Tumor Microenvironment

Composition of tumors

1. **Tumor parenchyma**

    - Source of the tumor cells
    - According to them => name of the tumor
    - Level of differentiation (degree of similarity with the starting tissue)

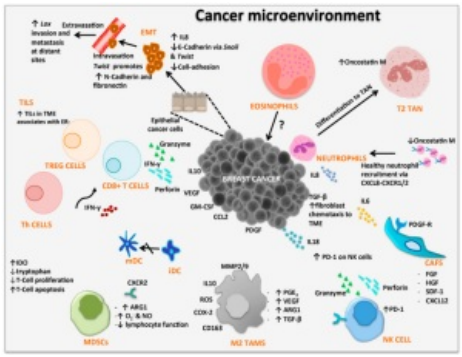
2. **Tumor stroma**

    - Fibroblasts, cells of the immune system , endothelial cells (vessels)
    - Provides nutrition and support
    - Transport functions (signal transmission, reservoir and leaching of growth factors, cytokines and others)
    - Key role in tumor angiogenesis and metastasis

The ratio between the parenchyma and the stroma determines the consistency of the tumor:

- **predominance of stroma** —> solid to hard tumor (scirhotic tumor)
- **predominance of parenchyma** —> soft (medullary tumor)

The formation of a tumor stroma takes place in parallel with the proliferation of tumor cells.

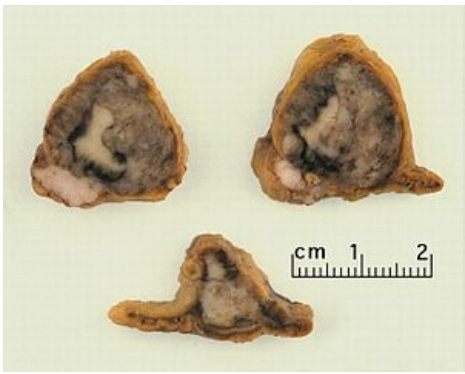


Communication in the tumor microenvironment

- The initial process is the leakage of plasminogen, fibrinogen and other coagulation factors from blood vessels due to increased capillary permeability (this is induced by the action of VEGF - vascular permeability factor, released by tumor cells)
- Thus, an extracellular fibrin gel is formed, into which fibroblasts enter , which, under the influence of other factors, proliferate and form a tumor stroma.
- Tumor cell proliferation and tumor growth are linked to a suitable microenvironment (stroma), but also dependence on the ability to migrate, penetrate blood vessels and metastasize - here is the key role of enzymes of the generic name metalloprotease (MMP) - a large family (collagenases, elastases, gelatinases and others).) and these arise predominantly in stromal cells (fibroblasts) in response to the presence of tumor cells.
- MMPs are significantly involved in the process of metastasis and angiogenesis.

Metastases

- Hidden spread to areas anatomically distant from the primary deposit
- The tumor can spread directly (if it grows into serous cavities), tumor cells can attach and proliferate on the surface of other organs (***implant metastases***) or spread through hollow organs (***porogenic metastases***)
- It is mostly a **multi-stage process**, taking place in 4 metastatic cascades and is the result of a disturbed balance between activating and inhibiting factors
- The trigger mechanism responsible for changing the cellular phenotype to metastatic is probably a mutation in the **ras** oncogene



Adrenal metastasis

Stages of the cascade

1. **Invasion of the tumor into the environment (necessary penetration of the tumor cell through the basement membrane and interstitial stroma)**

    - *Basement membrane* - contains type IV collagen and specific glycoproteins (laminin, fibronectin)
    - *Interstitial stroma* - collagen type I. and III., elastin , proteoglycan
    - Tumor cells interact with the basement membrane through receptors (receptors for laminin and mainly for integrins) - the cell adheres to the basement membrane through the receptor → self-disruption of the membrane by proteolytic enzymes (released from tumor cells) - mainly metalloproteases (mainly collagenases - collagen proteolysis IV .), serine proteases, cysteine proteases
    - After membrane disruption → invasion of tumor cells mechanically (at increased pressure inside the growing tumor)
    - The tumor cell penetrates the lymphatic and blood capillaries (key invasive factor: E-cadherin)

