Tumor suppressor genes

Tumor suppressor genes (also called antioncogenes or recessive oncogenes) play a crucial role in the malignant process. Their products regulate cell division. Disruption of cell cycle control results in the absence of both alleles of a particular suppressor gene (e.g., deletions), alterations in their structure (e.g., point mutations), or inactivation of the protein encoded by them. All of this can result in a malignant cell reversal.

General

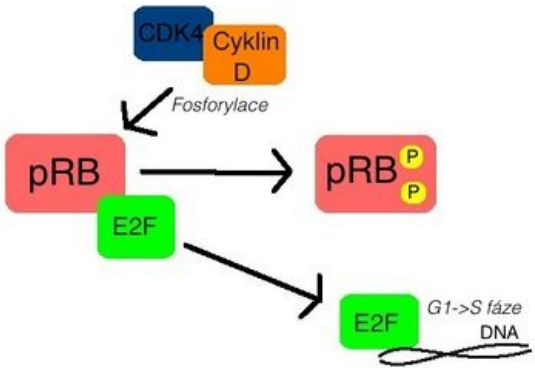
Mutations in tumor suppressor genes are **recessive**. Unlike oncogenes, the proteins encoded by antioncogenes have an antiproliferative effect, promoting differentiation and apoptosis.

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. Related to this is the so-called **two-hit theory** (first formulated by Knudson, when he explained the origin of a rare hereditary retinoblastoma). Unlike the much more common sporadic retinoblastoma, where there are random mutations of one and then the other allele in a retinal cell, one mutated allele is inherited in the hereditary form. The individual is a heterozygous who does not yet have an inherited tumor predisposition. However, when the second allele is mutated / eliminated, the development of a retinal cell tumor clone is initiated.

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

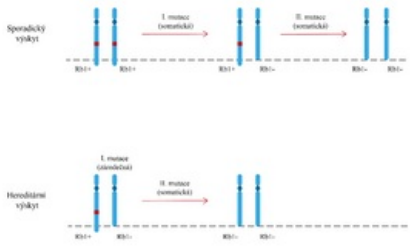
pRB

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 cycle of division**The retinoblastoma gene** (RB1) and another tumor suppressor gene **TP53, resp**. 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 during the development of hereditary retinoblastoma, or sequestration of its protein product in the presence of adenoviral E1A protein or E7 protein (in human papilloma virus 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).



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

Loss of 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 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 is not increasing yet. However, another genetic change causing **p19ARF** loss, **p53** mutation, or **bcl-2** overexpression leads to increased proliferation and decreased apoptosis. Gene products such as **E1b** (from adenovirus), large antigen from **SV-virus** and **E-6** antigen from papillomavirus, which bind to the p53 protein, contribute to this. Apoptosis, or the tendency to reduce it, is of key importance for the development of tumorigenesis.



two hit theory in RB1 mutation

p53

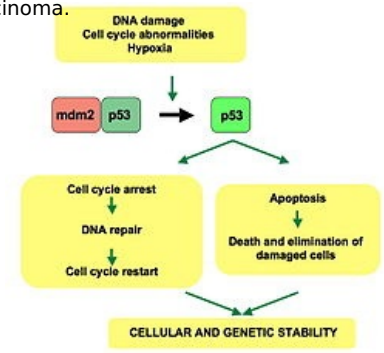
The tumor suppressor **gene TP53**, which encodes the p53 protein, is a key regulatory factor that monitors DNA damage. Inactivation of p53 is one of the first steps leading to malignant transformation in the development of many cancers. Patients with Li-Fraumeni syndrome usually have one mutant allele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

Located on the short arm of chromosome 17 (17p13.1, OMIM: 191170 (https://www.omim.org/entry/191170)), it contains 393 codons and regulates the course of interphase, also called the "guardian of the genome". It responds to DNA damage by temporarily suspending the cycle and thus enabling the repair of errors (so-called major repair). Controls the onset and duration of the resting stage through genes whose transcriptional activity is controlled by its p53 protein.

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

Overview of some tumor suppressor genes

Sign	Name	Tumor
APC	Gene Adenomatose Polyposes of the Colon	Colorectal carcinoma
BRCA1	Breast cancer type 1 susceptibility protein	Hereditary carcinoma of the breast/ ovary
BRCA2	Breast cancer type 2 susceptibility protein	Hereditary carcinoma of the breast/ ovary
CDH1	Gene for cadherin-1	Familial gastric cancer, lobular breast cancer
CDNK2A	Gene inhibitor of cyklin-dependent kinase 2A (p16)	Malignant skin melanoma
EP300	Gene of binding protein 300 kD-E1A	colorectal, pancreatic and breast carcinoma.



P53 pathways

Links

Sources

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