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Metastasis in Cancer and Tumor Cells

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

A crucial stage in the development of cancer is metastasis, which greatly increases patient morbidity and mortality. The process of metastasis involves several steps, starting with the local invasion of cancer cells into the surrounding tissues, then extravasation, colonization at distant sites, survival in the bloodstream, and intravasation. Changes in cell adhesion, modification of the extracellular matrix, migration, invasion, immune evasion, angiogenesis, and the creation of a favorable microenvironment are only a few of the molecular and cellular processes that cause metastasis. Tumor heterogeneity, interactions with the tumor microenvironment, genetic and epigenetic variables, and immunological reactions all have an impact on the process. As a prognostic signal and a barrier to early discovery and efficient treatment, metastasis has significant clinical ramifications. Promising targeted treatments to prevent metastasis include those that target important signaling pathways, immune checkpoint blocking, and anti-angiogenic drugs. New approaches that target cancer stem cells, the tumor microenvironment, and the use of nanoparticles for targeted medication delivery are also being investigated. Even with breakthroughs, there are still many elements of metastasis that are unclear, highlighting the need for more study to understand its complexities, find new therapeutic targets, and provide individualized therapies to prevent or treat metastatic cancer. For bettering cancer patient outcomes and easing the burden of this terrible disease, it is essential to comprehend metastasis and effectively address it.

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1. INTRODUCTION

Metastasis is the process by which cancer cells spread from the site of their initial formation to another area of the body. In metastasis, cancer cells separate from the main tumor and move through the blood or lymphatic system to develop a new tumor in various body organs or tissues. The main tumor's malignancy has spread to a new, metastatic tumor, for instance, if breast cancer spreads to the lung, the cancer cells there are those of the breast, not the lung. Despite being the leading factor in cancer therapy failure and mortality, metastasis is still not fully understood. Large quantities of cancer cells are discharged into the bloodstream every day in cancer patients, although melanoma research in animal models suggests that only 0.1% of tumor cells spread. Cancer cells must leave their primary site, travel through the circulation, endure blood vessel pressure, adapt to novel biological environments in a secondary site, and avoid lethal conflict with immune cells in order to produce metastases [1,2]. After all, more than 90% of cancer patients die from metastasis as the main cause of mortality. Understanding the mechanics of this process will make it easier to find molecular therapy targets that could potentially slow or stop the spread of cancer [1,3,4]. Cancer mortality and morbidity are primarily brought on by metastasis. The procedure involves complicated interactions between the inherent characteristics of cancer cells and various microenvironments. The result is the growth of a close-by or far-off discontiguous secondary mass. Metastatic cells acquire properties in addition to those required for neoplastic transformation in order to successfully disseminate. Determining the hallmarks of metastasis is extremely difficult due to the heterogeneity of the mechanisms involved, routes of spread, redundancy of the molecular pathways that might be used, and the capacity to benefit from the activity of nearby stromal cells [5].

