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REVIEW ARTICLE

Targeting tumor associated macrophages to alternate cancer stem cells and tumor microenvironment milieu

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ABSTRACT

Macrophages in the tumor microenvironment are involved in promoting cancer growth and enabling it to evade therapies. By acting as something like a tumor's "underground," these cells dampen down the "calls for help" that chemotherapy or radiotherapy might otherwise trigger. They also appear to enable some cells in the cancers to reset themselves into cancer stem cells (CSCs), allowing them to divide and differentiate. Cancer stem cells are compelled to initiate tumors and maintain their growth. In part, the tumor-associated macrophages (TAMs) effect this by secreting cytokines with well-established roles in regulating stemness, as well as proteins that govern cell migration and are known to help keep CSCs in the niche where the tumor formed and maintain the tumor. Prognostic studies have found that TAMs are associated with worse patient outcomes. This article reviews the existing knowledge on TAMs in supporting the survival and maintenance of CSCs, increasing tumor resilience and resistance to therapy. We did a systematic review using the keywords CSC, TAM, tumor microenvironment (TME), and extracellular matrix remodeling from the following databases: ScienceDirect, PubMed, NCBI, Nature, Google Scholar, and Oxford Academic for articles published between 2010 to 2026. The underlying premise of the current investigation is that macrophages facilitate the maintenance of the "stemness" characteristics of CSCs. The TAM-CSC alliance must be interrupted to improve therapeutic outcomes and reduce tumor recurrence. Our review focuses on addressing the difficulties presented by CSCs and TME through advanced research techniques and specific combination treatments. This alternative method offers a less harsh and more effective therapy that will improve the patient's outcomes by effectively eradicating tumor cells and modifying the tumor microenvironment to enhance the immune system's capability to combat the tumor.

Keywords: Immune cell, tumor microenvironment, epithelial-mesenchymal transition, infiltration, extracellular matrix remodeling

Abbreviations:
AM: Alveolar Macrophage
ARG: Arginine
CSC: Cancer Stem Cell
ECM: Extracellular Matrix
EGF: Epidermal Growth Factor
EMT: Epithelial-Mesenchymal Transition
FGF: Fibroblast Growth Factor
FGFR: Fibroblast Growth Factor Receptor
HGF: Hepatocyte Growth Factor
HIF-1α: Hypoxia-Inducible Factor-1 alpha
IDO: indoleamine 2,3-dioxygenase
IFN- γ: Gamma Interferon
IL: Interleukin
LPS: Lipopolysaccharides
MAPK: Mitogen-Activated Protein Kinase
MDSC: Myeloid-Derived Suppressor Cells
MMP: Matrix Metalloproteinases
NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells
NK: Natural Killer
NO: Nitrite Oxide
PD: Programmed Death
PDGF: Platelet-Derived Growth Factor
ROS: Reactive Oxygen Species
STAT3: Signal Transducer and Activator of Transcription 3
TAM: Tumor-Associated Macrophage
TGF-β: Transforming Growth Factor-Beta
TME: Tumor Microenvironment
TNF-α: Tumor Necrosis Factor-Alpha
VEGF: Vascular Endothelial Growth Factor
VEGFR: Vascular Endothelial Growth Factor Receptor

INTRODUCTION

Effective cancer management requires a multifaceted approach encompassing prevention, early detection, personalized treatment, and ongoing research. Personalized treatment options include targeted therapies that minimize damage to normal cells, immunotherapy that harnesses the immune system, and precision medicine tailored to the genetic makeup of an individual's cancer.[1] Ongoing research through clinical trials, biomarker identification, and combining chemotherapy with immunotherapy or gene therapy has become part of the strategic approach used in cancer treatment, which does not have a gold standard protocol approach.[2–5] Tumor-associated macrophages (TAMs) are central components of the tumor microenvironment (TME) that significantly impact cancer development and the spread of cancer cells.[6,7] Although TAMs have various purposes, one of their most crucial aspects is their interaction with cancer stem cells (CSCs).

Current studies have prioritized investigating the precise molecular and cellular interactions between TAMs and CSCs using sophisticated techniques such as single-cell RNA sequencing and spatial transcriptomics.[8,9] Tumor-associated macrophages play a complex role in the immune system's response to cancer, presenting both obstacles and opportunities for cancer treatment.[10,11] Utilizing different TAM phenotypes (e.g., M1 and M2) enables their reprogramming and shifting the equilibrium from a tumor-promoting to a tumor-fighting environment.[12] This alternative approach could specifically focus on eradicating CSCs.

