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Review

p53 and mitochondrial function in neurons ☆

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ABSTRACT

The p53 tumor suppressor plays a central role in dictating cell survival and death as a cellular sensor for a myriad of stresses including DNA damage, oxidative and nutritional stress, ischemia and disruption of nucleolar function. Activation of p53-dependent apoptosis leads to mitochondrial apoptotic changes via the intrinsic and extrinsic pathways triggering cell death execution most notably by release of cytochrome c and activation of the caspase cascade. Although it was previously believed that p53 induces apoptotic mitochondrial changes exclusively through transcription-dependent mechanisms, recent studies suggest that p53 also regulates apoptosis via a transcription-independent action at the mitochondria. Recent evidence further suggests that p53 can regulate necrotic cell death and autophagic activity including mitophagy. An increasing number of cytosolic and mitochondrial proteins involved in mitochondrial metabolism and respiration are regulated by p53, which influences mitochondrial ROS production as well. Cellular redox homeostasis is also directly regulated by p53 through modified expression of pro- and anti-oxidant proteins. Proper regulation of mitochondrial size and shape through fission and fusion assures optimal mitochondrial bioenergetic function while enabling adequate mitochondrial transport to accommodate local energy demands unique to neuronal architecture. Abnormal regulation of mitochondrial dynamics has been increasingly implicated in neurodegeneration, where elevated levels of p53 may have a direct contribution as the expression of some fission/fusion proteins are directly regulated by p53. Thus, p53 may have a much wider influence on mitochondrial integrity and function than one would expect from its well-established ability to transcriptionally induce mitochondrial apoptosis. However, much of the evidence demonstrating that p53 can influence mitochondria through nuclear, cytosolic or intra-mitochondrial sites of action has yet to be confirmed in neurons. Nonetheless, as mitochondria are essential for supporting normal neuronal functions and in initiating/propagating cell death signaling, it appears certain that the mitochondria-related functions of p53 will have broader implications than previously thought in acute and progressive neurological conditions, providing new therapeutic targets for treatment. This article is part of a Special Issue entitled: Misfolded Proteins, Mitochondrial Dysfunction, and Neurodegenerative Diseases.

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1. Introduction

p53 is a transcription factor that activates or represses the expression of multiple genes [1], but it is also found in the cytosol and mitochondria eliciting an increasing repertoire of extra-nuclear, non-transcriptional functions. p53 expression is upregulated in response to a diverse array of cellular stresses, including DNA damage, hypoxia, oxidative and nutritional stress, ribonucleotide depletion, disruption of nucleolar function and oncogene activation [2,3]. p53 regulates DNA repair, metabolism, cell cycle progression, senescence and apoptosis, thus playing a key role in tumor suppression, aging and neurodegeneration [4–7]. These multifaceted p53 functions are realized via a surprisingly large number of p53-regulated proteins and pathways with a significant fraction of them converging on the mitochondria. This review is focused upon p53 functions that directly or indirectly regulate mitochondrial physiology and its immediate up- and down-stream events (Fig. 1) and provides current, still very limited assessment of those functions in neurons.

2. p53-mediated apoptosis (Fig. 2A)

Numerous studies have established that p53 promotes apoptosis by transcriptionally activating or repressing the expression of a panel of pro- and anti-apoptotic proteins. For apoptotic processes involving mitochondria, p53 transcriptionally activates Fas/Fas ligand and DR5/KILLER for the extrinsic apoptotic pathway. For the intrinsic pathway p53 induces expression of PUMA, Noxa, Bid, Bad, p53AIP1, Bax and APAF1 among others [1,8,9], maintains basal expression of apoptosis-inducing factor (AIF) [10], and represses expression of Bcl-2 [11], Bcl-xL [12] and Mcl-1 [13], consequently triggering release of apoptogenic proteins including cytochrome c and AIF from the mitochondrial intermembrane space. These pathways contribute to neuronal cell death and neurodegeneration but the critical players mediating the pathway may vary depending upon the nature of the apoptotic stimulus [14–18].

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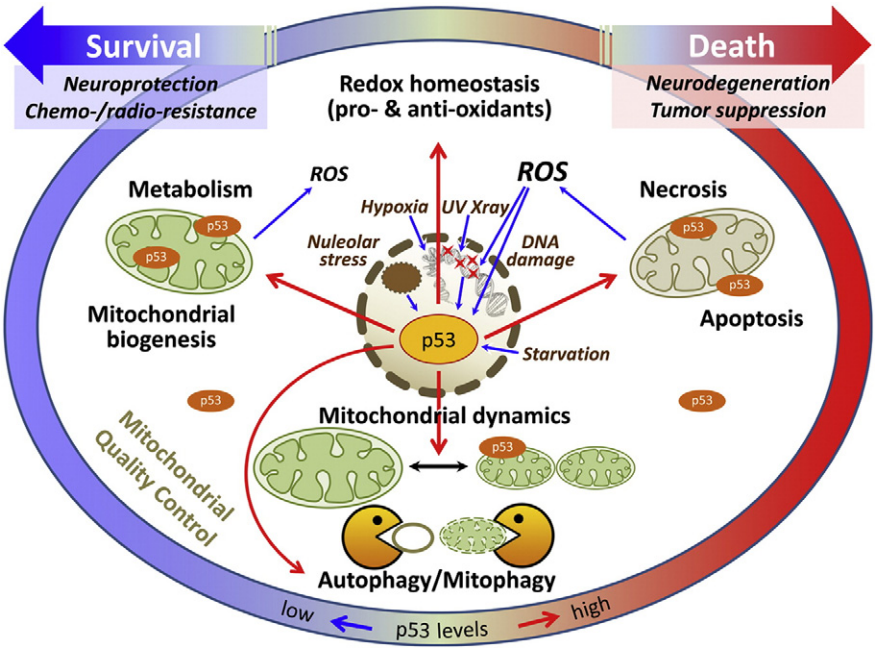

