The Influence of Tumor Microenvironment on the Spread and Growth of Lymphoma

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Abstract

In 2024, the American Cancer Society projected that about 89,190 people will be diagnosed with some kind of lymphoma in the United States. A tumor's microenvironment, or TME, is the foundation to the survival, growth, and spread of cancer in the body. The tumor and its microenvironment are constantly interacting with each other in the way that the TME provides for the tumor, giving it the space and the nutrients it needs to grow. However, sometimes the TME and the tumor can interact negatively. Understanding the structure, organization, and spatial composition of a TME is critical to finding the best treatment for specific tumors and cancers. This article will focus on the structure and function of a TME, the specifics on B-cell lymphoma tumor's TME, and what treatments paths that should be taken based on a tumor's microenvironment.

What Is a Tumor Microenvironment

A tumor microenvironment is made up of several different components to provide for the tumor consisting of different cells, an extracellular matrix, vasculature, and chemokines (Yang et al., 2021). Immune cells are considered one of the most important aspects of a tumor's microenvironment as they can either slow or encourage the growth of the tumor. They are placed in two categories: adaptive cells or innate cells. The innate immune cells (like macrophages, neutrophils and dendritic cells) are pro and anti tumorigenic based on complex communications within the TME (Yang et al., 2021). They are mostly a defense mechanism non-specific that deal with foreign antigens coming into the body. The adaptive immune cells, T-cells, B-cells and NK, are activated by specific antigens and evaluate the threat to enhance immune response (Anderson & Simon, 2020).

Stromal cells (like vascular endothelial cells, fibroblasts, adipocytes and stellate cells) are brought into the TME by the cancerous cells becoming a part of the crucial step in the formation of the tumor and furthering the cancer progression (Anderson & Simon, 2020). The vascular endothelium is composed of a monolayer of endothelial cells (ECs), assisting in the formation of blood vessels. This supplies the tumor with an environment to thrive, receiving water, nutrients, circulated blood for tissue, is able to maintain homeostasis, carry immune cells, and help create even more blood vessels (Anderson & Simon, 2020). EC's are also able to promote the migration, invasion, and metastasis of a cancer cell through immature blood vessels without proper cell to cell connections that allow cancer cells to extravasate (Anderson & Simon, 2020).

The structure of the tumor's microenvironment is established by the cancer associated fibroblasts (CAFs) that have a large influence on tumor progression and therapy (Yang et al., 2021). The CAF creates the connection of communication between the TME and the cancer cells. The stroma and cancer cells create growth factors that turn fibroblasts into CAFs in the TME. They play such a huge role because they are a majority of the extracellular components

and shape the TME. The CAF's four main jobs are tumor proliferation and metastasis, neoangiogenesis, ECM remodeling and immunosuppression (Anderson & Simon, 2020).
Of the non-cellular components, the extracellular matrix (ECM) has the most important function within the TME: promoting tumor cell dissemination. Especially in solid tumors that have large ECM deposits that take up more than half the tumor mass facilitating more spreading (Anderson & Simon, 2020). It not only takes control of the TME and provides a structure for the cells, it also has a big effect on the tumor's response to therapy (Henke et al., 2020).

B-cell Lymphoma Microenvironment

Lymphoma, which is cancer of the immune system cells, has two main entities: Hodgkin lymphoma (HL) and non-Hodgkin (B-cell lymphomas (B-NHL) and T-cell lymphomas (Menter & Tzankov, 2019). They are a diverse group of neoplasms coming from B and T lymphocytes, and natural killer (NK) cells that infiltrate lymphoid structures. The key aspects influencing the composition of microenvironment are lymphoma subtypes and the interactions between the lymphoma cells and the microenvironment (Kumar & Xu, 2018). For nutrients and growth, lymphoma uses the growth factors and cytokines from its microenvironment. In learning more about the structure and function of lymphoma genomics, we better understand its microenvironment and what effects it has on the progression and lymphomagenesis of the cancer (Menter & Tzankov, 2019). In recent years, the study in progression of lymphoma has had an increasing focus on the non-malignant cells in the tumor to better understand how to approach the TME of lymphoma (Mulder et al., 2019).
Ultimately, TME in B-cell lymphoma can be separated into the immune microenvironment and the non immune microenvironment. In the immune microenvironment, it contains T and B lymphocytes, tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), tumor-associated neutrophils (TANs), natural killer (NK) cells, dendritic cells (DCs) and more. These cells escape immunity and mediate the weakening immune system (Liu et al., 2021). In the non immune microenvironment, you will find stromal cells, like cancer-associated fibroblasts (CAFs), extracellular matrix (ECM), pericytes, mesenchymal stromal cells and molecules like growth factors, cytokines, chemokines and extracellular vesicles. These cells hold the biomarkers of the cancer and play a vital role in the development of the tumor and the prognosis of B-cell lymphoma (Liu et al., 2021).

