Journal of Cancer Research and Immuno-Oncology

OPEN ACCESS Freely available online

Opinion Article

Cancer Stem Cells: Their Role in Metastasis and Resistance

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DESCRIPTION

Cancer is no longer viewed as a uniform mass of rapidly dividing cells. Instead, it is now understood as a complex, evolving ecosystem composed of various cell types with distinct functions. Among these, Cancer Stem Cells (CSCs) have emerged as a particularly dangerous subset. These rare but powerful cells exhibit self-renewal, tumor-initiating capacity, and resistance to conventional therapies. Mounting evidence suggests that CSCs play a central role in both metastasis and treatment resistance, making them critical targets for future cancer therapies.

Seeds of metastasis CSCs spread cancer

Metastasis the spread of cancer from a primary site to distant organs is responsible for the majority of cancer-related deaths. The process is complex and multi-step cancer cells must detach from the primary tumor, invade surrounding tissue, survive in circulation, and eventually colonize new tissue. Not all cancer cells are equipped for this journey, but CSCs seem uniquely suited for it.

CSCs share many traits with normal stem cells, including plasticity and adaptability, which give them an edge during metastasis. These cells can enter a quiescent state, avoiding immune detection and surviving chemotherapy, only to later become activated in a new microenvironment. Their ability to undergo Epithelial-Mesenchymal Transition (EMT) a process in which epithelial cells acquire mesenchymal, migratory characteristics further enhances their metastatic potential. Studies in breast, colon, pancreatic, and prostate cancers have identified CSC-like cells in both primary tumors and metastatic lesions. For example, CD44(high)/CD24(low) cells in breast cancer display enhanced invasive potential and are more likely to initiate secondary tumors. This evidence suggests that CSCs may act as the "seeds" of metastasis, capable of initiating tumor growth in distant organs even after the bulk of the primary tumor is removed.

Moreover, the tumor microenvironment or "soil" also plays a crucial role. Signals from stromal cells, immune cells, and the extracellular matrix can support CSC survival and expansion in distant tissues, essentially nurturing their metastatic colonization. This interplay highlights the need for therapies that not only target CSCs but also disrupt the supportive niches that allow them to thrive.

Masters of evasion CSCs and therapy resistance

One of the most frustrating challenges in oncology is treatment resistance. Many tumors initially respond to chemotherapy, radiation, or targeted therapies, only to relapse later often more aggressively. CSCs are believed to be a major contributor to this phenomenon. Unlike the bulk of tumor cells, which may be rapidly dividing and thus more susceptible to treatment, CSCs can exist in a slow-cycling or dormant state. This makes them inherently less sensitive to therapies that target proliferating cells. Furthermore, CSCs often express high levels of drug-efflux pumps which actively remove chemotherapeutic agents from the cell.

Another hallmark of CSCs is their enhanced capacity for DNA repair. Treatments like radiation and certain chemotherapies work by inducing DNA damage. CSCs can efficiently repair this damage, thereby surviving therapies that would otherwise be lethal. Additionally, CSCs exhibit resistance to apoptosis due to alterations in key pathways such as Notch, Wnt/ β-catenin, and Hedgehog pathways that also govern normal stem cell function.

This resilience is not just theoretical. In glioblastoma, for example, CD133+CSCs have been shown to survive radiation therapy and regenerate tumors. In colorectal cancer, LGR5+stem-like cells resist chemotherapy and can repopulate the tumor even after apparent remission. Such cases exemplify how conventional therapies, while shrinking the tumor, may inadvertently enrich the CSC population and set the stage for relapse. Immunotherapy, a powerful new tool in the cancer arsenal, may also fall short against CSCs. These cells often express lower levels of immunogenic markers like MHC class I, making them less visible to cytotoxic T cells. Moreover, CSCs can secrete immunosuppressive factors that dampen the local immune response, creating a microenvironment where they can hide and persist.

If CSCs are indeed the root of metastasis and resistance, then eliminating them is essential for achieving durable cancer

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Received: 18-Feb-2025, Manuscript No. JCRIO-25-38368; **Editor assigned:** 20-Feb-2025, PreQC No. JCRIO-25-38368 (PQ); **Reviewed:** 06-Mar-2025, QC No. JCRIO-25-38368; **Revised:** 13-Mar-2025, Manuscript No. JCRIO-25-38368 (R); **Published:** 20-Mar-2025, DOI: 10.35248/2684-1266.25.11.241

Citation: Zhang E (2025) Cancer Stem Cells: Their Role in Metastasis and Resistance. J Cancer Res Immunooncol. 11.241.

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remission or cure. But this is easier said than done. One major challenge is identifying CSCs reliably, as markers can vary between cancer types and even between patients. Additionally, CSCs often overlap with normal stem cells, raising concerns about off-target effects that could harm healthy tissues.

Nonetheless, progress is being made. Therapies that target CSC-specific pathways (such as Wnt, Notch, and Hedgehog inhibitors), epigenetic regulators, and the tumor microenvironment are under investigation. Clinical trials are also exploring the combination of conventional therapies with CSC-targeted agents to eliminate both the bulk tumor and the stem-like cells driving recurrence.

CONCLUSION

Cancer stem cells represent one of the most insidious aspects of cancer biology. Their ability to drive metastasis and resist therapy makes them both dangerous and indispensable to understand. They challenge the traditional model of cancer as a homogenous mass and instead present it as a dynamic, hierarchical system with a small group of highly potent cells at its apex. To achieve lasting cancer control, future treatments must go beyond targeting the visible tumor and focus on eradicating these hidden instigators. Only by cutting the cancer off at its root its stem can we hope to stop its growth, spread, and return.