pairs of bases) in relation to the size of the microorganism with circular loops may overlap and form a series of independent topological domains, allowing the protection of the genetic content and preventing the rupture thereof [1]. Such knowledge has been used on a large scale by genetic engineering.

The term *genetic engineering* refers to the use of in vitro techniques to alter genetic material in the laboratory and may insert modified material into the original organism or into some other organism. The techniques involved in the use of the genetic material range from the fragmentation of specific segments by the action of restriction enzymes that discard the content that is not interesting, restricting the selected DNA fragment for observation and manipulation, even modifications in these, using restriction enzymes and modification, cloning, and mutagenic agents [2].

The majority of the mutagenic agents exhibit a spectrum of mutations that depend on a number of factors, including the nature of the primary DNA changes such as: base modifications, sugar or phosphate residues, filament breaks, or modified base incorporations, and the subsequent side effects caused by the body's response to these modifications [3].

Mi et al. [1] state that bacterial infections can cause damage to the DNA of host cells and induce certain pathogens such damage as part of its program through the multifaceted infection of bacterial DNA recombination into the host DNA, even generating cytotoxic enzymes. Additionally, signaling pathways involved in the host cell to DNA damage response (DDR) may be changed in response to an infection with the potential to trigger mutations and cancer.

Cancer arises from the acquisition of multiple genetic and epigenetic changes in host cells over many years, promoting oncogenic traits and carcinogenesis. In addition, it is important to note that the environment where tumors evolve provides a unique source of signaling signals that affect the growth, survival, movement, and metastasis of cancer cells [4].

In recent years it has become evident that the microbiota, and particularly the gut microbiota modulates the response to treatment of cancer and susceptibility to toxic side effects [5].

Aiming at these aspects, this paper aims to present the results of a systematic literature review on the main advances in knowledge about the interaction of bacteria and cancer, highlighting the main tools discovered to identify and combat cancer cells.

Methods

The systematic review gathered articles from two major databases: ScienceDirect. The search was done by means of the combination of keywords: Bacteria, cancer, modelers, regression shown in table 1. As inclusion criteria, articles were selected that referred to all information available about the relationship between Bacteria and Cancer, without limit of the year or linguistic restriction. Any other data or articles that did not live up to these inclusion criteria were excluded, totally avoiding the theme proposed in the present study or not directly related to the theme.

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Results and discussion

The influence of the microenvironment in the microbial potential

Over a century, it was observed that the bacterial activity causes tumor regression, either by its regulatory effects in the configuration of the tumor microenvironment, either through molecular markers for the tumor target or by nutritional competition with the cancer cells, or by the action of extracellular enzymes produced and secreted by bacteria or by immunostimulation and genetic modification increasing the potential anti-tumor action.

Microbial action with tumor target is one of the most effective tools of metabolic activities of bacteria that can generate positive effects in fighting cancer. An enlightening work was performed by Zheng et al. [6] with the use of carbon nitride (C3N4) in experimental models in rats. This compound is adsorbed by bacteria present in normal human biota such as Escherichia coli. These bacteria, abundant in the colon of homeothermic animals, are nitrate reducing agents (NO3-), which is used as a final electron acceptor in the process of anaerobic (or anoxic) respiration originating nitrite (NO2-), which is one of the natural metabolic pathways of the species. Exposed to carbon nitride (C3N4), E.coli metabolizes NO2 - producing nitrogen monoxide (NO), which has cytotoxic properties with antitumor effect, resulting in the reduction of tumors in 80% of the experimental rat population. The research showed that the bacteria were used as carriers of C3N4 and migrated to the tumor microenvironment, altering the composition of microorganisms by cytotoxic no synthesis.

It is observed in the previous work that exogenous influences in the metabolic pathways of normal biota microorganisms undergo biochemical alterations that develop new metabolic pathways, which produce and eliminate substances with differentiated effects, and an example is an antitumor effect. Therefore, one should consider the normal biota bacteria (or normal flora) as an important potential arsenal of substances against the development of abnormal cells such as a tumor, among other possible functions. Metabolic changes do not occur in a casual way, but due to the conditions imposed by the tumor microenvironment that can generate favorable conditions for the proliferation of some differentiated microorganisms with new metabolic pathways.

