STM JOURNALS

Recent Trends in
Infectious Diseases

Volume 1, Issue 2, 2024
July-December
DOI (Journals): 10.37591/RTID

https://journals.stmjournals.com/rtid

Review RTID

Navigating the Depths of Cancer Stem Cells: Unraveling Resistance Mechanisms and Emerging Therapeutic Strategies

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Abstract

In the past few decades, comprehensive evidence has convincingly established the presence of cancer stem cells (CSCs) as a minor subset within tumors, contributing to an unusually elevated level of cellular diversity within the malignancy. CSCs are functionally identified by their capacity for self-renewal and differentiation, frequently influenced by signals from their surrounding microenvironment. The interconnected transcriptional, post-transcriptional, metabolic, and epigenetic regulatory networks govern the biological characteristics of CSCs. CSCs contribute to tumor growth, therapeutic resistance, and disease recurrence by prolonged proliferation, invasion into normal tissue, angiogenesis enhancement, immune system evasion, and resistance to traditional anticancer therapy. As a result, understanding the molecular pathways behind cancer stem cell persistence, adaptability, and therapeutic resistance would increase our capacity to improve treatment.

Keywords: Cancer, Cancer stem cells, Tumor microenvironment, therapy resistance, Future perspectives

INTRODUCTION

Cancer stem cells (CSCs) are characterized as cells with the capacity for self-renewal and the generation of progeny. Consequently, the majority of the cancer mass comprises differentiated and proliferative progeny, while small populations of diverse CSCs coexist. Overcoming tumors remains a significant challenge for oncologists due to the advanced stages of most cancers and the presence of resistant CSC clones [3]. Various approaches have been developed to characterize CSCs and understand the mechanisms underlying their self-renewal [1].

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Received Date: December 08, 2023
Accepted Date: December 18, 2023
Published Date: December 30, 2023

Citation: Gajanan Sapate, Rutuja Shinde, Swaraj Tawale, Dipak Pawar. Navigating the Depths of Cancer Stem Cells: Unraveling Resistance Mechanisms and Emerging Therapeutic Strategies. Recent Trends in Infectious Diseases. 2024; 1(2): 14-18.

Typically, solid tumors are treated using surgical or medical methods, with additional options such as immunotherapies, chemotherapies, and radiotherapies. The recurrence of cancer poses a critical challenge, contributing to a high mortality rate, particularly because symptoms often remain silent until the disease has progressed significantly. Even with curative resection, the recurrence rate ranges from 30% to 70%, tied to symptoms that manifest only after the residual cells have sufficiently advanced to propagate the tumor [2, 3].

The notion of CSCs as the major actor in cancer responsible for resistance to conventional therapy stems from many observations made utilizing cell culture, animal models, and cancer patients. In the direct investigation of apoptosis in colon carcinoma

cell culture indicated that treatment triggered the death of differentiated cancer cells or non-CSCs. CSC, on the other hand, was able to withstand the therapeutic insults [4, 5]. Tumors represent intricate systems comprising malignant cells and the tumor microenvironment (TME), encompassing elements such as cancer-associated fibroblasts (CAFs), vasculature, infiltrating immune cells, and other constituents. Substantial efforts have been dedicated to replicating the complexity of cancer by incorporating the TME to explore tumor heterogeneity based on genetic and epigenetic variations [1]. According to the concept of cancer stem cells (CSCs), tumors exhibit a unidirectional cellular hierarchy akin to normal tissues, with CSCs positioned at the apex. These CSCs play a crucial role in sustaining tumorigenicity and reproducing the cellular diversity inherent in the original tissue.

