Microorganisms and cancer: scientific evidence and new hypotheses

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. Abstract

Summary

The involvement of microorganisms in human cancer has been known for over a century and different types of parasites, bacteria and viruses have been implicated in oncogenic processes. Within the bacteria, was first recognized as carcinogenic Helicobacter pylori, which causes gastric cancer and may be related to extra gastric cancers in humans. Helicobacter hepaticus has been associated with liver cancer using animal models. Other bacteria, such psitacii Chlamydia, Borrelia burgdorferi and Streptococcus bovis, have been associated with ocular tumors, skin and colorectal cancers, respectively. In addition, a human intestinal commensal bacteria, Bacteroides fragilis, has been linked recently with colorectal cancer using animal models.

Key words: Cancer. Microorganisms. Man.

Full Text

Introduction

The discovery that the disease producing organisms was one of the major milestones of microbiology in the nineteenth century and, at the end of that century, microbiologists have sought in these organisms the origin of many diseases, including cancer. Several authors have recently carried out reviews of the microorganisms that cause cancer in hombre1, 2.3, among which could be noted in Zur Hausen, winner of 2008 Nobel Prize in Medicine for his work on human papillomavirus and its implication cérvix4 in cancer, 5. Evidence that different parasites, viruses and bacteria are involved in human cancer are becoming more numerous (Table 1) and the latest research results indicate the need for further research into the role of microorganisms in cancer.

Table 1. Microorganisms that have been linked to various cancers

Location	microbial species or host	cancer
Vermin		
Female Gallbladder	Schistosoma haematobium	
Liver	viverinni Opisthorchis	Man
Liver	Female Clonorchis sinensis	

Bacteria
Mouse Colorectal Bacteroides fragilis
Borrelia burgdorferi Leather Man
Ocular Chlamydia psitacii Man
Gastrointestinal Female Helicobacter pylori
Helicobacter pylori Eye Man
Helicobacter pylori Mama Man
Hepatobiliary Helicobacter hepaticus mouse and man may
Streptococcus bovis Small Man

Virus
Epstein-Barr virus (EBV) B cell lymphomas, Burkitt's lymphoma, nasopharyngeal cancer man
Kaposi sarcoma herpesvirus 8 Man
Cervical papillomavirus and different sexual organs Man
Hepatitis viruses B and C (HBV and HCV) Liver Man
HTLV-1 Leukemia Virus Man
Liver SV40 monkey, mouse and hamster
Virus mouse mammary tumor (MMTV) Mama Mouse
Parasites were first

The first human cancer-related microorganisms were different parásitos4. Specifically, Opisthorchis felineus higado6 cancer, Bilharzia (schistosomiasis) and cancer Spirocerca vejiga7 lupi dog with granulomas can refer sarcomas8. Taking into account the results of all these and other studies, the IARC (International Agency for Research on Cancer) concluded that there is enough evidence to implicate in human cancer and Schistosoma haematobium Clonorchis viverrini9. Schistosoma haematobium is currently one of the leading causes of gallbladder cancer in Egypt and Opisthorchis and Clonorchis sinensis viverinni are important factors in cholangiocarcinomas and liver carcinomas in southeastern Thailand and southern China5.

After the virus

The following microorganisms involved in different types of tumors were virus4, 5, and in 1898 had published M'Faydan and Hobday transmission between animales10 warts. In 1911 Rous demonstrated the transmission of a solid tumor, sarcoma of the chicken, células11 free extracts. At this time, other viruses were related to the production of tumors in animals, such as mammary tumor virus ratón12, the poliomavirus13, a virus that causes erythroblastosis in mouse liver and SV40 adulto14 which, from liver monkeys, when inoculated into newborn hamsters, caused tumors in a few months invasivos15, 16. Although these tumors are not reproducing the virus, an antigen específico17 originated as was the case of tumors induced papilomavirus18.

In the case of man, the first oncogenic virus was described by Burkitt, a surgeon who worked in Africa and found lymphoma in children of certain areas geográficas19. Later it

was discovered that the cause was a virus20 later called Epstein-Barr, mononucleosis infecciosa21 responsible. The development of immunological detection of viral antigens to the discovery high titers of antibodies in patients with lymphoma and carcinomas Burkitt22 nasofaríngeos23.

