HIGH SCHOOL EDITION
Journal of Student Research
Volume 13 Issue 3 (2024)

A Mini-Review for Cancer Cell Migration and Cancer Metastasis

Siyan Guo

Shanghai Starriver Bilingual School, China

ABSTRACT

This mini-review addresses the critical issue of cancer metastasis, a process that significantly contributes to cancer-related mortality. The study delves into the molecular and cellular mechanisms underpinning cancer cell migration and metastasis, focusing on recent advances and key factors involved in each step of metastatic progression. The research highlights the complexity of cell migration, comparing single cell migration with collective cell migration and emphasizing their roles in developmental processes and disease progression. The study also provides a detailed analysis of the five key steps in cancer metastasis: infiltration, intravasation, survival in the circulatory system, extravasation, and colonization, elucidating the cellular and molecular events driving each step. Overall, the findings underscore the importance of understanding cell migration in cancer biology, offering insights into potential therapeutic targets and strategies to prevent tumor dissemination and enhance cancer treatment outcomes.

Introduction

Cancer metastasis, the dissemination of cancer cells from the primary tumor to distant locations in the body, stands as a primary contributor to cancer-related mortality. This process involves a series of intricate steps including cancer cell migration, invasion, intravasation into blood or lymphatic vessels, survival in the bloodstream, extravasation at the target site, and subsequent colonization and proliferation at the distant site (Zijl et al., 23).

This mini-review aims to provide an overview of the molecular and cellular mechanisms that drive cancer cell migration and metastasis. It will focus particularly on recent breakthroughs in our understanding of these processes, shedding light on key factors and pathways involved in each step of metastatic progression. Understanding these mechanisms is crucial for developing targeted therapies aimed at preventing or inhibiting cancer metastasis, ultimately improving patient outcomes.

Discussion

Cell Migration Fundamentals and its Role in Cancer Metastasis

Cell Migration and Its Four Steps

Cell migration plays critical roles in physiological and pathological processes like cancer metastasis. Cell migration is a complex and heterogeneous movement triggered by external chemical signals or mechanical signals (Lodish et al., 2850). Usually, cell migration is comprised of four steps (Fig. 1).

First, receiving signals. The cell receives the guidance of the chemical or mechanical signals and protrudes the lamellipodia towards the directions of the signals. Second, the Attachment of lamellipodia. The lamellipodia re-attaches and adhere at a new position, providing a pivot to support the cell moving forward. Third,

the movement of the cell body. Using the pivot the contraction generated by the actomyosin in the cytoskeleton pulls the cell body to move forward. At last, the deattachment of the cell rear. The rear of the cell deattaches from the extracellular matrix and follows the movement of the cell b33ody (Lodish et al., 2853).

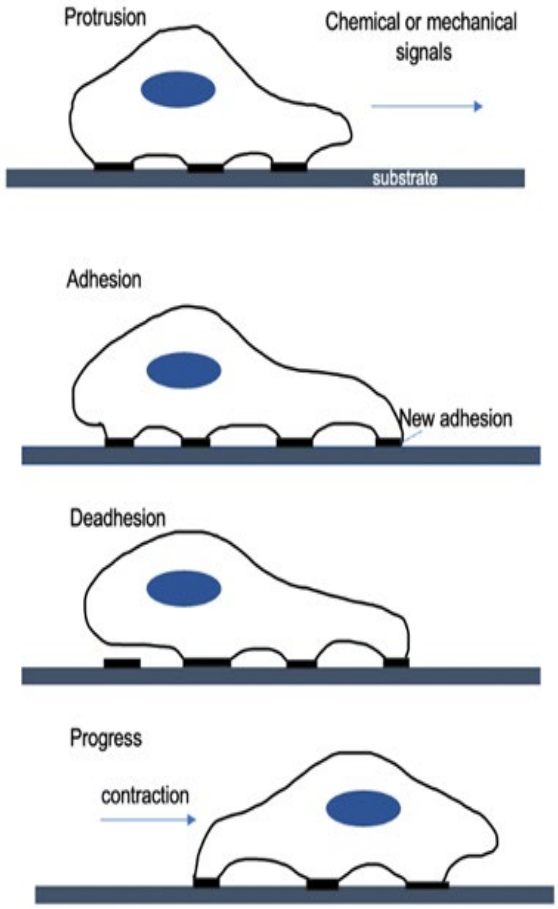

Figure 1. The four steps involved in cell migration: receiving signals, attaching lamellipodia, moving the cell body, and detaching the cell rear.

