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The Role of Cancer Stem Cells in Tumor Relapse and Resistance: Mechanisms, Challenges, and Therapeutic Strategies

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Abstract

Cancer is a complex disease defined by altered gene expression. The core issue driving cancer development is the persistent, unregulated proliferation of cancer cells. These cells fail to respond to the signals that control normal cell behavior, leading to uncontrolled growth and division. As a result, cancer cells invade normal tissues and organs and eventually spread throughout the body. Cancer stem cells (CSCs) represent a small subpopulation within tumors with the capacity for self-renewal, differentiation, and tumor initiation when transplanted into an animal host. They play crucial roles in cancer relapse and metastasis. This review article highlights the complex nature of CSCs in cancer biology and the ongoing efforts to develop targeted therapies to overcome their contribution to tumor relapse and treatment resistance.

Introduction to Cancer Stem Cells

Stem cells are defined by their ability to self-renew and differentiate into specialized cell types. Recent findings suggest a subset of stem-like cells within tumors, termed cancer stem cells (CSCs), which exhibit characteristics of both stem cells and cancer cells. CSCs can be identified within tumors by their unique cell division patterns and changes in gene expression. Researchers often use specific cell surface markers like CD44, CD24, and CD133 to detect and isolate CSCs from other tumor cells. CSCs pose a challenge due to their high expression of drug efflux pumps and enhanced ability to activate anti-apoptotic and pro-survival pathways, as well as DNA repair mechanisms. They are highly tumorigenic, capable of initiating tumor formation in animal models with very few cells. This ability underscores their critical role in tumor initiation and progression across various types of cancer, presenting a significant challenge in contemporary oncology. Moreover, CSCs are implicated in cancer relapse and metastasis, as their survival and dissemination to distant sites contribute to cancer spread and hinder long-term remission. Understanding CSC biology is essential for developing more effective cancer treatments that specifically target and eliminate these resilient cells, thereby improving patient outcomes and reducing the likelihood of tumor recurrence. When differentiated cells undergo certain essential processes, there is a potential for them to dedifferentiate. By inducing epithelial-

mesenchymal transition (EMT), these differentiated cells can acquire stem cell-like characteristics, leading to the formation of cancer stem cells (CSCs). This implies that tissues with a sufficient population of differentiated cells may be capable of undergoing these transformations.

Theory of Cancer Relapse

Cancer cells within an individual patient display extreme heterogeneity, varying in malignant potential, drug sensitivity, and capacity to metastasize and cause relapse. Among these, highly malignant cells known as stemness-high cancer cells or cancer stem cells (CSCs) have been identified in various tumor types. These CSCs are characterized by their high tumorigenicity, metastatic potential, and resistance to conventional chemotherapy and radiation treatments. Consequently, current cancer treatments often fail due to metastasis and relapse. Although chemotherapy can induce partial or complete cancer regression in some patients, these responses are frequently followed by relapse.

When cancer cells become resistant to treatment drugs, they can regrow and form tumors again, a process known as recurrence or relapse. This resistance can develop rapidly or emerge months or years after treatment initiation, arising from molecular changes in the cancer cells that make them less responsive to the drugs, either before treatment (intrinsic resistance) or during treatment (acquired resistance). Evidence indicates that CSCs are critically linked to drug resistance. For example, ionizing radiation has been shown to upregulate CD133+ CSCs in glioblastoma xenografts, and CSCs are enriched in breast cancer following radiation therapy. Additionally, acquired resistance to one drug can lead to cross-resistance to other chemotherapeutic agents. CSCs resist therapy due to their expression of multidrug resistance (MDR) transporters, enhanced DNA repair capabilities, and increased ability to avoid apoptosis compared to other cells. Therefore, research should focus on targeting CSCs to overcome therapy resistance.

Daunorubicin and Ara-C are chemotherapeutic drugs to which leukemia CSCs are resistant. In glioblastoma, treatment with temozolomide and bevacizumab has been shown to reduce tumorigenicity by targeting CSCs. A prime example of eliminating CSCs through targeting specific genetic alterations is the use of the HER1/HER2 inhibitor lapatinib in HER2-positive breast cancer, which addresses the amplification of the HER2 gene.

