Mechanisms of tumor formation

Mechanisms of tumor formation - Pathobiochemistry of tumor transformation (lecture notes: https://el.lf1.cuni.cz/p45782335/).

Basic characteristics of malignant transformation

A malignant tumor is a **genetic disease**. It arises on the basis of the **accumulation of somatic alterations** of certains genes (see below) caused by **genotoxic effects** of physical (ionizing radiation), chemical (genotoxc substances), or biological (failure of endogenous replication processes, and viruses). The development of a malignant tumor in an affected individual may be more or less accelerated by the existence of **hereditary mutations** (alterations in highly penetrant predisposing genes vs. alterations in genes with limited penetrance). They also have a significant impact on its development **epigenetic factors** influencing the expression of genetic information (mainly histone modifications).

The most significant characteristic of tumor cells is their uncontrollable **growth across the hierarchical construction plan of the organism** . This construction plan begins with the individual cells grouping into cell clusters, which make up the tissues that make up the individual organs, arranged in organ systems working in synchronism within the organism. Its control also corresponds to the body's construction plan - local regulation of individual cells within tissues is realized by means of **local signaling** (growth factors , cytokines , immunomodulatory molecules), while regulation of organs and their systems is controlled by **distant neurohumoral systems** (especially hormones).). The proper functioning of cellular components in the body is constantly monitored by the immune system . The development of a malignant tumor is a disorder of this homeostasis , which begins at the level of the genomes of cells of malignantly transformed tissue, which - in the event of failure of control immune mechanisms and due to distant metastases - can cause symptoms of systemic collapse leading to death . Although the process of tumor transformation varies from case to case, neoplastic tissue always shows some identical characteristics resulting from disorders of transforming cells at the level of:

- **Interpretation of local and system signaling.**
- **Internal homeostasis** - especially at the genome level.
- **Mutual local intercellular communicatione** and communication with the microenvironment.

These processes serve to regulate the basic behavior of individual cells within tissues:

- **Regulation of cell self-renewal** (cell replication, their aging and apoptosis).
- **Regulation of functional capacity within the tissue** (differentiation and migration of cells).

All this ensures **tissue homeostasis** – a dynamic balance of cell formation and extinction with respect to the current needs provided by the relevant tissue within the organism (ie the intact existence of a hierarchical construction plan, which is a condition of the physiological integrity of the organism). The failure of these processes leads in turn to the characteristic manifestations of transformed tumor populations:

- Autonomy in the production of growth signals.
- Decreased sensitivity to inhibitory growth signals.
- Diseases of apoptosis.
- Threshold-free replication potential (immortalization).
- Disorders in DNA repair (genomic instability).
- Significant angiogenesis.
- Ability of tissue invasiveness and metastasis.

Despite the deregulation of a number of intracellular signaling systems, uncontrolled tumor growth is the result of the failure of two critical events - the cell cycle (https://el.lf1.cuni.cz/bunecnycyklus/) and apoptosis (https: // el .lf1.cuni.cz / apoptosis /) complementary influencing tissue homeostasis (balance between new cell formation arising from cell cycle division and death of worn, unnecessary or damaged cells in the process of apoptosis characterizes the normal physiological state in the tissue of an adult organism). Tumor cells are always characterized by a disorder of this balance, which is caused by an increase in cell cycle rate and resistance to induction of apoptosis. Disorders of both processes are caused by mutations accompanied by epigenetic alterations of genes that control both processes (oncogenes or proto-oncogenes - involved in cell cycle stimulation and inhibition of apoptosis and counteracting tumor suppressor genes). Genetic alterations are tolerated in tumor cells because the third **critical condition** for tumor transformation is **deregulation of DNA repair mechanisms**. Failure of repair events causes genome instability, in which unrepaired genetic alterations accumulate, which can impair other regulatory mechanisms responsible for the formation of heterogeneous tumor populations with high malignant potential.

A note on the origin of tumor cells

What is the basis of the population from which the initial cluster of tumor-transformed immortalized cells arises? In each tissue, three major developmental populations can be traced (or at least assumed) that are necessary for physiological tissue regeneration during human life, because - with exceptions to the rule (eg pyramidal nerve cells) - the generation time of most cells is a fraction of the lifetime. organism:

- **Tissue specific stem cells** they carry time-indefinite replication potential in the tissue: they restore the supply of progenitor cells .