From the induction of changes in metabolic pathways followed the production and release of new substances, these microorganisms can enable efficient responses against the tumor itself, causing a decrease [7]. The human microbiota has an extremely important role in the homeostasis of the human body and may remain balanced for years, however, is always likely changes in response to pressures of their surroundings. Among the many factors that can cause metabolic changes in the microorganisms of the human microbiota are mentioned: use of antibiotics, exposure to toxic, diet type and extreme factors such as high and low temperatures and changes in environmental pH, among others [7]. Moreover, the microbiota acts as a true bio-indicator of the individual's health.

Among the alterations of the normal human microbiota by some types of cancers are those that destroy numerous microorganisms and are fundamental in the regulation of body homeostasis. Acute Lymphoblastic Leukemia, for example, alters the bacterial composition of the individual's fecal material by reducing the populations of Anaerostipes spp., Coprococcus spp., Roseburia spp. and Ruminococcus spp. Species of Anaerostipes spp. and Roseburias spp. are bacteria of the human microbiota that metabolize diet components and synthesize short-chain fatty acids like butyrate. This molecule acts on the motility of the colon contributes to the maintenance of the immune system and has anti-inflammatory properties. Changes in its concentration cause modifications of various metabolic pathways associated with irritable bowel, obesity, type two diabetes, allergies, gallstones. Coprococcus eutectic is a gram-positive, anaerobic, non-motile coconut from the normal biota that metabolizes carbohydrates, and studies with autistic children with gastrointestinal problems could be indicating a link between autism and the microbiota with a decrease in this genus [8].

On the other hand, squamous cell carcinoma of the head and neck (HNSCC), which is the fifth most common cancer in the world (annual incidence of 780,000 new cases) causes neoplasms in the oral cavity (buccal mucosa, gums, palate, tongue, oropharynx, nasopharynx, hypopharynx, nasal cavity and paranasal sinuses, glottic and supraglottic larynx and salivary glands). It is characterized by reducing the population of Neisseria spp., Aggregatibacter spp., Haemophilus spp. and Leptotrichia spp. which are normal in saliva. Furthermore, it is known that the consumption of tobacco and/or alcohol in excess constitute a high risk for the development of neoplasias [7]. Although advances in the treatment and survival of patients with HNSCC, the death rate still remains around 40%.

The tumor microenvironment may contain all the necessary tools to increase bacterial pathogenic potential, causing a real aggravation of the neoplastic disease. The effect of microorganisms in tumor development (or carcinogenesis) may be: i) alter the balance of proliferation and cell death; ii) orientation of the immune system function in favor of tumor development; iii) influence on host metabolism based on food standards and/or antibiotic ingestion, excessive use of alcoholic beverages and drugs, among others. There are so many mechanisms of the microorganisms that can influence the genomic stability of the cells, directly affecting the proliferation and cell death balance, as mentioned [9]. One of the more common examples relates to the *pks* gene expressed by the B2 group of E. coli present in the large intestine. Other gene products to the genetic material cited as causing damage are enterotoxin released by *Bacteroides fragiles*, cytolethal distending toxin (*Cytolethaldis tendingtoxin*) released by γ-ε- Proteobacteria [9]. Another example, cholangiocarcinoma (cancer of the bile ducts caused by mutant cells of the bile ducts draining bile from the liver to the small intestine) increases the abundance of *Stenotrophomonas spp.* whose metabolism causes tissue necrosis. Human papillomavirus (HPV), on the other hand, promotes a favorable environment for the proliferation of Lactobacillus spp. in the cervical mucus [7]. Lactobacilli are bacteria of the normal vaginal flora protective opportunistic infections and other potentially pathogenic microorganisms by competition for niches, foods, and control vaginal pH (pH maintained around 4). It concludes that the microenvironment characteristics directly influence the metabolic activity of microorganisms affecting different aspects of their physiology, such as the secretion of substances and mediation of these products can promote the development or delay of tumor growth. Thus, we believe in the modulating power of bacteria in the tumor microenvironment and can be a strong ally in anti-cancer therapies.

