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TP53 Mutation, Mitochondria and Cancer

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Abstract

Under normal conditions, basal levels of wild-type p53 promote mitochondrial function through multiple mechanisms. Remarkably, some missense mutations of p53, in contrast to the null state, can result in the retention of its metabolic activities. These effects are particularly prominent in the mitochondria and demonstrate a functional role for mutant p53 in cancer metabolism. This review summarizes accumulating data on the mechanisms by which p53 missense mutations can regulate mitochondrial metabolism and promote the viability and survival of both normal and cancer cells, thus acting as a double edged sword for the host. Greater understanding of these mechanisms may provide insights for developing new treatment or preventive strategies against cancer.

Introduction

Cancer is a disease driven by genomic instability that causes the accumulation of DNA mutations, which then promote its aberrant growth [1]. p53 protein, encoded by the human *TP53* gene, acts to suppress this process through various cellular mechanisms including DNA damage repair, cell cycle regulation, and cell death [2,3]. Based on the Cancer Gene Census mutation database, the pivotal role of *TP53* in tumorigenesis has been further underscored by the high frequency (36.1%) of its somatic mutations in cancer patients across 20 tissues, the most of any known gene [4]. Only PIK3CA (14.3%) and BRAF (10%), the second and third most frequently mutated genes, were altered in 10% or more of patients out of the remaining 197 cancer genes. The somatic mutations of *TP53* found in human cancers occur in domains of the gene that are most conserved amongst mammals, highlighting the importance of its wild-type activity in maintaining normal cells [5]. In contrast to other tumor suppressor genes, which frequently have frameshift or nonsense mutations, most mutations of *TP53* are missense mutations suggesting that altered forms of p53 protein may play a role in tumorigenesis [6].

In 1969, Li and Fraumeni described a familial cancer syndrome, inherited in an autosomal-dominant manner, with a predisposition to multiple primary tumors at an early age [7]. Li-Fraumeni syndrome (LFS) was found to be caused by germline mutations of the *TP53* gene

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[8]. Consistent with the higher frequency of missense *TP53* mutations in tumors, the majority of LFS patients also carry missense mutations. In addition, patients with missense mutations develop cancer at an earlier age compared with those carrying deletion mutations [9]. Thus, even from a clinical perspective, the loss of wild-type activity by a missense mutation in the *TP53* gene is not equivalent to a haploinsufficiency state caused by gene deletion. In the laboratory, mutant p53 has been shown to display gain-of-function activities through different mechanisms, including the interference of the transactivating activities of p63 and p73, and acquiring new transactivation target genes that promote cell proliferation such as *EGFR*, *MYC* and *MAP2K3* [10–12].

Within the past decade, there has been a resurgence of interest in the role of metabolism in cancer biology [13–15]. Mitochondrial metabolism in particular appears to be critical for the selection and survival of cancer cells, with varying outcomes dependent on factors like tumor type and microenvironment [16,17]. For example, parallel studies utilizing different approaches have demonstrated the prominent role of the mitochondria in glioblastoma, lymphoma and melanoma [18–20]. Mitochondria are regulated through multiple pathways by wild-type p53, so these recent reports of the role of mitochondria in cancer biology provide impetus for investigating whether mutant p53, commonly overexpressed in human cancers, can also regulate the mitochondria [21]. Here we summarize some of the findings of a growing body of work that suggests that mutant p53 can regulate metabolism and mitochondrial function.