2. MECHANISM OF CELL INVASION

Cancer cells invade other tissues either by moving collectively as epithelial sheets or detached clusters, or as single cells via mesenchymal or amoeboid cell types. Numerous tumor cells undergo morphological and phenotypic conversions that alter their plasticity as cancer progresses, such as the epithelial to mesenchymal transition (EMT), the collective to amoeboid transition (CAT), and the mesenchymal to amoeboid transition (MAT). During the past decade, EMT has come to be understood as a critical step in the development and metastasis of cancer. EMT, also known as type I, type II, and type III EMTs, is a highly conserved process that happens during embryogenesis, chronic inflammation, fibrosis, and the advancement of cancer, respectively. EMT is characterized molecularly by the loss of epithelial features and the simultaneous gain of a mesenchymal gene expression program. Accordingly, cells that have undergone EMT lose their epithelial integrity and acquire the capacity to separate from epithelial cell clusters and migrate as solitary mesenchymal cells. CAT, also known as collective to amoeboid transition, has been defined as the amoeboid migratory technique used to separate individual cells from cell clusters, particularly in melanoma. Amoeboid cells have less contact with the extracellular matrix (ECM) than other cell types, which enables them to pass through ECM barriers without the aid of ECM proteolysis. Breast cancer, melanoma, and fibrosarcoma all exhibit MAT, or the transformation of mesenchymal cells into amoeboid cells. MAT is dependent on Rac and Rho/ROCK signaling and is unrelated to activities of proteases like MMPs, serine proteases, and cathepsins. In fact, it has been demonstrated that inhibiting extracellular proteolysis causes MAT. In addition to being regulated by the tumor microenvironment, regulatory proteins like EphA2 kinase can also cause MAT. A nonproteolytic invasive program is activated coupled with a Rho-mediated cell rounding when EphA2 is re-expressed in mesenchymal melanoma cells, changing the plasticity to an amoeboid motility [6].

2.1 Collective Cell Invasion

Breast, endometrial, colorectal, and melanoma are epithelial malignancies that experience the bulk invasion of cancer cells. The overall invasion of cells has three distinguishing characteristics. First, during mobility, cell-cell connections are unharmed. Second, the traction force necessary for collective cell movement is produced by the multicellular coordination of polarity and cytoskeletal activity. Third, modification of the extracellular matrix (ECM) and changes to the basement membrane are caused by collective cell invasion. There are

many different types of collective cell invasion, such as the development of a monolayer that enables two-dimensional invasion, the development of cell strands for three-dimensional invasion, or even the dissociation of a collectively invading cell cluster from the initial tumor. For instance, in mammary tumors, where the loss of myoepithelial cells results in the collective cell movement that transforms in situ breast cancer into invasive breast carcinoma, luminal epithelial cells have diminished polarity. Force generation is required to pull or push cells from the front or back in order to mediate collective cell movement. Integrins that bind to substrates in leading cells produce the traction force. In order to attach to ECM elements like fibronectin, the leading-edge expresses integrins 1 and 3 to mediate focal adhesion complexes [6].

2.2 Mesenchymal Cell Invasion

Five steps make up the migratory cycle used by mesenchymal cells: pseudopod protrusion, focal contact creation, focalized proteolysis, actomyosin contraction, and ultimately, trailing edge detachment. Melanoma, glioblastoma, and fibrosarcoma all showed evidence of mesenchymal cell invasion. Mesenchymal cells mostly develop from epithelial cell clusters during EMT in cancer. Cancer cells become partially polarized as a result of the rearrangement of F-actin. The cell is firmly attached to the ECM by focal adhesions in the front, whereas the tail moves as a result of contractions of the retraction fibers. It has been demonstrated that transient TGF- signaling is what causes cancer cells to dedifferentiate and the subsequent separation of individual cells from a cell strand that is migrating collectively. Within the tumor, cells of various motilities are dispersed unevenly; in fact, only 5% of the cells are mobile. Time-lapse investigations that differentiated between collective clusters and individual moving cells found that individual mesenchymal cells exhibit active TGF- signaling as shown by nuclear Smad2 agglomeration. Smad2 was kept in the cytoplasm of non-motile or collectively moving cells, in contrast. Large lung metastatic colonies and lymph node-disseminated cell clusters lacked nuclear Smad2 accumulation. It's interesting to note that TGF-/Smad2 signaling was required for intravasation of individual mesenchymal cells into blood arteries because TGF- type II receptor inhibition prevented hematogenous metastasis. Cancer cell clusters could still be seen in the lymph system, and collective invasion was unaffected. By activating Smad4, the epidermal growth factor (EGF) receptor, Nedd4, M-RIP, FARP, and RhoC, this study showed that (i) TGF- is necessary to change cancer cells from a cohesive to a single cell motility, and (ii) the downregulation of TGF- at secondary sites is required for distal metastasis [6].