2. **Lymphatic / blood transport of tumor cells**
    - There are connections between the two vascular systems - the presence of a tumor cell in the node triggers an immune response (the node enlarges, it can also increase due to tumor infiltration, if the immune system has failed)
    - *Penetration into the circulation* - tumor cells are in an unfavorable environment (only a fraction survives) - cells are eliminated: non-specific destruction (macrophages , granulocytes), immunological mechanisms (T-lymphocytes , NK-bb.), mechanical factors (blood turbulence), so-called ***oxygen effect*** (increased oxygen tension in arterial blood and lung capillaries) and the effect of NO (released from activated macrophages, has a cytotoxic effect and induces apoptosis , on the other hand facilitates the attachment of tumor cells to the endothelium - causes vasodilation and potentiates aggregation) plates)
3. **Nidation of tumor cells and their penetration into the tissue**
    - Most often in the capillary network of parenchymatous organs
    - In the circulation, tumor cells form platelet aggregates, the aggregate is more easily trapped in the capillaries
    - Platelet adhesion (adhesion molecules: cytoadhesins, E-cadherin) and their degranulation (release of eg thromboxane A2); causes irreversible aggregation and fixation of the thrombus with tumor cells on the vessel wall
4. **Penetration of attached cells back into the tissue (similar to the first stage)**
    - PDGF (platelet- derived growth factor) stimulates, among other things, the proliferation of micrometastasis cells, and at the same time released serotonin can facilitate the penetration of tumor cells by altering the permeability of capillaries
    - The microembolus is resistant (compared to free tumor cells) because it is coated with fibrin (formed as a product of plasma coagulation), the coating protects the cells against mechanical trauma and masks the tumor cells from immunocompetent lymphocytes

Growth metastasis

- Cells can differentiate (eg in neuroblastoma) or nap at rest without losing their proliferative potential, or they can continue to metastasize (so-called ***metastasis metastases***)
- Proliferation of metastasis is linked to the presence of different ***proliferative (growth) factors*** , the concentration of which is different in different organs, as well as the concentration of inhibitors of these factors
- Examples of factors: PDGF, factors produced by own tumor cells, oncogene products - eg TGF-α, EGF, PDGF (c-sis, c-myc, c-erb) having growth factor activity
- Assuming the growth of metastasis: a continuous ***supply of nutrients*** and ***O 2***
- Simple diffusion is enough to feed a maximum of micrometastasis of 1-2 mm!
- Greater metastasis - needs its own vascular supply - this is ensured by new blood vessel formation: angiogenesis (tumor hypoxia stimulates angiogenesis)

Angiogenesis

- neovascularization
- application under physiological circumstances (embryo development, wound healing, menstrual cycle)
- multistage process (cascade) regulated by a set of humoral agents (cytokines, integrins, adhesion molecules, proteolytic enzymes, etc.)
- under normal circumstances, the stimulating factors are in balance with the angiogenesis inhibiting factors, loss of balance → disorder
- ***course of angiogenesis:*** first vasodilation, endothelial cell stretching, disruption of the basement membrane (enzymatically and mechanically), leakage of fibrinogen and plasminogen → conversion to fibrin and plasmin
- endothelial cells first form "buds" on the vessel, increased proliferative activity of endothelium allows the growth of a "shoot" on the matrix of fibrin fibers
- the newly formed vessel later stabilizes, pericytes are activated, and the basement membrane and lumen are formed
- migration of endothelium towards the tumor locus is induced by humoral stimuli from tumor angiogenic cells, they produce in addition to factors also proteolytic enzymes
- stromal and endothelial production of collagenase IV is important. - membrane disruption allows endothelial migration (tumor cells and metastasis)
- fibrinogen and plasminogen escape through the damaged vessel → extravascular deposits of fibrin are formed, which further form a matrix for the growth of a newly formed vessel (or tumor)
- vascularization of the tumor site will allow perfusion of the tumor and its further growth
- once the vessels reach the tumor site, the paracrine mechanisms by which both populations (tumor and endothelial) are affected
- endothelium produces a large number of mitogens and motogens (agents affecting motility) - hl. PDGF, IGF-, IL-6, IL-8 and others
- that is, there is a close relationship between angiogenesis and metastasis
- the more intense the angiogenesis, the higher the risk of metastases and the worse the prognosis of cancer
- the degree of angiogenesis may serve as a useful prognostic factor
- inhibition of angiogenesis - could be one of the treatment modalities

