# Studying the role of the tumor's microenvironment in cancer progression.

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## Abstract

This research paper delves into the crucial significance of the tumor microenvironment in cancer progression and treatment resistance. Focusing on tumor angiogenesis, immune cell interactions, and extracellular matrix modifications, the study highlights the need to comprehend the complex dynamics within the tumor microenvironment. Targeting these interactions presents promising avenues for developing effective cancer therapies. Disrupting angiogenesis, overcoming immune suppression, and addressing ECM alterations emerge as potential strategies to improve treatment outcomes. The research emphasizes the importance of exploring the tumor microenvironment to advance our understanding and pave the way for transformative cancer treatments in the future.

## I. Introduction

With an estimated 1.9 million new cancer cases and 609,360 deaths last year, cancer is the second leading cause of death in the country. Cancer is different from other illnesses since it is harder to treat and it refers to a collection of more than 100 different diseases. It is difficult to treat because the cancer cells can develop resistance to certain treatments. When that happens, patients are given a different treatment, however, the cancer could develop a resistance to the new drug and there may not be any alternative options left. So the question is how does the tumor develop resistance against treatment and continue to spread throughout the body? And would investigating how cancer develops resistance allow us to explore better treatment options? The short answer is yes.

## II. Metastasis

A primary reason that makes cancer so hard to treat is how quickly it spreads throughout the body and invades bodily tissue. Approximately 90% of cancer deaths are due to the movement of the primary tumor sites to distant parts of the body. This process is known as metastasis, in which cancerous cells escape the primary tumor site and spread to distant parts of the body. It's hard to say exactly why cancer cells leave the primary tumor site, however, conditions inside a tumor can be harsh due to the deficient blood supply. A deficient blood supply could mean lowered oxygen and nutrient levels as well as metabolic waste build up, which can contribute to an acidic environment. Cancer cells may also migrate in a response to treatments like chemotherapy. Cancers that disseminate in this aggressive manner are considered malignant and if left untreated they can spread further throughout the body and disrupt organ function.

So how exactly does metastasis work? Well, in order for metastasis to proceed, the cancer cells must be able to break away from neighboring cells and break through supporting tissues until they can reach a lymph or blood vessel. Upon entering a blood or lymph vessel, these cells can be transported throughout the body. To gain access to the channel, cancer cells must navigate through the extracellular matrix (ECM), a network of macromolecules that helps provide cellular structure. It's essentially a cellular mixture of water, polysaccharides, and fibrous proteins. When navigating through the extracellular matrix cancer cells will utilize enzymes, such as the enzyme group known as the matrix metalloproteinases, or stimulate the cells within the

extracellular matrix (ECM) to migrate through the channel with ease. Oftentimes, the tumor will spread “downstream” from their primary organ because of the structure of the circulatory system. The cancer cells will be carried inside the blood vessel until they find a suitable location to form a new tumor. The act of “setting up camp” at a new location is what can be referred to as colony formation. The new arrival cells must create a favorable surrounding in their new environment in order to ensure further growth and survival. However, a new environment will present challenges. The surrounding tissue(stroma) will be very different from their original site and will be unfriendly to our new cancer cells. If the cancer cells are unable to transform the stroma to fit their needs, they cannot metastasize any further and must stay dormant.

**III. Routes of Metastasis**

The three primary ways that tumors can spread to distant organs is through the circulatory system, lymphatic system, and through the body wall into the abdominal and chest cavities. The circulatory system serves as the primary route for metastasis and the lymphatic system provides a route to nearby lymph nodes. The route of metastasis varies from cancer to cancer; for example, bone and soft tissue tumors primarily travel through blood, while breast, lung, and gastrointestinal cancers spread through the lymphatic system. So why exactly do different types of cancers use different modes of transport? The simple answer is that different cancers travel to different locations. For example, breast cancer cells often develop secondary tumor sites in the liver because of the suitable environment for growth. This phenomenon was discovered in 1889 by Stephen Paget and is known as the Seed and Soil in which certain cancers only colonize selective organs due to their suitable growth environments. What creates a successful metastasis depends on the interaction between the metastasizing tumor cells and their target organ. Metastasizing tumor cells must be able to alter the environment, and if the cells are unsuccessful in doing so, successful metastasis is impossible. Some obstacles to metastasis include the inability to promote angiogenesis (formation of new blood vessels) or the inability to reproduce due to lack of interaction with the stroma. Investigating the interactions between the tumor and the stroma is quite challenging given the vast number of growth factors, cytokines, and other cells. On the other hand, the importance of the tumor microenvironment is fairly obvious.