Comparing Collective Cell Migration and Single Cell Migration

There are two types of cell migration, collective cell migration and single cell migration. Single cell migration means a single cell migrates by itself. Compared with single cell migration, the collective cell migration is more complex because of the involvement of the interaction and communication between cells (Friedl and Wolf, 11). Collective cell migration describes the transportation of groups of cells in collective behavior, required to perform specific functions. Collective cell migration is essential in developmental processes in the lives of multicellular organisms (Friedl and Wolf). Cells can migrate in cohorts in forms of individual cells contacting each other in collective signals, or migrate by having junctional interactions transiently in terms of adhesion in mesenchymal cells (Theveneau and Mayor, 3). On account of the high variability of the quantity of migrating cells and the indeterminacy of chemical signals via cell-cell or cell-matrix interactions, the study of collective cell migration has an openness to the question of preventing tumor transfer and spread, further affecting the treatment of cancer(Le and Mayor, 1733).

Cell migration is heavily involved in every step of cancer metastasis, in which cancer cells move from

their initial site to invade distant organs of the body. In the distant organs, the cancer cells settle down, start to proliferate, and finally form a new tumor derived from the original ones (Friedl and Wolf, 12). In detail, cancer cells initially detach from the primary tumor and acquire motile properties. Then, cancer cells migrate and infiltrate into the surrounding normal tissue and seek lymph nodes or blood vessels where they can metastasize further. Once the cancer cells leave the primary tumor and enter the vascular or lymphatic system, they move forward with the fluids, searching for a site where they can form a new tumor (Majidpoor and Mortezaee, 3).

All these processes together are termed 'metastasis'. Briefly, five steps are involved in the process of metastasis: (i) infiltration that can be defined as cancer cells infiltrate into the adjacent tissue; (ii) intravasation that refers to cancer cells invading vessels via penetrating the endothelium; (iii) circulation that provides a route through blood vessels for the detached cells to enter the circulatory system and metastasize to distant sites; (iv) extravasation that reverses the process of intravasation, i.e. cancer cells penetrate the endothelium from inside the vessels and finally migrate out from the vessels; (v) colonization that means cancer cells reach and form a new tumor in the distant organs. Intuitively, cancer cells keep migrating during all the steps of the cancer metastasis (Zijl et al., 23). Therefore, cell migration is pivotal for the process of cancer metastasis. In the following context, we will elucidate how cell migration is involved in the aforementioned each step of the cancer metastasis.

How Cell Migration Is Involved in Cancer Metastasis

First Step of Cancer Metastasis: Local Infiltration of Tumor Cells into The Adjacent Tissue

Infiltration means that tumor cells separate from the primary tumor and invade into the extracellular matrix (ECM) and the adjacent tissue. During the infiltration, four critical events happen to promote cancer cell migration: (i) cell selection through the gene mutations involved in epithelial-mesenchymal transition (EMT); (ii) invasion into ECM;(iii) ECM remodeling; and (iv) the involvement of mechanical forces (Novikov et al., 102). These four events are described in detail as follows.

Cell Selection Through Epithelial-Mesenchymal Transition (EMT) In Primary Tumor: EMT seemingly drives metastasis initiation, leading to the intrinsic differences between benign tumors and malignant tumors, i.e., the malignant tumors can migrate and invade connective tissues. In the process of migration, the genes originally expressed in mesenchymal cells that can promote cell migration are mutated and expressed in the epithelium-derived primary tumors to promote the migration of the tumor cells. This process is called epithelial-to-mesenchymal transition (EMT) (Majidpoor and Mortezaee, 4). The phenotype of EMT is more prominent in the boundary of the primary tumors, and the cells located in the boundary with EMT mutation become leader cells which can guide the inside tumor cells to follow the migration (Majidpoor and Mortezaee, 5).