Overview of the most important angiogenic factors

- **FGF** (fibroblast growth factor) - growth factor for fibroblasts, a significant mitogen of endothelial cells, released from activated T-lymphocytes, macrophages, tumor cells
- **VEGF** (vascular endothelial growth factor) - growth factor for endothelium, its release induces TGF-β in fibroblasts, also stimulation of MMP production
- **TNF-α** (tumor necrosis factor) - released from activated monocytes and macrophages, is used in the degradation of the basement membrane as an activator of MMPs, stimulates the release of some cytokines (IL-1) and adhesion molecules, induces intravascular coagulation and can cause vascular occlusion and tumor necrosis
- **MMP** - metalloproteases, enzymes, proteolytic effect on the basement membrane of endothelium and extracellular matrix, facilitate angiogenesis by creating space for a newly emerging vessel, support invasion of bb tumor into blood vessels (importance for angiogenesis and metastasis)
- **PDGF** - mitogen, stimulates fibroblast proliferation and collagen production, importance for the formation of a new lumen of the vessel
- **TGF-α** - activates protein kinases, stimulates endothelial proliferation
- **other factors:** angiogenin, angiopoietin, PD-ECGF, IL-1 (stimulation of mitogenesis), IL-6 (effect on tumor cell migration) and others

Anti-angiogenic factors

- their suppression will allow angiogenesis
- **thrombospondin** (produced by fibroblasts under the control of the suppressor gene p53 , when the gene is mutated in a growing tumor, its concentration decreases)
- **others:** angiostatin, endostatin, interferons (α, β) and others

Tumor immunology

- tumor cells - have altered antigenic composition
- it is important for the clinician whether the antigen is a specific marker for the given tumor (detection and monitoring of the tumor) or if it can fulfill the function of a "rejection" antigen (therapeutic purposes)
- immunological mechanisms - an important part of the processes by which the organism prevents the development of cancer, provided by a whole complex of specific and non-specific reactions
- in the case of cell-mediated immunity, a direct cytotoxic effect on the tumor cell is essential → it is realized by various immunocompetent cells and their products, whose activity is dependent on mutual interactions mediated by interleukins and cytokines
- specific response - T-lymphocytes , have a heterogeneous population
- macrophages : phagocytose and present antigen, after stimulation they start to produce IL-1 → it activates Th-lymphocytes (helper) in their gradual differentiation into cells producing IL-2 and other cytokines
- IL-2 responsible for the clonal expansion of subpopulations of lymphocytes, including Tc-lymphocytes (cytotoxic) - these are the terminal effector cells, responsible for the specific destruction of the tumor cell
- dendritic cells - arise from myeloid precursors by the action of hematopoietic factors, main role: antigen presenting cells (APC), produce cytokines important for the primary immune response (IL-1, IL-6, other IL)
- NK-cells - large granular lymphocytes, belonging to the T series, but independent of thymus, kill tumor cells or cells infected with the virus spontaneously without prior sensitization
- neutrophilic leukocytes - upon their entry into the tumor locus (supported by selectins and integrins) release chemokines and cytokines - these further modulate the reactions between humoral and cellular immunity
- humoral immune responses - the importance of B-lymphocytes , after stimulation with antigen and with the coordinated participation of helper T-lymphocytes mature into a plasma cell producing specific antibodies
- antibodies : either antitumor effect by themselves, but more often by binding and activation of complement they induce its cytotoxic effect

References

Related articles

- Mechanisms of cancer development
- Oncogenesis
- Molecular mechanisms of neovascularization

References

- Lecture: MUDr. Zikán
- KLENER, P, et al. *Klinická onkologie.* 1. edition. Praha : Galén, 2002. 686 pp. ISBN 8072621513.
- DEAN, M – FOJO, T – BATES, S. *Tumour Stem Cells and Drug Resistance: Drug Resistance in Cancer Cells* [online]. ©2005. The last revision 2006, [cit. 28. 12. 2009]. <https://login.medscape.com/login/sso/getlogin?urlCache=aHR0cHM6Ly93d3cubWVkc2NhcGUuY29tL3ZpZXdhcnRpY2xlLzUwMjgxNV81&ac=401>.
- Cleveland Clinic Foundation. *Chemotherapy Resistance* [online]. ©2005. [cit. 28. 12.

2009]. <http://chemocare.com/chemotherapy/what-is-chemotherapy/what-is-drug-resistance.aspx>.

- PEREZ-PLASENCIA, C – DUENAS-GONZALEZ, A. *Can the state of cancer chemotherapy resistance be reverted by epigenetic therapy? (Molecular Cancer 2006, 5:27)* [online]. ©2006. [cit. 28. 12. 2009]. <https://molecular-cancer.biomedcentral.com/articles/10.1186/1476-4598-5-27>.

Kategorie:Patobiochemie Kategorie:Onkologie Kategorie:Vnitřní lékařství Kategorie:Chirurgie