The p53 functional circuit

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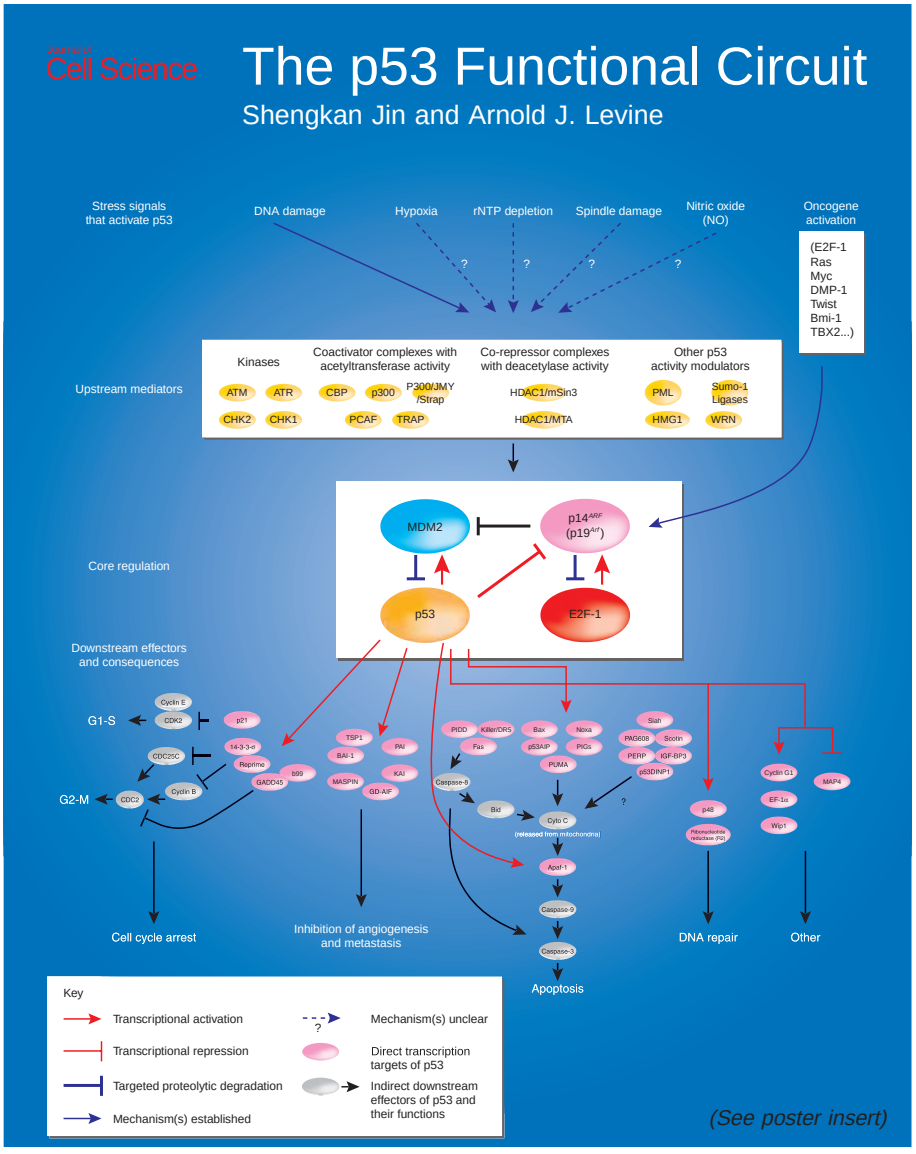
The *p53* gene is a tumor suppressor gene that plays a critical role in safeguarding the integrity of the genome. *p53* is mutated or part of its regulatory circuit is functionally inactivated in almost all cancers, which highlights its importance in preventing tumorigenesis. The p53 protein is a sequence-specific DNA-binding transcription factor that is kept at a low level in cells under normal circumstances. Various stress signals, such as DNA damage, can stabilize and activate p53. Upon activation, p53 binds to the enhancer/promoter elements of downstream target genes and regulates their transcription, through which it initiates cellular programs that account for most of its tumor-suppressor functions.

