The Role Of TME In Mesothelioma Progression

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ABSTRACT

Malignant Mesothelioma is a dangerous type of cancer that predominantly occurs due to asbestos exposure. Its development and drug resistance are mainly caused by the tumor microenvironment (TME). TME is a complex community of immune-suppressive cells, fibroblasts, and signaling factors. The TME shields the tumor, promotes metastasis, and suppresses immune responses. This review addresses how MM uses its microenvironment and explores new therapies against the TME, including immune checkpoint inhibitors, anti-angiogenic drugs, and fibroblast-disrupting therapy. By shifting focus from cancer cells to their milieu, researchers can uncover superior, multi-targeted therapies that improve MM patient outcomes and reimagine cancer treatment paradigms.

Introduction

Cancer is the leading cause of mortality worldwide. There are numerous reasons why it can result in death, but the main factor is metastasis. Cancer, which is colloquially referred to as a neoplasm or malignant tumor, starts its journey into the body through uncontrollable cell division. Firstly, the place where cancer forms in the body is called the primary site. The cells from the primary site break away from the origin and spread to other body parts. These cells can grow further and form other tumors. This is what is known as secondary cancer. (Cancer Research UK, 2023). Cancer cells spread to other parts of the body through the bloodstream. Unlike normal cells, cancer cells don't stick together, and this results in the production of substances that stimulate them to move. Once in the bloodstream, the cancer cells enter tiny blood vessels known as circulating tumor cells (CTCs). Through the CTCs, the cancer cells move along the bloodstream until they get stuck in a place. This can be due to proper conditions and nutrients for the cancer cells to grow and multiply. Cancer's ability to establish secondary tumors in body sites makes it one of the most challenging health problems worldwide. However, this invasive tendency is not uniform across all cancers, as it varies based on the type and location of the tumor. Cancers that are located near the breast or lungs have different invasive natures due to the vague differences in tissue structure, and differences in tissue structure.

Of these cancers, Malignant Mesothelioma (MM) is an extremely aggressive tumor and carries a dismal prognosis. Mesothelioma is a rather infrequent though highly malignant neoplasm in most cases resulting from many years of asbestos exposure. (Mayo Clinic, 2024). Asbestos is a naturally occurring mineral fiber that is harmful to the body. The malignant tendency begins from the mesothelial cells that provide the serous membranes surrounding several vital organs, including the lungs or pleura, abdomen or peritoneum, and heart or pericardium. Characterized by a rapid disease course, insensitivity to conventional therapies, and poor prognosis, with less than two years of survival in the majority of patients, the cancer is severe. According to the tumor site, common symptoms of MM include chest pain, breathing difficulties, and fluid accumulation. (Mayo Clinic, 2024). Symptoms usually appear only in an advanced stage since, in most cases, the latency period is very long, taking decades. Whereas most cancers can show variable tumor growth with the tissue environment, malignant mesothelioma exploits the special microenvironment provided by the mesothelial lining for its aggressive tumor growth and metastasis.

An important aspect in the study of MM is the study of the tumor microenvironment, which comprises immune cells, stromal cells, blood vessels, signaling molecules, and the extracellular matrix. (Biosignaling Biomed Central, 2020). The TME itself is the key to the advancement of cancer because it allows tumors to escape immune destruction, acquire a source for nutrients and growth, and metastasize. In the context of malignant mesothelioma, the TME is one of hostility, given that it inhibits immune functions and creates an inflammatory milieu that fuels tumor growth. This review discusses the role of the tumor microenvironment in the pathogenesis of malignant mesothelioma. Thus, based on how MM's behavior is influenced by the TME, this paper aims to identify targets for therapy in the microenvironment. The interaction between MM and its TME may offer new possibilities to develop treatments that are targeted at targets other than the tumor to target the wider ecosystem that fosters the growth and survival of the tumor.

Mechanics Of TME Support in Malignant Mesothelioma

Malignant mesothelioma (MM) is dangerous and resistant to treatment because of its overdependence on the tumor microenvironment (TME). The tumor microenvironment is a vast channel of immune cells, signaling molecules, fibroblasts, and extracellular matrix that surrounds and mixes with cancer cells. Rather than existing independently of this environment, MM cells thrive by co-opting the tumor microenvironment (TME) to their ends. This cancer microenvironment not only nourishes the cancer but also enables it to avoid detection and killing by the immune system (Williams Firm). In MM, the pleura and peritoneum mesothelial tissues are, by nature, fibrotic and typically poorly oxygenated (hypoxic). These characteristics are not hitchhikers; they are actively involved in MM cell increased invasiveness and resistance to apoptosis. Specifically, hypoxia promotes the upregulation of genes that facilitate angiogenesis and enable cancer cells to survive under unfavorable conditions (Biosignaling Biomed Central, 2020).

