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Review

Modulation of the ARF-p53 Pathway by the Small DNA Tumor Viruses

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KEY WORDS

ARF, p53, RB, PP2A, apoptosis, cell cycle arrest, DNA tumor viruses, polyoma small T-antigen, polyoma middle T-antigen, cancer

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ABSTRACT

The small DNA tumor viruses encode proteins that subvert many of the pivotal growth regulatory pathways within the cell to facilitate their own replication. The cell responds to viral infection/proteins by activating the p53 tumor suppressor pathway. Activation of p53 could impair a productive viral infection at many levels, including the inhibition of viral DNA replication and/or the premature death of infected cells. Therefore, DNA viruses encode proteins that inactivate the p53 tumor suppressor pathway. Understanding how DNA viral proteins activate/inactivate the p53 pathway has provided invaluable insights into tumorigenesis. Recent studies with polyoma virus have identified a viral protein (PyST) that inhibits ARF-mediated activation of p53, and revealed a novel role for PP2A in the regulation of the ARF-p53 tumor suppressor pathway.

THE ARF-p53 TUMOR SUPPRESSOR PATHWAY

The p53 tumor suppressor pathway is a critical cellular defense against neoplastic transformation. DNA damage or inappropriate growth signals can activate p53, which induces the transcription of downstream effectors that prevent the replication, or invoke the apoptosis, of aberrant cells (Fig. 1).[1,2] The replication of DNA viruses and tumor cells, which is driven by activated oncogenes, can trigger a p53 response that could terminate their genesis. Therefore, inactivation of the p53 pathway is believed to be a requisite event for the replication of both small DNA tumor viruses as well as tumor cells. The p53 pathway is inactivated by mutations in over 80% of human tumors, while the small DNA tumor viruses encode specific viral proteins to achieve the same end. Indeed, p53 was first identified as a cellular protein that interacted with SV40 Large T-antigen (SV40 LT),[3,4] and subsequently found to be also deregulated in tumor cells.

The p53 tumor suppressor pathway is disabled in many human tumors through either mutations in p53, or the loss of ARF, a critical upstream regulator.[5,6] ARF, which is specified by the Alternative Reading Frame of the p16 ^{INK4A} gene in the *INK4a* locus,[7] is not induced in normal cellular proliferation.[8] However, unscheduled proliferation or activated oncogenes induce the expression of ARF, which prevents MDM2-mediated degradation of p53.[8] The precise molecular mechanisms underlying ARF induction and function remain to be fully elucidated. How viral proteins activate/inactivate the p53 tumor suppressor pathway can reveal important insights into p53 regulation that could be modulated for tumor therapy. Recently, the Polyoma virus encoded Middle T-antigen (PyMT) and Small T-antigen (PyST) proteins have been demonstrated to have opposing effects on the ARF-p53 pathway. PyMT activates ARF and consequently p53,[9] whereas PyST inhibits ARF-mediated upregulation of p53.[10] This article will discuss recent studies with DNA viruses that are increasing our understanding of the ARF-p53 tumor suppressor pathway.

ACTIVATION OF p53 BY THE SMALL DNA VIRUSES

The small DNA tumor virus group includes Polyoma Virus (Py), Simian Virus 40 (SV40), Human Papilloma Virus (HPV) and Adenovirus (Ad), all of which are totally dependent on their ability to commandeer the host cell DNA synthesis machinery for their own replication. Various aspects of viral infection can induce the cell to activate the p53 pathway.[1,11] For example, p53 can be activated by a DNA damage response triggered by extensive viral DNA replication (Fig. 1). Viral genomes are recognized by the DNA damage/repair machinery in the cell due to, either their unusual DNA structures/intermediates,[12]

or in the case of adenovirus, the replication of naked double-stranded DNA termini.[13] Potential breaks in cellular DNA may also occur as a result of the cellular DNA repair machinery being overwhelmed by an overabundance of replicating viral DNA, leading to a DNA damage response (Fig. 1).[13,14] DNA damage activates ATM, which can result in the downstream phosphorylation and induction of p53.[15]

