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The p53 – microRNA-34a axis regulates cellular entry receptors for tumor-associated human herpes viruses

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Abstract

A growing number of reports indicate the frequent presence of DNA sequences and gene products of human cytomegalovirus in various tumors as compared to adjacent normal tissues, the brain tumors being studied most intensely. The mechanisms underlying the tropism of human cytomegalovirus to the tumor cells or to the cells of tumor origin, as well as the role of the host's genetic background in virus-associated oncogenesis are not well understood. It is also not clear why cytomegalovirus can be detected in many but not in all tumor specimens. Our *in silico* prediction results indicate that microRNA-34a may be involved in replication of some human DNA viruses by targeting and downregulating the genes encoding a diverse group of proteins, such as platelet-derived growth factor receptor-alpha, complement component receptor 2, herpes simplex virus entry mediators A, B, and C, and CD46. Notably, while their functions vary, these surface molecules have one feature in common: they serve as cellular entry receptors for human DNA viruses (cytomegalovirus, Epstein-Barr virus, human herpes virus 6, herpes simplex viruses 1 and 2, and adenoviruses) that are either proven or suspected to be linked with malignancies. MicroRNA-34a is strictly dependent on its transcriptional activator tumor suppressor protein p53, and both p53 and microRNA-34a are frequently mutated or downregulated in various cancers. We hypothesize that p53 – microRNA-34a axis may alter susceptibility of cells to infection with some viruses that are detected in tumors and either proven or suspected to be associated with tumor initiation and progression.

INTRODUCTION

Herpesviruses are a large family of DNA viruses that can cause latent or lytic infections in animals and humans, notably – often in immunocompromised patients. Epstein-Barr virus

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CONFLICT OF INTERESTS

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(EBV) and Kaposi's sarcoma-associated herpes virus (KSHV) are proven to play an important role in the development of various cancers (1, 2). Though the direct role of other human herpesviruses in oncogenesis has not been proven yet, their proteins and/or DNA sequences are frequently detected in tumors but not in adjacent normal tissues. Human cytomegalovirus (HCMV) has been found in tumor cells of patients with malignant brain tumors (gliomas), breast cancer, colon cancer, cervical cancer, prostate carcinoma, and EBV-negative Hodgkin's lymphoma (3). The finding of HSV-1 and-2 DNA in thyroid tumors (4) may be linked to the antiapoptotic activity of herpes simplex viruses (HSV) 1 and 2 and their ability to downregulate human telomerase reverse transcriptase (5–7). Human herpes virus 6 (HHV-6) has been connected with hematological malignancies (8, 9). It had been suggested that herpesviruses could initiate subtle changes, the so-called oncomodulation (10), which was defined as the ability of viral proteins and non-coding RNAs to promote oncogenic processes without direct oncotransformation but through disturbances in various intracellular signaling pathways. However, despite growing experimental evidence (11), the roles of HCMV, HHV-6 and HSV-1 and -2 as active participants in the tumorigenic processes continue to be debated. Additionally, it is not clear why the above-mentioned viruses can be detected in many but not in all tumor specimens.

Here we present a hypothesis that highlights a potential link between the major tumor suppressor p53, its transcriptional target microRNA-34a, and susceptibility of cells to infection with viruses that are either proven or actively studied for their possible role in the initiation or progression of cancers.

BACKGROUND

HCMV and human malignancies

HCMV is currently one of the most actively studied prooncogenic/oncomodulatory infectious agents (12). Its DNA sequences and proteins are detected in more than 90% of human gliomas, brain tumors with high morbidity and mortality. Many HCMV activities contribute to established hallmarks of cancer such as proliferative signaling, evasion of growth suppressors and resistance to cell death, genomic instability, activation of invasion, metastasis, angiogenesis, avoidance of immune destruction, and inflammation. However, HCMV is not characterized by the sustained expression of oncogenes or genomic integration, the features that are attributed to known oncogenic viruses (13). Hence, some additional factors, for example, genetic polymorphisms that render susceptibility to the oncomodulatory effects of HCMV, are proposed to play a role in the possible contribution of HCMV to oncogenesis. It has been hypothesized that, analogously to HSV-1, some haplotypes of HCMV-encoded *Fc*-like receptors may vary in their ability to bind to antibodies due to steric variations. The low-affinity binding interferes with the effector functions of antibodies, thus allowing HCMV-infected cells to avoid or to mitigate antibody-dependent cellular cytotoxicity, complement-dependent neutralization, and phagocytosis (14).