There exist two types of cancer cell migration, single cell migration and collective cell migration. The full EMT and the partial EMT are respectively corresponding to the single cell migration and collective cell migration. This is because the mesenchymal cells can not adhere to each other to generate the cell cluster. The full EMT induces the epithelial cells to become mesenchymal cells fully and lose the cell-cell adhesion (Wu et al.). The partial EMT remains both the features of epithelial cells and mesenchymal cells. The epithelial feature can help to keep the cell-cell adhesion to generate the collective cell invasion (Wu et al.).

In addition, tumor cells with EMT are more prone to acquire drug resistance. Also, induction of this phenotypic state in tumor cells requires cross-talking with stromal cells, especially with cancer-associated fibroblasts (CAFs). The presence of CAFs within the stroma indicates poor prognosis (Joshi et al.).

Extracellular Matrix (ECM) Dysregulation / Remodeling: During the cell selection step, the cancer cells gain the migratory phenotypes through EMT, but to infiltrate to the ECM and the adjacent tissue, another critical step is required, i.e., the alteration of cancer microenvironment – ECM remodeling that promotes tumor cell

migration. The ECM remodeling includes three major changes: 1. Increased ECM deposition; 2. Increased crosslinking, better alignment, and increased stiffness; and 3. ECM degradation. The increased deposition of fibrillar collagen in the ECM is the most common tumorigenic alteration of ECM homoeostasis (Lu et al.) (Fig. 2).

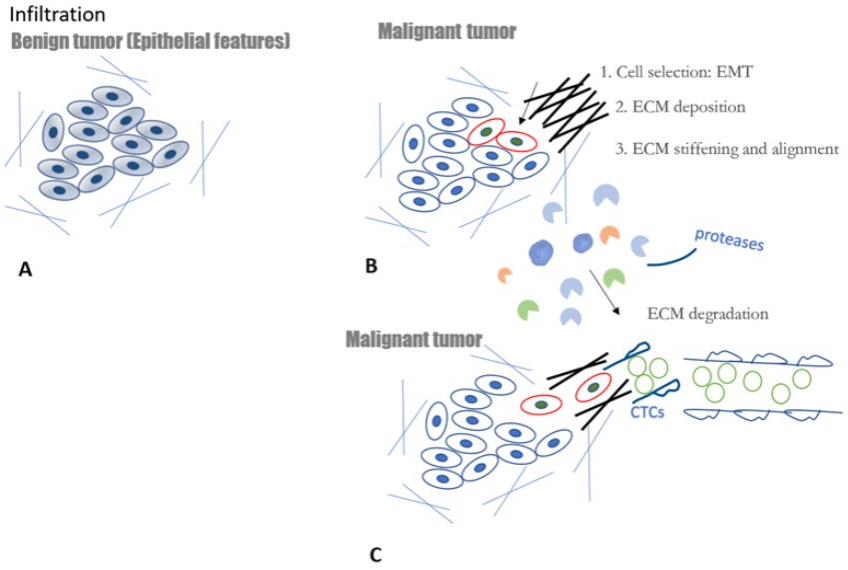

Figure 2. The four steps involved in cell migration.

1) Deposition

The predominant contributor for excessive ECM deposition is myofibroblasts. During the development of tumor malignancy, myofibroblasts are over-activated by pro-inflammatory factors secreted by immune cells and transforming growth factor TGF-β secreted by mesenchymal cells or epithelial cells. After the over activation of myofibroblast, they are stimulated to synthesize excessive ECM fibers, such as collagen-I and collagen IV (Lu et al., 10)(Fig. 2B). Thus, the synthesis of excessive ECM fibers leads to the abnormal extra ECM deposition (Fig. 2B).

