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The p53 Transcriptional Network Influences Microglia Behavior and Neuroinflammation

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Abstract

The tumor-suppressor protein p53 belongs to a family of proteins that play pivotal roles in multiple cellular functions including cell proliferation, cell death, genome stability, and regulation of inflammation. Neuroinflammation is a common feature of central nervous system (CNS) pathology, and microglia are the specialized resident population of CNS myeloid cells that initiate innate immune responses. Microglia maintain CNS homeostasis through pathogen containment, phagocytosis of debris, and initiation of tissue-repair cascades. However, an unregulated pro-inflammatory response can lead to tissue injury and dysfunction in both acute and chronic inflammatory states. Therefore, regulation of the molecular signals that control the induction, magnitude, and resolution of inflammation are necessary for optimal CNS health. We and others have described a novel mechanism by which p53 transcriptional activity modulates microglia behaviors *in vitro* and *in vivo.* Activation of p53 induces expression of microRNAs (miRNAs) that support microglia pro-inflammatory functions and suppress anti-inflammatory and tissue repair behaviors. In this review, we introduce the previously described roles of the p53 signaling network and discuss novel functions of p53 in the microglia-mediated inflammatory response in CNS health and disease. Ultimately, improved understanding of the molecular regulators modulated by p53 transcriptional activity in microglia will enhance the development of rational therapeutic strategies to harness the homeostatic and tissue repair functions of microglia.

Keywords

CNS ischemia; inflammation; macrophage; microRNA; neurodegeneration

I. INTRODUCTION: THE P53-SIGNALING PATHWAY AS A NETWORK

TP53 (and its mouse homologue Trp53) encode a 393-amino acid, 53-kDa protein that acts as a tumor suppressor and is a crucial player in the maintenance of genomic stability. That protein, p53, belongs to a family of highly homologous proteins, including p63 and p73, with a large array of isoforms that comprise the p53 regulatory network. The p53 signaling network regulates a variety of cellular processes including cell proliferation, cell death, and DNA repair. Since the discovery of p53 as a human tumor suppressor, extensive effort has

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been put forward to elucidate the molecular functions of this protein and its signaling pathway. Interest in p53 peaked when it was identified as the most frequently mutated gene in human tumors, and more than 25,000 p53 mutations have been reported.[1,2] Due to its prominent role in cancer and maintenance of cellular homeostasis, the field of p53 research has grown tremendously. As a multifunctional transcriptional regulator and cell-cycle coordinator, p53 is sensitive to intrinsic and extrinsic stress signals that modulate cellular homeostasis. These signals include DNA damage, hypoxia, mitotic spindle damage, inhibition of ribosome biogenesis, nutritional starvation, depletion of ribonucleotide triphosphates, and the activation of selected oncogenes (e.g., c-Myc, Ras, E2F-1, and Atc-Myc).[3] In response to these intrinsic and extrinsic signals, p53 orchestrates cellular functions that promote or maintain homeostasis, such asproliferation, cell-cycle arrest, and apoptosis.

The action of p53 in the cytosol is firmly regulated by several molecular mechanisms. Post-translational modifications on p53 (phosphorylation, acetylation, methylation, ubiquitination, summolation, and neddylation) are induced in cell-type and stressor specific patterns, leading to activation of p53-mediated transcription. For example, the murine double minute 2 (Mdm2) is an E3 ubiquitin ligase that promotes p53 ubiquitination and degradation by the proteosome. The discovery of Mdm2 as both a target of p53 transcriptional activation and a factor that inhibits p53 transactivation led to the definition of a novel negative feedback loop in the signaling pathway and another level of regulation on p53 functions.[4,5] Many post-translational modifications of p53 prevent Mdm2-p53 interactions and substantially increase protein half-life. Stabilizing p53 in the cytoplasm protects p53 from proteosomal degradation, promoting its translocation to the nucleus and binding to specific p53 response elements.[5,6] Therefore, post-translational modifications can impact p53 function and activity, modulating cellular responses to a wide array of extrinsic signals that may impact homeostasis.

