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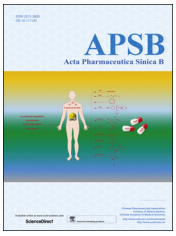

REVIEW

Cancer metastases: challenges and opportunities

Xiangming Guan*

Department of Pharmaceutical Sciences, College of Pharmacy, South Dakota State University, Brookings, SD 57007, USA

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Abstract Cancer metastasis is the major cause of cancer morbidity and mortality, and accounts for about 90% of cancer deaths. Although cancer survival rate has been significantly improved over the years, the improvement is primarily due to early diagnosis and cancer growth inhibition. Limited progress has been made in the treatment of cancer metastasis due to various factors. Current treatments for cancer metastasis are mainly chemotherapy and radiotherapy, though the new generation anti-cancer drugs (predominantly neutralizing antibodies for growth factors and small molecule kinase inhibitors) do have the effects on cancer metastasis in addition to their effects on cancer growth. Cancer metastasis begins with detachment of metastatic cells from the primary tumor, travel of the cells to different sites through blood/lymphatic vessels, settlement and growth of the cells at a distal site. During the process, metastatic cells go through detachment, migration, invasion and adhesion. These four essential, metastatic steps are inter-related and affected by multi-biochemical events and parameters. Additionally, it is known that tumor microenvironment (such as extracellular matrix structure, growth factors, chemokines, matrix metalloproteinases) plays a significant role in cancer metastasis. The biochemical events and parameters involved in the metastatic process and tumor microenvironment have been targeted or can be potential targets for metastasis prevention and inhibition. This review provides an overview of these metastasis essential steps, related biochemical factors, and targets for intervention.

Abbreviations: BM, basement membrane; CAFs, cancer-associated fibroblasts; CAMs, cell adhesion molecules; CAT, collective amoeboid transition; CCL2, chemokine (C–C motif) ligand 2; CCR3, chemokine receptor 3; Col, collagen; COX2, cyclooxygenase 2; CSF-1, chemokine colonystimulating factor–1; CTGF, connective tissue growth factor; CXCR2, chemokine receptor type 2; DISC, death-inducing signaling complex; ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, EGF receptor; EMT, epithelial–mesenchymal transition; FAK, focal adhesion kinase; FAs, focal adhesions; FGF, fibroblast growth factor; FN, fibronectin; HA, hyaluronan; HGF, hepatocyte growth factor; HIFs, hypoxia-inducible factors; IKK, IκB kinase; JAK, the Janus kinases; LN, laminin; MAPK, mitogen-activated protein kinase; MAT, mesenchymal to amoeboid transition; MET, mesenchymal–epithelial transition; MMPs, matrix metalloproteinases; PDGF, platelet-derived growth factor; PI3K, phosphatidylinositol 3-kinase; STATs, signal transducers and activators of transcription; TAMs, tumor-associated macrophages; TGF-β, transforming growth factor β; TME, tumor microenvironment; VCAMs, vascular cell adhesion molecules; VEGF, vascular endothelial growth factor; VN, vitronectin

*Tel.: +1 605 6885314; fax: +1 605 6885993.
E-mail address: Xiangming.guan@sdstate.edu

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1. Introduction

Cancer metastasis is a process in which cancer cells disseminate from the primary tumor, settle and grow at a site other than the primary tumor site. Most cancer deaths are caused by cancer metastasis not the primary tumor. Cancer metastasis is the primary cause of morbidity and mortality and responsible for about 90% of cancer deaths[1]. It is now accepted that tumor distribution and secondary site growth is not a matter of chance, but rather it is determined by the dependence of the 'seeds' (the cancer cells) on the 'congenial soil' (the target organ for metastasis) as proposed by the English surgeon Stephen Paget in 1889[2]. Until recently, cancer research has primarily focused on the development of methods/agents that can detect tumor at the early stage, and on agents that inhibit tumor growth. Advances in early cancer detection and treatment have rendered that most solid tumors are now manageable or curable if they are diagnosed and treated before metastasis. However, once cancers spread beyond the initial primary site, they are usually highly incurable and fatal[3]. Due to a lack of understanding of the mechanisms that underlie the metastatic process, limited success has been made on prevention and inhibition of cancer metastasis.

Metastasis is a complicated event that involves multiple sequential and interrelated steps and multi-biochemical events with much to be elucidated. Metastasis is facilitated by four essential steps: detachment, migration, invasion and adhesion. Cancer cells first detach from the primary tumor, undergo migration, invasion, and travel to different sites through blood and lymphatic vessels, then settle (adhesion) and grow. Metastasis is regulated by various signaling pathways and is affected by the surrounding extracellular matrix (ECM). It is now known that metastasis genes are stress-response genes that physiologically contribute to inflammation, wound healing, and stress-induced angiogenesis[4]. This review is aimed to provide an overview of the metastasis process and targets for intervention with a focus on cancer cell detachment, migration, invasion and adhesion. It is not the intent of this review to provide an in-depth description of each parameters related to the four essential steps and relevant intervention targets since each topic itself can be a lengthy review. It is hoped that this review can serve as a lead for readers who are interested in cancer metastasis and intervention.