Mutant p53 and metabolism

Hundreds of different somatic and germline mutations of *TP53* have been reported, but only a minority have been biologically characterized (IARC TP53 Database) [6]. Therefore, it is important to stipulate that the properties of one specific somatic or LFS germline mutation cannot be generalized to all variants of p53. This makes drawing general conclusions from studies of mutant p53 challenging, but nonetheless, specific p53 mutations can still be informative for investigating the role of aberrant mitochondrial activity in cancer biology. Under normal conditions, wild-type p53 is short-lived and expressed at low levels, but mutant p53 protein can accumulate to high levels in cancer cells [22]. The loss of wild-type p53 transcriptional activation of *MDM2* that destabilizes p53 protein can contribute to increased mutant p53 levels by eliminating a major negative feedback control. However, there also appear to be other factors involved in its abnormal accumulation [23]. From an evolutionary perspective of cancer development, the relatively late acquisition of *TP53* mutations and frequent overexpression of mutant p53 protein in colon cancer suggest that it may result in cellular fitness required for malignant progression in this specific type of tumor [1,24,25]. Compared to p53 null mice, those harboring LFS hot-spot mutations of p53 (human p53 R175H and R273H missense mutations) display a distinct tumor spectrum with more aggressive metastatic potential [26,27]. Similarly, skin carcinomas in mice harboring the p53 R172H missense mutation (human R175H homolog) are more aggressive and metastatic compared to that from p53 null mice [28]. These observations begin to describe the gain-of-function properties exhibited by mutant p53 which are distinct from p53 null state.

Increased glycolysis is observed in many types of cancer cells, but this metabolic shift can also cause increased oxidative stress and DNA damage [16,29–31]. One of the earliest p53-regulated metabolic genes identified was *TP53-induced Glycolysis and Apoptosis Regulator (TIGAR)*, which inhibits glycolysis by hydrolyzing an allosteric activator of the glycolytic enzyme 6-phosphofructo-1-kinase (PFK-1) [32]. This activity can indirectly increase antioxidant capacity by shunting glucose into the pentose phosphate pathway for glutathione biosynthesis. Therefore, TIGAR could be tumor suppressive by decreasing oxidative DNA damage [32]. On the other hand, a subsequent study has shown that the overexpression of TIGAR in human colon cancers can promote both tumorigenesis and the regeneration of normal tissue, demonstrating that cancer cells can also benefit from the metabolic activities of TIGAR [33]. p53 can also down-regulate other components of glycolysis through the destabilization of phosphoglycerate mutase and the repression of the glucose transporters 1, 3 and 4 [34,35]. In the absence of wild-type p53 activity, insulin receptor is overexpressed demonstrating another pathway by which p53 inhibits glycolysis [36].

The dissociation of wild-type p53 metabolic activities from classic cell cycle regulation has highlighted the importance of what was previously thought to be of lesser concern in tumorigenesis prevention. While cell cycle arrest, senescence and apoptosis are well-established tumor suppressive processes, a recent study elegantly demonstrated that even with the loss of these typical p53 cell cycle control pathways, its metabolic activities were sufficient to suppress thymic lymphoma development [37]. A p53 acetylation mutant mouse ($p53^{3KR/3KR}$) with the loss of three acetylation sites necessary for cell cycle arrest, senescence and apoptosis retains its capacity to inhibit glycolysis and reactive oxygen species (ROS) generation. Like wild-type p53, $p53^{3KR}$ can still upregulate mitochondrial glutaminase 2 (GLS2), which promotes mitochondrial metabolism and redox homeostasis, and repress the expression of *SLC7A11*, a cystine-glutamate exchanger which promotes ferroptosis in response to oxidative stress [38,39]. The delineation of important cellular processes through specific structural modifications of p53 has helped to define the various roles of p53 mutants in tumor metabolism and cell survival.

Mutant p53 regulation of mitochondrial biogenesis and function

The promotion of mitochondrial respiration by p53 was first attributed to its transcriptional regulation of *Synthesis of Cytochrome c Oxidase 2* (*SCO2*), an essential gene for the assembly of complex IV (cytochrome c oxidase) [40,41]. However, growing evidence indicates that p53 promotes mitochondrial respiration through multiple pathways that include both transcriptional and post-translational mechanisms involving mitochondrial biogenesis genes such as *Mitochondrial Transcription Factor A* (*TFAM*) (Figure 1) [21]. The marked decrease in swimming and running endurance of p53 null mice compared with p53 wild-type mice demonstrated the physiological importance of p53 in aerobic metabolism [41–43]. Notably, like $p53^{3KR}$, the LFS “hot-spot” *TP53* R175H mutation retains the mitochondrial biogenesis activities of wild-type p53 and can amplify them due to its unregulated expression [37,44]. Cells and tissues of *p53* R172H knockin mice (human R175H homolog) display a mutant allele dose-dependent increase in both mRNA and protein levels of *TFAM* and *SCO2* with a concomitant loss in the expression of *CDKN1A,* the prototypical p53 target gene encoding p21 [44]. This dissociation between the cell cycle

