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Review

Immunomodulatory Role of Stem Cells in Cancer: A Landscape of Tumor-Promoting and Tumor-Inhibitory Effects

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Abstract

Stem cell therapy has emerged as a transformative frontier in cancer treatment, harnessing the unique immunomodulatory capabilities of stem cells to reshape anti-tumor immune responses. Mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), induced pluripotent stem cells (iPSCs), and cancer stem cells (CSCs) dynamically interact with innate and adaptive immune systems within the tumor microenvironment (TME). MSCs secrete cytokines such as IL-6, TGF-β, and VEGF, which exhibit context-dependent effects on cytotoxic

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T lymphocytes (CTLs), regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs). These effects vary according to factors such as MSC tissue origin, tumor type, inflammatory status, and the cytokine milieu. MSCs can also modulate tumor-associated macrophage (TAM) polarization, but the direction of polarization toward pro-tumor M2-like or anti-tumor M1-like phenotypes is highly dependent on the surrounding TME. Conversely, CSCs drive immune evasion by expressing checkpoint molecules (e.g., PD-L1) and recruiting immunosuppressive cells, illustrating stem cells' paradoxical roles in cancer progression. Despite their promise, challenges persist: the TME's complexity, safety concerns (tumorigenicity, immune rejection), and a lack of standardized protocols impede clinical translation. Innovations such as genetically engineered stem cells for targeted drug delivery, their potential combination with immunotherapies such as CAR-T cells and checkpoint inhibitors, and personalized approaches tailored to tumor-specific profiles offer promising experimental strategies to enhance efficacy. This review underscores stem cells' potential role in rebalancing immune responses while emphasizing the need for further research to refine their therapeutic application. Although hematopoietic stem cell transplantation is clinically established for selected hematological malignancies, most other stem-cell-based immunomodulatory approaches remain preclinical or are under early clinical investigation.

Keywords
Stem cells; cancer; immunotherapy; immunomodulation; mesenchymal stem cells

1. Introduction

Stem cell therapy represents a frontier in regenerative medicine and cancer treatment, offering novel strategies to address the limitations of conventional therapeutic approaches [1]. Stem cells can self-renew and differentiate into diverse cell types, making them valuable for tissue repair, regenerative medicine, and targeted drug delivery [2]. Their ability to modulate the immune system has garnered considerable attention, particularly in cancer therapy [3].

Stem cells are undifferentiated cells characterized by self-renewal, enabling them to replicate and maintain a pool of undifferentiated cells, and differentiation, allowing them to mature into specialized cell types with specific functions. This dual capacity is fundamental to their role in tissue homeostasis, repair, and regeneration. Several types of stem cells with unique characteristics have therapeutic applications [4]. Importantly, mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), induced pluripotent stem cells (iPSCs), and cancer stem cells (CSCs) have fundamentally different roles in cancer immunity: MSCs mainly exert paracrine immunomodulatory effects, HSCs generate hematopoietic and immune-cell lineages, iPSCs provide a renewable source for generating specialized immune cells, whereas CSCs are malignant stem-like cells involved in immune evasion and therapeutic resistance [4].

Stem cell therapy has broad applications, including regenerative medicine, where stem cells are employed to repair or replace damaged tissues and organs, offering hope for treating conditions such as heart disease, neurodegenerative disorders, and spinal cord injuries [5]. In cancer therapy, stem cells can serve as therapeutic carriers for targeted drug delivery to tumor sites, selectively

target CSCs to eradicate the root of the tumor, and modulate the immune system to enhance anti-tumor immune responses [2, 6]. Immunomodulation in cancer therapy involves modulating the immune system to better recognize and eliminate cancer cells, shifting the balance from tumor-promoting inflammation to anti-tumor immunity [7, 8]. This can be achieved by stimulating anti-tumor immune responses, suppressing immunosuppressive mechanisms that protect cancer cells from immune attack, and restoring immune homeostasis to create an environment less conducive to tumor growth [9]. Stem cells, particularly MSCs, play a pivotal role in immunomodulation by interacting with various immune cells, secreting cytokines and growth factors that influence immune cell behavior, and influencing immune cell differentiation and function, shaping the immune landscape within the tumor microenvironment (TME) [6, 10]. By modulating the immune system, stem cells can improve cancer therapy efficacy, overcome therapeutic resistance mechanisms used by cancer cells, and improve patient outcomes, offering a more personalized, targeted approach to cancer treatment [8].

