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REVIEW

Genome guardian p53 and viral infections

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SUMMARY

Because virus infections elicit various cellular responses that inhibit viral replication and growth, viruses must intervene to attenuate antiviral measures in order to thrive. The genome guardian p53 plays a central part not only in DNA damage responses, inducing cell cycle arrest or apoptosis, but also in the innate host immune control of viral infections by orchestrating diverse signaling pathways originating from many different cellular receptors and sensors. Many viruses have acquired sophisticated mechanisms to regulate p53 functions by deploying subversive proteins and modulating its post-transcriptional status. In this review, we overview the mechanisms by which DNA and RNA viruses manage p53 signaling in favor of their continued survival. Copyright © 2012 John Wiley & Sons, Ltd.

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INTRODUCTION

Viruses intrinsically depend on their host cells during the course of infection. Cells infected by viruses utilize host surveillance mechanisms to ultimately block viral replication and dissemination. The coordinated genetic regulatory network in which a transcription factor p53 controls the expression of a set of diverse target genes is central to host defense. Actuary, p53-mediated apoptosis, which may be termed altruistic suicide, inhibits the further spread of infectious pathogens [1]. On the other hand, another important aspect of cellular responses is the immune system signaling elicited by infection with viruses, which usually leads to the production of type I IFN and inflammatory cytokines, resulting in elimination of the pathogens [2].

p53 is also activated in response to diverse cellular stresses such as DNA damage and oncogenic stress [3,4]. Induction of p53 triggers multiple cellular programs ranging from transient responses, such as DNA repair and cell cycle arrest, to terminal fates such as cell death and permanent cell cycle arrest, hence having central roles in tumor suppression and maintaining genomic integrity as a guardian of the genome [3,5,6].

Lane and Levine initially isolated p53 as a binding partner of SV40 LTag in 1979 [7,8]. Within a few years of its discovery, evidence of a cellular oncogene property appeared because the gene cloned from neoplastic cells could reproduce transformation [9]. Tumor-derived p53 mutants can promote cellular transformation through dominant-negative inactivation of endogenous wild-type p53, whereas wild-type p53 cannot [10]. Vogelstein and colleagues reported a common loss-of-heterozygosity at the p53 locus in human colorectal cancers [11], suggesting that p53 was actually a tumor suppressor gene rather than an oncogene. Indeed, p53 is mutated or lost in over 50% of human cancers [12], representing the most commonly mutated gene in human tumors.

In unstressed cells, p53 is kept at low levels by its negative regulator MDM2 (HDM2) through the ubiquitin-dependent proteasome pathway [13]. Upon DNA damage, p53 is phosphorylated to escape from proteasomal degradation [14], and then is stabilized and activated to function primarily as a transcription factor, consequently leading to cell

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Abbreviations used
Ad, adenovirus; DDRs, DNA damage responses; E6AP, E6-associated protein; HBX, hepatitis B virus X protein; HPV, human papillomaviruses; Inf., Influenza virus; KSHV, Kaposi sarcoma herpesvirus; LANA, latency-associated nuclear antigen; LTag, large T antigen; SV40, simian vacuolating virus 40; Vacc., vaccinia virus; VSV, Vesicular stomatitis virus.

cycle arrest or apoptosis through the p53-mediated gene expression cascades [4,15]. These cellular outcomes after stresses, including DNA damage, oncogene activation, hypoxia, nucleotide imbalance, and oxidative damage, are tightly linked to p53 dynamics mediated by both the levels and post-translational modifications of p53 [16,17]

Furthermore, p53 also contributes to immune responses that lead to eradication of pathogens such as viruses [18]. p53 directly transactivates the expression of several innate immunity-related genes such as IRF9, TRL3, ISG15, and MCP-1 [19–22], and interestingly, transcription of the p53 gene is induced by IFN-α/β signaling [1,23]. These findings suggest a positive feedback loop involving p53-mediated enhancement of IFN signals to boost antiviral immune responses. Viruses, in turn, have to evolve elaborate mechanisms to subvert IFN-mediated and p53-mediated host immune responses.

Viruses are grouped into two major categories: DNA and RNA viruses. Replication of viruses, especially RNA viruses, can induce type I IFNs, triggered by the production of dsRNA. On the other hand, DNA viruses activate DNA damage signaling, triggered by the production of viral DNA genomes. Viruses intervene at numerous stages in the pathways to attenuate the antiviral responses. Here, we review how viruses modulate p53 functions and its downstream signaling pathways during their propagation, the functional links between viral growth and post-translational status of p53, and the physiological importance of this interplay. The interplay between p53 and viruses is summarized in Figure 1.

