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Mini-review

Oncogenic virus-mediated cell fusion: New insights into initiation and progression of oncogenic viruses-related cancers

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ABSTRACT

Cell fusion is fundamental to the development and physiology of multicellular organisms, such as fertilization, placentation, development of skeletal muscle and bone. Oncogenic virus-mediated cell fusion, however, may lead to chromosomal instability (CIN) by various mechanisms when tumor suppressor p53 is deregulated and produce oncogenic aneuploid cells. It is worth noting that all human oncogenic viruses, including human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), Epstein-Barr virus (EBV), human herpesviruses-8/Kaposi sarcoma herpesvirus (HHV-8/KSHV) and human T-cell lymphotropic virus type 1 (HTLV-1), are capable of both inducing cell fusion and inhibiting the functions of p53 as well as pRb. Although it is now not clear whether a link between virus-mediated cell fusion and cancer established in experimental systems also exists in humans, the fact that the observation of tetraploid cells is more frequent in virus-positive than virus-negative premalignant lesions supports this link. Additionally, there are now no available vaccines against most oncogenic viruses except for HBV and HPV. Given these, developing fusion inhibitors is beneficial to cancer prevention and therapy of virus-associated cancers via inhibiting virus entry, spread and oncogenic role.

1. Introduction

Cancer statistics indicate that human tumor viruses and Helicobacter pylori are the primary causes of several cancers, which together account for about one-fifth of all human cancer cases in the world [1]. In recent decades, causation relation between certain virus and cancer has been widely accepted (Table 1), such as human papillomavirus (HPV) and cervical cancer, hepatitis B virus (HBV) or hepatitis C virus (HCV) and hepatocellular carcinoma (HCC) [1–3]. However, clear oncogenic mechanisms of these viruses remain elusive despite intense efforts and great advances in this field.

Virus can cause cancer by multiple mechanisms, such as mutations due to virus integration, expression of viral oncogenes as well as virus-mediated cell fusion [2–5]. Despite the knowledge that all oncogenic viruses are able to mediate cell fusion (Table 1), a definitive link between cell fusion and cancer has only been established recently in experimental systems [6,7]. Indeed, tetraploidy, a natural product of cell fusion, can result in cancer-associated aneuploidy, but the proliferation of tetraploid cells is limited by a variety of mechanisms. Although it has been debated whether a so-called 'tetraploidy checkpoint' exists [8], it is reported that tetraploid cells arrest their cell cycle and that this arrest is p53-dependent [9,10]. It is noteworthy that all oncogenic viruses can express proteins to damage p53 functions.

However, whether the above link in experimental systems also exists in human beings remains unclear. Despite the technical difficulty in directly detecting cell fusion in cancer patients, several clinical observations, such as tetraploid cells and premature chromosome condensation (PCC) [11] in virus-positive premalignant lesions, support the

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Table 1
Human oncogenic viruses with fusogenic activity.

Virus	Cancer association	Tetraploid cells in premalignant lesions	Fusogenic proteins[a]	References
HPV	Cervical cancer	Yes	E5	[19–21]
HBV	Hepatocellular carcinoma	Yes	Not found	[22,23]
HCV	Hepatocellular carcinoma	Yes	E1, E2	[22,24]
EBV	Nasopharyngeal carcinoma Hodgkin lymphoma Burkitt lymphoma	Yes Unknown Unknown	gB, gH, gL	[25,26]
HHV-8/KSHV	Kaposi sarcoma	Yes	gB, gH, gL	[27,28]
HTLV-1	Adult T-cell leukemia or lymphoma	Unknown	gp21	[29]

[a] "Fusogenic proteins" refers to proteins that able to mediate cell–cell fusion rather than virus-cell fusion. Human papillomavirus (HPV); hepatitis B virus (HBV); hepatitis C virus (HCV); Epstein-Barr virus (EBV); human herpesviruses-8/Kaposi sarcoma herpesvirus (HHV-8/KSHV); human T lymphotropic virus-1 (HTLV-1).

existence and potential importance of cell fusion in cancer development. In this review, we describe clinical works suggesting a potential role of virus-mediated cell fusion in mechanisms of cancer initiation. Additionally, we also discuss the development of fusion inhibitors targeting virus-mediated cell fusion for prevention and therapy of virus-related cancers.

