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Mini Review

Oncoviruses which are the Source of Human Cancer

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Abstract

Cancer has been seen to affect any tissue in the body is caused by various reasons, one of them being oncovirus. This includes seven different types of viruses- Epstein Barr virus, Hepatitis b, Hepatitis c, Human Immunodeficiency Virus, Human Papilloma Virus, Human Lymphotrophic Virus type 1 and Human Herpes Virus [1]. It has been seen that lymphomas are crucial for the study of these oncogenic viruses. Different types of tumors and mutations are developed in cancer. Development of a specific drug is also the biggest challenge in different cancer treatment. Specific cause of cancers is still unknown. This article primarily discusses the various aspects of these oncogenic viruses in development of cancer.

Keywords: *Oncoviruses; Human Cancer; Human Immunodeficiency Virus*

Introduction

Cancer refers to a group of about 200 complex diseases capable of affecting any of the tissues of the body. Cancers of different origin or source have different features, varied course and varied response to treatment. The most phenomenal feature of cancer is that each tumors is different. This uniqueness creates difficulty in the development of drugs to treat the disease. Cancer is primarily identified as unregulated growth of cells. There are different types of cancer which include solid cancers (carcinoma, sarcomas), liquid cancer (leukemia, lymphoma). Besides them, tumors and mutations are also present. Causes of cancer show great diversity. This includes genetics, neoplastic transformations, chemicals, radiations, microbes etc. A brief portion of oncogenesis by virus (microbes) has been discussed in the following section.

There are 7 commonly known oncoviruses [1]:

- Epstein Bar Virus (EBV)
- Hepatitis B
- Hepatitis C
- Human Immunodeficiency Virus (HIV)
- Human Papillomavirus (HPV)
- Human Herpes Virus 8 (HHV8)
- Human T lymphotropic virus type I (HTLV-I)

Neither of the viruses have been seen to lead the development of cancer as part of their viral cycle. 6 of these viruses have been discussed below.

Epstein Bar Virus

It is a fascinating human herpes virus which provides a unique insight into host: pathogen interactions and complex cellular molecular processes. It was the first identified human tumor virus [2]. In the infectious stage, EBV typically remains associated within the memory B-cells in a latent phase but may also be found in epithelial cells (oropharynx) as well as in subsets of T-cells and NK-cells. It is a causative agent for infectious mononucleosis and multiple lymphoid and epithelial malignancies including B-cell lymphoma, various T-cell/NK lympho proliferative disorders and nasopharyngeal and gastric carcinomas [3]. Latent membrane protein-1 (LMP) is a latent protein of EBV which has been considered tumorigenic due to its property to transform rodent fibroblast in mice. It is seen to be expressed in EBV-transformed lymphoblastoid cell lines, nasopharyngeal carcinoma (NPC) and in EBV-associated lymphoproliferative disorders (EBV-LPDs) [4].

Hepatitis B Virus

China depicts hepatitis B virus (HBV) as an important causative factor of hepatocellular carcinoma (HCC) [5]. Hepatitis B e-antigen positivity and high serum hepatitis B virus (HBV) DNA concentrations have been considered as strong risk factors for HCC recurrence after curative resection of HBV-related HCC. Antiviral therapy after curative treatment is aimed at improving the prognosis by preventing HCC recurrence and maintaining the liver function. Therapy with interferon and nucleotide analogs can be useful for preventing HCC recurrence and improving overall survival in patients undergoing curative resection for HBV-related HCC [6].

HIV

It has been seen that cancer is a leading cause of death among HIV infected people. The major risk factors includes tobacco use (associated with lung, colorectal, stomach, and liver cancer), overweight/obesity (breast and colorectal cancer), alcohol consumption (colorectal and liver cancer), and viral infections (liver, stomach, and cervical cancer) [7]. Highly active antiretroviral therapy or combination antiretroviral therapy has drastically decreased the mortality rate in case of HIV infected people [8].

