

Invasión del cáncer y metástasis

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Artículo completo

Introduction

Metastasis is defined as the transfer of disease from one organ or tissue to another not directly connected with it. Approximately 90% of all cancer patients die from metastases [1, 2]. The understanding of molecular mechanisms which lead to metastasis is not only a great challenge in experimental cancer research, it may also reveal key targets against which therapeutic strategies should be directed. The metastatic cascade is an ordered sequence of events required for metastasis to occur. The order of these events can vary among different types of cancer [3], e.g. in the mechanisms of invasion and types of metastasis. Some new aspects of cancer invasion and metastasis will be briefly outlined in this contribution.

Cancer Invasion

The existence of an invading cancer does not necessarily imply metastasis and a fatal outcome. Invasion is certainly a prerequisite for metastasis, e.g. without invasion no metastasis [1, 2, 4–6]. There are many steps in the cascade from the initiation of cancer to metastasis and death:

initiation] growth] angiogenesis] progression]
selection] detachment] adhesion at the basal membranes
] destruction of the basal membranes] motility
] adhesion at the basal membranes of vessels] migration
through the vessel wall] survival in the vessel and
embolization] destruction of the vessel membranes in
metastatic organs] local factors] invasion and growth
of metastasis.

Firstly, acquired genetic susceptibility enables the stepwise selection of variant sublines of cancer cells. In a minority of cells, loss of cell-cell adhesion will occur during growth. Proteins (e.g. RAGE, i.e. receptor for ad-

vanced glycation endproducts) and amphoterin have been identified as a receptor-ligand pair in molecular checkpoints that regulate invasiveness, growth and spread of tumor cells. Regulation of the molecular events necessary for invasion involves a spatial and temporal coordination, cyclic on-off processes (at the level of individual cells) and a motility coupled with regulated, intermittent adhesion to the extracellular matrix (ECM), which allows an invading cell to move through the three-dimensional matrix. Several gene families are involved in invasion: matrix metalloproteinases, urokinase plasminogen activator/receptor, integrins, cathepsins and many others, most of which are presently undetected. The functions of proteins encoded by the genes are the deregulation of adhesiveness of tumor cells with each other as well as of tumor cells with ECM, the synthesis of proteases, spread of tumor cells, cytoskeleton remodeling and the synthesis of new ECM components (ECM remodeling). In a tumor, the close proximity of neoplastic and non-neoplastic cells (e.g. fibroblasts, pericytes and inflammatory, endothelial and myoepithelial cells) affects the microenvironment of the ECM. The microenvironment is modified and remodeled by proteases. It has to be borne in mind that the host stroma is responsible for most of the increase in protease production, and cellular origins of the proteolytic machinery vary in different tumor types. A recent finding is that intratumoral hypoxia is correlated with an increased risk of invasion probably by the selection of mutations that promote invasion and by the expression of genes, the products of which promote invasion mediated by hypoxia-inducible factor 1 (HIF-1). A new finding is that the breakdown of epithelial cell homeostasis leading to aggressive cancer progression has been correlated with the loss of epithelial characteristics and the acquisition of a migratory phenotype [6]. This phenomenon, referred to as epithelial-mesenchymal transition (EMT) is considered a crucial event in late-stage tumorigenesis. A multitude of EMT models have been developed in different tissues. EMT is accompanied by loss of epithelial glycoprotein 2 (MOC-31), upregulation of matrix metalloproteinases and increased expression of N-cadherin. Recently, the diversity of molecular mechanisms contributing to the plasticity of epithelial cells has been studied. It has become evident that metastasis and angiogenesis are intrinsically connected. A further crucial element both in cancer invasion and in metastatic outgrowth is the interaction between tumor cells and stroma. Conventional wisdom assumed that invasion and metastasis are late events. The present knowledge is that invasion can be both early and clinically dormant.

Cancer Metastasis

The problem of cancer metastasis is connected with a series of open questions, a couple of which has not been completely answered. Do only few cancer cells have a metastatic potential or do most cancer cells have a metastatic potential? Is metastasis an early or a late phenomenon? A closer examination of the metastatic process reveals different types of metastases (table 1).

There is a certain probability that different mechanisms might be necessary for the different types of metastasis, assuming that the properties of cells with the ability to metastasize in a given cavity (e.g. peritoneum) might be different from those of cells which metastasize to lymph nodes or to distant organs via the bloodstream). There are new findings indicating a genetic heterogeneity of different cancer cells. Metastases isolated from different organs had different characteristic gene expression profiles [7] . Specific profiles were associated with a high metastatic potential. These profiles might be required for the primary hematogenous dissemination. Open questions are if these profiles are primary changes or results of secondary events during metastasis. It has been proposed that a subset of mutant alleles acquired by incipient tumor cells confer the selected replicative advantage and the proclivity to metastasize, a thesis supported by small and localized breast carcinomas with isolated tumor cells in the bone marrow, which have a strikingly similar gene expression pattern. Gene expression profiles of breast carcinomas predict with 90% accuracy whether a tumor will remain localized or metastasize. In mouse models, several oncogenes (*ras* and *myc*) were able to induce metastasis in cancer cells. Consequently, the tendency to metastasize may already be preordained by the spectrum of mutations that progenitor cells have acquired early in tumorigenesis, and genes and genetic changes specifically and exclusively involved in metastasis may not exist. Instead the genes involved in metastasis may be tumor suppressor genes and oncogenes. Because important components of metastasis occur early in tumorigenesis, even small primary tumor populations may already metastasize. Several factors, e.g. tumor suppressor gene inactivation, oncogene activation, intratumoral hypoxia and growth factors, affect the transcriptional activity of HIF-1, a major determinant of the invasive cancer phenotype. Metastatic heterogeneity is caused by cells with different metastatic properties. Clonal origin of metastasis is accompanied by intra- and interlesional heterogeneity. The microenvironment of the organ induces certain tumor types to metastasize to specific organs. This might be due to interactions between metastatic cells and the environment

of the organ, specific binding to endothelial cells and responses to local growth factors, all of which are influenced by chemokines. Chemokine signaling can lead to activation of RAS/MAPK pathways, intracellular actin polymerization, pseudopodial formation, cell motility, migration and tissue invasion.

A question which has not been answered experimentally is 'Do metastases themselves have the capacity to metastasize?' [8]. From a clinical point of view: yes! August et al. [9] presented a series of case studies in which they reported on 7 patients who had developed hepatic metastases from colorectal primary tumors. At laparotomy, metastatic disease was found in the lymph nodes of the hepatoduodenal ligament. It was suggested that the lymphatic metastasis was due to re-metastasis of the hepatic metastasis. Further examples are lymph node metastases in hilar lymph nodes of the lung in cases of lung metastases of colorectal carcinoma and without any other evidence of lymphatic or hematogenous spread. Experimental models have, however, been inconclusive [10].

Although isolated tumor cells from a primary tumor are frequently detected in the blood or different organs (mostly in bone marrow isolates), the number of micrometastases is much lower (1/40) [8], and only 1% has the ability to develop macrometastases [8, 11].

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Table 1. Types of metastases

Implantation metastasis

Intracavitary (peritoneal metastasis)

Intraluminal (e.g. transitional cell carcinoma)

Iatrogen

Lymph node metastasis in regional lymph nodes or non-regional lymph nodes

Hematogenous metastasis in distant organs (primary and secondary)