2. Cancer metastasis

Cancer metastasis is a process of dissemination of tumor cells from a primary tumor mass to a different site through blood vessels and lymphatic vessels (Fig. 1). It is a complex succession of a series of cell-biological events termed the "invasion–metastasis cascade". The cascade involves the development of new blood vessels (angiogenesis), departure of metastatic cells from the primary tumor (detachment and migration), invasion through the basement membrane (BM) and ECM surrounding the tumor, invasion of the BM supporting the endothelium of local blood and lymphatic vessels, intravasation of the metastatic cells into the blood and/or lymphatic vessels, adhesion of the circulating metastatic cells to the endothelium of capillaries of the target organ site, invasion of the cells through the endothelial cell layer and the surrounding BM (extravasation), and finally the settling and growth of secondary tumors at the target organ site[5,6]. Fig. 1 provides a brief overview of the process.

Metastatic cell dissemination requires that cells first detach from the primary tumor[7–9]. Under normal circumstances, epithelial and endothelial cells will undergo apoptosis (programmed cell death) when detached, a phenomenon referred to as anoikis (induction of apoptosis caused by detachment from the ECM)[10]. During the process of anoikis, both death receptor pathways and mitochondrial pathway are activated[10]. This is a mechanism designed to protect multicellular organisms from cells establishing themselves outside

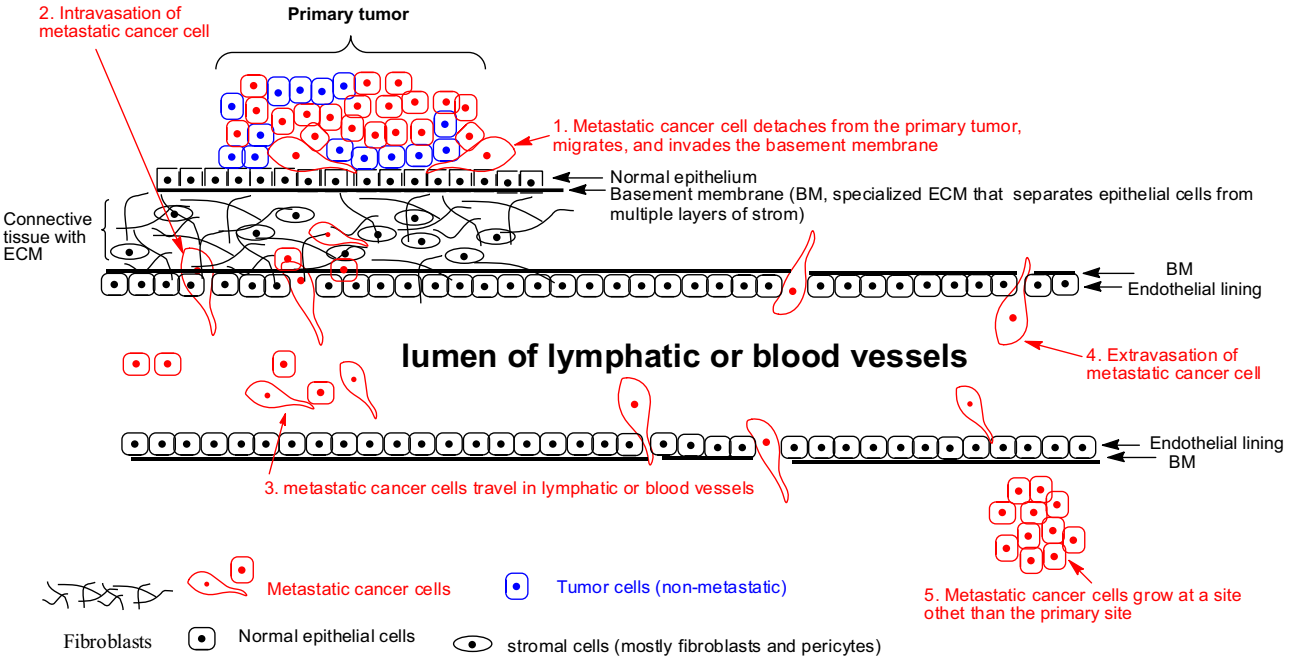

Figure 1 Metastatic cascade. Metastatic cells detach from the primary tumor site, migrate and invade through the BM and ECM, enter the blood or lymphatic vessels (intravasation), travel in the blood/or lymphatic vessels, leave the blood or lymphatic vessels (extravasation), adhere and grow at a distal site.