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Measles Virus: Association with Cancer

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Abstract

Measles virus (MV) is a member of the paramyxovirus family of enveloped RNA viruses and one of the most infectious viral pathogens identified. Despite initial optimism that vaccination programs would eventually eradicate measles, reduced vaccination coverage against measles continues to result in outbreaks of measles. Mild or asymptomatic measles infections are common among measles-immune persons exposed to measles cases and may be the most common manifestation of measles during outbreaks in highly immune populations. Persistent, asymptomatic MV infections commonly persist in apparently healthy individuals. MV has been detected in several malignancies, including lung, breast, and endometrial cancers, as well as Hodgkin's lymphoma. The presence of MV in these tumors was associated with distinct clinico-pathological characteristics: in lung cancer, older ages of patients and over expression of Pirh2, and in breast cancer, age less than 50 years, lower histological grade, and over expression of p53. Nectin-4 is the MV receptor in epithelial cells and is highly expressed in certain epithelial tumors. MV-associated tumorigenesis may be linked to the effect of MV-phosphoprotein on Pirh2, an E3 ubiquitin ligase of p53. By way of MV interaction with Nectin-4 and Pirh2, persistent MV infection may co-act with other factors in transforming cells to become malignant.

Keywords: Measles virus; Cancer; Pirh2; p53; MV-phosphoprotein

Introduction

Although viruses have long been implicated as a cause of cancer [1], their relevance to human cancer development has often been debated. An estimated 15 percent of all human cancers worldwide may be attributed to viruses [2], representing a significant portion of the global cancer burden. Both DNA and RNA viruses have been shown to be capable of causing cancer in humans. Epstein-Barr virus (EBV), human papilloma virus (HPV), hepatitis B virus (HBV), [3] human herpes virus-8 (HHV8) [4], and the recently identified Merkel cell Polyomavirus (MCPyV) [5] are DNA viruses that are capable of causing the development of human cancers. Human T lymphotrophic virus type 1 and hepatitis C viruses (HTLV1, HCV) [6,7] are the two RNA viruses that contribute to human cancers. It has been recognized that tumor-viruses induce oncogenesis by initiating a series of cellular events, which lead to immortalization and proliferation of the infected cells by disrupting the mitotic checkpoint upon infection of the host cell. This is often accomplished by functional inhibition or proteasomal degradation of many tumor suppressor proteins by virally encoded gene products. Although it is convenient to consider human tumor viruses as a uniform group of viruses, these viruses, in fact, have very different genomes, life cycles, and represent a number of virus families [8]. The path from viral infection to tumorigenesis may be slow and inefficient; only a minority of infected individuals progress to cancer, usually years or even decades after primary infection. Virus infection also is generally not sufficient for cancer, and additional events and host factors, such as genetic predisposition, immunosuppression, somatic mutations, and exposure to carcinogens also play key roles.

The criteria most often used in determining the causality of viruses in the development of cancer are mainly consistency of the association, either epidemiologic or on the molecular level, and oncogenicity of the agent in animal models or cell cultures [9]. It must be recognized however, that the use of these generally applied criteria in deciding on causality is selective, and the criteria may be weighted differently. Whereas for most of the tumor viruses the viral genome persists in an integrated or episomal form with a subset of viral genes expressed in the tumor cells, HCV is not inherently oncogenic, but infection leads to transformation of cells by indirect means. For some malignancies such as Burkitt's lymphoma, EBV appears to serve as a cofactor. For Hodgkin's lymphoma, the viral association with EBV is inconsistent. EBV may simply define subsets of Hodgkin's lymphoma, or while not causing the tumor, may act to modify the phenotype, contributing to tumor progression.

