Chapter 1

Introductory Chapter: Cancer Metastasis

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1. Introduction

In malignant evaluation of cancer cells, metastasis is a commonly used terminology in which cancer cells gain the invasion ability to neighboring tissues and distant secondary organs and finally colonize in these organs. Metastasis is estimated as the main reason of 90% of cancer-related mortality due to its incurability by surgical resection and resistance of tumor cells to chemotherapeutic agents. Cells that have metastatic capability disseminate by several ways as hematogenous spread, lymphatic spread, or seeding into body cavities. Although lymphatic spread of cancer cells is commonly observed in metastasis and represents as a prognostic factor, hematogenous spread represents the major way in human tumors. Seeding into body cavities is routinely observed in colorectal and ovarian cancers [1].

The process from the spreading of cancer cells to distant parts of the body, termed as the invasion-metastasis cascade, involves sequential and interrelated steps: (1) invasion of local tissue, (2) intravasation into stroma and blood vessels, (3) survival in vasculature circulation, (4) extravasation into the parenchyma of distant tissues, and (5) survival in a new microenvironment and colonization to form micro- and macro-metastasis (**Figure 1**). The steps of invasion-metastasis cascade are explained below [1, 2].

2. Dissemination and local invasion

Dissemination process includes the initial step of invasion-metastasis cascade. During dissemination, cancer cells acquire ability to leave the primary tumor location to invade nearby tissues and travel to secondary tumor locations. Invasion ability of tumor cells is used to distinguish malignant tumors from benign tumors. Invasive growth and associated signaling pathways have role in tumor progression as well as metastasis. It basically includes the entering of tumor cells

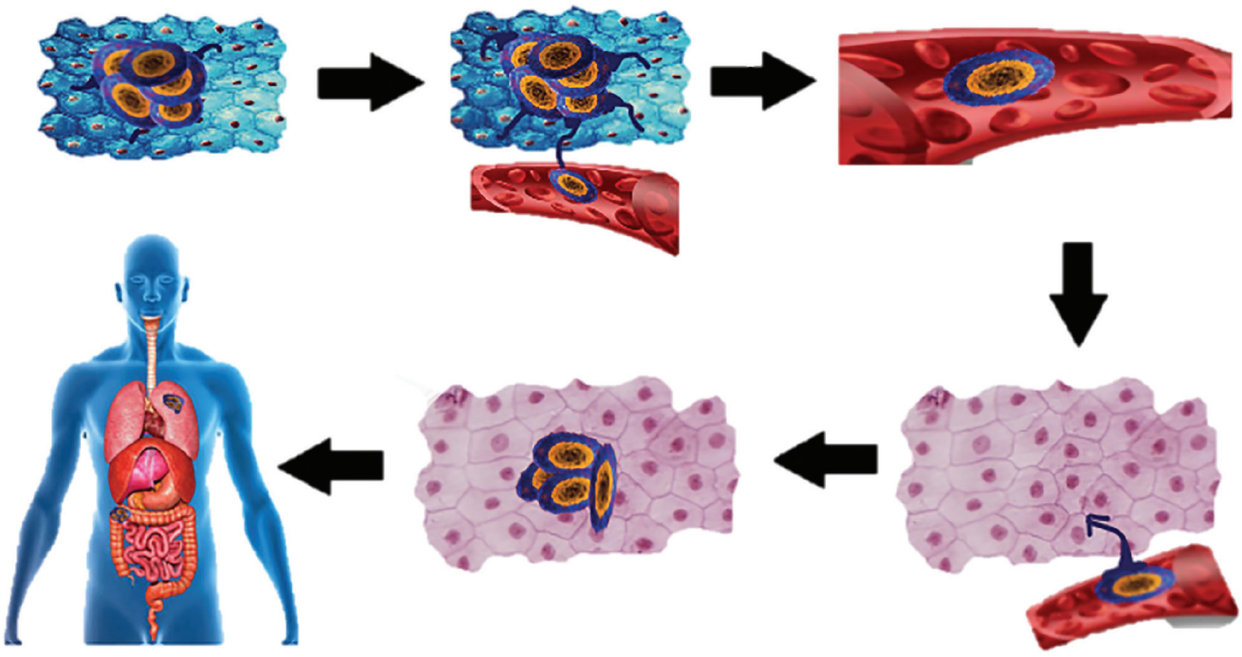

Figure 1. Steps of metastasis. During metastatic process, cells invade to local tissue (1), intravasate into the stroma and blood vessels (2), survive in the vascular circulation (3), extravasate into the distant tissues (4), survive and colonize to form micrometastasis (5), and finally form a clinically detectable macro-metastasis (6).

into the surrounding tumor stroma and adjacent normal tissue parenchyma. To gain invasion capability, cancer cells have to lose their adhesion ability to the adjacent cells and leave the primary tumor with gaining migratory feature. Therefore metastasis starts with the migration of tumor cells [3]. At this point, epithelial-mesenchymal transition (EMT), a process during the detachment of cancer cells from the epithelial stratum by losing of their epithelial markers and gaining motility, has a key role on the cancer progression. Gaining of EMT character and dissemination occur in early stage of metastasis. This complex process, EMT, is orchestrated by several EMT-inducing transcription factors such as Snail, Slug, Twist, Zeb1, Zeb2, Foxc2, Prrx1, etc. [4].

