Stem Cells in Oncology: Potential and Challenges in Cancer Therapies

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ABSTRACT

Cancer, recognized as a predominant etiologic factor contributing to mortality, affects millions of people worldwide each year. Surgical interventions, chemotherapy regimens, and/or radiotherapeutic modalities remain some of the conventional therapeutic approaches, each associated with a myriad of adverse effects. Consequently, therapeutic outcomes are frequently suboptimal. Alternatives are steadily advancing due to the constant innovation of personalized medicine, and stem-cell therapies are emerging as an important avenue for oncologic treatments. In this review, we examine the multiple advantages related to stem cell treatment and elucidate how various types of stem cells currently influence oncology. These innovative treatments can improve patient well-being; however, they are not exempt from limitations, including collateral damage to nontarget organs that may facilitate tumor recurrence, resistance mechanisms, and issues related to treatment specificity. A deeper understanding of these challenges and the formulation of feasible solutions are needed to make the transition from experimental research to clinical application possible and real.

Keywords: Stem cell therapy, Cancer stem cells, Mesenchymal stem cells, Hematopoietic stem cell transplantation, Induced pluripotent stem cells

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Background

Globally, a significant number of people are affected by cancer every year. In the year 2022, a minimum of 20 million novel cases and an estimated 9.7 million fatalities associated with this ailment were documented. Lung cancer ranks as the most common cancer, exhibiting an occurrence rate of 12.4% and being the foremost contributor to deaths associated with cancer at 18.7%. In the next position, breast cancer showed the greatest incidence (11.6%), with colorectal cancer (9.6%), prostate cancer (7.3%), and stomach cancer (4.9%) following thereafter. In our investigation into the critical mortality statistics, we find that colorectal cancer is especially notable (9.3%) following lung cancer, with liver cancer (7.8%), breast cancer (6.9%), and stomach cancer (6.8%) not far behind.[1]

As per a comprehensive definition derived from meticulous examinations of a myriad of resources, cancer is not merely a singular ailment but rather a kaleidoscope of disorders defined by the rampant growth and expansion of altered cells, which unfold through the intricate dance of natural selection.[2–4] At its core, cancer possesses a fundamentally genetic essence; within this framework, a typical cell undergoes mutations that bestow upon it the remarkable ability to achieve immortality, leading its cell cycle to spiral into chaos, permitting it to multiply without end, thereby transforming it into a cancerous entity. As a product of the transformed cell, multiple cells with heterogeneous and erroneous genetic characteristics are generated, forming the tumor. In this process, differentiation is inhibited, uncontrolled proliferation is stimulated and cells are given the ability to permanently colonize and invade normal tissues.[5–9] This context explains that the multifactorial nature of cancer originates through the force exerted by natural selection on mutations with selective pressures in a constantly changing environment.[2] In addition to genetic factors, multiple external elements significantly influence the onset and progression of cancer. Internal factors include biological agents (viral or bacterial infections), autoimmune response, and chronic inflammation. External influences encompass ecological elements, such as contact with carcinogenic substances, environmental pollutants, and ultraviolet rays, alongside lifestyle choices like poor nutrition, alcohol intake, tobacco use, and inactive routines.[10,11]

The extensive diversity of cancer types can be attributed to the variety of cell types they can affect and to the different risk factors involved. The molecular evolution of tumor cells also contributes to this diversity.[8] Thus, we can think of carcinogenesis as a complicated process consisting of numerous phases, determined by different underlying causes that influence different moments of cancer development.[12] This explains why universal cancer prevention, diagnosis, and treatment remain an almost insurmountable challenge.

For a long time, oncological therapies have predominantly been based on universal methodologies encompassing surgery, chemotherapy, and radiotherapy. These last two methods are often associated with significant side effects and a wide variability of results.[13] Surgery is the treatment of choice for localized solid tumors since it allows their direct removal. In a supportive way, radiotherapy achieves its impact by causing harm to the DNA of cancerous cells. At the same time, chemotherapy employs the administration of highly cytotoxic pharmacological agents to prevent or stop tumor proliferation, thus facilitating a multifaceted strategy in the fight against malignant neoplasms (Figure 1).[14]