Microenvironment Interaction

Cancer stem cells (CSCs) reside in niches, specific regions within the tumor microenvironment (TME). These niches maintain the core properties of CSCs, preserve their phenotypic plasticity, shield them from the immune system, and enhance their metastatic potential. Specialized and anatomically distinct, these niches play a critical role in cancer progression by producing factors that support CSC self-renewal, thereby maintaining their population. They also promote angiogenesis, supplying the tumor with the necessary nutrients and oxygen. Additionally, CSC niches recruit various immune cells and other stromal cells, which secrete factors that facilitate tumor cell invasion and metastasis, aiding cancer spread. By creating a supportive environment,

CSC niches not only protect CSCs from therapeutic interventions but also enhance their ability to drive tumor growth and progression.

Factors produced by CSCs and endothelial cells (ECs) within the TME can transform normal fibroblasts into cancer-associated fibroblasts (CAFs). These transformed fibroblasts play a crucial role in tumor progression by creating a supportive environment for cancer cells, contributing to tumor growth, invasion, and metastasis. CAFs, along with other cells within the niche, enhance stemness by activating the WNT and NOTCH pathways. The canonical WNT pathway is a key regulator of CSCs, promoting stemness in colon and other cancers. NOTCH signaling is also crucial for stem cell maintenance and cell fate decisions, preventing cells from responding to differentiation signals from their immediate environment.

Mesenchymal stem cells (MSCs) are multipotent stromal cells involved in various mechanisms that promote cancer cell proliferation and metastasis, encourage angiogenesis and create an immunosuppressive microenvironment. MSCs enhance cancer stemness through the NF-kB pathway by secreting CXCL12, interleukin (IL) 6, and IL8.

One of the most compelling areas of research today is the role of the CSC niche in modulating tumor immunity. The TME is characterized by chronic inflammation, which drives tumor cell proliferation and metastasis.

Challenges in targeting Cancer Stem cells

Despite significant advancements in understanding cancer stem cells (CSCs) and their role in tumor relapse and resistance, several challenges remain in effectively targeting them. These challenges arise from the complex biology of CSCs, their interaction with the tumor microenvironment (TME), and the limitations of current therapeutic strategies. CSCs are not a uniform population; they exhibit substantial heterogeneity even within the same tumor. This variability complicates the identification and targeting of CSCs, as different subpopulations may respond differently to treatments. CSCs can transition between stem-like and differentiated states. This plasticity allows them to evade therapies designed to target specific cell states, making it difficult to achieve complete eradication. Identifying reliable and specific markers for CSCs is challenging due to their overlap with markers of normal stem cells and other cell types. This makes it difficult to isolate and target CSCs without affecting normal stem cells. CSCs often express MDR transporters that actively expel chemotherapeutic drugs, reducing their intracellular concentrations and effectiveness. CSCs have robust DNA repair mechanisms, allowing them to survive genotoxic stress from chemotherapy and radiation, leading to treatment resistance. CSCs evade apoptosis through various mechanisms, including the activation of anti-apoptotic pathways and inhibition of pro-apoptotic signals. CSCs reside in specialized niches within the TME that protect them from immune surveillance and therapeutic interventions. These niches provide a supportive environment that enhances CSC survival and resistance. The TME, including cancer-associated fibroblasts (CAFs) and mesenchymal stem cells (MSCs), supports CSC maintenance and resistance through complex signaling networks. CSC niches promote angiogenesis, ensuring a steady supply of nutrients and oxygen, and recruit immune cells that create an immunosuppressive environment, further protecting CSCs.

Current preclinical models often fail to fully recapitulate the complexity of human tumors and the TME, limiting the predictability of therapeutic outcomes in clinical settings.

Therapeutics Strategies to Target CSCs

Targeting CSC by immunotherapy

With improved immunological characterization of cancer stem cells (CSCs) and a deeper understanding of the interactions between cancer tissue and the immune system, immunotherapy—particularly immunological cytotherapy—holds great promise for cancer treatment. Adoptive cell therapy, a type of cellular immunotherapy, utilizes the host's immune cells—specifically, those with direct anticancer activity—to eliminate cancer. This approach, known as adoptive T-cell therapy, incorporates tumor-infiltrating lymphocytes (TILs), chimeric antigen receptor (CAR)---engineered T cells, and T-cell receptor (TCR)--engineered T cells. Stem-like and differentiated tumor cells were targeted for elimination by adoptively transferring NK cells from healthy donors, which had been activated with IL-2 and IL-15.

