

## **p53 tumor suppressor: Regulation of transient cell cycle arrest and/or terminal silencing**

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Ageing is a complex and multifactorial process that involves not only a decline in the metabolic efficiency of various cells and tissues but may also predispose organisms to altered responses to environmental stressors. There is evidence that cells accumulate damage over a lifetime which induces a gradual reduction of growth rate and impairment of functions of the cells. Wild-type (wt) p53 protein, product of a tumour suppressor gene, responding to a variety of cellular and environmental stresses is known to induce either transient cell cycle arrest or apoptosis, thereby, preventing cancer development. However, increased wt p53 activity is also able to induce a terminal cell cycle arrest in cultured cells defined as senescence as well as organismal ageing.

In normal unstressed cells wt p53 protein is maintained at low levels. Under stress conditions distinct signaling pathways can be activated that directly target p53 for post-translational modifications and increase its stability resulting in the nuclear accumulation of wt p53 protein. Upregulated p53 protein induces a cell cycle arrest. The induction of a cell cycle block at G<sub>1</sub> and G<sub>2</sub> by p53 provides additional time for the cell to repair genomic damage before entering the critical stages of DNA synthesis and mitosis. However, in tissues where the stressors generate a severe and irrevocable damage, p53 can initiate apoptosis, thereby, eliminating damaged cells. Alternatively, wt p53 may mediate a terminal cell cycle arrest called senescence. Senescence observed in cultured cells is irreversible and is accompanied by enhanced p53 activity.

If wt p53 protein plays an essential role in regulating senescence, how might it perform these functions? It seems that a few additional proteins may regulate the stability and activity of wt p53 protein known to accelerate the process of ageing.

One of the putative candidates is hSIR2 (SIR1), the human homologue of the *S. cerevisiae* Sir2 protein known to be involved in cell ageing. hSIR2, an NAD-dependent deacetylase binds and deacetylates the p53 protein with a specificity for its COOH-terminal Lys382 residue, modification of which has been implicated in the transcriptional activation. Sir2 has been shown to enhance longevity if overexpressed. Inactivation of Sir2 conversely causes a reduction of the mean life span. A reduction of Sir2 mediated gene silencing with age leads to an increase in the generation of extrachromosomal rDNA circles, which appear to shorten the life span.

On the other hand, poly ADP-ribose) polymerase 1 (PARP-1) which contributes to the regulation of the intracellular NAD level may directly control the activity of SIR2 and the transcriptional competence of p53 protein and may additionally regulate the basal level of wt p53 in ageing cells. It has been shown that PARP-1 enhances the stability of wt p53 protein in unstressed cells. Inactivation of PARP-1 by gene disruption results in a pronounced reduction of p53 half-life. PARP-1 directly binds the COOH-terminal domain of wt p53 and masks the nuclear export signal (NES), thereby, preventing nuclear exclusion and degradation of p53 protein. In the absence of functional PARP-1 p53 is rapidly exported and proteolytically processed.

Thus, the evidences that hSIR1 and PARP-1 directly modulate p53 activity and stability raise the intriguing concept that they may affect longevity in mammals, at least partially, through a p53-dependent pathway. Mouse models of organismal senescence support the idea that wt p53 may in part regulate the longevity of organisms.