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Review Article

In Vivo Stem Cell Discoveries: Promising Implications in Cancer Therapy

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ABSTRACT

The remarkable regenerative abilities and versatility of stem cells have long attracted researchers. Recently, *in vivo* studies have revealed exciting results related to stem cells, particularly their use in cancer treatment. This review will provide an overview of these discoveries and their broader implications for the future.

There is growing *in vivo* evidence that stem cells have immense therapeutic potential in treating various diseases, including cancer, because of their self-renewal and differentiation capabilities. As a result of *in vivo* research, critical aspects of stem cell behavior within tumor microenvironments have been clarified, providing a deeper understanding of their potential therapeutic utility. Several *in vivo* studies have demonstrated the potential of stem cell-engineered tumor-targeting agents or therapeutic payloads for the precise delivery of medicinal drugs when these agents are engineered to express them in tumor cells. Through targeted therapies, off-target effects can be minimized, and the therapeutic index of the anti-cancer agents can be improved. Several stem cell-based delivery systems have shown remarkable efficacy in preclinical *in vivo* studies, including breast, lung, and pancreatic cancer, indicating their potential as a novel therapeutic strategy. Moreover, *in vivo* studies have revealed that the immunomodulatory properties of stem cells modulate the immune response and modify the tumor microenvironment to suppress it. In particular, using checkpoint inhibitor therapy with stem cells has paved the way for innovative immunotherapeutic strategies. Research on stem cells *in vivo* has also provided invaluable insights into stem cell biology and their interaction with cancer cells. Due to these findings, there is an increasing understanding of tumor initiation, progression, and resistance mechanisms, which has opened avenues for improving cancer treatment by developing more effective treatments. As a result of the *in vivo* studies that have taken place so far, there is a wealth of information regarding the potential of stem cells in cancer treatment. This research opens up exciting prospects for the future of oncology, from the delivery of targeted drugs to immunomodulation and improving our understanding of tumor biology.

1. Introduction

There are 9.6 million cancer deaths yearly in developed countries due to cancer's high mortality and morbidity rates[1]. Despite traditional therapies such as surgery, radiation, and chemotherapy, cancer recurrence remains challenging due to cancer stem cells' self-renewal characteristics[2]. Various strategies for cancer therapy have been trending, like immunotherapy with parasites, such as *Trypanosoma cruzi*, *Trichinella spiralis*, and *Echinococcus granulosus*; however, they need more experimental studies for finding the exact mechanism behind[3-6]. Even after chemotherapy, a small

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population of cancer stem cells (CSCs) remains within the tumor. There may be epigenetic mutations associated with the chemoresistance of healthy stem cells[7]. The CSCs also express specific markers that help identify these rare cells in brains, breasts, colonies, and pancreatic cancers[8]. Moreover, CSCs in tumor tissues cause metastasis, cancer growth, and recurrence[9]. In addition, recent reports have suggested that CSC may be derived from stem cells or may result from the differentiation of a non-committed progenitor cell[10,11].

New therapeutic approaches can be developed by better understanding CSCs and their niche profiles[12]. An approach targeting specific cancer cell populations can be practical in identifying CSCs[13]. As a result of alteration in these pathways, CSCs develop, leading to tumor growth, metastasis, and even recurrence after treatment because of their high self-renewal capacity, uncontrollable proliferation rate, and ability to alter the niche around them to accommodate their energy requirements[14]. The recurrence, development, and chemical resistance of the CSCs must be inhibited or suppressed with target-specific and efficient therapy[15]. A novel approach may be developed, or existing treatments can be combined with other treatments[16].