Currently, personalized or precision medicine in oncology is based on the idea that cancers are not homogeneous and that people respond differently to treatments due to internal and external factors already mentioned.[15] A key custom-fit strategy in the skirmish against cancer is immunotherapy, consisting of vaccines, monoclonal antibodies, checkpoint inhibitors, and cellular transplants. While immunotherapy has made extraordinary strides in improving clinical results, it faces significant hurdles due to its specificity and insufficient targeting of the tumor location, apart from scenarios with chimeric antigen receptor (CAR) effector cells, leading to

Fig 1 | Cancer patient receiving treatment

Table 1 | Types of stem cells by their differentiation capacity

Type of Stem Cell	Definition/Characteristics	Example	Differentiation Capacity
Totipotent	Highest level of plasticity; can differentiate into any cell type, including the three germ layers and extraembryonic structures like the placenta.	Fertilized egg	All organism cells and extraembryonic structures.
Pluripotent	Inability to generate extraembryonic structures but can differentiate into the three germ layers.	Embryonic stem cells and iPSCs	Any cell type from the germ layers.
Multipotent	Limited capacity to specialize into several cell lineages within a specific germ layer.	Hematopoietic stem cells	Several specific cell lineages.
Oligopotent	Limited differentiation to a specific set of cell types.	Myeloid lineage cells	Specific set of cell types (e.g., leukocytes).
Unipotent	Ability to generate only one cell type, but with high self-renewal potential.	Epidermal cells	A single cell type.

unfavorable outcomes, resistance to treatment, and relapses.[14,16–18] In addition, the ability of cancer cells to evade the immune reaction is a fundamental factor causing deficiencies in treatments. Although therapeutic strategies aim to selectively eradicate tumor cells without compromising adjacent healthy tissues, this goal has not yet been effectively achieved, which explains the persistent increase in cancer mortality rates annually.[19,20] Among the new approaches, cell therapies are positioned as one of the most innovative strategies in personalized medicine. In essence, therapies rooted in stem cells, celebrated for their ability to enhance the effectiveness of various treatments due to their remarkable precision, emerge as a beacon of hope in the relentless battle against cancer.[21]

This review article presents some current advances in stem cell research, emphasizing therapeutic applications, limitations, and advances with a look at the future of these therapies in the field of oncology. The analysis stemmed from a thorough exploration of scholarly repositories like PubMed and Google Scholar; considering that the largest number of selected articles were publications from recent years, the reference list contains publications mostly published between 2012 and 2024. Clinical and preclinical research and relevant reviews in English and Spanish were prioritized. Inclusion criteria considered peer-reviewed studies that addressed the above-mentioned points. This selection allowed for summarizing clinical and molecular perspectives, highlighting key findings and emerging areas in the field.

Stem Cells: Origin and Diversity

Stem cells represent a remarkable category of unspecialized (undifferentiated) cellular entities distinguished by their fundamental capacity to replicate themselves and evolve into various specialized cell forms. However, as they develop, this ability is diminished. Stem cells possess the remarkable ability to transform into over 250 unique types of cells, encompassing every cell that composes the organism as well as additional structures beyond the embryo, like the placenta. Totipotent stem cells, such as the fertilized egg, have the highest degree of plasticity.[22] This particular kind of cell possesses the remarkable potential to transform into any of the three fundamental germ layers. As they progress to a pluripotent state, they lose the ability to generate extraembryonic structures. The classification of stem cells encompasses the most happening fields of embryonic stem cells as well as induced pluripotent stem cells (iPSCs). IPSCs are synthesized from somatic cells have great potential in regenerative medicine. The capacity of multipotent stem cells, encompassing hematopoietic variants, to undergo transformation into various cellular phenotypes is recognized; however, their differentiation capability is considerably more limited in comparison to pluripotent stem cells, attributable to their origin from a specific germ layer. Conversely, oligopotent cells can transform into a defined array of cell types, such as myeloid lineage cells, which play a crucial role in forming distinct categories of leukocytes. Ultimately, unipotent cells, like those residing in the epidermis, can produce only a singular cell type, yet they exhibit remarkable capabilities for self-renewal, rendering them an invaluable asset in the realm of regenerative therapies.[23] The main characteristics and differentiation capacities of stem cells based on their levels of specialization are summarized in the following table (Table 1).