There are several lines of reasoning that associate measles virus (MV) with cancer development. MV is a ubiquitous RNA virus with highly contagious properties in unvaccinated populations and results in lifetime immunity after infection [10]. Despite the wide availability of a safe and effective live attenuated virus vaccine, measles continues to be an important cause of morbidity and mortality in many parts of the world [11-13]. During outbreaks in highly immune populations, mild or asymptomatic measles infections are common among measles-immune persons exposed to measles cases, and may be the most common manifestation of measles [14]. Asymptomatic MV infections that may be caused by MV mutants commonly persist in apparently healthy individuals [15,16]. Novel data shows that PVRL4 (Nectin-4), is the MV receptor in epithelial cells, and is highly-expressed in certain tumors [17,18]. It was also found that MV may hijack the p53 tumor suppression system by affecting Pirh2, an E3 ubiquitin ligase of p53 [19]. This review summarizes the data supporting a role played by MV in the development of several types of cancers. It is suggested that persistent MV infection may co-act with other factors in the

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malignant transformation of cells. Alternatively, MV may contribute to tumorigenesis by modifying the phenotype of an established tumor or by playing a key role in tumor progression rather than in tumor initiation.

The Measles Virus

Measles is a common infection in children, caused by MV, a non-segmented, single stranded; negative-sense enveloped RNA virus of the genus Morbillivirus within the family *Paramyxoviridae* [10]. It is spread by the respiratory route, and characterized by fever, photophobia, coughing, running nose, nausea, and a macular red rash. MV infection can confer lifelong immunity, and there is no evidence of latent or common persistent infection except for subacute sclerosing panencephalitis (SSPE). No animal reservoir has been identified.

MV has helical symmetry and encodes 8 proteins. Viral mRNAs are transcribed to encode a nucleocapsid protein (NP), a phosphoprotein (P), virulence factors (C and V), matrix protein (M), membrane fusion protein (F), the hemagglutinin/receptor binding protein (H), and an RNA polymerase (L) [20]. Surrounding the nucleocapsid is a membrane which contains the two viral glycoproteins, H and F. The H protein is required for viral attachment to the host cell receptor. The F protein mediates membrane fusion and the entry of molecules throught the host plasma membrane and is also responsible for syncytia (multi-nucleated cell) formation [21]. Interaction of the H protein of MV with a cellular attachment factor is the initial event of infection [22]. The binding of H to the host cell receptor triggers and activates the F protein to induce fusion between virus and host cell membranes [23]. The nucleoprotein (N) forms a helical nucleocapsid around the genomic RNA to form the ribonucleocapsid. The phosphoprotein (P) and large (L) polymerase protein are associated with the ribonucleocapsid and necessary for RNA synthesis after initiation of infection. The matrix (M) protein associates with the interior surface of the viral lipid envelope and links the ribonucleoprotein complex to the envelope glycoproteins during virus assembly. Two nonstructural proteins, C and V, are encoded within the P gene through an alternative translation initiation site and RNA editing. Neither C nor V is necessary for MV replication in tissue culture, but both proteins, along with P, interact with cellular proteins and regulate the response to infection.

The first protein identified as a cellular receptor for MV was membrane cofactor protein (CD46), which is ubiquitously expressed on human nucleated cells [24]. However, although CD46 functions as a receptor for laboratory-adapted and vaccine strains of MV, most wild-type MV strains do not bind to CD46. More than a decade ago, signaling lymphocyte activation molecule (SLAM, CD150) was identified as a receptor for both laboratory-adapted and wild-type strains of MV [25,26]. CD150 is expressed on subsets of thymocytes, macrophages, and dendritic cells, as well as B- and T-lymphocytes. Epithelial cells are critical to the process of infection and the spread of MV by aerosol droplets. Recently, the human PVRL4 (Nectin-4), a tumor cell marker found on breast, lung, and ovarian carcinoma cell lines, was identified as epithelial receptor for MV [17,18]. PVRL4 is expressed at low to moderate levels in normal tissues but is highly up-regulated on the surfaces of adenocarcinoma cells. Further experiments with differentiated primary epithelial cells in culture and the use of human epithelial explants are currently underway to validate the role of PVRL4 in infections of normal epithelial cells and establish its importance in measles pathogenesis.

