Review

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The emerging molecular machinery and therapeutic targets of metastasis

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Metastasis is a 100-year-old research topic. Technological advances during the past few decades have led to significant progress in our understanding of metastatic disease. However, metastasis remains the leading cause of cancer-related mortalities. The lack of appropriate clinical trials for metastasis preventive drugs and incomplete understanding of the molecular machinery are major obstacles in metastasis prevention and treatment. Numerous processes, factors, and signaling pathways are involved in regulating metastasis. Here we discuss recent progress in metastasis research, including epithelial–mesenchymal plasticity, cancer stem cells, emerging molecular determinants and therapeutic targets, and the link between metastasis and therapy resistance.

Hurdles in eliminating metastasis-associated mortality

Metastasis is a multistep process that begins when primary tumor cells break away from their neighboring cells, such as nearby stromal cells, and invade through the basement membrane. Subsequently, metastasizing cells enter the circulation (intravasate), either directly or via lymphatics, and then home to distant organs where they exit the vasculature (extravasate). Eventually, tumor cells that successfully adapt to the new microenvironment proliferate from micrometastases into clinically detectable metastatic tumors (Figure 1) [1]. Although great advances have been made in combating cancer, particularly in its early stages, metastasis remains a formidable and frequently fatal challenge [2–4]. It is becoming increasingly clear that the seeds of metastasis are present in many cases of early disease [3,5], leading to deaths that might be prevented. Numerous processes, factors, and signaling pathways have been implicated in regulating metastasis, including epithelial–mesenchymal plasticity, cancer stem cells, noncoding RNAs, cytokines, hormones, and receptor tyrosine kinase (RTK) pathways, with the list of determinants of metastasis still expanding. However, few molecules have been translated into effective metastasis prevention or treatment in the clinic.

Over 90% of cancer-related deaths are caused by metastasis. For instance, breast cancer, the most common malignant disease in women, begins as a local disease and later metastasizes to lymph nodes and other organs. The most common sites of breast cancer metastasis are vital organs such as the lung, liver, bone, and, to a lesser extent, the brain [6,7]. National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) data indicate that the percentages of patients with localized, regional, metastatic, or unstaged breast cancer at diagnosis are 61%, 32%, 5%, and 2%, respectively. Their corresponding 5-year survival rates are 98.5%, 84.6%, 25%, and 49.8%. However, many patients with localized or regional cancers show evidence of local invasion or disseminated micrometastatic tumor cells at diagnosis, meaning that it is too late to stop the early steps of metastasis [8]. Therefore, for those 93% of patients, preventing metastatic colonization – the growth from disseminated micrometastatic tumor cells to macroscopic metastases – holds the most therapeutic promise. For those 5% of patients with metastatic disease at diagnosis, shrinking established metastases must be the goal.

Surgery, radiation therapy, and chemotherapy can eliminate many primary tumors and thus approaches to preventing metastatic colonization should be most effective as adjuvant therapy [8]. The major roadblock to devising adjuvant metastasis prevention treatments is that the current clinical trial system is not designed to test metastasis preventive drugs [9]. In the current setting, running metastasis prevention trials on patients with early-stage cancer would be prohibitively lengthy and costly and would require many thousands of patients. Therefore, drugs today have to induce regression of established metastatic tumors in late-stage cancer patients in whom standard treatment failed, if those drugs are to receive regulatory approval and to be advanced to adjuvant metastasis prevention trials [2,9]. This is in contrast to the preclinical setting, where most antimetastatic agents that have been tested prevent the formation of metastases but do not shrink established metastatic tumors [2,9]. It has been suggested that the format of clinical trials be changed