**IV. Extracellular Matrix**

Before we go further in depth into the tumor microenvironment, it would be more appropriate to examine the extracellular matrix’s role in cancer progression. As I mentioned earlier, the role of the extracellular matrix (ECM) is to provide support to surrounding tissue and serves as a filler in between each densely packed cell in the tissue. The extracellular matrix also directs the morphology (shape) of a tissue by interacting with cell surface receptors and binding to growth factors that initiate signaling pathways. Tumors have an altered extracellular matrix and functions similarly as it would in the body. The extracellular matrix serves as a support for the tumor cells and directs cell to cell communication. ECM modifications can be triggered by hypoxia, acidosis, oxygen free radicals (unstable oxygen molecules) produced by inflammatory cells, or proteases released by tumor or stromal cells. Breast cancer cells have been known to induce chemical and physical signals in the extracellular matrix to promote their growth and development. These alterations in the extracellular matrix are often linked to poorer prognosis for patients. Malignant cancer cells have been known to contribute to ECM stiffness, and in return, alter the characteristics of the cancer cells. The extracellular matrix can act as a

protective barrier around cancer cells making them less susceptible to chemotherapy and other treatments which contribute to therapeutic resistance. A stiffened ECM can provide physical support to cancer cells and promote tumor growth, while softer ECM will be less supportive. ECM stiffness is a distinctive feature and a promising therapeutic target.

## IV. Tumor Microenvironment: Key Components and Interactions

To determine the resiliency of a cancer cell, scientists study the cellular composition of the tumor itself. The tumor mass is not only a collection of cancer cells but also hosts a variety of resident and host cells, secreted factors, and an extracellular matrix. Tumor cells must stimulate important chemical and physical changes within their host tissue to sustain cancer growth and progression. The composition of the tumor microenvironment varies but general components include immune cells, stromal cells, blood vessels and the extracellular matrix (ECM). The tumor microenvironment is an active promoter of cancer growth, and the relationship it establishes with the cancer cells promotes cancer cell survival, local invasion, and metastatic growth. To ensure a well-balanced tumor microenvironment and overcome the threats of hypoxia and an acidic environment, the tumor microenvironment coordinates a step by step measure that promotes angiogenesis to restore O2 levels , nutrient supply, and the removal of metabolic waste.

## V. Immune Cells

Immune Cells play a critical role in the tumor microenvironment and can either suppress or promote tumor growth. For instance, Tumor Associated Macrophages (TAMs) promote tumor growth by suppressing immune responses and promoting angiogenesis. Immune cells fall into two general categories: adaptive immune cells and innate immune cells. Adaptive immunity is initiated by the exposure to certain antigens and uses an immunological memory to evaluate the danger and implement the appropriate immune response (ex. T Cells, B Cells, NK Cells). Innate immunity refers to the non-specific immunity and is activated when foreign substances enter the body (ex. Macrophages, neutrophils, dendritic cells).

Stromal cells, also known as mesenchymal cells, are often found in the bone marrow but can be found in many other parts of the body as well. These immune cells are vital in tissue repair and tissue homeostasis and are the most responsive cell to tissue inflammation. However, these cells can also promote cancer progression as they can secrete various growth factors that promote angiogenesis and metastasis.

### 1. Endothelial Cells

Vascular endothelium is a thin single layer of endothelial cells (ECs) and aids in angiogenesis. Not only does vascular endothelium separate circulating blood from tissues, it also delivers water and nutrients, disposes metabolic waste and carries immune cells. During the initial stages of tumor development cancer cells rely on passive diffusion for gas exchange and the transportation of nutrients. Once tumors reach a certain volume, insufficient oxygen and a build-up of metabolic waste results in the tumor microenvironment (TME) becoming hypoxic