Gaining comprehension of TAMs and altering their functioning could result in therapies that effectively eradicate tumor cells and modify the tumor microenvironment to enhance the immune system's capability to combat these cells. This article reviews the existing knowledge on tumor-associated macrophages in supporting the survival and maintenance of cancer stem cells,

increasing tumor resilience and resistance to therapy.

METHODS

This review paper involved a thorough literature search on several search engines, i.e., Science Direct, PubMed, NCBI, Nature, Google Scholar, and Oxford Academic databases using the following keywords: CSC AND TAM AND TME AND EMT AND Extracellular matrix remodeling. Relevant English articles published from 2016 to 2026 were gathered from the mentioned search engines. Initially, 371,570 articles met the inclusion criteria, but ultimately, most of them were excluded due to duplication, access issues, and irrelevant topics, leaving 96 articles for analysis and synthesis (Figure 1). This review included peer-reviewed original research, systematic reviews, meta-analyses, selected narrative reviews, and clinical overviews to comprehensively cover mechanistic and therapeutic aspects of tumor associated macrophages and treatment strategies. Non-English articles and case reports were excluded.

Definition and role of TAMs in immune system

When cancer cells appear, a distinct subgroup of macrophages derived from circulating monocytes is reprogrammed and called tumor-associated macrophages (TAMs, Figure 2). These macrophages can facilitate tumor development by encouraging the formation of new blood vessels, proliferating cancer cells to reach other body parts, and suppressing the immune system. However, they can also regulate the immune system by inhibiting the body's anti-tumor responses through the release of the anti-inflammatory cytokines interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β).[13–17] Their presence makes them essential contributors to the advancement of cancer and the development of resistance to treatment. In most malignancy cases, the TAMs found are mostly polarized towards the M2 phenotype.[18]

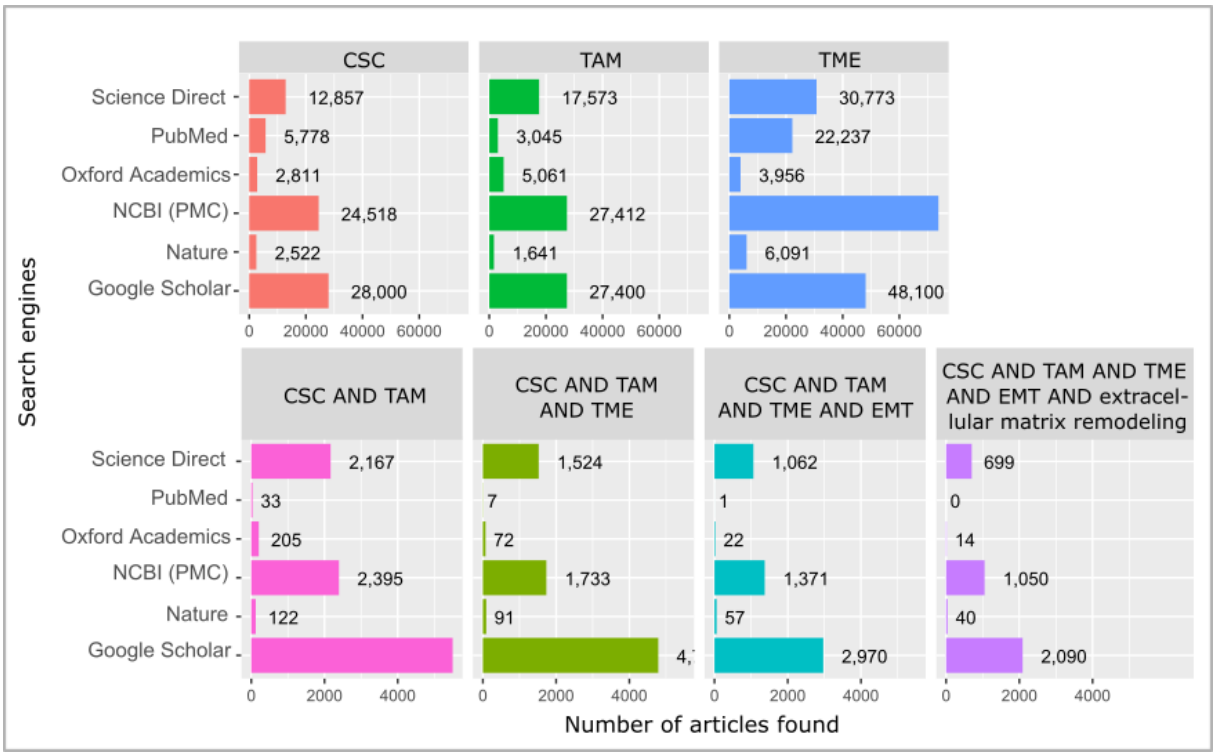

Figure 1. The numbers of articles found in different search engines using different keywords initially collected in this review

