**LECTURE SYLLABUS**

**(General medicine, dental medicine)**

**Pathophysiology of tumors**

Tumor (neoplasm) = structure developing by uncontrolled proliferation of abnormal cells

Also diffuse tumors - leukemia

* Loss of cell cycle control → autonomous proliferation
* Disorder of cell differentiation
* Tumor phenotype of the cells

**Tumor-like structures, pseudotumors**

- dif. dg.

* Hypertrophy, hyperplasia
* Pathological compound deposition
* Inflammatory pseudotumors - edema, cell proliferation
* Schloffer's tumor - inflammatory origin, around a foreign particle (e.g. surgical stitches)
* Hamartia - tissue segment not integrated into the organ structure
* Parasites - tapeworms (cestoda) - Echinococcus, Alveococcus
* Cyst
* Pseudocyst

**Tumor classification**

According to biologic features

* benign
* intermediary
* malignant

According to histogenesis

* epithelial
* mesenchymal
* from neural tissue
* mixed
* teratoma
* trophoblast-derived tumors

Typing

Grading

Staging

**Benign tumors**

Slow growth

Quite good differentiation

Delimited, often encapsulated

Expansive growth = volume increase, compression of surrounding tissue, but no infiltration

No metastases

→ Easy surgical ablation of the whole tumor = no tumor recurrence

Problematic localizations and features:

* Intracranial localization
* Endocrine activity
* Organ compression, duct obstruction, gut obstruction
* Risk of malignisation

**Malignant tumors**

* Rapid growth
* Cellular and nuclear irregularities, frequent mitoses
* No delimitation
* Infiltrative (invasive) and destructive growth = increase their volume and invade the surrounding tissue
* Metastases

→ Difficult complete surgical ablation of the whole tumor = surgery does not always mean complete healing

But:

E.g. the basalioma does not create metastases → benign from the clinical point of view

**Metastases**

= secondary tumor

A piece of tumor tissue, tumor cell, cell cluster separates from the primary tumor and moves to another place, where it is implanted and gives origin to a secondary tumor.

→ affection of more organs, enlargement of total tumor mass, source of disease recidive after surgical ablation of the primary tumor

Ways of metastatic process:

* hematogenic
* lymphogenic
* porogenic
* per continuitatem - e.g. prostate cancer spreads into the urinary bladder

**Tumor development**

* Clonal theory - a tumor originates from one transformed cell
* Mutation (somatic) - tumor initiation

→ tumor transformation of the cell - complex change of cell phenotype:

