Molecular mechanisms of metastasis

Metastatic initiation

The individual tissues are separated by two types of extracellular matrix (basement membranes, interstitial connective tissue). There are collagens, glycoproteins (laminins, fibronectins) and proteoglycans. Regulatory proteins and growth factors are also found in this matrix. The binding of epithelial cells to the basement membrane lamin and collagen polarized to the basal surfaces is mediated by **transmembrane integrins**. Under normal circumstances, genes whose products are integrins involved in the adhesion and quiescent differentiation of cells are expressed. When cancer develops, these genes are suppressed and other genes that express proliferation- and migration-promoting integrins are activated. In addition, integrins are also involved in signaling to and from cells into the extracellular matrix.

Tumour-cell invasion

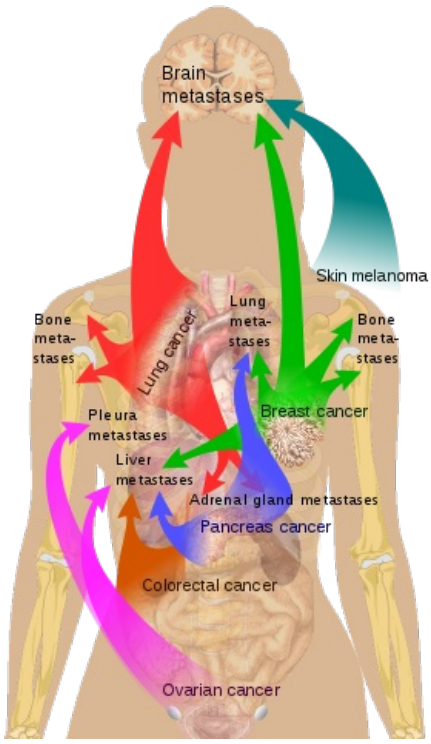
In order for a tumor subclone (metastasis) to form, tumor cells must cross several barriers. In tumors of epithelial origin, the basement membrane is disrupted, penetration through the interstitium, followed by vascular basement membrane disruption and penetration through the endothelium into the circulation. However, these steps are performed in reverse order by the tumor cells at the site of initial metastatic spread.
It is required for invasion:

1) **Release of tumor cells from interconnections and detachment from the basement membrane**

- Mutation in the gene for cadherin, which mediates intercellular junctions.
- Alteration in the expression of other integrins (see above). .

2) **Degradation of the extracellular matrix and binding to new components of the extracellular matrix**

- Proteolytic components (metalloproteinases, cathepsins, urokinase) are produced directly by tumor cells, or they are formed at the site of inflammation around the tumor after induction from tumor cells (consisting of inflammatory cells and fibroblasts).
- There are growth factors in the extracellular matrix that are released during ECM degradation and promote the growth, chemotaxis and neovascularization of tumor cells. The cleavage products of collagen and proteoglycans have the same function.
- Matrix proteolysis is also affected by molecules with inhibitory mechanisms (metalloproteinase inhibitors, serpins, cystatins). However, their level is not so high and the physiological balance is shifted towards ECM degradation.



Examples of metastasis of common tumors

3) **Tumor cell migration**

- The most important component of tumor cells are their **cytoplasmic projections - invadopodia**, which affect the passage of the extracellular matrix. They can alter adhesive molecules, contain some proteinases and are involved in migration.
- Tumor cells can invade the ECM in three ways:

1. by taking the form of mesenchymal cells ,
2. using pseudopodia (ameboid migration - the same as when leukocytes pass through the vascular bed),
3. if the tumor cells retain their intercellular junctions, they pass in bundles.

Intravasation of tumor cells and their movement in the vascular bed

When invading tumor cells into blood vessels (intravasation), the same mechanisms are applied as when entering through the basement membrane epithelium. Tumor cells penetrate the vessels that form de novo at the site of the primary tumor much better. These vessels have imperfectly formed endothelial connections. Tumor cells can enter the vascular bed individually or in groups. Their movement is passive, they can also move around the walls of the endothelium. Immune response mechanisms are involved in vascular clearance.(NK cells, monocytes). The physical properties of the blood also have a great influence (hydrostatic pressure, which can disrupt the wall of tumor cells). When tumor cells move in the vascular bed like microemboles (along with leukocytes, platelets, fibrin), they have a much better chance of survival than if they moved alone.

Colonization of tumor cells at sites distant from the primary tumor

In the capillaries of the vascular bed, tumor cells may stop due to their size. Tumor cells can be up to twice the diameter of capillaries. In addition, tumor cells also adhere to endothelial intercellular junction sites. After their attachment and retraction, apoptosis may occur, which was induced by a loss of adhesion to the stroma or an inappropriate reaction between the stroma and the cell. We call this state **anoikis**. The endothelium, which can produce nitric oxide that induces tumor cell death, is also involved in antimetastatic action.
Only a small proportion of the tumor cells that were in the vascular bed eventually become entrapped in the metastatic deposit. In addition to **the ability to survive** translocation through the vascular bed, **growth factors** located at the site of the emerging metastasis also play an important role. Some tissues and organs do not allow the growth of a metastatic clone. These include, for example: spleen, skeletal and cardiac muscle. Metastases occur here in the most aggressive tumors (small cell lung cancer). Last but not least, we must not forget to mention **the ability to induce new blood vessel formation** by tumor tissues.

Links

Related articles

- Tumors
- Mechanisms of tumor formation
- Neovascularization
- Tumor microenvironment

Bibliography

- POVÝŠIL, Ctibor – ŠTEINER, Ivo. *Obecná patologie.* 1. edition. Praha : Galén, 2011. vol. 290. ISBN 978-80-7262-773-8.