Several pathways regulate CSC proliferation, including Wnt/ β-catenin, Hedgehog (Hh), Transforming Growth Factor-β (TGF-β), Janus Kinase-Signal Transducers, and Activators of Transcription (JAK-STAT), Phosphatidylinositol-3-kinase/Protein kinase B (PI3K/Akt), Epidermal Growth Factor Receptor (EGFR), Nuclear factor-κB (NF-κB), Notch and B-cell- specific Moloney murine leukemia site 1 (Bmi-1)[17-19]. Self-renewal and differentiation of CSCs are controlled by transcriptional regulators such as Nanog, Myc, Klf4, and Oct4[20]. The CSCs develop when these pathways are altered, resulting in tumor growth, metastasis, and recurrence after treatment because of their ability to self-renew, multiply uncontrollably, and transform their surrounding niches to meet their energy needs[21]. The mechanisms and pathways controlling CSC functioning must be better understood to develop similar viable methodologies[22]. In addition, drugs and microRNAs are commonly used for each pathway, and potential therapeutic targets are identified to suppress the recurrence of CSCs [23]. A novel drug-free approach that uses stem cells and cell-free treatments is then explored, combined with our hypothesis to explore innovative yet target-specific approaches[24]. The tumor microenvironment plays an essential role in regulating the CSC phenotype[25]. The purpose of this review is to provide a concise overview of the characteristics, biology, modes of developing multidrug resistance, therapeutic implications, and metastasis of CSCs, as well as the need to target CSCs specifically with an emphasis on the various strategies that are currently being developed to do so.

2. Cancer stem cells origin and mechanism of action

Bonnet et al. (1997) provided the first experimental evidence for cancer stem cells in acute myeloid leukemia, demonstrating that the CD34+CD38- leukemia cells possessed stem cell-like properties, such as proliferating, self-renewing, and differentiation[26]. The stem cells can initiate acute myeloid leukemia (AML) when inoculated into non-obese diabetic/severe combined immunodeficient mice (SCID). As a result, CD34+CD38- leukemia cells were considered CSCs. Cancer stem cells were found in solid tumors, including breast, liver, lung, head and neck, colon, pancreatic, glioma, stomach, glioma, bladder cancer, melanoma, and hepatocellular carcinoma[27,28]. The surface tags on CSCs, self-renewal ability, and regulatory signaling are similar to those on normal stem cells. Therefore, CSCs could arise when dormant normal stem cells are transformed into malignant cells by oncogenic mutations acquired over time, and this increasing mutational load plays a vital role in tumorigenesis and tumor growth[29]. CSCs may also be transformed through epigenetic changes (abnormal methylation or histone modifications), genetic mutations, and epidermal mesenchymal transition (EMT)[30]. A handful of embryonic stem cells (ESCs)-like cells may exist in other tissues or blood. An alternative theory proposes that stem cells become misplaced in the stroma due to basement membrane lesions, resulting in invasive tumors from these misplaced stem cells[31-33].

An embryonic stem cell is the quintessential pluripotent cell. ESCs originate from blastocysts and can differentiate into virtually any cell found in an embryo's three germ layers: mesoderm, ectoderm, and endoderm[34]. Their ability to generate diverse cell lines makes them a valuable resource for regenerative medicine and cancer therapy. Cancer research uses ESCs to study oncogenesis' fundamental mechanisms *in vivo*[35,36]. These models can be used to study the mechanisms underlying cancer initiation metastasis progression and provide insight into the genetic alterations and molecular pathways involved in malignant transformation. Furthermore, ESCs play a crucial role in drug discovery, helping to identify novel anti-cancer agents and high-throughput screening therapeutic targets[37].

Mesenchymal stem cells (MSCs) can differentiate into adipocytes, osteoblasts, and chondrocytes, among other mesodermal lineages[38]. As a result of their ability to modulate the tumor microenvironment (TME), MSCs have received considerable attention in recent years[39-41]. It is important to note that MSCs have a dual nature when used to treat cancer. Alternatively, engineered MSCs may deliver targeted drugs directly to metastatic tumors, such as oncolytic viruses or cytotoxic agents[42]. As a result of their immunomodulatory properties, they may also have potential as cancer therapies aimed at enhancing immune function[43-45].