Transcriptionally active p53 binds to a specific DNA sequences termed the p53-responsive element (RE), where it regulates the expression of target genes. The crystal structure of the p53 core domain bound to DNA was elucidated in 2008.[7] This structure showed the p53 residues that make contact with p53-RE and revealed how different tumor-associated mutations on p53 obliterate this binding. A p53-RE is composed of a consensus sequence RRRCWWGYYY-(0–21 nucleotides)-RRRCWWGYYY, where R is a purine, W is adenine or thymidine, and Y is a pyrimidine.[8] Specific post-translational modifications (e.g., ubiquitination by MDM2) not only influence p53 half-life and stability but also influence the selectivity of DNA binding, enabling further specification of the p53 target gene network.[8] Several studies have established that the p53 signaling network plays key roles in DNA repair,[9–11] antioxidant defense [12] energy metabolism,[13,14] and anti-angiogenesis,[15] which all contribute to the role of p53 in tumor suppression. Therefore, p53 activity is influenced by the ability of the p53 core domain to interact with a p53-RE, where specific patterns of modifications on activated p53 can promote expression of target genes to modulate cellular responses to stress or promote cell cycle arrest or apoptosis.

The p53 tumor suppressor protein belongs to a family of proteins that work together to modulate gene expression in response to an array of stress signals. Protein homologs in the same family, p63 and p73, actively contribute to different branches of the same regulatory

network. Similar regulatory post-translational modifications that drive transcriptional activation signals on p53 are recapitulated on p63 and p73. These family members are similarly responsive to oncogenic and physiological stress (i.e., DNA damage). For example, using an Alzheimer's Disease mouse model to study tau (τ) phosphorylation, loss of one p73 allele *in vivo* has been linked to hyperphosphorylation of the τ protein at the τ-1 epitope as well as reduced motor and cognitive function.[16] Therefore, the p53 family of transcriptional activators constitutes a unique signaling network, mediating key cellular responses, including cell proliferation and stress responses.

II. MICRORNA EXPRESSION: A CRITICAL COMPONENT OF THE P53 SIGNALING NETWORK

As a transcriptional activator, p53 regulates expression of genes that orchestrate cell behavior, including microRNAs (miRNAs) specifically involved in modulating levels of effector proteins that in turn affect cellular functions (Figure 1).[4,17] MiRNAs are the smallest (~22 nucleotides) identified ribonucleic acid carriers of highly specific genetic regulatory information. Although first discovered in the early 1990s as regulators of *Caenorhabditis elegans* development,[18] miRNAs were not systematically studied until after the discovery of RNA interference (RNAi). Mature miRNAs contribute to the epigenetic regulation of gene expression involved in both normal physiology and pathologies.[19] MiRNAs post-transcriptionally regulate gene expression through complementary binding to the 3′ untranslated region (3′UTR) of messenger RNAs (mRNAs). MiRNAs can regulate expression of many genes by forming imperfect base pairing with sequences in the 3′ UTR of a target mRNA. Binding of mature miRNA associated with the RNA-induced silencing complex (RISC) at the 3′UTR of mRNA interrupts mRNA translation or causes degradation of the targeted mRNA.[20] Each individual miRNA has the potential to target multiple mRNAs. Therefore, a single miRNA will modulate the expression of a large number of proteins and thus may exert profound influence on a gene expression network involved in determining a specific pattern of cellular behavior.

In 2007, several groups reported that p53 transcriptional activity directly influences expression of miR34 family members of miRNAs (Figure 1).[21,22] The miR34 family consists of miR34a, miR34b, and miR34c, which are encoded by two different genes. miR34a is encoded by an individual transcript and is expressed in a majority of tissues, while miR34b and miR34c share a common primary transcript and are mainly expressed in the lung.[4,21] Ectopic expression of miR34a promotes apoptosis, cell cycle arrest, and senescence in transformed cell lines, whereas inactivation of endogenous miR34a strongly inhibits p53-dependent apoptosis in these cells. Yamakuchi et al.[21] showed that miR-34a mediated suppression of NAD-dependent protein deacetylase sirtuin-1 (SIRT1) promotes apoptosis in wild-type human colon cancer cells but not in human colon cancer cells lacking p53. Furthermore, the same group also showed that miR-34a itself is a transcriptional target of p53, suggesting a positive feedback loop between p53 and miR-34a. Therefore, p53 may function as a tumor suppressor and modulate key cellular functions via miR-34a and other miRNAs.