and metabolic activities of p53 also helps to conceptualize the important distinction between the p53 mutant and p53 null states. There is an opposite effect on exercise capacity between the homozygous states of p53 null (*p53-/-)* and p53 R172H mutation (*p53H/H*) mice compared to p53 wild-type mice (Figure 2) even though p21 transactivation is similarly lost in these two models [42–44]. In a translational study of patients with Li-Fraumeni syndrome, noninvasive P-31 magnetic resonance spectroscopy of skeletal muscle showed evidence of increased oxidative phosphorylation capacity as measured by phosphocreatine recovery kinetics after exercise [44]. These observations were further supported by mitochondrial studies using both blood and skeletal muscle needle biopsy specimens, therefore indicating that general observations in mouse LFS models may be applicable to humans in the clinics.

Besides transactivating *SCO2* expression, p53 is also known to transcriptionally regulate other mitochondrial biogenesis genes such as *Apoptosis-Inducing Factor* (*AIF*) gene, which is involved in complex 1 assembly, and *Ferredoxin Reductase* (*FDXR*), which is responsible for the maturation of Fe-S proteins essential in electron transfer reactions [41,45–48]. While the regulation of AIF and FDXR by mutant p53 has not been reported, the mitochondrial citrate transporter protein (CTP, encoded by *SLC25A1*) is induced by several mutant forms of p53, including the LFS *TP53* R175H and R273H mutations, but not by the p53 null state [49]. CTP, localized in the inner membrane, facilitates the exchange of mitochondrial citrate for cytosolic malate, which stimulates respiration and helps maintain inner membrane integrity [50]. CTP is required for tumor proliferation, and it has been proposed to serve as a negative prognostic marker as its level and activity are elevated in human cancers [49,50]. p53 also regulates fatty acid metabolism through genes such as *Sphingosine Kinase 1* (*SPHK1*) and *Lipin 1* (*LPIN1*), which can promote cell growth and mediate nutritional and genotoxic stress signals [51,52]. In summary, p53 displays multiple transcriptional activities in promoting mitochondrial function, which is important for cell viability as well as human fitness. However, the retention and augmentation of these activities by the overexpressed mutant p53 in cancer cells ultimately compromises longer term organismal survival.

Mitochondrial genomic maintenance

The mitochondrial genome (mtDNA) encodes only 13 proteins, however, maintaining its integrity is paramount because each protein is essential for respiration and oxidative phosphorylation [53]. Like its role in maintaining the nuclear genome, there is increasing evidence that p53 is also involved in mtDNA homeostasis. mtDNA depletion is observed in both cultured cells and tissues with p53 deficiency, which has been attributed to p53-inducible ribonucleotide reductase 2 (p53R2) and TFAM down-regulation [43,54,55]. p53R2 functions to supply deoxyribonucleotides and repair nuclear DNA damage, but it is also necessary for mtDNA maintenance [56,57]. Paradoxically, high p53R2 expression was also observed in a number of different cancer types, and is associated with more malignant characteristics, thus raising speculation that mutated p53 may play a role in upregulating *p53R2* expression [58].