The functional signal transduction circuit of p53 consists of the upstream mediators (which sense and relay stress signals to p53), the core regulation components (which form the core circuitry maintaining and regulating p53 levels) and the downstream effectors (which initiate cellular response programs).



The core regulatory circuitry consists of p53, Mdm2, $p14^{ARF}$ ($p19^{Arf}$ in the mouse) and E2F-1. These are organized into two interactive feedback loops. p53 and Mdm2 form one feedback loop, in which p53 positively regulates Mdm2 by activating *Mdm2* transcription, and Mdm2 negatively regulates p53 by promoting p53 ubiquitination and degradation. E2F-1 and $p14^{ARF}$ form a similar feedback loop, in which E2F-1 activates *ARF* transcription, and $p14^{ARF}$ facilitates proteolytic degradation of E2F-1. These two feedback loops are connected in two ways. First, $p14^{ARF}$ interacts with Mdm2, inhibiting Mdm2-mediated p53 ubiquitination and degradation, thereby stabilizing p53. Second, p53 represses transcription of the *ARF* gene. This complex circuit is essential for maintaining and regulating p53 intracellular levels and activities. Some aspects of this circuit are defective in all cancers. Missense mutations of *p53*, amplification of *MDM2*, silencing or deletion of *ARF* and/or the loss of E2F-1 regulation through *RB* mutation are the most common mechanisms by which tumor cells alter the circuitry.

Cellular stresses signal to p53 by perturbing the p53 core regulatory circuitry directly or indirectly. Several stresses activate p53, including DNA damage, oncogene activation, hypoxia, cellular ribonucleotide depletion, mitotic spindle damage and nitric oxide (NO) production. DNA damage activates p53 through p53 upstream mediators, which include protein kinases, transcriptional coactivator complexes with histone (protein) acetyltransferase activity, transcriptional co-repressor complexes with histone (protein) deacetylase activity, and other p53 activity modulators, such as Sumo-1 ligases, PML complex, Werner's Syndrome protein (WRN) and HMG-1 protein. Most of these upstream mediators target p53 for post-translational modification. For example, DNA damage activates the protein kinases ATM, ATR, CHK1 and CHK2, which in turn phosphorylate p53 and/or Mdm2. Phosphorylation of p53 and/or Mdm2 activates p53 through three mechanisms: (1) stabilizing p53 by disrupting p53-Mdm2 interaction; (2) regulating p53 transactivation activity; (3) promoting p53 nuclear localization. Activated p53 recruits transcriptional

coactivator or co-repressor complexes to the enhancer/promoter regions of its downstream target genes, facilitating or repressing their transcription, respectively. These transcription co-factor complexes can either acetylate or deacetylate p53 itself, which increases or decreases p53 stability and its DNA-binding affinity, respectively. In addition, another post-translational modification, sumoylation, of p53 appears to modulate p53 levels and activity. In contrast, oncogenes usually regulate p53 by altering transcription and/or activity of the *ARF* gene. For example, the oncogenes E2F-1, Ras, DMP1 and Myc enhance *ARF* transcription, whereas Twist, Bmi-1 and TBX2 downregulate it. The mechanisms by which other stresses activate p53 are not fully understood.

Upon activation, p53 in turn activates or represses the transcription of its downstream effector genes, through which it may trigger several cellular programs, including cell cycle arrest, apoptosis, inhibition of angio-genesis/metastasis, and DNA repair. p53 may induce G1-S arrest by activating p21, a CDK2 inhibitor, or it may trigger G2-M arrest by inducing 14-3-3σ, GADD45, Reprimo and b99, which leads to CDC2 inhibition. p53 induces apoptosis by activating many pro-apoptosis genes, which ultimately activate Apaf-1 and caspase 9 through several pathways. p53 can activate anti-angiogenesis genes such as *TSP1*, *BAI-1*, *MASPIN*, *GD-AiF* and anti-metastasis genes such as *KAI*. p53 can also activate genes involved in DNA repair, including *p48* in the nucleotide excision repair (NER) pathway and non-S-phase ribonucleotide reductase (R2). Finally, p53 can activate or repress genes that have undefined functions. Among these are those that encode cyclin G, EF-Iα, Wip1 and Map4. Different types of cellular stress in cells of different tissue types appear to regulate different transcriptional programs by activating a subset of these genes and their products.

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