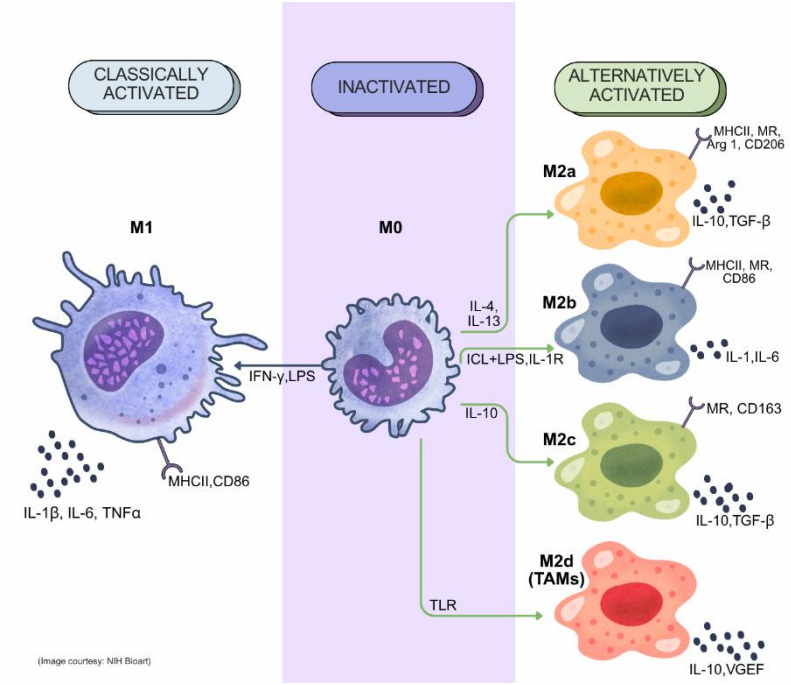

Figure 2. Macropfferentiation is stimulated by the microenvironment.[19] LPS or IFN-γ results in the differentiation of macrophages toward the M1 type, while other interleukins (IL-4, IL-13) and IL-10 evolve in the polarization of macrophages toward the M2 type.

Due to their ability to promote immunological suppression within the tumor microenvironment, directing therapeutic interventions towards TAMs has become a viable option to improve the effectiveness of cancer immunotherapies. One approach entails reprogramming them to transition from a phenotype that promotes tumor growth to one that combats tumor development. Another approach centers on inhibiting the signals that attract them to the tumor, decreasing their accumulation, and mitigating their influence. Additionally, focusing on the survival routes and roles of TAMs can hinder their ability to inhibit the immune response, potentially restoring the body's ability to combat the tumor.

Association between increased TAMs and poor prognosis in cancer

Tumor-associated macrophages perform numerous roles extending beyond essential immune functions. Research has shown a consistent link between a high presence of TAMs within tumors and poorer outcomes for cancer patients. This connection is driven by direct and indirect interactions with cancer cells, especially CSCs, and several other pathways. Tumor-associated macrophages support tumor development through several biomolecular pathways (Figure 3).[38] They produce anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which clamp the immune response and create an immunosuppressive TME, reducing the effectiveness of cytotoxic T cells and natural killer (NK) cells against tumor cells. Tumor-associated macrophages also secrete chemokines, such as CCL2, CCL5, and CXCL12, which recruit additional macrophages and other immune cells to the tumor site, where they are then differentiated into pro-tumor M2 macrophages under the influence of the local microenvironment shaped by CSCs.[39] Cancer stem cells , in turn, promote the dispersal of TAMs to the M2 phenotype by secreting cytokines like IL-10 and IL-4, which are critical mediators in suppressing the immune response and enhancing the pro-tumorigenic activities of TAMs. Additionally, TAMs support cancer cells' epithelial-mesenchymal transition (EMT), a vital step in metastasis, by releasing TGF-β, IL-6, and IL-1β. Tumor-associated macrophages maintain a supportive niche for CSCs by secreting cytokines and growth factors, including EGF, VEGF, and HGF. TAMs promote angiogenesis by secreting vascular endothelial growth factor (VEGF), which induces the formation of new blood vessels that supply the tumor with oxygen and nutrients, facilitating its growth and providing routes for metastasis.[40]