1.1 Literature Search Strategy

This narrative review was based on literature searches conducted in PubMed, Scopus, and Google Scholar using combinations of the terms “stem cells,” “mesenchymal stem cells,” “hematopoietic stem cells,” “induced pluripotent stem cells,” “cancer stem cells,” “cancer,” “immunomodulation,” “tumor microenvironment,” “T cells,” “NK cells,” “macrophages,” “regulatory T cells,” “myeloid-derived suppressor cells,” and “immune evasion.” We considered studies published primarily between 2009 and 2026, and included relevant earlier studies when necessary. We included original studies, clinical studies, and relevant reviews on stem-cell-mediated cancer immunomodulation, and excluded studies without a clear link to cancer immunity or outside the scope of this review.

2. Cross-Talk of Stem Cells and the Immune System in Cancer

2.1 Overview of Immune Responses in Cancer

The immune system plays a complex and multifaceted role in cancer, characterized by both protective and promoting effects that significantly influence tumor development and progression [11]. Understanding the intricate interplay between innate and adaptive immunity is paramount for devising effective immunotherapeutic strategies that harness the immune system’s anti-tumor potential.

Innate immunity constitutes the body’s initial line of defense against pathogens and aberrant cells, including cancer cells, and involves a diverse array of cells such as macrophages, natural killer (NK) cells, and dendritic cells (DCs) [12]. Macrophages, versatile phagocytes, can engulf and digest cancer cells, while also presenting tumor-associated antigens to adaptive immune cells, thereby initiating a targeted anti-tumor response. NK cells, specialized cytotoxic lymphocytes, can directly recognize and kill cancer cells without prior sensitization, providing rapid and broad-spectrum anti-tumor activity [13]. DCs function as professional antigen-presenting cells (APCs), capturing, processing, and presenting tumor-associated antigens to T cells, thereby bridging the innate and adaptive immune responses and initiating a targeted anti-tumor response [14]. Myeloid-derived suppressor cells (MDSCs), a heterogeneous population of immature myeloid cells, represent

another component of the innate immune system, but they typically exert immunosuppressive effects within the TME, suppressing anti-tumor immune responses and promoting tumor growth and metastasis [15].

Adaptive immunity, a more refined and targeted defense mechanism, involves T and B lymphocytes, which recognize specific tumor-associated antigens and mount tailored immune responses to eradicate cancer cells [16]. T cells, including cytotoxic T lymphocytes (CTLs) and helper T cells, directly kill cancer cells and coordinate immune responses by secreting cytokines that modulate other immune cells [6]. B cells, responsible for humoral immunity, produce antibodies that can neutralize tumor antigens, activate the complement system to destroy cancer cells, and mediate antibody-dependent cell-mediated cytotoxicity (ADCC), recruiting immune cells to eliminate antibody-coated cancer cells. Regulatory T cells (Tregs), a subset of T cells, suppress immune responses to maintain immune homeostasis and prevent autoimmunity, but in cancer, they can also inhibit anti-tumor immunity within the TME, protecting cancer cells from immune attack [17].

2.2 Interaction Between Stem Cells and Immune Cells

Different stem cell populations interact with immune cells, influencing the balance between anti-tumor immunity and immune suppression and thereby affecting tumor growth and progression [18, 19]. For MSCs, these interactions are mainly mediated by cell-cell contact, cytokine secretion, and other signaling mechanisms and can either stimulate or suppress immune-cell activity depending on the surrounding microenvironment [20]. HSCs primarily contribute through hematopoietic and immune-cell generation, whereas iPSCs can serve as a source of differentiated immune effector cells. CSCs, in contrast, predominantly interact with immune cells to facilitate immune evasion. For example, mesenchymal stem cells (MSCs), known for their immunomodulatory properties, can interact with NK cells, suppressing their proliferation, cytokine secretion, and cytotoxicity, thereby potentially dampening the innate immune response against cancer [21]. However, activated NK cells can also lyse MSCs, highlighting a complex bidirectional interaction in which NK cells can eliminate MSCs that may pose a threat. MSCs can modulate DC differentiation, maturation, and function, influencing their ability to present tumor-associated antigens to T cells and initiate a targeted adaptive immune response [20, 22].

