

The Role of the p53 Gene in Apoptosis and Cancer

p53 Gene and Apoptosis

1. Activation of the p53 Gene in some cells initiates Apoptosis: programmed cell suicide (fig. 1, below and on the left of fig. 2 page 2)
 - p53 is Activated by
 - a. Damage to DNA, e.g. radiation
 - b. Cellular invasion, e.g. Viruses
 - c. Normal chemical signals during embryonic development
 - Apoptosis helps to prevent the reproduction of genetically damaged cells
2. **Apoptosis** removes unneeded cells when activated by normal chemical signals during development (on the left in fig. 2 on page 2). Some examples....
 - Tail of tadpole during metamorphosis
 - Webbing between fingers during human embryonic development
 - Human lens during embryonic development
 - Human skin cells
 - Uterine lining during menstruation

p53 Gene as a Tumor Suppressor Gene

3. In some cells the p53 gene acts as a **Tumor Suppressor Gene** (in the middle in fig. 2 on page 2)
 - The “normal” p53 gene product inhibits cells from proceeding from the G₁ or G₀ phases of the cell cycle to the “S” phase of the cell cycle
 - Helps to regulate the cell cycle—i.e. acts as the “brakes” to keep cells from dividing unnecessarily
4. **Mutant p53 gene** (on the right in fig. 2 on page 2)
 - Mutant gene product does not stop a cell from proceeding from G₁ or G₀ phases of the cell cycle to the “S” phase of the cell cycle
 - May lead to _____?

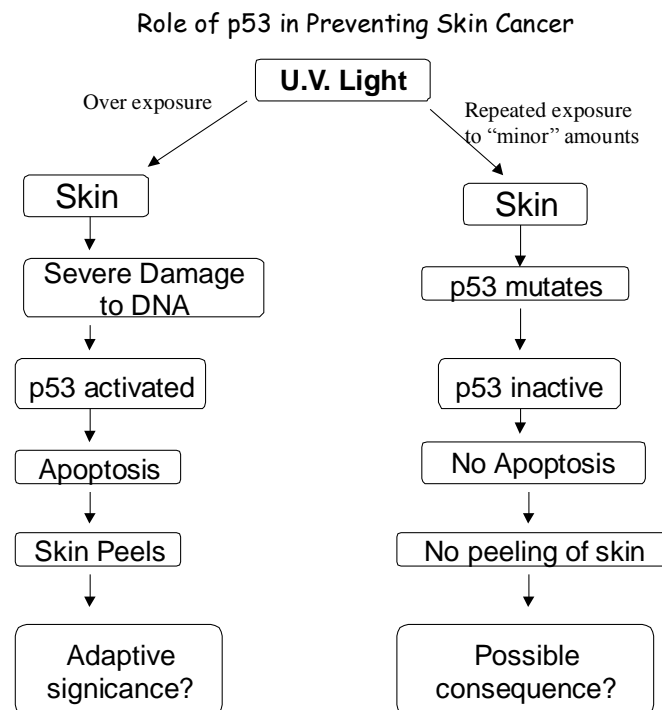


Figure 1. The role of the p53 gene in apoptosis and in helping to prevent skin cancer.
Adapted from *Scientific American*, 9/96

