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CAN A VIRUS CAUSE CANCER?

A LOOK INTO THE HISTORY AND SIGNIFICANCE OF ONCOVIRUSES

Niema Rważavian

THE IMPORTANCE OF ONCOVIRUSES

Cancer, a disease caused by unregulated cell growth, is often attributed to chemical carcinogens (e.g. tobacco), hormonal imbalances (e.g. high levels of estrogen), or genetics (e.g. breast cancer susceptibility gene 1). While cancer can originate from any number of sources, many people fail to recognize another important etiology: oncoviruses, or cancer-causing

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viruses. Oncoviruses are often overlooked because current preventative measures against cancer focus on modifiable lifestyle risk factors, such as diet and exercise. Despite limited awareness, oncoviruses are nevertheless important because they represent over 17% of the global cancer burden (Parkin 2006). Studies have demonstrated that if these pathogens were eliminated, there would be 23.6% fewer cases of cancer in developing countries and 7.7% in developed countries, leading to a Preduction of 1.5 million and 390,000 cases of cancer per year, respectively (Parkin 2006). Given their significant yet surprising role in human cancer, oncoviruses are considered to be the second-most important risk factor after tobacco consumption for cancer development in humans (zur Hausen 1991). Currently, six viruses have been proven to cause over ten types of cancer in humans (see Table 1).

THE HISTORY OF ONCOVIRUS RESEARCH

The discovery of oncoviruses dates back to the early 20th century, when in 1908 Oluf Bang and Vilhelm Ellerman, researchers at the University of Copenhagen, demonstrated that leukemia could be induced in healthy chickens by treating them with a filterable extract containing the avian leukemia virus (Javier and Butle 2008). Despite their results, the discovery of the first known tumor virus was credited to Payton Rous, who proved that the Rous sarcoma virus caused cancer in Plymouth Rock chickens

(van Epps 2005). Although many in the scientific community were unconvinced of the role of viruses in cancer, research on the subject nevertheless continued. In 1933, Richard Shope discovered the first mammalian oncovirus, cottontail rabbit papillomavirus (CRPV), which could infect cottontail rabbits, and in 1936, John Bittner discovered the mouse mammary tumor virus (MMTV), which could be transmitted from mothers to

pups via breast milk (Javier and Butle 2008). By the 1960s, with the additional discovery of the murine leukemia virus (MLV) in mice and the SV40 virus in rhesus monkeys, researchers began to acknowledge the possibility that viruses could be linked to human cancers as well. The growing concern

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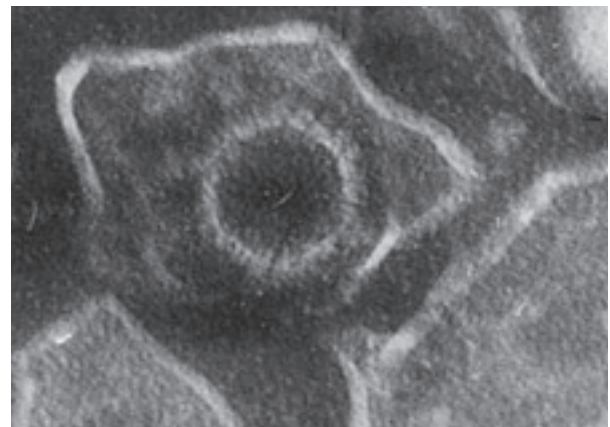


Figure 1. An electron micrograph of two Epstein Barr Virus virions. The dark sphere in the middle contains the virus' genome.

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Figure 2. A doctor administers the Human Papillomavirus Vaccine.

Then in 1965, a major breakthrough in the search for human oncoviruses occurred when Tony Epstein and Yvonne Barr discovered herpesvirus-like particles in cell lines (i.e. cells grown under controlled conditions) derived from the tumor of a patient diagnosed with Burkitt's lymphoma (a cancer of the lymphatic system). This virus, known as the Epstein-Barr virus (EBV), or human herpesvirus 4 (HHV-4),

initiate or promote the carcinogenic process, which was consistent with the notion that cancer develops from the accumulation of multiple cooperating events (Javier and Butle 2008).

went on to develop Burkitt's lymphoma. Furthermore, it was found that EBV only caused Burkitt's lymphoma when it was present in conjunction with other unknown cofactors. These findings demonstrated that rather than serving as distinct carcinogens, human oncoviruses acted to initiate or promote the carcinogenic process, which was consistent with the notion that cancer develops from the accumulation of multiple cooperating events (Javier and Butle 2008).

The notion that viruses could cause human cancers was solidified by the discoveries of hepatitis B virus (HBV) in 1975 as a causative agent in hepatocellular carcinomas (liver cancer) and the human papillomaviruses (HPV16 and HPV18) in 1983 as the causative agent for nearly 70% of all cervical cancers worldwide (Frazer et al. 2007). Since the early 1980s, three additional oncoviruses have been found: human T-cell leukemia virus (HTLV), which causes adult T-cell leukemia, hepatitis C virus (HCV), which like HBV causes hepatocellular carcinoma, and Kaposi's sarcoma herpesvirus (KSHV), which is highly associated with the development of Kaposi's sarcoma in individuals with AIDS.

