

## p53, ROS and senescence in the control of aging

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**Abstract:** In addition to its function as a tumour suppressor, p53 is also involved in an increasing number of pathology associated with aging. Several activities of p53 appear contribute to its role in aging; one function that might be particularly relevant in this context is the regulation of senescence. The control of ROS and senescence by p53 may help to explain how p53 can function to both restrain and promote aging.

p53 functions as a longevity assurance gene (by virtue of its strong tumor suppressor activity) and a regulator of aging. In several mouse models, persistent low-level activation of p53, either through deregulated expression of p53 itself or in response to constitutive stress like DNA damage/telomere erosion, leads to premature aging [1,2]. However, mice with normal basal p53 levels that have been engineered to show a heightened ability to mount a p53 response show a very strong resistance to tumorigenesis without evidence of premature aging [3]. Indeed, in several of these models a decreased level of aging related damage is observed, indicating that p53 may also help to promote longevity. The control of aging reflects numerous activities of p53, including the modulation of the IGF1R pathway through interplay between full-length p53 and N-terminally truncated splice variants of p53 [4] and the ability of p53 to restrict stem cell function [5]. p53 is also a key regulator of senescence, a central stress response that plays an important role in tumour suppression, but may also help to promote cancer development by inducing an inflammatory response [6]. The ability to control senescence is consistent with p53's function in restraining cancer development, but can the mechanisms through which p53 regulates senescence also contribute to the control of aging?

Induction of senescence by p53 is associated with the regulation of p53-dependent genes that can participate in cell cycle arrest. While depletion of these components can impact senescence induction – supporting their role in mediating this response – the inhibition of cell cycle progression alone does not explain how this arrest can be turned into the definitive and permanent proliferation block that is characteristic

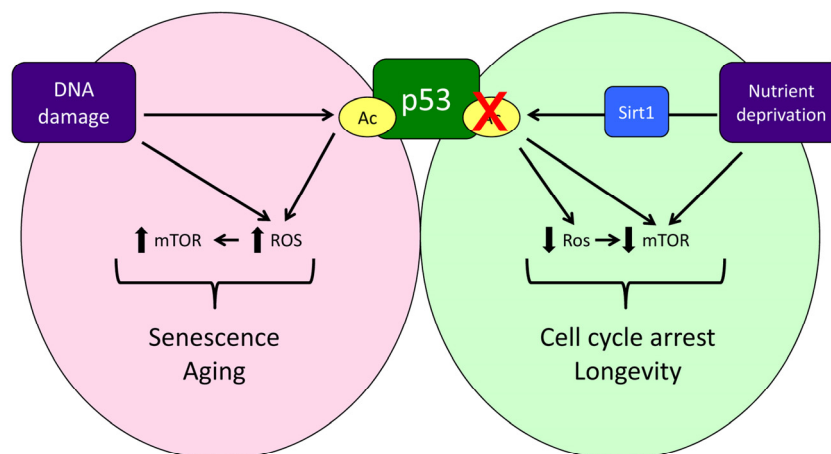
of senescence. Furthermore, despite the clear documentation of p53's ability to induce senescence, more recent evidence shows that p53 can also function to inhibit senescence while promoting cell cycle arrest [7]. So how can p53 both suppress and promote senescence? An important component of this may be the ability of p53 to control cell growth and metabolic stress through different pathways, including the regulation of ROS levels and the activity of mTOR (Figure 1). The ability of p53 to promote ROS production has been shown to participate in the induction of apoptosis by p53 [8]. But ROS are also known to be critical for senescence [9] and the p53 target genes that increase ROS may also play an important role in senescence induction. However, p53 also promotes the expression of a number of antioxidant genes, accounting for p53's ability to control oxidative stress in cells and mice [10]. So p53's ability to decrease and increase oxidative stress likely contributes to its dual effect on senescence. Another factor that influences the outcome to p53 activation is mTOR. While mTOR is normally associated with cell growth, activation of mTOR can contribute to and be essential for certain types of senescence [11,12], and the maintenance of mTOR signalling under conditions of cell cycle arrest leads to senescence in cultured cells [13]. p53 inhibits the mTOR pathway at several levels [14], contributing to the anti-senescence activity of p53 [15]. Furthermore, mTOR can be activated by ROS [16], so p53's antioxidant activities may reinforce the dampening of mTOR and senescence (Figure 1).

One of the main responses to mTOR inhibition is the induction of autophagy, a response that allows survival

under conditions of nutrient deprivation. There are several possible links between autophagy and senescence. Inhibition of autophagy results in the accumulation of protein aggregates, ER stress and mitochondrial dysfunction, each of which could promote senescence. However, other studies suggest that autophagy may be required for an efficient senescence response [17]. In either case, the ability of p53 to both enhance and inhibit autophagy [18] provides a further mechanism for the modulation of senescence.

The activity of p53 is regulated through many mechanisms, but of particular interest with respect to the control of senescence and aging is a role for the histone deacetylase Sirt1, whose expression is strongly down regulated in senescent cells [19]. In contrast nutrient deprivation, which inhibits mTOR and can impede cellular senescence [13], has been shown to increase Sirt1 levels [20]. One way in which Sirt1 functions is to deacetylate p53, modulating p53 activity and decreasing senescence [21]. Deacetylation inhibits p53's ability to transcriptionally activate some, but not all, target genes - including those involved in apoptosis

induction, ROS production [22,23], and presumably also senescence (Figure 1). The presence of a chronic DNA damage response (as may be seen in cancer cells), which is linked to the induction of senescence [24], can directly increase p53 acetylation by inducing the phosphorylation of the N-terminus of p53 and so promoting the interaction with the acetyl transferases CBP/p300. Mouse models have shown that expression of phosphorylation resistant p53 inhibits the induction of senescence [25], while cells harbouring p53 with acetyl-mimicking mutations of the last seven lysine residues have an accelerated entry into senescence and are very resistant to senescence bypass [26], although the cell cycle arrest response in these cells remains normal. Phosphorylation and acetylation of p53 is also seen to be important during Ras-induced or replicative senescence [27,28]. Under these circumstances, it would seem that deacetylation of p53 by Sirt1 impedes the induction of senescence, as well as apoptosis. Taken together there is good evidence that acetylation of p53 promotes senescence and apoptosis, so inhibitors of the deacetylation enzymes might be useful drugs for the reactivation of these p53 responses for cancer therapy [29].



**Figure 1. A model of how acetylation, oxidative stress and mTOR activity might influence the response to p53.** Note that this model does not account for all published observations (e.g. reduction of the initial burst of mTOR activity during oncogene induced senescence [17]) and represents an oversimplification of these signalling pathways.



