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Short Communication

Fibrosis and its Impact on Pancreatic Tumor Growth, Metastasis and Therapeutic Resistance

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DESCRIPTION

Pancreatic cancer, particularly Pancreatic Ductal Adenocarcinoma (PDAC), is known for its aggressive nature, poor prognosis, and high resistance to standard therapies. One of the major factors contributing to the malignant behaviour of PDAC is the fibrotic stroma that surrounds and infiltrates the tumor [1,2]. This dense Extracellular Matrix (ECM) is not merely a passive scaffold but actively participates in tumor progression, metastasis, and resistance to therapy. Understanding the role of the fibrotic stroma in pancreatic cancer can provide novel insights into how to overcome its challenges and improve patient outcomes [3,4].

Fibrotic stroma

The tumor microenvironment in pancreatic cancer is predominantly made up of Cancer-Associated Fibroblasts (CAFs), immune cells, endothelial cells, and a dense Extracellular Matrix (ECM) [5]. The ECM consists of collagen, fibronectin, hyaluronic acid, and proteoglycans, all of which contribute to the physical and biochemical properties of the tumor microenvironment. In PDAC, the stroma is particularly abundant and often described as desmoplastic, meaning it exhibits excessive collagen deposition and tissue stiffness [6].

Impact on tumor metastasis

Pancreatic cancer is notorious for its early metastatic spread. The fibrotic stroma not only promotes local tumor growth but also plays a pivotal role in the ability of the cancer cells to invade surrounding tissues and disseminate to distant organs. One of the key mechanisms by which this occurs is through the remodeling of the ECM [7]. Tumor cells secrete Matrix Metalloproteinases (MMPs), enzymes that degrade ECM proteins like collagen and fibronectin, allowing tumor cells to migrate through the stroma and invade adjacent tissues. The dense stroma also facilitates tumor cell intravasation the process by which cancer cells enter blood vessels and spread to distant organs, such as the liver, lungs, and peritoneum.

Therapy resistance: Role of the stroma

One of the most significant challenges in treating pancreatic cancer is the resistance of tumors to conventional therapies, including chemotherapy, radiotherapy, and targeted therapies [8]. The fibrotic stroma plays a major role in the development of therapy resistance through several mechanisms.

Physical barriers to drug delivery: The dense and stiffened ECM in pancreatic tumors acts as a physical barrier that prevents effective drug penetration. The ECM acts to limit the access of chemotherapeutic agents to the tumor cells, particularly in the tumor core, where blood vessels are poorly developed [9]. The high interstitial pressure in the tumor further complicates drug delivery, leading to an insufficient concentration of therapeutic agents in the tumor. This poor perfusion reduces the effectiveness of treatments and is a primary reason for the failure of chemotherapy in many pancreatic cancer patients.

Hypoxia-induced resistance: The hypoxic conditions in the fibrotic stroma activate various survival mechanisms within the tumor cells. In particular, the Hypoxia-Inducible Factors (HIFs) induce the expression of genes involved in angiogenesis, cell survival, and drug resistance. Hypoxia also triggers the upregulation of ATP-Binding Cassette (ABC) transporters, which actively pump out chemotherapeutic drugs from cancer cells, reducing their intracellular concentrations and effectiveness [10]. As a result, pancreatic tumors can become highly resistant to chemotherapy and other treatment modalities.

Immune evasion and stromal interference: The stroma also contributes to immune evasion by limiting the infiltration of immune cells such as cytotoxic T-cells and Natural Killer (NK) cells. The dense ECM acts as a physical barrier, preventing immune cells from reaching the tumor and mounting an effective immune response. Additionally, Myeloid-Derived

Suppressor Cells (MDSCs) and regulatory T-cells (T_{regs}) within the stroma can further suppress immune activity and promote tumor survival. This immune-suppressive microenvironment

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further exacerbates therapy resistance and hinders the effectiveness of immunotherapies.

CONCLUSION

The fibrotic stroma is a critical player in the progression and therapy resistance of pancreatic cancer. It not only provides structural support for tumor growth but also facilitates metastasis and impedes the effectiveness of conventional and improved therapies. Targeting the fibrotic stroma presents a requiring strategy to enhance the treatment response in pancreatic cancer. By modulating the tumor microenvironment, researchers hope to overcome the major challenges posed by tumor stiffness, immune evasion, and therapy resistance, ultimately improving patient outcomes and survival rates in this devastating disease.

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