2.3 Amoeboid Cell Invasion

The ability to chemotactically and the loss of entire cell polarity are two characteristics of amoeboid cell invasion. Breast cancer, lymphoma, small-cell lung and prostate carcinomas, as well as melanoma and sarcoma, all exhibit single amoeboid cell invasion. Amoeboid cancer cells differ from mesenchymal cells in that they are rounded, develop in suspension, don't generate stress fibers, don't remodel the ECM, and don't have focalized integrins. When compared to mesenchymal cells, which move at a rate of 0.1–1 m/s, amoeboid cells exhibit the fastest migration phenotype, reaching a speed of up to 20 m/min. Amoeboid-like motility is protease-independent, whereas mesenchymal and collective cell invasion depend on protease activities. Cells use actomyosin-based mechanical forces to physically displace matrix fibrils rather than destroying them. It is believed that protease-independent amoeboid cell invasion specifically takes place when collagen network structural holes fail to exhibit the stabilizing covalent crosslinks that govern ECM rigidity. Amoeboid cancer cells are restricted in their movement by structural limitations because they are unable to pass through collagen pores that are smaller than the size of their nucleus. Even in vivo and in vitro, naturally crosslinked collagen necessitates MT1-MMP (MMP14) dependent proteolytic activity for amoeboid cell movement. This shows that several movements can be enjoyed concurrently and jointly rather than being mutually incompatible [6].

3. HALLMARKS OF METASTASIS

Given that tumor cells make use of biological mechanisms, signaling pathways, and chemicals that are common to normal cells, it has been difficult to assign distinct hallmarks to either the metastatic process or the emergence of metastatic lesions. Normal and malignant cells both make use of the same cellular machinery, with the exception of driver mutations. The fact that cancer has proven to be so challenging to properly prevent or treat without considerable toxicity is one of the main causes behind this.

The majority of the time, cancer cells behave normally, but in the wrong situations.

3.1 Motility and Invasion

Cells must be able to move if they are to escape from a main tumor. Cancer cells can escape in a variety of ways, but the ability to move is essential for metastasis. While other cells can assist in cellular migration, metastatic cells must have the innate capacity to migrate, either as a single cell or as a community of cells. Malignancy, by definition, necessitates that cells pass through a basement membrane. As a result, metastatic cells must somehow be able to infiltrate. However, this ability need not be intrinsic; it may instead arise through the usurpation of immune cells' invasive properties or from changing the behavior of nearby stromal populations. Also critical, is recognition that motility is necessary, but not sufficient, for invasion [5].

3.2 Modulation of the Microenvironment

The ability of metastases to restructure local tissue is a striking trait. They can do this by enlisting new cells into the local microenvironment, inducing the mobilization of immune/inflammatory cells, telegraphing the restructuring of other tissues, changing the metabolism of the stroma around them, blocking immune system responses that would otherwise be anti-tumor, controlling the behavior of other cancer cells, changing the extracellular matrix, or co-opting the normal behaviors of other cells [5].

