Chapter

Introductory Chapter: Molecular Mechanism of Cancer Metastasis

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1. Introduction

Neoplastic cells' capacity to spread and colonize distant tissues is their most dangerous trait. Most malignancies are curable when detected early and have not spread outside of the original tissue. However, cancer is frequently incurable when tumor cells have created colonies elsewhere. Tumor progression is the transformation of a healthy cell into a metastatic cancer cell that poses a threat to life. Neoplasia is a cellular illness, and research has been done to better understand the molecular mechanisms underlying the early stages of the progression that lead to the formation of cancer. The molecular mechanisms underpinning the behavioral changes that distinguish a metastatic cell from cells that are still at the site of tumor formation are now understood to reflect a fraction of cells that have left the primary tumor and are known as metastases [1, 2].

Tumor cells go through predominant steps and reach metastasis: invasion, intravasation, delivery, extravasation, and metastatic colonization. Further, tumor cells communicate with the surrounding microenvironment or tumor-associated stroma [3]. Tumor microenvironment affects tumor cells' metastatic ability and subpopulation of cancer stem cells, angiogenic vascular cells, cancer-associated fibroblasts, and infiltrating immune cells, the process additionally affects primary tumor metastatic capacity to distant locations [2, 4].

The spread of malignant cells to distant or disjointed secondary sites, where they multiply to create a mass, is known as metastasis. For almost every characteristic that is measured, tumor heterogeneity exists [1–3]. Positional, temporal, and genetic heterogeneity are the three forms that can exist inside a tumor. The accessibility of a cell to heterogeneous extrinsic stimuli influences positional heterogeneity. Regarding alterations in cells brought on by cycle signals, temporal heterogeneity is important. Genetic diversity is a result of the characteristics that tumor cells have by nature. Single-cell clone isolation proves that there are fundamental variations among the subpopulations that make up a single tumor mass [1].

2. Formation of metastatic cell

2.1 Invasion by perturbing cell: Cell and cell matrix adhesion

Invasion initiates as a result of tumor cell breaking of the basement membrane and penetrate underlying stroma. Tissues architecture forms from epithelium, basement membrane, and stroma. Catherins adhere cells to each other through catenins inside the cell. Integrin receptors attach cells to fibronectin at the extracellular matrix and

fibronectin attaches to collagen. Normally epithelial cells are maintained by cell–cell anchoring junctions: tight junctions- adherent junctions attached to actin and keratin, respectively, whereas cell matrix anchoring junctions hemidesmosomes attached to keratin intermediate filaments like cell-anchoring factor desmosomes. Changes in cell–cell and cell-matrix adhesion are necessary for invasion; these changes must be coordinated with matrix breakdown and cellular mobility. All these molecules provide cell integrity, and therefore, cell adhesion proteins are the target of oncogenes as well as the tumor suppressor proteins that regulate the signaling pathways.

Cadherin functions as tumor suppressor and suppresses tumor cell metastasis at distant sites. Integrins pin cells to basement membrane—extracellular membrane, and cells break free from the binding site during metastasis. Integrins affect the cytoskeleton by binding to actin and key kinases like FAK (Focal Adhesion Kinase). Actually, FAK mediates cell motility and activates the RAS pathway. Therefore, enhancing integrin expression in tumor cells induces mobility and invasion of metastasizing cells. Degradation of extracellular matrix and stroma for invasion of tumor cells to the nearby tissue also depends on proteases [1, 3].

Epithelial-mesenchymal transition involves changes in shape and confers metastatic properties and this process is accompanied by enhancing mobility, invasion, and resistance to apoptotic stimuli. The change provides cells to migrate to distant sites. Epithelial-mesenchymal transition associates with loss of E-cadherin from the adherens junctions and a switch from the expression of keratins to the mesenchymal intermediate-filament vimentin [5].

2.2 Invasion through matrix degradation

One of the hallmarks of the malignancy is the disruption of basement membrane and enzymes extruded from tumor cells degrade matrix for invasion. These enzymes form a diverse family, including serine/cysteine proteinases, cathepsin, disintegrin, ADAM metalloproteinases, and matrix metalloproteinases (MMP). Increased MMPs are considered poor prognosis in several cancer types and correlate to invasion and metastasis. Cathepsins, proteinase inhibitors, and cysteine proteinase inhibitors regulate proteolysis. Both tumor and stromal cells play roles in the inhibitory mechanism [1, 5].