Numerous studies have been conducted to identify the genetic signatures that determine CSC self-renewal[46,47]. It has been shown that several signaling pathways and genes play essential roles in cancer stem cells and regulate normal[48]. There are several signaling pathways and genes that play an essential role. Notch is a transmembrane receptor that controls self-renewal, Hedgehog is a glycoprotein family associated with pro-survival pathways, wnt/β-catenin is from the a family of proteins that regulate

self-renewal, and Bmi-1 is a transcriptional repressor factor that regulates the expression of telomerase[49-51]. It has been shown that, in the absence of Wnt signaling, β-catenin remains in the cytoplasm, where it forms a complex with glycogen synthase kinase GSK-3β, able to phosphorylate β-catenin, which undergoes degradation[52]. When the Wnt pathway is activated, GSK-3β is inhibited, blocking β-catenin phosphorylation[53]. Unphosphorylated β-catenin is stable and translocates to the nucleus; it binds to and activates T cell factor-lymphoid enhancer factor (TCF-LEF), which in turn dramatically increases the proliferation and self-renewal of CSCs when unphosphorylated [54].

CSCs in the ovary have CD24+ and CD133+, acute myeloid leukemia stem cells are CD34+, CD38-, head and neck CSCs are CD44+[55-57].

3. Targets and drugs regulating cancer stem cells

3.1 Signaling pathways

In cancer, several pathways responsible for stem cells growing, replicating, self-renewing, and differentiating poorly in a healthy environment are triggered or blocked abnormally[58]. Various endogenous and exogenous molecules, as well as miRNAs, regulate the complex pathways[59]. Several downstream genes are triggered by signaling pathways, including apoptosis, proliferation, cytokines, and even metastasis[60]. Several of the genes in this group are interconnected by network signaling pathways that regulate the growth of CSCs[61,62]. Multiple pathways regulate CSC differentiation and self-renewal, including Hh, Bmi-1, Wnt/catenin, Bone Morphogenetic Protein (BMP), Notch, PI3K/Akt, and JAK-STAT signaling[19,63].CSCs are, however, resistant to DNA damage-induced cell death and are prevented from dying through anti-apoptotic signaling. A Notch pathway is involved in CSCs radioresistance[64-66]. Hence, Notch's γ-secretase (GSI) inhibition enables glioma CSCs to become radiation-sensitive[67]. By inactivating PI3K/Akt and increasing the levels of McCl-1 protein, radiation causes this DNA damage response to be triggered. Several transcription factors expressed in embryonic stem cells, including Nanog, Klf4, Oct4, c-Myc, and Sox2, may also be modulated to control CSC stemness development, ss, and proliferation[68,69]. Post-clinical tests and pathway-targeting strategies can provide a promising approach to eradicating CSCs within tumor niches. Various small compounds or drugs and endogenous miRNAs can be used to target CSCs and be effective with fewer side effects[70].

3.2 The notch pathway

Several cancers were associated with CSCs through the Notch pathway[71]. Evidence shows that gamma-secretase inhibitors (GSIs) effectively eliminate CSCs in medulloblastoma, breast cancer, and glioma[72]. These inhibitors inhibit the protease necessary for Notch cleavage and activation. As a result of the Notch inhibition in intestinal stem cells, GSIs were found to be relatively nonselective drugs with dose-limiting gut toxicity (secretory diarrhea). Highly specific mAbs targeted Notch ligands and receptors with single target specificity[73]. CSCs (EpCAM+/CD44+/CD166+) can be reduced with antiDeltalike four ligands (DLL4, a membrane-associated Notch ligand) antibodies, alone or in combination with irinotecan. Breast cancer recurrence was suppressed more effectively by siRNA targeting Notch4 rather than Notch1[74].

