Review Article

Do p53 stress responses impact organismal aging?

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Abstract: p53 is a transcriptional regulator that responds to cellular stresses to suppress oncogenesis, but some of these responses can have unintended consequences that influence non-cancer-related aging processes. The impact of these consequences is not well understood—partly due to the many complex processes that influence p53 function and partly due to the vast array of processes that p53 affects. p53 has the potential to both accelerate and hinder cellular aging processes, which would likely have antithetical biological outcomes with regard to organismal aging. To accelerate aging, p53 induces apoptosis or cell cycle arrest as a prerequisite to cellular senescence; both can impair the mobilization of stem and progenitor cell populations. To suppress aging, p53 inhibits unregulated proliferation pathways that could lead to cellular senescence and a senescence-associated secretory phenotype (SASP), which creates a pro-inflammatory and degenerative tissue milieu. A review of mouse models supports both possibilities, highlighting the complexity of the p53 influence over organismal aging. A deeper knowledge of how p53 integrates and is integrated with various biological processes will improve our understanding of its influence over the aging process.

Keywords: p53; stress response; cellular senescence; aging

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General p53 function and post-translational modifications

p53 is a transcriptional regulator that suppresses oncogenesis in response to a variety of stresses including DNA damage, oxidative reactions, hypoxia, compromised energy levels and oncogenic signaling (1-6). p53 transcribes a diverse set of genes that promote apoptosis (*53BP1*, *BAX*, *Killer*, *Scotin*, *FAS*, *BBC3*, *PERP*, *LRDD*), cell cycle arrest (p21, 14-3-3, GADD45, RPRM), PMAIP1) and oxidative phosphorylation (SCO_2, AIF), suppress aerobic glycolysis (GLUT1, TIGAR, Hexokinase, Phosphoglycerate mutase) and cell growth (PTEN, TSC2, AMPK beta, IGF-BP3) (7) and modulates protein synthesis [sestrins 1 & 2 (8-10)]. In addition, p53 has activities that are distinct from transcription, including the regulation of microRNA processing (11), DNA repair (12), mitochondrial function (13) and ribosome biogenesis (14,15). Thus, p53 is a multi-functional protein that responds to a diverse array of stresses.

Post-translational modifications to p53, in response to stress, regulate its activity (16). Among the best-known p53 regulators are MDM2 (murine double minute 2) and MDM4 (a.k.a. MDMX). MDM2 is a ubiquitin ligase, while MDM4 enhances p53 ubiquitination in a complex with MDM2. MDM2 regulates p53 stability, while MDM4 regulates p53 activity (17), with tissue-specific differences (18). Deletion of either MDM2 or MDM4 is embryonic lethal due to widespread cell cycle arrest and apoptosis, and deletion of p53 rescues these mutant embryos (19-22). Thus, unfettered p53 activity is toxic to a developing embryo.

A variety of protein kinases phosphorylate p53 on multiple Ser/Thr residues in response to stress. For example, in response to DNA damage, ATM and other kinases phosphorylate Ser 15 (Ser 18 in mouse p53) and Ser 20 (Ser 23 in mouse). These modifications interfere with MDM2 binding, resulting in increased expression of p53. Interestingly, mice carrying a modified p53 (S18A) that can no longer undergo phosphorylation exhibit late-onset cancer and accelerated aging; fibroblasts from these mice undergo premature replicative senescence, suggesting that this response suppresses aging as well as cancer (23). Similarly, mice carrying p53 T21D and S23D (which activate p53) show reduce stem cell populations and early aging (24). Depletion of the pro-apoptotic p53 target, PUMA rescues this phenotype, suggesting that apoptosis reduces stem cell populations to accelerate aging.