2) ECM alignment and stiffening

The excessive ECM deposition under the tumor microenvironment could be featured with alignment of fibers towards a specific direction. Another feature of the tumor microenvironment is the increased stiffness. These ECM fiber alignment and tissue stiffening have been reported to promote the development of tumor malignancy and induce the tumor cell infiltration. The stiffening can promote the formation of invadopodia to enable the invasion of cancer cells through the extracellular matrix (Henke et al., 14).

3) ECM degradation

During tumor cell invasion into the basement membrane, cancer cells and some cancer-associated cells, including fibroblasts and infiltrating immune cells such as macrophages, can secrete and maintain a sustained presence of proteolytic enzymes. These enzymes can degrade the matrix to provide a pathway for the intrusion of the tumor cells. Proteolytic enzymes, including matrix metalloproteinases (MMPs), disintegrins and other proteases, can cleave and reconstitute ECM to erode and destroy the envelope of the primary tumor, i.e., the basement membrane (Lu et al., 6).

Invasion into Extracellular Matrix (ECM) And Adjacent Tissue: Invasion is the first step of cancer cell metastasis. The processes of the cell selection and the ECM remodeling provide cancer cells necessary and sufficient

conditions for their invasion into the ECM. During the cell selection, cancer cells experience EMT to adopt a plastic phenotype. This plastic phenotype enables epithelial cancer cells to express the features of mesenchymal cells that promote the cell migration. Besides these alterations inside the cancer cells, the cancer microenvironment also changes to facilitate the invasion, i.e., ECM remodeling. It has been reported that ECM remodeling, including stiffening, alignment, and degradation, can promote the cancer cell invasion (Clark and Vignjevic).

Invasion occurs at the tumor-stroma margin and has two manifestations, monoclonal migration and polyclonal migration. In single-cell migration, tumor cells lose their cell-cell adhesion and become single cells during the process of invasion. In contrast, during collective cell invasion, intercellular adhesion remains (Zijl et al.). Cancer cell cluster as multicellularity requires cohesive behavior to achieve efficient metastasis for collective cell invasion (Zijl et al., 26).

Second Step Of Cancer Metastasis: Intravasation

Intravasation is an important step for tumor cells to penetrate the vascular wall and enter the circulatory system, becoming circulating tumor cells (CTCs) that are responsible for delivering cancer cells to distal tissues (Zavyalova et al.). Two steps are required for the invasion of tumor cells into the vasculature. First, cancer cells can express which attracts C-X-C chemokine receptor type 4 (CXCR4) (Zavyalova et al., 763). CXCR4 as a receptor can interact with C-X-C chemokine ligand 12 (CXCL12) that is expressed by the endothelial cells. The interaction between CXCR4 and CXCL12 is stimulated under the hypoxia microtumor environment (Zavyalova et al.). Thus, the vascular wall secretes the ligand CXCL12 to form a gradient signal which attracts the cancer cells to migrate towards the vasculature (Zavyalova et al.). This process of tumor cell migration induced by the CXCL12 gradient is termed 'Chemotaxis' (Zavyalova et al.). The extrinsic factors include ECM remodeling and degradation as forementioned (Zavyalova et al.).

After the tumor cells arrive at a likely point of intravasation, they interact with the endothelial cells located on the vascular wall via the ligand-receptor (CXCL12- CXCR4) axis to develop stronger adhesion. Then, cancer cells release proteases that erode the connection between endothelial cells, likely leading to the leaking vasculature. Lastly, the tumor cells penetrate the endothelium and invade into the vasculature through the leaking points.