and acidic. To overcome hypoxia and acidification, tumors must develop their own blood supply. Hypoxia leads to the activation of hypoxia inducible factors (HIFs), transcription factors critical in coordinating cellular responses to low O2. Vessel sprouting is a common mechanism used by tumors to induce the growth of new vessels. Specifically, HIFs initiate vessel sprouting by instructing ECs to secrete angiogenesis supporting factors such as, platelet derived growth factors (PDGF), epidermal growth factors (EGF) and VEGF. The VEGF stimulates migration of ECs to form new blood vessel lumen and the endothelial cells secrete proteins to form new basement membranes. Blood vessels in the TME often fail to achieve the final stages of maturation, resulting in faulty blood vessels. Beyond angiogenesis, endothelial cells are critical in promoting cancer cell migration, invasion and metastasis. ECs are highly plastic in nature and can differentiate into CAFs . During tumor progression, ECs undergo endothelial-mesenchymal transition to become cancer associated fibroblasts (CAFs). The transition from an EC to a CAF is organized by TGF-β, a major regulator of numerous cellular functions including cellular immunity,  and bone morphogenetic protein (BMP) and leads to loss of cell-to-cell connections, detachment and elongation, enhanced migration and loss of endothelial properties. CAFs are critical in stimulating migration and invasion of tumor cells .

## 2. Macrophages

Macrophages are responsible for engulfing and digesting foreign substances that include any harmful matter including cellular waste and invading cells. Based on the condition of the cellular environment, monocytes give rise to mature macrophages, and when they are recruited into the tumor microenvironment and if conditions allow, they are converted into tumor-associated macrophages (TAMs). Generally, macrophages come in two main groups called classically activated macrophages (M1) and alternatively activated macrophages (M2). The former type typically inhibits cancer growth and kills off cancer cells while the latter promotes cancer metastasis and angiogenesis. M2 tumor-associated macrophages not only lack the function of phagocytizing tumor cells but also help tumor cells in spreading them to other parts of the body and preventing them from being killed. TAMs have proved to be a promising area for developing cancer treatment.

## 3. T lymphocytes (Tregs, effector T cells)

Regulatory T cells (Tregs) are essential to regulating homeostasis in the immune system and act to suppress immune response responses thereby maintaining homeostasis and self-tolerance. They control the immune response to self and foreign particles and prevent autoimmune diseases. There are two main types of Tregs: Tregs produced by the thymus are termed “ natural” whole cells produced outside the thymus are termed “adaptive”. And it has been found that Tregs can suppress anticancer immune response thereby hindering effective cancer treatment and encouraging tumor growth. Identifications of such factors influencing the function of these cells is critical to understanding cancer development and growth. The manipulation and modifying of these cells would be a promising cancer therapeutic strategy but would require further research. Currently, there have been strides made to create genetically modified Tregs for cancer therapy such as, altering the specificity of the T-receptor or introducing antibody recognition in the chimeric antigen receptors (CARs).

### 4. Myeloid-derived suppressor cells (MDSCs)

Myeloid-derived suppressor cells (MDSCs) are immature myeloid cells that suppress immune responses and undergo massive expansion during tumor growth. MDSCs can be categorized into two major groups: granulocytic/polymorphonuclear MDSCs (PMN- MDSCs) and monocytic MDSCs (M-MDSCs), grouped according to their origin from either the granulocytic or monocytic cell lineages. A recent report suggests that a percentage of PMN-MDSCs might have differentiated from a distinct monocytic myeloid cell lineage, but the possibility that the PMN-MDSCs differentiate from other precursors requires further investigation.These cells aid cancer cells in suppressing anti-cancer immune responses, tumor expansion and invasion, and resist treatment and are indicators of malignant tumors. MDSCs have proven to have negative effects on treatment efficiency; treatments such as chemotherapy, radiotherapy, and immunotherapy. Treatment strategies targeting MDSCs have proven to have positive outcomes on the patient.

