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Commentary

Impact of Tumor Microenvironment on Cancer Stem Cell Maintenance

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DESCRIPTION

Cancer Stem Cells (CSCs) have emerged as a pivotal subpopulation within tumors that possess the unique ability to self-renew, differentiate and drive tumor initiation, progression and recurrence. These cells are implicated in therapy resistance and metastasis, making them critical targets in cancer research. However, the behavior and maintenance of CSCs are profoundly influenced by their surrounding Tumor MicroEnvironment (TME) a dynamic and complex milieu comprising stromal cells, immune cells, ExtraCellular Matrix (ECM), signaling molecules and vascular networks. The TME provides essential niche signals that sustain the CSC phenotype and promote their survival under hostile conditions such as hypoxia and chemotherapy. Interactions between CSCs and various components of the microenvironment orchestrate a finely tuned balance between quiescence, proliferation and differentiation, ultimately influencing tumor heterogeneity and aggressiveness.

One of the hallmark features of the TME is hypoxia, or low oxygen tension, which commonly occurs due to aberrant tumor vasculature. Hypoxia-Inducible Factors (HIFs) activated under these conditions enhance the expression of stemness-related genes such as *OCT4*, *SOX2* and *NANOG*, reinforcing the CSC phenotype. Hypoxia also triggers metabolic reprogramming, favoring glycolysis, which supports CSC energy demands and survival. Moreover, hypoxia modulates the secretion of cytokines and growth factors that recruit stromal and immune cells, further shaping the niche. Cancer-Associated Fibroblasts (CAFs) constitute a major stromal cell type within the TME and play a vital role in CSC maintenance. CAFs secrete a variety of soluble factors including Transforming Growth Factor-beta (TGF-β), hepatocyte growth factor (HGF) and interleukins, which activate signaling pathways such as Wnt, Notch, and Hedgehog in CSCs. These pathways are crucial for maintaining stemness and promoting resistance to chemotherapy. CAFs also remodel the ECM, influencing the mechanical properties of the niche, which has been shown to regulate CSC behavior through mechanotransduction.

Immune cells in the TME present a double-edged sword with regard to CSC regulation. Tumor-Associated macrophages (TAMs), for example, often adopt an immunosuppressive M2 phenotype that supports CSC survival by secreting cytokines such as IL-10 and TGF-β. These factors not only dampen anti-tumor immune responses but also directly enhance CSC self-renewal and invasion. Conversely, effector immune cells such as cytotoxic T lymphocytes can target CSCs; however, CSCs often evade immune surveillance by upregulating immune checkpoint molecules like PD-L1. Exosomes and extracellular vesicles represent another layer of complexity in TME-CSC communication. These vesicles transfer proteins, lipids and nucleic acids including microRNAs from stromal cells to CSCs, modulating gene expression and promoting stemness, drug resistance and metastatic potential. For instance, exosomal miR-21 derived from CAFs can suppress tumor suppressor genes in CSCs, enhancing their survival and invasiveness.

The vascular niche within the TME also plays a critical role in CSC maintenance. Endothelial cells secrete factors such as Vascular Endothelial Growth Factor (VEGF) and nitric oxide, which support CSC self-renewal and promote angiogenesis, thereby facilitating tumor growth and dissemination. In turn, CSCs contribute to neovascularization by differentiating into endothelial-like cells or pericytes, further illustrating the reciprocal relationship between CSCs and their microenvironment. Importantly, the plasticity of CSCs is influenced by dynamic changes in the TME. CSCs can transition between stem-like and non-stem-like states in response to environmental cues such as inflammation or therapy-induced stress, complicating therapeutic targeting. Understanding the bidirectional crosstalk between CSCs and the TME is thus essential for developing more effective treatments.

CONCLUSION

The tumor microenvironment profoundly impacts the maintenance, plasticity and function of cancer stem cells, thereby influencing tumor progression, therapeutic resistance and metastasis. By providing biochemical signals, structural support and immune modulation, the TME acts as a nurturing niche that sustains CSC populations and enhances their malignant potential. Therapeutic strategies targeting the TME components that regulate CSCs such as inhibiting CAF-secreted factors, modulating immune cells, disrupting hypoxia pathways,

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or interfering with exosome communication hold promise in overcoming CSC-mediated treatment resistance. Additionally, normalizing the aberrant vasculature and remodeling the ECM to disrupt CSC niches may sensitize tumors to conventional therapies.

As the intricate relationship between CSCs and their microenvironment continues to be elucidated, it becomes clear that future cancer treatments must adopt a dual approach: targeting not only the cancer cells themselves but also the supportive niche that enables their persistence and evolution. Integrative therapies combining CSC-targeted agents with TME modulators could offer a more durable and effective means to prevent tumor relapse and metastasis. Ongoing research, supported by advanced technologies such as single-cell sequencing, spatial transcriptomics and 3D tumor organoids, will provide deeper insights into the cellular and molecular mechanisms underpinning CSC-TME interactions. Such knowledge will be crucial for designing innovative, precision therapies that disrupt the cancer stem cell niche and improve clinical outcomes for patients worldwide.