

Viruses and cancer:
**Should we be
more afraid?**



UNIVERSITÉ DE
SHERBROOKE



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During the past 30 years it has become exceedingly clear that several viruses play significant roles in the development of various cancers in humans. For instance, 99% of cervical cancers are caused by certain strains of human papillomavirus (HPV). In fact, approximately 15% to 20% of all types of cancers are associated with viral infections. To date, Epstein-Barr virus (EBV), Kaposi's sarcoma-associated herpesvirus (KSHV), human papillomaviruses (HPV), Merkel cell polyomavirus (MCPV), hepatitis B virus (HBV), hepatitis C virus (HCV) and Human T-cell Lymphotropic virus type 1 (HTLV-1) have been classified as cancer-inducing infectious agents. These viruses are implicated in many types of human cancer such as liver cancer (HBV and HCV), cervical cancer (HPV), Burkitt's lymphoma and nasopharyngeal carcinoma (EBV), leukemia (HTLV-1), stomach cancer (EBV), skin cancer (MCPV), and Kaposi's sarcoma (KSHV). Many researchers around the globe are currently trying to identify the molecular and cellular mechanisms that are necessary for a virus-infected cell to become cancerous. With the advent of new technologies allowing better genetic identification, there is also a lot of interest in determining whether other viruses may play an important causative role in other types of cancer (such as breast cancer and leukemias for instance).

How do viral infections lead to cancer?

Although cancer-inducing viruses utilize diverse strategies to contribute to cancer development, they nonetheless share many common features. One key feature is their ability to infect, but not completely kill, the infected cell. Indeed, all viruses are parasites that

require a host cell to replicate. Once inside a cell, viruses typically hijack the cellular machinery to make copies of themselves. This usually results in the production of large amounts of new virus particles, the destruction of the host cell, and the spread of viruses to other cells (in the same host or in a different host). In contrast to many other viruses that cause disease, cancer-inducing viruses have the tendency to establish long-term chronic infections which does not result in the destruction of the infected cell. In fact, cancer-causing viruses typically produce very few viral particles following infection. The process by which a virus can cause cancer requires multiple steps in addition to virus infection and is quite complex. Therefore, the latency period (from viral infection to the appearance of the tumor) can be many years. Consequently, cancer-inducing viruses have evolved numerous strategies for evading the host immune response, which would otherwise clear the virus during these chronic infections.

Viruses typically initiate cancer by altering the expression of the genes in the cells that they infect or by integrating their own genetic materials in key regions of our DNA. They can also induce inflammation or produce viral proteins which will eventually lead the infected cells to start multiplying uncontrollably. Infection with cancer-inducing viruses frequently involves the activation of cellular genes that drive cell division forwards (oncogenes), or suppressing cellular genes that restrict cell division (tumour suppressor genes). This ability of cancer-inducing viruses to drive host cell division forwards predisposes the cell to further genetic mutations, thereby increasing the likelihood of cancer development. It should also be

noted that some viruses act indirectly as tumour viruses. Infection by these viruses does not result in the disruption of the host cell cycle machinery. Instead, these viruses set up an environment within the body that makes disruption from other viruses more likely. For example, infection with the human immunodeficiency virus (HIV) results in the depletion of an individual's immune system, thereby making that individual more susceptible to cancer caused by direct tumour viruses such as KSHV.

Should we be afraid of cancer-inducing viruses?

It is nearly impossible to identify what causes cancer in any individual, because most cancers have multiple possible causes. There are numerous causes and risk factors for cancer such as genetic mutations, hormonal changes, immune dysfunctions, tobacco use, alcohol consumption, obesity, dietary factors, physical inactivity, environmental pollutants, and radiations. During the past few years, researchers studying cancer-inducing viruses have clearly demonstrated that for many virus-induced cancers, infection by the virus appears to be necessary, but not necessarily sufficient, for tumor development. The current interpretation is that viruses usually do not behave as complete carcinogens (substances that induce cancers), but rather act as initiating or promoting factors. Additional modifications must therefore accumulate to complement those encountered during viral infection in order to disable the cellular machinery and to lead to cancer. Consequently, it is not surprising that cancer development is not an inevitable outcome of virus infection. Indeed, the vast majority of individuals naturally infected with a cancer-inducing virus will never develop a cancer. For instance, although more than 90% of humans are infected with EBV, the chances of developing an EBV-associated cancer (gastric cancer and/or head & neck cancer) is relatively rare unless the individual becomes immunocompromised. Similarly, although 40% of sexually active women will be infected with a high-risk