3.3 The hedgehog pathway

The activation of the Hedgehog (Hh) pathway has been associated with CSC maintenance and tumorigenesis in various tumor types, including multiple myeloma, myeloid leukemia, colorectal cancer, gastric cancer, and gliomas [75]. As a result, several targeted therapies were developed. In certain types of cancer, such as brain and pancreatic cancer, an antagonist of the Hh coreceptor Smoothened (SMO), cyclopamine, can decrease CSC proportions or even eliminate CSCs [76]. Aside from that, studies have shown that GDC0449 (also known as Vismodegib), an orally active SMO antagonist, is bioavailable in brain and basal cell carcinomas. With IPI269609, the SMO inhibitor, the proportion of ALDHbri CSCs in pancreatic tumor xenografts could be reduced[77]. Several therapeutic strategies targeting Hh pathways and combined inhibitors of the pathway have drawn the medical community's attention. Combined treatments with gemcitabine, cyclopamine, or cyclopamine, rapamycin, and chemotherapy might reduce pancreatic CSC numbers *in vivo* to virtually undetectable levels[78,79].

3.4 The Wnt/ β -catenin pathway Aberrant

Cancerous cells with abnormally activated Wnt/catenin pathways were closely linked to tumorigenesis. Deficiency in clonogenicity and tumorigenicity of tumors caused by an antibody that targets frizzled7, a Wnt receptor [80]. It has been found that Dickkopf1 (Dkk1), a primary secreted antagonist of Wnt signaling, binds to low-density lipoprotein receptor-related protein6 (LRP6), an essential coreceptor for canonical signaling [81]. An antibiotic potassium ionophore, salinomycin, has been shown to inhibit breast CSCs and block LR P6's phosphorylation to block the Wnt pathway [82] (Figure 1).

4. Cancer stem cells and metastasis

Primary solid tumor cells invade adjacent and distant tissues, eventually growing into secondary tumors, which is the process of metastasis[83]. There is no conclusive way to determine cancer cell metastatic potential simply by accumulating genetic alterations and expressing factors from the cancer cells [84]. It is also important to note that cancer cells interact with extracellular matrix components (ECM) and stromal tissue compartments, which are