p53 has been shown to interact with mitochondrial matrix proteins and participate in the repair of mtDNA damage primarily through base excision repair (BER) [21,59]. p53

interacts with DNA polymerase γ (POLG), TFAM, and single-stranded DNA-binding protein 1 (SSBP1) to repair and maintain mtDNA [60–62]. At least three different mechanisms have been proposed to explain how p53 translocates into mitochondria under non-apoptotic conditions [63–65]. One mechanism of interest is the import of p53 into the mitochondria via the coiled-coil-helix-coiled-coil-helix domain-containing protein 4 (CHCHD4), a carrier of the respiration-driven disulfide relay system [65]. Because electron transfer during active respiration may be associated with ROS generation, this import mechanism could sub-cellularly target p53 to the site of DNA damage where its repair activities are needed. Indeed, the accelerated repair of oxidative mtDNA damage has been shown to be dependent on the Cys-135 amino acid residue of p53 that is necessary for interaction with CHCHD4 and import into the mitochondria [65]. Given the multifaceted roles of p53, the CHCHD4 mediated translocation of p53 represents an ideal homeostatic mechanism by which its mtDNA repair activity can be targeted to the site of oxidative stress.

The CHCHD4-mediated repair of oxidative mtDNA damage is preserved in the p53 R175H mutant, both *in vitro* and in mouse tissues [65]. Remarkably, recent work has demonstrated decreased prevalence of mtDNA mutations in colon tumors, which frequently harbor *TP53* mutations, relative to adjacent normal tissue [66]. Thus, it could be of interest to correlate such an observation with *TP53* mutation status of the primary tumors. One prediction would be that colon cancers with p53 alterations that preserve CHCHD4 interaction and are sufficiently functional to exist as both somatic or germline mutation, such as p53 R175H, would maintain mtDNA integrity. On the other hand, tumors with severe p53 mutations that disrupt its translocation into mitochondria and are only encountered as somatic mutations, such as p53 C135Y, may show greater mtDNA instability [65].

Other mechanisms of mitochondrial regulation by mutant p53

There is further evidence that the translocation of p53 into the mitochondria impacts mitochondrial function and homeostasis. A mitochondrial pool of p53 has been reported to interact with the oligomycin sensitivity-conferring protein (OSCP) to promote complex V (F_1F_0-ATP synthase) assembly, increase respiration, and decrease ROS production [67]. Parkin, an E3 ubiquitin ligase responsible for initiating mitophagy of damaged mitochondria, can be both transcriptionally and post-translationally regulated by p53 [68,69]. Because cytosolic p53 is known to inhibit autophagy, the significant correlation between the high level of cytosolic mutant p53 expression and increased autophagy inhibition suggests that mutant p53 may also modulate parkin-mediated autophagy and mitophagy [70,71].

The role of p53 in regulating metabolism is becoming increasingly difficult to define and predict as there can be contradictory results in cultured cells and tissues dependent on the type of cellular stress, p53 expression levels and p53 mutation status. Under normal, relatively unstressed conditions, p53 promotes mitochondrial respiration that is essential for redox homeostasis, while highly induced p53 can be pro-oxidant and apoptotic [30,72]. This dual nature is exemplified by p53 modulation of the master mitochondrial biogenesis regulator, peroxisome-proliferator-activated receptor γ co-activator-1α (PGC-1α), expression levels [73,74]. Basal levels of wild-type p53 can stimulate PGC-1α expression

and mitochondrial biogenesis in mice, while severe cellular stress associated with telomere dysfunction and increased p53 levels can repress both PGC-1α and PGC-1β expression [42,75]. DNA interaction studies show that p53 binds to the −2317 region on the mouse PGC-1α promoter and can increase PGC-1α expression, while its binding to elements at −564 and −954 suppresses its expression [75,76]. In addition to its dosage or activation state, p53 mutation status is also likely to be critical for determining how p53 interacts with the cis regulatory elements of *PGC-1α*.

