

CANCER STEM CELLS AND TUMOR MICROENVIRONMENT: IMPLICATIONS FOR THERAPY RESISTANCE AND NOVEL STRATEGIES

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Background. Cancer stem cells (CSCs) represent a distinct subpopulation of tumors, characterized by self-renewal capacity and multilineage differentiation potential. These cells interact dynamically with the tumor microenvironment (TME).

Objective of the study. To elucidate the interactions between CSCs and the TME, highlighting their roles in tumor progression, metastasis and treatment resistance, as well as the need for targeted therapies.

Materials and Methods. An extensive review of the existing literature was conducted by gathering and analyzing scientific articles sourced from multiple databases, including PubMed, HINARI, Google Scholar and Medline.

Results: CSCs are key drivers in multiple aspects of tumor development, including the initiation of tumor formation, its subsequent progression, metastasis and therapeutic resistance. Their intrinsic resistance to conventional anticancer treatments significantly contributes to tumor relapse and treatment failure. Several signaling pathways, including WNT/ β -catenin, Hedgehog, Notch, nuclear factor kappa B (NF- κ B), JAK/STAT, *transforming growth factor beta* (TGF- β), phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT), and peroxisome proliferator-activated receptor (PPAR), regulate CSCs function, influencing tumorigenesis, metastasis, and tumor heterogeneity. CSCs are primarily located within specialized tumor niches, where hypoxia, aberrant angiogenesis, and chronic inflammation promote their survival and expansion. Stromal cells, such as cancer-associated fibroblasts (CAFs), mesenchymal stem cells (MSCs), endothelial cells, and adipocytes, contribute to TME maintenance by stimulating angiogenesis, facilitating extracellular matrix (ECM) remodeling, inducing therapeutic resistance, and enhancing metastatic dissemination. Within the tumor microenvironment (TME), various immunosuppressive cell populations, including tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), cancer-associated fibroblasts (CAFs), and regulatory T cells (Tregs), play a pivotal role in modulating immune responses. These cellular components collectively suppress antitumor immune reactivity and create a permissive environment that facilitates tumor progression and immune evasion.

Conclusions: A bidirectional relationship is established between CSCs and the TME, where the TME sustains CSCs survival, while CSCs modulate the structure of the TME, promoting an immunosuppressive environment. These interactions compromise the efficacy of current cancer therapies, emphasizing the need for novel therapeutic strategies targeting both CSCs and the TME, ultimately improving treatment outcomes.

Keywords: cancer stem cells, tumor microenvironment, tumorigenesis, metastasis, therapeutic resistance, anticancer therapy, CSC-targeted therapies.