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Interplay between viruses and bacterial microbiota in cancer development

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ABSTRACT

During the last few decades we have become used to the idea that viruses can cause tumors. It is much less thought of and discussed, however, that most people infected with oncoviruses will never develop cancer. Therefore, the genetic and environmental factors that tips the scales from clearance of viral infection to development of cancer is currently an area of active investigation. Microbiota has recently emerged as a potentially critical factor that would affect this balance by increasing or decreasing the ability of viral infection to promote carcinogenesis. In this review, we provide a model of microbiome contribution to the development of oncogenic viral infections and viral associated cancers, give examples of this process in human tumors, and describe the challenges that prevent progress in the field and their potential solutions.

1. Introduction

As the human lifespan lengthens, the incidence of cancer worldwide is also increasing. The World Health Organization predicts the frequency of cancer occurrence to increase by 70% over the next two decades [1,2], indicating a rise in the global cancer epidemic. One of the established causes of cancer is viral infection, which is responsible for 20% of the global cancer burden [3]. Among those, the most common are Human Papilloma Virus (HPV), Hepatitis C and B viruses with others such as Epstein-Barr Virus (EBV), Human Immunodeficiency Virus (HIV), and Kaposi Sarcoma Herpesviruses (KSHV) contributing to less than 3% of cancers worldwide [4]. These viruses use two different strategies to cause cancer: first, by directly affecting host cell machinery (e.g HPV); and second, indirectly, by inhibiting the human immune system (e.g. HIV) [5,6]. It is common knowledge that the development of some cancers require viral infection such as HPV for cervical cancer. It is less known, however, why most people infected with oncogenic viruses will never develop cancer.

A hint in solving this puzzle may come from studies demonstrating the crucial role of microbiota (collection of microorganisms living with the host) in the course of viral infections [7–10]. Moreover, microbiota have been recently implicated in different diseases associated with aberrant immune responses ranging from diabetes and autoimmunity to obesity and cancer [11,12]. For example, a recent epidemiologic study reported an association between antibiotic exposure and development of several malignancies such as esophageal, gastric, pancreatic, lung, prostate, and breast cancers [13].

Studies thus far have placed emphasis on gastrointestinal microbiota and its role in the development and progression of gut-associated malignancies [14]. For example, *Helicobacter pylori* causes gastric adenocarcinoma and is a classic case of oncogenic bacteria [15]. Intestinal infections with other bacteria such as *Salmonella typhi* [16] and *Streptococcus gallolyticus* (*bovis*) [17] were also linked to development of hepatobiliary and colorectal cancers, respectively. These studies represent additional support for specific microbiota members as an understudied environmental factor contributing to protection from or development of virus-associated cancers. Even though the gut microbiome represents the majority of bacteria in the human microbiome [18], other body sites such as the vagina and oral cavity have been explored for their participation in cancer development and progression.

Oncogenic properties of virus and bacteria, individually, are popular fields of investigation. However, the interaction between those two in the context of cancer has not been well investigated. Nevertheless, in recent years we have witnessed an increasing number of attempts to interrogate this three-way interaction, particularly the influence of microbiota on the progression and acquisition of oncogenic viral infections. But the question remains, are bacteria the good or bad guys? In this review, we provide a model of microbiome contribution to the development of oncogenic viral infections, discuss examples of this process in human tumors, and describe obstacles in the field and their potential solutions.

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2. Model description

The role of bacteria (and bacterial microbiota) in viral infections leading to cancer can be assigned to two broad categories: bacteria influencing the viral particles or affecting host interaction with the viral infection. On the one hand, healthy microbiota was shown to contribute to infections by interacting with viruses directly and through bacterial by-products [7–10]. It was reported that commensal microbiota augment the transmission of mouse mammary tumor virus [19,20], bacterial lipopolysaccharides enhance virion stability of poliovirus [21], and enteric bacteria promote norovirus infection through histo-blood group antigen-like substances [9,22]. On the other hand, healthy microbiota are critical for immune system development, especially on mucosal surfaces [23]. Antibiotic-treated mice exposed to mucosal influenza virus was observed to have impaired innate and adaptive antiviral immune responses and delayed clearance of the virus [24]. These and other studies define microbiota as a putatively important factor for development of virus-associated cancers.

Herein we propose a model for the three-way interaction between bacteria, virus, and mammalian host, highlighting two distinct mechanisms for the contribution of microbiota to virus-associated cancers. The first involves direct effect of interaction of bacteria and bacterial products on viruses, primarily affecting their infectivity (Fig. 1A). The second involves bacteria-host interactions leading to changes in host gene expression and subsequent activation/repression of viral expression or direct promotion of inflammation synergizing with tumorigenic effects of virus (Fig. 1B). There is evidence to suggest that the role of bacteria can be positive or negative in terms of disease progression with each of these cases. In this review, we discuss conventional tumor viruses and explore the role of gut, vaginal, and oral microbiota components in both of these mechanisms.