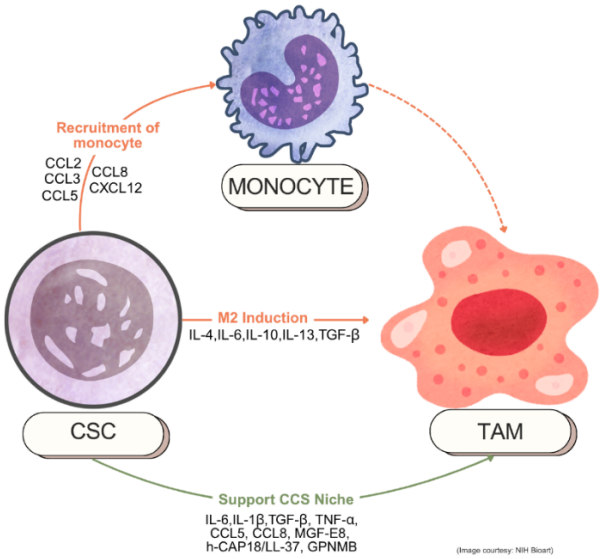

Figure 3. The mechanism of TAMs in facilitating cancer stem cell (CSC) survival

Epidermal growth factor (EGF) produced by TAMs stimulates tumor cell proliferation and invasion by interacting with the EGF receptor (EGFR) on tumor cells.[42–44] Matrix metalloproteinases (MMPs) released by TAMs degrade the extracellular matrix (ECM), creating pathways for tumor cell invasion and metastasis.[45–48] Cathepsins, another type of protease released by TAMs, also contribute to ECM degradation and facilitate tumor cell migration.[49–52] Tumor associated macrophage express immune checkpoint molecules such as programmed death-ligand 1 (PD-L1), which binds to PD-1 receptors on T cells, hinders their activity and allow tumor cells to evade immune detection.[53–61] B7-H4, another inhibitory molecule expressed by TAMs, suppresses T cell-mediated immune responses.[62,63] Metabolic reprogramming by TAMs involves the expression of arginase-1 (ARG1), which depletes arginine, an amino acid necessary for T cell proliferation and function, and the catabolism of tryptophan by indoleamine 2,3-dioxygenase (IDO), leading to T cell suppression and promoting Tregs expansion.[64–66] Signal transduction pathways such as the STAT3 and NF-κB pathways are activated in TAMs, encouraging the assertion of pro-tumorigenic genes intricate in cell survival, proliferation, and angiogenesis. Tumor-associated macrophages sustain hypoxia-inducible factor-1 alpha (HIF-1α), upregulating genes involved in angiogenesis, glycolysis, and survival under low oxygen conditions in the hypoxic TME.[67–72] These pathways collectively enhance tumor progression by promoting immune evasion, angiogenesis, and tissue remodeling, providing a supportive niche for tumor growth and metastasis.[73] Understanding these mechanisms is compelling for altering targeted therapies to inhibit TAM function and reprogram them towards an anti-tumor phenotype.

TAMs impact on tumor progression and metastasis

Tumor-associated macrophages significantly impact drug resistance, tumor growth, metastasis, angiogenesis, and immunosuppression through the complex release of cytokines, chemokines, and growth factors (Figure 4). These mediators activate various biochemical signaling pathways that collectively promote the malignancy and complexity of tumors. For instance, TAMs secrete IL-6 and IL-10, which activate the STAT3 and NF-κB pathways in cancer cells.[69–71] These pathways upregulate anti-apoptotic mechanisms and drug efflux pumps, enhancing resistance to chemotherapy. Tumor-associated macrophages also release growth factors such as EGF, HGF, and PDGF, which stimulate cancer cell proliferation and survival through the MAPK and PI3K-Akt pathways, further supporting tumor growth and facilitating extracellular matrix remodeling. Metastasis is fostered by TAM-driven secretion of TGF-β and other molecules that induce the EMT, enabling cancer cells to access migratory and invasive characteristics through the Smad and non-Smad signaling pathways. VEGF and FGF are released by TAMs, which act on vascular endothelial cells to promote neoangiogenesis by activating the VEGFR and FGFR signaling pathways.[74]