p53 can also be induced by the aberrant proliferative signals that drive viral DNA replication. The RB family of tumor suppressor proteins (RB, p107, p130) bind the critical S phase transcription factor E2F, thereby repressing E2F activity.[16-17] In normal cellular proliferation, RB is inactivated by a series of phosphorylation events, mediated in a staged and tightly regulated manner, by cyclin dependent kinase (cdk) complexes.[18] The small DNA viruses infect quiescent cells, but unlike DNA viruses with larger genomes, have a limited genetic capacity, and do not specify all the necessary DNA replication enzymes necessary for their propagation. The small DNA viruses have evolved a common strategy to invoke unscheduled S phase entry thereby replicating the viral genome together with the host cellular DNA. Each of these viruses specifies a protein (Py Large T-antigen (PyLT), SV40 large T-antigen, HPV E7, Ad E1A) that binds and inactivates the retinoblastoma family of tumor suppressor proteins, irrespective of cdk activation.[19] This results in the inactivation of RB proteins and the release of a number of factors, including E2F, which activates the transcription of genes necessary for S phase entry (Fig. 1).[20] Such unscheduled S phase entry can induce the activation of p53.

ARF is a critical tumor suppressor protein that activates the p53 checkpoint in response to oncogenic stress.[21] Both E1A and PyMT activate ARF and consequently p53 (Fig. 1). The induction of ARF by E1A is mediated, at least in part, through E1A binding and inactivation of the RB family of tumor suppressor proteins (Fig. 1).[22] Whether other viral oncogenes also induce ARF as a consequence of RB inactivation, for example HPV E7, PyLT, or SV40 LT, has yet to be reported. Nevertheless, although ARF is an E2F target, it is not induced in normal cellular proliferation (in which RB is inactivated by phosphorylation), but is specifically induced by aberrant proliferative signals or activated oncogenes.[8,23] This suggests that there may be either a qualitative/quantitative difference in how oncogenes functionally inactivate the RB checkpoint, or alternatively, that they also perturb an additional cellular factor that acts together with E2F to induce ARF. For example, oncogenes such as E1A, PyLT and SV40 LT also perturb chromatin remodeling factors such as p300 and p400.[24-26]

The viral oncogene, PyMT, has also been shown to induce ARF.[9] Although PyMT has no intrinsic enzyme activity, it binds and modulates a number of cellular proteins involved in critical growth factor mediated signaling pathways. PyMT activates PI3 Kinase, PLC-γ and the RAS-Raf-MAP kinase pathway to induce cellular transformation.[27-28] Through its inappropriate activation of one or more of these growth stimulatory pathways, PyMT induces ARF, and consequently invokes the p53 checkpoint.[9] Understanding the mechanism whereby ARF is induced by viral oncogenes could reveal novel therapeutic modalities that selectively target abnormal proliferation in tumor cells but leave proliferating normal cells unharmed. Viral oncogenes such as E1A and PyMT provide us with invaluable tools with which to realize this goal.

