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Understanding the role of p53 in cancer

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Our main goal is to elucidate the biochemical and biological processes that underlie the activity of the p53 tumor suppressor protein. Within this frame we are also interested in the mdm2 gene - an oncogene whose protein product serves as the main negative regulator of p53 within living cells.

The p53 gene is mutated in about half of all human tumors. p53 is a transcription factor whose activity gives rise to a variety of cellular outcomes, most notably cell cycle arrest and apoptosis, eliminating cancer-prone cells from the replicative pool. Usually, p53 protein is present within a cell in minute amounts. It is very labile, with a half-life sometimes as short as a few minutes. The Mdm2 oncoprotein binds to the N-terminus of p53 and represses its transcriptional activity. Most notably, Mdm2 promotes the ubiquitination and rapid degradation of p53. Upon genotoxic and other stresses, p53 levels increase, mainly through post-translational modifications, as well as through altered protein-protein interactions, which increase the half-life of p53.

Upon DNA damage, p53 is phosphorylated on multiple residues. We found that following treatment of cells with ionizing radiation, Mdm2 also undergoes rapid phosphorylation by the ATM kinase. The phosphorylated Mdm2 is less able to promote p53 degradation. Our findings imply that, in response to DNA damage, ATM promotes p53 stability and activity by mediating the simultaneous phosphorylation of both partners of the Mdm2-p53 negative autoregulatory loop.

Activated oncogenes also affect p53 activity. Interestingly, we found that deregulated excess activity of β-catenin induces accumulation of active p53. This occurs through induction of another tumor suppressor protein - ARF- by the deregulated β-catenin. As a consequence, excess β-catenin triggers a p53-dependent growth inhibitory response. Aberrant accumulation of nuclear β-catenin has been documented in a variety of human tumors, including colorectal cancer. We propose that aberrant activation of β-catenin, which happens in initial stages of colorectal carcinogenesis, may alert p53 and increase its anti-proliferative activity. This would provide a safeguard against oncogenesis, imposing a selective pressure for mutational inactivation of either ARF or p53 itself. Indeed, in the absence of either ARF or p53, β-catenin exerts prominent oncogenic effects in tissue culture transformation models.

The ARF protein itself is also likely to be subject to extensive regulation within living cells. As a first step towards understanding the exact roles and regulation of ARF, we have purified ARF-binding proteins. Several of these proteins have been identified, and are presently being characterized in more detail.

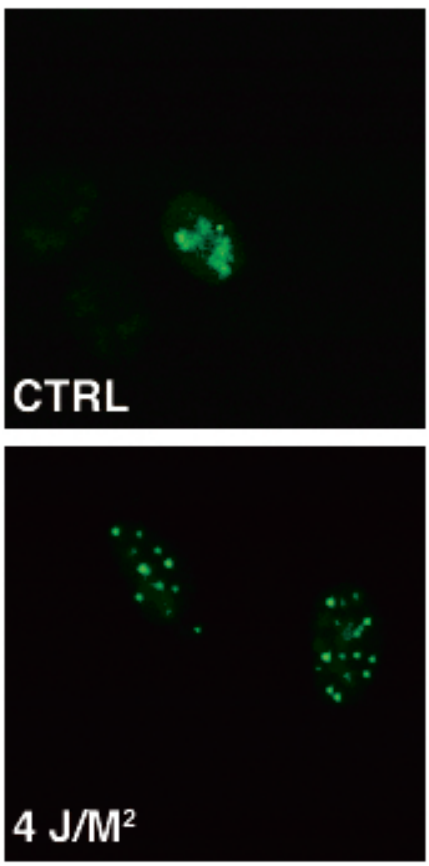

Fig. 1 *UV causes redistribution of WRN protein from the nucleolus to nucleoplasmic foci. Cells were transfected with a plasmid encoding a GFP-WRN fusion protein, and either irradiated with 4J/m2 of UV, or left untreated (CTRL).*

Numerous studies have suggested that p53 plays an important role in the orchestration of replicative senescence. Werner syndrome is a premature aging disorder. Mutations in the wrn gene predispose to accelerated aging. We found that WRN protein interacts specifically with p53. Importantly, the activation of p53 by several types of DNA damaging agents is impaired in cells of Werner syndrome patients. Moreover, the WRN protein itself is dramatically affected by DNA damage, and changes its intracellular localization from the nucleolus to nucleoplasmic foci (Fig. 1). These findings support the existence of a cross-talk between WRN and p53, which may be important for maintaining genomic integrity and for preventing the accumulation of aberrations that can give rise to premature senescence and to cancer.

All this places p53, along with its negative regulator Mdm2, at the heart of a regulatory network (Fig. 2), aimed at assuring an effective response against cancer-promoting processes.

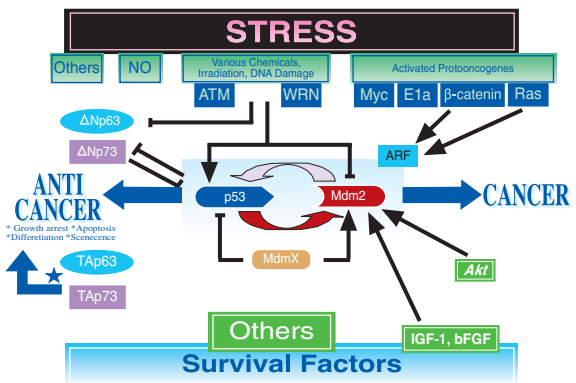

Fig. 2 *The p53 network. p53 induces mdm2 gene transcription, whereas Mdm2 inactivates p53. The p53-Mdm2 module serves as an integration hub for a variety of incoming signals. Arrows indicate positive inputs; horizontal bars indicate inhibitory inputs.*

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Acknowledgements

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