In the 70's got the characterization of a virus isolated from myeloid leukemia aguda24 and detected the presence of mammary tumor virus in mouse milk of women and mama25 cancer. Later it was discovered the involvement of hepatitis B virus in hígado26 cancer, retrovirus identified in a rare form of leukemia humana27, it was discovered the involvement of papillomavirus in cervical cancer women4, 5, the involvement of the virus hepatitis C and cancer hígado28 herpesvirus 8 as the most likely agent Kaposi29 sarcoma.

Bacteria after viruses

Although developed Bacteriology Virology long before the last microorganisms involved in human cancer were bacteria, and not until 1905 that published the first results on the isolation of bacteria from tumors, the surgeon called Doyen30 Micrococcus neoformans. Even prepared a vaccine, he said, cured cancer and was applied by Wright, who described this vaccine cure a case of inoperable31 cancer. Wright's group observed that the characteristics of this bacterium were consistent with those of the genus Staphylococcus32. Obviously, the techniques of that time to cancer diagnosis or identification of bacteria were not confident enough to engage Staphylococcus bacteria in cancer, even causing infections in patients with cáncer33, 34, has been isolated, together with other bacteria, in solid tumors, such as mama35.

The interest aroused by the involvement of various viruses in different cancers relegated the study of bacteria in these diseases into the background and, to the late twentieth century, no bacteria was clearly related to the production of tumors, with Helicobacter pylori first bacterium known to be carcinogenic to humans. His involvement in gastric cancer was discovered in 199136,37,38,39 and in 1994 was recognized H. carcinogénico9 pylori agent. Some years later it was discovered that the ability to produce gastric cancer was related to the presence of certain regions in the genome of the bacterium, called pathogenicity islands because their ends are directly repeated DNA sequences that set them apart from the rest of the genome. These regions are absent in nonpathogenic strains, which may acquire by transfer genética40, 41. The islands belong to Helicobacter pylori secretion system IV42, 43, present in other pathogenic bacteria such as Agrobacterium tumefaciens, responsible for tumor formation in plants superiores44.

Since the discovery of the involvement of H. pylori in gastric cancer, several bacteria have been identified in various tumor types, but has not yet been shown to be the direct cause of carcinogenesis, as in the case of Chlamydia psitacii and various types of cancers oculares45, Borrelia burgdorferi and piel46 lymphomas, different species of Streptococcus and colon cancer and other cancers digestivos47, 48 and, finally, between Bacteroides fragilis and colorrectal49 cancer.

Koch's postulates in cancer

Already in the twenty-first century research on bacteria possibly involved in cancer has continued, although basically centered on Helicobacter pylori, on which there are numerous recent reviews publicadas50, 51.52. Prove that a microorganism is capable of inducing cancer is difficult because an infectious agent may trigger the initial events of oncogenesis but absent in the tumor final1, 5. Since Robert Koch enunciated his famous postulates that must be met to ensure that a microorganism is responsible for an infectious process, only in the case of Helicobacter pylori have been demonstrated in man and only in the case of gastritis. And yet, since it was first observed in the human gut bacteria linked to Marshall showed úlceras53 until Koch's postulates had to spend more than a siglo54. However, the recognition of this bacterium as carcinogenic class I got only 9 years tarde9. Today, Koch's postulates can only be met using animal models, but often can not even isolate the organism responsible and must be used to study microbial genes present in cancerous tissue samples. Therefore, it might be convenient to redefine the Koch's postulates when microorganisms may not be present in tumors at the time of detection.

Bacteria involved in gastrointestinal cancer

After two decades of research, is now fully accepted the role of H. pylori in certain types of gastric cancer and therapy for the eradication of bacteria is part of the treatment of these cánceres55, 56.57. Numerous studies have been conducted to try to establish the specific mechanisms of interaction of this bacterium with hombre58, 59, his virulencia60 factors, 61 and the secretion system to which belong the islands of patogenicidad62, 63. It has been shown that the risk of gastric cancer caused by H. pylori is increased in patients infected with strains carrying the cagA gene located on an island patogenicidad64. However, the wide distribution of this island in the population infected with H. pylori casts doubt on these findings, it seems that there are differences between the types of cancers, most notably a relationship of strains carrying the island with gastric tumors with morphological similarity with the related intestinal tissue p53 mutations found in cancer intestino65. However, in diffuse-type gastric cancers are involved in both strains carrying the island and those who did not contienen66. In addition certain alleles of vacA gene, involved primarily in gastritis, are also associated with cancer gástrico67, 68. Although variations have been found in the sequences of the genes of the cag island of H. pylori in some populations, which could impede its use in the diagnosis of virulent strains of this bacteria69, 70, what does seem clear is that the presence of the entire island in H. pylori is associated with gastric symptoms more intensos71. Very recently it has also confirmed that gastrin is an essential cofactor of gastric cancers induced by H. animales72 pylori models.