On the other hand, stem cell transplants can be classified according to the source from which they come. When they are obtained from the patients themselves, they are called autologous.[24,25] If they come from an identical twin, they are called syngeneic, while those obtained from another person who is neither the patient nor an identical twin are known as allogeneic.[26]

Cancer stem cells (CSCs) have the unusual ability to initiate and sustain cancer progression.[6,27] Unlike typical tumor cells, CSCs lack the regulatory systems that restrict normal stem cell proliferation, but they do share traits with normal stem cells, such as self-renewal and differentiation.[28] As a result, cancer can survive, recur, and metastasize to other tissues because they are

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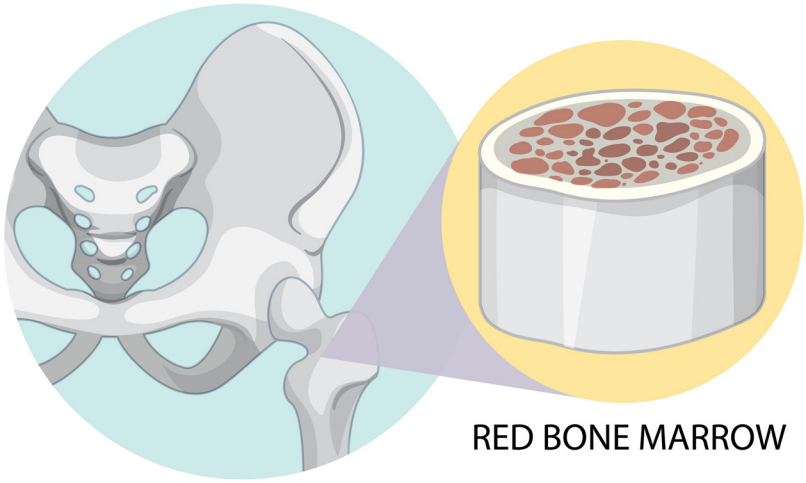

Fig 2 | Human bone marrow

resistant to traditional treatments, which do not effectively eradicate them.[29] These cells play an important role in acquired resistance to chemotherapy and intratumoral heterogeneity.[6] Chemotherapy primarily kills sensitive tumor cells during treatment, but resistant CSCs can persist and hinder disease progression.[30,31] CSCs can enter a state in which their metabolic functions are diminished. This state reduces their susceptibility to treatments designed to inhibit cell division.

Furthermore, CSCs possess mechanisms such as overexpression of ABC transporters that expel drugs out of the cell,[33] efficient repair of damaged DNA, reduction of reactive oxygen species levels, and evasion of apoptosis by overexpression of antiapoptotic proteins such as Bcl-2 and Bcl-xL, allowing them to resist various chemotherapeutic agents.[34] Recent discoveries have shown that CSCs can interact with their microenvironment and with immune system cells to avoid being detected and destroyed.[35] Furthermore, signaling pathways such as Notch, Wnt/β-catenin, and Hedgehog are involved in the self-renewal and survival of these cells, making them potential therapeutic targets. However, because CSCs share many characteristics with normal stem cells, it is difficult to develop treatments that specifically attack them without damaging healthy tissues.[34]

Therapeutic Advances of Stem Cells in the Antitumor Context and Their Challenges

Stem cells have facilitated the development of numerous innovative strategies in cancer therapy. These original techniques consist of the production of immune protector cells, the assimilation of stem cells as restorative mediums, the infusion of mesenchymal and hematopoietic stem cells, the application of extracellular vesicles (EVs) originating from stem cells, alongside several additional strategies.

Hematopoietic Stem Cell Transplantation (HSCT)

In the 1950s, the first HSCT, commonly referred to as bone marrow transplantation, took place (Figure 2). This treatment method involves administering healthy hematopoietic stem cells to individuals whose bone marrow is either dysfunctional or severely compromised.[36] Its advantages include restoration of bone marrow function and elimination of cancerous tumor cells, depending on the state of the disease.[37]

Many hematologic diseases are treatable by allo-HSCT (allogeneic), but efficacy is contingent on disease status.[26] This procedure has mainly been utilized as a conventional method for treating leukemia, multiple myeloma, and lymphomas following several cycles of high-dose radiotherapy or chemotherapy.[38] Allo-HSCT tends to produce magnificent results when acute myeloid leukemia and acute lymphoblastic leukemia attain swift and complete remission, especially in high-risk individuals.[26,39] Those with chronic myeloid leukemia not reacting to tyrosine kinase inhibitors may see improvements with HSCT.[40] For those grappling with myelodysplastic syndromes, HSCT remains the foremost remedy, particularly among younger individuals and those diagnosed in the nascent phases of the ailment.[26]