Tumor-associated macrophages (TAMs), a prominent component of the TME, interact extensively with CSCs to promote tumor progression, maintain CSC stemness, and enhance their resistance to therapy [23]. TAMs can secrete growth factors, cytokines, and other factors that enhance CSC self-renewal, proliferation, and drug resistance, while CSCs recruit macrophages into the TME, creating a self-reinforcing loop that promotes tumor growth and immune evasion. The interactions between TAMs and CSCs exemplify the complex interplay between stem cells and immune cells within the TME, highlighting the challenges in developing effective cancer immunotherapies [24].

3. Mechanisms of Immunomodulation by Stem Cells in Cancer

Stem cells, particularly MSCs, exert immunomodulatory effects in the TME through multifaceted mechanisms, including the secretion of cytokines (e.g., IL-6, IL-8, VEGF, TGF-β, IL-10) and chemokines (e.g., MCP-1, MIP-1), direct cell-cell interactions, and recruitment of immune cells such

as neutrophils, macrophages, T cells, Tregs, and MDSCs [25, 26]. These secreted factors modulate immune responses by influencing immune cell differentiation, activation, and function: pro-inflammatory cytokines can enhance anti-tumor immunity by recruiting cytotoxic T cells and NK cells, while immunosuppressive cytokines like TGF-β and IL-10 suppress T cell activity and promote tolerance. MSCs also alter macrophage polarization, shifting the balance between anti-tumor M1 (pro-inflammatory) and pro-tumor M2 (anti-inflammatory) phenotypes, and regulate T cell function [25, 27, 28]. Importantly, MSC-mediated regulation of Tregs, MDSCs, macrophages, and effector lymphocytes is context-dependent and can either enhance or suppress anti-tumor immunity according to MSC origin, activation status, tumor type, and the surrounding cytokine milieu. The complexity and context-dependence of these interactions, including their impact on the inflammatory landscape and immune cell dynamics, underscore the need for further research to optimize stem cell-based therapies for enhancing anti-tumor efficacy while mitigating immune suppression in the TME [29] (Table 1).

Table 1 Studies on the immunomodulatory role of stem cells in cancer.

Author(s)	Stem cell type	Cancer type	Main findings	Reference
Yu et al.	HCT116 (colon cancer stem cells)	Colon Cancer	TP5 reduces stemness in HCT116 cells, enhancing the cytotoxic effect of oxaliplatin by decreasing stemness-related markers and altering Wnt/β-catenin signaling.	[30]
Casbon et al.	HSC	Breast Cancer	Tumor-derived G-CSF directs hematopoietic stem cells to produce immunosuppressive neutrophils, contributing to immune evasion.	[31]
Pont et al.	HSC	Hematological Malignancies	The study demonstrates the immunotherapeutic potential of donor T cells post-alloSCT and the necessity of analyzing antigen distribution to avoid adverse effects.	[32]
Lullo et al.	HSC	Multiple Myeloma	IMiDs reduce pro-tumor T cell subsets in MM during autologous transplantation, suggesting an anti-inflammatory role.	[33]
Sayed et al.	HSC	Various Murine Tumors	Activation of myelopoiesis and MDSC differentiation in tumor models lead to immunosuppression.	[34]