- ↑ proliferation ability

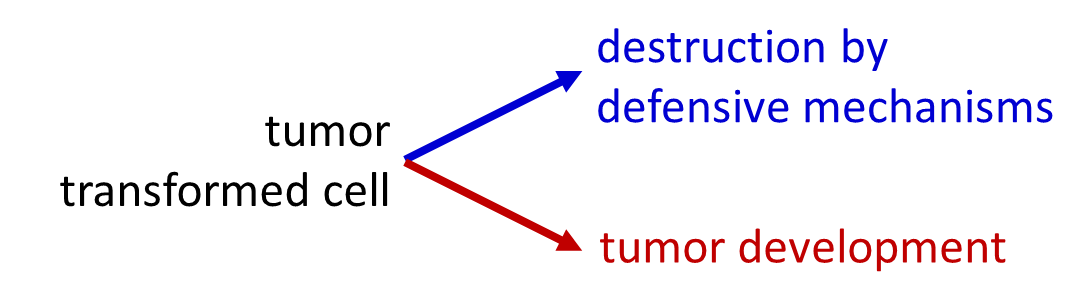
- ↓ or abnormal differentiation

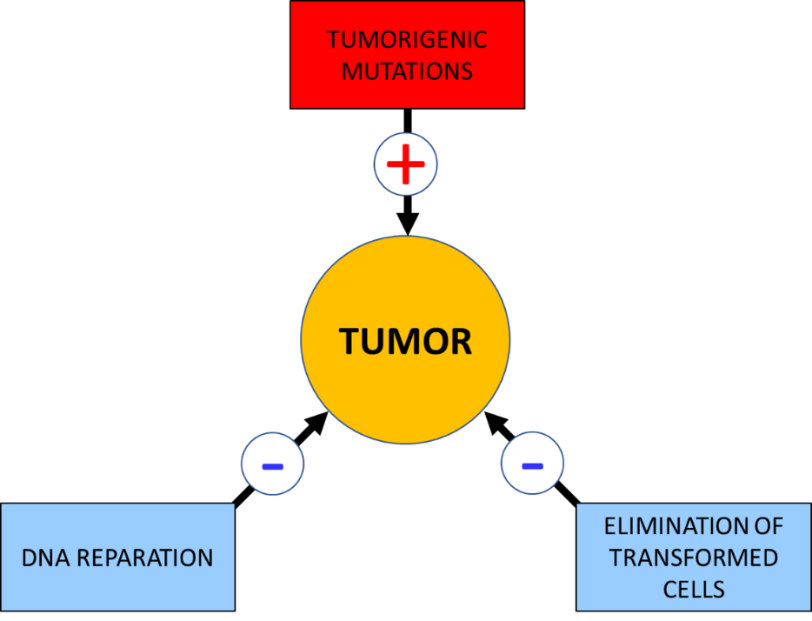
- ↓ apoptosis

- telomerase activity

- changed interaction with cells and extracellular matrix

Tumorigenesis is a process having several steps, more mutations are needed.



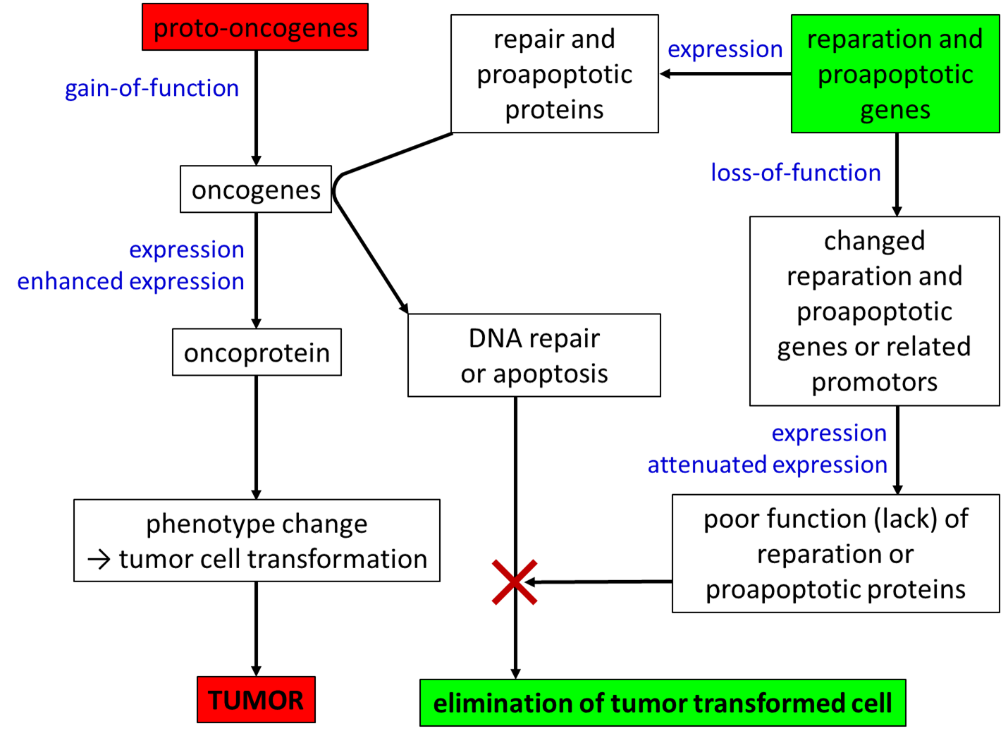


**Protoonkogenes**

* growth factors
* growth factor receptors
* intracellular signal pathway proteins
* transcription factors

**Tumor suppressor genes, anti-oncogenes**

* cell division inhibition
* differentiation promotion
* DNA reparation
* proapoptotic proteins



**Mutation character**

- mutation (usually more mutations in one cell are necessary) of proto-oncogenes, tumor suppressor genes

In the case of recessive mutations, change of both alleles is necessary.

- mutation in protein structure-encoding DNA sequence or change of gene expression control

* point mutations
* sequence insertion
* gene amplification
* translocation
* etc.

Philadelphia chromosome

= translocation of terminal parts of long arms of chromosomes 9 and 22

→ *abl* and *bcr* fusion → *bcr-abl*

→ protein having enhanced tyrosine-kinase activity

→ chronic myeloid leukemia

**Genetic instability of tumors**

In the frame of tumor transformation, defective DNA repair and defective induction of apoptosis in the case of irreparable mutation develop.

