Acta histochemica **112** (2010) 3—25

Available online at www.sciencedirect.com

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acta histochemica

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REVIEW

Molecular interactions in cancer cell metastasis

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Received 2 October 2008; received in revised form 13 November 2008; accepted 13 November 2008

KEYWORDS
Cancer metastasis;
Review;
Integrins;
Cathepsins;
Selectins;
Proteinases;
Angiogenesis

Summary

Metastasis, the process by which cancer cells leave the primary tumour, disseminate and form secondary tumours at anatomically distant sites, is a serious clinical problem as it is disseminated disease, which is often impossible to eradicate successfully, that causes the death of most cancer patients. Metastasis results from a complex molecular cascade comprising many steps, all of which are interconnected through a series of adhesive interactions and invasive processes as well as responses to chemotactic stimuli. In spite of its clinical significance, it remains incompletely understood. This review provides an overview of some of the molecular interactions that are critical to metastasis. It summarises the principle molecular players in the major steps of the metastatic cascade. These are: (1) tumour angiogenesis, (2) disaggregation of tumour cells from the primary tumour mass, mediated by cadherins and catenins, (3) invasion of, and migration through, the basement membrane (BM) and extracellular matrix (ECM) surrounding the tumour epithelium, and subsequent invasion of the BM of the endothelium of local blood vessels. This is mediated through integrins and proteases, including urokinase form of plasminogen activator (uPA), matrix metalloproteinases (MMPs) and cathepsins, (4) intravasation of the tumour cells into the blood vessels prior to hematogeneous dissemination to distant sites, (5) adhesion of the circulating tumour cells to the endothelial cell lining at the capillary bed of the target organ site. This occurs through adhesive interactions between cancer cells and endothelial cells involving selectins, integrins and members of the immunoglobulin superfamily (IgSF), (6) invasion of the tumour cells through the endothelial cell layer and surrounding BM (extravasation) and target organ tissue and (7) the development of secondary tumour foci at the target organ site.

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doi:10.1016/j.acthis.2008.11.022

Contents

Introduction

Metastasis results from a complex molecular cascade through which cancer cells leave the site of the primary tumour mass and disseminate to distant anatomical sites where they proliferate and form secondary tumour foci. Disseminated disease is the most usual cause of death in cancer patients and is, therefore, a very serious clinical problem. It remains poorly understood. Robert Weinberg (1999) in his book 'one renegade cell' says 'our understanding of metastasis is still fragmentary. The principles that guide the migratory routes of most cancer cells are as mysterious as those that guide the monarch butterfly. For the cancer researcher, the process of metastasis remains *terra incognita*, still largely unexplored', and almost a decade later, in spite of some significant advances, this remains mostly true.

Metastasis is often described as a 'cascade' of events, since there are many steps, all of which are interconnected through a series of adhesive interactions and invasive processes, as well as responses to chemotactic stimuli. A metastatic tumour cell needs to successfully complete the entire cascade, and it is widely believed that the vast majority of cancer cells are unable to do so (Fidler, 1970; Luzzi et al., 1998; Wong et al., 2001). Until recently, the accepted paradigm was that owing to the inherent genetic instability of tumour cells, as cancers progressed, individual cells gradually acquired characteristics such that eventually metastatic sub-clones emerged (e.g. see Fidler, 2003). Recent research has challenged this idea. Gene microarray experiments seeking 'signatures' or profiles of genes that are associated with metastatically competent, poor prognosis tumours show promise in being able to identify individual patients at high risk of metastatic disease who would benefit from early aggressive adjuvant therapy. These studies have also, intriguingly, provided evidence that predictive profiles of metastasis-associated genes are present at an early stage in tumorigenesis, rather than acquired later as disease progresses. Metastatic competence may, therefore, be 'hardwired' into tumours from an early stage (Ramaswamy et al., 2003; Glinsky et al., 2005; Glinsky, 2006; Weigelt et al., 2005). Moreover, there is currently a debate over the existence of cancer stem cells, inherently resistant to current therapies, which have the ability to repopulate primary or metastatic tumours following treatment (Behbod and Rosen, 2005; Wicha et al., 2006; Jordan et al., 2006; O'Brien et al., 2007; Ricci-Vitiani et al., 2007).

The steps involved in the metastatic cascade are illustrated in Figure 1 and are well described by Chambers et al. (2002) and (Fidler, 2003). They can be summarised as follows:

(1) The development of a new blood supply to the growing tumour (angiogenesis).
(2) The escape of tumour cells from the primary tumour mass.
(3) Invasion of, and migration through, the basement membrane (BM) and extracellular matrix (ECM) surrounding the tumour epithelium, and subsequent invasion of the BM supporting