In addition to the miR-34 family, p53 also directly regulates the transcriptional expression of miR-145 through direct binding to the p53 promoter response elements (p53-REs) (Figure 1).[17,23,24] miR-145 was first recognized as a tumor suppressor miRNA that is transcriptionally regulated by p53.[25] miR-145 originates from a bicistronic cluster in the 5q33.1 region along with miR-143. These two miRNAs have been extensively studied for their role in neoplastic transformation.[26] MiRNAs miR-143 and miR-145 are also involved in the phenotypic switch of vascular smooth muscle cells to mesenchymal cells and have been associated with atherosclerosis. Another critical miR-145 target is c-Myc, which may contribute to the observation that miR-145 influences tumor cell growth both *in vitro* and *in vivo.*[23] In the CNS, miR-145 is significantly increased after transient cerebral ischemia, a state known to induce p53 activation.[27] However, transient ischemia is also associated with a large inflammatory response involving both an inflammatory infiltrate and activation of the resident myeloid population, the microglia cells. Profiling studies of miRNAs induced by inflammatory activation of microglia demonstrated increased expression of miR-145 after treatment with IL-4 [28] while inflammatory activation in astrocytes leads to suppression of miR-145 expression.[29] Taken together, these findings suggest that induction of miR-145 by CNS ischemia may come predominantly from microglia or infiltrating immune cells. Additionally, they support a potential role for p53 as a mediator of miRNA expression in the setting of inflammatory responses.

III. THE P53 SIGNALING NETWORK INFLUENCES INFLAMMATORY RESPONSES

The downstream impact of p53 transcriptional activity has been thoroughly studied in the context of cell cycle arrest and apoptosis. More recently, however, p53 has been implicated in novel biological processes ranging from metabolism and autophagy to influencing the immune response. In addition to its role in tumor suppression, p53 has recently emerged as a key modulator of the immune response in several cell types, including lymphocytes, macrophages, and microglia.[30–34] Downregulation of p53 in response to antigen stimulation has been reported to be critical for antigen-specific T-cell proliferation.[33] Furthermore, inhibiting Mdm2 to promote sustained p53 activity prevented antigen-specific T-cell proliferation.[33] In addition to what might have been an expected role for p53 in regulating lymphocyte proliferation, we and others have demonstrated that transcriptional activity mediated by p53 and p53 family members can modulate a variety of innate immune responses unrelated to p53 involvement in regulation of the cell cycle.[35–37] More specifically, p53 modulates responses to DNA damage by activating cells of the innate immune system to remove damaged or dead cells.[30,38] In addition, p53 duplication in mice confers enhanced viral immunity, suggesting a role for p53 in the host response to viral infection.[39] In macrophages, p53 was recently reported to suppress M2 macrophage polarization through regulation of c-Myc expression.[34] Another mechanism by which p53 transcriptional activity influences innate immune responses is through modulating the expression of the Toll-like receptor (TLR) family of pattern recognition receptors. De Almodovar et al. demonstrated that nearly all members of the human TLR family (TLR1–10) have canonical or non-canonical p53 REs within 5 kb of the beginning of the transcription site.[40] The non-canonical (or half-site) p53 RE is predicted to provide weak-to-

modest p53 responsiveness.[40] By regulating expression of critical innate immune receptors, such as TLRs, p53 may play a significant role in innate immune responses. Furthermore, the p73 member of the p53 family has been reported to promote activation of a subset of p53 target genes and apoptosis in response to ionizing radiation.[36] Many p73-/p53-dependent genes induced by thymic radiation are involved in inflammation and are transcriptionally co-regulated by the pro-inflammatory transcription factor NF-κB. For example, caspase 4/11 requires both p53 and NF-κB for full induction after DNA damage. Furthermore, p73 shows increased interaction with the p65 RelA subunit of NF-κB.[36] Taken together, these reports demonstrate that the p53 signaling network influences a variety of molecular mediators that participate in innate immune response mechanisms. Therefore, p53 influences immune activation through modulating expression of effector genes involved in the immune response.