MODES OF INFECTION: DNA AND RNA ONCOVIRUSES

Oncovirus research has demonstrated that although these viruses do not directly cause cancer, their actions do promote cancer development. The method by which oncoviruses cause cancer varies by the oncovirus' genetic material. Oncoviruses that have a DNA genome (e.g. HPV, EBV, KSHV, HBV) induce uncontrolled cell growth by interfering with

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marked the discovery of the first human tumor virus. Interestingly enough, researchers found that not all individuals infected with EBV went on to develop Burkitt's lymphoma. Furthermore, it was found that EBV only caused Burkitt's lymphoma when it was present in conjunction with other unknown cofactors. These findings demonstrated that rather than serving as distinct carcinogens, human oncoviruses acted to

the tumor suppressor gene p53. The protein product of p53 is frequently referred to as the “guardian of the genome” because it controls the cell cycle, apoptosis (the process of programmed cell death or cell “suicide”), and DNA repair. Thus, by preventing genetic instability, p53 effectively impedes tumor growth and proliferation. Cells infected with DNA oncoviruses, however, have their p53 repair system

knocked out, leading to the gradual accumulation of mutations that affect the cell cycle (de Oliveira 2006).

RNA oncoviruses, on the other hand, insert their genetic material into the infected cell's genome: using the enzyme reverse transcriptase, viral RNA is converted into DNA, which can then be added into the host's genomic DNA. Given this mode of infection, RNA oncoviruses are classified as retroviruses. In fact, RNA oncoviruses were the first class of retrovirus discovered, and it was the work with these viruses that led to the discovery of reverse transcriptase (Javier and Butle 2008). The main method by which these viruses promote uncontrolled cell growth is through the long terminal repeats (LTRs) encoded in their RNA. LTRs function as powerful promoters that, upon insertion into cellular DNA, increase the transcription of viral genome and thus permit more frequent encoding of the virus. Uncontrolled cell proliferation occurs when these LTRs, along with viral DNA, are inserted close enough to proto-oncogenes (genes that typically control cell growth) such that transcription up-regulates both the production of virus and proto-oncogene. Thus, through the up-regulation of genes controlling cell growth, cells grow unrestrained, eventually leading to tumor formation.

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VIRUS	ASSOCIATED CANCER
Hepatitis B, Hepatitis C	Hepatocellular Carcinoma (liver cancer)
Human T-lymphotropic virus	Adult T-cell Leukemia
Human papillomaviruses	Cancers of penis, cervix, skin, anus
Kaposi's sarcoma-associated herpesvirus	Kaposi sarcoma, Body cavity lymphoma
Epstein-Barr virus	Burkitt's lymphoma, Hodgkin's lymphoma, Nasopharyngeal carcinoma

Table 1. Known Oncoviruses and Their Associated Cancers

VIRUS FAMILY	VIRUS
Adenoviridae	Adenovirus subgroups B,C,D
Papillomaviridae	HPV (other types)
Polyomaviridae	SV40, BKV, JCV, MCPyV
Retroviridae	XMRV, HERVs, HMTV

Table 2. Potential Oncoviruses (Javier and Butle 2008)

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FRONTIERS IN ONCOVIRUS RESEARCH

According to the World Health Organization (WHO), more than 30% of cancer deaths can be prevented (WHO 2009, Danaei et. all 2005). One of the main methods of cancer prevention is through HBV and HPV vaccination (WHO 2009). Given that viral infection can typically be prevented through vaccination, many researchers and pharmaceutical companies have began searching for vaccinations against oncoviruses. The first major breakthrough came with the creation of the HBV vaccine in 1976, which was the first cancer vaccine ever developed. The next cancer vaccine came in 2006, when the FDA approved Gardasil for the prevention of HPV, which is responsible for causing nearly all cases of cervical cancer in women (zur Hausen 2002). As more and more research strengthens the link between viruses

and cancer, new methods of preventing viral infection will be developed.

Finally, another major part of oncoviral research is proving the causal relationship between viruses, often thought of as benign, and human cancer. Current research is focusing on substantiating the link between various viruses and cancers. Researchers suspect that JC virus (JCV) as well as BK virus (BKV) are linked to brain/colon cancers. They also believe in the link between simian virus 40 (SV40) and Non-Hodgkin's lymphoma. Additional potential oncoviruses are listed in Table 2 (Brower 2004).

The notion that viruses can cause cancer has transformed from a hypothesis with circumstantial evidence into an undeniable fact. It was through the work of scientists such as Rous, Epstein, and zur Hausen, that the significance and impact of these viruses could no longer be ignored. Through over a century of oncovirus research scientists have not only learned more about these viruses, but they have also gained further insight into the pathogenesis of cancer itself. Future research in this burgeoning field is sure to uncover additional information on the mechanisms of infectious disease, and may even reinvent our views on the biology of cancer.

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