This process provides the tumor with essential nutrients and oxygen, thereby aiding in the proliferation of cancer. Regarding immunosuppression, TAMs utilize many mechanisms, such as the secretion of IL-10 and TGF-β, which engage signaling pathways to inhibit cytotoxic T cell and NK cell functions. They also express high levels of PD-L1, engaging the PD-1 receptor on T cells, which leads to T cell weariness via the PD-1/PD-L1 signaling axis.[75] This multifaceted biochemical interplay directly enhances tumor progression and modifies the TME to create a protective niche for cancer cells, complicating therapeutic interventions and contributing to poor patient outcomes.

Strategies for disruption of TAM-CSC alliance

Disrupting the relationship between CSCs and TAMs is becoming a critical tactic in the fight against cancer (Figure 5).[77] The interaction within TMEs is crucial in promoting cancer growth, metastasis, and resistance to treatment.[78,79] Researchers concentrate on cutting-edge approaches to disrupt this alliance by targeting TAMs and their connections with CSCs.[80–84]

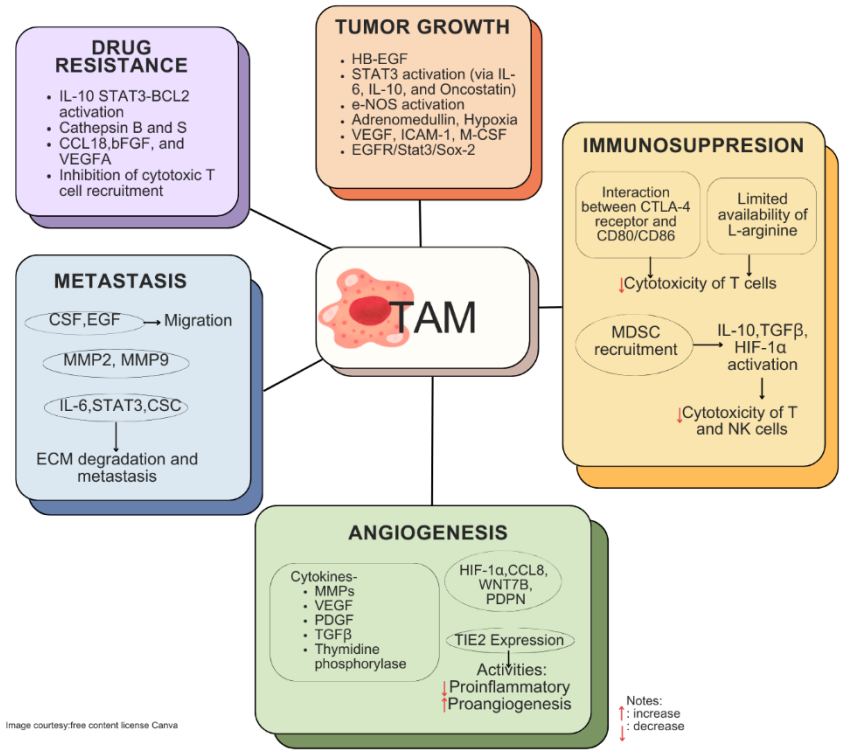

Figure 4. Mechanisms of TAM-mediated CSC survival.[76] TAMs facilitate tumor progression by promoting tumor cell proliferation, invasion, migration, angiogenesis, immunosuppression, and metabolism.

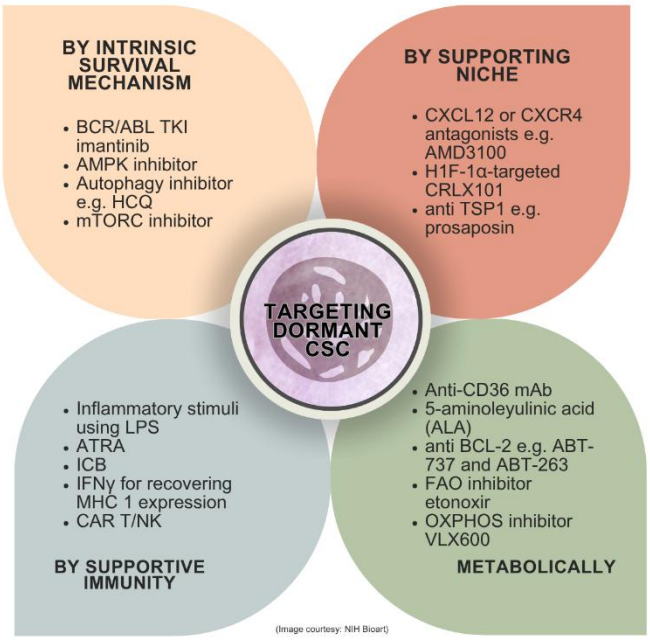

Figure 5. Therapeutic targeting and mechanisms of action disrupting TAM-CSC alliance [85]

