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Review

Human Viral Oncogenesis: A Cancer Hallmarks Analysis

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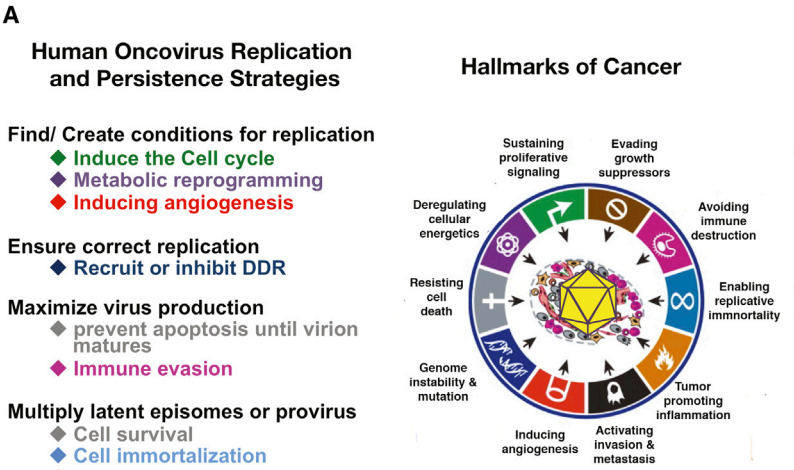
Approximately 12% of all human cancers are caused by oncoviruses. Human viral oncogenesis is complex, and only a small percentage of the infected individuals develop cancer, often many years to decades after the initial infection. This reflects the multistep nature of viral oncogenesis, host genetic variability, and the fact that viruses contribute to only a portion of the oncogenic events. In this review, the Hallmarks of Cancer framework of Hanahan and Weinberg (2000 and 2011) is used to dissect the viral, host, and environmental cofactors that contribute to the biology of multistep oncogenesis mediated by established human oncoviruses. The viruses discussed include Epstein-Barr virus (EBV), high-risk human papillomaviruses (HPVs), hepatitis B and C viruses (HBV and HCV, respectively), human T cell lymphotropic virus-1 (HTLV-1), and Kaposi's sarcoma herpesvirus (KSHV).

Introduction

Approximately 12% of human cancers worldwide are caused by oncovirus infection, with more than 80% of cases occurring in the developing world (Bouvard et al., 2009; Boyle and Levin, 2008; de Martel et al., 2012). Despite their prevalence, public health importance, and suitability for immunoprophylaxis and targeted therapies, understanding and managing virus-induced cancers still faces formidable challenges. This is due to limited animal models of disease, the disparate nature of viral-induced cancers, the very distinct types of viruses that cause them, and the complex nature of the virus-host cell interactions leading to cancer development (zur Hausen, 2009).

Human viral oncogenesis has common traits (Bouvard et al., 2009; zur Hausen, 2009): (1) oncoviruses are necessary but not sufficient for cancer development, so cancer incidence is much lower than virus prevalence in human populations; (2) viral cancers appear in the context of persistent infections and occur many years to decades after acute infection; (3) the immune system can play a deleterious or a protective role, with some human virus-associated cancers increasing with immunosuppression and others appearing in the context of chronic inflammation. The Hallmarks of Cancer framework developed by Weinberg and Hanahan allows the dissection of the malignant phenotype into specific cellular capabilities that are acquired during the carcinogenic process (Hanahan and Weinberg, 2000, 2011). Each cancer "hallmark" represents a biological consequence of oncogenic alteration(s) that underlies the tumor's phenotypic characteristics (Figure 1). For instance, oncogenic mutations that constitutively activate RAS, a potent regulator of the MAPK and PI3K-AKT-mTOR cascades, convey proliferation, survival, angiogenesis, and metabolic-related hallmarks to a tumor cell. Mutations that inactivate the tumor suppressor gene p53 (*TP53*), a DNA damage-induced activator of growth inhibition and apoptosis, enables uncontrolled growth and genetic instability hallmarks. The Hallmarks of Cancer framework also helps to explain the multistep nature of human carcinogenesis (Vogelstein and Kinzler, 1993), which outlines the time dependence for the development of a cancer that requires the progressive acquisition of all necessary cellular hallmarks that constitute a malignant phenotype. This results from the accumulation of somatic oncogenic alterations, sometimes referred to as "oncogenic hits," caused by spontaneous mutations or mutations as a consequence of exposure to environmental carcinogenic factors in the context of the genetic background of the host and the selective pressures imposed by the tissue microenvironment (Hanahan and Weinberg, 2000, 2011). The cancer hallmark model, therefore, is also a powerful tool to organize and understand the process of human virus-associated carcinogenesis. Early studies with acutely transforming viruses suggested that viruses are sufficient to cause cancer because they carry powerful oncogenes. Human oncoviruses, however, appear to be necessary but not sufficient to cause cancer and are rarely fully oncogenic per se. This indicates that within the context of multistep carcinogenesis, viral infection provides only a subset of the required oncogenic hits. Additional cofactors such as immunosuppression, chronic inflammation, or environmental mutagens are generally necessary for malignant transformation (Bouvard et al., 2009; zur Hausen, 2009). The Cancer Hallmarks framework helps to discern the contribution to the oncogenic process of viral genes, of the host response to the infection, and of acquired somatic mutations. In this review, we will analyze oncogenesis mechanisms and identify host and environmental cofactors contributing to full development of malignancy for each of the major human viruses defined in the last IARC report as Group 1 Biological carcinogenic agents for which there is "sufficient evidence of carcinogenicity in humans"