MV Infection in Vaccinated Populations

Measles is a leading cause of vaccine-preventable childhood mortality worldwide. Even in countries where vaccination has significantly reduced mortality, rates may remain high. Despite optimism that vaccination programs would eventually eradicate measles, reduced vaccination coverage against measles resulted in outbreaks of measles in many western countries. In the US, two major types of outbreaks have been described: those in which most of the cases occurred among preschool-age children (those under 5 years of age), and those in which most of the cases occurred among school-age persons (those 5 to 19 years of age) [27]. Most outbreaks occurred within small clusters, were acquired outside of the United States, and involved individuals who had not been vaccinated [28]. Although indigenous measles was declared to have been eliminated in North, Central, and South America, rural Canada is still regarded as having minor endemic status [29]. In many European countries, measles outbreaks continue to produce a major health problem. The European measles cases have largely (73%) been in individuals who have not received the vaccine [30]. Although the peak incidence is in the age range of 1-4 years, the vast majority of cases occurred in individuals over the age of 4 years. In Israel, despite the implementation of a pulse vaccination policy, outbreaks of measles continue to occur [31]. A recent outbreak that included hundreds of cases has been reported among Jewish ultra-orthodox communities in Jerusalem [13]. As a result of measles infection, immunity against MV was thought to be life-long. The measles vaccination was also considered to induce life-long immunity. It has been recognized, however, that the MV can infect previously immune individuals, producing a wide range of illnesses such as typical measles, mild modified measles, and asymptomatic infection. Helfand et al. [14] studied the frequency of mild or asymptomatic measles infections among 44 persons exposed to a student with measles during a 3-day bus trip. All participants had detectable measles-neutralizing antibodies, and none developed classic measles symptoms. Ten of the exposed (23%) were IgM positive for measles, indicating recent infection. The authors concluded that mild or asymptomatic measles infections are probably very common among measles-immune persons exposed to measles cases and may be the most common manifestation of measles during outbreaks in highly immune populations. Molecular epidemiological investigation of measles outbreaks can document the interruption of endemic measles transmission and is useful for establishing and clarifying epidemiological links between cases in geographically distinct clusters. Although measles virus (MV) is serologically monotypic, the genetic characterization of wild-type viruses has identified eight classes (A-H), which have been divided into 22 accepted genotypes and one proposed genotype [32]. There are no known biological differences between viruses of different genotypes, and specific measles genotypes are not associated with differences in severity of disease, or likelihood of developing sub acute sclerosing panencephalitis (SSPE).

At least three studies have shown the presence of MV infection in tissues of asymptomatic individuals. Sonoda et al. [33] detected MV genome by RT-PCR in peripheral blood mononuclear cells in 40 of 159 samples from healthy volunteers who had been immunized more than 2 months before, and in seven of 26 individuals after natural infection. Similar findings were found in bone marrow aspirates performed for evaluation of malignant involvement in 179 adult patients with a variety of hematological neoplasms [16]. The MV genomes were detected in 17 (9±5%) of 179 individuals by RT–PCR of the bone

marrow aspirates and 28 (15±6%) through hybridization, and were all in the same cluster, D5, the viral strain circulating during the study period. The authors concluded that asymptomatic infections of MV are common in adults and the presence of the MV genome is not be related to the pathogenesis of illness. These results contrast to the MV genome detected in chronic brain infection which is related to the wild-type virus circulating at the time of initial infection, and not to the type circulating at the time of onset of symptoms [34,35]. Katayama et al. [15] detected MV mRNA by RT-PCR in 23 (45.1%) of 51 autopsy subjects. MV genome was found in the brain, kidney, spleen, liver, and lung with the detection rates in each tissue ranging from 8 to 20%. Sequence analysis revealed frequent mutations in the corresponding viral protein. The authors concluded that MV mutants commonly persist in apparently healthy individuals.

