Oncogenes and Proto-oncogenes

Proto-oncogenes are genes responsible for cell and tissue proliferation.

They are involved in the regulation of **cell proliferation**, cell cycle progression, differentiation, development, aging, programmed cell death (apoptosis), immune responses, and carcinogenesis at all levels of **signaling pathways**.

Proto-oncogene products

Growth factors

- The **proto-oncogene sis** encodes part of the **biologically active** b-chain of the growth factor **PDGF** (platelet-derived growth factor)
- The **proto-oncogene hst** encodes **FGF** (fibroblast growth factor)
- In breast, esophageal, and malignant melanoma tumors, hst is amplified and its increased expression contributes to **malignant transformation**.

Growth factor receptors

- These receptors most often have **tyrosine kinase activity**: tyrosine kinases are enzymes that phosphorylate the tyrosine residues of target proteins or proteins with **tyrosine kinase domains**.
- This group of proto-oncogenes includes the **HER-2 / neu proto-oncogene** (human epidermal growth receptor)
- It belongs to a family of 4 proto-oncogenes encoding **epidermal growth factor** receptors (EGFR) with tyrosine kinase activity.
- In a mutated **hyperactive form**, it occurs in gliomas. Amplification (overexpression) of this gene is also seen in **breast cancer cells**.

GTP-binding proteins - G-proteins

- These are **intracellular proteins** (GTPases) that act together with tyrosine kinases.
- They are involved in the regulation of **cell proliferation**.
- G-proteins include, for example, **proto-oncogene products of the ras family**.
- **Mutated proto-oncogenes** (c-ras oncogenes) encode a protein whose activity is not regulated by the **alternating binding** of GTP or GDP (activation or inactivation of ras protein respectively) - as a result, the ras **oncoprotein** is unable to terminate the **cell growth stimulating signal**.
- They are found in the cells of **various tumors**.

Tyrosine kinases located in the plasma membrane

- The **abon** and **src** proto-oncogene products are proteins with tyrosine kinase activity.
- They allow the propagation of extracellular signals from the plasma membrane to the **cytoplasm**.

Cytoplasmic proteins

- These proteins are responsible for the transmission of **signals from the cytoplasm** to the nucleus. These signals are initiated by growth factors, differentiation hormones, cytokines, mobilization of calcium ions, and oxygen radicals or other DNA damaging substances. The resulting signaling cascades are regulated by the products of many **proto-oncogenes**.
- Together with the **products of the proto-oncogenes** of the ras family, the transmission of these signals in the cytoplasm ensures the expression of the **proto-oncogene raf-1** for example.
- Its product - protein kinase Raf-1, or the first MAP-kinase, has a **regulatory role** in the protein kinase-mediated signal transduction **cascade**.

Transcription factors

- The proto-oncogenes fos, jun, erb-A, and myc encode proteins with a specific function - **transcription factors**.
- They are activated by **MAP kinases** and their products stimulate or suppress the transcription of **target genes** for the regulation of individual parts of the **cell cycle**.

Proteins controlling the course of the cell cycle

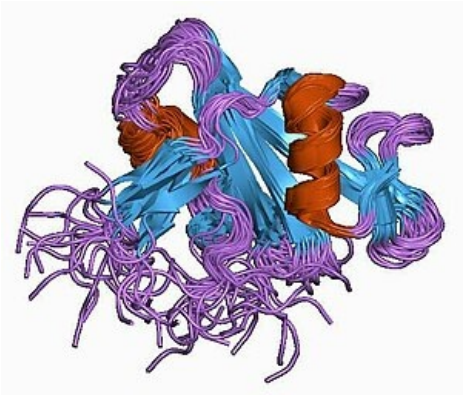
- myc and myb proto-oncogenes stimulate the **transition from G1 to S phase**, and their increased expression leads to a shortening of the G1 phase before entering the S phase of the cell cycle.
- This limits the time for **DNA repair** (limitation of the so-called large repair)

For various proto-oncogenes, great **similarities** have been found between different animal species, such as humans, mice, yeasts, or Drosophila. A **mutation** in one of the paired proto-oncogenes on homologous chromosomes is **sufficient to alter** the regulation of cellular activity in which that proto-oncogene participates. Mutations in proto-oncogenes have so far been predominantly detected only in **somatic cells** and have the character of a **dominant mutation**.

Oncogenesis

If a proto-oncogene is abnormally expressed or has undergone a gain-of-function mutation, its protein product will be overly expressed or active. The result is excessive cell division. This mutated form of a proto-oncogene is called an **oncogene**. The proto-oncogene may be activated as a result of:

- **Point mutations**
- **Amplification** (increase in proto-oncogene copy number)
- **Translocation to a transcriptionally active site** (e.g., in Burkitt lymphoma)
- **Formation of a chimeric (fusion) gene due to chromosomal rearrangement** (e.g., Philadelphia chromosome).