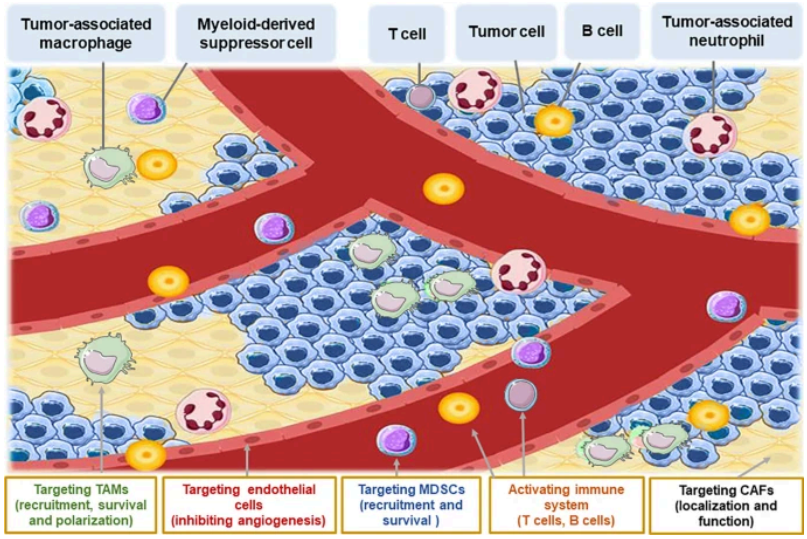

Figure 1 - the diagram above displays the contents of a typical tumor microenvironment of B-cell lymphoma including all major cellular and non-cellular components. At the bottom of the figure, shows the approaches to attacking and targeting specific parts of the B-cell lymphoma TME as of now (Liu et al., 2021).

Since the cancer cells are actively shaping their microenvironment for their needs, the composition of a lymphoma's TME indicates the extent to which the tumor cells rely on the TME cells for proliferation and survival. There are three major patterns ('re-education', 'recruitment' and 'effacement'), but aside from that, the varying degree of "interplay" between the malignant and immune cells within the TME is attributed to the type of lymphoma (Mulder et al., 2019). Specifically, Large B-cell Lymphoma has tumor cells, including NKs, DCs, macrophages, and T-cells), that have genetic mutations that make them independent to survival signals from their TME. These cells, specifically T-cells, however, are a big predictor for patient prognosis and may have a possible role in lymphomagenesis. Low T-cell infiltration seems to correspond to poor survival as well as high infiltration with increased survival. Understanding of different aspects of a tumor's microenvironment can lead to better approaches in treatment and disease progress like how T-cell infiltration can suggest potential benefits of treatment with ICB (Immune checkpoint blockade) (Mulder et al., 2019).

Treatment and TMEs

Over the recent years, research of tumor microenvironments has grown and has improved the approach to cancer treatments targeting these tumors. Instead of previous methods that targeted the tumor as a whole, there has been a new approach with therapeutic strategies that target specific cells in the TME (Anderson & Simon, 2020). Overall, therapeutic strategies under three categories: depleting existing cells, preventing cells from being recruited to tumor sites, and reprogramming cells into antitumor subtypes (Liu et al., 2021). As previously mentioned, one of the new therapeutic strategies is ICB, or Immune checkpoint blocking, which

blocks receptors to dull T-cell activation and function. However, knowing the specifics of the TME a doctor is dealing with is very important as ICB only works for patients that have the relevant biomarkers to actually benefit from the treatment. While this approach has its benefits, more advancement in efficiency is still necessary to make this a viable treatment for more patients (Anderson & Simon, 2020). The ECM plays a critical role in evading treatments due to its stiffer and denser physical properties allowing it to shield clusters of tumor cells from the incoming therapy (Henke et al., 2020). If one targets the ECM with enzymes, it will cause collagen degradation, could delay the process of tissue regeneration and influence the survival, expansion and progression of tumors (Liu et al., 2021).

Biomarkers prove to be useful in finding which antiangiogenic drugs certain patients will benefit from compared to other targeted therapies. Found in a study done by Rakesh K. Jain and his colleagues, the normalization of blood vessels and ECM increased survival and lowered the growth of the TME, but they still stress the need for more testing and research to be done in this treatment type. They also bring up the point of the possible benefits of combining the treatments of antiangiogenic drugs and chemotherapy to target the different types of cells (Jain, 2013). It is also important to consider a global approach to the TME in terms of treatment due to the complicated cross talk between malignant B cells and immune cells that leads to immune escape (Ng et al., 2022).

Conclusion

A tumor's microenvironment plays a crucial role not only in the survival of lymphoma cancers, but also in its growth and spread. TMEs are the vital structure for a tumor to receive its nutrients and contain components that overall influence the treatment an individual must receive to get rid of it. By learning about the structure and components of TMEs, specifically in B-cell lymphoma tumors, doctors and researchers have the ability to better approach the therapies and treatment that each individual needs to go through to have the best chance at survival and increasing their health. With more and more research, we will be better suited to help improve the situation of all different types of TMEs we are faced with.

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