2. Physiological cell fusion and virus-mediated cell fusion

Physiological cell fusion is significant for fertilization; the development of muscle, bone, and placenta; the immune response and aspects of stem cell-mediated tissue regeneration [12]. Combination of genetic and epigenetic information of fusion partners and subsequent reprogramming lead to diversity and genetic complementation, which underlie the roles of cell fusion [13,14]. Cell fusion, however, is a tightly controlled process and restricted to only a few cell types which produce only terminally differentiated multinuclear cells incapable of proliferation [12].

In addition to its occurrence in normal physiology, cell fusion is also essential for the progression of different pathological events and, possibly, cancer initiation and progression. Virus-mediated cell fusion is one effective manner for virus spread between host cells. It also contributes to pathogenic changes of many virus-related diseases, such as giant cell formation in measles pneumonia [15]. Although virus infection and replication are often associated with apoptosis [16] which is generally disadvantageous to virus persistence, human oncogenic viruses encode proteins which can both mediate cell fusion and inhibit apoptosis (Tables 1 and 2). The fused cells made by oncogenic virus *in vitro* have abnormalities including unstable genomes, unstable gene expression and other properties not found in a normal cell, and they can cause tumor in mice, suggesting that virus-mediated cell fusion may contribute to carcinogenesis [6,7].

Despite the importance of cell–cell fusion in numerous physiological and pathological processes, little is known of its mechanistic underpinnings. So far, only a limited number of viral and cellular fusogens, proteins that fuse membranes, have been isolated and characterized [17]. Additionally, a large number of factors, including integrins, vacuolar ATPase, receptors and their ligands, as well as different signaling intermediates have been associated with cell fusions [17,18]. In spite of the diversity of viruses and cell types that undergo fusion, the underlying cellular processes, including cell–cell adhesion, alignment and membrane fusion, are similar. Taking human immunodeficiency virus-1 (HIV-1) as a model, the viral genome encodes envelope (Env) proteins, which bind to cell surface receptors and assist the virus in entering the cell. The infected cell commences to synthesize Env proteins, which, upon insertion in the plasmalemma, engage receptor proteins in neighboring cells and initiate cell–cell fusion [17].

Table 2
Cell cycle regulatory proteins and apoptosis are perturbed by the human viral oncoproteins.

Virus	pRb	p53	Pro-apoptotic proteins	References
HPV	E7	E6	E5, E6, E7	[43,44]
HBV	HBx	HBx	HBx, HBc	[45–48]
HCV	NS5B	NS5A, NS3	NS2, 3, 5A, 5B, E2, core	[49–56]
EBV	EBNA-3C, 5, 6	EBNA-3C, 5	LMP2a, EBNA-3 A, C, BHRF1	[57–63]
HHV-8/KSHV	LANA	LANA	LANA, KSBCL-2, K7	[63–67]
HTLV-1	Tax	Tax	Tax	[68–70]

3. Tetraploid cells in premalignant lesions

Observation of tetraploid cells has been established as a prognostic factor that allows to estimate the relative progression risk into more advanced lesions [19,30]. Further investigations to some virus-related cancers found that the observation of tetraploid cells is more frequent in virus-positive than virus-negative premalignant lesions [20,22], suggesting that virus appears to play an important role in tetraploid cell formation, at least in these cancers.

Epidemiological data clearly indicates that persistent high-risk HPV (especially HPV-16 and -18) infection is a risk factor for the development of cervical cancer and its precursor, cervical premalignant lesions [3]. According to different grades of severity, cervical premalignant lesions are stated successively as atypical squamous cells of unde-