

# [P53 gene and cancer relationship](https://assignbuster.com/p53-gene-and-cancer-relationship/)

In 1979, the protein p53 was discovered, binding to the SV40 (simian virus) large T antigen. However, because it was found excessively in its mutant form, it was initially believed to be an oncogene. Not until ten years later in 1989 was the protein determined to be major factor in tumor suppression. The p53 protein is encoded by the p53 gene located on chromosome 17 and binds directly to DNA. It is composed of 393 amino acids and has four main binding domains: the N terminus (1-43), the beginning of the chain that regulates gene expression, the DNA binding domain (110-286) that is associated with gene sequencing, the tetramerization domain (326-355) that regulates oligamorization, and the C-terminus (363-393), the end of the chain that appears to play a major role in the maintenance of p53.

In normal cells, p53 remains in a latent, standby mode stage with a very low half-life of about twenty minutes. It interacts with more than 150 other proteins, some that restrict its production and eliminates its excess. A major protein involved with it is mouse double minute-2 (MDM2). MDM2 binds to p53 as a tag for ubiquintination, or degeneration of it in the proteasome, which keeps the tumor suppressor at relatively low levels. Because MDM2 is also negatively regulated by p53, their relationship continues in a cycle, where both proteins keep one another in check. Another related protein is MDM4, which also lowers p53 but directly and not through ubiquintination.

P53 signaling is initiated by genotoxic stresses such as DNA damage, oncogene activation, hypoxia, ribosomal alterations, and temperature shock. Although each stress, along with its associated kinases, contain similarities in their response, each leads ultimately to varied pathways and cause the cell to interpret p53 in different ways. For example, the stresses of DNA damage and oncogene activation form distinct paths. DNA damage signals for ATM/ATR kinases for phosphorylation while oncogenes signal for ARK, which in return signals MDM2 for maintenance. ATM also activates the kinases CHK1 and CHK2.

When p53 is activated, it builds up in the nucleus and stimulates the production of another protein p21, which, in return, initiates the cell division-stimulating protein (cdk2) for cell arrest at G1/S or G1/M. The process is supported to give time for cell repair. When the cell has experienced repeated, excessive damage and is determined unfixable, the p53 protein signals it to perform apoptosis, programmed cell suicide, or senescence. Because of its wide, regulatory functions it has been given the nickname the “ guardian of the genome.”

Mutations of p53 are associated with approximately fifty percent of cancers, including those of the breast, bladder, lung, and neck. Seventy-three percent are missense mutations, ninety percent of which occur in the DNA binding domain.

Mutant p53 can have three general effects on wild-type p53. The most common is the dominant-negative effect, where the mutant attacks wild-type p53’s cell-moderating ability. Another is the null effect, where mutant p53 does not directly block wild-type formation. This effect occurs when the mutant protein is present in relatively low levels. The last is the dominant-positive effect, where the mutant displays a gain of function. An example would be its function of preventing DNA repair. Mutants with a gain of function can also suppress its family members p63 and p73 that play similar roles as transcription factors and tumor suppressors and similar structures. Such properties are shown to create much more lethal tumors than those of null p53.

Mouse models are considered great help in p53 investigations because they demonstrate similar gene expression patterns to those of humans. Thus, observing how lack, mutation, or excess p53 in them can give researchers a general idea on how p53 functions within actual people. Models include knock-out, knock-in, over expression, and crossed. Knock-out models exclude the p53 gene or its family members while knock-in models include the p53 gene or its family members. Over expression amplifies the gene, and crossed intermingles the gene with another.

The protein’s role in cell moderation has given it much recognition in cancer chemotherapy and target research. High accumulation of mutant p53, for one, is not present in normal cells and can, thus, be an accurate, malignancy biomarker. Some scientists believe that restoring the mutant p53’s original tumor-suppressing function will help lead to anti-cancer drugs. Further research has identified the low-molecular-weight compound PRIMA-1 to be a possible way to reactivate apoptosis by p53 to massively cancerous cell.

P53, as a major tumor suppressor, is responsible for the prevention of uncontrollable cell proliferation. Despite present, conflicting results, further studies targeting the protein’s varied signaling network and distorted function may one day lead to effective cancer chemotherapy and a better understanding of tumor formation.