Bacteria as cancer modellers

According to Trinchieri et al. [5], the role of bacteria in carcinogenesis is complex, since pro- and anticarcinogenic functions have been attributed to microorganisms.

The flora is mainly composed of commensal bacteria and other microorganisms living in the epithelial barriers of the host and the intestine, and are involved in the initiation, progression and spread of cancer in both epithelial cells and in sterile tissue [5]. Although the tumor etiology induced by tumor viruses, such as human papillomavirus, hepatitis B virus and hepatitis C virus, is well documented, only one bacterial species, *Helicobacter pylori*, is currently considered by the WHO as a human carcinogen of class I [10]. Thus, stomach cancer is considered the fifth most common cancer and the third most common cause of death associated with cancer worldwide the incidence is highest in the Far East, in countries such as China, Japan, and Korea, and in South American countries such as Colombia and Chile, which are also regions where *Helicobacter pylori* infection is endemic [11].

In colorectal cancer models, it is known will interaction between *Escherichia coli*, usually belonging to the subphylum B2, the colibactin genotoxins producers. Raisch et al. [12] identified the influence of *E. coli* belonging to the B2 filogroup proto-tumors activities of macrophages since these organisms are associated with the prostate cancer cells and induce the expression of COX-2 (cyclooxygenase-2 enzyme-cycle or prostaglandin-endoperoxide synthase 2, encoded in humans by the Ptgs2 gene) into macrophages. Infection in macrophages themselves by *E. coli* and COX-2 production is not related to colibactin, however, the influence of these bacteria in the tumor development was observed since the treatment against *E. coli* producing session COX-2. COX-2 is usually a gene associated with colorectal cancer, suggesting that the expression of this gene in bacteria contributes to tumor progression when mutated.

Kramer et al. [13] have observed the influence on the expression of PPARγ (Peroxisome Proliferator-Activated Receptor Gamma) in tumor angiogenesis in epithelial cell cancer. Nepelska et al. [14] studied the influence of commensal bacteria on intestinal activity, where the gene expression of PPARγ was linked to the presence of butyrate and propionate, two of the main metabolites of intestinal fermentative bacteria. It is believed that this interaction is due to the activity of PPARγ as the key nuclear receptor of the lymph nodes linking metabolism and inflammation to the microbiota.

The relationship between chronic obstructive pulmonary disease (COPD) and cancer is already recognized. Schmidt observed in mice models induced cytokine deficiency epithelial interleukin-17C (IL-17C), responsible for the recruitment of neutrophils in inflamed and doubly deficient tissues at Toll-like 2 and 4 receptors (TRL-2/4). Cytokines are the molecules that directly exert the function of communication between the cell and the immune system. TRL receptors are responsible for the reception of these signals and the signaling, maturation, and development of the signaled cell. These are responsible for the adaptation of the immune system to a model of metastatic lung cancer. In these models, it was observed that the administration of *Haemophilus influenza* (NTHi) organisms commonly found in COPD patients, IL-17 is dependent on TRL-2/4. That is, IL-17C increased the expression of NTHi and tumor necrosis factor-α of neutrophil choices, promoting neutrophil inflammation of the tumor microenvironment, pathologically binding to the microbiota and aiding in tumor growth.

Chan et al. [15] identified significant differences in microbiota in women with breast cancer and control women, through aspiration of the fluid present in the mammary gland and canals. In the group with breast cancer, the prevalence of bacteria of the genus Alistipes, formed by strict anaerobic, pigment-producing gram-negative bacteria, was observed in the collected material, while the women of the control group had a prevalence of the genus Sphingomonadacea, which includes thirteen species of gram bacilli-negative aerobic, non-fermenters, the *Sphingomonas paucimobilis* being the only species described in human infections. The enzymatic activity of β-glucuronidase was identified in women with breast cancer, showing a relationship between the enzyme and the development of this cancer and the enzyme produced by Sphingomonadacea. The microbiota found in women without cancer is typically found in healthy people because these bacteria belong to natural breast channels of women.