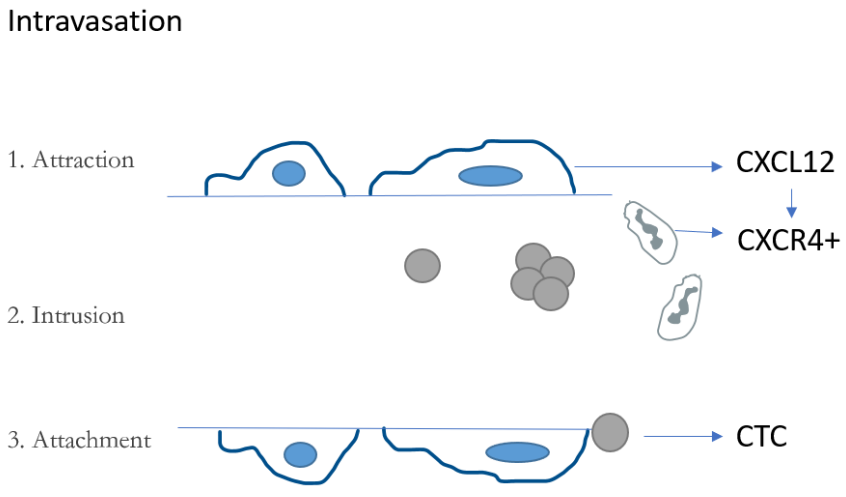

Figure 3. The intravasation of cancer metastasis

Third Step of Cancer Metastasis: Survival in The Circulatory System

During metastasis, cancer cells from the primary tumor may invade neighboring tissues or lymph nodes; from

there, some may reach the bloodstream or lymphatic system. CTCs maintain an invasive phenotype and are attacked in circulation by the immune system and other environmental stresses after entering the circulatory system. These circulating tumor cells (CTCs) must overcome several obstacles to persist in the bloodstream, including physical shear stress, which can damage and rupture their fragile membranes, and immune surveillance, which can identify and eliminate abnormal or foreign cells. A minority of cancer cells survive within the circulation (Sturgess et al., 2).

To avoid further die-off, metabolic reprogramming will be induced to increase glucose uptake and other energy. CTCs may acquire genetic or molecular alterations that enable them to hide from or suppress immune cells, such as downregulating surface markers or secreting immunosuppressive factors, to evade the immune system (Sturgess et al.).

In addition, CTCs may resist the physical and chemical stresses of circulation by adapting their shape, size, and metabolism and by activating stress-response pathways, such as the heat shock protein pathway or the unfolded protein response pathway. CTCs may also benefit from the assistance of other blood components, such as platelets, which can provide a protective shield and improve their survival, and immune cells or stromal cells, which can produce a favorable microenvironment for CTC growth and proliferation. CTCs may colonize distant organs or tissues by adhering to and invading endothelial cells that line blood vessels or by interacting with the local microenvironment, such as by releasing growth factors or cytokines that stimulate angiogenesis or inflammation (Sturgess et al.).

Overall, the ability of CTCs to persist in the circulation and metastasize to distant sites is a complex and dynamic process involving multiple cellular and molecular interactions and represents a significant challenge for cancer diagnosis, prognosis, and treatment.

Fourth Step of Cancer Metastasis: Extravasation

In extravasation, cancer cells leave the circulatory system and enter the surrounding cells. adhesion and stable binding of CTCs and endothelial cells promote extravasation (Cheng and Cheng, 2).

Adherence of disseminated tumor cells (DTCs) to endothelial cells (ECs) lining blood vessel walls is the initial stage in cancer cell extravasation. Adhesion molecules like selectins and integrins play a role in this process after being increased by TGF-signaling. Before being more securely adhered to the vessel wall, the DTCs bond weakly to the ECs as they roll along the wall. DTCs then produce proteases like matrix metalloproteinases (MMPs), which play a role in separating ECs from the basement membrane. These proteases break down the extracellular matrix, and holes or pores are formed in the EC layer, allowing the DTCs to escape into the surrounding tissue. The third phase involves the translocation of DTCs beyond the basement membrane and into the surrounding tissue, a process known as transendothelial migration (TEM). The DTCs' ability to extend protrusions or filopodia aids in this process by allowing them to traverse the pores and spaces made by the proteases. In the fourth stage, the DTCs may enter a dormant condition in which they remain inert or develop much slower for a considerable amount of time (Cheng and Cheng).