Relevance to health and cancer

Generally, metabolic genes function to maintain the homeostasis of cells for growth and adaptation to their environment. It is clear that p53-regulated metabolism under normal conditions contributes to cellular homeostasis without which there are gross deficiencies in cellular and physiological function. Some examples include mtDNA depletion in p53 null cells and tissues and the poor intrinsic exercise capacity or adaptation to exercise training of p53 null mice, both of which could be critical for survival during evolution [41–43,54,55]. Some germline LFS *TP53* mutations may retain or amplify p53 metabolic function, with resultant improvements in bioenergetic, thermogenic or antioxidant capacity that could be beneficial to both cellular and organismal survival under stressful conditions [44]. However, these advantages could be deleterious to the *TP53* mutation carrier when normal cells transform into cancer cells which can use this mechanism for aggressive growth. In support of this notion, recent studies have shown that *PGC-1α* expression mediates increased mitochondrial respiration and resistance to oxidative stress in cancer cells and correlates with their metastatic potential [20,77]. A genetic analysis of the multi-cancer TCGA datasets comprised of >9000 primary and metastatic tumor samples have demonstrated the potential clinical significance of mutant p53-regulated *SCO2* expression [78]. Both mutated *TP53* state and high *SCO2* mRNA expression, as well as amplification of *SCO2* gene, significantly correlated with poor patient survival [78]. These observations of mutant p53 promotion of mitochondrial activity and correlation with poor clinical outcomes suggest that targeting the mitochondria may be one avenue for restraining tumorigenesis. Indeed, growing evidence from disparate investigations suggest that increased mitochondrial biogenesis and antioxidant capacity are conducive for cancer progression, while disrupting mitochondrial function inhibits it [79–84]. The effect of mutant p53 on metabolic regulation appears to be important for tumorigenisis and thus, as recently suggested for therapy-resistant cancers, may represent a selective vulnerability that can be used to inhibit their growth [85]. Cancer cells are adept at utilizing the double edged sword of mutant p53, but as with most advantages there are also disadvantages to which cancer is not immune.

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* of special interest

** of outstanding interest

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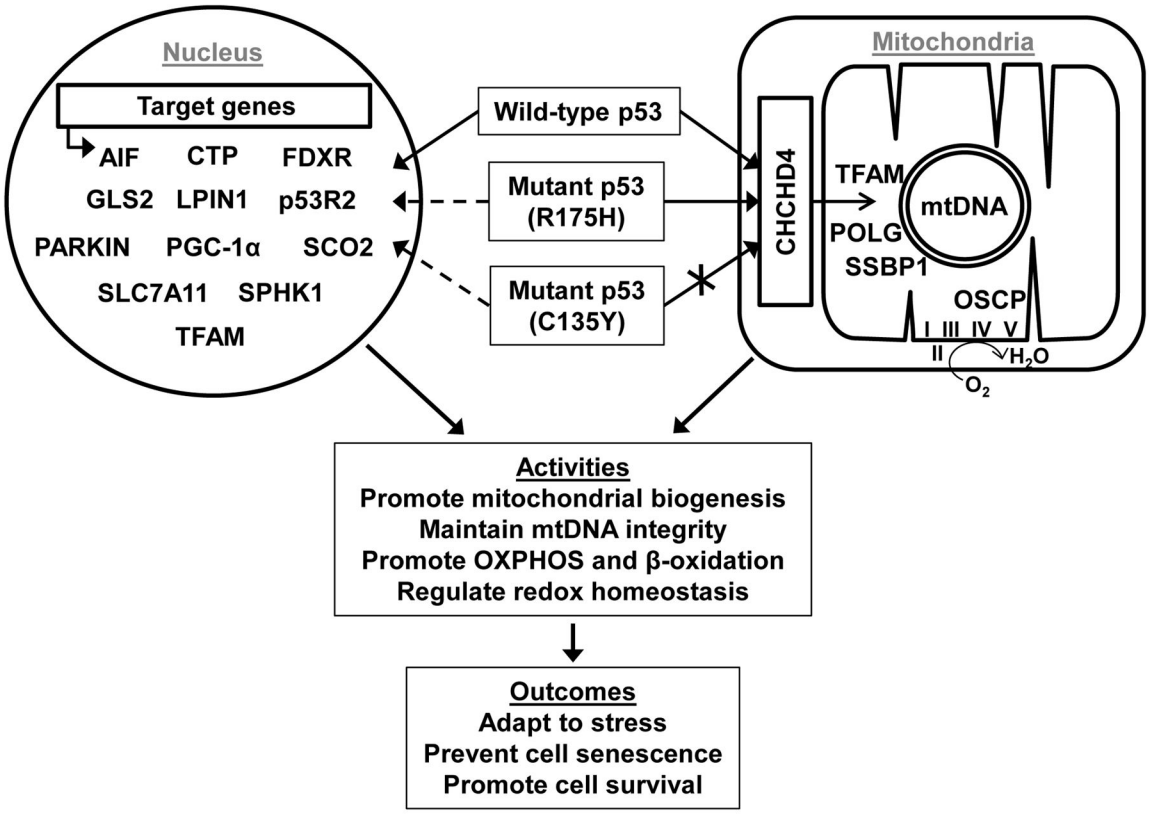