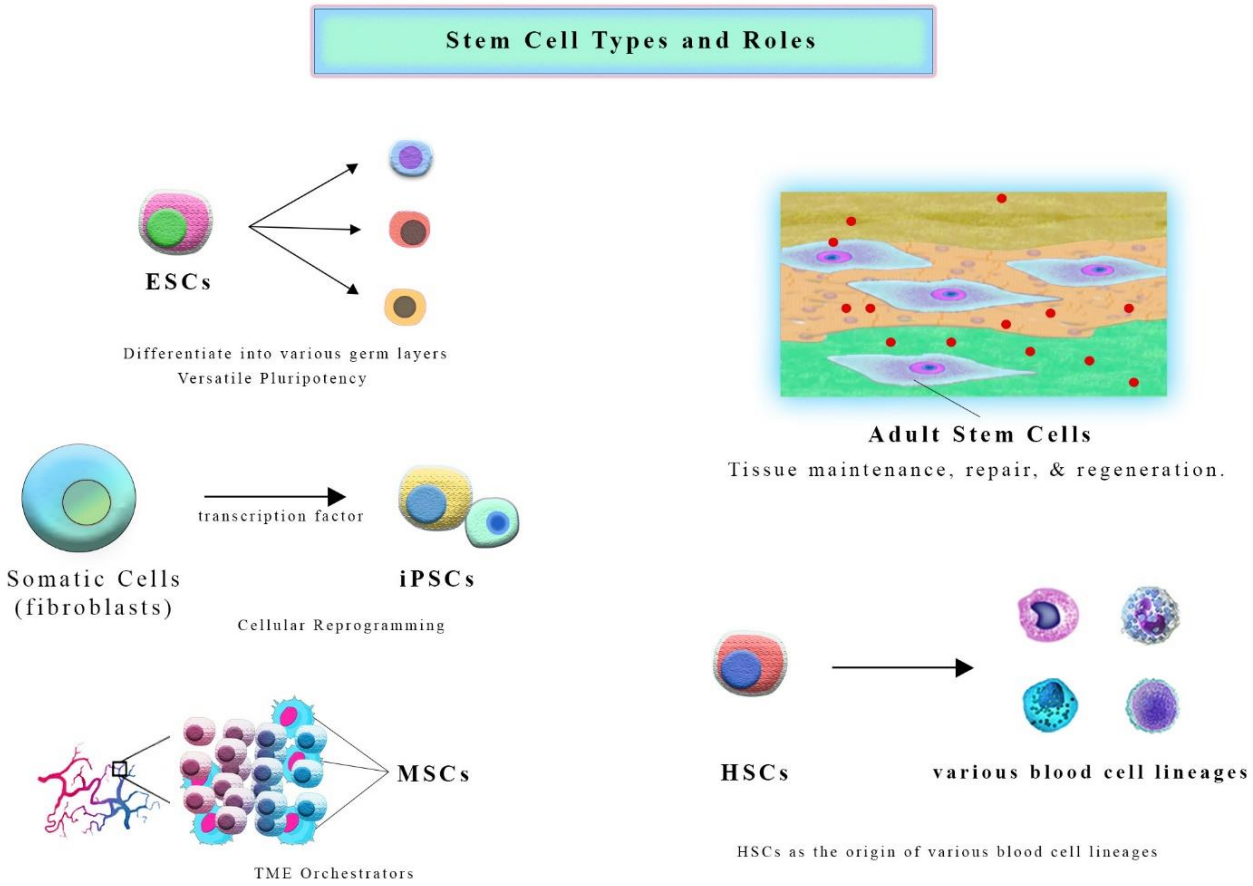

Figure 1. Diverse spectrum of stem cell types and their pivotal roles in cancer therapy and regenerative medicine. The figure portrays the remarkable pluripotency of Embryonic Stem Cells (ESCs), the cellular reprogramming process of Induced Pluripotent Stem Cells (iPSCs), the niche-specific locations of Adult Stem Cells within tissues, the dual nature of Mesenchymal Stem Cells (MSCs) in the tumor microenvironment, and Hematopoietic Stem Cells (HSCs) as the progenitors of various blood cell lineages. Each depicted stem cell type showcases its unique attributes and contributions, offering insights into their potential applications in the field of oncology and regenerative medicine."

essential for metastasis [85].

During the early stages of metastasis, establishing the 'pre-metastatic niche' independent of the signals emanating from the stromal microenvironment may be the first indication of the spreading of cancer cells. It is a highly specialized microenvironment that facilitates the migration of tumor cells to distinct sites, homing and colonization of tumor cells at the new site, and subsequent enhancement of tumor cell proliferation and disease development, similar to the CSC niche at the primary tumor site. Studies have revealed similarities between metastatic stem cells (MetSCs) and primary CSCs[86]. Analysis of large-scale genome sequencing has also revealed that metastasis-promoting mutations are accumulated in primary cancers. Through site-specific delivery of CSCs, researchers demonstrated that cellular bookmarking resulted in pre-metastatic niches (permissive niches) in target organs[87]. Metastatic mutations associated with relapse and poor prognosis are identified through gene expression signatures in primary tumors[88]. A breast cancer patient's stem-cell markers were inoculated into immunodeficient mice, forming bone, lung, and liver metastases[89]. In studies, metastases originate from early-stage cancer cells with long-term self-renewal capacities, quiescent and chemotherapy-resistant[90,91]. In melanoma, the presence of MetSCs has even been reported that does not appear to follow a hierarchical structure [92]. studies support the idea that primary tumors and metastases arise from different cell types; Metscs are likely simply developing from the CSCs that developed throughout tumor progression or through MetSC regeneration[93].