Lee et al.	HSC	Ovarian Cancer	CD8α+ dendritic cells from HSCs enhance antitumor immune activity against ovarian cancer.	[35]
Rossnagl et al.	Osteoblasts	Various cancer	EDA-FN from osteoblasts increases arginase in myeloid-derived cells, promoting cancer growth via immune modulation.	[36]
Witte et al.	MSC	Lung Cancer	MSCs trigger immunomodulation through phagocytosis by monocytic cells, suggesting a mechanism for their therapeutic effects despite their rapid disappearance.	[37]
Wellhausen et al.	HSC	Acute Myeloid Leukemia, B cell lymphoma, Acute T cell leukemia	Development of epitope edited CD45 CAR T cells enables universal therapy against blood cancers; protects HSCs from CAR T cell recognition and destruction.	[38]
Rueff et al.	HSC	Plasma Cell Myeloma	Rapid recovery of NK cells after autologous HSCT correlates with protection from relapse in patients.	[39]
Zhang et al.	MSC	Various	Tumor-conditioned MSCs display hematopoietic differentiation, with a diminished Ca^{2+} influx facilitating the conversion to immune cells like macrophages.	[40]
Giles et al.	MSC	Metastatic Tumors	HSPCs contribute to immunosuppression within pre-metastatic niches, impacting tumor dissemination.	[41]
Wu et al.	Hematopoietic Stem and Progenitor Cells	Various cancers	The study reveals that HSPCs in cancer patients are myeloid-biased, contributing to the accumulation of MDSCs and disease progression.	[42]

3.1 Cytokine and Growth Factor Secretion

Stem cells exert significant immunomodulatory effects in cancer by secreting cytokines and growth factors, soluble mediators that influence immune cells, tumor cells, and other TME components, ultimately affecting tumor growth and the overall immune response [43]. These secreted factors can act locally within the TME or systemically, influencing immune cell trafficking, differentiation, and function.

Cytokines are signaling molecules that mediate communication between cells and play a crucial role in regulating immune responses, orchestrating the complex interactions among immune cell types and influencing the balance between pro-inflammatory and anti-inflammatory responses [44]. Stem cells, particularly MSCs, secrete a wide array of cytokines that can either promote or suppress immune responses, depending on the specific context and the target cells involved. For instance, MSCs secrete IL-6, which can have dual effects depending on the context, promoting tumor growth and angiogenesis in some cases, while contributing to inflammatory immune activation under other conditions [45, 46]. The net effect depends on tumor type, the cellular source of IL-6, its concentration, and activation of downstream pathways such as STAT3. Similarly, IL-8 secreted by MSCs can attract neutrophils and other immune cells to the TME, modulating the inflammatory landscape and potentially influencing tumor progression [47].

TGF-β is another important cytokine secreted by MSCs, known for its immunosuppressive properties, inhibiting the activation and proliferation of T cells, promoting the differentiation of Tregs, and suppressing the activity of NK cells. These effects can contribute to immune evasion by cancer cells. However, TGF-β can also have anti-tumor effects by inhibiting tumor-cell proliferation and inducing apoptosis, particularly during earlier stages of tumorigenesis, highlighting the complex and context-dependent nature of cytokine signaling in cancer [48].

Stem cells also secrete growth factors that influence tumor growth, angiogenesis, and immune cell function, shaping the TME and influencing the course of tumor development. VEGF is a key growth factor secreted by stem cells, promoting angiogenesis and tumor vascularization, providing tumors with the nutrients and oxygen they need to grow and metastasize. By promoting angiogenesis, VEGF can enhance tumor growth and metastasis. However, VEGF can also modulate immune cell function by suppressing the maturation of DCs and inhibiting T cell responses, further contributing to immune evasion [49, 50].

The specific effects of stem cell-derived cytokines on tumor growth and immune response depend on several factors, including stem cell type, the TME, and the specific cytokines involved, making it challenging to predict the overall impact of stem cell therapy on cancer progression [51]. Understanding these complex interactions is crucial for developing effective stem cell-based immunotherapies that can harness the beneficial effects of cytokines while minimizing their potential to promote tumor growth. For example, human Wharton's jelly stem cells (hWJSCs) secrete cytokines that inhibit the proliferation of ovarian cancer cells in vitro, suggesting their potential as a therapeutic agent. These hWJSC extracts decreased the expression of oncogenic cytokines, chemokines, and growth factors, thereby inhibiting OVCAR3 cells, demonstrating their ability to modulate the cytokine milieu within the TME [52].

3.2 Regulation of Tumor-Associated Macrophages

TAMs are a key component of the TME and play a critical role in tumor progression and immune evasion, influencing angiogenesis, metastasis, and therapeutic resistance [53]. Stem cells can influence macrophage polarization, affecting the balance between M1 and M2 macrophages, which have opposing roles in tumor immunity, with M1 macrophages generally exhibiting anti-tumor activity and M2 macrophages promoting tumor growth [54].