  Charasteristics: replication potential comparable to the lifetime of the whole organism; tissue concentration very low; unlimited but low mitotic potential; the absence of most of the phenotypic traits of mature cell populations.

- **Progenitor cells** - supplement the need for continuously declining worn-out specific mature tissue cells.

  Charasteristics: have limited generational potential; rapid division; ability to migrate; the ability to differentiate into specialized cell populations of the relevant tissue. In their phenotypic equipment, according to the degree of their differentiation, we encounter the characteristics of mature cells.

- **Specialized tissue cells** resulting from the differentiation of their progenitors make up> 99.9% of the cell population in the tissues.

  Characteristics: they perform tissue-specific functions; they have a low replication potential (they age during their several divisions and must be replaced by a new population of new cells resulting from progenitor differentiation); terminal and specialized phenotype; limited or no ability to migrate (applies to solid tissues).

Given the known characteristics of tumor cells (unlimited replication potential, loss of contact inhibition , migration, incomplete expression of phenotypic traits of fully differentiated tissue cells, etc.), it is likely that the primary clone of tumor-transformed cells (**tumor stem cells**) results from a gradual accumulation of genetic and epigenetic alterations. At the level of stem or progenitor cells rather than the majority of populations of fully mature tissue cells.

Disorders (failure) of intracellular signaling leading to tumor transformation

If cell cycle control disorders and apoptosis are the basis of tumor transformation , while inactivating DNA repair mechanisms, which specific genes and signaling processes are involved? Although thousands of somatic alterations in DNA and epigenetic insults have been described, it can be assumed that there are some signal transduction pathways whose disorders are critical for tumor transformation.

Disorders of mitotic signaling and cell cycle failure

Disorders of cell cycle control , with regard to the mechanism of its regulation, mainly affect the initial phase - entry into the cell cycle and regulation of cell cycle checkpoints. Promitotic signaling involves the detection, transmission, propagation, and amplification of a mitotic signal that ultimately initiates changes in the gene expression of the stimulated cell that induce the synthesis of protein regulators that control the cell cycle (e.g., cyclins). At the biochemical level, these processes are expressed by signaling cascades involving their own signaling molecules (ligands), their protein receptors, and possibly transducers transmitting a mitotic signal to systems of mutually communicating kinases modulating the activity of specific transcription factors(TFs), which regulate gene expression of genes responsible for cell cycle passage. Representatives of these events are, for example, signaling:

- **Growth factors (GFs)** and their receptors (RTKs) - receptors with intrinsic - tyrosine kinase (TK) activity including RF> RRFs> adapters (Grb / Sos)> transducers (Ras)> kinase system (MAPKKK> MAPKK> MAPK) and target TFs (Elk). All of these components stimulate the cell cycle.
- **Cytokines** and their receptors - as an example of a direct signaling pathway, typically based on cytokine receptor activation (without intrinsic TK activity), which (due to ligand-induced conformational change) associates with a membrane-bound molecule Both kinases phosphorylating the receptor itself and subsequently phosphorylating STAT protein molecule (signal transducers and activators of transcription). Activating phosphorylation of STAT proteins allows their dimerization and translocation to the cell nucleus, where they directly play the role of specific TFs.
- **Signaling involving protein kinase B (AKT)** - integrating signaling from a number of membrane receptors (RTKs, cytokine receptors) and affecting not only the cell cycle but also the process of apoptosis.
- **β-catenin signaling**- regulated by contact inhibition mediated by adhesive molecules (cadherins and β-catenin) or stimulated by signaling molecules of secretory (often autocrine) signaling molecules of Wnt proteins interacting with their receptor complex (Frizzled / LRPs) and influencing differentiation processes in the cell .
- others - Notch, Hedgehog, NFκB (nuclear factors κB), nuclear and intracytoplasmic receptors of lipophilic signaling molecules (eg steroid hormones)

Mutations in oncogenes encoding individual protein components of signaling pathways that cause activation of their encoded proteins regardless of the presence of stimulation by the parent signaling molecule are a typical sign of somatic alterations in tumor cells (eg **EGFR** , **k-Ras** , **PI3K** gene mutations) and cause promitotic hyperstimulation independent on the presence of a superior control signal. Gene amplification (multiplication of allele copies) of genes encoding individual transduction cascade proteins (eg ErbB-2 encoding the her2 / neu receptor, heterodimerizing with other members of the EGFR family) has a similar effect.