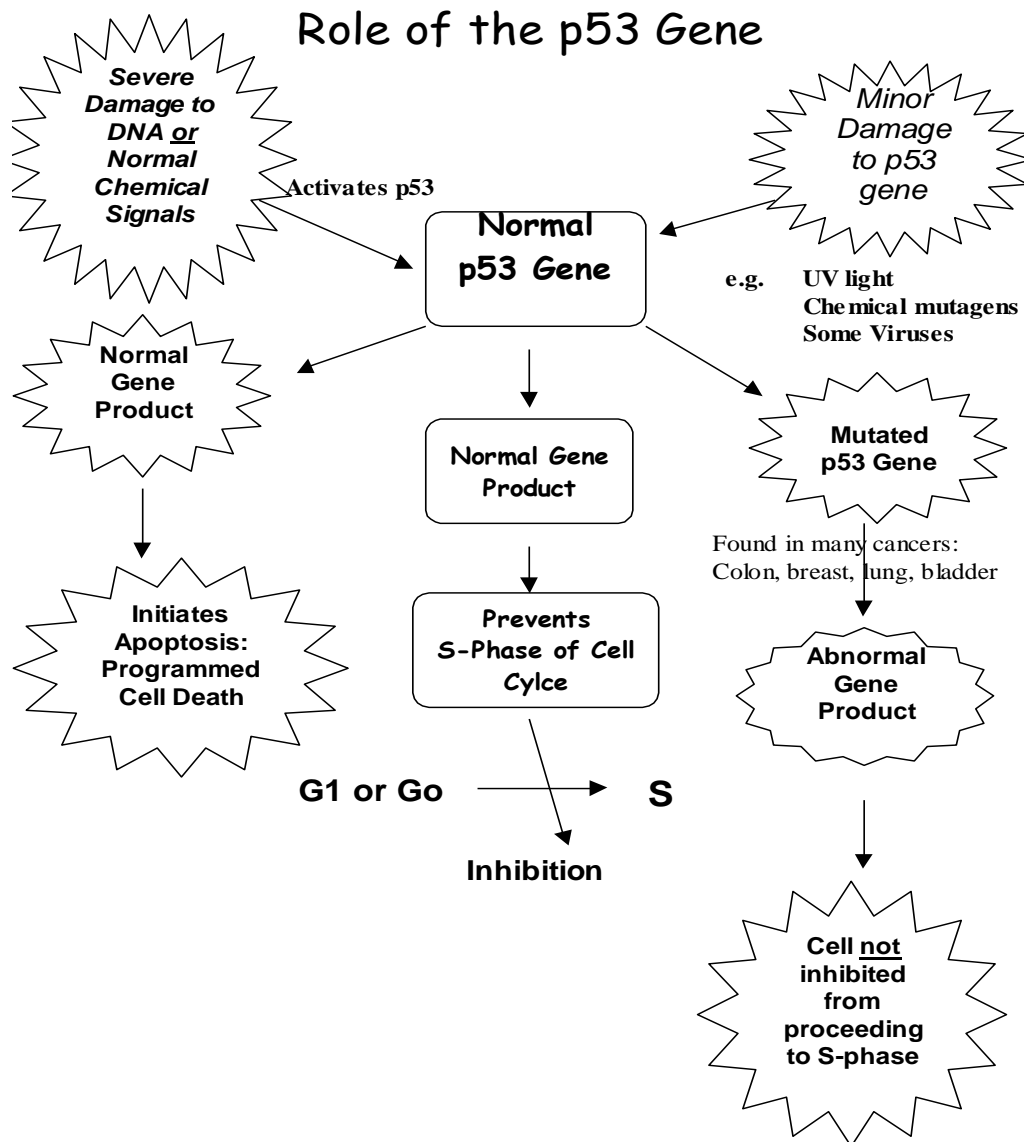


Figure 2. The role of the p53 gene in apoptosis and as tumor suppressor gene. Adapted from *Scientific American*, 9/96

Self-Test Questions

p53 Gene and Apoptosis:

1. List the three major things that activate the p53 gene to initiate apoptosis (cell suicide).
2. What roles do the p53 gene and apoptosis play in helping to prevent skin cancer?
3. Explain why the over-exposure to UV light causes a person's skin to peel. Of what adaptive value does the peeling of skin have?
4. What effect might repeated exposure to UV light have on the p53 gene? What are the possible consequences of this? Why?
5. What is the role of the p53 gene in removing unneeded cells during embryonic development?

The p53 Tumor Suppressor Protein

The **p53 gene** is a **tumor suppressor gene**, i.e., its activity stops the formation of tumors. If a person inherits only one functional copy of the p53 gene from one of their parents, they are predisposed to cancer and usually develop several independent tumors in a variety of tissues in early adulthood. This condition is rare, and is known as Li-Fraumeni syndrome. However, mutations to the p53 gene are found in most tumor types, and so contribute to the complex network of molecular events leading to tumor formation.

The p53 gene has been mapped to chromosome 17. In the cell, **p53 protein** binds DNA, which in turn stimulates another gene (the p21 gene) to produce the **p21 protein**, a protein that interacts with a cell division-stimulating protein (cdk2). When p21 forms a complex with cdk2 the cell cannot pass through to the next stage of cell cycle. A **mutant p53** can no longer bind DNA in an effective way, and as a consequence the p21 protein is not made available to act as the '**stop signal**' for cell division. Thus cells divide uncontrollably, and form tumors.

Help with unraveling the molecular mechanisms of cancerous growth has come from the use of mice as models for human cancer, in which powerful 'gene knockout' techniques can be used. The amount of information that exists on all aspects of p53 normal function and mutant expression in human cancers is now vast, reflecting its key role in the pathogenesis of human cancers. It is clear that p53 is just one component of a network of events that culminate in tumor formation.

Source (accessed 11-12-09):

<http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gnd&part=thep53tumorsuppressorprotein>

Self-Test Questions

P53 Gene as a Tumor Suppressor Gene

6. Test your knowledge about the mechanism behind how the p53 acts as a tumor suppressor gene by completing the following sequence of events.

Activation of _____ gene on Chr 17 → _____ produced → _____ gene activated → _____ produced → _____ complexes with cdk2 protein → cell _____

7. The p53 gene can thought of as the “brakes” or “stop signal” of the cell cycle. Explain how the p53 gene acts to suppress cells from going from the G₀ or G₁ phase of the cell cycle to the S-phase.
8. Why might a mutant (dysfunctional) p53 gene lead to cancer (e.g. cancer of the colon, breast, lung and bladder)?
9. Why does inheriting a mutant p53 gene drastically increase the chance of getting cancer?
10. Why must the must both “a” and “b” below happen within a normal cell for it to become a cancer cell?
- Both copies of the p53 gene mutate
 - The telomerase gene must be become active

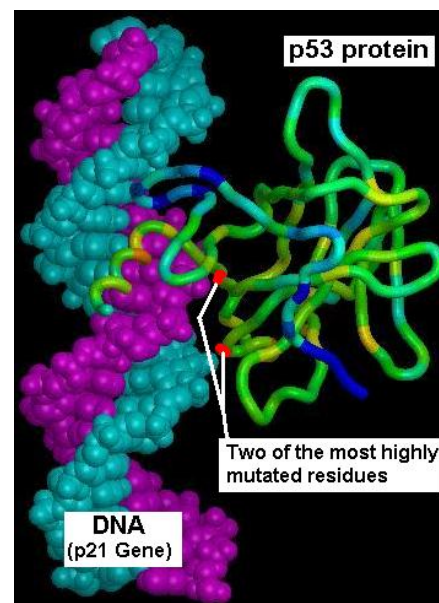


Figure 3. p53 protein bound to DNA. The p53 protein is color-coded according to frequency of observed mutations in tumors (blue, very few; red, many). Two of the most mutated residues are indicated.