Lysine acetylation is another p53 modification. Potential p53 deacetylases include p300, CBP, PCAF, TIP60 and hMOF (25). Acetylation stabilizes p53 by interfering with the MDM2 interaction (26). Acetylation can also recruit cofactors influencing p53 activity. Deacetylases counteract acetyltransferase activity. In particular, SIRT1 deacetylates K382 to negatively regulate p53-mediated apoptosis. This deacetylation could impact aging since a natural molecule found in wine, resveratrol (3,5,4'-trihydroxystilbene), activates SIRT1 (27) and improves survival for multiple species, including mice fed a high fat diet (28). Thus p53 post-translational modifications could influence the aging process and longevity.

The integration of p53 with anti-growth interventions that improve survival

Rapamycin, a bacterial metabolite, was the first chemical to reproducibly extend longevity in mice (29-31). At least part of the life span extension was due to cancer suppression (32,33), but rapamycin also ameliorated other age-related maladies (31,34,35). Furthermore, rapamycin improved survival for species that do not develop cancer (36). Rapamycin inhibits mTOR (mechanistic Target of Rapamycin), a highly conserved serine/threonine kinase in the same family as ATM (37-40). mTOR forms a complex with multiple proteins, including Raptor to form mTORC1 (mTOR complex 1). mTORC1 promotes cell growth (mass) and proliferation (cell division) in response to mitogenic signals. Rapamycin inhibits mTORC1 by binding to the protein folding chaperone FKBP12 (FK506 binding protein); the rapamycin/FKBP12 complex binds to and inhibits mTORC1 (41-43). Thus, rapamycin improves survival in mice and other species by inhibiting mTORC1-anabolic signaling (44).

p53 also inhibits mTORC1, but as a part of a stress response that does not involve FKBP12. Instead, p53 induces the transcription of sestrins 1 and 2 to activate a negative mTORC1 regulatory pathway involving AMPK and TSC2 (5' adenosine monophosphate-activated kinase and tuberous sclerosis 2) (8). As a negative regulatory loop, mTORC1 elevates p53 function after DNA damage (44), similar to the activity of ATM. These data indicate that mTORC1 induces p53 in response to DNA damage, thereby coupling the genotoxic stress response to energy levels (44). Because p53 and rapamycin inhibit mTORC1 through different mechanisms, their impact should be additive. In support this prediction, p53 enhanced rapamycin's ability to suppress the ionizing radiation-induced senescence-associated secretory phenotype (SASP) in human cells (45). In mice, p53 levels directly correlate with rapamycin's ability to extend life span, although a higher rapamycin dose extends the life span for $p53^{-/-}$ (46), suggesting that the activity of rapamycin is not p53-dependent and that the dose of rapamycin and p53 can affect outcome. Indeed, escalating rapamycin concentrations proportionately increase life span (47) and suppress intestinal adenomas (33), whereas p53 haploinsufficiency leads to cancer (48). These findings indicate that p53 and rapamycin likely blunt mTORC1 activity through different pathways and therefore have additive effects (*Figure 1*).

The above results showing that p53 enables rapamycin to extend longevity might seem antithetical to its role in establishing cellular senescence (permanent G_1 arrest). In response to stress, p53, acting in part by stimulating p21 transcription, induces a G_1 checkpoint to drive cells into quiescence (reversible G_1 arrest). In DNA repair defective mice, p53 is constitutively active (49) and essential for the rapid senescence of fibroblasts from those mice (50,51). Yet as noted above, p53 also suppresses the SASP in conjunction with rapamycin in human cells (45). In addition, p53 overexpression suppresses senescence in p21-overexpressing cells to maintain quiescence (52), and elevated mTORC1 activity, achieved through TSC2 knockdown, induces quiescent cells to enter senescence after nutlin-3a-mediated growth arrest (53). Nutlin-3a is a cis-imidazoline analogue that disrupts the p53-MDM2 interaction to enhance p53 stability. Rapamycin reversed this growth arrest, indicating that mTORC1 can promote senescence. Similarly, TSC1 maintains naive T cells in quiescence (54). Thus, it appears p53 drives cells into quiescence in response to stress, and suppresses mTORC1-induced senescence (44,55).