5. Cancer stem cells and angiogenesis

Numerous studies have examined the relationship between angiogenesis and CSCs[94]. In a study, Conley et al.2012, as well as Chau and Figg, presented a hypothesis that inhibiting angiogenesis could cause hypoxia, which would result in increased tumor growth rates and metastases as a consequence of an increase in the CSC population through activation of the Akt/β catenin pathway[95,96]. Researchers found that CSCs produce vascular endothelial growth factor (VEGF) higher under normoxic or hypoxic conditions than non-CSCs in tumors[96]. By increasing VEGF levels, endothelial cells migrate faster, forming new blood vessels. As a result of bevacizumab administration *in vivo*, hemorrhages and vascular growth

from CSC xenografts were inhibited[96]. Individuals with angiogenesis and CSCs can have a mutually beneficial relationship, and antiangiogenic therapy may increase the number of CSCs and increase VEGF production. A study by Bao et al. [97] indicated that stem cell-like gliomas (SCLGC) with CD133+ CSCs develop dense vascular networks. In the CD133+ plus SCLGC complex, VEGF expression was ten times higher, but tumor growth was reduced by bevacizumab treatment. There is a possibility that similar phenomena develop in cancers that affect other organs as well. The Notch pathway used by CSCs is believed to be involved in angiogenesis and CSC self-renewal, based on a review by Zhao et al. 2011 The STAT3 signaling pathway promotes the angiogenesis of tumors, and activation of NF-kB by CSCs could result in these cells degenerating into functional endothelial cells[98]. Angiogenesis markers (VEGF, Ang1 and Ang2, Tie, VEGF-C, PL-EGF) correlate with many CSC biomarkers.

Additionally, it has been found that CSCs express VEGFR, resulting in the nesting of these cells in significant metastatic sites, also referred to as vascular niches[99,100]. Additionally, VLA-4 is expressed by VEGFR1+. Fibronectin is the ligand that promotes the adhesion of circulating tumor cells[101,102]. This niche consists of potential properties essential for the survival of CSCs, including self-renewal and differentiation, as well as providing a potential site for cancer metastasis[103-105]. An antibody against VEGF1 can partially prevent metastases by destroying the vascular niche[106]. It has been determined that inflammatory cytokines, such as IL-17, are responsible for the self-renewal of CSCs and cancer metastasis[107,108]. A recent study shows that combination therapy with trastuzumab (anti-HER2 monoclonal antibody) and salinomycin effectively targets CSCs and cancer cells expressing HER2[109]. It has been demonstrated that overexpression of HER2 is closely associated with increased expression of VEGF in human tumor cells[110].

Additionally, salinomycin inhibits angiogenesis (blood vessel formation) for the metastasis and growth of cancer. Tao Li and colleagues say salinomycin inhibits tumor angiogenesis with intense and exciting pieces of evidence[111]. Several aspects of angiogenesis, including migration and capillary structure formation endothelial cell proliferation, have been inhibited by salinomycin *in vitro* at relatively low concentrations in this study[111]. Salinomycin was shown to act directly on both tumor cells and tumor endothelial cells. It has been shown that salinomycin inhibits ATP binding to the binding pocket of the VEGFR2 to inhibit multiple aspects of vascular endothelial angiogenic signaling[111].

In conclusion, salinomycin exerts its antiangiogenic effect via the VEGFR2 signaling pathway. Furthermore, salinomycin suppresses angiogenesis and tumor growth in a mouse model of human gastric cancer xenografts[112] (Figure 2).