Allo-HSCT presents certain constraints when addressing lymphomas and multiple myeloma; nevertheless, it holds promise under particular circumstances. While less intensive protocols tend to experience increased relapse rates, they pose reduced risks in the realm of multiple myeloma.[41] However, the high mortality associated with HSCT, which can range from 30% to 50%, limits the frequent use of this approach.[42] In the realm of solid tumors, there are instances where patients battling metastatic renal cell carcinoma have demonstrated enduring recurrences through HSCT intervention, although these findings are still in their nascent stages.[43,44] The emergence of graft-versus-host disease (GVHD) following HSCT from allogeneic sources remains a formidable obstacle, typically managed with immunosuppressive medications that often yield limited efficacy and intense side effects.[45]

Mesenchymal Stem Cells (MSCs)

MSCs have the innate capacity to move toward primary and metastatic cancers. They are regarded as promising vehicles for targeted medication administration in the treatment of cancer.[46,47] However, because they can have both tumor-promoting and tumor-suppressing actions, there is debate regarding their safe therapeutic use.[48] This intriguing duality arises from the remarkable ability of MSCs to adjust their secretory profile in response to signals from the tumor microenvironment, thereby influencing immune response, apoptosis, and angiogenesis.[49] Their involvement is pivotal in tumor development, spreading, and metastasis, facilitated by their amicable connections with stromal and tumor cells.[50] The dual nature arises due to MSCs' skill in adjusting their secretory profile about stimuli from the tumor microenvironment, which can affect immune response, apoptosis, and angiogenesis.[49]

Variables, including the MSCs' source, the timing and method of delivery, the experimental models employed, and the cell dose, may all contribute to variations in preclinical study outcomes.[48,51,52] Overcoming

these variations and standardizing procedures is imperative to promoting the safe and efficient use of MSCs in cancer treatments.

To tackle the intricate hurdles associated with MSCs, notably their paradoxical roles in either fostering or thwarting tumors, the innovative application of CRISPR gene editing is suggested to reshape crucial pathways like TGF-β and VEGF. Furthermore, the design of experimental models that combine MSCs with functionalized nanoparticles could improve tumor specificity, minimizing secondary risks.

MSC as oncolytic virus (OV) vehicles

Oncolytic viruses (OVs) have an incredible ability to multiply only in tumor cells, effectively killing them while leaving healthy cells intact, making OV therapy a hopeful option in the fight against cancer.[53,54] However, the patient's immune reaction and the challenge of accessing the tumor can restrict their effectiveness.[55] Due to their easy culture, metabolic activity that promotes viral multiplication, and innate ability to move toward tumors, MSCs are suggested to be the best vehicles for OV delivery.[46,56,57] Moreover, to function as OV carriers, MSCs have immunosuppressive qualities that can enhance viral therapy by preventing immune responses that would limit the growth of these viruses.[58]

In addition, they have inherent anticancer properties that increase the therapeutic impact, such as causing cancer cells to undergo apoptosis.[59] According to preclinical research, OV-loaded MSCs can precisely target tumors, reduce tumor size, and increase survival rates in experimental animal models.[60–63] However, some issues need to be addressed, such as the possibility that MSCs may increase tumorigenicity in specific situations, the possibility of premature lysis of MSCs caused by excessive viral replication, and patient antiviral reactions, which may reduce treatment efficacy.[57] Nevertheless, despite these challenges, the use of MSCs as OV vehicles is a novel approach that has the potential to greatly improve therapeutic outcomes for cancer patients.

MSC-Derived EVs

The EVs that come from MSCs are important for how cells communicate and can have a mixed effect on cancer by either blocking or aiding tumor development.[64] An example is how they act on tumor angiogenesis. Zhu et al. found that exosomes from human bone marrow-derived MSCs (hBMSC) could promote the growth of gastric and colon tumors in mice by activating pathways like ERK1/2 and p38 MAPK, increasing the expression of VEGF and CXCR4.[65] On the flip side, another research team found that these exosomes could reduce blood vessel formation in breast cancer cells by transferring miR-16, which lowers VEGF expression.[66]

Furthermore, EV derived from MSCs can have direct effects on how tumor cells grow and die. It is noted that exosomes from hBMSC can promote apoptosis and slow down the growth of hepatocellular and ovarian cancers. Some special miRNA found in exosomes from human adipose-derived MSCs have been shown to increase apoptosis in ovarian cancer cells, emphasizing how important the RNA content in these vesicles is.[64]