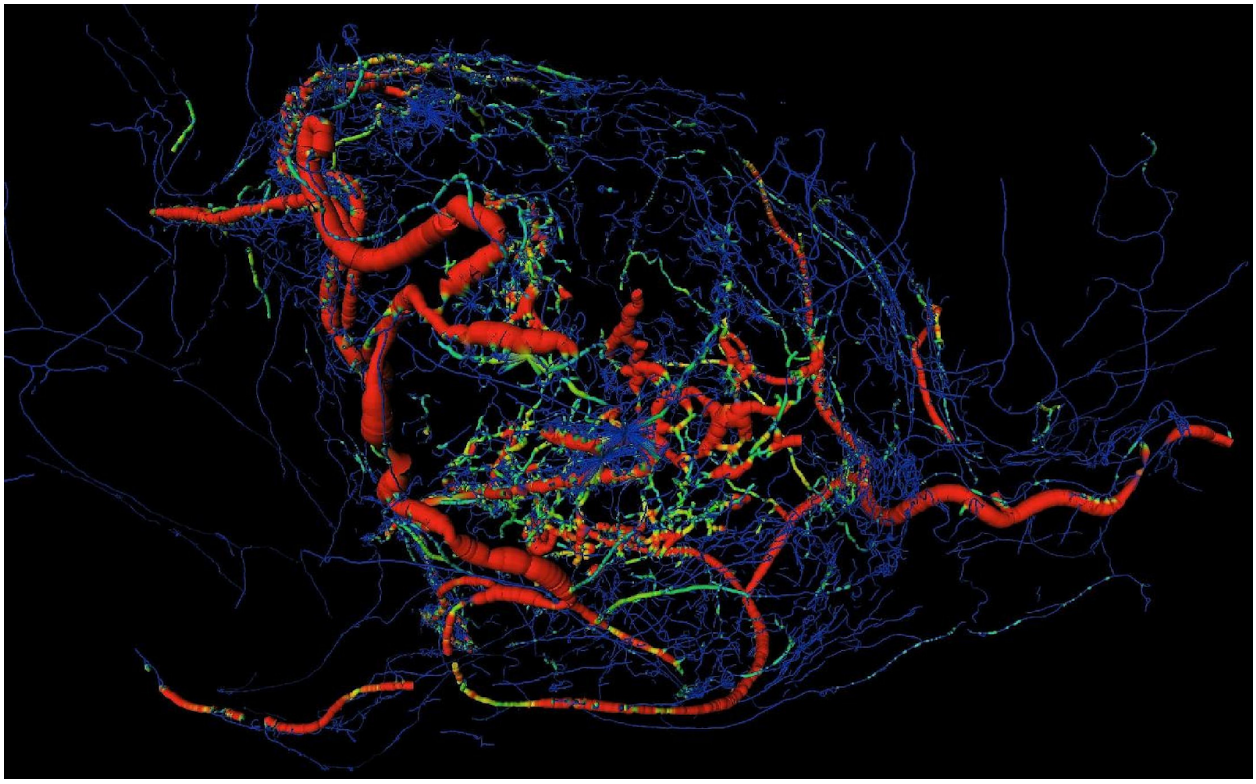
## VI. Inflammation

Inflammation is a type of natural body response that involves activation and the initiation of cell innate and adaptive immunity. Some of its primary functions lie in protecting the body from invading pathogens and tissue repair. And it has been found that inflammation plays a role in cancer progression and cancer therapy. In recent years, oncologists have shifted its perspective from a ”cancer-centric” view to a broader context that places cancer cells in a network of various molecular components and immune cells known as the tumor microenvironment.(TME) Cancer development and its response to treatment is regulated by inflammation, which either promotes or suppresses tumor progression. Inflammation has a profound effect on the tumor microenvironment because the cells inside are highly plastic and continuously change their function and appearance. Chronic inflammation facilitates tumor progression and treatment resistance, whereas acute inflammation often stimulates the maturation of dendritic cells (DCs) leading to anti-tumor immune responses. Pro-tumorigenic inflammation promotes cancer by impeding anti-cancer immunity. Given that the immunity system can play pro and anti-tumorigenic roles throughout each stage of tumorigenesis, treatments that redirect the immune system’s response to cancerous cells prove to be beneficial. These approaches include immunological “checkpoint” blockade, cancer vaccines, and oncolytic virus therapy. Oncolytic virus therapy refers to the use of viruses to infect and destroy cancerous cells. However, immunotherapy is still ineffective for many patients. In the present, immunotherapy has largely been used on patients with advanced cancers so the effectiveness against less developed cancers is yet to be determined.

## VII. Tumor angiogenesis and its drivers

Earlier in the article you were introduced to tumor angiogenesis and its significance in the the tumor microenvironment; now we will discuss the mechanisms of tumor angiogenesis more deeply. The process of angiogenesis is facilitated by chemical signals in the body. Throughout a person’s lifetime the body will simulate growth and repair of these blood vessels. However, tumors are also able to do this and use tumor angiogenesis to provide nutrients and oxygen to itself. The process can be broken down into four distinct steps: degradation, migration,

dissemination, and formation. (1) Degradation of the supporting membranes by enzymes (2) Migration of endothelial cells (3) Dissemination of endothelial cells (ECs). (4) Formation of new basement membrane and blood vessels. And what results is a complex system of blood vessels that seem to stem out uncontrollably around the tumor as shown by the illustration below.