IV. P53 MODULATES MICROGLIA-MEDIATED INFLAMMATORY RESPONSES

Microglia are the tissue-resident population of innate immune effector cells in the central nervous system (CNS). In microglia, p53 expression and activity can be rapidly increased in response to a wide range of stresses, including DNA damage, hypoxia, oncogene activation, microtubule disruption, and oxidative damage.[41] DNA damage from reactive oxygen species (ROS) leads to activation of p53, which is important for modulating microglia responses to inflammatory stimuli *in vitro* and in an *in vivo* ischemic stroke model.[35,37,42] We have identified microglia as an unusual cell type, with endogenous p53 transcriptional activity in the basal state.[32] We began evaluating a potential role for p53 in regulating microglial behavior when we unexpectedly observed that p53-deficient microglia were neuroprotective in an *in vitro* model of HIV-induced neurodegeneration.[37] Further investigation revealed that patients with HIV-associated neurocognitive disorders (HAND) demonstrated extensive p53 activation in microglia as well as increased immunoreactivity for several known p53 target genes.[43] We determined that p53-deficient microglia demonstrate increased expression of mRNA for proteins involved in anti-inflammatory and tissue repair functions as well as a remarkably blunted activation of pro-inflammatory functions in response to pro-inflammatory cytokines.[32] In addition, p53-deficient mice developed an increased number of microglia expressing alternative activation markers and morphology during the post-stroke recovery period following the middle cerebral artery occlusion (MCAO) model of ischemia followed by reperfusion.[32] This series of studies suggests the hypothesis that p53 is required for activation of microglia pro-inflammatory behaviors and the absence of p53 leads to increased microglia tissue repair functions.[32,44] To begin to understand the mechanism by which p53 regulates microglial behavior, we performed global gene expression analysis. Bioinformatic evaluation of that data for additional transcriptional signaling pathways regulated by p53 suggests that p53 negatively regulates c-Maf, a transcription factor previously described as an activator of anti-inflammatory functions in macrophages and lymphocytes.[44]

Because p53 is generally known as an obligate transcription factor when activated, we hypothesized that p53 suppresses c-Maf through a miRNA intermediate. As described above, p53 promotes expression of a number of miRNAs that negatively regulate a variety of genes involved in promoting proliferation and cell survival, thus enhancing its ability to

promote cell-cycle arrest and apoptosis (Table 1). For example, one well-described p53 transcriptional target is the miR-34 family.[45] miR-34 has been shown to be directly regulated by p53 and to contribute to p53-mediated biological effects including apoptosis, G1 arrest, and senescence.[45] Several additional miRNAs regulated by p53 have been reported to modulate the function of cells involved in innate and adaptive immunity.[30] For example, miR-155 was shown to play an important role in the differentiation of B, T, and dendritic cells[46] and recently was proposed to have a feedback effect on p53 activity mediated by Socs1.[47] Two other p53-dependent miRNAs, miR-143 and miR-145, have been proposed to play a role in growth-suppression in response to DNA damage, promoting innate immune functions.[17]

In addition to its role as a direct transcriptional activator, p53 may influence immune cell function by impacting miRNA expression at the post-transcriptional level. For example, p53 interacts with Drosha, a protein in the miRNA-processing complex that mediates the processing of pri-miRNA transcripts into pre-miRNAs.[48] Drosha requires RNA-associated proteins such as DEAD box RNA helicases p68 and p72 (also known as DDX17) to carry out its function. p53 was shown to promote the Drosha-mediated processing of certain miRNAs with growth-suppressive functions in cells in response to DNA damage.[48]

Microglia are also influenced by the p53 signaling network via miRNA intermediates. Recently, our laboratory has identified a novel mechanism in which p53-dependent miRNAs play a critical role in regulating microglial proinflammatory responses.[44] As described above, we observed that adult microglia from p53-deficient mice have increased expression of the anti-inflammatory transcription factor c-Maf, and we hypothesized a miRNA intermediate. We examined the impact of p53 on the known miRNA regulator of c-Maf, miR-155. MiR-155 was reported to target c-Maf for degredation in lymphocytes.[46] We determined that the IFN-γ mediated induction of miR-155 was significantly higher in wild-type murine microglia compared with p53-deficient microglia. This finding suggests that induction of miR-155 in microglia is dependent on p53. The mechanism by which p53 regulates miR-155 expression in microglia has not been determined. It has been reported that p53 can directly regulate the transcription of certain miRNAs, but there is no clear consensus RE sequence for p53 binding in proximity to the bic/miR155 gene. The helix-loop-helix transcription factor Twist2, is an additional known regulator of c-Maf expression.[49] We determined that p53-deficient microglia express increased Twist2, so again, we hypothesized a miRNA intermediate. We identified recognition sites in the 3′UTR of Twist2 mRNA that interact with two p53-dependent miRNAs: miR-34a and miR-145. We demonstrated that both miR-34a and -145 are expressed in microglia, are regulated by p53, and negatively regulate Twist2 expression.[44] Thus, p53 activation in microglia may suppress the anti-inflammatory response by promoting expression of miRs-34a, -145, and -155. Taken together, our findings support our hypothesis that p53 activation (potentially induced by local ROS or accumulated DNA damage) influences microglia behavior and that one specific molecular target of p53-dependent miRNAs in microglia is c-Maf.

