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Review Article

Microbial Carcinogenesis

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Abstract: Carcinogenesis is a multistep process and multifactorial disease. It is estimated that in developing countries upto 25% of tumours are associated with various microbes. Microbial carcinogenesis is a major public health problem. Viruses are now accepted as bonafide aetiologic factors of human cancer. A formidable level of evidence has determined that there exists a relationship between certain bacteria and cancers. This article focuses mainly on human oncogenic viruses as well as emerging role of bacteria in cancer.
Keywords: Carcinogenesis; Virus; Bacteria; candidiasis; parasites.

INTRODUCTION

Carcinogenesis is a complex process involving the contribution of many different factors. The suggested categories of cancer causation include spontaneous, hereditary, environmental and interaction of gene and environment. Infectious agents cause almost 20% of cancers worldwide, 10 – 15% of them are caused by viruses [1].Microbial carcinogenesis is a major public health problem. Though many infectious agents causes cancer but Human papilloma virus, Hepatitis B and C virus and Helicobacter pylori, a bacterium that triggers stomach cancer causes lion's share [2,3]. The mechanism by which infectious agents might cause cancer include: (1) Induction of chronic inflammation or rapid cell proliferation. (2) Direct carcinogenesis through DNA damage. (3) Suppression of immune responses against cancer. (4) Immune stimulation of cancer growth factors [3].

The link between cancer and inflammation was proposed by Virchow in 1860's and since then the potential relationship between cancer and inflammation have been studied [4].Viruses are now accepted as bonafide aetiologic factors of human cancer [5].

Viruses and cancer

Though a number of RNA and DNA viruses have proved to be oncogenic in animals but the main viruses that have been linked with human cancer are:

Oncogenic DNA Viruses

Human papilloma virus (HPV)
Hepatitis B virus (HBV)
Epstein Barr virus (EBV)
Kaposi's sarcoma associated herpes virus (KSHV, HHV-8)

Oncogenic RNA Viruses

Human T-Cell Leukemia Virus Type 1
Hepatitis C Virus (HCV) [4]

Host response modulation

Viruses may contain genes that have the potential to modulate host responses. The various viruses bypass their hijack from immune system or prevent themselves from being detected by immune system by a number of viral strategies which are as follows: (1) Restricted expression of viral genes and proteins thus making infection nearly invisible to host. (2) Escape from antibody and T cell recognition through antigenic variation. (3) Infection of sites that are relatively inaccessible to immune responses. (4) Infection of immune cells. (5) Down regulation of expression of host MHC class I molecules in infected cells. (6) Blocks p53 dependent apoptosis [6].

Perhaps the most prevalent cancer causing virus is Human Papilloma Virus. The high risk HPV's (types 16 and 18) have been linked in the genesis of several cancers, mainly cervical squamous cell carcinoma and carcinoma of anogenital region. The products of two viral genes, E6 and E7 are related to the oncogenic potential of HPV. The E6 binds to and inactivates the tumour suppressor p53, while E7 binds to and degrades the tumour suppressor pRb. The inactivation of p53, therefore, results in the

dysregulation of the cell cycle and allow cellular mutations to occur. These two oncoproteins subvert key cell cycle and regulatory processes such as cyclin, cyclin dependent kinases (CDKs) and cyclin dependent kinase inhibitors (CDIs) to transform and immortalize the host cell [4, 7].

Epstein - Barr virus (EBV), named after it discoverers Michael Epstein and Yvonne Barr was the first human virus to be directly implicated in carcinogenesis. It has been linked in the pathogenesis of several human tumours namely: the African form of Burkitts lymphoma, B-cell lymphomas in individuals with immunocompromised conditions, Hodgkin's lymphoma (not all forms but a particular subset), carcinoma of nasopharyngeal region and some gastric carcinomas and rare form of T cell lymphomas and natural killer cell lymphomas. EBV infects B lymphocytes and epithelial cells of oropharynx. The molecular basis involves hijacking of several normal signalling pathways. One EBV gene, latent membrane protein-1 (LMP-1) acts as an oncogene. LMP-1 contributes to inhibition of p-53 mediated apoptosis in B-lymphocytes by activating bcl-2. It also activates the NF-kB and JAK/STAT signalling pathways and promotes B-cell survival and proliferation [4, 8].

EBV also encodes several nuclear proteins designated as EBV nuclear antigen 1-6 (EBNA 1-6) that could interfere with tumor suppressor proteins function. EBNA-2 is a transcriptional coactivator of several host genes including cyclin D [8].

Epidemiologic studies have suggested chronic infection with hepatitis B (HBV) and C (HCV) causesliver cancers but the precise mechanism through which it acts is still not understood. The oncogenic effects of HBV and HCV are multifactorial. A more likely scenario is that many virus - infected liver cells are destroyed as a result of immunological attack. Such damage stimulates the remaining cells to grow and divide, thereby increasing the risk of genomic damage. Thus the more andmore dominant effect seems to be immunologically mediated chronic inflammation [4].