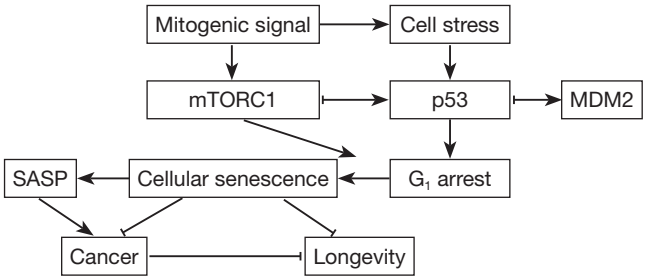

Figure 1 p53 integrates multiple stress signals to induce a G1 arrest and inhibit mTORC1. Mitogenic signals induce a pro-growth pathway that enables G1 arrested cells to become senescent and exhibit a SASP. Cellular senescence prevents the cell from developing a cancer, but the SASP can alter the tissue microenvironment to fuel the development of cancer from non-senescent cells, promote tissue degeneration and reduce longevity.

Caloric restriction (CR) improves survival and ameliorates aging in many species, including mammals (56). p53 does not appear to be a major player in CR-mediated life span extension. Yet, CR promotes SIRT1-mediated deacetylation of p53, thereby facilitating MDM2-induced degradation of p53 (57,58). Further, CR improved the survival of $p53^{-/-}$ mice (59) even when initiated late in life (59).

p53 mouse models show a diverse impact on aging and longevity

Mouse models reveal a contradictory impact of p53 on aging and longevity. These models were originally designed to study cancer but some appear to impact aging and longevity as well. They range from complete p53 null mutations to truncations or point mutations that alter activity. A comparison of these models reveals the complex influence p53 has over organismal aging—which can be independent or a consequence of its tumor suppressor role.

The initial mouse models were simple knockouts that produced null alleles (no protein). These $p53^{-/-}$ mice exhibited a developmental defect that killed a subset of animals by reducing apoptosis in the mid-brain, leading to exencephaly (60). Yet, most $p53^{-/-}$ embryos developed into apparently healthy adults, almost all of which succumb to cancer in about half a year. Heterozygous ($p53^{+/-}$) mice develop cancer at a later age (61). Cancer development in $p53^{+/-}$ mice is often due to loss of heterozygosity (spontaneous inactivation of the wild type copy). But there is also evidence for haploinsufficiency (reduced protein levels) since some cancers from $p53^{+/-}$ mice retain p53 function (62). p53 mutation is also sensitive to genetic background, as measured by cancer onset and spectrum, and to environmental conditions, as seen with exposure to carcinogens (63-66). Due to cancer-related death at a young age, p53-null mice cannot be studied for late-onset maladies that are typically seen in old wild-type mice (67,68).

Since simple p53-deletion increases cancer, simple overexpression should reduce cancer. Indeed, mice harboring an extra *p53* gene contained within a BAC (bacterial artificial chromosome) had a lower incidence of cancer with no obvious effect on aging (69). Furthermore, increased gene dosage of p53 together with Arf lowered the cancer incidence and improved overall survival (70). ARF elevates p53 levels by inhibiting MDM2 (71,72). Similarly, mice with a hypomorphic MDM2 allele, which increased p53 levels, showed a reduced cancer incidence without deleterious side effects (73). Thus, enhanced p53-mediated cancer suppression was not toxic to adult mice. It is possible that the pro-aging side effects of p53 are manifest only when p53 overwhelms the many regulatory mechanisms that modulate its activity.