V. P53 AND ITS SIGNALING NETWORK INFLUENCE NEURODEGENERATION

Many studies have suggested that inflammation influences injury and neurodegeneration in the CNS. A growing number of studies support the idea that neuroinflammation negatively impacts disease progression and outcome. As a recently described regulator of inflammatory responses, p53 has been an interesting target of investigation in microglia. Continued efforts toward identifying the key immune modulators regulated by p53 transcriptional activity are likely to uncover important therapeutic targets.

An emerging theme in the field of neuroinflammation is that glial cells may act as essential cellular arbitrators in neurological diseases through non-cell autonomous mechanisms.[50] Two current theories have been proposed regarding the processes of non-cell autonomous neurodegeneration. First, intrinsic glial mutant protein expression leads to the distribution of normal glial function and/or changes in glial responses that subsequently trigger downstream damage to vulnerable neurons. Second, neuronal toxicity itself instigates toxic responses from neighboring glia.[51] For example, HAND develops in a subset of HIV infected individuals,[50] which correlates with accumulation of p53 protein, as observed in CNS tissue from HAND patients.[52] In HAND brain tissue, the alternative (anti-inflammatory) activation marker CD163 was expressed in a subset of microglia separate from those demonstrating p53 accumulation.[32] This finding, in conjunction with aforementioned studies defining p53-mediated mechanisms that suppress alternative activation of macrophages, supports the hypothesis that p53 influences microglial behavior in disease, skewing microglia into a proinflammatory state. Therefore, microglia may act to propagate CNS disease due to uncontrolled inflammatory responses instigated or supported by the activation of the p53 signaling network.

The p53 protein serves as a key orchestrator of microglial activation phenotypes in response to extrinsic signals (e.g., ROS) that may promote a pro-inflammatory activation characterized by secretion of inflammatory cytokines. In the absence of p53, microglia demonstrate a blunted response to IFN-γ. Microglia from p53 knockout mice fail to upregulate expression of genes associated with pro-inflammatory activation or secrete pro-inflammatory cytokines.[32] Interestingly, moderate dietary restriction, but not extreme dietary restriction, reduces p53-mediated neurovascular damage after hypoxia/ischemia and confers long-term protection in the neonatal brain.[53] Increased expression of genes associated with anti-inflammatory functions, phagocytosis, and tissue repair in p53-deficient microglia were observed compared with those cultured from strain-matched p53-expressing mice. Microglia from p53 knockout mice demonstrate increased phagocytic activity *in vitro* and expression of markers for alternative macrophage activation both *in vitro* and *in vivo*.[32] Therefore, p53 serves as a key orchestrator of microglia activation phenotypes, promoting a specific pattern of inflammatory behaviors *in vitro* and *in vivo*.

Several groups have identified novel roles for p53 function in the pathogenesis of CNS disease, including novel roles of p53 function in microglia. In one example, pharmacological inhibition of p53 attenuated microglial-evoked neurotoxicity following exposure to beta-amyloid (Aβ), the peptide that accumulates in Alzheimer's disease (AD) plaques.[35]

Additionally, p53 stabilization, which enables both immune detection and transcriptional activation, has been shown to increase in association with inflammatory activation of microglia. Activation of microglia with chlorogenic acid, lipopolysaccharide, or Aβ peptides results in microglial stress, culminating in apoptosis.[54–58] This activation-induced apoptosis has also been reported during LPS stimulation of microglia activation.[59] The process of microglial apoptosis may cause shedding of substances such as soluble Fas ligand, which can then induce and promote neuronal apoptosis.[60,61] Taken together, these findings suggest that preventing microglial stress and subsequent apoptosis is neuroprotective. Thus, controlling microglial stress pathways may be beneficial in neurodegenerative diseases, in which microglial activation and apoptosis occurs.

It has recently been reported that activation of p53-mediated transcription in microglia supports pro-inflammatory behaviors that potentiate neurodegeneration through synapse deterioration.[62] Jebelli et al. demonstrated that in microglia, p53 mediated pro-inflammatory responses influence neuronal synapse integrity *in vitro*. These studies revealed that microglial activation resulted in a significant reduction in expression of neuronal synaptic markers (synaptophysin and debrin) that are dependent on p53 transcriptional activation. The removal of pro-inflammatory cytokine–secreting microglia and pharmacological inhibition of p53 maintained synaptic marker integrity. These studies demonstrate that p53 function in microglia contributes to a non-cell autonomous mechanism that can exacerbate neurodegeneration induced by CNS inflammation.[62]

In addition, several reports have linked p53 family members to Alzheimer's Disease (AD) pathophysiology. Loss of one allele (+/−) of the p53 family member, p73, yields mouse models of aging or AD more susceptible to neurodegeneration.[16] In aged mice, microglial density was higher in $p73^{+/-}$ brain than in the wild type. In addition, intralysosomal accumulation of the oxidative stress biomarker lipofuscin was also higher in the aged $p73^{+/-}$ brain.[16] These findings also suggest a role for p73 in age-related CNS pathology.