Converting TAMs to an anti-tumor phenotype

A highly promising strategy involves converting TAMs from a pro-tumor (M2-like) state to an anti-tumor (M1-like) state by reprogramming. It is feasible to prompt a change in the characteristics of TAMs by modifying their surroundings or employing targeted signaling inhibitors, including NF-kB and STAT3.[86] This transformation diminishes their capacity to sustain cancer cells and can actively transform them into cells that attack the tumor.

Eliminating TAMs from TME

An alternative strategy involves reducing the quantity of TAMs accessible to support the tumor by applying therapies targeting TAM survival pathways or stimulating their apoptosis.[87–89] Therapeutic agents such as clodronate liposomes, taken up by macrophages and trigger cell death, are currently under investigation.[90] By reducing the consistency of TAMs in TME, the support system for CSCs is weakened, impeding the tumor's ability to proliferate and metastasize.

Another strategy is preventing TAMs from being recruited to tumors by inhibiting chemokine signals attracting monocytes to the tumor location.[91] For instance, inhibitors that specifically target the CCL2/CCR2 or CXCL12/CXCR4 chemokine pathways have demonstrated the potential to decrease the movement of monocytes toward tumors.[92,93] This technique seeks to deprive the cancer of crucial support and immunosuppressive capabilities that TAMs offer by limiting the entry of additional TAMs.

Focusing on the colony stimulating factor 1 CSF1/CSF1 receptor (R) pathway

Ultimately, focusing on the colony stimulating factor 1 and its receptor (CSF1/CSF1R) pathway offers a precise method to interfere with the function and continuance of TAMs.[94] Colony stimulating factor 1 and its receptor are vital in macrophages' survival, recruitment, and functioning. Inhibiting CSF1 or CSF1R can decrease TAM populations inside TME and impede their ability to support CSCs survival and tumor growth. These solutions offer a distinct approach to breaking the harmful TAM-CSC partnership to advance the development of more efficient cancer therapies and enhance patient outcomes by weakening a fundamental element of tumor resistance.

Implications and future prospects

Tumor-associated macrophage current research is mainly directed at comprehending the genetic and epigenetic alterations in CSCs that play a role in resistance. By mapping these alterations, scientists can formulate more accurate treatments targeting particular pathways, potentially overcoming the CSCs' capacity to resist therapy.

Another important aspect is developing ways to manage side effects by enhancing symptomatic treatments and developing medications that exhibit more selectivity towards cancer cells, minimizing damage to healthy tissues. Advancements in drug delivery systems, such as the utilization of nanoparticle technology, provide hopeful opportunities to achieve precise medication administration that minimizes harm to healthy cells.

Targeted therapies are a fundamental aspect of contemporary oncology, which selectively attack specific molecular targets linked to cancer. The ongoing progress of targeted therapies depends on their constant improvement, specifically in identifying novel targets inside TME and CSCs. As our knowledge of the molecular makeup of cancer becomes more extensive, there are increasing possibilities to interrupt the vital pathways that support cancer cells, offering more efficient and less harmful treatments.

CONCLUSION

The future of cancer therapy is evolving into a complex and diverse process, which entails improving our existing knowledge and venturing into uncharted territory in research and practical implementations. Our focus is addressing the difficulties presented by CSCs and TME through advanced research techniques and specific combination treatments. With each step, this method brings us closer to less harsh and more effective medicines, which should improve patient outcomes. The dynamic nature of this changing environment emphasizes the vital importance of continuous research, collaboration, and innovation in our ongoing battle against cancer.

Conflict of Interest

Competing interests: No relevant disclosures.

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Authors' Contributions

M – Conception, drafting the article. SIW, NS - Critical revision of the article. FCI – Drafting, Final approval of the version to be published. All authors have read and agreed to the published version of the manuscript.

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Declaration of AI Usage in Scientific Writing

Nothing to declare.

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