Macrophages exhibit remarkable plasticity, adapting their phenotype and function in response to environmental signals, and can differentiate into functionally distinct phenotypes, primarily classified as M1 and M2 macrophages [55]. M1 macrophages are classically activated by stimuli such as IFN-γ and lipopolysaccharide (LPS) and exert anti-tumor functions, producing pro-inflammatory cytokines such as IL-12 and TNF-α, mediating cytotoxicity, and promoting T cell responses. In contrast, M2 macrophages are alternatively activated by stimuli such as IL-4 and IL-10 and promote tumor progression, secreting anti-inflammatory cytokines such as IL-10 and TGF-β, promoting angiogenesis, and suppressing T cell responses [56].

MSCs can influence macrophage polarization in a context-dependent manner, potentially shifting macrophages toward either M1-like or M2-like phenotypes. For example, MSCs can secrete factors (e.g., TNF-α, IL-1β, IL-6, IL-12, IL-23, and CXCL10) that promote M1 polarization, enhancing anti-tumor immunity and increasing pro-inflammatory cytokine production [57]. Conversely, stem cells can also promote M2 polarization, contributing to immune suppression and tumor progression by secreting factors that suppress T cell activity and promote angiogenesis [58]. Thus, the inflammatory environment, tumor-derived signals, and the functional state of MSCs determine MSC-mediated macrophage polarization.

TAMs play a critical role in tumor progression and immune evasion, influencing various aspects of tumor biology. M2 macrophages promote tumor growth by secreting growth factors and cytokines that stimulate tumor cell proliferation and angiogenesis, providing tumors with the resources they need to grow and metastasize [59]. They also suppress anti-tumor immune responses by inhibiting T cell activation and promoting the differentiation of Tregs, creating an immunosuppressive environment that protects cancer cells from immune attack. TAMs can also contribute to CSC maintenance and drug resistance, promoting tumor recurrence and therapeutic failure [60].

Targeting TAMs has emerged as a promising strategy for cancer immunotherapy, aiming to reprogram their function and enhance anti-tumor immunity. Strategies include depleting TAMs, inhibiting their recruitment to the TME, and reprogramming M2 macrophages to M1 macrophages, shifting the balance from tumor-promoting inflammation to anti-tumor immunity [61]. Preclinical approaches targeting innate immune signaling pathways, including STING activation, can also alter TAM function [24]. Stem cells can deliver therapeutic agents directly to TAMs, modulating their function and promoting anti-tumor immunity, offering a targeted approach to reprogram the TME. For instance, MSCs can deliver oncolytic Newcastle disease virus (NDV) to enhance therapeutic effects by altering the TME and promoting apoptosis, demonstrating stem cells' potential to modulate TAM function [62]. However, clinicians have not yet established durable MSC-mediated TAM reprogramming.

3.3 Modulation of T-Cell Responses

T cells are critical components of the adaptive immune system, recognizing and eliminating cancer cells through direct cytotoxicity and the secretion of cytokines that coordinate immune responses. Stem cells can influence T-cell activation, differentiation, and function, affecting their ability to mount effective anti-tumor responses and impacting the course of cancer progression [63].

T-cell activation is a complex process that requires multiple signals, including antigen presentation by APCs and co-stimulatory signals that provide the necessary cues for T-cell proliferation and effector function [64]. Stem cells can modulate T-cell activation by influencing APC function, altering the expression of co-stimulatory molecules (i.e., CD80/CD86, CD40, PD-L1, ICOS-L, and CTLA-4), and secreting cytokines that affect T-cell signaling pathways [65]. For example, MSCs can suppress T-cell proliferation and activation by secreting TGF-β and IL-10, inhibiting pro-inflammatory cytokine production and dampening the overall immune response [66].

Stem cells also influence T-cell differentiation, the process by which T cells acquire specialized functions, affecting the balance among T-cell subsets such as CTLs, helper T cells, and Tregs [67]. CTLs are critical for directly killing cancer cells, while helper T cells coordinate immune responses through cytokine secretion, activating other immune cells and enhancing anti-tumor immunity. Tregs, on the other hand, suppress immune responses to prevent autoimmunity but can also inhibit anti-tumor immunity in the TME, protecting cancer cells from immune attack [68].