Previous work has also demonstrated a role for p53 in mediating the inflammatory response to mouse models of CNS ischemia. Ipsilateral to the middle cerebral artery occlusion (MCAO) model of stroke, p53 immunoreactivity was observed specifically in cortical neurons in regions positive for TUNEL staining, signifying DNA damage.[63] We have identified a novel pathway, which involves the p53-mediated pro-inflammatory network in microglia, utilizing an ischemia/reperfusion paradigm involving MCAO followed by removal of the occluding filament and reperfusion of previously ischemic tissue (MCAO/R).[32,44] We observed that in $p53^{-/-}$ animals, microglia are more likely to adopt a ramified morphology and express markers of alternative activation in the ischemic penumbra.[32] We further observed that microglia isolated following brief MCAO/R demonstrate activation of p53-dependent miRNAs (miR-155 and miR-34a) during the stroke recovery period.[44,64] These findings suggest that p53 influences the microglia response to ischemia, promoting pro-inflammatory behaviors and suppressing expression of molecules associated with alternative activation behavior patterns (Figure 2). We hypothesize that when p53 is activated in microglia by ROS (in response to ischemia/reperfusion), spontaneous DNA damage, or cellular stress associated with CNS disease and injury, the effectors of such activation work together to suppress anti-inflammatory and tissue-repair behaviors, at least

in part through the miRNA-mediated suppression of c-Maf. This molecular response supports microglia pro-inflammatory behaviors that can be injurious to surrounding neural cells. Therefore, the p53 network skews microglia to attain pro-inflammatory phenotypes and suppress anti-inflammatory and tissue repair behaviors.

While we and other groups have described the role of p53 in microglia-mediated inflammation, few animal models are available to selectively study the deletion of p53 in microglia *in vivo*. Recently, a research group generated mice expressing tamoxifen-inducible Cre recombinase-EYFP fusion protein driven by the *CX_3CR1* promoter, allowing for microglia specific alteration of gene expression *in vivo*.[65] These mice can be utilized for many studies requiring conditional gene manipulation in CNS microglia, as well as other *CX_3CR1*-expressing myeloid cell populations. Therefore, it is now possible to ask questions that allow the field of neuroinflammation as a whole to identify the impact of p53-mediated gene regulation on the microglial inflammatory response in mouse models. Future studies on the specific loss of microglia p53 in acute CNS injury, chronic neurodegeneration, and CNS tumor models will likely answer key questions regarding the balance of protective and destructive functions of microglia in these disorders.

VI. CONCLUSIONS

The tumor suppressor protein p53 is a crucial player in the maintenance of genomic stability, cell proliferation, and death. Recently, p53 has also been identified as a regulator of the immune response. In this review, we have highlighted the canonical roles of p53 and recent findings of the prominent role of p53 in regulating microglia function including removing amyloidogenic proteins, fighting CNS pathogens, recruiting or suppressing adaptive immune responses in the CNS, and promoting tissue repair. In microglia, p53 modulates expression of effector genes required for regulation of the inflammatory response. We predict that p53 target genes (including miRNA targets) could be manipulated to influence microglial activity and to attenuate CNS tissue destructive inflammation in disease or injury. Understanding the ways in which the diverse molecular signaling pathways the influence microglia activation is pivotal for advancing neuroinflammation research and future development of targeted therapeutics. Furthermore, we suggest that study of p53 dependent microRNAs, including miR-155, will advance the identification of therapeutic targets and disease biomarkers for several CNS disorders.