→ higher probability of accumulation of other mutations

→ malignisation of a benign tumor

→ creation of secondary cell clones in the tumor

→ tumor cell population heterogeneity

**p53**- mutation in 50 - 60% of human malignant tumors

Non-functioning p53 = selection advantage for a tumor cell

**Defense against the tumor and its creation**

* tumor suppressor genes
* immune system - namely NK-cells, Tc-lymphocytes

**Precancer (precancerosis)**

= pathological change of the tissue close to a cancer or preceding cancer development

Example: Barrett‘s esophagus

= intestinal metaplasia of the esophageal mucous membrane

(squamous epithelium → cylindrical epithelium)

* a consequence of the gastroesophageal reflux → irritation, inflammation

**Etiologic and risk factors**

factors that increase probability of mutations + factors reducing efficiency of defensive mechanisms

* radiation
* chemical carcinogens, including free radicals
* biological factors - viruses, etc.
* states connected with intensive cell proliferation
* heredity
* immunodeficiency
* ↓ protective factors (tissue quality, antioxidants, dietary fiber...)

Most of these factors are present permanently in some levels

Intensity + time of exposure + factor combination + individual sensitivity

**Radiation**

UV, RTG, α, β, γ

* DNA damage = mutations
* tissue damage = ↑proliferation

**Chemical cancerogens**

* interaction with DNA
* oxidative injury
* tissue irritation
* food
* water
* air pollutants
* medicaments (e.g. cytostatic)
* smoking

→ determination of the most frequent tumor lacalizations

Precancerogenes = converted by metabolism to cancerogenes

Protective substances: antioxidants, dietary fiber, some vitamines

**Viral etiology of tumors**

* insertion of viral DNA into the cell genome (RNA viruses - reverse transcription)

= direct mutagenic effect

→ oncogene insertion

→ active promotor insertion in front of a proto-oncogene

→ damage of a tumor suppressor gene

Indirect effects:

e.g. HIV (immune deficiency), hepatitis B (damage and abnormal reparation of the tuissue)

**Other microorganisms**

* tissue irritation (Helicobacter pylori)
* production of cancerogenic substances (molds)

**States of intensive cell proliferation**

* Chronic irritation, tissue damage, inflammation, (gastroesophageal reflux, liver cirhosis...)
* Hormonal stimulation

**Heredity of tumors**

* Disposition for tumors in general or for a particular tumor type
* An inherited mutation → in all cells → ↑ probability, that in one of them other mutations necessary to complete tumor transformation appear by chance, or mutation of the second allele
* An inherited mutation can lead to genome instability and increased sensitivity to mutagenic factors or reduced immune system capacity

Retinoblastoma

* mutation of the *Rb* suppressor gene
* AD heredity
* loss of heterozygosity

Li-Fraumeni syndrome

* p53-encoding gene mutation

→ disposition for tumors in an early age

Neurofibromatosis

* *NF1* gene mutation (morbus von Recklinghausen, peripheral type of neurofibromatosis) or *NF2* gene mutation (central type)

Familiar adenomatous polyposis of the large intestine

Lynch syndrome – colorectal cancer

**Tumor stroma and vascular bed**

- fibroblasts, vessels, extracellular matrix = tumor niche

- production of angiogenic growth factors VEGF, FGF, impact on metastatic process, increase of resistance of tumors to cytostatic treatment

- Vessels in the tumor are often abnormal – irregular lumen, higher vessel wall permeability.

**The impact of tumors on the organism**

* infiltration and destruction of the organ, replacement of the functioning tissue with the tumor
* bone destruction + Ca release
* organ compression (e.g. intracranial hypertension) → functional deficits, organ damage
* lumen obstruction
* cachexia
* chronic bleeding into the GIT, urinary tract → anemia
* hormone production
* production of pathological protein - myeloma → paraprotein
* pain ← compression, occlusion, tissue damage, bone fractures

**Paraneoplastic syndromes**

= tumor manifestations, that are not caused by growth of the primary tumor or its metastases directly in the organ

→ change of functions of organs in that the tumor is not localized

* Production of hormones by tumor originating from non-endocrine tissues

- e.g. small-cell lung cancer → ACTH, PTHrP

* Changed cytokine production
* Changed immune system function
* Synthesis of proteins similar to sequestered antigens (CNS!) → autoimmunity → paraneoplastic encephalomyelitis, ataxias...
* Suppression of erythropoietin secretion, vit. B12 and folic acid consumption → anemia
* Penetrance of tumor cells into the circulation, tissue factor expression → DIC
* Cachexia

**Tumor markers**

= substances present in the organism as a consequence of a malignant tumor

* released parts or secrets of tumor cells

→ detectable in the blood → diagnosis, therapy evaluation

**Alfa-fetoprotein (AFP)**

* liver cancer
* but also in the liver cirrhosis

**Carcinoembryonic antigen (CEA)**

* adenocarcinomas, namely colorectal c.
* but also inflammations

**Prostatic specific antigen (PSA)**

* prostate cancer