Taking into account the severity and the increase of gastric cancer in the last decade in some regions of mundo73, including that produced by H. pylori eradication has been proposed for this bacterium in all patients in whom this is found, but has not developed cancer, as this is a long process, in the early stages may manifest only as a atrófica74

gastritis and have been shown to cure virtually all patients with gastric lymphoma MALT57 type. However, other types of gastric cancer, eradication of this bacterium only gets reduced by one third its prevalencia75. Furthermore, the eradication of this bacteria is not achieved in all cases and patients infected with strains carrying the pathogenicity islands present greater vacA and cagA erradicación61 failure. Thus, we have conducted numerous studies on the mechanisms involved in host immune response to the infección76 to facilitate the development of a vaccine to prevent cancers caused by Helicobacter pylori77.

Taking into account the relationship of H. pylori with stomach cancer, has raised the possible involvement of this bacterium in cancer-related bodies digestive system, as has been found in bile and gallbladder, postulating the involvement of H. pylori in the liver and kidney cancers in hombre78. However, more detailed studies and more standardized protocols to detect bacterial DNA or anti-Helicobacter bacteria in order to relate this with biliar79 tract cancers, 80. Several studies have found DNA from H. pylori in human liver carcinomas, but in some cases not established the exact species of Helicobacter present in mismos81, 82.83. Another species of the genus Helicobacter, H. hepaticus, has been implicated in hepatobiliary cancer animales78 models, 79,84,85. Very recently, using techniques of molecular biology and immunology have described the presence of H. gallbladder hepaticus in patients with various digestive ailments, including cancer gástrico86. With regard to pancreatic cancer, the results are contradictory, although it has found a positive relationship between the presence of H. pylori and this type of tumors in non-smokers or bebedores87. In the case of the esophagus and larynx results indicate no association with this bacteria88, 89.

The increased risk of colorectal cancer has been linked to infection with various microorganismos90, including bacteria include H. Streptococcus bovis92 pylori91 and in man, and H. hepaticus in ratón93. However, further studies are needed to elucidate whether the latter species can cause cancers such humanos94. In the case of Streptococcus bovis, their relationship with colorectal cancer is well established since the mid-7047.95, although currently some strains of this species have been reclassified in S. infantarius and S. gallolyticus96. According to epidemiological studies have found a very high in the case of S. gallolitycus colon cancer, while S. infantarius has higher correlation with cancers of other organs related to digestive system, such as pancreatic duct and biliares96. Other very recent studies have found that S. gallolyticus plays an essential role in the progression of normal colorectal mucosa, adenoma and cancer a colorrectal97. Since endocarditis caused by Streptococcus are associated with cancer colorrectal47, 48.95, has been proposed that colonoscopy should be mandatory in cases of endocarditis caused by these microorganismos98.

In addition to these bacteria has recently been published tumor induction by Bacteroides fragilis, an intestinal commensal bacteria from man, whose role in colorectal cancer could be similar to that of H. pylori in gastric cancer. It has been shown that enterotoxigenic strains of these bacteria produce colitis and induce the formation of tumors in the colon of mice via activation of T helper type lymphocytes may be involved in the production of cancer also humanos49.

Bacteria involved in extra gastric cancers

Although the first bacterium described as cancer-producing agent may correspond to Staphylococcus aureus and some authors have attempted to relate mama32 cancer has never been shown their involvement in human cancer, even in a recent study using cell cultures have shown that an extracellular protein involved in the adherence of S. aureus can prevent cancer bone metastases mama99. However, recently there have been reports of infection with S. aureus concomitant with breast cancer that is not very clear the relationship between the two enfermedades100. In addition, recently described the presence of human papillomavirus type 16 (HPV-16) in the genomes of different bacteria, including Staphylococcus aureus, isolated from cérvix101 cancer. The authors suggest that the presence of these viruses in the bacterial genome could explain the progression of an infection with HPV-16 in cervical cancer using the bacterium as vector101.

Recent research has also linked to H. pylori extra gastric cancers, including lung and mama102, 103.104 mainly via induction of gastrin, which, apart from a hormone, a factor involved in carcinogenesis, tumor growth and metastasis of these two types of tumores102, 103. Together, stress and mast cells located in the BBB can trigger a series of reactions that facilitate the development of brain metastases from lung tumors and mama105. H. pylori is involved in this process and has proposed that its eradication may prevent this type of metastasis cerebrales106.

