Untangling the p53 network

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p53 is a tumor suppressor protein capable of eliminating cancer-prone cells from the replicative pool. Our main goals are:

1. To elucidate the biological and molecular processes that underlie the activation of p53 functions.

2. To elucidate the outcome of p53 activation in cellular and molecular terms.

Within this frame, we are particularly interested also in the Mdm2 protein, the product of an oncogene, which can negatively regulate p53. Mdm2 ubiquinates p53 and promotes its degradation. As shown in Figure 1, p53 and Mdm2 are components of an intricate signaling network. This network can promote p53-dependent transcriptional activation which, depending on the specific genes activated by p53, can lead to one of a variety biological outcomes. Some of the frequent biological outcomes following cellular stress are growth arrest and apoptosis. We are also interested in other outcomes such as regulation of the levels of reactive oxygen species (ROS). Thus, we have identified a novel target of p53, the AIF gene, which helps to maintain low ROS levels under normal conditions, but facilitates p53-dependent apoptosis under severe stress. Regulation of ROS levels by p53 may serve a dual role: cytoprotection and growth advantage on the one hand, and elimination of undesirable cells on the other hand.

Different types of stress can result in activation of p53 (Figure 1) via distinct molecular pathways. Many of these pathways culminate in inactivation of Mdm2, often through protein-protein interactions, e.g. the well-documented ARF-Mdm2 interaction. A yeast two-hybrid screen has enabled us to identify novel Mdm2 interacting proteins, intensifying our understanding of the p53-Mdm2 network. Thus, we found that Lats2, a tumor suppressor in its own right, can associate with the central domain of Mdm2, leading to Mdm2 inactivation and thus to p53 activation. Lats2 mediates a p53-dependent growth

Fig. 1 Selected events in the network regulating p53 and subsequent biological outcomes. In this scheme of the p53 network, red arrows indicate transcriptional activation events; the red blocked arrow indicates repression of transcription; green blocked arrows indicate protein-protein interactions with Mdm2 which lead to the repression of the ability of Mdm2 to promote the degradation of p53; blue blocked arrows indicate inhibitory activities promoting degradation; blue lines indicate ubiquitination events; light blue blocked arrow indicates an inhibitory RNA:RNA interaction.
arrest following mitotic machinery stress (G1 tetraploidy checkpoint). Furthermore, Lats2 is a transcriptional target of p53, Thus Lats2, Mdm2 and p53 constitute a fragmented feedback loop most likely designated for optimizing the p53 response to mitotic machinery stress.

We also identified additional Mdm2-interacting proteins, including two ribosomal proteins. While several other ribosomal proteins have been reported to interact with Mdm2 and activate p53 following ribosomal stress, one of our ribosomal proteins can be ubiquitinated by Mdm2 and therefore may be regulated by it. Another novel Mdm2 interactor is a protein residing in the endoplasmatic reticulum (ER). Mdm2 can promote the degradation of this protein. Therefore, it is likely that under stress conditions Mdm2 may influence additional pathways. We are currently examining the possibility that the additional effects of Mdm2 serve to optimize the p53 response.

While protein-protein interactions are well documented in determining the balance between p53 and Mdm2, we have obtained evidence for regulation also at the RNA level. Thus, we have identified an antisense transcript complementary to the Mdm2 transcript. Surprisingly, like the Mdm2 sense transcript, the antisense transcript can also be regulated by p53. Given the anticipated role of this antisense transcript in down regulation of Mdm2, we are currently investigating its importance in maintaining an optimal ratio between Mdm2 and p53 following the onset of cellular stress.

A major ongoing effort is directed towards understanding the role of p53 in modulating transcription. We are studying the potential role of p53 in regulation of genes encoding micro RNAs, and are also testing the p53-dependent transcription profile at distinct cell cycle stages. Furthermore, to better understand the impact of p53 phosphorylation on its transcriptional activation potential, we intend to perform a functional screen with a combinatorial library of p53 phosphorylation site mutants. Finally, we are also addressing the role of p53 and p63 (an additional member of the p53 family) in the cross-talk between tumor cells and host tissues, and particularly the tumor stroma. In this context, we found that stromal p53 may regulate cancer cell migration. The mechanism and biological significance of this finding are being currently investigated.

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