Proto-oncogene product

Another mechanism of tumor growth is mutations in antiproliferative **tumor suppressor genes**. These always occur as two copies in the genome, and the **mutation of both copies** is necessary for oncogenesis. However, proto-oncogenes differ in this **aspect**. Mutation of **one copy** of a proto-oncogene (transformation to an oncogene) is sufficient to cause manifestations - **dominant mutation character**.

Proto-oncogenes can encode a very wide variety of proteins with many different functions (cell differentiation genes, signaling molecules, surface receptors, regulatory genes). If, for example, the signaling pathway protein is damaged, the reactivity of the cells to the action of growth factors may change. Significant cell division follows. This can be caused by several mechanisms:

1. The protein is expressed in cells in which it does not normally appear;
2. The protein is produced in cells that normally produce it, but in excessive amounts;
3. The protein is produced as a form that cannot be regulated by normal mechanisms.

New research has found that the activation of proto-oncogenes to oncogenes can occur via the action **microRNAs**. These are RNA segments of 21-25 nucleotides. They can control the expression of these genes by down-regulating them. In the future, they could possibly be used to block the action of oncogenes.

Currently, 40 proto-oncogenes are known. Of these, 16 of them have been shown to be directly related to tumor growth. These include:

Proto-oncogene	tissue
Her-2/ neu	breast tumors
K-ras	tumors of the esophagus, colon, and pancreas
beta-Catenin	tumors of the pancreas and colon
Cyclin E	liver tumors
B-Raf	melanomas

Examples of (proto-)oncogenes

Oncogenes include, for example, mutant forms of the growth factor PDGF, growth hormone receptors, or intracellular signaling pathway proteins. All of the affected cells exhibit similar behavior - they react as if they are constantly receiving signaling instructions for division. The cells thus completely deviate from the regulatory process.

The oncogenes also include the viral src gene. Cancer-associated viruses are called **transformation viruses** (these are often retroviruses). Normally, the src gene regulates cell division. The individual structures of the oncogene and proto-oncogene differ in several amino acids.

Viral oncogenes	Normal proto-oncogene function	Tumors caused by mutation
oncogene abl	Tyr-specific protein kinase	pre-B-cell leukemia
erb-B	epidermal growth factor (EGF) receptor	erythroleukemia
fos, jun	regulation of gene expression	osteosarcomas, fibrosarcomas
myc	regulation of gene expression	sarcomas and carcinomas
src	Tyr-specific protein kinase	sarcomas

Rous sarcoma (oncogene study model)

- Detailed **research about the viral oncogene** v-src (retrovirus associated with Rous sarcoma of chickens) by the method of molecular genetics clarified its **origin**.
- **Proviral DNA** was cloned in a bacteriophage. After obtaining a sufficient amount of proviral DNA, it was digested with **restriction endonucleases**.
- The v-src gene was isolated, inserted into a **plasmid** and amplified.
- Pure DNA carrying v-src was used to **transform chicken fibroblasts**.
- **Transformation of fibroblasts** with the isolated v-src gene was successful.
- **DNA hybridization**, which allowed for the comparison of the structure of the v-src oncogene with DNA isolated from normal chicken cells, **showed** that the v-src oncogene was **not of viral origin**, but was a copy of a gene found in **all chicken cells**.
- The v-src oncogene is thus a **copy of the exons** of one of the cellular **proto-oncogenes**.
- The **viral oncogene** was probably originally part of the **genome of the eukaryotic cell** and was randomly obtained from the genetic material of the **host cell** by transduction in a **Rous virus** ancestor.
- Based on the methodology used in this study, other viral **oncogenes** were identified from the **tumors in various animals**.
- This discovery indicated the **existence of cellular genes** with hidden **oncogenic potential**.
- Later on, a whole class of **cellular proto-oncogenes** related to v-onc retrovirus genes was discovered.
- Furthermore, **oncogenes** of tumor cells were isolated and identified - **cellular oncogenes** (c-onc), which were created by mutations of **cellular proto-oncogenes**.
- More than 1**00 different human oncogenes** have currently been identified in tumors.

References

Related articles

- The cell cycle
- Hereditary tumor syndromes
- Mutation
- Proliferation
- Tumor suppressor genes
- Chromosomal aberrations in the etiology of neoplasms

External links

- What are Proto-Oncogenes (https://www.news-medical.net/life-sciences/What-are-Proto-Oncogenes.aspx)
- Proto-Oncogenes to Oncogenes to Cancer (http://www.nature.com/scitable/topicpage/proto-oncogenes-to-oncogenes-to-cancer-883)

Used Literature

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- KUMAR, Vinay, Abul K ABBAS a Nelson FAUSTO, et al. *Robbins basic pathology.* 8. vydání. Philadelphia : Saunders/Elsevier, 0000. 0 s. ISBN 978-1-4160-2973-1.