However, it has also been evidenced that these EVs can facilitate tumor growth and metastasis. Research indicates that exosomes sourced from hBMSC facilitate the proliferation and movement of nasopharyngeal carcinoma cells by initiating EMT through the FGF19-FGFR4-ERK route.[67] Exosomes containing microRNAs like miR-410 and miR-130b-3p from hUCMSC have been correlated with the promotion of tumor growth in lung cancer.[68]

Regarding the induction of latency and chemotherapy resistance, it was found that exosomes from hBMSC can transfer miR-23b to metastatic breast cancer cells, inducing a latent state by inhibiting the oncogene MARCKS, allowing cancer cells to evade treatments and potentially lead to relapses.[69]

iPSCs and CAR-T

The advent of iPSCs as a groundbreaking therapeutic weapon has unveiled a novel frontier in the battle against cancer. These remarkable cells possess the ability to morph into a multitude of cell types, including those that can embrace immune traits like dendritic cells, NK, T, Tγδ, iNKT, and MAIT cells, which are adept at orchestrating formidable defenses against daunting tumors.[65,70,71] In addition, they present advantages such as a low probability of developing GVHD and a high capacity to identify and eliminate transformed cells. However, iPSCs also present risks, such as chromosomal changes and genetic abnormalities during culture, which can induce malignant transformations.[72] Concerns persist about the presence of undifferentiated cells after transplantation, which could generate teratomas.[73] Innovative in vitro techniques have been introduced to tackle these obstacles, including altering growth conditions, eliminating undifferentiated cells, and creating cell-free approaches to avert contamination; however, numerous elements remain beyond our control within the physiological context.[74]

A vital obstacle lies in guaranteeing that lymphocytes derived from iPSCs can enduringly thrive within the tumor microenvironment and triumph over the forces of tumor suppression. Gene editing has enabled the persistence and functionality of iPSC-derived T and NK cells to be improved by removing inhibitory genes and introducing specific receptors.[75,76] However, further research is still required to determine the ideal duration of their in vivo activity and their clinical impact.

In their pursuit of innovation, T cells derived from iPSCs have been harnessed to forge the future of CAR-T therapies. These innovative treatments aim to transcend the challenges posed by solid tumors, including the diverse array of antigens, the suppressive nature of the immune environment, and the imposing physical obstacles within the tumor's microecosystem, such as the following:[77]

- They identify a variety of tumor antigens, thereby minimizing unintended toxicity.
- They defy the whispers of immunosuppressive signals, weaving in immune checkpoint inhibitors and proinflammatory cytokines like IL-12 to amplify their antitumor prowess.
- They better infiltrate tumors because they use enzymes that degrade the extracellular matrix and chemokine receptors designed to overcome the physical barriers of dense tumors.
- They improve efficacy in complex clinical contexts and are being evaluated in clinical trials.

Below is a summary table of the stem cell therapeutic strategies in oncology and associated challenges addressed in this review article (Table 2).

Some Challenges Associated with Clinical Implementation

The clinical implementation of stem-cell-based therapies faces multiple challenges that limit their adoption on a large scale. A significant hurdle lies in their limited accessibility, primarily driven by their steep price tag. In the case of THSC, autologous transplants range from $36,000 to $88,000 (USD) for the initial

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Table 2 | Stem cell strategies and associated challenges in oncology

Therapeutic Strategy	Description	Advantages	Challenges
HSCT	Administration of hematopoietic stem cells to restore damaged bone marrow, mainly in leukemia and lymphoma.	Improves bone marrow function, high curative potential in leukemia.	High cost, risk of -GVHD, high mortality in some cases.
MSCs	Used to modulate the tumor microenvironment and as therapeutic vehicles.	Ability to migrate toward tumors, immunomodulatory potential.	Dual function (can promote or inhibit tumors), lack of standardization in protocols.
MSCs as Oncolytic Virus Carriers	MSCs are used to transport viruses that destroy cancer cells.	Increase the effectiveness of OVs, prevent premature immune responses.	Risk of tumorigenicity, possibility of premature MSC lysis, patient antiviral response.
MSC-Derived EVs	Exosomes derived from MSCs can influence tumor progression or inhibition.	Potential for targeted therapy without the risk of tumorigenicity.	Lack of standardization in production, some exosomes may promote tumors.
iPSCs	Differentiation of iPSCs into immune cells such as NK and T lymphocytes to attack tumors.	Personalized therapies, lower risk of -GVHD.	Risk of genetic mutations, potential for teratoma formation.
CAR-T Therapy Based on iPSC	Genetic modification of iPSC-derived T cells to attack tumors.	High specificity, better infiltration capacity in solid tumors.	High costs, tumor microenvironment immune suppression.