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ABBREVIATIONS

TPp53	tumor protein p53
Mdm2	mouse double minute 2 homolog
miRNAs	micro RNA

RISC	RNA-induced silencing complex
ROS	reactive oxygen species
MCAO/R	middle cerebral artery occlusion and reperfusion
Twist 2	Twist family BHLH transcription factor 2
c-Maf	transcription factor MAF/proto-oncogene c-Maf
AD	Alzheimer's disease
HAND	HIV-associated neurocognitive disorders

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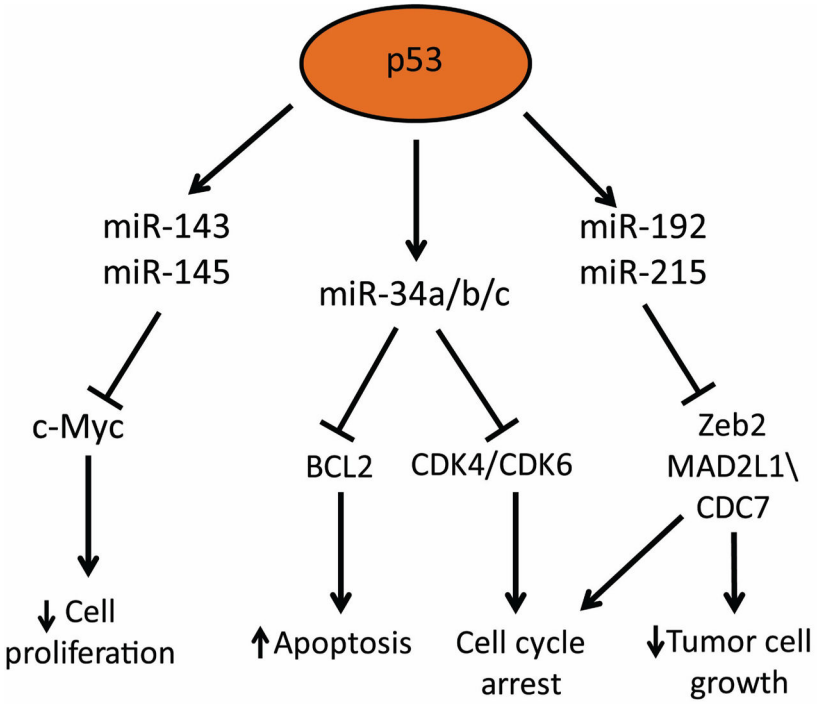

FIG. 1.

p53-dependent miRNAs modulate key cellular functions. P53 regulates expression of several miRNAs with known roles in critical cellular functions. MiR-145 and miR-143 negatively regulate expression of the c-Myc transcription factor that modulates cell-cycle progression. P53 additionally orchestrates expression of miR-34 cluster miRNAs that target genes involved in apoptosis, cell-cycle arrest, including Bcl2 and cyclins. Additionally, p53 promotes expression of miRNAs that suppress tumor cell transformation and growth. These miRNAs, miR-192 and miR-215, downregulate expression of CDC7, MD2L1, and CUL5, genes involved in tumorgenesis.

