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The Mechanism of RNA Virus-mediated Tumorigenesis

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Various RNA viruses could lead to tumorigenesis. Since these viruses belong to different genera, they have evolved distinct mechanisms of tumorigenesis, with unique interactions among key oncoproteins, oncogenes and hosts factors. This article reviews the tumorigenic mechanism of two well-known human RNA tumor viruses, and explores the potential tumorigenic effects of SARS-CoV-2, which is also an RNA virus.

Introduction

Malignancy is a life-threatening disease. Over the years, oncology research has revealed that viral infections play a significant role in human tumorigenesis with RNA viruses being particularly critical to tumor pathogenesis. RNA tumor viruses，also known as retroviral tumor viruses, are characterized by the presence of reverse transcriptase in their particles. These viruses can replicate in host cells without disrupting cell division and are capable of transforming both animal and human cells，inducing tumor formation . Retroviral tumor viruses are widespread in nature and exhibit a broad range of tumorigenic effects across various species, including reptiles, birds, mammals, and primates. Rous sarcoma virus (RSV)is an RNA tumor virus first discovered by Rous in 1911[1, 2]. RNA tumor viruses are classified into two categories:acute transforming RNA tumor viruses and chronic RNA tumor viruses. Acute transforming RNA tumor viruses are not oncogenic in humans but can induce tumors in animals. These viruses lack replicative capacity and induce tumors rapidly by expressing viral oncogenes captured from the host cell genome. For example, murine leukemia virus (MuLV)produces the oncogene V-MOS and causes leukemia and neurological disease in mice by integrating its genome into the host's genome through reverse transcription[3]. RSV leading to sarcoma formation in chickens[4]. In contrast，chronic RNA tumor viruses do not carry oncogenes but can replicate and activate cellular proto-oncogenes by inserting viral long terminal repeat sequences near proto-oncogenes, inducing tumors with long latency.Examples include mouse mammary tumor virus and the avian leukosis virus[5].

Furthermore, some studies suggest that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA virus that causes COVID-19, may integrate into the genome of infected human cells[6]. In this review, we will introduce the mechanism of RNA virus-mediated tumorigenesis with two RNA viruses associated with carcinogenesis: Human T-cell leukemia virus type 1 (HTLV-1) and hepatitis C virus (HCV). We also explore the potential tumorigenic effects of SARS-CoV-2 and discuss future research directions and trends in the study of RNA virus-mediated tumorigenesis.

The Mechanism of HCV-mediated Tumorigenesis

HCV is a single-stranded RNA virus in the family Flaviviridae that induces chronic inflammation and progressive liver fibrosis, creating an oncogenic tissue microenvironment.It is one of the leading causes of hepatocellular carcinoma (HCC). HCV consists of three structural proteins (Core, E1 and E2) and seven non-structural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B)7. The core proteins forms the nucleocapsid of the viral genome and the envelope of HCV are composed of the envelope glycoproteins E1 and E2. NS3 exhibits serine protease and helicase activities and,in conjunction with NS4A,cleaves downstream NS proteins. NS4B is a component of the membrane-associated cytoplasmic HCV replication complex. NS5A is is critical for the assembly of the HCV replication complex and viral particles. NS5B is an RNA-dependent RNA polymerase that synthesizes viral RNA. Since HCV's genetic material cannot integrate into the host genome, it is commonly believed that HCV interacts with host cytokines through its constituent proteins, participating in cell signaling, transcription, and directly or indirectly promote cell proliferation and apoptosis7.HCV promotes inflammation, dysregulation of the metabolic system leading to steatosis, and fibrosis through activation of hepatic stellate cells. Additionally, it induces malignant transformation of hepatocytes through accumulation of genetic damage and epigenetic dysregulation, while also impairing immune cell response,leading to immune escape7. As cells proliferate to replace those destroyed by chronic inflammation, they may acquire tumorigenic mutations8. This inflammation-driven tumorigenesis is a slow and complex process9, often taking decades to develop.

