Untangling the p53 Network

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The tumor suppressor p53 acts to eliminate cancer-prone cells from the replicative pool. It sits at the junction of an extremely complex network of cellular signaling since different input signals such as oncogene activation, DNA damage, mitotic impairment or oxidative stress must be assimilated by p53 to initiate the correct cellular response including DNA repair, cell cycle arrest, senescence or apoptosis.

In non-stressed conditions, the rapid turnover of p53 is predominately due to the antagonistic action of the Mdm2 oncogene. Mdm2 is an E3 ubiquitin ligase that binds specifically to p53 and promotes the ubiquitination and proteasomal degradation of p53. Mdm2 is also a target of p53 transcriptional activity, thus defining a negative feedback loop. Numerous proteins affect the p53 pathway by influencing Mdm2 activity. For this reason, our laboratory performed a yeast two-hybrid screen in order to identify novel Mdm2 interacting proteins. One such Mdm2 interacting protein is the tumor suppressor Lats2. We showed that Lats2 mediates a p53-dependent growth arrest in response to mitotic stress in order to prevent the accumulation of potentially tumorigenic tetraploid cells. Another Mdm2 interactor that we uncovered is the ribosomal protein L26. L26 functions in a dual pro-p53 manner to augment cellular p53 levels and activity; binding to Mdm2 to interfere with its ability to downregulate p53 and also binding directly to p53 mRNA to enhance its translation.

Approximately half of all cancers bear p53 gene mutations, the vast majority of which impair its ability to act as a sequence-specific transcriptional activator. This underscores the important role of p53's transcriptional targets in tumor prevention. In an effort to understand the contribution of different p53 response genes, our laboratory is currently working to demonstrate that p53 regulates the expression of several antioxidant genes in response to mitochondrial oxidative stress. This may prevent the accumulation of reactive oxygen species (ROS) and protect DNA from ROS-induced mutations. Moreover, supervision of ROS levels by p53 may have a more universal function, beyond tumor suppression, in promoting cell survival of noncancerous cells.

In addition to regulating the expression of a multitude of protein-coding mRNAs, p53 also modulates the trancription of microRNAs (miRs). MiRs are small RNAs that mediate posttranscriptional gene silencing through translation inhibition or mRNA degradation. Specifically, p53 can directly drive the expression of miR-34a. miR-34a promotes apoptosis, at least partially via inactivation of Bcl-2 expression. Hence, miR-34a is a direct proapoptotic transcriptional target of p53 that can mediate some of p53's biological effects. Perturbation of miR-34a expression, as occurs in some human cancers, may thus contribute to tumorigenesis by attenuating p53-dependent apoptosis.

Beyond acting within a single cell to prevent tumerogenic transformation, p53 can also exert effects that contribute to tumor suppression in neighboring cells (non-cell-autonomous effects). Our laboratory recently reported that p53 represses the transcription of the chemokine SDF-1. SDF-1 produced by stromal fibroblasts promotes the migration and invasiveness of tumor cells that express its cognate receptor, CXCR4. We propose that this may represent a mechanism by which p53 exerts a non-cell-autonomous tumor suppressor function.

As mentioned above, the p53 tumor suppressor gene is mutated in over half of all human cancers. This is considered a critical event in cancer development. Once p53 is mutated, the mutant p53 protein not only loses its tumor suppression activity, but it also acquires new oncogenic functions, manifested by accelerated growth and protection from apoptosis (mutant p53 "gain of function"). We found that mutant p53 can augment the transcriptional activity of a promoter carrying multiple Vitamin D receptor (VDR) response elements. Furthermore, we found that mutant p53 interacts physically with the VDR protein and increases its nuclear retention following Vitamin D3 treatment.

Since p53 primarily acts as a transcription factor, our laboratory is focused also on elucidating various universal mechanisms of transcriptional regulation. For instance, chromatin structure and histone remodeling have an immense effect on transcriptional output. We are directing efforts in our laboratory towards understanding epigenetic events that affect p53 transcription and transcription patterns in general.

Global transcription patterns are also being examined exploiting bioinformatic methodology. For instance, we are investigating the potential crosstalk between miRs and molecular mechanisms that regulate gene expression at the transcriptional and posttranscriptional levels. These regulatory networks portray several recurring architectures, a common one being transcription factors and miRs that together regulate a large set of common genes and that also regulate one another. Another computational project analyzes the meaning and regulation of noise in transcription regulatory networks. Biological circuits need to be sensitive to changes in environmental signals but at the same time buffer rapid fluctuations (noise) that might be imposed on this input. We are analyzing the interplay between sensitivity to signals and the ability to buffer noise in different network motifs.

Selected publications

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