The interaction of these organisms with cancer is an important link between both. The understanding of this interaction may develop tools for the implementation of appropriate policies in the administration of the same in diagnostic and therapeutic means effectively.

Bacterial Cancer Therapy

Gene therapy is known for the use of nucleic acids to repair, replace, or regulate genes to prevent or treat disease. Hundreds of genes have been investigated as potential candidates for gene therapy in cancers [16].

This therapy is based on the transfer of therapeutic genes to the cancer cells in order to delay or stop the malignancy of progress and they are classified into three categories: corrective gene therapy, gene therapy inducing toxin/apoptosis and suicide gene therapy [16–18].

The corrective approach applies cancer therapeutic genes to cancer cells to adjust the profile of the disrupted gene and, therefore, moderate or stop cell proliferation. Tumor suppressor genes, such as p53 or genetic interference agents that interfere with the proliferation of cancer cells (for example, siRNA or miRNA), are two prominent examples of this gene therapy approach [18].

The gene therapy inducing toxin/apoptosis is a simple and direct way in which the transgene product delivered results in a protein (e.g. diphtheria toxin or TNF) that causes cell death. The main weakness of corrective gene therapy and inducing toxin/apoptosis gene therapy is that only cancer cells that received the therapeutic gene are affected and those who did not receive the therapeutic gene continue to proliferate [18].

However, this practice becomes especially problematic for nanomedicines that depend exclusively on these two gene therapy strategies because both cannot penetrate deeply into tumor tissues in the face of physiological tumor conditions and high interstitial fluid pressure. As a result, not all cancer cells of tumors can be eliminated, and this significantly increases the likelihood of cancer recurrence. Generally, the toxicity outside the target and lack of access to all cancer cells in the tumor environment are the main obstacles to the successful treatment of cancer [18,19].

Microorganisms are also applied in gene therapy, aiming at therapeutic potential and act as vectors. A vector acts as a "drug" and as soon as it reaches the target begins to direct the synthesis of a new protein that properly restores a defective cellular process. They do not cause adverse effects because the vectors carry specific antineoplastic agents, for example, chemotherapeutics or enzymes useful in the destruction of cancer cells. They are thus used to transfer a chemotherapeutic agent directly to the tumor as well as the use of their secretory products, such as toxins [20,21].

Currently, a wide variety of vectors are being employed in gene therapy protocols, including recombinant viruses, plasmids, and nanoparticles. An important point in the use of microorganisms as vectors for gene therapy is safety because what is desired in this technique is to combat disease, such as cancer and not harm the patient's body treated with a pathogen. Thus, microorganisms are deprived of

their pathogenicity; (e.g., they are cultured under appropriate biotic conditions or treated with certain substances that result in mutation or weakening, and/or loss of pathogenic properties) [21,22]

The vector to be chosen in therapy depends on factors related to the disease, the therapeutic gene, the target market, and the transfer route. For example, the requirements for the vector used in the treatment of hemophilia are different from those designed for the treatment of cancer, since carcinomas are aimed at the death of tumor cells and the vector must be responsible for the delivery of a therapeutic gene, where the permanent expression of this gene is not necessary and may even be damaging to healthy cells. Therefore, a well-designed vector has a great impact on the performance of gene transfer and the success of the therapeutic approach [20,21].

Therefore, given the ability of the virus to bind to a host cell and to transfer its genetic material into the same, these organisms are now used as vectors. Taking advantage of the unique characteristic of viruses, scientists have begun to modify them so that their infective capacity is maintained in the modification process because this allows the beneficial DNA is inserted into host cells. The viruses used are retroviruses, lentiviruses, adenoviruses and adeno-associated [16,23,24].

Vectors often attributed to gene therapy of cancer are the adenoviruses, which are also employed to vaccines for expression of different antigens. Adenovirus vectors may be defective in replication, certain essential viral genes are deleted and replaced with a cassette expressing a foreign therapeutic gene. Vectors that are oncolytic are designed to replicate preferentially in cancer cells and to destroy them through the natural lytic virus replication process in which the vector is reproduced using the host cell machinery. Briefly, both clinical trials and clinical studies show the efficacy of cancer treatment with the use of a viral vector (Adenovirus) [25].