The presence of Borrelia burgdorferi DNA in lymphomas has led some to suggest a relationship of this bacterium with non-cutaneous Hodgkin46. The bacteria can survive in the skin of patients for decades and occasionally can develop B cell lymphomas and, additionally, other type neoplasis carcinoma, so it has proposed a relationship of B. burgdorferi with this type of tumores107.

In recent years also been associated with different bacteria ocular108 cancers among which we highlight H. pylori and Chlamydia. In MALT ocular tumors have found conflicting results regarding the involvement of H. pylori, as some studies suggest an involvement of this bacteria109, 110, while others show negativos111 results. It seems that Chlamydia is most probably involved in eye cancers and has proposed its elimination, along with that of H. pylori, as pretreatment therapies agresivas46, 109. Chlamydia psittaci is the only species identified by the time type MALT109 ocular tumors, 111.112, and some authors have found differences geográficas111, being positive relationship between this bacterium and ocular cancers and negative Austria112 Italia46 and Unidos113 States. It is thought that these discrepancies may be due to the methodology used for the detection of bacterias114. Some authors have found that other species, Chlamydia trachomatis, may be a risk factor when it coexists with some types of human papillomavirus carcinomas115. In the case of ovarian cancer appears that this bacterium could induce an inflammatory response that would lead to different types of cancer, although the authors recommend further studies amplios116.

Metagenomics, a new way of detecting tumor-producing bacteria

It is now recognized that bacteria may be involved in different types of cancers, but not easy detectarlas1 due to multiple reasons, including the fact that cancer is not the result of an acute infection and thus the causal agent can not recover from tumor5. However, viral or bacterial DNA may persist for some time, either in the tumor itself, either in the peritumoral area, so that molecular techniques based on the amplification of bacterial DNA in tumor tissues are the most commonly applied for detection and identification of bacteria in tumors. Even techniques have been proposed based detection "find" the exogenous DNA sequences corresponding to the tumor after sequencing DNA fragments mismo117, 118.119. It is seldom necessary to assume that they will be able to fulfill Koch's postulates, because although disposes of pure cultures, confirmation of the carcinogenic potential of microorganisms must be obtained in animal models, as has happened recently in the case of the bacteria Bacteroides fragilis, whose role is carcinogenic in man assumed from the findings in ratón49.

Molecular biology techniques that allow the identification of microorganisms in the absence of insulation is known as metagenomics and are based on the amplification of microbial genes directly from a sample, whose subsequent sequencing allows the identification of microorganisms present in the misma120, 121 . Some metagenomic techniques have the advantage of allowing analysis of microorganisms in complex ecosystems such as cavity or intestino123 oral122. To analyze these samples can be applied several techniques, such as DGGE124 or SSCP125, respectively based on the different electrophoretic mobility changes in the pattern of distortion or secondary formation of DNA single strand 16S ribosomal gene, whose sequence is the basis for classification and identification of bacteria. However, for the analysis of complex populations are especially useful intergenic spaces located between the 16S and 23S ribosomal genes (ITS) in bacteria and between 18S and 28S genes in fungi, which can be separated electrophoretically in a technique called RISA (ribosomal intergenic spacer analysis). Since the size of the ITS in bacteria is highly variable, RISA technique permits the separation of the ITS of most bacterianos126 groups. The subsequent sequencing of the separated fragments allows identification of bacteria, as they are sequenced in all pathogenic bacteria and major hombre126 diners. Using this technique we have analyzed the intestinal bacterial populations in individuals affected by cancer and laringe126 colorrectal127.

Metagenomic techniques have the advantage of allowing identification of cultivated and uncultivated microorganisms present in the human microbiome both healthy subjects and those affected by processes tumorales128, 129. During these are changes in the microbiome resulting from the process itself tumoral129 for antibióticos130 treatments, 131 or radiation treatments and quimioterápicos130, 132. Therefore, metagenomics is the most promising tool in the investigation of the microorganisms present in tumors, since new massive sequencing techniques (next-generation sequencing) enable the analysis of millions of sequences in record time and at competitive prices. There is no doubt that this type of techniques that allow the detection of microbial genes in any sample, contribute substantially to the knowledge of the microorganisms involved in the

production of tumors.

Conflict of interest

The authors declare no conflicts of interest.

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