In the next sections, we present an update on CSC intrinsic and extrinsic regulators, including transcriptional and post-transcriptional control, epigenetics, metabolism, and the TME, which have influenced our knowledge of how CSCs work to promote tumor development and treatment resistance. We also discuss recent advancements in CSC-based therapeutics and clinical trials [1]. CSC-targeting strategies are thought to be significant for studying the evolution of cancer treatment and the future of therapeutic techniques. However, identifying and comprehending this cell subgroup, which promotes tumor formation and progression, remains difficult. The first challenge in exposing patients to targeted treatment is defining their unique markers. ALDH, which exhibits greater metabolic activity, is one of the most recently regarded indicators for CSCs. CSC definition and key features. With adequate time, individually cultured subpopulations of stem, basal, or luminal cells can gradually emulate phenotypic ratios that encompass the other two cell types, mirroring the heterogeneity observed in clinical breast cancer [1].

THE TRANSCRIPTIONAL REGULATION OF CSCs

CSCs may self-renew and differentiate, making them tumorigenic and plastic enough to develop drug/radiation resistance after treatment [1].

OCT4, which is encoded by the POU5F1 gene, is involved in a variety of activities, including stem cell maintenance and embryogenesisOCT4 is consistently upregulated in cancer stem cells (CSCs) across various human malignancies, and its association with carcinogenesis, resistance to therapy, and unfavorable prognoses in cancer patients has been established.

SOX2 dysregulation is linked to cancer etiology and various cancer cell characteristics such as proliferation, EMT, CSC development, resistance to apoptosis, and chemotherapy. Furthermore, mounting evidence suggests that SOX2 is important in the control of CSC self-renewal, tumor development, and therapeutic resistance [1].

KLF4, a zinc finger transcription factor, participates in diverse cellular functions, such as regulating the cell cycle and preserving cellular pluripotency. MYC proteins, including c-MYC, N-MYC, and L-MYC, play critical roles in carcinogenesis and drug resistance. c-MYC is one of these MYC members that is commonly dysregulated in human carcinogenesis, making it a prospective therapeutic target [10].

Wnt signaling is a critical cascade in the regulation of embryonic development, as well as self-renewal, carcinogenesis, and CSC metastasis. Several Wnt signaling pathway components, including LEF1, cyclin D1, -catenin, and TCF-4, are expressed at significantly greater levels in CSCs than in non-CSCs. The absence of Wnt1 in breast cancer stem cells (CSCs) led to the reduced expression of stemness-associated genes CD44, ALDH1, and ATXN1. This deficiency also resulted in diminished CSC subpopulation and impaired formation of tumor spheres [1]. STAT3 is a critical molecular driver in numerous signaling systems that are dysregulated in several human malignancies. Janus kinases (JAK) phosphorylate STAT3 at tyrosine (Tyr) 705 to control dimerization, nuclear accumulation, and DNA binding, ultimately commencing transcriptional regulation.

Technological and methodological breakthroughs have increased our understanding of post-transcriptional changes, which constitute a second mechanism that regulates gene expression in cancer. According to new findings, epi transcriptome control is critical in CSC maintenance and cancer progression [1]. The CSC niche comprises several components that can keep CSCs dormant and govern cell plasticity and quiescence through the activation of multiple signaling pathways. The signaling pathways within the cancer stem cell (CSC) niche represent the interconnected map or network of interactions among cells and components within the niche. The significance of signaling pathways encompasses the majority of traits.

CANCER RESISTANCE: CSCs AND THE TUMOR MICROENVIRONMENT

TME research continues to be of great interest and importance in solid tumors due to TME's important involvement in tumor resistance and progression. It has been split into several components, which can be seen by histological investigation, where the linkages between normal and tumor tissue appear to prevail niches through different cell types dispersed in other tumor locations may form a dynamic cancer environment [2]. CSCs can form a dense network of linkages between the tumor and normal tissue, providing a distinct role for each niche that is readily connected by dependency relationships. A specific niche frequently emerges in hypoxic circumstances, which is the true driver for stemness mediators. CSCs can survive due to their high metabolism and attraction to nutrients like glucose, which promotes tumor migration and dispersion, producing hypoxia and necrosis [2].

Recent research links Snail and Twist expression to cell adhesion loss and enhanced cell [2] Proliferation. CSC, like healthy stem cells, live in niches that supply microenvironmental elements such as autocrine signaling and signals from stromal fibroblasts (cancer-associated fibroblasts, CAF), immunological cells, endothelial cells, and extracellular matrix components [9, 10].