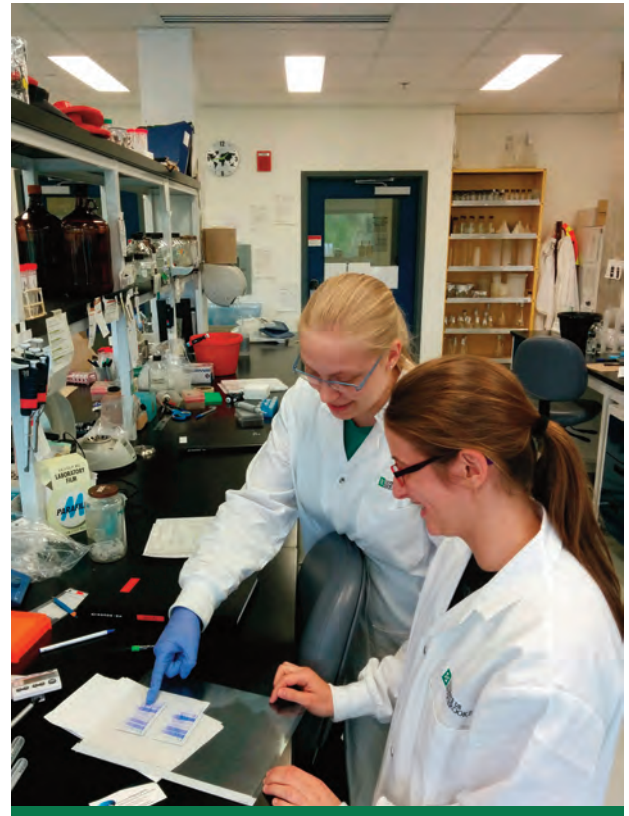


Fig. 1. Understanding cancer-inducing viruses. Graduate students at the Université de Sherbrooke (Canada) are trying to decipher the molecular mechanisms used by viruses to induce cancer in humans. Understanding the molecular mechanisms used by viruses to induce cancer is key for the development of novel strategies to fight cancer.

HPV at some point in their lives, infection with a high-risk HPV presents a woman with about a 3% lifetime risk of developing cervical cancer. At the other end of the spectrum, it has been estimated that Japanese males have a lifetime estimated risk of developing liver cancer of 20% in HBV chronic carriers and 30% in HCV carriers. Fortunately, as mentioned previously, the latency period from viral infection to the appearance of cancer can be many years for most cancer-inducing viruses. Prolonged latent periods are typically the norm between the time of initial virus infection and



Fig. 2. Studying cancer-inducing viruses with new technologies.

Bioinformatic approaches are currently under investigation to understand the numerous molecular changes that lead to cancer following infection by viruses. Researchers can now investigate the gene expression profiles of patients with tumours and compare them with healthy individuals.

tumor appearance in normal individuals. For instance, although most HTLV-I infections are acquired in infancy, adult T-cell leukemia usually arises in people in their forties and fifties. Similarly, individuals with chronic HBV infections acquired as newborns usually develop liver cancer beyond the age of 50.

Viral vaccines to control cancer?

