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Mini-review

Viruses and human cancer: From detection to causality

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ABSTRACT

The study of cancer is incomplete without taking into consideration of tumorigenic viruses. Initially, searches for human cancer viruses were fruitless despite an expansion of our knowledge in the same period concerning acute-transforming retroviruses in animals. However, over the last 40 years, we have witnessed rapid progress in the tumor virology field. Currently, acknowledged human cancer viruses include Epstein–Barr virus, hepatitis B virus, hepatitis C virus, high-risk human papilloma viruses, human T-cell lymphotropic virus type 1 and Kaposi's sarcoma-associated herpesvirus. Extensive epidemiological and mechanistic studies have led to the development of novel preventive and therapeutic approaches for managing some of these infections and associated cancers. In addition, recent advances in molecular technologies have enabled the discovery of a new potential human tumor virus, Merkel cell polyomavirus, but its association with cancer remains to be validated. It is anticipated that in the next few decades many additional human cancer viruses will be discovered and the mechanisms underlying viral oncogenesis delineated. Thus, it can be expected that better tools for preventing and treating virus-associated cancer will be available in the near future.

1. Introduction

At the end of the 19th century, viruses were classified as small infectious agents that, unlike cells and bacteria, pass through fine-pore filters. Subsequently, in 1911 Peyton Rous evidenced an association between cancer and viruses by demonstrating that filtered cell-free tumor extracts could be used to propagate tumors in chickens. Shortly after, however, study of the Rous sarcoma virus (RSV) was suspended and interest shifted to chemical and physical initiators of cancer. In 1933, Richard Shope and E. Weston Hurst reported a virus-causing wart on the skin of wild cottontail rabbits. The tumorigenic nature of the disease, now understood to be induced by cottontail rabbit papillomavirus, was subsequently confirmed in collaboration with Peyton Rous. To date, over 100 types of human papillomavirus (HPV) have been identified, several etiologically linked to human cancer. The significant role of viruses in cancer was acknowledged finally in the second half of the past century after various rodent tumorigenic viruses were discovered, and evidence had accumulated supporting an association between viruses and human cancer. Indeed, the Nobel Prize was awarded to Rous in 1966 in recognition of his seminal discovery of tumor-inducing viruses. In addition, almost at the same time, a Special Virus Cancer Program (VCP) was launched by the US congress in 1964 providing enormous funds for intensive research into the supposed role of viruses in human cancer. This program, criticized by some investigators as being a political moonshot-style plan, failed to identify candidate human cancer-causing viruses, yet generated fundamental information about the molecular biology

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and mechanisms underlying, in particular, virus-related animal cancer, and cancer in general [1].

Currently, six human viruses have been classified by the International Agency for Research on Cancer (IARC) as "carcinogenic to humans" (Group 1) based on sufficient evidence supporting their etiologic association with human cancer: Epstein–Barr virus (EBV), hepatitis B virus (HBV), HPV of several types, human T-cell lymphotropic virus type 1 (HTLV-1), hepatitis C virus (HCV), and Kaposi's sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8) (Table 1, adapted from [2]). The human immunodeficiency virus type-1 (HIV-1) is also listed as a group 1 cancer-causing agent. However, HIV-1 increases primarily the risk of certain malignancies associated with KSHV, EBV and HPV by causing immune suppression. Recent advances in molecular technologies have led to the discovery of a new putative human cancer virus, Merkel cell polyomavirus (MCPyV) [3], though further evidence is required to establish its carcinogenicity. Overall, 12% of the global cancer burden is conservatively estimated to be virus-attributable, with an even higher proportion in developing countries [4]. Since human cancer viruses are often ubiquitous and yet produce tumors in infected individuals only rarely, accumulating enough evidence to establish causal association between any given virus and cancer is a challenge. Therefore, it is likely that the burden of virus-related cancers is underestimated and future research will reveal new associations between already known viruses and human cancer and/or new cancer viruses [5].

Here we review the approaches taken to discover human cancer viruses and promising methods for detecting new viruses. We also discuss how causal association is established and possible cofactors that influence development of virus-associated cancers.

2. Discovery of human cancer viruses

Most of the known human cancer viruses were discovered thanks to unique clinical and epidemiologic clues that pointed to the involvement of an infectious agent in the development of the cancer. Various approaches, ranging from classical virological methods to the most advanced molecular techniques, were used to establish the association between cancer and a given virus. The background and methods underlying the discovery of each human cancer virus are reviewed in this section. Present and future approaches for discovering unknown cancer viruses are presented in Section 3.

2.1. Epstein–Barr virus (EBV)

EBV was the first human virus to be classified as carcinogenic, a definition based on years of clinical, epidemiological and cell biology studies. Initially, Denis Burkitt reported in the 1950s the appearance of a novel form of childhood B-cell lymphoma in the African malarial belt and hypothesized that the etiologic agent of this disease could be a virus transmitted by an arthropod vector [6]. Then in 1965, Tony Epstein and Yvonne Barr established cell lines from Burkitt's lymphomas and demonstrated by electron microscopy the presence of herpesvirus-like particles in a small fraction of the cells. Werner and Gertrude Henle proved that this virus was biologically and antigenically distinct from other known viruses. However, the high seroprevalence of EBV in human populations worldwide dissuaded researchers from concluding that the virus could be a pathogenic agent underlying African Burkitt's lymphoma. Nevertheless, the initial causal link between EBV and Burkitt's lymphoma was corroborated by the elevated levels of antibodies to EBV antigens present in

Table 1
Human cancer viruses.

Virus	Year of Discovery	Disease associated with primary infection	Acknowledged associated human cancers	Suspected associated human cancers
Epstein–Barr virus (EBV, human herpesvirus 4 [HHV-4])	1965	Asymptomatic infection, Infectious mononucleosis	Burkitt's lymphoma, Nasopharyngeal carcinoma, Hodgkin's lymphoma, immunosuppression-related non-Hodgkin lymphoma, extranodal NK/T-cell lymphoma	Gastric carcinoma, lymphoepithelioma-like carcinoma, leiomyosarcomas
Hepatitis B virus (HBV)	1967–1968	Asymptomatic, acute hepatitis, long-term chronic infection of the liver	Hepatocellular carcinoma	Cholangiocarcinoma, non-Hodgkin lymphoma
Human T-cell lymphotropic virus type 1 (HTLV-1),	1980		Adult T-cell leukemia and lymphoma	
Human papillomavirus (HPV) (high-risk types)	1983		Carcinoma of the cervix, vulva, vagina, penis, anus, oral cavity, and oropharynx and tonsil	Cancer of the larynx, and some head and neck cancers
Hepatitis C virus (HCV)	1989	Asymptomatic, acute hepatitis	Hepatocellular carcinoma, non-Hodgkin lymphoma	Cholangiocarcinoma
Kaposi's sarcoma-associated herpesvirus (KSHV, human herpesvirus 8 [HHV-8])	1994		Kaposi's sarcoma, primary effusion lymphoma	Multicentric Castleman's disease
Merkel cell polyomavirus (MCPyV)[a]	2008			Merkel cell carcinoma

[a] Further evidence required for unquestionable inclusion as an etiologic agent of cancer.