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Review

Does bacterial infection cause genome instability and cancer in the host cell?

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ABSTRACT

Research of the past several decades suggests that bacterial infection can lead to genome instability of the host cell often resulting in cancer development. However, there is still a substantial lack of knowledge regarding possible mechanisms involved in the development of genomic instability. Several questions remain unanswered, namely: Why has the causative relationship between the bacterial infection and cancer been established only for a small number of cancers? What is the mechanism responsible for the induction of genome instability and cancer? Is the infection process required to cause genome instability and cancer?

In this review, we present a hypothesis that the bacterial infection, exposure to heat-killed bacteria or even some bacterial determinants may trigger genome instability of exposed and distal cells, and thus may cause cancer. We will discuss the mechanisms of host responses to the bacterial infection and present the possible pathways leading to genome instability and cancer through exposure to bacteria.

Contents

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1. Introduction

While smoking remains the number one cause of lung cancer, infection with pathogens is the second largest preventable cause of cancer in humans [1]. Although viral infection is by far the main reason of pathogen-induced cancers, bacterial infection also makes a significant contribution to the occurrence of cancer. In general, the association of infectious agents with genome instability and cancer has been known for a while.

Early observations identified bacteria at the site of carcinomas [2]. For example, in 1772, an observation was made that bronchogenic lung carcinomas frequently appear in the areas of pulmonary scars from tuberculosis, thus implicating *Mycobacterium tuberculosis* as one of the causes of lung cancer [3]. In the middle of 19th century, Rudolf Virchow made one of the first epidemiological observations on the relationship between a parasitic disease and cancer, noting a high frequency of bladder carcinoma among patients infected with *Schistosoma haematobium* in endemic regions in the North Africa [4]. In 1910, Peyton Rous showed that an avian sarcoma could be transmitted to healthy animals through a filterable agent [5]. In 1939, it was also Rous who described the oncogenic potential of the cottontail rabbit papillomavirus [6]. Rous was the first scientist who demonstrated that cancer might have an infectious agent by showing in his research that an RNA virus caused carcinogenesis.

Despite an original interest in the field, research into infectious agents causing cancer failed to show any significant advances until the 1950s–1960s. Work of Renato Dulbecco, David Baltimore, Howard Temin and many other researchers demonstrated that some RNA viruses could cause cancer by getting into cells, integrating into the genome and causing mutations or changes in transcriptional regulation. In the late 1960s, a response to the field of infectious cancer-causing viruses sparked the US Government to create the US Special Virus Cancer Program. Since that time, numerous papers have demonstrated the causative relationship between viral infections, genome instability and cancer [7–9]. Over the past half-century, research has expanded in the field of epidemiology and biology of infectious diseases, epidemiological and serological methods, and the biological knowledge base for understanding infectious agents [1]. In 1991, it was estimated that a large fraction of human cancers might be associated with viral infections, including cervical cancer caused by human papillomaviruses, T-cell leukemias and lymphomas caused by human T-cell leukemia viruses, liver cancer caused by the hepatitis B virus, and Burkitt's lymphoma and nasopharyngeal carcinoma caused by the Epstein–Barr virus [10]. Later on, it was estimated that up to 15% of cancers worldwide have originated from an infectious agent, amounting to over a million cases per year of the global total [11]. A theory emerged that a significant portion of cancers being treated today is preventable, although this requires a well-understood relationship between the presence of a causative agent, the process of infection, and the development of a particular cancer.

Unfortunately, research on possible effects of bacterial infection was largely left behind. Although early studies identified bacteria at the sites of carcinogenesis, most of the researchers were not able to isolate bacteria from the site of infection. Since carcinogenesis is often a long process, it is difficult to establish the link between the initial infection process and carcinogenesis. In this review, we first will briefly describe both the effect of viruses on genome stability and cancer and the effect of bacterial infection, including the processes of inflammation and immune response, on genome stability and cancer.

2. Viral infections and carcinogenesis

Viral infection is proposed to induce genome instability and cancer through several major mechanisms, with chronic inflammation, direct cell transformation and immunosuppression being the most important ones. First, a virus is able to integrate its genomes into the host genome by either physically disrupting tumor suppressor genes or inserting themselves close to regulatory elements of pro-oncogenes or tumor suppressor genes, which leads to their activation or inactivation [12]. This phenomenon of a direct viral transformation of the host cell results in an inability of the host cell to effectively regulate cell cycle progression, causing an increase in proliferation and promoting tumorigenesis.

Moreover, a continuous presence of an infectious agent such as a hepatitis C virus in the organism leads to chronic inflammation [13]. Inflammatory cells form and release reactive oxygen and reactive nitrogen species, ROS and RNS, respectively. Another source of cytotoxic mediators such as ROS and RNS are phagocytes [14]. Radicals have multiple effects on the cell. A massive amount of ROS and RNS are able to cause all sorts of DNA damage, with double-strand breaks being the most dangerous [15]. Radicals have the ability to alter the enzymatic activity and gene expression and form DNA–protein crosslinks [16]. Smaller concentrations of radicals play a critical role in signaling and are able to deregulate the process of cell division and cell response to stress. In addition, radicals are able to prime cells rendering them either more tolerant or more vulnerable to future infections [17]. These three mechanisms of action of radicals in an inflammatory cell contribute profoundly to DNA damage and carcinogenesis [18].

Finally, viruses that induce immune suppression (such as the human immunodeficiency virus (HIV)) contribute to the aggressiveness of tumorigenesis. The innate immunity and adaptive immunity are two primary protection mechanisms against cancer. The first line of defense includes protective digestive enzymes, macrophages and natural killer cells, whereas the second line of defense involves cytotoxic T lymphocytes. HIV infection severely suppresses both lines of defense. The co-infection of HIV with human papillomavirus (HPV) results in up to a 22-fold increase in cervical cancers as compared to HPV infection alone [19].

How often does a virus induce oncogenesis? Viral infections are very common in nature, but virus-associated malignancies are much more rare, at least the established connection between viral infection and cancer is relatively rare [20]. It is often difficult to establish a link between viral infection and cancer. Acute infection processes rarely lead to cancer; it is chronic infection that is typically associated with oncogenesis. Thus, although the link between viral infection and the oncogenesis process is undeniable, it is still believed that infections are relatively minor causative agents in the development of oncogenic processes.

3. Bacterial infection and carcinogenesis

The ability of bacteria to induce cancer is still a highly debated subject. Several parameters must be met to "pin" a pathogen to cancer. When bacterial infection persists chronically, as in the case of infection with (*Helicobacter pylori*), then it is easier to establish its possible association with carcinogenesis. In contrast, when infection is acute, it is difficult to relate it to cancer development, especially if there is a significant time between the infection process and carcinogenesis. Thus, the first parameter to be met is the establishment of the link between the infection process and carcinogenesis. Second, an infectious agent has to be found at the tumor site, although this does not guarantee the causal relationship. Third and this may only be relevant for viral pathogens, pathogen