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Editorial

Virus-Based Human Cancers: Another Look

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EDITORIAL

With 4,204,424 infections and 288,472 deaths, as of May 12 2020, the COVID-19 pandemic is turning the entire world upside down, directly and indirectly. It is just a small (125 nm), RNA virus that is causing havoc on the whole world. Compare this to Hepatitis B virus (HBV) that is the most common risk factor for Hepatocellular Carcinoma (HCC)-commonly known as liver cancer [1-3]. Over 400 million people are infected with this virus all over the world [2]. Its counterpart, Hepatitis C Virus (HCV) has infected over 170 million people [2]. Each year over half a million get the liver cancer and in 2018, 700,000 died due to it, out of 800,000 incidences. Another virus causing cancer is Human Papilloma Virus (HPV), which is one of the main causes for cervical cancer. In 2018, 570,000 women had cervical cancer and 311,000 died out of it.

So, did Nature, with all its wisdom and function, and conserving resources, made these and other viruses for a purpose, other than just infecting and killing people? Checking the origin of viruses indicates that they were formed around 3.4 billion years ago, shortly after life first emerged on the planet 3.5 million years ago [4]. Today, with all the things happening, it's tempting to think of viruses as mere pests, that is causing only diseases and sufferings. But one speculation indicates that more than 100 million years ago, a viral infection in a primitive mammal uploaded a gene that helped the placenta evolve, as syncytin is a protein made only by cells in the placenta that viruses used to fuse cells together in order to hop from one host cell to the next. In mammals it fused placenta cells with the uterus, allowing the fetus to draw nutrients from its mother [4].

What are these viruses? Virus is a small organism (varying in size from 40 nm to 450 nm), with just nucleic acids. They are of two types: Deoxyribonucleic Acid (DNA) viruses and Ribonucleic Acid (RNA) viruses. Each of them can be classified into single-stranded (ss) and double-stranded (ds). In addition, they could be with or without envelopes, covering their protein coats [1-3]. For example, HPV is a small, non-enveloped, double stranded, DNA virus that preferably infects skin or mucosal cells. This circular viral genome has approximately 7.9-kbase pairs [3]. Compare this with COVID-19 virus, which is an enveloped, single stranded, RNA virus. There are over 320 types of HPVs and only HPV-16 and HPV-18 play a major role in cervical cancer, the fourth most frequent cancer in women, and the third leading cause of death in women. In addition, HPV causes vaginal, vulvar, anal, skin, head and neck, pharyngeal and penile cancers. Other viruses that cause human cancer include Human Herpes Virus 8 (HH8), Epstein-Barr Virus (EBV), Human T-cell Lymphotropic Virus 1 (HTLV-1). Through their mutagenic activity or their effects on cell behavior, viruses play a significant role in the development of various human cancers. Viruses can disrupt cell behavior in various ways [2], including DNA damages/mutations, disturbing cell regulation. Table 1 shows a partial list of oncoviruses and cancers caused by them in humans.

Table 1: Major Viruses and human cancer [1].

Virus	Genome	Human Cancer
HPV	Double stranded DNA 8k base pairs	Cervical, skin, head and neck cancers, anal, oral, pharyngeal and penile cancers
HBV	Double stranded DNA 3.2k base pairs	Hepatocellular Carcinoma (HCC)
HCV	Double stranded RNA 9.6k base pairs	Hepatocellular Carcinoma (HCC)
HHV-8	Double stranded DNA 165k base pairs	Kaposi's sarcoma, primary effusion lymphoma, and Castleman's disease
EBV	Double stranded DNA 172k base pairs	Burkitt's lymphoma, nasopharyngeal carcinoma, post-transplant lymphomas and Hodgkin's disease
HTLV-1	Double strand DNA 9k base pairs	Adult T-cell Leukemia

Head and Neck Squamous Cell Carcinoma (HNSCC) in non-smokers is identified to be due to HPV-16 and 18, as HPV has a specific tropism for squamous epithelium. HPV infection plays a major role in the pathogenesis of a unique subset of oropharyngeal HNSCCs. These tumors primarily emerge from the lingual and palatine tonsils in the oropharynx. HPV-positive HNSCC has an

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improved prognosis and response to therapy than HPV-negative HNSCC [3]. In a recent meta-analysis, HPV genomic DNA was detected in ~26% of HNSCC. Other studies indicate up to 50% or more of oropharyngeal tumors contained HPV genome. A multinational study by the International Agency for Research (IARC) indicated 18% of oropharyngeal tumors are HPV-positive, indicating geographical variation. HPV-16 accounts for 90% to 95% of HPV-positive tumors [3]. This knowledge that HNSCC could be caused by HPV helps to diagnose and treat tumors in non-smokers. HPV-related cancer is a distinct established entity that can be reliably diagnosed. A meta-analysis of chromosome aberrations in human HCC shows the several specific gains and losses that correlate with etiology and histological grade [3], which can be used to devise novel therapeutics.

Using the knowledge that cancer cells have viral genes and normal cells don't have them could be used for treatment options, in addition to vaccines and other non-viral agencies. Our innate and adaptive immune systems also play a major role in converting the infection into a carcinoma [5]. In addition, electrical pulses, with/out a chemo drug could be used for advanced, recurrent, inoperable, chemo resistant tumors of HNSCC and liver cancers [6,7]. Considering that up to 15% of all cancers are caused by viruses and the cancer drug revenue totals over one hundred billion dollars, virus-based cancer is a still fertile field to devise new and alternate vaccines and therapies for safe, economical and efficacious clinical applications.

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