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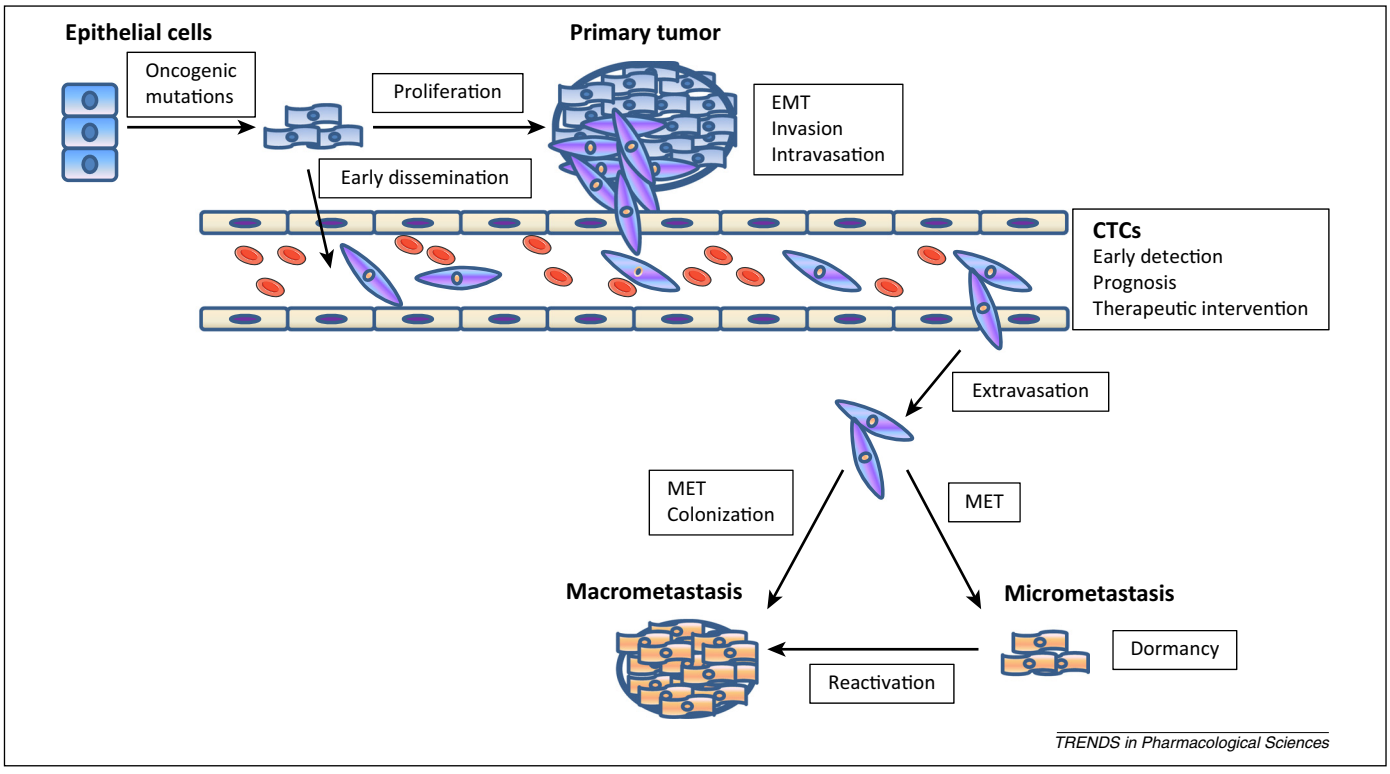

Figure 1. Schematic of the invasion–metastasis cascade. Metastasis involves a succession of discrete steps, beginning with local invasion, then intravasation of cancer cells into blood and lymphatic vessels and transit of circulating tumor cells (CTCs) through the vasculature, followed by extravasation to the parenchyma of distant organs, and finally proliferation from micrometastases into macrometastases.

to accommodate metastasis preventive drugs [9], but to do so would require a new approach to defining patient eligibility and to predicting drug response.

Ideally, trials of metastasis preventive drugs would enroll patients with early-stage disease who are at high risk of developing metastases as well as those who already have metastases and are at risk of developing more [9]. One major obstacle to this ideal, however, is that we have no good means of identifying these high-risk patients. We also do not know how to select patients who might benefit from specific metastasis preventive agents. To surmount these barriers and facilitate metastasis prevention trials, we need to find better prognostic markers for metastasis, effective antimetastatic drugs, and predictive markers for drug response.

In addition to the lack of appropriate clinical trials for metastasis prevention, the heterogeneity of metastatic tumor cells may account for the failure in therapeutic targeting of a specific pathway, since different subpopulations of metastatic tumor cells could employ distinct molecular machinery. For instance, treatment of patients with triple-negative breast cancer (TNBC), which metastasizes more frequently than other breast cancer subtypes and is associated with poor clinical outcomes, has been challenging due to the heterogeneity of this disease and the lack of well-defined therapeutic targets [10]. Thus, there is a pressing need to understand tumor heterogeneity and elucidate the mechanisms by which different metastases originate from different subpopulations of cancer cells coexisting within a tumor.

In this review we dissect the processes of metastatic progression. These processes depend on genetic and epigenetic aberrations in tumor cells and alterations in the associated microenvironment. In addition to reviewing the emerging molecular determinants and therapeutic targets at each step of the invasion–metastasis cascade, we discuss the molecular basis of the cellular plasticity of tumor cells. Such plasticity is likely to underlie therapy resistance and metastatic relapse, which suggests the importance of understanding tumor heterogeneity and the need to develop new combination therapies to target all types of cancer cell subpopulations, including cancer stem cells (CSCs), circulating tumor cells (CTCs), disseminated tumor cells (DTCs), and differentiated cancer cells.

Role of epithelial–mesenchymal plasticity and cancer stem cells in metastasis

The ability of cancer cells to metastasize depends on their genetic and epigenetic alterations as well as the microenvironmental cues they receive. Recent studies suggest that many of the properties associated with invasion and metastasis do not arise as purely cell-autonomous processes; instead, the surrounding tumor stroma becomes 'activated' during primary tumor progression and begins to release signals such as transforming growth factor beta (TGF-β), hepatocyte growth factor (HGF), tumor necrosis factor (TNF) alpha, Wnt, and platelet-derived growth factor (PDGF). Subsequent adaptation of carcinoma cells to these heterotypic signals can lead to the acquisition of highly malignant cell-biological traits