

## METASTASIS — QUO VADIS?

Metastasis development is a dramatic clinical stage of malignant tumor progression. It is the end product of a process, in which genetic instability of tumor cells, interactions between cancer cells and their microenvironment yield alterations that allow tumor cells to surmount physical boundaries of primary affected organ, to disseminate and colonize the distant organ. Tumor cells, which are capable to metastasize, are generated as a result of complex molecular and cellular processes driven on the genetic and epigenetic levels. Metastatic features of tumor cells define their ability to invade normal organs and tissues, penetrate via the walls of blood vessels to the bloodstream (intravasation), survive in the process of circulation, and to get into the new organ for colonization.

Not all tumors are metastatic, and nor all cells within metastatic tumors are capable of metastasizing. Tumors of comparable size and histology can have widely different metastatic potential, depending on their genotype (determining specific cellular adhesion and tumor cell motility, spectrum of secreted proteolytic proteins, pro-angiogenic factors, growth factors and cytokines) and local microenvironment, created by target organ and the whole organism. The metastatic expansion of tumor cells is a highly ineffective process as only less than 0.05% of circulating tumor cells develop into metastatic colonies. Nevertheless, the prevention of metastasis development assures the success in treatment of cancer patients.

The mechanisms underlying the causes of metastasis are still unclear, despite of comprehensive studies of tumor cell biology. It is mainly due to the lack of research in the field of primary tumor cell microenvironment (second “player of the process”) and/or features of metastasis target tissues. By other words, to find the solution to a problem of malignant tumor metastasis, scientists should carry out the fundamental research on the advanced molecular and cellular methodological level in the field of “tumor-organism” relationships, formulated in XX century by academician R.E. Kavetsky and his scientific school.

The evidence suggests that tumor cells might begin conditioning distant tissues for colonization by establishing a so-called pre-metastatic niche, which provides “comfortable” metabolic media for following colonization by tumor cells. Tumor cells could penetrate host tissue barriers (e. g.: walls of blood vessels) with the help of proteolytic enzymes, synthesized by normal cells, which were locally activated by tumor cells. The appearance of the new malignant cells in the invaded tissue is associated with a local reorganization

of the stroma, blood vessels, lymphatic and epithelial cells morphology, changes in the reactions of nonspecific and specific host immune responses and in the metabolism of the whole organism.

It was also shown that the preference of tumor cell for metastasizing to specified target organs is highly connected with the special features of these organs. Circulating tumor cells could respond on the soluble factors, which are locally secreted by potential target tissue. For example, the high level of insulin-like growth factor-1 (IGF-1) in liver and lung tissue attract metastatic tumor cells of breast cancer. Muller *et al.* (2001) proposed that chemokines and their receptors have a critical role in determination of the metastatic destination of tumor cells. In particular, breast cancer cells metastasis to regional lymph nodes, bone marrow, lung and liver is regulated by receptor-ligand interaction between CXCR4 and CXCL12. *In vitro* stimulation of breast cancer cells by CXCL12 mediates the development of features that promotes invasion: pseudopodia formation and actin polymerization. *In vivo*, the interactions of CXCL12 and CXCR4 were neutralized by anti-CXCR4 monoclonal antibodies, which significantly impaired metastasis of breast cancer cells.

Therefore, the molecular and biochemical regulation of metastasis development is not already a “black box” to a full extent. But still there are some principal questions remaining to be answered:

- Why tumor cells in specified primary tumor get different abilities for invasion and metastasis?
- Which factors determine the colonization of specified target organ by different tumor cells?
- What are the reasons of the development of resting metastasis? Which factors could stimulate them? Which factors govern the duration of resting period?
- Is there any relation between the changes in target tissue stroma, induced by tumor cells, and pharmacokinetics of anti-tumor, anti-angiogenic and biotherapeutic drugs?

At last, the new methods should be developed to identify the “critical points”, which distinguish the locally distributed tumor from disseminated tumor, and to find out the biomarkers of invasion and tumor metastatic potential.

Getting the answers to the stated questions would improve and expand the approaches to effective cancer prevention and treatment of patients with malignant tumor metastasis.

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