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Mini-review

Virus induced inflammation and cancer development

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ABSTRACT

Chronic inflammation as a result of viral infection significantly increases the likelihood of cancer development. A handful of diverse viruses have confirmed roles in cancer development and progression, but the list of suspected oncogenic viruses is continually growing. Viruses induce cancer directly and indirectly, by activating inflammatory signalling pathways and cytokines, stimulating growth of infected cells and inhibiting apoptosis. Although oncogenic viruses induce inflammation by various mechanisms, it is generally mediated by the MAPK, NFκB and STAT3 signalling pathways. This review will explore the unique mechanisms by which different oncogenic viruses induce inflammation to promote cancer initiation and progression.

1. Introduction

Viruses contribute significantly to cancer development worldwide, with up to 15% of human cancers attributed to chronic viral infection [1,2]. Human papillomavirus (HPV) and hepatitis B virus (HBV) are the most significant contributors, but the list of tumourigenic viruses is much longer [1]. Epstein–Barr virus (EBV), human T-lymphotropic virus-I (HTLV-I), hepatitis C virus (HCV), Kaposi's sarcoma herpesvirus (KSHV) and Merkel cell polyomavirus (MCV) all have confirmed roles in cancer induction, with a significantly longer list of viruses also suspected to play a role in tumourigenesis.

The acute inflammatory response to virus infection is an essential component of the antiviral response, inducing genes responsible for antiviral activity, immune cell recruitment and cell fate [3]. Unfortunately, excessive inflammation can arise during persistent infection and is generally damaging, having mutagenic effects on the host genome [4]. Chronic inflammation plays a role in a number of disease states, including diabetes, arthritis, Alzheimer's disease, and over a longer period, cancer [5]. In the context of cancer development, chronic inflammation has been linked not only to tumourigenesis, but also to increased cell proliferation, survival, invasion, angiogenesis and metastasis [5,6].

Tumourigenesis usually follows the accumulation of mutations in gene coding regions, resulting in uncontrolled cell growth. It is estimated that around 100 coding region mutations are present in a typical cancer genome, including 10–20 in genes actively contributing to oncogenesis [7,8]. This implies that cancer development is usually a slow process, largely unaffected by acute infections which resolve. For this reason, viruses and bacteria with the potential to develop chronic infections are significantly over-represented among tumourigenic pathogens [9].

Cancer initiation during viral infection can generally be divided into two categories, based on the capacity of the virus to directly contribute to oncogenesis. Oncogenic viruses encode proteins that stimulate cell proliferation and/or interfere with cell apoptosis, and therefore play a direct role in carcinogenesis [10]. Most viral oncogenes target similar cell growth pathways to counteract the growth arrest that occurs in response to viral infection. Other viral oncogenes inhibit apoptosis and immune cell recognition, thus allowing ongoing viral replication.

Viral carcinogenesis can also occur indirectly, if chronic infection leads to oxidative stress and inflammation [10]. Cytokine secretion by the infected cell and surrounding tissues creates an inflammatory milieu which can promote cancer development, principally mediated by IL-1B, TNF-α and IL-6 [4,11]. Inflammatory stimuli and direct effects of the virus activate signalling pathways responsible for cancer development, including NF-κB, STAT3 and the MAPKs [12,13].

Inflammation alone can increase the oncogenic potential of a cell, but the combination of direct and indirect factors present during chronic viral infections explains the high rates of virus-associated cancers. This review will focus on the role of virus-induced inflammation in cancer development, highlighting the similarities and differences among oncogenic viruses.

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2. Oncogenic viruses of the liver: HBV and HCV

HBV and HCV are both hepatotropic viruses which can establish persistent infection. HCV is unusual among oncogenic viruses, as it does not integrate into the host genome or demonstrate viral latency, yet sustains chronic infection in approximately 50–80% of untreated individuals [14]. Chronic HCV infection dramatically increases the likelihood of developing liver fibrosis (scarring) and steatosis (fat accumulation), with approximately 20% of patients developing cirrhosis, and 4% developing hepatocellular carcinoma (HCC) [15]. In countries where HBV is not endemic, including the United States, Europe, Egypt and Japan, HCV contributes to 60% of diagnosed HCC [16]. Conversely, approximately 54% of HCC cases worldwide are attributed to HBV, particularly in endemic regions such as East Asia and sub-Saharan Africa where up to 8% of the population have chronic HBV infection [17–19].

HCV (*Flaviviridae* family) and HBV (*Hepadnaviridae* family) have significantly different genomes, which contribute to their unique mechanisms of establishing chronic infection in the liver and eventually cancer. The HCV genome is a single positive RNA strand, which is replicated by a low fidelity RNA polymerase, creating a diverse population of quasispecies capable of evading the immune response [20,21]. In contrast, after entering the nucleus, the double stranded DNA HBV genome forms covalently closed circular DNA (cccDNA), which is very stable and persists as an episome [18,22]. HBV is capable of integrating into the host genome [23], which is not required for HBV oncogenesis, but is seen in approximately 80% of HBV related HCCs, and increases in frequency with chronic inflammation [24,25].