Figure 1. Transcriptional and post-translational regulation of the mitochondria by p53 is determined by multiple factors including its mutation status and translocation into the mitochondria

Depicted are three possible genotype states: wild-type p53, mutant p53 (R175H) that can translocate into the mitochondria; and mutant p53 (C135Y) that cannot translocate into mitochondria (crossed arrow) due to disruption of its interaction with the disulfide relay protein import carrier CHCHD4. Proteins that have been reported to interact with p53 inside the mitochondria are shown along with schematic representations of circular mtDNA and respiratory complexes. p53 of all three indicated genotypes can translocate into the nucleus, but the ability to transactivate the indicated genes involved in mitochondrial function may be altered (dashed arrows) depending on its mutation status and the specific p53 target gene. Abbreviations: I, II, III, IV, and V, mitochondrial OXPHOS complexes; AIF, apoptosis-inducing factor; CTP, citrate transporter protein; FDXR, ferredoxin reductase; GLS2, mitochondrial glutaminase 2; LPIN1, lipin 1; p53R2, p53-inducible ribonucleotide reductase 2; PGC-1α, peroxisome-proliferator-activated receptor gamma co-activator-1α; SCO2, synthesis of cytochrome c oxidase 2; SLC7A11, solute carrier family 7 (cationic amino acid transporter, y+ system), member 11; SPHK1, sphingosine kinase 1; SSBP1, single-stranded DNA-binding protein; TFAM, transcription factor A, mitochondrial; OSCP, oligomycin sensitivity-conferring protein; OXPHOS, oxidative phosphorylation.

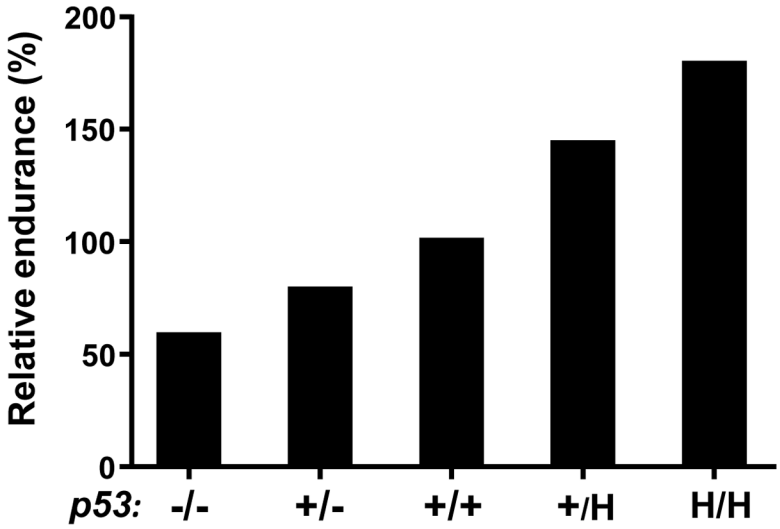

Figure 2. Effect of *p53* genotype on relative exercise endurance as a marker of aerobic metabolic capacity

This is a schematized composite graph based on the maximal treadmill exercise times of mice that are heterozygous or homozygous for *p53* gene deletion or R172H knockin mutation (mouse homolog of the human LFS R175H mutation) compared to wild-type mice (set at 100% relative endurance) [43,44]. *p53* wild-type (*+/+*), heterozygous knockout (*+/−*), homozygous knockout or null (*−/−*), heterozygous R172H knockin (+/H), homozygous R172H knockin (H/H).