Fig. 1. p53 plays numerous distinct roles in mitochondria-related processes, such as apoptosis/necrosis, autophagy/mitophagy, mitochondrial quality control and cellular redox regulation, depending on its expression levels, subcellular localization, availability of cell-specific binding partners, and cellular state (i.e. resting versus stressed). Nuclear p53 is activated (upregulated and/or stabilized) by cellular stress including DNA damage, hypoxia, oxidative stress (ROS), nucleolar stress and starvation, and transcriptionally activates or represses p53 target genes, leading to a variety of downstream effects. p53 can also translocate to the cytoplasm and to mitochondria, where it can directly bind to and activate or inhibit proteins and pathways related to mitochondrial function. p53 actions related to mitochondrial quality control (to the left) are largely functional at basal (physiological) levels of p53 expression, while its pro-death function (to the right) requires higher levels of p53. The same is generally true at the individual gene/protein level within any specific category of p53 function where pro-survival actions are seen with physiological levels of p53 expression, while pro-death actions are induced by upregulated levels of p53.

The last decade of research, however, has revealed a role for p53 as a non-transcriptional inducer of apoptosis, which involves its direct action at the mitochondria [19,20]. In this model, a cytoplasmic pool of p53 rapidly translocates to the surface of the outer mitochondrial membrane in response to stress, where it behaves like a BH3-only protein physically interacting with anti-apoptotic (Bcl-xL, Bcl-2, Mcl-1) and/or pro-apoptotic (PUMA, Bax, Bak) members of the Bcl-2 family. These interactions eventually facilitate Bax/Bak-mediated permeabilization of the outer mitochondrial membrane leading to release of cytochrome c and the activation of the caspase cascade. Consistent with p53 acting directly at mitochondria, p53 protein has been localized in mitochondrial fractions after stress [21–23] and directly targeting p53 to the mitochondrial outer membrane is sufficient to promote apoptosis in the absence of any external stress [21,24]. While the evidence for a direct action of p53 at the mitochondria is compelling, it was derived from studies using normal and tumor cells of non-neuronal origin.

Evidence for a direct mitochondrial action of p53 in neurons is not as abundant and remains inconclusive. Although initial studies appeared to have established that p53 immunoreactivity is confined to the nucleus in neurons destined to die [15,25–27], in agreement with nuclear p53 function being essential for apoptosis induction, there have been several reports describing cytoplasmic accumulation of p53 in neurons, but with no demonstration that this had functional consequences for viability [28–30]. Subsequent to the demonstration of extra-nuclear apoptotic activity of p53 in non-neuronal cells, several studies have since demonstrated a potential role for mitochondrial p53 in mediating neuronal apoptosis using various in vitro and in vivo models [31–37]. However, none of these studies has provided definitive proof for a mitochondrial site of p53 action in neurons. Definitive evidence in support of a mitochondrial site of action for p53 would include its physical association with mitochondria and its molecular interaction with either members of the Bcl-2 family of proteins or other intrinsic mitochondrial proteins. The evidence available from these studies is still not conclusive in that a mitochondrial association for p53 has principally been demonstrated by immunofluorescence colocalization. When data is presented in support of p53's physical association with mitochondria and/or its molecular interaction with an appropriate protein in mitochondrial fractions, the results cannot be strictly associated with neurons because the analysis has been done using whole brain tissue. In this regard, Endo et al. [31] used micro-dissected CA1 pyramidal cell layer tissue to demonstrate a p53-Bcl-xL interaction in mitochondrial fractions and, therefore, the result is more likely to represent a neuronal event. A functional contribution of mitochondrial p53 to apoptosis has been demonstrated by using pifithrin compounds. Pifithrin-α [38] and pifithrin-μ [39] specifically inhibit the nuclear (transcriptional) and mitochondrial (non-transcriptional) actions of p53, respectively, although their specificities have not been critically tested in neurons. The results obtained with these inhibitors are not consistent and suggest context-dependent, variably proportionate contributions of nuclear and mitochondrial p53 to neuronal apoptosis [31,32,35–37]. A shift in sensitivity from pifithrin-α to pifithrin-μ is also observed as neurons mature in culture [34]. Collectively, these studies appear to suggest that mitochondrial p53 action contributes to neuronal apoptosis but to a variable extent. Results from some of these studies [31,32,36], however, suggest that the action of pifithrin-α and pifithrin-μ may not be exclusively confined to their expected sites of action, nucleus and mitochondria, respectively, although some "non-specific" effects of pifithrin-μ on nuclear p53 activity may be explained by a potential increase in nuclear p53 concentration when p53 translocation to mitochondria is blocked by pifithrin-μ. Pifithrin-α has been widely used to inhibit the nuclear, transcriptional activity of p53, but it may possess some nonspecific actions [40–42]. Caution must be taken when assessing mitochondrial p53 function solely on the basis of the sensitivity to pifithrin-μ because the specificity of this compound has recently been challenged. Leu et al. [43] demonstrate that the direct target of pifithrin-μ action is actually heat shock 70 kDa protein (HSP70). Pifithrin-μ disrupts the association between HSP70 and its cofactors and client proteins, the latter of which include p53, APAF1 and autophagy-related proteins (p62, LAMP2). This results in compromised activation of both the caspase cascade and autophagy as well as reduced localization of p53 to mitochondria. Also, pifithrin-μ