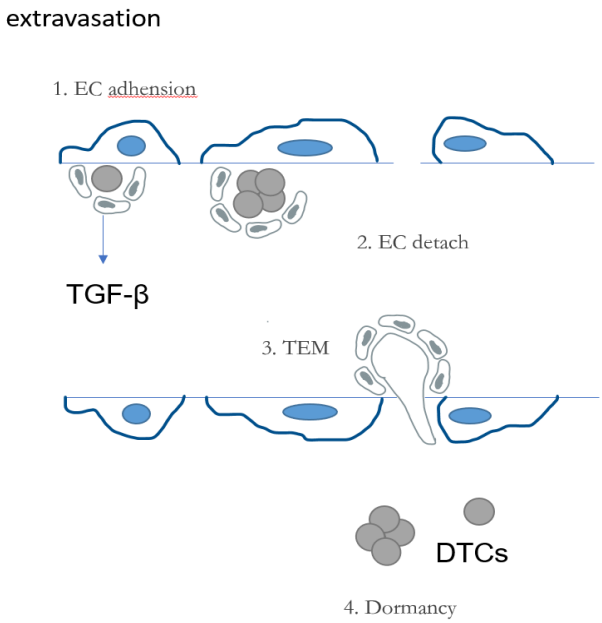

Figure 4. The extravasation of cancer metastasis

Fifth Step of Cancer Metastasis: Colonization

Colonization is the final step in the process of cancer metastasis. After selecting target organs and metastatic sites, cancer cells choose to go dormant or continue to proliferate. The proliferating cancer cells will make the tumor gradually become larger (Lambert et al., 676).

The arrival of disseminated tumor cells (DTCs) in a distant place is the first stage in colonization. These cells could have entered the bloodstream or lymphatic system and spread to their new location. To establish themselves and thrive, DTCs must attach to and pierce the walls of blood or lymphatic vessels and adapt to the new microenvironment. This entails several cellular and molecular modifications, such as changes in gene expression, metabolism, and signaling pathways, which allow the cells to respond to new environmental signals while evading immune monitoring.DTCs can proliferate and create a new tumor if adapted to their new milieu. This process may include the development of new blood vessels, known as angiogenesis, to deliver nutrition and oxygen to the growing tumor (Lambert et al., 676)..

As the tumor grows, it has the potential to spread and infect adjacent tissues, resulting in organ malfunction and other consequences.

Conclusion

To sum up, cell migration is a fundamental process involved in various physiological and pathological phenomena, such as cancer metastasis. This paper comprehensively discussed the four steps of cell migration, highlighting the intricate mechanisms and signaling pathways underlying this process. Moreover, it compared single cell migration with collective cell migration, emphasizing the complexity of collective cell behavior and its significance in developmental processes and disease progression.

The discussion delved into the crucial role of cell migration in cancer metastasis, outlining the five key steps involved: infiltration, intravasation, survival in the circulatory system, extravasation, and colonization. Each step was meticulously examined, elucidating the cellular and molecular events that facilitate cancer cell migration and metastasis.

Furthermore, the paper emphasized the importance of understanding cell migration in the context of cancer biology, as it offers insights into potential therapeutic targets and strategies for preventing tumor dissemination and improving cancer treatment outcomes. Overall, this study contributes valuable knowledge to the field of cell biology and cancer research, paving the way for further investigations and advancements in understanding and controlling cell migration in disease contexts.

Acknowledgments

I would like to thank my advisor for the valuable insight provided to me on this topic.

References

Cheng, Xiao, and Ke Cheng. "Visualizing Cancer Extravasation: From Mechanistic Studies to Drug Development." *Cancer Metastasis Reviews*, vol. 40, no. 1, Mar. 2021, pp. 71–88. *PubMed Central*, https://doi.org/10.1007/s10555-020-09942-2.

Clark, Andrew G., and Danijela Matic Vignjevic. "Modes of Cancer Cell Invasion and the Role of the Microenvironment." *Current Opinion in Cell Biology*, vol. 36, Oct. 2015, pp. 13–22. *ScienceDirect*, https://doi.org/10.1016/j.ceb.2015.06.004.