To improve the precision of therapeutic approaches, ligands or antibodies are frequently chosen to target surface markers, stemness markers, and signaling pathways specific to cancer stem cells (CSCs). For instance, delivering intracellular antibodies against structural maintenance of chromosome protein 2 (SMC2) has shown efficacy in reducing malignancy in CSCs from colorectal cancer (HCT116), triple-negative breast cancer (MDA-MB-231), and pancreatic cancer (PANC-1) cell lines.

Targeting Metabolism

Cell division and dysregulated growth are fundamental features of cancer. Cancer cells increase nutrient uptake to support biosynthetic pathways, modulate diverse metabolic processes, and maintain redox homeostasis. Therefore, metabolic reprogramming, driven by the pivotal role of various metabolic pathways in malignant transformation and tumor progression, has recently emerged as a hallmark of cancer. By using the metabolic characteristics, smart and effective drug delivery systems could be designed to target therapeutic agents to CSCs

Targeting microRNAs

MicroRNAs (miRNAs) are noncoding RNA sequences that regulate gene expression and have been implicated in tumorigenesis. They play a crucial role in a wide range of cancer-related processes such as cellular proliferation, DNA damage response, cell cycle arrest, senescence, and apoptosis. As such, modulating the expression levels of oncogenic or tumor suppressor miRNAs is fundamental in the treatment of cancer stem cells (CSCs). In acute myeloid leukemia, miRNA miR-126 maintains leukemia stem cells in a quiescent and primitive state by repressing PI3K signaling. This restriction prevents entry into the cell cycle, enhances self-renewal capabilities, and reduces differentiation. Conversely, loss of miR-126 activity leads to increased proliferation and differentiation by activating PI3K signaling [58]. Similarly, miRNA miR-10b regulates stem cell markers in breast cancer cell lines by targeting PTEN.

Targeting tumor microenvironment

Cancer stem cells (CSCs) and the tumor microenvironment engage in intricate, specific interactions influenced by the types of cells or proteins present, contributing to metastasis and drug resistance in unique ways. Targeting the CSC niche in tumors or interfering with the CSC-niche interactions may improve treatment efficacy.

Targeting surface markers

Identifying and isolating rare subpopulations of cancer stem cells (CSCs) using specific surface markers is indeed crucial for developing targeted therapeutic approaches. By targeting these markers, researchers can potentially design treatments that specifically attack CSCs, which are often responsible for tumor initiation, progression, and recurrence. This approach holds promise for more effective cancer therapies that aim to eradicate the cells driving tumor growth and metastasis. Researchers have demonstrated a molecular connection between stem cell markers like MDR-1 and the hyaluronan receptor CD44 in breast and ovarian cancers. Consequently, investigations have explored hyaluronic acid (HA)--based drug conjugates as potential strategies for targeting cancer stem cells (CSCs).

Conclusion and Future Perspectives

Cancer stem cells are central to the challenges of tumor relapse and therapy resistance. By understanding the mechanisms that enable CSCs to survive and thrive, researchers can develop targeted therapeutic strategies to overcome these obstacles. Focusing on disrupting CSC niches, inhibiting critical pathways, and enhancing the effectiveness of existing treatments holds the potential to improve outcomes for cancer patients. However, numerous obstacles must be overcome to effectively eradicate CSCs.

Eliminating CSCs (Cancer Stem Cells) poses numerous challenges that require careful consideration and innovative solutions. These hurdles include identifying and targeting CSC-specific markers without affecting normal stem cells, understanding the complex microenvironments that support CSC survival and resistance to therapy, developing therapies that can penetrate and effectively target CSCs in heterogeneous tumors, and addressing the potential for CSCs to adapt and evolve resistance mechanisms. Overcoming these challenges is crucial for advancing cancer treatment strategies toward more effective and sustainable outcomes. CSCs pose a significant challenge to cancer therapy across various types. Effective strategies, including direct CSC inhibitors and targeted delivery systems, are key to enhancing treatment success and outcomes for cancer patients.

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