DNA VIRUSES

Most DNA viruses replicate their genomes in nuclei and usually elicit DDRs, resulting in phosphorylation and stabilization of p53. Some exploit the DDR to facilitate their own genome replication, but in other cases, the DDR presents a block to viral replication, which must be overcome. Thus, DNA viruses employ a variety of strategies to inactivate or degrade p53 or sometimes to utilize p53 function for their proliferation. The prevention of p53 functions by virus, in turn, contributes to tumor progression in a certain tissue.

The high-risk HPV, which is associated with human cervical cancer, E6 protein can recruit the cellular E3 ubiquitin ligase E6AP, a prototype member of the homologous to the E6-associated protein carboxyl terminus (HECT) family, to a trimeric complex with p53 [24] that is degraded through the ubiquitin–proteasome pathway [25,26]. Degradation of p53 by the E6–E6AP complex reduces the net levels and then allows viral replication by inhibiting p53-mediated antiviral responses including DDR, apoptosis, and other stress signals.

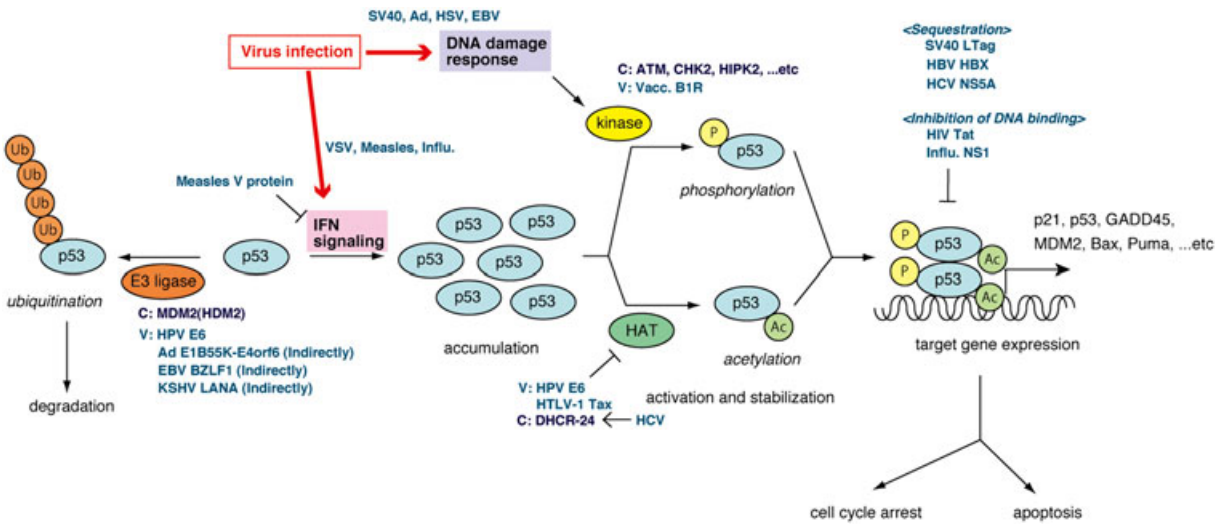

Figure 1. Intervention of viral proteins in p53-mediated antiviral responses. The viruses interfere with the p53 functions at several steps to permit a successful viral life cycle. Although infection with pathogens induces antiviral signaling pathways that stabilize and activate p53, viral factors manipulate these pathways by mimicking post-translational modifications of p53 and/or disrupting its downstream signals

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Many oncogenic DNA viruses including Ad, EBV, and KSHV also share the p53-inhibiting strategy that leads to p53 degradation through the ubiquitin–proteasome pathway. Ad E1B55K associates with E4orf6 to ubiquitinate p53 [27]. The EBV BZLF1 protein can function as an adaptor of the Elongin B/C-Cul2/5-SOCS-box protein (ECS) complex, which facilitates p53 degradation that has previously been phosphorylated in C-terminal region responses [28–30]. The KSHV-encoded LANA interacts with p53, resulting in inhibition of p53-mediated apoptosis and increased chromosome instability [31–33]. Thus, preventing p53 destruction by viral proteins might be a potent therapeutic target to combat virus-related carcinoma.

SV40 possesses tumorigenic properties in non-permissive cells. This transformation potential depends on the activity of LTag interacting with several cellular tumor suppressors, including p53 and pRb. Lilyestrom *et al*. reported the structure of p53 bound to LTag [34], featuring a circular Tag helicase domain hexamer with a p53 DNA-binding domain bound to the outside surface of each subunit, forming a pinwheel-like structure [34], suggesting that LTag subverts p53 function by preventing it from binding to DNA for appropriate regulation of p53.