Stem-cell-based approaches can modulate T-cell-mediated anti-tumor immunity, although the direction of this effect depends strongly on the stem cell type and experimental context. Engineered MSC-based strategies may promote CTL responses, whereas unmodified MSCs frequently suppress T-cell activation through immunoregulatory mediators. Similarly, their effects on Tregs may vary according to the cytokine environment and MSC activation state [69]. By modulating T-cell responses, stem-cell-based approaches may influence the efficacy of cancer therapies [70].

The potential therapeutic effects of stem cells on T-cell-mediated anti-tumor immunity have been demonstrated, providing evidence that they can enhance T-cell activity and promote tumor regression. For instance, MSCs loaded with oncolytic NDV can enhance E7-specific lymphocyte proliferation and CD8+ cytolysis, increasing the number of T cells targeting tumor-associated antigens and enhancing their cytotoxic activity [71]. Additionally, a strategy combining 4-methylumbelliferone (4Mu) with an adenovirus encoding interleukin-12 (AdIL-12) elicited a potent anti-tumor effect and prolonged animal survival by promoting cytotoxic-specific T cell responses, demonstrating the ability of stem cells to enhance T cell-mediated immunity [72].

3.4 Regulation of Regulatory T-Cells and Myeloid-Derived Suppressor Cells

As mentioned, Tregs and MDSCs are major players in immune suppression in the TME, inhibiting anti-tumor immune responses and promoting tumor growth and metastasis. These cells use various mechanisms to suppress immune cell activity, creating a protective shield around cancer cells and hindering immune elimination. Stem cells, particularly MSCs, can modulate the function of Tregs and MDSCs; however, these effects may be either suppressive or supportive depending on the surrounding inflammatory and tumor context [73]. Tregs can inhibit anti-tumor immunity, promoting tumor growth and immune evasion by suppressing the activity of effector T cells and other immune cells that would otherwise target and kill cancer cells [74]. Tregs suppress T-cell activation and proliferation via inhibitory cytokines (TGF-β, IL-10), metabolic disruption

(adenosine/CD39-CD73), and CTLA-4-mediated competition for co-stimulatory signals (CD80/CD86); inhibit NK cell activity by downregulating activating receptors (e.g., NKG2D) through TGF-β/IL-10 and inducing exhaustion via PD-1/PD-L1 or granzyme B; and promote MDSC differentiation through GM-CSF, CD40-CD40L interactions, and miRNA transfer, amplifying their arginase-1/iNOS-dependent immunosuppression. This establishes a self-reinforcing network within the TME, bolstered by crosstalk with M2-like macrophages, CAFs, and chemokine-driven recruitment of suppressive cells [75].

Also, MDSCs inhibit T cell activation and proliferation, promote Treg differentiation, and suppress NK cell activity, contributing to generalized immune suppression within the TME [76]. MDSCs also promote angiogenesis, tumor cell proliferation, and metastasis, facilitating tumor progression and dissemination to distant sites [77]. MSCs can regulate Tregs and MDSCs through several context-dependent mechanisms [78, 79]. Although some experimental conditions have been associated with reduced suppressive activity, MSC-derived factors such as TGF-β and IL-10 can also support Treg-mediated immunosuppression. Similarly, MSC effects on MDSCs vary according to tumor-derived signals and the inflammatory environment. Therefore, MSC-mediated regulation of Tregs and MDSCs should not be considered uniformly anti-tumor [79].

The mechanisms by which stem cells inhibit immune suppression in cancer are complex and context-dependent, requiring further investigation to fully elucidate their intricacies and optimize their therapeutic potential [80]. Understanding these mechanisms is crucial for designing effective stem cell-based immunotherapies that can selectively target Tregs and MDSCs while sparing other immune cells, maximizing anti-tumor immunity and minimizing off-target effects. For instance, oncolytic NDV delivered by MSCs can increase infiltration of $CD11b^{+}Gr1^{+}$ MDSCs, suggesting a modulation of the TME and a potential shift in MDSC function [81]. Additionally, SF2523, a dual PI3K/BRD4 inhibitor, blocks tumor immunosuppression and promotes adaptive immune responses by reducing the infiltration of MDSCs and the polarization of immunosuppressive macrophages, highlighting the potential of targeted therapies to modulate immune cell activity [82] (Figure 1).