Kaposi's sarcoma - associated herpes virus (KSHV) also known as human herpes 8(HHV-8) belongs to Herpesviridae family. It is associated with Kaposi's sarcoma, one of the most common tumorin human immune deficiency virus infected patients, primary effusion lymphoma and some type of multicentric Castleman's disease [9].

Human T-Cell Leukemia virus Type 1 (HTLV-1) is currently the only retrovirus accepted as having an etiologic role in a specific human cancer. It appears to act indirectly in the development of T cell leukemia or lymphoma. The CD4 + T subset of T cells is the major target for neoplastic transformation as this virus has tropism for these cells. HTLV-1 genome contains a specific tax gene. The products of this gene stimulates transcription of viral mRNA and host cell genes involved in proliferation and differentiation of T cells. It also dysregulate the cell cycle by enhancing cyclin D activation and inactivation of cell cycle inhibitor p16/INK4 [4].

A previously unknown virus, Merkel cell polyoma virus was discovered recently, 4 years back which causes a rare form of skin cancer, Merckel cell carcinoma [10].

Bacteria and Carcinogenesis

Various laboratory based and epidemiological studies have shown that several bacterial species have been associated with different cancers. The complex relationship between bacteria and humans is demonstrated by Helicobacter pylori and Salmonella typhi infections [11].

Helicobacter pylori was isolated from the human stomach for the first time in 1982. It has been widely recognized as cause of stomach ulcers, but it is now thought to also cause gastric cancer [12]. Once tumour develops there is an increased risk of bacterial infection, often it can be difficult to determine if the bacteria has caused the tumour or if the tumour has developed before the bacterial infection [12].

Possible Pathways for Bacterial Carcinogenesis

The important mechanisms by which bacterial agents may induce carcinogenesis include chronic infection, immune evasion and immune suppression [11].

It has been believed that several bacteria can cause chronic infections. The infection could increase the chances of cell transformation and rate of tumour development through increased rate of genetic mutations by inducing cell proliferation and DNA replication through activation of mitogen activated kinase (MAPK) pathways and cyclin D1. Moreover several infections modulate the expression of Bcl-2 family proteins or inactivates retinoblastoma protein, pRb leading to suppression of apoptosis and allow the partially transformed cell to evade the self -destructive process and progress to higher level of transformation, ultimately becoming tumorigenic [13].

Several species of bacterial strains particularly, Escherichia coli are capable of catalysing nitrosonation in which microbial cells catalyse the formation of N-nitoso compounds from precursor nitrites, amine and amides [14]. The favourable mechanism relevant to the oral cavity is metabolism of potentially carcinogenic substances by the bacteria. The pre-existing local microflora may facilitate tumorigenesis by converting ethanol into acetaldehyde to levels capable of inducing DNA damage [14, 15].

Recent studies have suggested that periodontal disease may promote progression of oral squamous cell carcinoma(OSCC) via podoplanin-dependent pathway. Podoplanin is a small mucin-like transmembrane protein expressed in various specialised cells throughout the body. The periodontal disease causing bacteria produce an extracellular metabolite, Butyric acid thatplays an important role in the progression of periodontal disease. The podoplanin expression will be increased by this butyric acid and ultimately cell migration in certain oral squamous cell carcinoma cell lines suggesting the possibility that periodontal disease promotes the progression of oral squamous cell carcinoma through this pathway [14, 15, 16].

Helicobacter pylori is not the only bacterium now under suspicion as a cause of malignancy but research continues to associate bacteria with other lesser known cancers. Chronic infections with other bacteria like Salmonella typhi can also facilitate development of gall bladder cancers, Chlamydia pneumoniaeis thought to be associated with lung cancer and Chlamydia trachomatis infection with development of carcinoma of cervix, Streptococcus bovis has been linked with malignancy of colon [11].

However, the role of microbiota in the oral cavity is not known. Studies have revealed that microbial flora on the healthy oral mucosa differ from malignant sites. Certain oral bacterial species have been linked with malignancies, but the further evidence is required to support this link. The search goes on for new infectious agents which may play a role in causing cancer [14].

The fungal infections particularly mucocutaneous candidiasis is also known to associate with the development of cancer mainly in patients with a rare genetic disease called autoimmune poly – endocrinopathy – candidiasis ectodermal dystrophy.

The epidemiologic observations have also suggested the role of parasites particularly bilharziasis sometimes termed schistosomiasis haematobium in the causation of cancer. Schistosome are trematode worms that live in the blood stream of human beings. An association between urinary bilharziasis and bladder cancer has been described by the ancient Egyptians and Ferguson in 1911. However the precise role of parasite in the development of cancer remains controversial [17].

CONCLUSION

The multistep nature of microbial oncogenesis provides ample opportunities for interventions to mitigate the process and prevent cancer. The role of viruses in the induction of cancer is well established. Better understanding of the role of microbes in human cancer will have therapeutic implications as control can be instituted. The best strategy is to prevent infection by preventing exposure to oncogenic agents and keep an eye on chronic inflammation. Finally our challenge for the future is to better understand the steps in microbe-induced cancers to optimize both prevention and therapy.

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