3.3 Plasticity

All forms of cancer are diverse. Furthermore, selection pressures vary the composition and cellular behavior, making measurements of tumor composition at any one time only a snapshot. In addition to normal stroma, tumor cells also communicate with one another. Neoplastic cells can affect other cells' growth rates, medication resistance, and propensity to spread. Communication can take place either directly with another tumor cell or through a middle cell. Regardless, communication occurs between tumor cells and between tumor cells and host cells, which leads to altered behavior and plasticity. As a result, heterogeneity is heterogeneous both spatially and temporally. . Cellular plasticity offers a selective advantage in terms of evolution. The multitude of microenvironments that dispersing cells must pass through along the metastatic cascade make this especially true. Similarly, the ability to adapt is necessary for plants to be able to grow in many types of soil. Cells must react to continuously shifting matrices, environmental factors (such as pO2, nutrition, sheer, etc.), and insults along the metastatic cascade. Cells with the most tools in their toolbox have a distinct competitive advantage because to the redundancy of mechanisms that can complete any step in the metastatic process. Cells that can use alternate adhesion molecules or recognize another matrix component have a selective advantage over those that can only use a single integrin heterodimer for attachment. A further method that spreading cells can metastasize is the capacity to adapt and use a different protease to enter the body. It is crucial to keep in mind that the development of a metastatic locus is not always a binary process. It goes without saying that a cell cannot effectively complete the metastatic cascade if it cannot finish the first step. However, efficiency is low but the opportunity to metastasis still exists if a cell has even a modicum of capacity for each stage. The continuum of states between epithelial and mesenchymal states emphasizes this notion. Between these phenotypic' extremes, neoplastic cells seem to be present. The rate of change between states may be important, but this is not yet known. Moving from one area of the body to another, nevertheless, necessitates the capacity to adjust to constantly shifting circumstances. According to current research, the inability to adapt (i.e., terminal differentiation into adipocytes) can actually prevent the ability to metastasis [5].

3.4 Colonization

The difference between the words "dissemination" and "metastasis" is among the most important distinctions when identifying the hallmarks of metastasis. Because metastasis can refer to both a process and an endpoint, confusion frequently results. From a clinical standpoint, the result is what matters most. Since the patient won't get cancer as long as the primary tumor is removed, it is unimportant if a cell starts the process but is unable to finish it (i.e., produce a macroscopic lesion). Survivability, however, drastically decreases if a dispersed cell successfully colonizes a tissue. Therefore, we highly advise separating the term "metastasis" from the simple spread of cells. It is erroneous to compare circulating tumor cells (CTC) or disseminated tumor cells (DTC) to

metastases. The majority of CTC and DTC never multiply to produce a macroscopic lesion. Although they all have the ability to, they have not yet done so. The capacity to colonize in a discontiguous site includes the capacity to control the microenvironment as well as adapt to growth elsewhere, just like with these other hallmarks of metastasis [5].

4. THE ROLES OF MICROBIOME IN CANCER METASTASIS

High-malignancy tumor cells have the potential to start metastatic foci and almost certainly cause patients' deaths. Promoting cell viability through epigenetic states (like EMT), microenvironmental variables (like cancer-activated immune cells), physical factors (like FSS), or genetic modifications (like DDR) might increase the survival of these harmful cancer cells. Indolepropionic acid (IPA), cadaveric amines, and sodium butyrate (NaB) are examples of microbial metabolites that play important roles in the metastasis of breast cancer, melanoma, prostate cancer (PC), and colorectal cancer (CRC) through a variety of mechanisms [3].

4.1 Microbiome Influences Cancer Metastasis through Epithelial-Mesenchymal Transition (EMT)

By lowering -linked proteins and stimulating the Wnt signaling pathway, the microbiome can cause EMT and aid in cancer spread [7–9]. Epithelial-mesenchymal transition (EMT) is a cellular reprogramming process whereby epithelial cells lose their adhesion to surrounding cells and the extracellular matrix (ECM) and simultaneously acquire mesenchymal characteristics needed for invasion and migration [3,10]. It happens when cancer cells spread to other parts of the body and is distinguished by a significant molecular and cytomorphological change. EMT is related to medication resistance, tumor invasion, and metastasis. EMT is used by carcinoma cells to hasten the dissociation from primary tumors and the dissemination into blood circulation necessary for the development of an invasive phenotype for the metastatic course of cancer [3,11].

