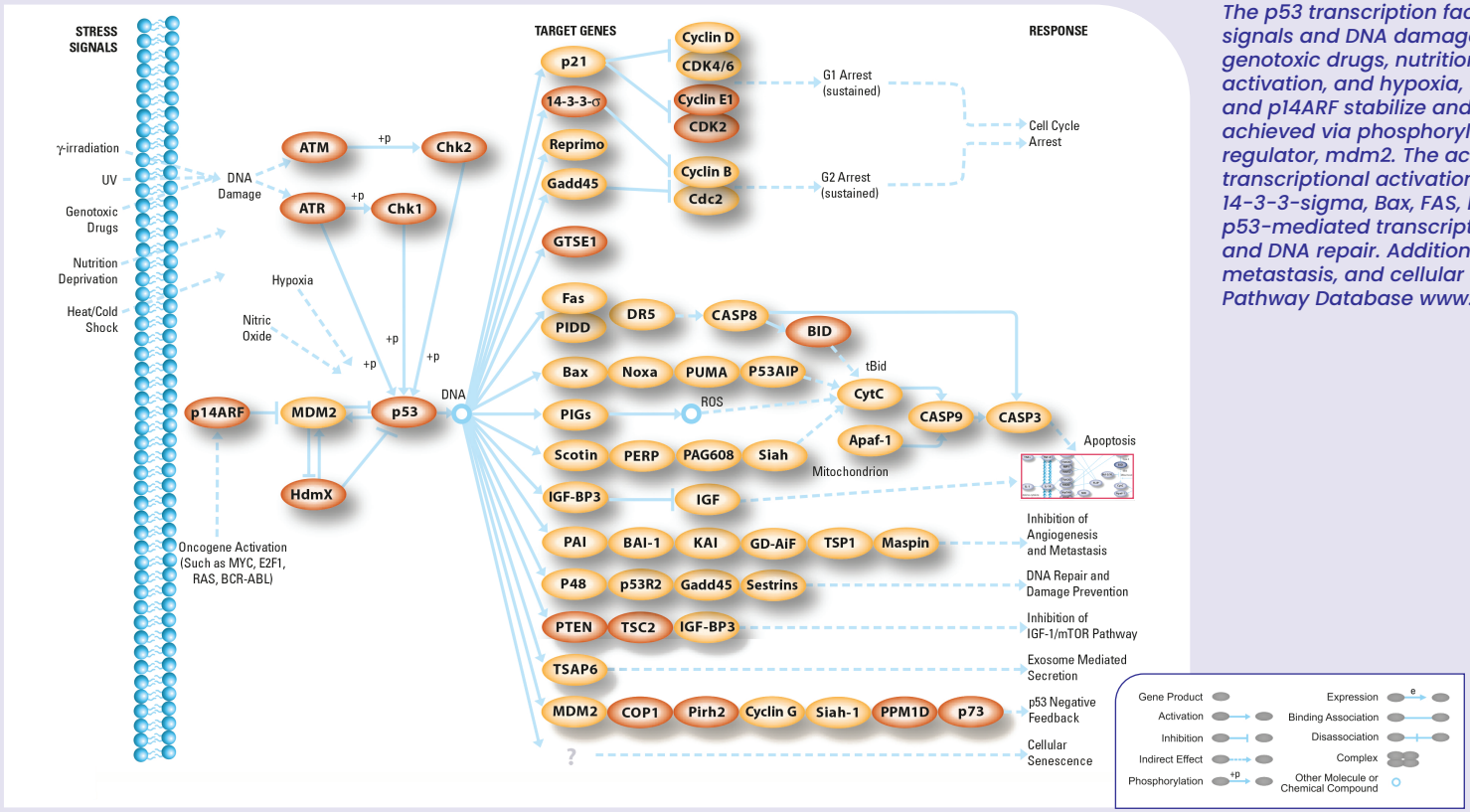
p53 PATHWAY

Due to its status as the most frequently mutated gene in human cancer, p53 is one of the most extensively studied proteins. Although not completely understood, much detail is known about the structural and functional characteristics of p53 as well as the upstream pathways and associated proteins which regulate its activity. p53 function is regulated on two fronts: protein stability, and transcriptional activity (*reviewed in*[1]). Regulation of p53 takes place at the post-transcriptional level and relies on post-transcriptional modifications of p53 as well as its major regulator, Mdm2. The major post-translational modification that occurs in response to genotoxic stress signals and oncogene activation is phosphorylation of p53. Phosphorylation is mediated by ATM/ATR, Chk1, Chk2, Jun NH-2 terminal kinase (JNK), p38, and other kinases. The phosphorylation of p53 influences both its activity and stability. Phosphorylation is also important to the activity of Mdm2. In unstressed cells Mdm2 functions as an E3-ligase and negatively regulates p53 activity by targeting p53 for ubiquitin-dependent degradation. In response to stress, Mdm2 is posttranslationally modified via de-sumoylation and phosphorylation resulting in self-ubiquitination and degradation. Destabilization of the Mdm2-p53 interaction results in p53 stabilization. Several other proteins regulate the stability of p53 by influencing the interaction between p53 and Mdm2 such as Mdm4 (HdmX) and p14ARF. Mdm4 (HdmX) regulates p53 by inhibiting its transactivational activity; p14ARF interacts with MDM2 and restricts MDM2-mediated degradation of p53. Once stabilized in response to stress or DNA damage, p53 activates transcriptional programs that promote cell cycle arrest, apoptosis, or DNA repair. The importance of p53 as the guardian of the genome and its role in the protection from cancer has become clear. Modulation of the pathways which regulate the stability and activity of p53 will be key to the development and application of successful cancer therapies (*reviewed in*[2]).

References

1. M. F. Lavin and N. Gueven, Cell Death. Differ. 13, 941-950 (2006).
2. A. Dey, C. S. Verma, D. P. Lane, Br.J Cancer. 98, 4-8 (2008).

The p53 gene is the prototypic tumor suppressor gene and is referred to as the "guardian of the genome". Mutations in the p53 gene have been found in about half of human cancers demonstrating its importance in the protection from cancer.



The p53 transcription factor mediates responses to genotoxic stress signals and DNA damage. In response to gamma- and UV-irradiation, genotoxic drugs, nutrition deprivation, heat and cold shock, oncogene activation, and hypoxia, upstream regulators of p53 such as ATM, Chk2, and p14ARF stabilize and activate p53. p53 stabilization and activation is achieved via phosphorylation of p53 and the dissociation of its negative regulator, mdm2. The accumulation and activation of p53 results in the transcriptional activation of a number of target genes such as p21, 14-3-3-sigma, Bax, FAS, IGF-BP3, Mdm2, and PTEN. The responses of p53-mediated transcription mainly include cell cycle arrest, apoptosis, and DNA repair. Additional responses can include angiogenesis, metastasis, and cellular senescence. (Figure adapted from the KEGG Pathway Database www.genome.jp/kegg/pathway/hsa04115.html).

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