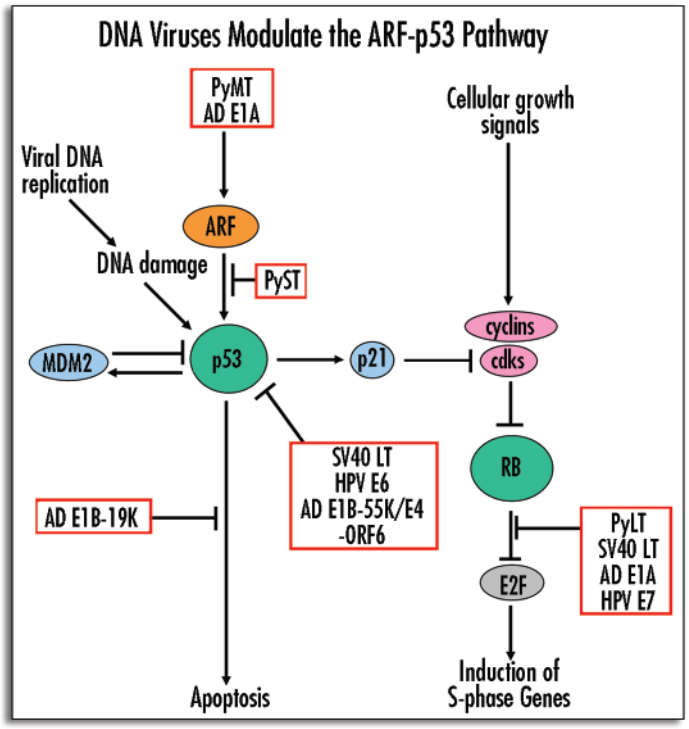

Figure 1. DNA viruses modulate the ARF-p53 pathway. The positive and negative effects of the different small DNA tumor viral proteins (boxed) on the ARF-p53 pathway are shown. The small DNA viruses can induce both genotoxic and oncogenic stress that can activate p53 resulting in the transcription of downstream effectors, such as p21 and MDM2. Activation of p53 can result in either cell death by apoptosis or cell cycle arrest. The small DNA tumor viruses can activate p53 in at least two ways. One is by eliciting a DNA damage response via viral DNA replication. Another is exemplified by the viral oncogenes, PyMT and AD E1A, that induce ARF, and consequently p53, as a result of inappropriate activation of cellular signaling pathways. The induction of cell cycle arrest/apoptosis by p53 could inhibit new virus production. Therefore, the viruses have evolved a number of different strategies to inactivate or override the p53 pathway. PyLT, SV40 LT, AD E1A and HPV E7 bind and inactivate RB and thus bypass the ability of p53 induced p21 to mediate cell cycle arrest. The Ad E1B-19K protein can prevent p53-mediated apoptosis. SV40 LT, HPV E6 and Ad E1B-55K/AD E4-ORF6 also target p53 directly, by binding and inhibiting its activity, or provoking its degradation. PyST inhibits ARF-mediated activation of p53 through its PP2A domain. Although PyST has been shown to inhibit PyMT induced ARF signaling to p53, it remains to be determined whether PyST will also inhibit ARF induced by E1A or cellular oncogenes-mediated activation of p53.

DNA VIRUSES HAVE EVOLVED VIRAL PROTEINS THAT INACTIVATE THE ARF-p53 TUMOR SUPPRESSOR PATHWAY

DNA tumor viruses can trigger p53 activation at multiple levels, an event that could have a devastating impact on viral replication. For example, p53 activation could inhibit DNA replication, or induce the premature death of infected cells resulting in an abortive infection. Therefore, the DNA tumor viruses encode proteins that inactivate the p53 pathway, and which are believed to play a requisite role in their viral replication. The study and use of DNA viral proteins that inactivate p53 have provided fundamental insights into tumorigenesis. Although the Adenovirus E1B-19K protein can block apoptosis downstream of p53,[29] most of the small DNA tumor viruses encode proteins that target p53 directly (Fig. 1). SV40 LT binds and inactivates p53 directly,[30-32] and p53 was first identified

as a cellular protein that interacted with SV40 LT.[3-4] Adenovirus encodes two viral proteins, E1B-55K and E4-ORF6 that form a complex, and together with cellular proteins involved in ubiquitination (cullin 5, RBC, Elongin), bind and degrade p53.[33-35] The HPV E6 protein also degrades p53 by binding to both p53 and the cellular E3 ubiquitin ligase, E6AP. While E6AP does not normally function to degrade p53, HPV E6 recruits and redirects its ubiquitin ligase activity to degrade p53.[36-38] Thus, disparate DNA viruses have functionally converged to encode proteins that bind and inactivate p53, underscoring the importance of the p53 tumor suppressor pathway in monitoring normal cell growth and DNA replication.

Polyoma virus and SV40 are both closely related members of the Polyomavirus family. Nevertheless, in contrast to SV40, polyoma is unusual among the small DNA tumor viruses in that none of its three early region proteins (PyLT, PyMT, PyST) directly bind and inactivate p53.[39] Nevertheless, PyMT induces ARF and consequently activates a p53 checkpoint that prevents PyMT-mediated transformation of primary mouse cells, and also of rat REF52 cells.[40] However, when either p53 or ARF is inactivated, PyMT expression alone can induce transformation in these cell types. In the first reported demonstration of oncogene cooperation, PyMT was also observed to transform primary mouse or REF52 cells when PyLT and PyST were coexpressed.[40-42] This has subsequently been explained by the finding that although PyMT induces ARF in these cells, p53 is not upregulated when PyST and/or PyLT are also present.[9] A recent study demonstrates that PyST is the critical Py protein that prevents the upregulation of p53, despite PyMT mediated induction of ARF.[10] This study also resolves the disparity and singularity of polyoma viral proteins that apparently fail to directly bind to and inactivate p53 or disrupt the p53 downstream pathway, and shows that PyST prevents the activation of p53 by its key upstream regulator, ARF (Fig. 1). The PyST PP2A interacting domain plays a critical role in preventing ARF mediated activation of p53, implicating a previously unrecognized role for PP2A in the modulation of the ARF-p53 tumor suppressor pathway.[10]