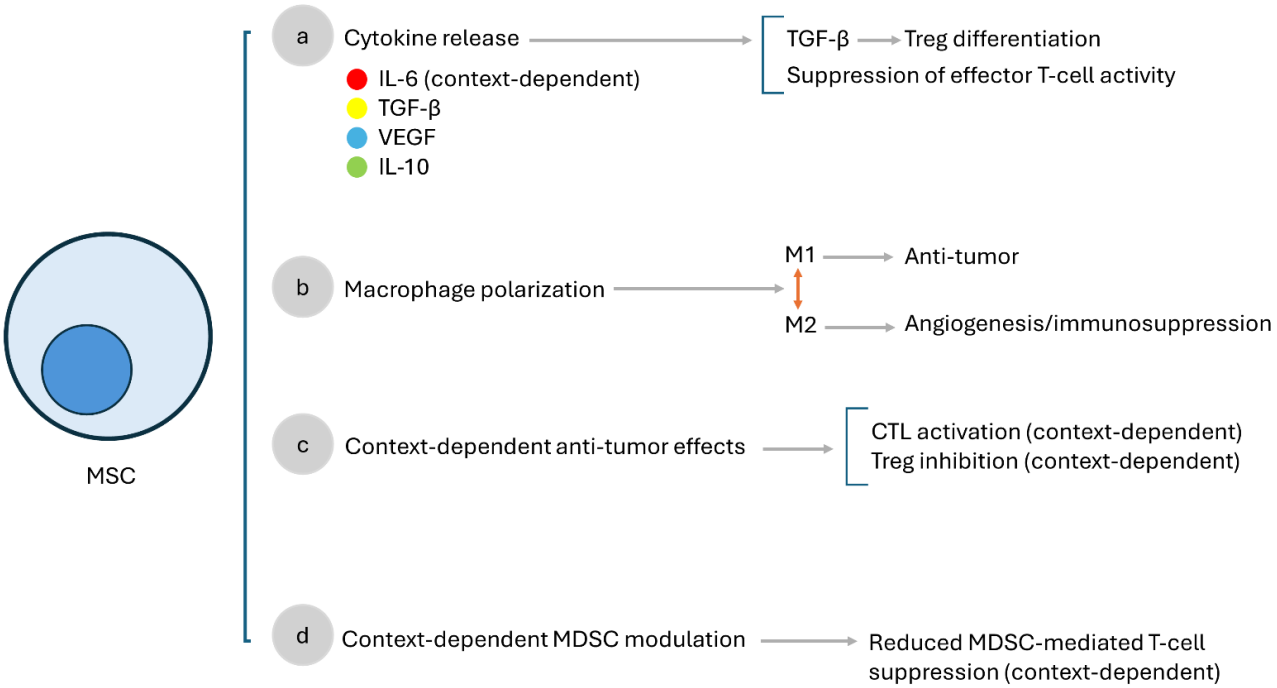

Figure 1 Mechanisms of MSC-mediated immunomodulation in cancer. This schematic illustrates the context-dependent effects of mesenchymal stem cells (MSCs) on immune responses within the tumor microenvironment (TME). (a) Cytokine release: MSCs release interleukin-6 (IL-6), transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), and interleukin-10 (IL-10). The predominant immunoregulatory effects of MSC-derived TGF-β include regulatory T-cell (Treg) differentiation and suppression of effector T-cell activity. IL-6 has context-dependent effects, whereas VEGF promotes angiogenesis and IL-10 contributes to immunosuppression. (b) Macrophage polarization: MSCs influence tumor-associated macrophage (TAM) polarization toward M1-associated anti-tumor activity or M2-associated angiogenesis and immunosuppression. (c) Context-dependent anti-tumor effects: Under specific conditions, MSC-mediated modulation may promote cytotoxic T-lymphocyte (CTL) activation and inhibit Treg activity; these effects are distinct from the predominant immunosuppressive effects of MSC-derived TGF-β. (d) Context-dependent MDSC modulation: MSCs may reduce myeloid-derived suppressor cell (MDSC)-mediated T-cell suppression under specific conditions. Solid arrows indicate activation or differentiation, inhibitory lines indicate suppression, and dashed arrows indicate indirect or context-dependent immunomodulatory effects. Context-dependent effects are additionally identified by explicit labels. Abbreviations: MSC, mesenchymal stem cell; TME, tumor microenvironment; IL, interleukin; TGF-β, transforming growth factor-beta; VEGF, vascular endothelial growth factor; TAM, tumor-associated macrophage; Treg, regulatory T cell; CTL, cytotoxic T lymphocyte; MDSC, myeloid-derived suppressor cell.