MV in Cancer

Despite the controversy in regard to the presence of MV in Hodgkin's lymphoma (HL), the presence of MV in various cancers and its association with distinct clinicopathologic characteristics remain the most convincing evidence associating MV with cancer. In western countries, classic HL generally shows a bimodal, age-specific incidence curve [36], with the first peak in young-adults linked to high social class, a high level of maternal education, small family size, and early birth order [37]. It has been proposed that such factors diminish an individual's exposure to infectious agents in early childhood and thereby increase susceptibility to developing a virus-induced pathogenesis later in life-the so-called late host response model. Since less than 25% of young adult cases are Epstein-Barr virus (EBV)-associated, EBV is not the elusive agent implicated in this model [38,39]. In recent years, there has been a persistent increase in the incidence rate of HL in young adults in Israel, and annual rates of incidence, especially in female young-adults have surpassed that of any other western country [40].

Benharroch et al. [41] reported the presence of MV in Hodgkin's Reed-Sternberg (HRS) cells in classical HL in Israeli patients. MV proteins were detectable by immunohistochemistry (IHC) in 82 (54.3%) of 154 patients using at least two antibodies. MV RNA was also detected by RT-PCR and *in-situ* hybridization in a significant minority of the cases. Subsequently two studies failed to confirm the presence of MV in HRS cells. MV was not detected in a series of HL cases from Scotland and Newcastle [42], nor was MV detected in microdissected HRS cells from biopsies of 18 German and 17 Israeli HL cases [43]; the Israeli cases had previously scored positive for MV antigens. As HRS cells are typically scarce among inflammatory background, it remains uncertain whether issues related to methodology or to study populations (or both) are responsible for these discrepancies.

MV was subsequently studied in other solid cancers including lung, endometrial, and breast cancer. Sixty-five newly-diagnosed patients with non–small cell lung cancer of all stages were studied for the presence of MV antigens on IHC [44]. Expression of at least one MV antigen was found in 54 of 65 (83%) cases. MV was associated with older age of patients, improved survival and overexpression of Pirh2. Thirty-six patients with endometrial carcinoma were studied to detect fingerprints of MV [45]. Twenty-six (72%) cases showed the presence of MV antigens in the tumor cells. Sixteen of 21 (76%) cases were positive for MV RNA by *in-situ* hybridization, and type I tumor was more positive for viral particles than type II. In 131 patients with invasive breast cancer IHC was used to evaluate the presence of two MV antigens, hemagglutinin and nucleoprotein [46]. Both MV antigens were detected in 64% of the tumors. MV was associated with younger age of patients, lower histological grade and overexpression of p53, but not with hormone receptor status or Her2/neu. All biopsies containing a ductal carcinoma *in-situ* (DCIS) component showed MV in both the DCIS and the invasive breast cancer components. MV antigens were studied in several other tumors including malignant melanoma, malignant pleural mesothelioma, glioblastoma multiforme, and peripheral T-cell lymphoma. MV antigens were detected in 80% of malignant melanoma cases but in none of the other three tumor types (unpublished data).

Pirh2 may link MV to cancer

The tumor suppressor p53, known as "the guardian of the genome", plays a key role in eliciting cellular responses to many signals of cell stress. By promoting cell cycle arrest, apoptosis, senescence and DNA repair, p53 helps in preventing cancer development [47]. p53 is subjected to a variety of post-translational modifications, including phosphorylation, acetylation, methylation and ubiquitylation [48]. Pirh2, also known as ring finger and CHY zinc finger domain-containing 1 (Rchy1), is a member of the RING finger family of E3 ubiquitin ligases. Pirh2 facilitates p53 degradation via the ubiquitin-proteasome pathway, independent of MDM2 [49]. Notably, Pirh2 degrades active p53 under conditions of DNA damage when Mdm2 dissociates from and fails to degrade p53 [50], and p73, another member of the p53 system [51]. Pirh2 is highly expressed in multiple cancers and in cell lines regardless of p53 status [52]. A mechanism by which MV may control the p53 signaling system was described by Chen et al. [19], analogous to the mechanism by which oncogenic viruses commonly deregulate cellular homeostasis by hijacking the p53 system, promoting an aberrant cell-proliferation or blocking apoptosis [53-56]. MV-phosphoprotein was able to specifically interact with and stabilize the ubiquitin E3 ligase hPirh2 by preventing its ubiquitination, but had no effect on the stability or ubiquitination of an alternative ubiquitin E3 ligase, Mdm2. This mechanism may link persistent MV infection, altered p53 function and cancer [19].