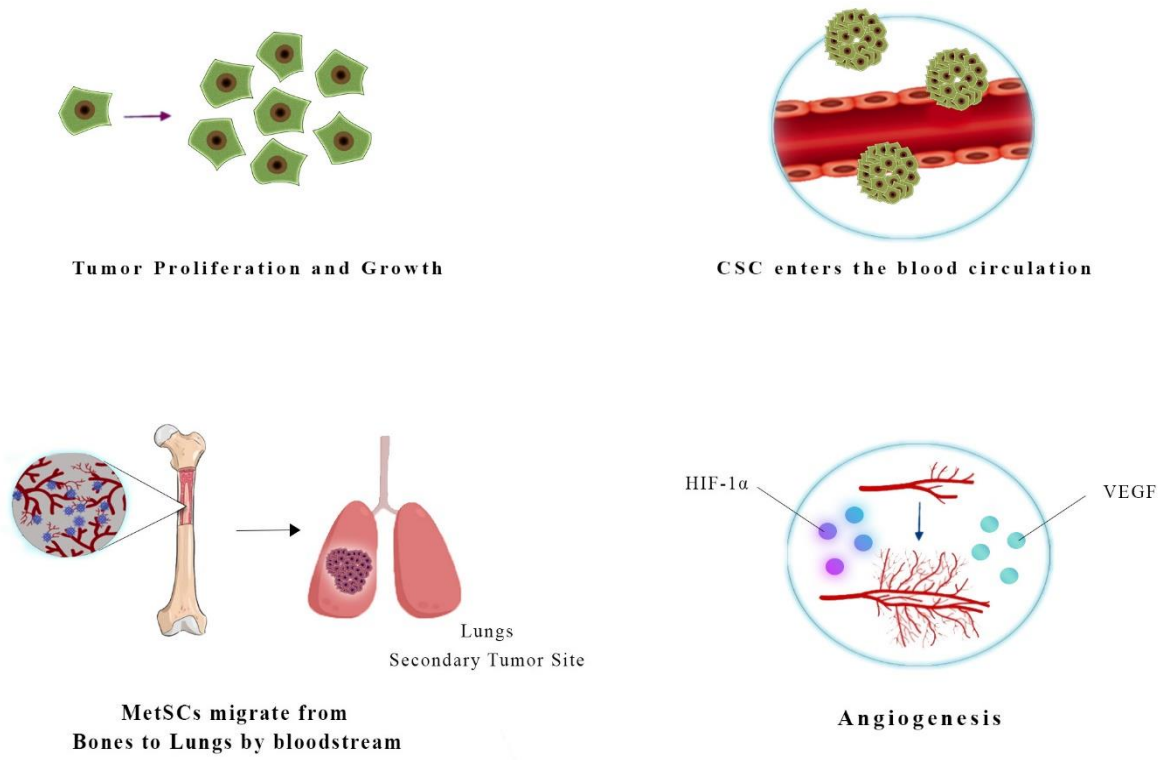

Figure 2. Metastatic stem cells (MetSCs) and their role in the metastasis process. This illustration details the critical steps in metastasis initiated by MetSCs. Within the bone marrow, distinct MetSCs are highlighted with unique markers, setting them apart from normal cells and cancer cells. The blood circulation pathway is emphasized, showcasing how MetSCs detach from the primary tumor site and enter the bloodstream. Their journey through the bloodstream is a crucial phase in the metastasis process. Upon arrival at a secondary tumor site, such as the lungs, MetSCs adhere to the blood vessel walls and commence the formation of a new tumor. This figure provides a comprehensive visual narrative of MetSCs' involvement in metastasis, from their origin in the bone marrow to their role in establishing secondary tumors.

6. Future Prospects

The CSC (Cancer Stem Cell) model provides a novel perspective on cancer, different from the conventional view that treats cancer as a dysfunction of somatic (normal) cells. According to the CSC hypothesis, cancer is not just a disease of bulk tumor cells; rather, it is rooted in a small population of specialized cells within tumors known as cancer stem cells. These cells possess unique properties similar to normal stem cells, including self-renewal and differentiation capabilities. Unlike other cancer cells, CSCs have the ability to initiate tumor formation, drive cancer progression, and resist conventional cancer treatments. One of the key reasons conventional cancer therapies struggle to eradicate cancer completely is their inability to effectively target CSCs. Standard treatments like chemotherapy and radiation primarily target rapidly dividing cells, which are common in most tumors. However, CSCs divide slowly and are often resistant to these therapies. When the bulk of the tumor is destroyed, CSCs can survive and regenerate, leading to disease relapse and metastasis. This phenomenon explains why cancer can reoccur even after seemingly successful treatments.

Moreover, CSCs are known to develop multidrug resistance, making them highly challenging to eliminate. Several factors contribute to the development of this resistance, including genetic mutations, activation of specific molecular pathways, and the presence of protective niches within the tumor microenvironment. These niches provide a supportive environment for CSCs, allowing them to evade the immune system and resist the toxic effects of chemotherapy drugs.