Another hypothesis is based on the fact that PDGFRA is an obligatory cellular entry receptor for HCMV. Viral attachment to PDGFRA elicits a potent cellular interferon-like response, which, in turn, activates downstream growth-factor-like receptor tyrosine kinase and integrin signaling pathways (13). Phosphorylation of PDGFRA upon its binding with HCMV glycoprotein B, and HCMV-mediated activation of human epidermal growth factor receptor trigger downstream signaling molecules PI3K/Akt and focal adhesion kinase, which are the components of the pro-oncogenic signaling network. PDGFRA deletion or blocking by antibodies, or targeted inhibition of its kinase activity abrogates HCMV internalization and gene expression, as well as the above-mentioned signaling cascade (13, 15). PDGFRA is essential for neural development, self-renewal of neural stem/progenitor cells and

gliomagenesis (16–19). The extent of PDGFRA signaling apparently corresponds to tumor malignancy: PDGFRA amplification is detected in about 13% of brain tumors (20), and PDGFRA overexpression can be observed in all phenotypes of glioblastoma (21, 22), though it is rather associated with secondary than with primary glioblastomas (23). The PDGFRA promoter region contains a total of 10 polymorphic sites that give rise to five distinct haplotypes. As these haplotypes are characterized by varying levels of PDGFRA promoter activity, the second hypothesis suggests that PDGFRA haplotype differences confer differential susceptibility to HCMV infection as well as predisposition to gliomagenesis or progression of gliomas in humans (13, 18).

Tumor suppressor protein p53 and viral replication

p53, a key tumor suppressor protein and a master transcriptional regulator, influences the expression of a variety of genes that are involved in cell cycle progression, cell growth, differentiation and death, cell motility and migration, cellular senescence, DNA repair, energy metabolism, cell–cell communications, angiogenesis and immune response (24, 25), in particular, innate antiviral immunity (26, 27)

During the process of evolution, viruses adopted different strategies to manipulate the host cells to ensure that all the steps in the viral life cycle are complete (28). As cellular stress responses and apoptosis are mediated in large part by p53, viruses utilize a variety of mechanisms aimed to inactivate p53 in order to prevent cell death and abortion of viral replication. Among them are interactions between p53 and viral proteins, p53 phosphorylation, ubiquitination of p53 by viral E3-ubiquitin ligases, prevention of p53 acetylation, downregulation of p53 by interferons, interaction with p53 regulatory proteins, inhibition of p53 dependent transcription, and activation of Hdm2 (29–33). p53 is frequently mutated in many cancers in the so-called hotspots of its DNA-binding domain. These gain-of-function mutants act oppositely to their wild-type counterpart not only by failing to transactivate its usual target genes but also by de-repressing or transactivating a plethora of oncogenes (29, 34). Human immunodeficiency virus-1 replication (35–37), and the host response to hepatitis C virus (38, 39), respiratory syncytial virus (40), influenza (41), vesicular stomatitis virus (42), and Rift Valley fever virus (43) were reported to vary depending on whether the cells harbored wild-type or mutant p53. Integration of adeno-associated viral vectors was higher in p53-negative cells as compared to normal ones (44). Loss of p53 confers enhanced susceptibility to reoviral and myxoma infectivity and replication (45). The role of p53 status appears to be even more essential for the replication of viruses that are implicated in tumorigenesis: human papillomaviruses (46–48), hepatitis B virus (49–52), gallid herpesvirus 2, which causes T-cell lymphomas in chickens (53), human adenoviruses (54, 55), and HSV-1 (56).

However, little is known about the mechanisms by which p53 abnormalities (either mutant or nonfunctional “negative” p53) influence the susceptibility of cells to viral infection.

Though some HCMV effects are reported to be independent of p53 status (57), it has been observed that the pre-existing genetic lesions, p53 mutations in particular, could explain the differential response of glioma cell lines to HCMV infection or overexpression of HCMV proteins (58–61). p53 is involved in regulation of HCMV replication (62, 63), and specifically, the onset of a lytic cycle (64). It influences expression of 22 HCMV genes (65), inhibits cell division and DNA synthesis upon overexpression of HCMV IE86 protein (61, 66) and regulates HCMV UL94 gene, which is activated during productive HCMV infection (67). It has been suggested that p53 mutations might represent one of the mechanisms by which HCMV contributes to the transformation of primary baby rat kidney cells in cooperation with the adenovirus E1A protein (3, 68). Wild-type p53 has been shown to inhibit HCMV major immediate-early promoter-enhancer as well as several other viral

promoters, including the HSV-1 UL9 promoter, and the long terminal repeat promoters of Rous sarcoma virus, human immunodeficiency virus-1, and human T-cell lymphotropic virus type 1. Conversely, mutations at any of the five "hotspot" amino acid positions 143, 175, 248, 273, and 281 release the repression of viral promoters to a variable extent (69–71). Altogether, p53 appears to provide wide-ranging impacts on the virus-host interaction from regulating expression of viral genes to maintaining the balance between latency and lytic infection.

