

Mechanisms of cancer development

Characteristics of the formation and growth of tumors

For tumor growth, as well as for healthy tissue, it is due to the relation (**balance**) of cell division and cell death.

- **tumor growth is not linear**, it depends on the supply of oxygen and nutrients - indirectly on genetic and epigenetic changes that lead to stimulation of tumor angiogenesis and escape of apoptosis and on the interaction with the tumor stroma, which also leads to stimulation of tumor angiogenesis and tumor invasion.
- **tumor stem cell** - the initial tumor population probably arises from a tissue-specific stem cell or close progenitor cell

Features that a tumor cell needs to acquire for metastasis:

1. ability to **release the stroma**
2. **angiogenesis** - penetration of blood vessels into the tumor and penetration of the tumor into the blood vessels (difference of tumor vessels)
3. **adhesion ability**
4. **hypoxia** tolerance

Regulation of angiogenesis, metastasis

Angiogenesis

- **angiogenesis** = use/ stimulation of endothelial cells from existing vessels
- **vasculoneogenesis** = activation of endothelial cell precursors
- can be excessive or insufficient, leading to a number of pathologies (rheumatoid arthritis, blindness, psoriasis, malignant tumors, skleroderma, peptic ulcer disease, sterility)
- **activators** (growth factors - VEGF, PlGF, FGF, EGF and others) and their receptors and **inhibitors** (especially *statins*) and their receptors are used in the **regulation** of angiogenesis and vasculogenesis
- the expression of mainly proangiogenic factors can be regulated by a number of oncogenes, the expression of mainly antiangiogenic factors can be regulated by tumor suppressor genes
- new vessels formation consists of several steps (disruption of the basement membrane, proliferation, migration, maturation) and both stimulation and inhibition of angiogenesis are used
- **tumor vessels** do not have a typical structure - a substantial part of the wall can be formed directly by tumor cells (there is a possibility of metastasis)
- the interaction of tumor stromal cells and adjacent tissue (tumor microenvironment) is significantly involved in tumor angiogenesis
- **inhibition of angiogenesis** (and other cell pathways in general) can occur at several levels:
 - growth factor inhibition (antibody)
 - receptor acceptor site inhibition (antibody)
 - receptor functional domain inhibition (tyrosine kinase inhibitors)
 - downstream pathway inhibition
 - inhibition of factor-producing factors initial conditions for initiating angiogenesis (inhibition of matrix metalloproteinases)

Metastasis

The tumor population is monoclonal but heterogeneous.

The formation of metastases takes place in several steps. To fill them, the tumor must acquire the required features:

1. *angiogenesis*
2. *ability to move*
3. *intravasation*
4. *adhesion*
5. *extravasation*
6. *angiogenesis in a distant organ*

Selection of resistant tumor clones

- **apoptosis** - how can a tumor escape apoptosis (what mutations of which genes)? How can a tumor escape hypoxia?
- **„multidrug resistance“** - are there any specific mutations or genes leading to drug resistance?
- **therapy** - how can we affect resistance? Is it related to the mechanism of resistance (targeted therapy, influencing the epigenetic background targeted molecular examination of the tumor)

References

Sources

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