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The work of tumor angiogenesis was pioneered by Harvard Medical School professor Dr. Judah Folkman. In 1971 in the New England Journal of Medicine, he reported that solid tumors were dependent on the development of the host's blood vessels to grow (SeagateWorld). He proposed that by stopping the growth of nearby blood vessels you could stop the growth of the tumor. Folkman first discovered this phenomenon when working with his lab partner Dr. Robert Langer when investigating a tumor's reaction to different injected substances. It was upon injecting the tumor with shark cartilage that the blood vessels began to shrink away from the site of injection. Although shark cartilage has been shown to reduce tumor size, it has not proven to be effective for cancer treatment.

## VIII. Therapeutic Applications

Numerous studies have shown the effectiveness of anti-angiogenic treatment on suppressing cancer growth and metastasis. Angiogenesis inhibitors can reduce the size of the tumor and stabilize the disease. It can be administered for long periods of time and is not subject to drug resistance because it's directed towards endothelial cells rather than cancer cells. Early

development of anti-angiogenic treatment began in the 1980's after the discovery of the first angiogenesis inhibitors from natural and endogenous origin. The early inhibitors include recombinant human platelet factor 4, AGM-1470 ( from a certain species of fungus), and marine cartilage.

## IX. Conclusion

Throughout the research paper you were introduced to the many components of the tumor microenvironment from the basic immune cells to the different processes that occur. By studying the role of the tumor microenvironment on cancer progression scientists can understand what makes cancer such a resilient disease. Targeting the tumor microenvironment offers promising avenues for developing effective cancer therapies. By disrupting angiogenesis, overcoming immune suppression, and addressing ECM alterations, researchers can pave the way for innovative treatments to improve patient outcomes.

## References

1. Richard. (2016, September 14). Angiogenesis of tumors, its history. Retrieved 11 August 2023, from Seagate World | A look into the human side of Seagate website: https://www.seagateworld.com/2016/09/angiogenesis-of-tumors/.
2. Anderson, N. M., & Simon, M. C. (2020). The tumor microenvironment. *Current Biology: CB*, *30*(16), R921–R925. doi:10.1016/j.cub.2020.06.081
3. Huang, J., Zhang, L., Wan, D., Zhou, L., Zheng, S., Lin, S., & Qiao, Y. (2021). Extracellular matrix and its therapeutic potential for cancer treatment. *Signal Transduction and Targeted Therapy*, *6*(1), 153. doi:10.1038/s41392-021-00544-0
4. Extracellular matrix. (2017, September 8). Retrieved 11 August 2023, from Biology Dictionary website: https://biologydictionary.net/extracellular-matrix/.
5. Gupta, M. K., & Qin, R.-Y. (2003). Mechanism and its regulation of tumor-induced angiogenesis. *World Journal of Gastroenterology: WJG*, *9*(6), 1144–1155. doi:10.3748/wjg.v9.i6.1144
6. Greten, F. R., & Grivennikov, S. I. (2019). Inflammation and cancer: Triggers, mechanisms, and consequences. *Immunity*, *51*(1), 27–41. doi:10.1016/j.immuni.2019.06.025
7. Sharpe, M., & Mount, N. (2015). Genetically modified T cells in cancer therapy: opportunities and challenges. *Disease Models & Mechanisms*, *8*(4), 337–350. doi:10.1242/dmm.018036
8. Singh, Yogendra. “(PDF) Tumor Angiogenesis: Clinical Implications.” *ResearchGate*, https://www.researchgate.net/publication/282782201_Tumor_Angiogenesis_Clinical_Implications.

9. Pan, Y., Yu, Y., Wang, X., & Zhang, T. (2020). Tumor-associated macrophages in tumor immunity. *Frontiers in Immunology*, *11*, 583084. doi:10.3389/fimmu.2020.583084
10. Zhou, J., & Shi, Y. (2023). Mesenchymal stem/stromal cells (MSCs): origin, immune regulation, and clinical applications. *Cellular & Molecular Immunology*, *20*(6), 555–557. doi:10.1038/s41423-023-01034-9