However, **mutations in tumor suppressor genes** under physiological circumstances that inhibit (silence) signaling cascades can lead to the same result . For example:

- Mutations in neurofibromin (NF-1) cause a loss of GAP activity (GTPase activating proteins), allowing a prolonged existence of activated Ras-GTP and thus promitotic hyperstimulation.
- Inactivating mutations in APC , whose gene product APC (adenomatous polyposis coli) protein normally inactivates β-catenin signaling by β-catenin retention in the cytoplasm , allow β-catenin to be released and translocated to the cell nucleus with transcription of cell cycle regulators.
- Mutations in the **PTEN** tumor suppressor gene cause inactivation of the phosphatase PTEN (phosphatase and tensin homolog) dephosphorylating 3,4,5-phosphatidylinositol triphosphate (PIP3), which is a condition for activation of the PKB / AKT kinase cascade, to signal-inactive 4,5-phosphatidylinositol diphosphate (PIP). Prolonging the half-life of PIP3 activates the AKT kinase cascade regardless of the absence of superior pacing signals.

The results of recent years suggest that microRNA (**miRNA**) molecules acting as oncogenic and tumor suppressor signals also play an important role in the regulation of gene expression of signaling regulators influencing mitotic signaling. Their mutations or changes in their gene expression are probably involved in the pathogenesis of many cancers.

In addition to mutations, negative regulators of mitotic stimulation may also be affected by epigenetic changes at the level of hypermethylations (eg hypermethylation of promoters of SOCS proteins that physiologically inhibit cytokine signaling).

Cell cycle disorders (in addition to the above-mentioned mitotic signaling disorders) also affect the control of the cell cycle itself. At the level of cell cycle entry, we often encounter deregulation of the major checkpoint in the G1 phase. Its molecular basis is to overcome the inhibitory effect of the **Rb protein** , physiologically achieved by sufficient mitotic stimulation leading to early gene synthesis (eg E2Fs) and subsequently delayed / late (group D and E cyclins) responses. Cyclins forming active complexes with CDKs hyperphosphorylate the Rb protein, thereby preventing its interaction (and thus inhibition) by a number of regulatory proteins (e.g., TFs of the E2Fs family). The Rb protein can be pathologically inhibited at the level of mutations in the gene (see retinoblastoma - hereditary inactivation) or pathological hyperexpression of cyclins (by amplification of their genes, less often by mutation) hyperphosphorylating (inactivating) Rb protein.

Another important mechanism of cell cycle deregulation in tumor cells is the **inactivation of inhibitory factors** that, under physiological circumstances, block cell cycle passage during mitotic hyperstimulation, S-phase DNA replication disorders, or M-phase chromosome segregation disorders . These factors mainly include tumor suppressor gene products from the CIP / KIP (cyclin-dependent inhibitor protein / kinase inhibitor; p21, p27, p57) and Ink4 (Inhibitors of kinases; p15, p16, p18, p19) families. In addition to their direct inactivation by mutations, functional inactivation of these negative cell cycle regulators at the level of alterations in signaling pathways and TFs that control their gene expression (eg **TGFβ / SMAD**) is **a common disorder in tumor cells** and p53).

Disorders of apoptosis

The growth of malignant cells within the initial clonal expansion of the primary locus of transformed cells is also made possible by the impaired ability to initiate apoptotic mechanisms. **Disorders of apoptosis** include initiation of the extrinsic pathway (involving the assembly of the DISC complex) - eliminating the regulatory effect of immunocompetent cells, intrinsic part of apoptosis activation (characterized by apoptosome formation) - enabling the existence of a tumor cell and its division through damage to its genomic DNA cascade cascade.

The formation of the **DISC** (death-inducing signaling complex) is enabled by trimerization of death receptors (DRs) expressed on the surface of all cells (except immunologically privileged tissues) stimulated by death ligands (DL) - signal ligands membrane-bound on the surface of immunocompetent cells. This interaction is inhibited in tumor cells by reducing the expression of DRs at the level of their gene expression, for example by inactivating their TFs (inhibition / mutation / ubiquitination of p53, inhibitory phosphorylation of FOXO TFs transactivating the CD95 / Apo1 / FasR promoter) or inhibition of DL based on decoy receptors (DR lacking an intracytoplasmic portion containing DD, which allows the association of adapter molecules and the formation of an active DISC complex).