4.2 Microbiome Influences Cancer Metastasis by Modulating Immunity

The innate and acquired immune systems play a key role in the development of cancer and have the ability to promote or prevent tumor spread. The relationship between the microbiome and the human immune system may be disrupted by changes in the microbiome's composition or development (ecological dysbiosis), which could ultimately result in altered immune responses that may be the cause of a number of inflammatory disorders in humans. Everyone agrees that innate immunity is characterized by inflammation. MHC class I and II and co-stimulatory molecules, as well as a large number of inflammatory chemokines and cytokines, are upregulated when innate immunity is activated by invading microbial and viral components. Through multiple antigen receptors, they also attract and trigger the activation of NK-cells and T-cells. However, a variety of immune escape mechanisms that tumor cells have developed have diminished the abilities of immune cell effectors. Numerous studies have demonstrated that the microbiota influences cancer spreading by altering immunity and facilitating or obstructing immune escape from tumor cells. For example, Parhi et al. [12] found that Fn colonizes breast tumors and causes a decrease in CD4+ and CD8+ T cells through the abundant Gal-GalNAc (also known as Thomsen-Friedenreich antigen) on tumor cells, so it is reasonable to speculate that Fn not only inhibits NK cells and tumor-infiltrating T cells killing of cancer cells, but also inhibits the accumulation of tumor-infiltrating T cells and promotes tumor growth and metastatic progression. Additionally, in colorectal cancer liver metastasis (CRCLM) tissues, the presence of Fn was linked to a lower density of CD8+ T cells and a higher density of bone marrow-derived suppressor cell (MDSC) markers [13]. This shows that the microbiota can help tumor cells suppress MHC class I expression on the cell surface, limiting antigen-dependent T cell activation and cytotoxic CD8+ T lymphocyte (CTL) elimination. Staphylococcus aureus has also been observed to be strongly related with the production of regulatory T cells in PC, which limit the activation and multiplication of effector T cells and weaken the immune system. Fn may reduce immunity to promote cancer spread. They may be responsible for PC metastasis by triggering immune suppression, increasing inflammation, and controlling the expression of prostate cancer stem cells (PCSCs) [14]. In contrast to the microbiota, which weakens the immune system and promotes cancer metastasis [3], the stimulation of stem cell development and survival pathways, as well as immunological defenses like cytotoxic T cells and natural killer T (NKT) cells, boost the metastatic proliferation of tumor cells [15].

4.3 Microbiome Affects Cancer Metastasis by Influencing Fluid Shear Stress (FSS)

During the metastatic phase, the microbiome can aid tumor cells in adjusting to the biochemical and biophysical elements of the tumor microenvironment. For instance, one well-known physical element that leads to the spread of tumor cells is the shear stress caused by fluid flow. Furthermore, it has been demonstrated that the microbiome alters the actin cytoskeleton in a way that makes tumor cells more resistant to FSS [16]. Tumor hydrodynamics has developed more quickly as a result of the expanding use of microfluidics and mechanical measurement in tumor research. There is growing evidence that FSS has a major impact on hydrodynamics and plays a substantial role in metastasis. FSS, which frequently leads to apoptosis in metastatic cancer cells, occurs, especially after venous entry into the circulatory system. Under physiological conditions, intracellular bacteria can travel through the circulation with cancer cells and greatly aid in the colonization of metastatic sites According to research by Fu et al., *S. xylosus, L. animalis*, and *S. cuniculi* alter the actin cytoskeleton in a way that increases tumor cells' resistance to FSS. This increases host cell survival and thus breast cancer of lung metastasis. In particular, interference with intracellular bacteria reduces metastasis, but not primary tumor growth [3].

4.4 Microbiome Influences Cancer Metastasis by Regulating Matrix Metalloproteinases (MMPs)

The intracellular and membrane-bound endopeptidases known as matrix metalloproteinases (MMPs) are zinc (Zn2+) dependent. The proteome of humans contains most of the 26 MMPs that have been identified [17]. Gelatinases, collagenases, stromelysins, and membrane-type matrix metalloproteinases are just a few examples of the different kinds of MMPs family members that can be found. The proteolytic activity of several MMPs is crucial for unchecked tumor growth, local invasion, and the spread of cancer to distant sites. By releasing matrix factors, cytokines attached to the cell surface, growth factors, or their receptors, they alter tissue integrity, immune cell recruitment, and tissue regeneration [18]. Thus, MMPs mainly affect the steps in cancer metastasis that separate from the primary tumor site and enter and survive in the circulatory or lymphatic system.