Understanding the CSC model is crucial for developing more effective cancer therapies. Researchers are exploring targeted therapies that specifically aim to eradicate CSCs or disrupt the supportive microenvironments that sustain them. By targeting the root cause of cancer – the CSCs – scientists hope to develop treatments that not only shrink tumors but also prevent relapse and metastasis, ultimately leading to more successful and long-lasting outcomes for cancer patients.Additionally, tumor cells' ability to undergo EMT and spread throughout the body, resulting in metastasis and distant tumor formation in various parts of the body, poses the most significant challenge to treatment. Hence, targeting CSCs is essential to overcoming the limitations of conventional chemo and radiotherapy. Surface biomarkers have facilitated the identification and targeting of CSCs. Targeted therapy only applies to CSCs of specific phenotypes because there is no universal CSC marker. Many strategies have been used to target CSCs. However, most of these studies were conducted *in vitro*, and they have yet to be tested in clinical settings, primarily due to the non-specificity of the strategies and potential toxicity to normal cells and stem cells. Various natural products have been proven to inhibit CSC by modulating the critical signaling pathways implicated in drug resistance, CSC self-renewal, and differentiation. It has also been shown that combinations of two or more drugs can overcome CSC drug resistance. Combining small molecules with conventional therapies can target both CSCs and differentiated cancer cells simultaneously, resulting in complete eradication of the cancer with a low chance of recurrence. The development of nanoparticles targeting CSCs has also gained interest. Recently, targeting specific CSC genes with RNA structures such as hairpin loops or miRNAs has gained considerable attention. Nanoparticles conjugated with ligands that bind specifically to CSC surface markers, cytotoxic drugs (or combinations of such drugs or small molecules) to eradicate CSCs, inhibitory molecules to overcome drug resistance or block key signaling pathways, and imaging agents to facilitate tumor diagnosis and the spread of nanoparticles in the body will undoubtedly prove effective strategies for targeting CSCs. The future challenges include developing better experimental systems, developing novel and specific strategies for targeting CSCs and avoiding toxicity to somatic cells and normal stem cells, improving the efficiency of CSC identification, and developing new carriers for delivering drugs efficiently to CSCs.

7. Conclusion

Recent *in vivo* research has illuminated the remarkable potential of stem cells in cancer treatment. Stem cells, with their unique regenerative and differentiation capabilities, have emerged as versatile tools with transformative implications for cancer therapy. They can be engineered to serve as precise tumor-targeting agents, revolutionizing drug delivery by homing in on cancer cells and releasing therapeutic agents within the tumor microenvironment. This precision enhances drug efficacy while minimizing harm to healthy tissues. Stem cells also exhibit immunomodulatory properties that enhance cancer immunotherapy. When combined with checkpoint inhibitor therapy, they offer innovative ways to boost the body's immune response against cancer, expanding the impact of immunotherapy. Furthermore, *in-vivo* research has deepened our understanding of the complex interplay between stem cells and cancer cells, shedding light on tumor biology, initiation, progression, and resistance mechanisms. This knowledge provides a foundation for the development of more tailored and effective cancer treatments. In conclusion, these *in-vivo* discoveries herald a promising future in cancer treatment, with more effective, patient-centered approaches on the horizon.

Declarations

Competing interests

The authors declare no conflict of interest.

Authors' contributions

The conceptualization of the research was spearheaded

by Mohammad Moeen Babayi, laying the foundation for the study. Subsequently, the initial draft of the manuscript was skillfully crafted by Shimen Gevargiz Sangar, Negar Agahi, and Alireza Azizi, who dedicated themselves to the writing process. The refinement and perfection of the document were entrusted to Nikoo Sadat Hasheminezhad, Emad Ghannad, and Parmida Nafei, who meticulously reviewed and edited the content. The project's funding was self-acquired, ensuring its independence. Throughout the research process, Mohammad Moeen Babayi provided vital supervision and guidance.

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Ethical considerations

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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