On the other hand, HBX inhibits p53-mediated cellular processes by sequestration of p53 from the nucleus to the cytoplasm [35,36]. The EBV latent protein EBNA1 contributes to repress p53-dependent DDR by competing for the binding site of deubiquitinating enzyme USP7 with p53 [37]. The vaccinia virus-encoding Ser/Thr kinase B1R is able to directly hyperphosphorylate p53 in several residues including Thr 18 [38]. Interestingly, phosphorylation by B1R results in p53 degradation in an MDM2-dependent manner [38], illustrating the complexity of the structure of the p53 N-terminus region. Downregulation of p53 promotes viral DNA synthesis in cells infected with vaccinia virus [39] and also prevents p53-mediated responses, such as apoptosis [40]. Taken together, the complex between viral and cellular proteins suppresses p53 functions by distinct mechanisms that block p53 activity independently at various steps, suggesting that it is important for viruses to disrupt p53 activity in order to perform their efficient replication and dissemination.

However, it should be noted that some viruses require p53 for their replication. The cells infected with human cytomegalovirus (HCMV) in the absence of p53 produce fewer infectious viral particles, with delay in viral protein production and trafficking [41]. The HCMV genome has 21 potential p53 responsive sites [42]. The available data suggest that HCMV gene expression is influenced by p53 molecules bound to the HCMV genome at immediate-early and early stages of infection, which could explain the mechanism of reduced and delayed production of virions in p53-negative cells. Indeed, p53 has been demonstrated to be involved in regulation of viral UL94 protein expression [43]. Furthermore, in early stages of the EBV lytic infection, the inactive form of p53 cooperates with viral factors including BZLF1 protein to stimulate virus replication [44,45], although active p53 is ubiquitinated by BZLF1-ECS ubiquitin ligase complexes and degraded in a proteasome-dependent manner to inhibit apoptosis in the middle and late stages [30]. Therefore, virus has to well-organize p53 functions in both time-dependent and status-dependent manners for its efficient replication.

Some DNA viruses including HSV-1/2 and adenovirus induce the antiviral innate immune response that leads to type I IFN production [46]. Taniguchi and colleagues showed that IRF5 is critical for antiviral immunity by showing that *Irf5*$^{-/-}$ mice are highly vulnerable to HSV-1 infection, accompanied by a decrease in type I IFN induction in the sera [47]. The connections between the p53 family and IFN-mediated innate antiviral immunity have been established [1]. IFN signaling drives increased p53 mRNA and protein levels in order to evoke more robust p53 responses that trigger apoptosis of infected cells and restrict virus replication. This is also supported at the level of gene expression, as several gene targets of the IFN system are also subject to regulation by the p53 family [48,49]. Indeed, IRF5 is identified as a direct p53-target gene [50]. These findings indicate the crosstalk between p53 and the IFN pathway in the innate immunity.

RNA VIRUSES

Most RNA viruses undergo their entire replicative cycle in the cytoplasm except for two principal types, retroviruses and influenza viruses, both of which have an important replicative step in the nucleus. Infection with most RNA viruses induces antiviral responses mediated by IFN signaling.

VSV infection induces marked phosphorylation of mouse p53 at Ser 18 through ATM [1], and then,

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some p53-inducible genes are upregulated in wild-type but not IFN-α/β receptor 1-deficient mouse embryonic fibroblasts (MEFs), although phosphorylation of p53 is found in the latter. Thus, IFN does not activate p53 but contributes to enhancement of p53 responses by inducing the p53 gene [1]. Furthermore, the virus yield was found to be more than 30-fold higher in $p53^{-/-}$ than in wild-type MEFs, suggesting that p53 contributes to limiting virus replication. Thus, the p53 response to virus infection constitutes a critical aspect of antiviral protection and its replication. In the case of measles virus infection, the V protein binds to IFN signaling proteins, STAT1 and STAT2, allowing efficient evasion of the host IFN-induced antiviral immune response [51,52].

Furthermore, the HCV core, NS3, and NS5A proteins have been shown to associate with p53, modulating its functions without targeting p53 for degradation [53]. Knockdown of p53 actually enhances the HCV replication [54]. In addition, chronic HCV infection results in persistent liver inflammation and induces endoplasmic reticulum and oxidative stress, thought to contribute to hepatocarcinogenesis [55] due to increased risk of DNA damage and missegregation of chromosomes in proliferating cells. HCV causes expression of DHCR24 (also known as seladin-1), which catalyzes the reduction of sterol intermediates during cholesterol biosynthesis [56] in human hepatocytes, resulting in resistance to oxidative stress-induced apoptosis and suppressed p53 activity [57]. DHCR24 inhibits acetylation of p53 at Lys 373 and 382 in the nucleus without the modulation of phosporylated status of p53 [57]. Thus, expression of DHCR24 suppresses the p53 response to oxidative stress, consistent with the previous report that inactivation and mutation of p53 play a role in the development of hepatocellular carcinoma (HCC) [58]. Genetic inactivation of p53 is associated with late stage HCC [58] and HCV RNA levels are notably lower in cancerous tissues from HCV-positive HCC patients than in noncancerous tissues [59]. Thus, impairment of p53 function by HCV-induced overexpression of DHCR24 might play a crucial role in early stage disease progression, implying the relationship between p53 inhibition by virus and pathogenesis.