A suggested model linking MV with cancer

Despite the wide implementation of measles vaccine programs, reduced vaccination coverage against measles continues to result in outbreaks of measles in many western countries. Although the exact scale of mild or asymptomatic measles infection during outbreaks of measles is unknown, these modes of MV infection cannot be ignored, and persistent MV infection in otherwise asymptomatic individuals is apparently not a rare phenomenon. MV is probably not oncogenic in the generally-applied criteria causality, as only a minority of infected individuals progress to cancer, usually years or even decades after MV infection. The mechanism by which MV-phosphoprotein modifies p53, via its effect on Pirh2, may explain how persistent MV may support tumorigenesis. Also MV infection is probably not sufficient for cancer, and additional events and host factors, such as genetic predisposition, immunosuppression, somatic mutations, and exposure to carcinogens are probably essential cofactors with MV to produce cancer. In cases of Hodgkin's lymphoma, MV may act in concert with EBV in the lymphomatous transformation of cells. Cigarette smoke may act along with MV in the course of development of lung cancer among smokers, and MV maybe a cofactor with a UV light-induced, *B-RAF* mutation that results in invasive melanoma. Recently, the MV-receptor, PVRL4 was shown to be overexpressed in several epithelial tumors. Although the presence of MV in cancer might simply indicate

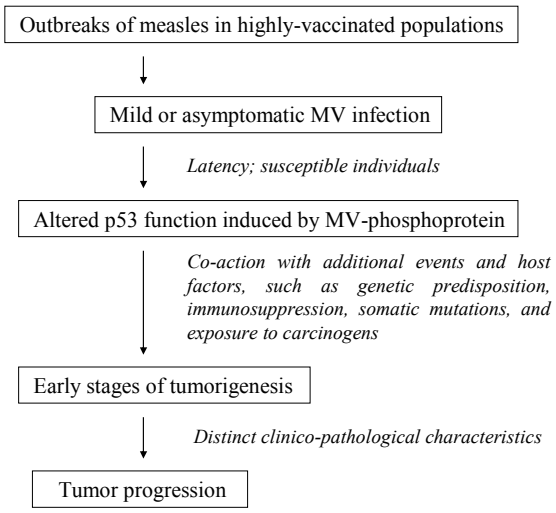

Figure 1: Diagram showing the suggested measles virus model of tumorigenesis.

MV infection of already transformed cells, data showing that MV-infected tumors show clinicopathological characteristics distinct from uninfected tumors support the hypothesis that MV plays a role in early stages of tumorigenesis. Figure 1 summarizes the suggested MV model of tumorigenesis.

Conclusions and Future Directions

Confirmation of the proposed model requires confirmation of the presence of MV in tumors in additional populations, as well as development of an animal model which could also be used to study the long-term sequelae of persistent MV infection. Future studies will need to address questions that may be raised by the suggested model such as: (i) the exact magnitude of persistent MV infection in previously-vaccinated populations; (ii) defining populations that are most susceptible to develop persistent MV; (iii) pursuing interactions between MV and additional events or factors in transforming cells to become malignant; and (iv) clarifying whether additional MV mechanisms to the effect of MV-phosphoprotein on Pirh2 are involved in MV-induced tumorigenesis. We suggest that the data presented in the current review justify the initiation of additional laboratory and epidemiologic studies that may further substantiate the association between MV and cancer.

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