With the effect of EMT-related transcription factors, cancer cells present various alterations in gene expression. They lose their apical-basal polarity due to the loss of adhesion molecules (such as E-cadherin and integrins) and intercellular junctions; the remodeling of intracellular cytoskeleton molecules begins to form cellular protrusions; invasive growth and penetration into the surrounding stromal matrix start with the degradation of basal membrane and lacking intercellular contacts. Tumor cells, which have migratory and invasive feature, are more resistant to chemo- or radiotherapy than other cancer cells [5, 6].

3. Intravasation

Invasive and motile cancer cells invade into the vessels to travel through blood flow and access the secondary metastatic sites, where they may form micro- and macro-metastasis. During

intravasation, tumor cells pass through tissue and reach the endothelial vessel [7]. Intravasation can be facilitated by specific transcription factors, signaling molecules, enzymes (proteases), cells in tumoral microenvironment, and biophysical conditions of microenvironment and vasculature. The route of intravasation is led by the structural differences between blood vessels and lymphatics. Blood vessels have tighter junctions than lymphatics; therefore invasion through blood vessels and their connective tissue may be limited [7].

4. Survival in the circulation

When the cancer cells have achieved to intravasate into the blood vessels, they travel in the venous and arterial circulation, known as circulating tumor cells (CTCs). Survival in the bloodstream is crucial step for metastasis. Millions of tumor cells move from the tumor bulk and enter the circulation. CTCs travel as a single cell or CTC clusters, and they undergo molecular alterations to change their phenotype. However the relationship between immune system and tumor cells cannot be excluded; natural killer cells, monocytes/macrophages, and neutrophils mediate a clearance of CTC from the blood circulation. Therefore the success rate of metastasis is low due to the rare amount of CTCs [8]. Over time, cancer cells have developed various strategies to escape from the immune system. These strategies include the loss of immunostimulatory molecules and gain of immunoinhibitory molecules and increased expression of apoptosis-related molecules [9]. Also platelets, tiny blood cells that function against bleeding, facilitate the survival of CTCs by reacting to main threats in blood as shear stress and natural killer cells. Molecules related with coagulation such as tissue factor and thrombin lead activation of platelets, and this activation forms the platelet-cancer cell aggregates [10]. The popularity of CTCs is increasing in recent years due to their potential use in cancer diagnosis as well as prognosis. Up-to-date technological advances pave the way for detection of circulating tumor cells.

5. Extravasation

After the survival in the harsh blood stream, tumor cells become arrested at a secondary location and extravasate into parenchyma of distant tissues. Extravasation, which requires a tumor cell transendothelial migration, involves adhesion of tumor cells to endothelial cells and the transmigration through the endothelial wall. Endothelial cells can either allow or block the adhesion of tumor cells, as well as possible transmigration. Therefore endothelial cells are essential due to their role in the determination of secondary tumor location and regulation of metastatic formation. But still their all function in the metastatic cascade is still unclear [11]. Permeabilization of vascular structure is provided by the ATP production by active platelets and angiopoietin-like 4 (ANGPTL4) production. Increased transendothelial migration ability enhances the metastatic outgrowth. Also other molecules as VEGF, MMPs, ADAM12, and CCL2 disrupt the vascular integrity and increase both intravasation and extravasation. However, requirements can be various for different locations to achieve a successful extravasation process [4].

6. Micrometastasis and colonization

Extravasated cancer cells have to survive to form micrometastasis in the secondary locations. The microenvironment of secondary location is different from the microenvironment of primary tumor location due to the different types of stromal cells, extracellular matrix components, cytokines, chemokines, and growth factors, and metastatic cancer cells have to adapt to this secondary microenvironment of their new homes.

In 1889, Stephen Paget proposed "seed and soil" hypothesis for metastatic dissemination, which depends on numerous interactions between certain types of cancer cells and organ-specific homeostatic mechanisms of microenvironment. According to him, although tumor cells can disseminate in many locations, selected metastatic cancer cells (seeds) tend to form metastasis in one or more particular distant organ locations (soils) for survival and proliferation [12, 13].

Before the arrival of metastatic cancer cells to the secondary locations, an establishment process of a pre-metastatic niche was proposed for the survival and adaptation of tumor cells. Primary tumor cells induce the formation of their own pre-metastatic niches by releasing systemic signals that activate organ-specific orientation of resident tissue fibroblasts. Induced pre-metastatic niche is an essential parameter for metastatic propensity and tissue tropism [1].

7. Detectable macro-metastasis

Even if tumor cells can survive in the secondary locations, the proliferation of tumor cells and formation of macro-metastasis are not certain. They can be in long-term dormancy state and stay as microcolonies and also face with attrition problem due to the failure on the triggering neoangiogenesis. Because of this poorly understood attrition, high apoptotic rate balances continuously the proliferation rate [14].

Angiogenic switch is an essential need for the transformation of micrometastatic tumors (or dormant tumors) to macro-metastatic tumors. Reformed vasculature originate from the existing blood vessels or develop by endothelial progenitor cells [15]. With the existence of advantageous pre-metastatic niche and angiogenic signals, clinically detectable metastases are the final result of highly complicated invasion-metastasis cascade.

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