Both HBV and HCV encode proteins that affect signalling pathways mediating cell growth, apoptosis and antiviral immunity, thus favouring viral replication and facilitating chronic infection. Most notable are the HCV proteins core, NS5A and NS3/4A; and HBV proteins HBx and pre-S2. These proteins restrict immune recognition and response, increase cell survival and proliferation, and inhibit apoptosis [16,26]. However, HCC resulting from HCV and HBV infection typically takes decades to develop, and is often associated with cirrhosis and steatosis [18,27,28]. Therefore the main driving force in HBV and HCV induced liver cancer is most likely chronic liver damage, resulting from years of inflammation, oxidative stress, cell death and regeneration [16,29,30].

A major source of harmful, pro-inflammatory cytokines during chronic HBV/HCV infection is liver infiltrating lymphocytes [31]. Viral persistence causes enrichment in the liver of both pro-inflammatory T cells and innate immune lymphocytes, including natural killer (NK) cells [32,33]. Many infiltrating lymphocytes display a high level of activation and low level of specificity, resulting in the inflammatory pathologies associated with chronic infection [31]. Following HBV and HCV infection, hepatocytes and infiltrating lymphocytes secrete increased amounts of TNF-α, IL-6 and IL-1β, all of which are associated with HCC development and progression [34–39].

Inflammation and leukocyte infiltration trigger activation of resident hepatic stellate cells, making them responsive to transforming growth factor β (TGF-β) [40,41]. TGF-β promotes hepatic fibrogenesis and apoptosis, and is associated with HCC carcinogenesis, progression and prognosis [42,43]. Interestingly, both HBV and HCV increase TGF-β mediated signalling, but shift it from a tumour suppressive (apoptotic) phenotype to a proliferative, pro-fibrotic phenotype [41,44,45].

HBV and HCV induced inflammation is tightly linked to oxidative stress [18,30]. Both HBV and HCV infection induce endoplasmic reticulum (ER) stress, which increases intracellular levels of reactive oxygen species (ROS), leading to an increase in inflammatory gene expression by activating NF-κB, AP-1 and STAT3 [46–50]. HCV core induces lipid accumulation, increases ROS and inflammation due to lipid peroxidation, and promotes development of HCC in transgenic mice [51,52]. Inflammation associated NF-κB not only promotes growth and suppresses apoptosis, but stimulates growth factor production, resulting in oncogenesis and cancer progression [53]. Pro-apoptotic JNK signalling is also activated by inflammation, but during chronic viral hepatitis is likely inhibited by viral oncoproteins [16]. Since HBV and HCV do not infect the entire liver, JNK signalling in uninfected "bystander" hepatocytes may result in cell death, as they lack "protective" viral oncoproteins [54,55]. The death of uninfected hepatocytes appears to drive compensatory cell proliferation, further stimulating cancer progression [56].

Taken together, these data demonstrate that chronic HBV/HCV infection induces an inflammatory phenotype, characterised by perpetual cell death and regeneration in the liver. Antiviral treatment to reduce viral replication can considerably reduce inflammation in the liver, but is expensive and can be associated with side effects [57]. There is nonetheless hope for reduced HCC rates in the future as antiviral treatments improve. The development of direct acting antivirals against HCV has increased cure rates to over 70%. The likely availability of all oral, interferon free options in the next few years would provide effective, convenient treatment with fewer side effects, which should increase community take up rates and reduce HCC incidence. New oral antivirals against HBV effectively inhibit viral replication for many years, with minimal side effects, reducing the risk of HCC. However complete eradication of HBV with treatment is still rare, reinforcing the importance of HBV vaccination and education programs [58,59].

3. Human T lymphotropic virus (HTLV-1)

Following an exhaustive worldwide search for a human retrovirus, HTLV-1 was identified in 1980 [60,61]. HTLV-1 was the first retrovirus to be associated with human cancer, termed adult T-cell leukaemia (ATL) [62]. The HTLV-1 genome is positive sense RNA, which is reverse transcribed and integrates randomly into the genome of predominantly CD4+ T cells [63]. Following integration, clonal expansion of the infected T cells is induced by the viral transactivator protein Tax, which interferes with the NF-κB, AKT, p53 and pRb signalling pathways, to name a few [64]. Although Tax is required to immortalise cells *in vitro*, it is often silenced following progression of ATL *in vivo*, and is seen in only 40% of cases [65,66]. Conversely, viral HTLV-1 basic leucine zipper factor (HBZ) transcripts are found in all ATLs, and it is thought that HBZ may be responsible for maintaining the leukaemic state [67].

HTLV-1 Tax and HBZ contribute directly to T cell oncogenesis by increasing growth potential, modulating immune recognition and increasing genetic instability. Nonetheless, HTLV-1 induced ATL is rare, occurring in only 5–10% of infected individuals over a lifetime [60,63]. Persistent activation of NF-κB by the Tax protein occurs following HTLV-1 infection *in vitro* and *in vivo*, and contributes significantly to the oncogenic potential of the virus [68,69]. Tax activates IKK, which phosphorylates the IκB regulators of NF-κB, targeting them for proteosomal degradation and activating NF-κB [70–72]. HBZ on the other hand does not affect the regulatory components of NFκB signalling, and instead inhibits the canonical NF-κB pathway by interacting directly with p65, leaving the non-canonical pathway stimulated by the Tax protein alone [73].

HTLV-1 stimulates the expression of a number of cytokines that stimulate both the canonical and non-canonical NF-κB pathways, including IL-1, IFN-γ, TNF-α/β, and Bcl-3 [74–78]. However, few studies have examined the association between inflammatory cytokine production and ATL initiation and progression. Elevated