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Review

Drug development against metastasis-related genes and their pathways: A rationale for cancer therapy

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ABSTRACT

It is well recognized that the majority of cancer related deaths is caused by metastatic diseases. Therefore, there is an urgent need for the development of therapeutic intervention specifically targeted to the metastatic process. In the last decade, significant progress has been made in this research field, and many new concepts have emerged that shed light on the molecular mechanism of metastasis cascade which is often portrayed as a succession of six distinct steps; localized invasion, intravasation, translocation, extravasation, micrometastasis and colonization. Successful metastasis is dependent on the balance and complex interplay of both the metastasis promoters and suppressors in each step. Therefore, the basic strategy of our interventions is aimed at either blocking the promoters or potentiating the suppressors in this disease process. Toward this goal, various kinds of antibodies and small molecules have been designed. These include agents that block the ligand-recepter interaction of metastasis promoters (HGF/c-Met), antagonize the metastasis-promoting enzymes (AMF, uPA and MMP) and inhibit the transcriptional activity of metastasis promoter (β-Catenin). On the other hand, the intriguing roles of metastasis suppressors and their signal pathways have been extensively studied and various attempts have been made to potentiate these factors. Small molecules have been developed to restore the expression or mimic the function of metastasis-suppressor genes such as NM23, E-cadherin, Kiss-1, MKK4 and NDRG1, and some of them are under clinical trials. This review summarizes our current understanding of the molecular pathway of tumor metastasis and discusses strategies and recent development of anti-metastatic drugs.

Contents

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1. Introduction

Cancer is the second leading cause of death in the USA, and more than half a million people succumb to the disease every year [1]. Despite significant improvements in screening methods and treatment options, the majority of cancer patients are still diagnosed at an advanced stage, and more than 90% of patients ultimately die from sequel of metastatic disease. Therefore, metastasis is a hallmark of malignancy, and no effective therapeutic option is currently available for those patients. Although the clinical importance of tumor metastasis is well recognized, advances in understanding the molecular mechanism involved in metastasis formation have lagged behind other developments in the field of cancer research. This is attributed to the fact that cancer cells are extremely heterologous in nature and that metastasis involves multiple steps with a high degree of complexity, and each step requires coordinated action of many promoters and suppressors. However, extensive efforts in the past decade have led to the discoveries of many previously unknown factors involved in metastasis and also unveiled several novel concepts in this research field [2,3]. These findings have shed new light on molecular pathways of metastasis, which also provided valuable information about potential targets for the treatment of metastatic disease. This review discusses our current understanding of molecular mechanism of metastatic process and summarizes recent information of drug development specifically targeted to the metastatic pathways.

2. Tumor metastasis involves multi-step process with high complexity

A primary tumor generally consists of heterogeneous cell types including a small number of cancer stem cells that are able to perpetually proliferate without responding to tumor suppressor function. The current theory predicts that these cancer stem cells originate from a normal stem cell or a cancer cell, which acquired a stem cell-like ability [4]. When a tumor grows more than 1 mm^3 in size at the primary site, it acquires active supply of oxygen and nutrients by promoting angiogenesis. Tumor cells accomplish this task by generating hypoxic environment followed by secretion of angiogenic growth factors (Fig. 1). Tumor cells that gain growth advantage further proliferate and acquire metastatic phenotypes due to additional mutations. The first step in metastasis is the detachment of these tumor cells from the primary tumor mass by acquiring an invasive phenotype that results in the loss of cell-cell adhesion and cell-extracellular matrix adhesion followed by proteolytic degradation of the matrix (Fig. 1) [5]. It is believed that autocrine motility factor (AMF) and hepatocyte growth factor (HGF) are critical components of motility and that degradative enzymes including serine-, thiol-proteinases, heparanases and metalloproteinases such as MMP2 and 9 play critical roles in the invasion [6–8]. When tumor cells intravasate surrounding tumor vasculature and neighboring lymphatic vessels, they must survive in this hostile environment that includes mechanical damage, lack of growth factor from the original environment and the host immune system (Fig. 1) [9]. Tumor cells in the circulation often aggregate with platelets and fibrin, and they embolize in the capillaries or directly adhere to the endothelial cells by a mechanism similar to leukocyte adhesion at the inflammatory site [10–12]. In some cases, arrested tumor cells extravasate before proliferating themselves using the same hydrolytic enzymes that are used in the initial step of invasion (Fig. 1) [13]. However, in many cases, cancer cells actually proliferate within the lumen of vessels to create a considerable tumor mass that can eventually obliterate the adjacent vessel wall by pushing aside the barrier composed of endothelial cells, pericytes and smooth muscle cells that previously separated the vessel lumen from the surrounding tissue [14,15]. After extravasation, cancer cells lodge at the secondary sites, where the cells must also proliferate and colonize for successful metastasis (Fig. 1). These processes are controlled by various metastasis promoters and suppressors, and they must be well coordinated to establish successful distant metastasis (Table 1) [2]. Recent advancement of research in this field has revealed the complex interplay of metastatic factors and many novel concepts of signal pathways leading to metastasis (Fig. 2 a,b). Based on this information, the current research is gradually moving toward translational stage by aiming at development of targeted anti-metastatic drugs (Table 1). The following sections summarize up-to-date information of the promoters and suppressors of metastasis that are currently under active investigation for drug development.

3. Metastasis promoters

3.1. Amf

Autocrine motility factor (AMF) was originally isolated as a C-*X*-*X*-C cytokine that stimulates random or directed motility of AMF-

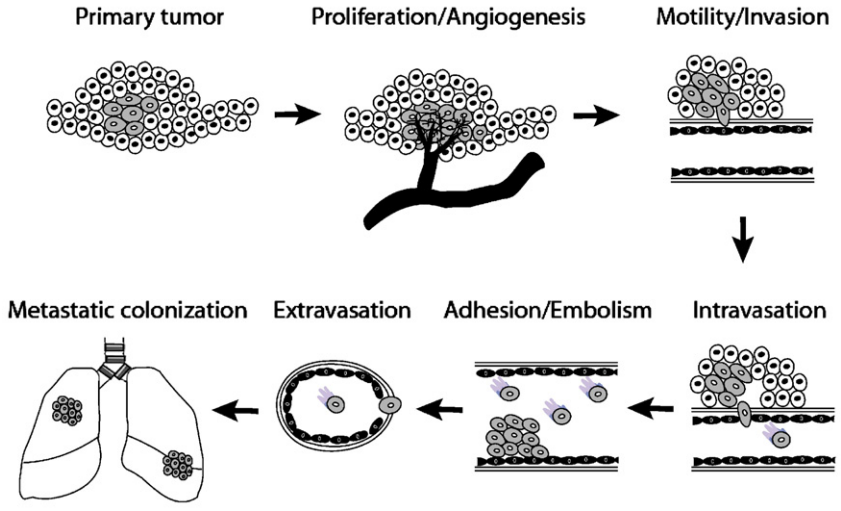

Fig. 1. Process of tumor metastasis. As primary tumor grows, tumor cells induce angiogenic factors to promote vessel formation which facilitates tumor growth and cell invasion into the circulatory system. Some tumor cells gain an invasive ability by expressing motility factors and proteases followed by breaching the basement membrane. Tumor cells then enter the blood vessel where they often aggregate with the platelets and cause embolize. When cells migrate to a distant organ, they adhere to endothelial cells and extravasate by inducing proteases. Cells then colonize and establish metastasis at the distant organ site where appropriate growth factors are provided.