Human Papillomavirus (HPV)

Human papillomavirus (HPV) is sexually transmitted infection, which is strongly associated with risk of cervical cancer and genital warts. HPV is also known to cause genital cancers, vaginal, including vulvar and anal carcinomas [9]. Both HPV 16 and 18 account for approximately 70% of cervical cancers. HPV infections usually occurs within the first years of sexual activity [10]. Condoms decreases the risk of transmission. But it is seen that women having sexual contact with men using condoms, are still at risk, as condoms are not 100% protective. The HPV virus is also transmitted by direct skin-to-skin contact [9]. The infection has also been reported in self-reported "virgins". Other factors include 30 and above age, infection with multiple HPV subtypes, parity, smoking, immunosuppression, and oral contraceptive use. Quadrivalent HPV vaccine is recommended for all girls in the age group of 11 to 12 along with catch-up vaccination for women up to age of 26. It is seen that it treats 70% of cervical cancers and 90% of genital warts [11]. HPV vaccination reduces rate of HPV-related cancers and precancerous lesions.

Human Herpes Virus 8 (HHV8)

Human Herpes Virus 8 (HHV8) causes Kaposi's Sarcoma (KS) usually in immunosuppressed individuals. It is a malignancy which involves epithelial circulatory systems. KS forms masses in the skin, other cells (*e.g*. B cells) of the lymphatic and lymph nodes or other organs. The lesions are generally purple in colour. They can occur both in a limited area and in a large area. The disease may worsen either gradually or quickly [12]. HHV8 infection alone does not cause clinical K [13]. Individuals with significant immune dysregulation (*e.g*. HIV infection with low $CD4^+$ T cell counts or immunosuppression following organ transplantation) are usually identified with KS lesions [14]. Lytic genes induces the some KS malignant phenotypes such as immune evasion, genetic instability and anti-apoptosis. Several new targets for potential future therapies have been identified, which includes inhibitors of viral replication, inflammation, cell signalling and angiogenesis. For the treatment of KS highly active antiretroviral therapy is used.

Human T lymphotropic virus type I (HTLV-I)

HTLV-I is a cause of lymphoproliferative disease such as adult T cell leukemia/lymphoma (ATL) and it also disturbs the immune responses resulting in HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP). HTLV-I was the first discovered human retrovirus [15]. Nearly HTLV-I infects 10 - 20 million people worldwide [16]. The HTLV-I is known to be an enveloped dimeric positive sense single-stranded RNA virus and the linear genome encodes the structural properties and enzymes such as gag, env, and pol [17]. It contains

a unique region pX at the 3' end which encodes regulatory proteins, such as Tax, HBZ and Rex. The tax protein induces or represses the expression of a large variety of cellular genes and also regulates viral gene expression [18]. Tax protein serves as the primary oncogenic mediator of HTLV-I. Tax protein also induces cell immortalization and transformation in vitro along with tumor formation in transgenic mice [19]. HTLV-I can infect T cells, B cells, and synovial cells. The infection is transmitted via three major routes, which are (1) mother-to-infant transmission (mainly breast-feeding), (2) sexual transmission (3) parental transmission. ATL in most of the cases is accompanied by visceral involvement and lytic bone lesions. Drugs developed to treat this infection includes pralatrexate and mogamulizumab.

Conclusions

Oncoviruses are responsible for 12% of all human cancers. Though these viruses are present in a wide number of individuals, very few actually go to develop cancers.

Viral cancers do not develop acutely after infection, but instead take a time span of about 15 - 40 years for the developmental process. An exception is a rare form of EBV-associated lymphoproliferative disease, which has the chances of occurrence shortly after infection. In cancer cells, viral replication has either ceased or is absent, as active replication would lyse the host cell thus preventing tumorigenesis. The virus may exists intracellularly as naked nucleic acid in the form of a plasmid, episome, or cellular-integrated genome [1]. Lymphomas have been assigned a crucial role in the history of oncoviruses, since both, the first human oncovirus (EBV) and the first human retrovirus (HTLV-1) were discovered from isolates taken from patients with unique lymphoma syndromes [20]. Through the process of development, still a lot is yet to be discovered regarding these special oncogenes.

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