EXPERIMENTAL CELL RESEARCH 319 (2013) 1604–1610

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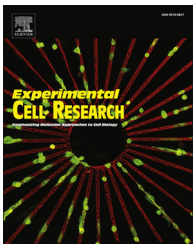
journal homepage: www.elsevier.com/locate/yexcr



Review Article

Metastasis: New insights into organ-specific extravasation and metastatic niches

*Anja Irmisch, Joerg Huelsken**

Ecole Polytechnique Fédérale de Lausanne, Swiss Institute for Experimental Cancer Research and National Center of Competence in Research "Molecular Oncology", 1015 Lausanne, Switzerland

ARTICLE INFORMATION

Article Chronology:
Received 8 February 2013
Accepted 15 February 2013
Available online 21 February 2013

Keywords:
Metastasis
Niche
Cancer stem cell
Extravasation
Colonization

ABSTRACT

The appearance of clinically detectable metastases is the end-point of a complex set of biological processes only few cancer cells are capable to complete. Metastatic colonization comprises the most inefficient metastatic steps as it requires a fine-tuned crosstalk between the disseminated cancer (stem) cells and their host microenvironment. The origin of the cancer cell and its intrinsic properties are factors that together with the organ microenvironment and circulation patterns determine the site of metastatic spread, the dormancy period and the extent of metastasis formation. Recent advances provide novel insights into the molecular components required for organ-specific infiltration, the composition of growth-supportive metastatic niches in different tissues and the cancer cell-niche crosstalk.

Contents

**Corresponding author.* Fax: +41 21 693 0770.
E-mail address: joerg.huelsken@epfl.ch (J. Huelsken).

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http://dx.doi.org/10.1016/j.yexcr.2013.02.012

Introduction

Many tumors are capable of metastatic spread to distant organs. Due to its systemic distribution and resistance to existing drugs, metastasis is still largely incurable [1]. Thus improved understanding of the mechanisms involved in each step of metastasis is necessary to unravel novel drug targets and prognostic markers of distant relapse.

Cancer progression towards metastasis involves a sequence of events termed the metastatic cascade. This cascade is initiated by single or groups of cancer cells leaving the confined primary tumor to invade the surrounding extracellular matrix (ECM) and stroma. After intravasation either into lymphatic or blood vessels and survival in the harsh environment of the circulation, tumor cells become arrested at a distant site and extravasate into the surrounding tissue [1]. There they must adapt to the foreign tissue environment to survive. In a process termed metastatic colonization few cancer cells progress to form micrometastases. Alternatively, disseminated cancer cells might initiate growth intravascularly and form micrometastases which eventually disrupt the vessel wall [2]. In the final step of the cascade, micrometastatic colonies proliferate to form clinically detectable macrometastases. The progression from micro- to macrometastatic growth thereby requires the metastatic colony to undergo an "angiogenic switch"—an induction of a transcriptional program producing pro-angiogenic signals that will recruit new vasculature to ensure sufficient oxygen and nutrient supply [3].

This review will highlight recent advances in understanding the mechanism of the later steps of the cascade: organ-specific extravasation, organ colonization and macrometastasis formation.

Inefficiency of metastasis and dormancy

It is well known from clinical and experimental observations that the metastatic cascade is a highly inefficient process. When B16F1 melanoma cells are injected intraportally to target the liver of mice only about 0.02% of the injected cells develop into liver macrometastasis 13 days after injection. Whereas 82% of melanoma cells survive in the circulation and extravasate, only 2.5% form micrometastases and of these only 1% develop into macrometastases [4]. This suggested that the most rate-limiting steps in the metastatic cascade occur after extravasation during metastatic colonization and the outgrowth of macrometastases. Whereas the high efficiency of extravasation was confirmed by other studies, it appears that the most rate-limiting step depends on the metastasis assay and cell type used. B16F1 melanoma cells injected into the vena cava of mice develop few micrometastases in their lungs but these grow efficiently into macrometastases [5]. Similarly Panc-1 human pancreatic cancer cells injected for liver metastasis assays are efficient in macrometastasis outgrowth whereas Capan-1 pancreatic cancer cells in the same assays are inefficient in micro- and macrometastasis formation (C. Urech, our own unpublished observation).

Consistent with the notion of metastatic inefficiency, in a pooled analysis of 4703 breast cancer patients, 30% presented with hundreds to thousands of bone marrow micrometastasis, as indicated by the presence of pan-cytokeratin-positive cells in bone marrow aspirates, but of these only 50% developed distant macrometastasis in the 10-year period after primary tumor removal [6]. Similarly, in prostate cancer and melanoma distant relapse might occur years to decades after surgical resection of primary tumors [7]. This implies that cancer cells had disseminated from the primary tumor prior to its removal and survived as solitary cancer cells or micrometastasis for years in a stage of dormancy. During this period the disseminated cancer cells and/or their new microenvironment are thought to undergo changes which eventually allow outgrowth of macrometastases.

Which factors lead to evasion or persistence of dormancy and which pathways are required for survival of dormant cells are clinically important questions which are mostly unanswered. Several mechanisms have been proposed to explain the period of metastatic dormancy. Extravasated, solitary tumor cells which encounter a non-orthotopic microenvironment might enter a G0–G1 growth arrest phase ("cellular dormancy") if they are unable to interpret signals from the microenvironment and/or remodel it into a supportive niche [8]. One elegant study of dormant breast cancer cells in mice revealed how a gain of function in the dormant tumor cells enables them to induce a metastasis-supportive environment. Dormant breast cancer cells in the bone can over time evolve to express the cell adhesion receptor VCAM-1 and secret its soluble form. By interacting with the $\alpha4\beta1$-receptor, VCAM-1 attracts $\alpha4\beta1$-positive osteoclast progenitors and promotes osteoclast activity. This initiates a vicious cycle of bone degradation and growth factor release from the bone matrix, which promotes further cancer cell proliferation [9].

In different scenarios, disseminated cells proliferate and undergo apoptosis at the same rate resulting in no increase of the net colony size ("mass dormancy"). Here a change in survival signaling induced by alterations in the stroma may tip the balance and lead to metastasis outgrowth. In a process termed angiogenic dormancy, micrometastases are thought to reach a certain size but then fail to induce an "angiogenic switch" to attract neovasculature. Thus hypoxia and nutrient depletion lead to high levels of apoptosis which are compensated by proliferation. Furthermore, the immune system can prevent the expansion of a proliferating micrometastatic colony. In mouse models this effect is mediated by cytolysis induced by cytotoxic $CD8^+$ T cells. However, cancer cells can evade immunosurveillance-induced dormancy e.g., through reduced expression of tumor antigens [8].

Nonetheless, not all tumor types undergo a period of long metastatic dormancy. For example lung and pancreatic adenocarcinomas might form metastases within months of primary tumor diagnosis. This suggests that cancer cells disseminating from these primary tumors either rapidly acquire metastatic traits or that primary tumor cells are already highly metastasis-competent [7].

Cancer stem cells in metastasis

The observation that extravasated solitary or small groups of cancer cells can outgrow to macrometastases, in some cases even years after their extravasation, suggests the involvement of metastatic cancer stem cells (mCSCs). Although many studies have analyzed the cancer stem cell (CSC) phenotype in primary tumors (see [10] for review), knowledge on cancer stem cells in metastasis is just beginning to emerge.