The capacity of CSCs to withstand conventional anti-cancer medicines implies that innovative and effective therapeutic techniques to destroy CSCs specifically are required. Targeting specific pathways responsible for generating and expanding cancer stem cells (CSCs), including Wnt, Shh, JAK/STAT3, and PI3/AKT signaling pathways that regulate thyroid CSC self-renewal and tumor development, could serve as a potential approach. Although preliminary evidence suggests that medicines that block CSC pathways lower thyroid cancer cell proliferation and improve cellular sensitivity to both targeted and conventional treatment.

THE MOLECULAR MECHANISMS SWITCHING ON CSCs AND METASTASIS

A hundred years ago, the dominant hypothesis proposed that metastasis primarily resulted from cell fusion between macrophages and tumor cells. Subsequent investigations have presented evidence supporting the idea that cell fusion can indeed play a role in the initiation and spread of tumors. This process can produce two distinct hybrid types: heterokaryons and synkaryons. In heterokaryons, the genetic information of the parent cells remains separated in distinct nuclei, leading to the creation of bi- or multi-nucleated hybrids. This occurrence was initially observed in vitro using the Sendai virus, where murine Erlich ascites cells were fused with human HeLa cells.

POTENTIAL THERAPEUTIC TARGETS FOR BLADDER CSCs

There are two types of therapeutic resistance mechanisms in cancer: intrinsic and acquired. Intrinsic mechanisms are caused by underlying cancer factors that exist before any therapy, rendering some therapies worthless. Drug resistance develops throughout therapy. A growing body of data suggests that the production of stemness markers is critical for tumor maintenance and that this molecule also controls resistance In many instances, the recurrence of tumors is attributed to a resilient cancer stem cell (CSC), whether intrinsic or acquired, within the primary tumor, along with its capabilities for sphere formation and self-renewal [7]. The heightened recurrence rates observed in papillary non-muscle-invasive bladder cancer (NMIBC) and the elevated invasion and metastasis seen in muscle-invasive bladder cancer (MIBC) to regional lymph nodes and distant organs are associated with CSCs. Recurrent bladder

cancer also exhibits resistance to conventional treatments [5, 6]. Chemoresistance may arise due to challenges in medication penetration into the core of tumor tissues for the eradication of all CSCs or as a result of the elevated stemness of bladder cancer. Consequently, a promising approach for bladder cancer treatment involves a combination of chemotherapy and targeted therapy directed at CSCs [4].

Given the high recurrence rate in NMIBC and the low survival rate in MIBC, novel treatment strategies based on CSCs are imperative. While CSC-focused treatments are in the early stages of development and are distant from clinical application, they hold promise for overcoming drug resistance and impeding cancer dissemination. Therefore, a comprehensive exploration of CSC genomic profiles is essential to identify CSC-related genes and potential intervention targets [2].

Tumors are recognized as complex entities composed of a diverse array of cells, including CSCs. According to the clonal evolution hypothesis, all tumor cells are physiologically similar and have the potential to self-renew and form new tumor cells [8, 9]. The cancer stem cell hypothesis argues that tumor-initiating cells (TIC) begin tumor development, with CSCs being a tiny fraction with self-renewal and differentiation capabilities that display resistance to chemotherapy, radiation, and immunotherapy [15].

Temozolomide-based chemotherapy is a recognized standard in the combination treatment of glioblastoma. However, recurrences are largely certain during the first year of therapy. This brief duration of remission shows that some GBM cells survive the therapy. GSCs appear to be good candidates due to their quiescent state, which implies limited proliferation and consequently low activity of DNA synthesis, factors that chemotherapy may target. Indeed, Liu et al. evaluated the impact of chemotherapy on CD133+ GSCs against CD133-negative GBM cells. GSCs exhibited greater chemoresistance than CD133-negative tumor cells [12, 14].