ARF MEDIATED ACTIVATION OF p53

The mechanism(s) whereby ARF induces p53 remain to be definitively elucidated. The initial model, based on the ectopic over expression of ARF, postulated that ARF binds and sequesters MDM2 in the nucleolus, thereby preventing MDM2 mediated inactivation/degradation of p53.[43-46] However, although ARF binds to MDM2 in vitro,[46] there is mounting evidence that ARF may stabilize p53 independently of MDM2 nucleolar sequestration.[9,47,48] Consistent with the latter, the induction of endogenous ARF by PyMT, or indeed Raf, does not lead to the nucleolar sequestration of MDM2.[9] ARF is a highly basic protein, that can bind and immunoprecipitate MDM2, even when extracts from cells in which ARF and MDM2 were expressed in the absence of each other, are mixed together post-lysis (O'Shea and Fried, unpublished data). Although this in no way excludes a functional interaction between ARF and MDM2 in vivo, it makes co-immunoprecipitation studies difficult to interpret. Therefore, it is conceivable that ARF may affect the ability of MDM2 to degrade p53, through both direct and indirect means. For example a direct but transient interaction of ARF with MDM2, or indeed other cellular proteins such as p300, MDMX or PP2A, could perhaps affect the ability of MDM2 to bind and degrade p53.

The mechanism by which PyST prevents ARF mediated induction of p53 could therefore, reveal important insights into the ARF-p53 tumor suppressor pathway. The PP2A binding domain of PyST is critical for its ability to prevent ARF mediated induction of p53.[10] These data indicate a potentially novel role for PP2A in regulating the ARF-p53 tumor suppressor pathway. PP2A is a hetero-trimeric complex comprised of different A, B and C subunits, of which there are at least 80 possible combinations. PyST displaces the PP2A B regulatory subunit, which is thought to modulate the substrate specificity of PP2A. Thus, PyST may perturb a novel function of PP2A function in regulating the induction of p53 by ARF. Both p53 and MDM2 are phosphorylated at multiple sites, which may affect their interaction and/or activity.[49-51] Therefore, PyST may affect a function of PP2A in regulating the phosphorylation of either p53 or MDM2 directly. Indeed, Cyclin G has been shown to recruit PP2A complexes containing B' subunits to dephosphorylate MDM2, thereby stimulating MDM2 mediated degradation of p53.[52,53] Therefore, it will be intriguing to determine if PyST promotes cyclin G/PP2A mediated dephosphorylation of MDM2 to induce the increased degradation of p53, despite the presence of ARF. Alternatively, PyST may affect the phosphorylation/activity of as of yet unknown cellular proteins, or indeed ARF itself, that play a critical role in regulating p53. In addition, it remains to be determined if PyST also affects ARF functions that are independent of p53.[54] It is significant that divergent DNA viruses encode proteins, for example Ad E4-ORF4 and SV40 ST that also bind to the B regulatory subunit of PP2A.[55-57] In addition, PP2A subunit mutations have been found in a subset of tumors.[58,59] Understanding how different viral proteins modulate PP2A activity may yield important insights into the many roles PP2A plays in normal and tumor cell growth, including the ARF-p53 tumor suppressor pathway.

SUMMARY

Revealing the interaction of DNA viral proteins with cellular pathways has revealed fundamental insights into tumorigenesis. This is particularly exemplified in the case of the ARF-p53 tumor suppressor pathway. The replication of viral genomes can activate a DNA damage signaling pathway to p53. E1A and PyMT activate cellular growth signaling pathways in an inappropriate manner, which results in the induction of ARF and consequently p53. Therefore, DNA viruses have had to evolve strategies to inactivate p53. Adenovirus, HPV and SV40 encode viral proteins that bind and inactivate p53 directly. In contrast to the other small DNA viruses, PyST targets p53 indirectly, by inhibiting ARF mediated induction of p53 (Fig. 1). The PyST PP2A domain plays a critical role in preventing ARF signaling to p53, implicating a previously unrecognized role for PP2A in regulating the ARF-p53 tumor suppressor pathway.

The p53 checkpoint is at the nexus of a web of integrated cellular processes that regulate its function, many of which are targeted by DNA viral proteins. Tumor cells are also likely to target the p53 pathway at similar levels. Understanding the various mechanisms whereby viral proteins modulate the ARF-p53 tumor suppressor pathway could identify critical tumor targets and strategies for therapeutic intervention. The continued study of small DNA tumor viruses promises to reveal novel insights into the regulation of the ARF-p53 tumor suppressor pathway that may one day be exploited for novel therapeutic modalities.

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