hospitalization that requires a single-intervention treatment. Other procedures such as myeloablative allogeneic that require an unrelated donor can exceed $200,000 (USD) in the first year.[78] More advanced personalized treatments such as CAR-T therapies can exceed $500,000 only with their initial implementation (USD).[79] Most stem-cell therapies, despite having proven their effectiveness, present a major limitation of having high initial costs. They require subsequent medical monitoring, which further decreases their accessibility and effectiveness. The high initial cost of these therapies is offset by the cost of other types of pharmacological treatments that are carried out over a longer period and are less effective.[78] However, the evidence of the long-term effectiveness of advanced stem-cell therapies is insufficient, so the estimated cost-effectiveness ratio has been associated with significant uncertainty; more studies are needed that reflect the follow-up of patients several years after being treated.[80]

Conversely, as noted earlier, a considerable threat of tumor formation looms, as research has demonstrated that MSCs cultivated for extended durations can metamorphose into cancerous cells.[81] However, strategies are being designed to reduce these risks, such as treatment with high-dose radiation, which has shown promising results in human iPSC cultures.[82] Another obstacle is the lack of scalability since current protocols are not designed to meet the needs of massive clinical applications. Not to mention, there are regulatory barriers that represent a major problem since the absence of international standards hinders the global approval and integration of these therapies into the health system.[81] To overcome these challenges, various strategies are proposed. Initially, it is crucial to nurture partnerships among the realms of industry, academia, and regulatory bodies in order to create expansive frameworks that lower expenses and enhance the effectiveness of treatments. Implementing automated technologies that allow the mass and standardized production of stem cells and their derivatives is also proposed, thus optimizing manufacturing processes. Finally, it is essential to establish international regulations that unify regulatory criteria, which would facilitate the approval and clinical adoption of these innovative therapies at a global level.

Strategies for a Promising Future of Stem Cells in Oncology

The design of genetically modified MSCs has shown promising results as a therapeutic strategy, an example of which was demonstrated by expressing apoptotic ligands such as TRAIL in lung cancer models, which was effective in reducing tumor progression, thus improving the therapeutic precision of conventional MSC transplantation.[83]

Furthermore, the creation of exosomes loaded with specific therapeutic molecules, such as siRNA or chemotherapeutics, offers a localized approach to treating resistant tumors, minimizing adverse effects.[82,84] Other advances include the development of programmable stem cells that dynamically respond to signals from the tumor microenvironment.[85] Finally, the implementation of next-generation CAR-T, with dual constructs and resistance to immunosuppressive signals, has the potential to overcome the challenges presented by solid tumors.[77]

Conclusion

This article highlights the transformative potential of stem-cell therapies in oncology, addressing their current advances and challenges. Effectively treating cancer requires a deep understanding of its complexity. Classic treatments like surgery, chemotherapy, and radiation remain foundational but often cause significant side effects and yield inconsistent outcomes.

Personalized medicine and immunotherapy mark a major advance, offering targeted and potentially more effective treatments. However, these innovations still have limitations, including issues of specificity and varying effectiveness across tumor types and patient populations. Challenges such as immune evasion and treatment resistance further emphasize the need for novel strategies.

Stem-cell therapies hold great promise in oncology. The area of HSCTs has notably boosted the survival possibilities for those facing blood cancers, even amidst ongoing risks like GVHD. MSCs show potential as therapeutic vehicles due to their tumor-homing ability, though their dual role in tumor suppression and promotion warrants careful consideration. The development of iPSCs enables the creation of personalized immune cells, potentially overcoming the limitations of existing treatments. However, concerns regarding genetic stability and unintended differentiation highlight the need for rigorous research.

EVs originating from stem cells introduce a new layer of healing possibilities. Their ability to influence tumor dynamics—either by suppressing or promoting proliferation—suggests that mastering their application could unlock new therapeutic strategies.

While remarkable progress has been achieved in the realm of cancer exploration, considerable obstacles continue to linger. Overcoming scientific and clinical barriers, such as process standardization, genetic stability, and tumor risk mitigation, is crucial. With advances in gene editing and targeted biomarkers, stem-cell therapies could become indispensable tools in the fight against cancer, offering more personalized and effective solutions.

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