3. Gastrointestinal microbiome

The gut microbiome is the largest microbial community of the human body. Recent discoveries show its involvement in a variety of functions, including immune system training and metabolism regulation [25–27]. Separate members of gut microbiota as well as dysbiosis (i.e. non-specific alterations of mammalian microbial community) have been implicated in disease development and progression. Among most prominent examples are diabetes [28], irritable bowel disease [25], and cancer [29,30]. Additionally, intestinal microbiota has been implicated in modulating the effect of different anti-cancer treatments [31–33]. Helicobacter species, in particular *Helicobacter pylori*, is the most well studied bacterial member of the gut community that causes cancer [15].

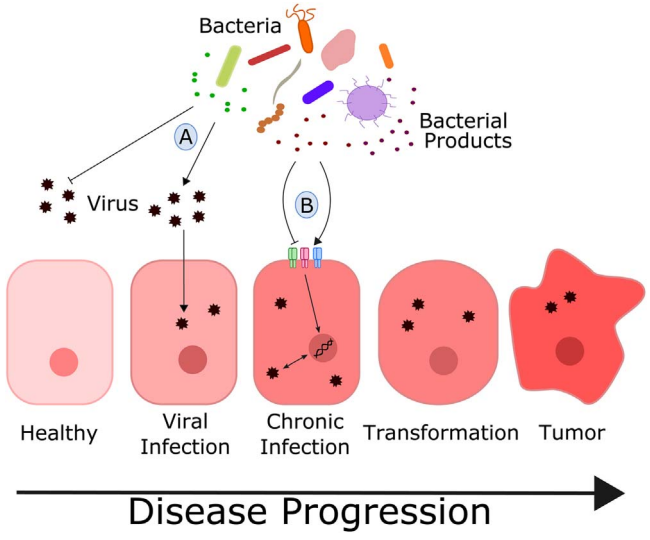

Fig. 1. Model of bacteria-virus interactions in cancer development and progression: (A) direct interaction between bacteria or bacterial by-products and virus resulting in inhibition or promotion of viral infection into host cell; (B) indirect interaction between bacteria and virus mediated by host-response to bacterial stimuli.

3.1. Hepatitis viruses

The second leading cause of cancer mortality is liver cancer [34]. The most prevalent histologic type of primary liver cancer is hepatocellular carcinoma (HCC) [35] primarily caused by chronic infection with hepatitis B (HBV) or hepatitis C (HCV) virus [36]. Although both viruses can cause cancer, HCV currently attracts stronger interest from the scientific community possibly due to absence of the vaccine against HCV.

The pathogenicity of both HBV and HCV involves a combination of direct and indirect mechanisms. The HCV encoded core, nonstructural protein 5A (NS5A) and NS3, and HBV encoded X antigen (HBx) are able to promote host cell proliferation. Both viruses are similarly capable of blocking cell immune response, inhibiting apoptosis while promoting angiogenesis and metastasis. By contrast, chronic inflammation caused by oxidative stress also contributes to the process of carcinogenesis [6].

While HCV is oncogenic, not all patients suffering from chronic hepatitis C will develop cancer. One of the first indications that bacteria may be a critical parameter in this cancer came with the observation that mice infected with Helicobacter-like bacteria were developing strong inflammatory responses leading to hepatocellular carcinoma [37]. Another group later found an association between *H. pylori* specific antibody levels and hepatocellular carcinoma [38]. Helicobacter DNA was also found in liver and was associated with hepatitis C induced cirrhosis [39] which indicates the ability of *H. pylori* to invade the liver and putatively contribute to the disease development (Fig. 2B). However, a more recent study conducted on mice colonized with *H. pylori* found no indication of bacteria translocation into the liver and no promotion of tumorigenesis. Why this experimental system failed to promote carcinogenesis remains unknown.

Another *Helicobacter* species, *Helicobacter hepaticus,* was demonstrated to cause chronic hepatitis and liver cancer in rodents [37]. In the following study, Fox et al. have shown that presence of *H. hepaticus* in the gut lumen promotes development of hepatocellular carcinoma in HCV infected mice, acting synergistically with viral infection [40]. This process did not require bacterial invasion. *H. hepaticus* was able to activate nuclear factor-κB (NF-κB) pathways in the bowel and liver which led to cell survival and proliferation in the liver [6,40] (Fig. 2C,D). This bacteria, detected in both human intestine [41] and liver [42–44], is suspected to contribute to not only cirrhosis [45] and HCC [42], but also to a set of other conditions such as inflammatory bowel disease [41] and prostate cancer [46]. Consequently, this data suggests a synergistic relationship between *H. hepaticus* and HCV in human cancers.

The link between HBV related oncogenesis and gut microbiota has also been reported. In 2011, Chen et al. found that enteric fungi diversity was positively correlated with a worsened disease state in chronic HBV infection [47]. More recently, Chou et al. reported that in a mice model of age-related HBV infection, sterilization of gut microbiota with antibiotics reduced the ability of adult mice to clear HBV infection [48]. Furthermore, two other human studies observed that a decrease in fecal Bifidobacterium populations was correlated with liver disease progression of HBV infection [49,50]. Interestingly, Bifidobacterium species have been shown to eliminate HBV in vitro [51] and promote antitumor immunity in a mouse model [52]. Thus, it is plausible that Bifidobacterium plays a protective role against liver and other cancers (Fig. 2A). However, further experimentation is warranted to establish how antiviral and antitumor effects of these bacteria contribute to overall protection against malignancy.