Since viral infection can lead to cancer, there is now an opportunity to develop preventive measures to inhibit virus infection, thereby reducing the risk of cancer in the population. Vaccines are clearly the most effective preventive approach against viral infections, and vaccination against cancer viruses clearly has the potential of reducing the global cancer rate. Vaccines can stimulate the immune system of an individual to produce antibodies to fight a disease. In fact, many vaccines are currently used to prevent

various infectious diseases caused by viruses (such as the flu, measles or polio for instance). Preventive (or prophylactic) cancer vaccines are now used in many industrialized countries (UK, Canada, etc.) in order to prevent viral infections associated with the development of cancer. These vaccines are designed to stimulate the immune system to attack viruses before they cause an infection. Such vaccines have now been developed against HPV and HBV. These vaccines can be given to healthy individuals before cancer develops to prevent cervical cancer related to HPV and liver cancer associated with HBV. These preventive vaccines commonly use viral proteins found on the surface of the virus to stimulate the immune system to produce antibodies against the viral proteins. If individuals encounter these viruses during their lifetimes, their immune system will already be equipped to fight the incoming virus. By preventing the viruses from infecting body cells, these cancer vaccines efficiently block the process that might eventually result in cancer.

Viruses to fight cancer?

Treating cancer patients is a challenging problem. Cancer is typically treated by surgery, radiotherapy and/or chemotherapy. Surgery is clearly the most effective treatment in the early stages of some types of cancer but is not applicable to all cancers. Radiotherapy and chemotherapy use radiation or chemicals to kill cancer cells but these approaches frequently lead to important side effects (such as hair loss) during treatment. During recent years, researchers have identified viruses that have the ability to specifically destroy cancer cells while not harming normal tissue. These viruses (oncolytic viruses) can infect cancer cells, destroy them, and release new viral particles that will attack other cancer cells in the body. Interestingly, these oncolytic viruses are not only killing cancer cells, but they also stimulate the immune system of the host to recognize and destroy cancerous tissues.

Oncolytic viruses typically fall into two classes. The first class encompasses viruses that replicate preferentially in cancer cells and are mostly nonpathogenic in humans. These include parvoviruses, myxoma virus, Newcastle disease virus, reovirus, and Seneca valley virus. The second class of oncolytic viruses encompasses viruses that are genetically manipulated by researchers to specifically destroy cancer cells and not harm healthy cells. A number of viruses including adenovirus, reovirus, measles virus, herpes simplex, Newcastle disease virus, Maraba virus and vaccinia virus have now been clinically tested as oncolytic agents and have shown great promise in the fight against cancer. More research is clearly needed to know which of these viruses might be best, how they should be administered and which cancers they might target efficiently.

Research opportunities and future directions

Research on cancer-inducing viruses has played a major role in cancer research over the past few decades. The study of these viruses has led to the identification of their importance as causative agents of cancer. It also allowed researchers to better understand cellular and growth control pathways that are modified during the establishment of cancer. With the advent of new technologies, research on cancer-inducing viruses will likely progress at a rapid pace in the next few years. Several areas of opportunity and avenues of investigation will likely keep cancer-inducing viruses at the forefront of cancer research. For instance, additional studies are clearly needed to uncover the nature of the additional cofactors that are necessary to lead to cancer following viral infection. Another serious challenge for the future will be the identification of new cancer-inducing viruses and/or unsuspected tumor associations involving viruses that are already known. Finally, for many cancer-inducing viruses, the exact molecular mechanisms by which these viruses cause cancer remain largely unexplored and will need to be uncovered.

Although only a small proportion of virus-infected individuals develop cancers, the total burden of infection-associated cancer is very large, with an estimated 2 million new cases of virus-induced cancer worldwide each year. Funding agencies, research foundations, and corporations will definitely need to continue their investment in this exciting research field during the next decades in order to improve the quality of life of the world population.

Profile



Pr Martin Bisailon is an expert in biochemistry and virology. He obtained a PhD in Microbiology and Immunology at the Université de Montréal in 1999. He then completed his post-doctoral training at the Sloan-Kettering Institute in New York City before directing a research team in the pharmaceutical industry aimed at developing antiviral agents. He is currently Chair of the Biochemistry Department at the Université de Sherbrooke (Canada).



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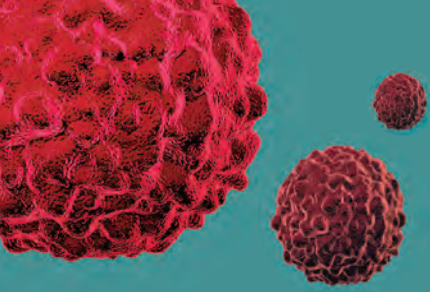
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