Because most active DRs complexes result in variable signaling complexes depending on the actual presence of adapter molecules in the cell, **altering the gene expression of adapter proteins** can critically affect the ability to induce apoptosis. E.g. while binding of FADD (Fas-associated protein with death domain) containing both DD and death effector domain (DED) allows completion of DISC complex activation by binding of procaspase-8 and its activation to caspase 8, association of activated DRs trimer with TRAFs (TNF receptor-associated adapters) factors) initiates (via several protein kinases) a "signal switch" leading, for example, to the activation of transcription factors NFκB with markedly antiapoptotic effects.

The formation of the apoptosome (APAF1 activation and procaspase-9 binding) in **the intrinsic part of apoptosis** is influenced by the translocation of cytochrome C from the intermembrane space of the mitochondria into the cytoplasm. The main group of proteins regulating this process is **the Bcl-2 family of proteins** including both proapoptotic (Bax) and anti-apoptotic (Bcl-2) proteins associated with the outer mitochondrial membrane. The ratio of pro- and anti-apoptotic proteins sensitively regulates the ability to induce apoptosis in its intrinsic part. Hyperexpression of antiapoptotic agents (eg due to amplification of their genes) and decreased expression of proapoptotic members of the Bcl-2 family (eg induced by impaired gene expression by inhibition of TFs that regulate their gene expression - typically mutations in the p53 gene encoding p53 protein transactivating Bax gene expression) PUMA (p53-upregulated modulator of apoptosis; BBC3) and NOXA encoding proapoptotic proteins) prevent the initiation of the intrinsic part of apoptosis.

Caspase activation disorder is another mechanism of inhibition of apoptosis in tumor cells. Inhibition of proximal caspase -8 (FLICE) activation in the extrinsic pathway of apoptosis may occur due to increased expression of **CFLAR** protein (Caspase-8 and FADD-like apoptosis regulator) lacking proteolytic activity, which competes with the procaspase-8 molecule for entry into the DISC complex and thus prevents its activation. The activity of executive caspases (caspase-3) is inhibited in many tumor cells by inhibitors of apoptosis (eg BIRC5 - baculoviral IAP repeat-containing protein 5 - survivin) overexpressed in many tumor cells .

Disorders of DNA repair mechanisms

Alteration of genes regulating the cell cycle and apoptosis is made possible in tumor cells due to **disorders of DNA repair mechanisms**, whose full activity would, under physiological circumstances, prevent the accumulation of gene insults and their tolerance. Under physiological circumstances, DNA repair mechanisms thus form an effective protective barrier preventing the formation of malignantly transformed cells. Repair processes are closely linked to the regulation of the cell cycle and apoptosis, because (1) under physiological circumstances only a cell with intact genomic DNA can enter the cell cycle, (2) passing through the cell cycle and advancing to its final phase can be performed correctly and accurately. replicated genomic DNA and (3) intrinsic mitosis and final cytokinesis can only occur in cells symmetrically segregating duplicate genetic material. If these conditions are not met, the cell cycle is stopped, allowing genomic DNA to be repaired and, in the event of its failure, to initiate apoptotic mechanisms. At the molecular level, the relationship between cell cycle regulation, DNA repair and apoptosis is represented by regulatory proteins that affect signaling in all of the above signaling pathways (eg protein kinase **ATM** (ataxia-telangiectasia mutated), activated by double-strand breaks in DNA, not only initiates activation of DNA repairs (phosphorylation of eg BRCA1 protein) , but thanks to phosphorylation of p53 protein activates this transcription factor, which is responsible for rapidly increasing expression cip1 , but also apoptosis stimulating members of the Bcl-2 family (Bax , PUMA, NOXA)).

Disorders of DNA repair mechanisms in tumor cells can affect all DNA repair systems:

- Disorders of repair mechanisms at the base level (**BER / NER system**) resulting in micromutations (missense / nonsense).
- Very important are alterations in the repair of double-stranded DNA breaks repaired either by a less precise non-homologous end joining (**NHEJ**) mechanism or by a highly efficient **HR** (homologous recombination) process, which inactivates chromosomal translocations / losses / amplifications of genetic material in tumor cells that cause physical destruction of alleles of tumor suppressor genes and amplification of chromosomal regions encoding oncogenes.