The TME also generates a highly inflammatory yet immunosuppressive milieu. This paradox, wherein inflammation occurs but the immune system is unable to mount an effective response, allows MM cells to continue proliferating while crippling the body's defenses (PMC, 2021). Normal immune function is suppressed by tumor-secreted and surrounding stromal cell-secreted signals and factors. Mesothelioma does not simply exist in its environment—it controls it. It suggests that the TME not only passively sustains the tumor but also actively evolves together with it, creating a feedback loop that propagates malignancy. Having recognized the TME as a partner in tumor development, researchers are pursuing therapies that not only target the tumor cells but also disrupt this support network.

Apart from aiding in the growth of the tumor, the MM tumor microenvironment also plays an important role in protecting against standard treatments, such as chemotherapy and radiation. Cancer-associated fibroblasts (CAFs) are one of the important components in such resistance. CAFs release structural proteins and chemical signals that form a dense "shield" of cells around the tumor, acting as an effective physical barrier for drugs (Crown Bioscience, 2025). But it's not just that, CAFs are also known to secrete survival factors that enhance the resilience of tumor cells against therapy-induced stress. In so doing, the TME essentially educates the tumor in survival when under attack.

In addition, immune evasion is another important advantage provided by the TME. In MM, the microenvironment becomes professionalized with immune-suppressive cells like regulatory T cells (Tregs), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs). These cells directly repress the immune system's efforts to identify and destroy cancer (PMC, 2021). Instead of resisting, the immune system is shocked or even hijacked to help the tumor grow. This explains why many patients with MM are unable to react to immunotherapies like checkpoint inhibitors. The problem isn't the tumor, but it's the environment around it and protecting it. According to a Nature article, inhibition of the tumor-associated macrophages, particularly of the M2 subtype that promotes growth and inhibits inflammation, may offer a new MM treatment option (Nature, 2018).

The more researchers know about MM's tumor microenvironment, the more a new era of treatments draws near. They don't target the cancer cells directly; they aim to dismantle the support mechanism that allows these cells to proliferate. Scientists, for example, are attempting to prevent or "reprogram" CAFs, disrupting the physical bar that envelops the tumor and allowing chemotherapy drugs to penetrate (PMC, 2021). Another promising approach is anti-angiogenic therapy, which targets the blood vessels that tumors employ to obtain oxygen and nutrients. Starving the tumor from the inside out by severing its supply of blood, doctors could kill the tumor.

Putting these techniques in concert with current therapies has already proved to be highly promising in clinical trials. One of the most significant was the recent approval of pembrolizumab (Keytruda) and chemotherapy in malignant pleural mesothelioma patients by the FDA. This checkpoint inhibitor "unmasks" the cancer cells so that the immune system can identify them and kill them. The Phase 3 trial that resulted in the approval showed a statistically significant overall survival advantage in patients receiving the combination versus chemotherapy alone (MarketWatch, 2024). Significantly, this therapy also aims to reprogram the TME through interference with the immune-suppressive signals that shield the tumor.

Even more sophisticated treatments are being developed, including nano-vaccines, cold atmospheric plasma treatment, and gene-edited viruses that selectively target and kill MM cells and induce an immune response (PMC, 2023). Although the majority of them are at the preclinical or phase one level of clinical trials, they have the potential to cure MM from a systems biology perspective, which targets not only the cancer but also its microenvironment.

Conclusion

The resistance to growth and treatment of malignant mesothelioma is incomprehensible without examination of the tumor microenvironment that supports its survival. Ranging from immunoevasion to the creation of physical and chemical barriers shielding the tumor, the TME is pivotal in the malignancy and therapeutic failure of the disease. Each feature, hypoxia and fibrosis, immune-suppressive cells, which work not as a standalone mechanism but as part of a coordinated system that fuels MM's growth and resistance. Where the standard treatments fall short, new methods aimed at the TME, immune checkpoint inhibitors, anti-angiogenic therapy, and CAF-inhibiting therapy are beginning to redefine the research landscape in mesothelioma.

However, there are constraints. Much of the work remains in trial phases, and the extremely variable nature of individual TMEs between patients prevents standardizing the therapies. In addition, the majority of the current studies are conducted on pleural mesothelioma, and the peritoneal and pericardial forms remain poorly understood. Thus, further, more extensive, high-statistics studies are needed to validate and tailor these encouraging therapies.

Looking at MM from the vantage point of its microenvironment isn't fighting an orphan disease, it's a way to rethink how we're fighting cancer in the first place. By shifting our focus away from the cancer cells and onto the environment they thrive in, researchers are uncovering new avenues to overcome resistance and improve outcomes. This review seeks to spur further research into the TME, which may yield multi-targeted treatments that extend survival and offer hope to patients long assigned to the incurable.

Lastly, understanding the tumor microenvironment of MM not only enhances our scientific enlightenment but also holds the promise to save lives in the real world as well. As we uncover this secret partner in cancer's success, we draw closer to therapies that demolish not only the tumor, but the world it builds to survive.

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