Another perspective is the strategy of using the viral vector as the treatment agent itself. Oncolytic viruses, for example, in the face of the evolution of genetic engineering are able to restrict infection and replication, ensuring that these processes occur only in target cells, such as tumor cells. With this approach, the tumor cell becomes a factory new viral particle which are released after cell lysis. These new particles, in turn, infect more tumor cells, amplifying the lytic process and consequently destroying the tumor cells. With this strategy, healthy cells are not affected by oncolytic viruses, which have preferably only by cancer cells [20,21].

The development of research on the use of microorganisms against tumors is comprehensive, especially in the new directions of the discovery of these microbiological tools. However, there is scarce literature noting the major advances in this area.

Camacho et al. [26] have observed the properties as an antitumor agent of a Salmonella strain and have highlighted its ability to proliferate within tumors. The investigations were carried out with potential cell copies commonly found in cancer specimens. The authors developed an inducible autolysis system based on the lysis ability of phage lambda that, in response to the anhydrotetracycline antibiotic, lysis Salmonella releasing its plasma content that contributes to the chain production of salicylate and observes that it can be concluded in the association between the development of this post-release effect of the cytoplasmic contents of Salmonella.

The salicylate chain promoted good efficiency in the death of tumor cells, resulting in promising expectations of the therapeutic potential of the same and the use of this bacterial line in cancer therapy, emphasizing that salmonella is an enteropathogenic agent that causes diarrhea, usually self-limited.

Subramaniam et al. [27] observed the action of the bacterium *Mycobacterium indicus* in tumor regression and complete recovery of lung and bladder cancer in rats. The action of these microorganisms occurred mainly after his death, releasing the intracellular content, particularly a cytotoxic substance that promoted apoptosis in cell types of cancer by the action of ADP-ribose polymerase and DNA fragmentation. The cytotoxic effect did not reach normal cells.

Bhave et al. [28] observed the cytotoxic effects of *Clostridium sporogenes* content of the plasma in colorectal cancer cell lines in two-dimensional platforms (in vitro specimens as Petri dishes) and three dimensional (in mice) and observed the death of 26.2% of the cell's colorectal cancer of the three-dimensional model in the first 72 hours of application.

Zymosan-A, complex proteins, and carbohydrates synthesized by *Saccharomyces cerevisiae* act on gram-positive and gram-negative bacteria promoting their lysis. It has been shown to be efficient in the release of cytotoxic compounds from such bacteria after causing their lysis and it has been found that these microbial substances have a cytotoxic effect on tumor cell lines. The mode of action would be due to the stimulation in Toll and phagocytic receptors leading to a strong synergy and, consequently, in the temporary or permanent elimination of some tumor cells [29].

The activity of histone deacetylases has a strong relationship with expression and poor prognosis in prostate cancer, and this knowledge can represent a gateway to the development of an effective therapy against the activity of these proteins.

Sun et al. [30], observing these aspects, used the Chromopeptide-A, a peptide with activity regulating the expression of the histones in the bacterial DNA, found in the bacterium *Chromobacterium sp.* for the treatment of T-cell lymphoma. The effects showed selective inhibition of the chromopeptide-A of histone deacetylase. The desacelitases histones are generally badly expressed in prostate cancer, promoting the uncontrolled tumor growth. In mice, after the in vitro test phase, the action of chromopeptide-A was observed in suppressive activity in the tumor growth, revealing itself as a mutagenic potential for the abnormal development of tumor cells.

Conclusion

The information obtained in the present study allowed to visualize in a general way the current state of the researches on bacterial activities related to cancer. Bearing in mind the role of the microbiota in the major human systems and their influence on the health of individuals, we have found research with evidence of its activity regarding tumor diagnosis and treatment. However, there have been no conclusive studies where the therapeutic potential, already recognized, has been consolidated, which suggests the need for investments in the development of the same that aim at the applicability of these microorganisms in procedures against cancer.

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