Retroviruses have a unique strategy for their propagation by which the viral genome is replicated to produce DNA from RNA genome templates by viral reverse transcriptase. The intermediate DNA is then transported to nuclei and incorporated into the host chromosomal genome by a virus-encoding integrase. This integration process elicits DDR [60,61]. Thus, retroviruses more directly affect events occurring in the nuclei of infected cells than other RNA viruses. The HTLV-1 Tax is crucial for viral replication and for initiating malignant transformation leading to development of adult T-cell leukemia [62]. Tax downregulates the p53 signaling through directly repress of p53 transcription [63,64]. However, the half-life of p53 protein is increased in the majority of Tax-transformed cells, suggesting functional inactivation [65]. Tax can activate expression of individual kinases as a transcriptional activator and then regulate both the phosphorylation status and transactivational functions of p53. This might be one of the mechanisms by which Tax can immortalize virus-carrying T-cells of HTLV-1-infected individuals. Thus, Tax inhibits p53 pathway by the control of p53 protein functions and by the decrease in p53 mRNA levels. Moreover, HIV-1 regulatory proteins Tat [66], Nef [67], Vpr [68], and Vif [69] modulate p53 for HIV-1 infection and replication. Although several distinct roles have been proposed for p53, the total effects of p53 on HIV-1 propagation remain controversial.

Infection with influenza virus induces apoptotic cell death in numerous cell types with an increase in p53 protein levels [70]. The nonstructural NS1 protein, which has multiple accessory functions including suppression of host immune and apoptotic responses [71], binds to p53 and suppresses p53-dependent transcription, leading to inhibition of p53-mediated apoptotic cell death [72] and presumably also to enhancement of viral replication. Indeed, the p53 pathway is overall downregulated by different subtypes of influenza A viruses [73]. In the case with H5N1 infection, a decrease in p53 mRNA expression is detected [73]. Intriguingly, in the human lung cell line, inhibiting p53 activity leads to elevated virus replication, potentially through the decrease in IFN signaling [74], suggesting that p53 is involved in the IFN-mediated antiviral response to influenza infection. Consistent with these findings, $p53^{-/-}$ mice show a more severe influenza A virus-induced disease compare with their wild-type counterparts [75]. Therefore, in addition to its established functions in tumor formation, p53 also serves as an antiviral factor that might be modulated to improve therapy and vaccines.

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CONCLUSIONS

Viral infection is tightly linked with host cell condition. Perhaps not surprisingly, given the central role of p53 attributed to various pathways in cells, changes in the activity of this protein by pathogens often alter the properties of cells such as cellular environment and cell fate in virus-infected cells.

A major conclusion of the work on cell proliferation and apoptosis is that loss of p53 functions may contribute to the initiation of virus-mediated cancer from these cells. The causative viruses of human cancer possess several distinct mechanisms to inactivate p53 functions and signaling by the alterations of post-transcriptional modification, localization, binding partner, turn over, and transcriptional activity. The activity of p53 is strictly controlled through a multistep process. Viruses have collectively acquired an impressive repertoire of molecules that target almost every aspect of the p53-mediated signaling pathway. An interesting aspect of these observations is that there are different ways of p53 inhibition within species, suggesting that virus obtained and adapted the mechanisms independently during its course of evolution. The connection between p53 and viral proteins is well established, but there are only a few demonstrations of the importance of these interactions in the control of biological processes related to p53 function. Purvis *et al*. recently demonstrate that p53 dynamics affects cell fate decision [17]. It would be interesting to investigate whether the interaction between p53 and viral factors influences the quality of signal in the cells. To clarify this, further studies are required.

Some studies have already provided evidence for the p53-mediated antiviral response. Infection of host cells with virus induces production of IFN-α/β and cytokines that concomitantly contributes to boost p53-mediated responses via accumulation of p53 protein. To counteract this, virus has to perturb the p53 functions. The antiviral effects by p53 are likely dependent on its ability to promote more rapid pro-inflammatory and antiviral gene expressions, strongly supporting the concept that enhancement of p53 functions as a host resistance factor against virus infection may be used as a host-targeted therapeutic strategy to develop antiviral therapies and vaccine adjuvants.

However, p53 is also necessary to construct a cellular environment for virus production before the onset of viral replication [41,42,45,69,76]. Taken together, the data indicate that, as a strategy for efficient virus survival and growth, it is important to maintain a delicate balance between activation and inhibition of p53 pathways.

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CONFLICTS OF INTEREST

The authors have no competing interest.

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