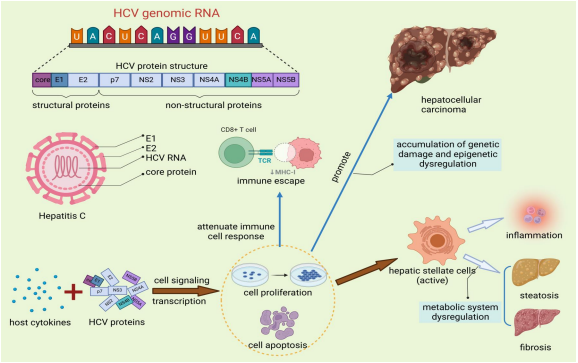

Fig1. The+Mechanism+of+DNA+Virus-mediated+Carcinogenesis

The Mechanism of HTLV-1-mediated Tumorigenesis

Human T-cell leukemia virus type 1 (HTLV-1) was the first confirmed pathogenic human retrovirus and is the causative agent of adult T-cell leukemia lymphoma (ATL) and a progressive myelopathy called HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)10.HTLV-1 is spherical, approximately 100 nm in diameter, containing viral RNA and reverse transcriptase at its core.The outer viral envelope, which exhibits helical symmetry, is surrounded by a 20-sided symmetric capsid protein.HTLV-1 consists of two identical single-stranded RNAs (ssRNAs) with short repetitive sequences at both ends and structural genes in the middle （gag, pol and env）, along with several accessory genes,including tax, rex, p12, p21, p30, p13 and HTLV-1 bZIP factor (HBZ)10. Studies have demonstrated the critical roles of Tax and HBZ genes in cellular transformation and leukemogenesis of HTLV-110. Tax is a trans-viral regulatory protein with pleiotropic functions in viral replication and cellular transformation. HTLV-I binds to CD4+ T cells and activates them, leading to the expression of IL-I2 receptors on their surface. Viral reverse transcriptase then converts viral RNA into DNA, which integrates into the host chromosome to form a provirus. In the presence of the Tax protein, CD4+ cells abnormally express IL-2 and its receptor gene abnormally, resulting in the proliferation of infected cells. Due to the diversity of viral DNA integration sites, host cells with the provirus can transform into different cell clones. As proliferation continues, mutations in the DNA of one clone may result in leukemic cell formation, ultimately giving rise to a leukemic cell clone. However, since Tax is the primary target of cytotoxic T lymphocytes (CTL), most ATL cells do not express Tax during the later stages of transformation, due to mechanisms that result in its loss, allowing the cells to evade CTL attack. In contrast, the HBZ protein, which is less immunogenic than the Tax protein10, facilitates infection spread by suppressing major HTLV-1 regulatory genes, including tax, and aiding the virus in escaping immune surveillance10.

Tumorigenic potential of Coronavirus

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus has caused an global pandemic since December 2019.As of the time of writing (August 2022), more than 500 million people worldwide have been diagnosed with COVID-19, resulting in over 6.45 million deaths (New York Times, 2022).SARS-CoV-2 is an envelope-positive single-stranded RNA virus11. Like other RNA viruses, SARS-CoV-2 infection may induce or accelerate the progression of tumors and diseases. A study by Rudolf Jaenisch's group at MIT found that the RNA of SARS-CoV-2 may integrate into the human genome via a LINE-1-mediated transposition mechanism, following infection of human cells, and that chimeric transcripts can be detected after integration6. This suggests the potential for SARS-CoV-2 to integrate into the human genome and possibly induce tumorigenesis in patients.

However, a team led by Geoffrey J. Faulkner at the University of Queensland in Australia has challenged these findings 12.They argue that although the theory of LINE-1-mediated retrotransposition of SARS-CoV-2 sequences into the human genome appears plausible, it is unlikely to occur in practice. This is because the cellular environment of HEK293T used by Jaenisch's group for SARS-CoV-2 infection promotes LINE-1 activity, compared to SARS-CoV-2-infected patient samples. Additionally, extensive cell death following in vivo infection further reduces the likelihood of sustained integration of SARS-CoV-2 into the human genome. Therefore, they concluded that there is insufficient evidence to support the integration of SARS-CoV-2 into the human genome. Whether SARS-CoV-2 viruses can mediate human tumorigenesis remains uncertain.

Conclusions and Perspectives

There are various mechanisms of RNA virus-mediated tumorigenesis, in which viral oncoproteins interact directly or indirectly with host cytokines, affecting the expression and/or activity of the cytogenetic material. This interaction causes multilevel and continuous damage to the host cell, ultimately leading to alteration of the host cell genetic material. However, the mechanism of RNA virus tumorigenesis remain poorly understood. The absence of a clear mechanism of RNA virus gene sequences into the host cell genome, and whether tumorigenic RNA viruses cause epigenetic modifications in addition to genetic changes, require further investigation. Advancing our understanding of the tumorigenic mechanism of RNA viruses, will enhance insights into the molecular etiology of tumorigenesis and the viral mechanisms of oncogenesis.It may also provide a new theoretical basis and application areas for us to use viral vectors in gene-level tumor therapies and to develop virus-based tumor vaccines to prevent and treat malignancie

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