Disorders of DNA repair mechanisms are one of the earliest manifestations of the initial stages of carcinogenesis . In the case of sporadic (ie non-hereditary) cancers, many of the genes encoding proteins involved in repair processes are inactivated by somatic mutations (point mutations and large deletions affecting entire genes) and / or by hypermethylation of the respective promoters . Relatively rare hereditary mutations in these genes are the basis of a number of severe inherited tumor syndromes (usually accounting for <5-10% of tumors; eg MSH / MLH genes, ATM, BRCA 1/2, MRE11, and many others), where pre-existing alterations usually one of the alleles of the gene significantly increases the risk of malignant transformation in the predilection tissue.

Importance

The number of cancers in our population is constantly increasing. Understanding the causes of the origin and development of cancer is an important issue not only for research in molecular oncogenetics, but it is an important prerequisite for the rational use of targeted **biological treatment** , which is, unlike conventional chemotherapy, directed against selected molecular features (e.g., overexpressed her2 / neu receptor; mutated k-Ras or B-Raf oncoproteins) in a particular patient with a particular cancer. Although this new treatment strategy is delivering good results, its often dizzying price strictly requires deployment only in indicated patients who have a good chance of a positive response. This a priori question must be rationally answered by an oncologist, who for a valid decision must necessarily understand the strict biological criteria based on the molecular nature of the treated cancer and the phenotype / genotype of the tumor cells in a particular patient.

Another area that is significantly changing due to advances in the molecular biology of tumors is **oncological diagnostics** . Disclosure of the molecular nature of cancer allows the use of **molecular taxonomy** for the classification of cancer, which is likely to allow a more appropriate grouping of individual forms of cancer, better suited to their biological nature than has been the case in purely pathological and immunohistochemical analysis. An important diagnostic area is also the **detection of pathogenic mutations in tumor predisposing genes** , which form a small but high-risk group of people.

For example, solving the question of the origin of cell populations in a malignant tumor is not only a significant theoretical problem, but its solution can bring significant progress in oncological therapy. Although most current treatment strategies often allow the elimination of major tumor cell populations, they are unlikely to be adequately effective on tumor stem cells. Their persistence in tissues is probably a common cause of disease recurrence.

Finally, restoring negative cell cycle regulation and increasing sensitivity to proapoptotic mechanisms in the tumor cell is a basic general concept of conventional anti-tumor chemo- and radiotherapy .

Links

Related article

- Cell signaling
- Cell cycle
- Proto-oncogenes

REferences

- OMIM. *Online Mendelian Inheritance in Men* [online]. [cit. 21. 12. 2009]. <https://www.ncbi.nlm.nih.gov/omim>.
- GenomeNet. *KEGG PATHWAY Database* [online]. [cit. 21. 12. 2009]. <https://www.genome.jp/kegg/pathway.html>.
- BioCarta. *Pathways* [online]. [cit. 21. 12. 2009]. <https://www.blogger.com/blogin.g?blogspotURL=http://www.biocarta.com/genes/index.asp>.
- KRAUS, G. *Biochemistry of Signal Transduction and Regulation.* 4. edition. New York : Wiley-VCH, 2008. ISBN 978-3527313976.
-
- DENG, Shan – CALIN, George Adrian – CROCE, Carlo M. , et al. Mechanisms of microRNA deregulation in human cancer. *Cell Cycle* [online]. 2008, vol. 7, no. 17, p. 2643-6, Available from <https://www.ncbi.nlm.nih.gov/pubmed/18719391>. ISSN 1551-4005.
- BARTEK, J – BARTKOVA, J – LUKAS, J. DNA damage signalling guards against activated oncogenes and tumour progression. *Oncogene* [online]. 2007, vol. 26, no. 56, p. 7773-9, Available from <https://www.ncbi.nlm.nih.gov/pubmed/18066090>. ISSN 0950-9232 (print), 1476-5594. DOI: 10.1038/sj.onc.1210881 (http://dx.doi.org/10.1038%2Fsj.onc.1210881).

}}

Source

- ws:Mechanismy vzniku nádorů