The p53-null and p53-elevated mouse models support a simple notion of function; that is, p53 suppresses cancer without toxic side effects. However, other p53-altered mouse models confound this notion. First, p53 caused lethality in Mdm2- or Mdm4-deficient mouse embryos (20-22). This observation is in stark contrast to the p53-overexpressing mice described above and suggests that p53 regulation is essential to prevent toxicity. Furthermore, p53 levels influenced aging in mice defective for BRCA1 (breast cancer susceptibility gene 1). BRCA1 repairs DNA double strand breaks (DSBs) created during DNA replication as a part of the homologous recombination repair pathway (74). Deleting one copy of p53 rescued *brca1*$^{-/-}$ mice from embryonic lethality but these mice displayed an early aging phenotype (75,76). Moreover, decreased capacity to repair DSBs by nonhomologous end joining caused p53-dependent early cellular senescence in cells and early organismal aging (50,77-79). Another genetic alteration that implicates p53 in aging is REGγ (REG: 11S regulatory particles, 28-kDa proteasome activator) (80). REGγ-deficient mice display early aging. Elevated p53 might contribute to this phenotype because REGγ is a proteasome activator that regulates p53. These mice accumulate casein kinase (CK) 1δ, which degrades MDM2, resulting in elevated p53 levels. A $p53^{+/-}$ background ameliorated the aging phenotype in REGγ-mutant mice, establishing unregulated p53 as causal. Finally, skin-specific MDM2 deficiency resulted in p53-induced senescence in epidermal stem cells and precocious

skin aging (81). These examples are interesting contrasts to the MDM2 hypomorphic allele described above, which reduced cancer without side effects (73), and suggests that different aspects of p53 regulation, coupled with genetic and environmental variances, can drive distinct biological outcomes.

Further complicating the picture, there are multiple p53 isoforms and family members (p63 and p73) generated from variant promoter usage, alternative splicing and alternative translation initiation (82,83). How these isoforms differ functionally is not fully understood (84). There is evidence that some of these isoforms could influence aging. For example, expression of the N-terminally truncated p53 isoform in mice lowered cancer risk at the expense of early aging (85,86). These mice showed poor tissue regeneration, implicating a defect in stem and progenitor cells (87). Supporting this possibility, old $p53^{+/-}$ mice exhibited increased levels of hematopoietic stem and progenitor cells, but not if N-terminally truncated p53 was present (88). The truncated p53 likely forms a tetramer with full-length p53 to improve stability and nuclear localization (89). Another isoform stabilized p53 in the presence of MDM2 (90). Thus, p53 isoforms have the potential to influence p53 function in a manner that affects aging.

A polymorphism in human p53 that improves survival in spite of enhanced cancer risk

A polymorphism in human p53 supports the notion that p53 can influence longevity independent of suppressing cancer, as suggested by some of the mouse models described above. In the human population, the p53 amino acid 72 can be either an Arg (most common) or Pro. Arg72 is better at inducing apoptosis than Pro72 (91). As expected, p53 Pro72 is associated with an increased cancer risk, but surprisingly is also associated with increased survival (92,93). Since cancer shortens life span, the increased survival supports the possibility that p53-mediated apoptosis has unintended consequences that lowers survival for people with p53 Arg72, possibly by limiting stem/progenitor cell pools. This observation is consistent with the mouse model that expresses N-terminally truncated p53, which shows early aging and lower levels of stem and progenitor cells (87-90).

Conclusions

p53 is a tumor suppressor that responds to numerous stresses to regulate a myriad of cellular outcomes that protect the organism by either cell maintenance or removal. This protection is best known in the light of tumor suppression, but might also have an impact on aging independent of cancer. Interestingly, p53's non-selected (not subject to evolutionary pressure) impact on aging might promote or inhibit aging phenotypes, depending on the genetic background and environment. Indeed, p53 both promotes and inhibits cellular senescence by inducing a reversible G_1 arrest that is a prerequisite for senescence and by inhibiting mTORC1-mediated growth and the SASP. p53-altered mouse models show diverse phenotypes with regard to aging, supporting the general notion that p53-mediated responses can result in contrasting biological outcomes with regard to aging.

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Footnote

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