MicroRNA-34a

MicroRNAs are short noncoding RNAs that regulate gene expression by targeting the 3'-untranslated region of mRNAs and inducing mRNA degradation or inhibiting its translation (72). microRNA-34a is a part of the p53-network (73), and a potent tumor suppressor, which is frequently downregulated in various cancers (74–78). microRNA-34a has previously been shown to control the same groups of genes that are regulated by p53 (79). It is encoded within the chromosome region 1p36, whose loss is shown to be associated with gliomas, neuroblastomas, pancreatic cancer, and chronic myeloid leukemia (80). According to the database *TargetScan*, microRNA-34a has a total of 512 conserved sites. In turn, p53 is believed to regulate between 1500 and 3000 genes (25). Either the loss of microRNA-34a or mutations within the p53-DNA binding domain that render p53 unable to transactivate its usual targets (including microRNA-34a) may result in significant changes of expression profiles across the whole genome.

In silico analysis of microRNA-34a target sites

By analyzing the databases *TargetScan* and *MicroCosm,* we have found that microRNA-34a targets a group of genes with one common trait: they encode cellular entry receptors for human herpesviruses that are actively studied for their possible role in the initiation or progression of cancers. The target sites for microRNA-34a have been identified on the following genes: platelet-derived growth factor receptor-alpha (PDGFRA) – HCMV cellular entry receptor; complement component receptor 2 (CCR2) – EBV cellular entry receptor; herpes simplex virus entry mediators A, B, and C (HVEM-A, -B, -C); and CD46 protein, which is a cellular entry receptor for HHV-6 (Figure 1). The matching positions for microRNA-34a within 3'-UTR and the corresponding NCBI Reference Sequence numbers of the targeted mRNAs are shown in Table 1. It is noteworthy that analogously to herpesviruses human adenoviruses are also investigated for their possible contribution to oncogenic processes through oncomodulation. According to *TargetScan* and *MicroCosm* databases CXADR mRNA has no predicted target sites for microRNA-34a. However, microRNA-34a has a highly conserved target site on *phosphoprotein enriched in astrocytes-15* (PEA15), which has been reported to upregulate the expression of coxsackievirus adenovirus receptor (CXADR) (81), the cellular entry receptor for all other serological groups of human adenoviruses. Of interest, is also the presence of a conserved miR-34a target site on CXADR pseudogene 2 (http://www.microrna.org).

HYPOTHESIS

We propose that tumor suppressor protein p53 regulates cellular entry receptors for HCMV as well as EBV, HSV-1 and -2, HHV-6 and adenoviruses. The effect of p53 on cellular entry receptors is mediated by its transcriptional target microRNA-34a. Thus, the status of the p53 – microRNA-34a axis may be considered as a pre-existing host condition that influences cell susceptibility to viral infections and accounts for the variable presence of HCMV and other herpesviruses in human tumors.

EVALUATION AND IMPLICATIONS

It is interesting to mention that HCMV immediate early 1 protein has been detected in nearly all glioblastomas and 82% of low-grade (less malignant) gliomas, while HCMV DNA could be identified in about 94% of clinical glioma specimens (13). These numbers are close to the frequency of altered p53 signaling in brain tumors – about 87% (19). As recently has been reported, repression of microRNA-34a upregulates PDGFRA (82). Overexpression of PDGFRA due to p53 or microRNA-34a abnormalities may increase the probability of HCMV infection of the tumor cells, as well as the potential cells of tumor origin. Furthermore, p53 inactivation or p53 mutations may significantly enhance HCMV replication due to de-repression of its promoter and thus create favorable conditions for HCMV to unfold its pro-oncogenic potential, which may further aggravate the already formed malignant glioma phenotype (11).

The microRNA-34a promoter has a *bona fide* binding site for wild-type p53, and microRNA-34a is recognized as a p53 downstream effector (73, 79, 83–85). In some cases, however, microRNA-34a levels can be elevated without functional p53. Inactivation of p53 by siRNAs was shown to lower basal levels of microRNA-34a transcript, but did not block microRNA-34a upregulation in response to oncogene-induced senescence (86). In p53-null K562 cells phorbol-esters could transactivate an alternative microRNA-34a promoter, which was located about 20 kb upstream of the classical microRNA-34a transcription start site, and produced a longer pri-microRNA-34a transcript (80). Recently it has been reported that CCAAT enhancer binding protein alpha (C/EBPα) and nuclear factor-kappa B (NF-κB) also bind to their appropriate sites and activate microRNA-34a, the NF-κB-mediated effect on microRNA-34a being p53-dependent (87, 88). Still, the overwhelming number of reports evidences microRNA-34a as a part of p53 network, thus allowing us to consider these two important tumor suppressor factors as the “p53-microRNA-34a axis.