5. FACTORS INFLUENCING METASTASIS

The spread of cancer cells from the main tumor to distant organs or tissues is known as metastasis, and it is a complicated process controlled by a variety of variables. The propensity for metastatic spread is influenced by a number of important factors, including genetic and epigenetic changes, tumor heterogeneity, the tumor microenvironment, and interactions between cancer cells and the host immune system.

5.1 Genetic Mutations

Genetic alterations are very important in encouraging metastasis. Oncogene, tumor suppressor, and DNA repair pathway mutations can impair regular cellular functions and provide cancer cells the ability to spread to new sites in the body. For example, TP53 gene alterations have been associated with enhanced metastasis in a number of cancer types. The proliferation, invasion, and metastasis of cells can also be aided by the activation of oncogenic signaling pathways such the Ras-MAPK and PI3K-AKT pathways.

5.2 Epigenetic Modifications

The capacity for metastatic spread can be affected by epigenetic modifications such as DNA methylation, histone modifications, and non-coding RNA expression. These alterations can change the way that genes are expressed and encourage phenotypes that are linked to metastasis. For instance, metastasis in several tumors has been linked to DNA hypermethylation of tumor suppressor genes, such as CDH1 and BRMS1 [19]. DNA methyltransferases and histone deacetylases are two epigenetic regulators that are frequently dysregulated in metastatic cancer cells, which contributes to their invasive activity.

5.3 Tumor Heterogeneity

A significant factor in metastasis is intra-tumor heterogeneity, which is the existence of genetically and phenotypically distinct cancer cell populations within a tumor. Genetic alterations, chromosomal instability, or microenvironmental selection pressures can result in subclones that have unique metastatic capacities. Targeted

therapies have difficulties due to tumor heterogeneity since some subclones may develop resistance or have increased metastatic potential. Breast and lung malignancies have both been linked to high levels of tumor heterogeneity [20].

5.4 Tumor Microenvironment

The extracellular matrix, immune cells, stromal cells, and soluble substances that make up the tumor microenvironment have a significant impact on metastasis. The tumor microenvironment can help metastatic cells establish a favorable habitat for survival, invasion, and colonization in distant locales. For instance, extracellular matrix-degrading enzymes and growth factors are secreted by cancer-associated fibroblasts (CAFs), which promote tumor invasion and angiogenesis [21]. Metastasis can also be impacted by the presence of an inflammatory milieu and immune cell infiltration, including tumor-associated macrophages or regulatory T cells [22].

5.5 Interactions with the Host Immune System

The immune system can either prevent or promote the spread of cancerous cells through metastasis. Through a variety of strategies, including the suppression of antigen presentation or the activation of immunological checkpoints, cancer cells can avoid immune monitoring. Immune cells, on the other hand, can also have anti-metastatic effects by removing circulating tumor cells or halting the colonization of metastatic sites. Anti-PD-1 and anti-CTLA-4 antibodies are examples of immune checkpoint medications that have been effective in treating metastatic melanoma and other malignancies.

6. CONCLUSION

In summary, research on metastasis in cancer and tumor cells has paved the way for significant improvements in cancer diagnosis, therapy, and prevention by shedding light on the intricate mechanisms behind the disease's growth. The understanding of important molecular pathway and the role of several factors has allowed for the development of better targeted medicines and immunotherapies, providing new hope for patients with metastatic disease. Metastasis still remains a significant issue in the management of cancer. To enhance outcomes and pave the way for a time when metastatic cancer may be effectively controlled and avoided, further study is required to address the heterogeneity and treatment resistance linked to metastasis.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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