

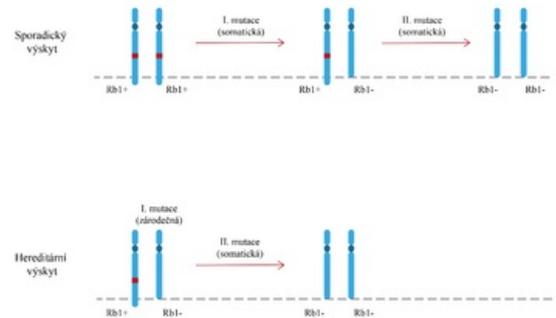
# Tumor suppressor gene

**Tumor suppressor genes'** (also called anti-oncogenes or recessive oncogenes) have an essential role in the malignant process. Their products regulate cell division. The loss of both alleles of a certain suppressor gene (e.g. deletion), a change in their structure (e.g. point mutation) leads to a disorder of cell cycle control ) or inactivation of the protein encoded by them. All this can result in a malignant transformation of the cell.

## General

Mutations in tumor suppressor genes have a ``recessive character. *Unlike oncogenes, proteins encoded by anti-oncogenes have an antiproliferative effect, promote differentiation and apoptosis.*

There are about 40 tumor suppressor genes in each somatic cell. To become tumorigenic, both of their alleles must be mutated – hence the name recessive oncogenes. This is related to the so-called *double hit theory* (first formulated by Knudson when explaining the occurrence of rare hereditary retinoblastoma). In contrast to the much more common sporadic retinoblastoma, where there are random mutations of one and then the other allele in the retinal cell, in the hereditary form one mutated allele is inherited. The relevant individual is a heterozygote in whom the inherited tumor predisposition is not yet manifested. However, if the second allele is mutated/eliminated, the development of a tumor clone of retinal cells is initiated.



The principle of the two-hit theory in retinoblastoma

This process is called ``loss of heterozygosity (*LOH - loss of heterozygosity*).

## pRB

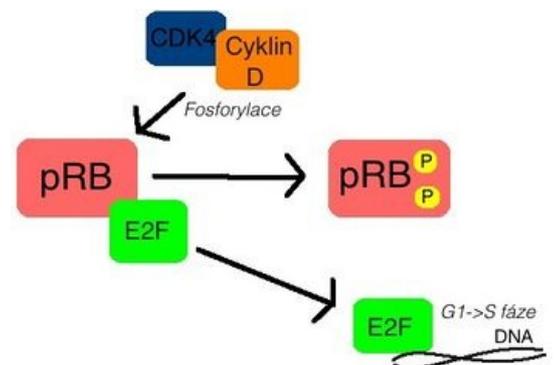
The first discovered tumor suppressor gene was **called the retinoblastoma gene (*RB1 gene*)'** and its product **RB-protein (pRB)**. It occurs in every cell, where it regulates the cell division cycle.

**Retinoblastoma gene (*RB1*) and another tumor suppressor gene *TP53*, respectively. their products act as a kind of brake on cell proliferation. *RB1* negatively regulates the important transcription factor *E2F*. Deletion of the ``*RB1* gene, which occurs in hereditary retinoblastoma, or sequestration of its protein product in the presence of adenoviral protein *E1A* or protein *E7* (in human papillomavirus infection) induces unblocking of *E2F* suppression. In contrast, *p53* acts by promoting the expression of *p21/CIP*, which is a potent inhibitor of cell cycle-regulating kinases (cyclin-dependent kinases).**

Loss of the regulatory function of the Rb gene in the cell cycle or overexpression of c-myc leads to increased proliferation, but also to increased apoptosis of the affected cells. Virogenic products such as ***E1A*** (adenovirus infection), ***T121-antigen'*** (from SV-virus) or ***E7*** (from human papillomavirus) bind to Rb and then have a similar effect. At this stage, the number of transformed cells does not increase yet. However, another genetic change, causing loss of *p19ARF*, mutation of *p53*, or overexpression of *bcl-2*, leads to increased proliferation and reduced apoptosis. Contributing to this are gene products such as *E1b* (from adenovirus), large antigen from SV-virus and *E-6* antigen from papillomavirus, which bind to the ***p53*** protein. Apoptosis, or the tendency to decrease it, is of key importance for the development of tumorigenesis.

## p53

The tumor suppressor gene *TP53*, which encodes the protein *p53*, is a key regulatory factor that monitors DNA damage. Inactivation of *p53* is usually one of the first steps that leads to malignant transformation in the development of a number of cancer diseases. Patients with Li-Fraumeni syndrome usually have one mutant allele in their germ cells and thus an increased risk of developing sarcomas, leukemia and carcinoma of the mammary gland] .



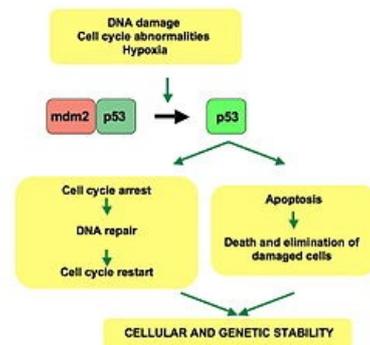
The CDK4/Cyclin D complex phosphorylates the pRB/E2F complex and thereby releases the E2F transcription factor, which further enables the cell to transition from G1 to S phase

Located on the short arm of chromosome 17 (17p13.1, OMIM: 191170 (<https://www.omim.org/entry/191170>)), contains 393 codons, regulates the course of interphase, also called "guardian of the genome" . It reacts to DNA damage by temporarily suspending the cycle and thus enables error repair (the so-called big repair). ⚠ It controls the initiation and duration of the quiescent stage through genes whose transcriptional activity is controlled by its p53 protein.

The p53 gene is also used in the 2nd interphase checkpoint - by pausing the cell cycle in this period, it enables the so-called post-replication repair. Furthermore, it induces and coordinates apoptosis when DNA repair is not successful.

Overview of some recessive oncogenes causing cancer

Symbol	Name	Cancer disease
APC	Adematous polyposis colon gene	Colorectal carcinoma
BRCA1	Family Breast/Ovarian Cancer Gene 1	Hereditary Breast/Ovarian Cancer
BRCA2	Family Breast/Ovarian Cancer Gene 2	Hereditary Breast/Ovarian Cancer
CDH1	Cadherin 1 gene	Familial gastric cancer, lobular breast cancer
CDNK2A	Cyclin-dependent kinase 2A inhibitor gene (p16)	Malignant melanoma of the skin
EP300	300 kD-E1A binding protein gene	Colorectal, pancreatic, breast carcinomas



P53 pathways

## Links

### Source

- ŠTEFÁNEK, George. *Medicine, diseases, studies at the 1st Faculty of Medicine, UK* [online]. [cit. 2010-02-11]. <<https://www.stefajir.cz/>>.
- MASOPUST, Jaroslav. *Pathobiochemistry of cells* [online]. ©2003. [cit. 2011-03-17]. <<http://dotdiag.cz/img/prednasky/bunka.pdf>>.

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