CONCLUSION AND FUTURE PERSPECTIVES

The maintenance of stemness and dormancy, fundamental to the capability of cancer stem cells (CSCs) to resist therapy, is a characteristic common to multiple molecular processes associated with therapy resistance mediated by CSCs. Other methods include drug efflux, anti-apoptotic mechanisms, DNA damage repair mechanisms, and CSC niche, immune evasion by TME manipulation [3].

One of the most intriguing fields of study is cancer therapeutic techniques. According to logical recommendations, the gold standard treatment includes surgery in the early stages and chemotherapy/radiotherapy in the later stages. CSCs appear to be important in cancer recurrence [11, 13]. It has also emphasized the significance of targeting this subpopulation of cells, because standard oncological therapies are ineffective against CSCs, which may live in a dormant condition and proliferate after damage, such as that caused by chemotherapy. As a result of the necessity to target CSCs, researchers.

REFERENCES

1. Huang T, Song X, Xu D, Tiek D, Goenka A, Wu B, Sastry N, Hu B, Cheng SY. Stem cell programs in cancer initiation, progression, and therapy resistance. Theranostics. 2020;10(19):8721.
2. Aramini B, Masciale V, Grisendi G, Bertolini F, Maur M, Guaitoli G, Chrystel I, Morandi U, Stella F, Dominici M, Haider KH. Dissecting tumor growth: The role of cancer stem cells in drug resistance and recurrence. Cancers. 2022 Feb 15;14(4):976.
3. Li Y, Wang Z, Ajani JA, Song S. Drug resistance and Cancer stem cells. Cell Communication and Signaling. 2021 Dec;19(1):1-1.
4. Abugomaa A, Elbadawy M, Yamawaki H, Usui T, Sasaki K. Emerging roles of cancer stem cells in bladder cancer progression, tumorigenesis, and resistance to chemotherapy: a potential therapeutic target for bladder cancer. Cells. 2020 Jan 17;9(1):235.
5. Das PK, Islam F, Lam AK. The roles of cancer stem cells and therapy resistance in colorectal carcinoma. Cells. 2020 Jun 3;9(6):1392.

6. Makena MR, Ranjan A, Thirumala V, Reddy AP. Cancer stem cells: Road to therapeutic resistance and strategies to overcome resistance. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2020 Apr 1;1866(4):165339.
7. Zhou HM, Zhang JG, Zhang X, Li Q. Targeting cancer stem cells for reversing therapy resistance: Mechanism, signaling, and prospective agents. Signal transduction and targeted therapy. 2021 Feb 15;6(1):62.
8. Oshimori N. Cancer stem cells and their niche in the progression of squamous cell carcinoma. Cancer science. 2020 Nov;111(11):3985-92.
9. Arnold CR, Mangesius J, Skvortsova II, Ganswindt U. The role of cancer stem cells in radiation resistance. Frontiers in oncology. 2020 Feb 20;10:164.
10. Jing N, Gao WQ, Fang YX. Regulation of formation, stemness, and therapeutic resistance of cancer stem cells. Frontiers in Cell and Developmental Biology. 2021 Apr 7;9:641498.
11. Gianì F, Vella V, Tumino D, Malandrino P, Frasca F. The possible role of cancer stem cells in the resistance to kinase inhibitors of advanced thyroid cancer. Cancers. 2020 Aug 11;12(8):2249.
12. Biserova K, Jakovlevs A, Uljanovs R, Strumfa I. Cancer stem cells: significance in origin, pathogenesis and treatment of glioblastoma. Cells. 2021 Mar 11;10(3):621.
13. Marzagalli M, Fontana F, Raimondi M, Limonta P. Cancer stem cells—Key players in tumor relapse. Cancers. 2021 Jan 20;13(3):376.
14. Ju F, Atyah MM, Horstmann N, Gul S, Vago R, Bruns CJ, Zhao Y, Dong QZ, Ren N. Characteristics of the cancer stem cell niche and therapeutic strategies. Stem Cell Research & Therapy. 2022 Dec;13(1):1-7.