A



B

VIRUS	CANCER	V-ONC	PATHWAYS	CANCER HALLMARK
EBV	BL	EBNA-1		
	NHL, PTLD, NPC	LMP-1	NFkB	
		LMP-2A	PI3K-AKT-mTOR, ERK	
HPV	CxCa, HNCC	E6	p53, mTOR, hTERT	
		E7	Rb	
		E5		
HBV	HCC	HBx	p53, Rb, Wnt, src, DNMTs, ras, PI3K JNK, NF-κB, ERK1/2, TGFβ, HDACs	
HCV	HCC	Core, NS3, Ns5A	p53, PARP, hTERT, TGFβ, HDACs,	
HTLV-1	ATL	Tax	NFkB, CREB, PI3K, DDR	
		HBZ	c-jun, E2F	
KSHV	KS	vFLIP	NFkB	
		LANA	p53, Rb, HIF, Notch, Wnt	
		vGPCR	PI3K-AKT-mTOR, ERK, p38, JNK, NFkB,	
		vIRF-1	αIFN, p53, ATM, Bim	

Figure 1. Cancer Hallmarks Activation by Human Oncoviruses

(A) Oncogenic risks of strategies for viral replication and persistence. Many of the molecular mechanisms deployed by human oncoviruses to maximize replication and persistence imply hijacking the host cell's signaling machinery, leading to acquisition of cancer hallmarks. The main strategies for viral replication and persistence are listed (on the left). Below each of them are the cellular responses that the virus induces to undertake each of these strategies. Virally induced cell responses are color coded according to the Hallmarks of Cancer to which they correspond (on the right). The picture on the right is a reproduction from the review by Hanahan and Weinberg (2011).

(B) Activation of oncogenic pathways by viral oncogenes leads to acquisition of cancer hallmarks by the infected cell. The table shows established viral oncogenes, the main cellular pathways they regulate, and the cancer hallmarks they can potentially induce. Hallmarks are color coded as the wheel in (A). Data from tumor models were given preference. HBV and HCV are potentially able to activate all hallmarks depending on HCC stage as described in the text and Figure 4.

(Bouvard et al., 2009). These include hepatitis B virus, (HBV), hepatitis C virus (HCV), Epstein-Barr virus (EBV), high-risk human papillomaviruses (HPVs), human T cell lymphotropic virus-1 (HTLV-1), HIV, and Kaposi's sarcoma herpesvirus (KSHV). Since HIV acts as a cofactor of AIDS-defining cancers that are associated with EBV and KSHV, it will be discussed within the context of these other viruses.

Oncovirus Replication and Persistence Strategies Involve Activation of Cancer-Causing Pathways

Coevolution of oncoviruses and their hosts is a fight for survival. Hosts evolved immune defenses against viral infections, while viruses have coevolved to evade host immune response and other host restrictions. Human oncogenic viruses rely on persistence to disseminate and thus deploy powerful immune evasion programs to establish long-term infections. As part of their replication and immune evasion strategies, human oncoviruses have evolved powerful anti-apoptotic and proliferative programs that can directly induce cancer hallmarks in the infected cell (Figure 1A) (Moore and Chang, 2010; zur Hausen, 2009). When these viruses overcome the ability of the host to maintain homeostasis, they trigger cellular changes ultimately leading to cancer. The underlying mechanisms include:

(1) Signaling mimicry: Viruses encode proteins that are able to subvert, in a dominant manner, host-signaling mechanisms that regulate cell growth and survival (Figures 1A and 1B). These are generally the same signaling pathways that, when deregulated, provide antiapoptotic and antiproliferative hallmark capabilities in nonviral cancers (Figure 1B).

(2) Effects on the DNA damage response (DDR): Recognition of viral genomes or replicative intermediates by the host leads to induction of DDR, which many oncoviruses need for their replication. As a consequence, however, host cells acquire genetic instability, which increases their mutation rate and accelerates acquisition of oncogenic host chromosomal alterations (McFadden and Luftig, 2013) (also see review in this issue by Weitzman and Weitzman [2014]).

(3) Chronic inflammatory responses to persistent viral infection: inflammation drives reactive oxygen species (ROS) generation that promotes the acquisition of mutations. This is observed in chronic HBV and HCV infections, where virus-triggered inflammatory responses lead to