Despite the *in silico* prediction data, the abilities of microRNAs to downregulate their transcriptional targets may vary significantly between tissues and depend on many factors including the accessibility of target sites, which is influenced by the complexity of RNA secondary structure and protein binding, on the levels of transcripts and other factors. (89). Contrary to the case with PDGFRA, the only route for HCMV, other herpesviruses may utilize alternative receptors that are not identified yet and are not controlled by microRNA-34a. Finally, expression of viral cellular entry receptors may vary in infected and non-infected cells, and even be downregulated upon their binding with viral proteins (90), probably in order to prevent superinfection followed by cell death. Notwithstanding the complexity of the issue, it should be acknowledged that the relatively slow evolution of DNA viruses and their long-term co-divergence with human hosts resulted in the development of mechanisms for controlling viral infectivity, replication and latency in host cells (91). It is recognized that though the known oncogenic viruses or other infectious agents are widely present in humans, only a small fraction of infected individuals develop cancer, apparently because of yet unidentified additional risk factors.

The ability of the viruses to enter non-infected cells in the first place is defined by the expression levels of their cellular entry receptors, which, in turn, may depend on the variations of the host’s genetic backgrounds. We suggest that p53 and microRNA-34a are important biomarkers that reflect genetic predisposition to HCMV infection and influence replication of HCMV and probably other human herpesviruses, such as EBV, HHV-6, HSV-1 and -2, and adenoviruses. Remarkably, all these viruses have been reported to have pro-oncogenic properties, although to a variable extent. Our speculations bring in another possible explanation of the inconstant detection of human herpesviruses, and specifically HCMV, in various tumors. Impaired p53 status, deletion of microRNA-34a, C/EBPα

mutations, mutations within p53-binding sites, or aberrant CpG methylation in the microRNA-34a promoter (87, 88, 92) could probably expedite viral entry via upregulation of the appropriate cellular entry receptors. Consequently, herpesviruses, which cause lytic or latent infections, may further contribute on a circumstantial basis to oncotransformation, formation of malignant phenotypes and tumor progression. The relevance of our hypothesis needs to be validated on the appropriate cell models and clinical tumor samples.

In the case of HCMV and its debatable role in the development of malignant brain tumors it has been stressed that studies addressing possible environmental and/or genetic factors, which increase the risk and elucidate the mechanisms underlying the input of HCMV into glioma pathology, need to be conducted (13). The present hypothesis may stimulate further studies in order to address the questions of whether the p53-microRNA-34a status may account for the development of glioma in only a small percentage of the population with latent HCMV, and if matching between miR-34a and several viral receptors simply reflects an evolutionary juxtaposition of herpesviruses or substantially diminishes their pro-oncogenic potential.

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Figure 1. Predicted microRNA-34a seed matches to viral entry receptors mRNAs

Results of *in silico* analysis suggesting the presence of microRNA-34a (miR-34a) target sites on the genes encoding cellular entry receptors for the following viruses: platelet-derived growth factor receptor-alpha (PDGFRA) – cellular entry receptor for human cytomegalovirus; complement component receptor 2 (CCR2) – for Epstein-Barr virus; CD46 – for human herpes virus 6 and human adenoviruses group B; and herpes simplex virus entry mediators A, B, and C (HVEM-A, -B, -C). *Phosphoprotein enriched in astrocytes-15* (PEA15) is a positive regulator for coxsackievirus adenovirus receptor, the cellular entry receptor for all other than group B serological groups of human adenoviruses.

Table 1

MicroRNA-34a matching positions and NCBI reference numbers of the targeted mRNAs.

Virus	Cellular receptor	Reference number	Matching positions
HCMV	Platelet-derived growth factor receptor-alpha	NM_006206.4	6269–6278; 6292–6306
EBV	Complement component receptor 2	M26004.1	3364–3370
HSV-1 and-2	Herpes simplex virus entry mediator A	NM_003820.2	1531–1537
HSV-1 and-2	Herpes simplex virus entry mediator B	NG_029149.1	47320–47341
HSV-1 and-2	Herpes simplex virus entry mediator C	NM_002855	2585–2591; 3900–3910
HHV-6, Human adenoviruses group B	CD46	NM_172361.2	2463–2469
Human adenoviruses	Coxsackievirus adenovirus receptor, upregulated by *phosphoprotein enriched in astrocytes-15* (81)	NM_003768.3	1729–1736