2.3 Motility

Actin filament assembly and treadmilling through coordinated polymerization and depolymerization provide cellular locomotion. However, tumor cells stimulate motility through lysophospholipase D in an autocrine fashion. *C-met* and hepatocyte growth factor interact and induce invasive epithelial cells chemokinetic activity. Chemotactic/haptotactic effect correlates to directional motility [1, 6]. Structures so called invadopodia determined in invading cells and represent the physical convergence of adhesion, proteolytic, and motility components of invasion. Therefore, invapodia is the essential structure for cancer invasion; however, if a tumor cell can not complete subsequent steps, it cannot go through metastasis [1].

2.4 Intravasation

Entry of a tumor cell into either blood or lymphatic vessels by serine and metalloproteinase action is called intravasation. After proteinase activity, tumor cells pass

from endothelial cells into the bloodstream. Tumor cells may travel either alone or as emboli (clumps with platelets) within the direction of blood flow.

Once in the vessels, most of the tumor cells are killed by monocytes or natural killer cells. Larger size of the tumor cells at the capillaries encounters a problem—hemostatic shear force. Smaller vessels break tumor cells by shear forces due to hydrostatic pressure.

Further, when tumor cells bind to endothelium via E-selectin, the cells are attached/overlapped. In this case, arrested tumor cells can go through apoptosis. This attachment may lead tumor cells to release NO and the process also drives the cells to apoptosis [2, 7].

2.5 Extravasation

The escape of a tumor cell from the vessels is named as extravasation. Tumor cells invade from the interior of a vessel into the organ parenchyma. There is a debate in the literature about whether extravasation is necessary for metastases process. One key evidence for this dilemma originates from lung endothelium-attached tumor cells. The cells survive and grow intravascularly; therefore, further experiments are required to elucidate the molecular mechanism [1, 3].

2.6 Metastatic colonization

Metastatic colonization is an inefficient metastatic cascade step in which progressively growing tumor forms at distant ectopic sites. This process involves the formation of new blood vessels to provide nutrients and oxygen. Micrometastasis contrast with colonization do not constantly grow but stays dormant for longer times. Metastatic colonization is the rate-limiting step of metastasis [3].

2.7 Metastasis and angiogenesis

Formation of new blood vessels from pre-existing vessels, angiogenesis, and augment metastatic colonization. Angiogenesis is essential for metastasis so that tumor cells get oxygen and nutrients as tumor cells exceed a minimum size, nutrients and oxygen can no longer reach through diffusion. By the same token, metabolism end products (lactate, ammonia, and lactate) cannot diffuse easily [3].

3. Conclusion

Elucidating the molecular mechanism of metastasis can improve efficient drug design and therapies. Currently, no distinguishable cellular behavior detected between normal and metastatic cells. Further, invasion is not a unique property for cancer cells. However, invadopodia may provide some insights and metastatic cells also proliferate without differentiating. Plus, the colonization stage of metastasis provides therapeutic opportunities as the cells are proangiogenic for long periods. All these differences may provide targets for both drug design and therapeutic approaches. In spite of all these differences, it is relatively easy to compare two distinct stages/properties of the tumor and may provide plethora of data.

Conflict of interest

The author declares no conflict of interest.

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References

[1] Matrisian LM, Welch DR. Invasion and metastasis. In: Mendelsohn J et al., editors. The Molecular Basis of Cancer. 3rd ed. Saunders: Elsevier; 2008. pp. 253-266. ISBN: 978-1-4160-3703-3. Ch19

[2] Rankin EB, Giaccia AJ. Cellular microenvironment and metastases. In: Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, editors. Abeloff's Clinical Oncology. 6th ed. Elsevier; 2019. pp. 47-55. Ch 3

[3] Pecorino L. Molecular Biology of Cancer. Mechanisms, Targets, and Therapeutics. 3rd ed. UK: Oxford; 2012. p. 365. ISBN: 978-0-19-957717-0

[4] Schulz DA. Molecular Biology of Human Cancers. 1st ed. Dordrecht, The Netherlands: Springer; 2005. p. 489. ISBN: 1-4020-3185-8

[5] Ruddon RW. Cancer Biology. Fourth ed. New York: Oxford; 2007. p. 545. ISBN: 978-0-19-517543-1

[6] Weber GF. Molecular Mechanism of Cancer. 1st ed. Dordrecht, The Netherlands: Springer; 2007. p. 644. ISBN: 978-1-4020-6015-1

[7] Weinberg RA. The Biology of Cancer. 1st ed. New York: Garland Science, Taylor & Francis Group; 2014. p. 963. ISBN: 978-0-8153-4219-9