

Cancer Lab p53 – Teacher Background on p53 Tumor Suppressor Protein

Note: The Teacher Background Section is meant to provide information for the teacher about the topic and is tied very closely to the PowerPoint slide show. For greater understanding, the teacher may want to play the slide show as he/she reads the background section. For the students, the slide show can be used in its entirety or can be edited as necessary for a given class.

What Is p53 and Where Is the Gene Located?

While commonly known as p53, the official name of this gene is Tumor Protein p53 and its official symbol is TP53. The *TP53* gene codes for the TP53 (p53) protein which acts as a tumor suppressor and works in response to DNA damage to orchestrate the repair of damaged DNA. If the DNA cannot be repaired, the p53 protein prevents the cell from dividing and signals it to undergo apoptosis (programmed cell death). The name p53 is due to protein's 53 kilo-Dalton molecular mass. The gene which codes for this protein is located on the short (p) arm of chromosome 17 at position 13.1 (17p13.1). The gene begins at base pair 7,571,719 and ends at base pair 7,590,862 making it 19,143 base pairs long. (1, 2)

What Does the p53 Gene Look Like When Translated Into Protein?

The *TP53* gene has 11 exons and a very large 10 kb intron between exons 1 and 2. In humans, exon 1 is non-coding and it has been shown that this region could form a stable stem-loop structure which binds tightly to normal p53 but not to mutant p53 proteins.

The *TP53* gene provides the base pair sequence from which to code for the tumor protein p53, which is 393 amino acids long. The gene codes for a protein which contains several different domains which include:

- a) a transactivation domain at the amino (N) - terminus which activates transcription followed by a proline-rich segment.
- b) The proline-rich domain mediates the p53 response to DNA damage through apoptosis. A common polymorphism is the substitution of an arginine for a proline at codon #72 but it isn't clear if this substitution is related to cancer or not.
- c) The core domain is the DNA-binding domain and is the section of the protein that recognizes specific DNA sequences so it can bind to the DNA.



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d) It is followed by the tetramerization domain and consists of a beta-strand, which interacts with another p53 monomer to form a dimer. This dimer formation is followed by an alpha-helix which mediates the dimerization of two p53 dimers to form a tetramer which is essential for activating p53.

e) The carboxyl (C) -terminus acts in a regulatory role recognizing damaged DNA, such as misaligned base pairs or single-stranded DNA.

(1, 2, 3, 7)

How Does the p53 Protein Function?

Tumor protein p53 acts as a tumor suppressor and was identified in 1979 by Arnold Levine at Princeton University, David Lane at Dundee University (UK), and William Old at Sloan-Kettering Memorial Hospital. The p53 phosphoprotein is located in the nucleus of each cell and works to in response to DNA damage to orchestrate the repair of the damaged DNA. If the DNA cannot be repaired, the p53 protein prevents the cell from dividing and signals it to undergo apoptosis. (2)

p53 plays a central role in the coordination of cellular response to stress, such as exposure to UV radiation and reactive oxygen species (ROS). ROS are chemically reactive molecules containing oxygen, such as oxygen ions and peroxides. Other examples of stress are heat shock, viral infection, and nutrient depletion.

The *MDM2* gene is the target gene of the transcription factor p53 protein. The encoded MDM2 protein is a nuclear phosphoprotein that binds and inhibits transactivation by the p53 protein, as part of an auto-regulatory negative feedback loop. If *MDM2* gene is overexpressed, it can result in the excessive inactivation of the p53 protein and thus diminishing its functions. (8)

What Role Do Mutations in the p53 Gene Play in Causing Cancer?

About 50% of the cases of adult human cancers contain a mutation in the p53 gene. This includes point mutations (missense and nonsense) and insertions/deletions in the DNA of the gene. Changes in the DNA mean a transcription into mRNA and translation of that mRNA into a protein which is different than normal p53. With a different sequence of amino acids in this new protein, it will potentially fold improperly and function abnormally or not at all.

About 20% of the mutations in p53 are concentrated at 'hot-spot' codons, such as arginine (A) 175, 248, 249, 273, and 282 and glycine (G) 245, mostly in the DNA-binding domain. The most common mutation occurs at arginine 248 which normally forms a strong stabilizing interaction with DNA by fitting into the minor groove. With changes in amino acids at the DNA-binding sites, it means that the p53 protein won't be able to bind to the DNA to initiate repairs of damaged DNA and more importantly, won't be able to initiate apoptosis in cells with mutated or damaged DNA. There also will be no regulation of arresting cell division in the cells with mutated or damaged DNA. In patients in New England, 90% of squamous cell carcinomas and more than 50% of basal cell carcinomas contained UV-like mutations in the p53 tumor suppressor gene. These somatic mutations are differently encountered within the body. In some cases, differences in frequencies of mutations at a specific site may reflect an enhanced growth



advantage for a tumor in a particular tissue. For example, the mutation of p53 at amino acid 175 is common in colon cancer but is rarely seen in lung cancer. (6, 7, 9, 10)

Li-Fraumeni syndrome appears to be the only inherited syndrome associated with mutations in the p53 gene. There are more than 60 different mutations that have been identified in individuals with this syndrome. Since the mutation(s) is inherited from a parent, it appears in all of the body's cells, unlike someone who develops a somatic mutation in the p53 gene in a specific organ of the body. Inheritance is autosomally dominant so a person who inherits a PP or Pp genotype would be affected and a person who inherits the pp genotype would be normal. (P = mutated p53 gene and p = normal p53 gene). This syndrome was named after two physicians, Li and Fraumeni, who studied the pedigrees of families with cases of childhood sarcomas. They identified this syndrome in those families where one individual had a sarcoma, at least two immediate relatives had cancer before age 45, and multiple cancers, such as breast, brain, and leukemia, were found elsewhere in the family.

Cells of individuals with this syndrome usually have one normal p53 allele and one inherited mutated p53 allele. It is unclear in the scientific literature if one or two mutated genes are necessary to cause the cancerous growth. It could be that the normal gene makes enough p53 protein to repair the damaged DNA and until a mutation occurs in that gene, everything functions well enough. Or it could be that the one normal gene cannot keep up with the DNA damage and cancerous growths occur even when there is only one mutation. More research is necessary to fully understand. (1, 10)

What Other Tumor Suppressor Genes Are There?

In addition to p53, other tumor suppressor genes include *APC*, *BRCA1*, *BRCA2*, *p16*, *p21*, and *RB*. Other DNA repair genes include *BLC2* and *XP*. Each gene is named after the cancer it causes if mutated. For example, *APC* stands for Adenomatous Polyposis Cancer (also known as Familial Adenomatous Polyposis or FAP) which causes colon cancer; *BRCA1* and *BRCA2* stand for Breast Cancer Susceptibility Genes 1 and 2; *RB* stands for Retinoblastoma, a cancer of the eye; *BLC2* stands for B-cell lymphoma 2; and *XP* stands for Xeroderma Pigmentosum, a skin cancer. Mutations in any of these genes can cause the associated cancer or disease.

Bibliography

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