Friedl, Peter, and Katarina Wolf. "Plasticity of Cell Migration: A Multiscale Tuning Model." *The Journal of Cell Biology*, vol. 188, no. 1, Jan. 2010, pp. 11–19. *PubMed Central*, https://doi.org/10.1083/jcb.200909003.

Henke, Erik, et al. "Extracellular Matrix in the Tumor Microenvironment and Its Impact on Cancer Therapy." *Frontiers in Molecular Biosciences*, vol. 6, Jan. 2020, p. 160. *PubMed Central*, https://doi.org/10.3389/fmolb.2019.00160.

Joshi, Rushikesh S., et al. "The Role of Cancer-Associated Fibroblasts in Tumor Progression." *Cancers*, vol. 13, no. 6, 2021. *ProQuest*, https://doi.org/10.3390/cancers13061399.

Lambert, Arthur W., et al. "Emerging Biological Principles of Metastasis." *Cell*, vol. 168, no. 4, Feb. 2017, pp. 670–91. *ScienceDirect*, https://doi.org/10.1016/j.cell.2016.11.037.

Le, Hoang Anh, and Roberto Mayor. "Cell–Matrix and Cell–Cell Interaction Mechanics in Guiding Migration." *Biochemical Society Transactions*, vol. 51, no. 4, Aug. 2023, pp. 1733–45. *PubMed Central*, https://doi.org/10.1042/BST20230211.

Lodish, Harvey, et al. *Molecular Cell Biology*. W. H. Freeman & Company, 2021.

Lu, Pengfei, et al. "Extracellular Matrix Degradation and Remodeling in Development and Disease." *Cold Spring Harbor Perspectives in Biology*, vol. 3, no. 12, Dec. 2011, p. a005058. *PubMed Central*, https://doi.org/10.1101/cshperspect.a005058.

Majidpoor, Jamal, and Keywan Mortezaee. "Steps in Metastasis: An Updated Review." *Medical Oncology*, vol. 38, no. 1, Jan. 2021, p. 3. *Springer Link*, https://doi.org/10.1007/s12032-020-01447-w.

Novikov, Nikita M., et al. “Mutational Drivers of Cancer Cell Migration and Invasion.” *British Journal of Cancer*, vol. 124, no. 1, Jan. 2021, pp. 102–14. *www-nature-com.libproxy2.usc.edu*, https://doi.org/10.1038/s41416-020-01149-0.

Sturgess, Victoria, et al. “Vascular Regulation of Disseminated Tumor Cells during Metastatic Spread.” *Biophysics Reviews*, vol. 4, no. 1, Mar. 2023, p. 011310. *PubMed Central*, https://doi.org/10.1063/5.0106675.

Theveneau, Eric, and Roberto Mayor. “Cadherins in Collective Cell Migration of Mesenchymal Cells.” *Current Opinion in Cell Biology*, vol. 24, no. 5, Oct. 2012, pp. 677–84. *PubMed Central*, https://doi.org/10.1016/j.ceb.2012.08.002.

Wu, Jia-shun, et al. “Plasticity of Cancer Cell Invasion: Patterns and Mechanisms.” *Translational Oncology*, vol. 14, no. 1, Oct. 2020, p. 100899. *PubMed Central*, https://doi.org/10.1016/j.tranon.2020.100899.

Zavyalova, M. V., et al. “Intravasation as a Key Step in Cancer Metastasis.” *Biochemistry (Moscow)*, vol. 84, no. 7, July 2019, pp. 762–72. *Springer Link*, https://doi.org/10.1134/S0006297919070071.

Zijl, Franziska van, et al. “Initial Steps of Metastasis: Cell Invasion and Endothelial Transmigration.” *Mutation Research*, vol. 728, no. 1–2, July 2011, p. 23. *www.ncbi.nlm.nih.gov*, https://doi.org/10.1016/j.mrrev.2011.05.002.