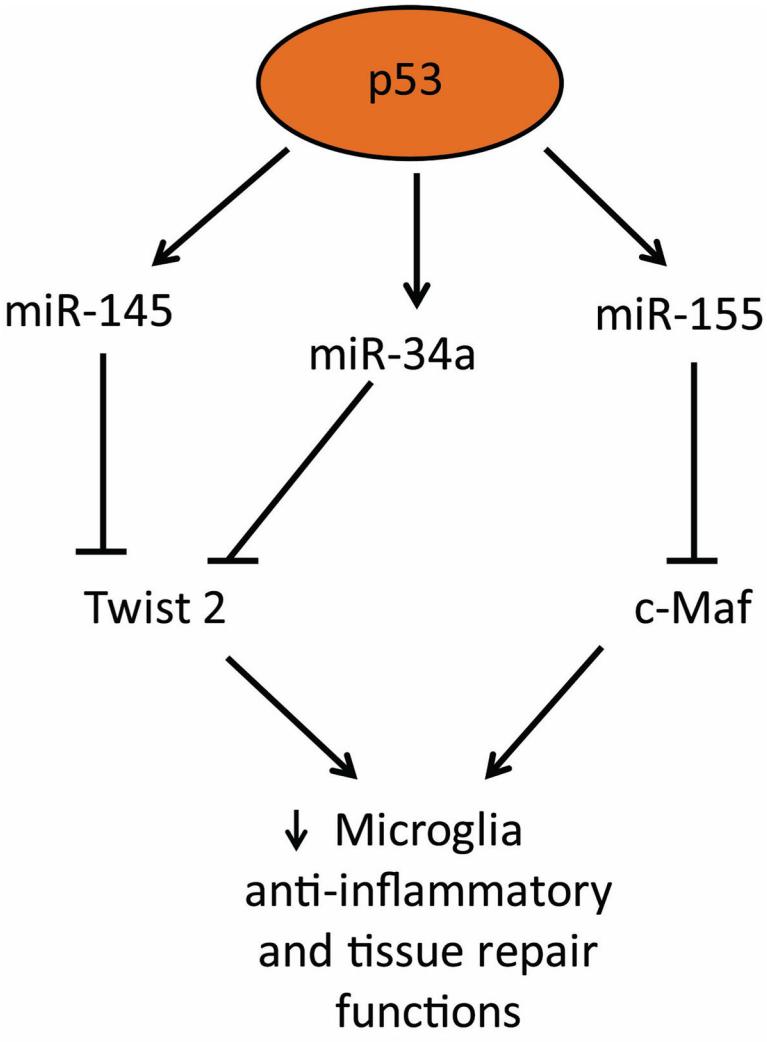

FIG. 2.

p53-dependent miRNAs modulate c-Maf in activated microglia. The p53-signaling network in microglia modulates c-Maf expression and promotes pro-inflammatory functions. p53 is activated in microglia by ROS, spontaneous DNA damage, or cellular stress associated with CNS disease and injury. p53-mediated transcriptional activity is required for the induction of p53-dependent miRNAs, miR-145, and miR-34a. These miRNAs target a transcriptional regulator, Twist2, for suppression, inhibiting the expression of the anti-inflammatory transcription factor c-Maf. In the absence of p53, microglia fail to induce expression of miR-155 in response to cytokine stimulation. MiR-155 also directly targets c-Maf mRNA for degradation.

TABLE 1

p53-dependent miRNAs with demonstrated function in CNS and systemic malignancies. MiRNAs with reported roles as modulators of cell cycle, cellular senesce, microglia, and macrophage activation in the CNS, hematopoiesis, the immune response, and regulation of miRNA processing are listed. This table consolidates key targets modulated by p53-dependent miRNAs, miR-155, miR-145, miR-143, miR-34a/b/c, miR-192, miR-215 and miR-107 that have been validated in the literature by reporter assays and qPCR

	Mature sequence (MiR Base Id)	Target genes	Functions in CNS & Periphery	References
miR-155	5′UUAAUGCUAAUUGUGAUAGGGGU3′ (MI0000177)	SPI(PU.1) IRF8 SOCS1 c-Maf	Hematopoiesis Microglia differentiation, Innate immune response	Hu et al., 2010[66] Pareek et al., 2014[67] Cardoso et al., 2012[68] Su et al., 2014[69]
miR-145	5′GUCCAGUUUUCCCAGGAAUCCCU3′ (MI0000169)	Twist-2 Sox2 c-Myc	Microglia anti-inflammatory functions, Embryonic stem cell renewal, Cell cycle progression, Apoptosis and cellular transformation	Su et al., 2014[69] Wang et al., 2013[70] Sachdeva et al., 2009[71]
miR-143	5′GGUGCAGUGCUGCAUCUCUGG3′ (MI0000257)	Prkce Vcan Kras Rreb1 MDM2	Cardiogenesis Cancer	Momand et al., 1992[72] Kent et al., 2014[73]
miR-34a/b/c	34-a 5′UGGCAGUGUCUUAGCUGGUUGU3′ (MI0000584) 34-b 5′AGGCAGUGUAAUUAGCUGAUUGU3′ (MI0000404) 34-c 5′GGCAGUGUAGUUAGCUGAUUGC3′ (MI0000403)	MYC SIRT1 BCL2 CREB1 CDk4 NOTCH1 MET	Apoptosis Cell cycle arrest Senescence	Chen et al., 2007[74] Ferlito et al., 2008[75] Hao et al., 2008[76] Manara et al., 2009[77] Wang et al., 2011[78] Yao et al., 2012[79] Cai et al, 2010[80]
miR-192	5′CUGACCUAUGAAUUGACAGCC3′ (MI0000551)	Zeb2	Cell cycle arrest/decrease tumor cell growth	Braun et al., 2008[81] Kim et al., 2011[82]
miR-215	5′AUGACCUAUGAUUUGACAGAC3′ (MI0000974)	Zeb2 MAD2L1 CDC7	Cell cycle arrest/decrease tumor cell growth	Braun et al., 2008[81] Georges et al., 2008[83] Kim et al., 2011[82]
miR-107	5′ GCUUCUCCUGGCUCUCCUCCCUC3′ (MI0000250)	HIF1 CDK6 DICER1	Decrease tumor cell growth/hypoxia signaling, Cell cycle arrest, miRNA processing	Yamakuchi et al., 2010[84] Bohlig et al., 2011[85] Martello et al., 2010[86]