4. Types of Stem Cells Enrolled in Cancer Immunomodulation

4.1 Mesenchymal Stem Cells

MSCs are multipotent stromal cells that can differentiate into various cell types, including osteocytes, chondrocytes, and adipocytes, making them valuable for regenerative medicine and tissue engineering [83]. MSCs possess inherent immunomodulatory properties, making them attractive candidates for cell-based therapies in cancer, where they can modulate the immune system to enhance anti-tumor responses [84]. MSCs exert their immunomodulatory effects through diverse mechanisms, including the secretion of cytokines, direct cell-cell interactions with immune cells, and the modulation of immune cell function, creating a complex interplay between MSCs and the immune system [85]. MSCs can secrete immunosuppressive cytokines such as TGF-β and IL-10, which inhibit T cell proliferation and activation, dampening immune responses and promoting immune tolerance [86]. They can also modulate immune cells such as macrophages, NK cells, and DCs, influencing their activity and shaping the immune landscape within the TME [87].

Studies on MSC-based cancer immunotherapy have shown promising results predominantly in preclinical settings, demonstrating their potential to modulate the immune system and enhance anti-tumor responses. MSCs can be used to deliver therapeutic agents directly to tumor sites and modulate the immune system [83]. However, unmodified MSCs may also promote immunosuppression, angiogenesis, and tumor progression in certain tumor microenvironments; therefore, their anti-tumor versus pro-tumor effects depend on MSC origin, phenotype, tumor type, and cytokine exposure [88].

4.2 Hematopoietic Stem Cells

HSCs are multipotent stem cells that give rise to all blood cell types, including immune cells, making them essential for immune system function and reconstitution following damage or disease [89]. HSCs are primarily used in hematopoietic stem cell transplantation (HSCT) to restore the immune system in patients with hematological cancers, such as leukemia and lymphoma, where the patient's own immune system has been compromised by disease or treatment [90]. HSCT represents an established clinical application of stem cells in oncology, unlike many other stem-cell-based immunomodulatory strategies that remain experimental.

The immunotherapy potential of HSCs in hematological cancers lies in their ability to reconstitute the immune system and promote tumor rejection, allowing for the establishment of a new, healthy immune system that can target and eliminate cancer cells [91]. Allogeneic HSCT, where HSCs are derived from a donor, can induce a graft-versus-tumor (GVT) effect, where donor-derived immune cells recognize and kill tumor cells, providing a potent anti-tumor response [92]. HSCs can also be genetically modified to express T-cell receptors (TCRs) or chimeric antigen receptors (CARs) that target tumor-associated antigens, enhancing their ability to recognize and kill cancer cells [93].

4.3 Induced Pluripotent Stem Cells

Induced pluripotent stem cells (iPSCs) are generated from adult somatic cells through reprogramming, a process that reverses their differentiation and returns them to an embryonic stem cell-like state, capable of differentiating into any cell type in the body [94]. iPSCs offer

significant potential for personalized therapies, as they can be derived from a patient's own cells, reducing the risk of immune rejection and enabling patient-specific cell therapies [95].

Emerging research on iPSCs in immunotherapy focuses on their potential to generate immune cells with anti-tumor activity, creating a renewable source of immune cells that can be tailored to target specific cancers [96]. iPSCs can be differentiated into NK cells, T cells, and DCs that can be used to target and kill cancer cells, offering a versatile platform for developing novel immunotherapies [97]. Recent advances in NK-cell expansion, activation, and genetic engineering have further strengthened the potential of stem-cell-derived NK-cell platforms for cancer immunotherapy [98]. However, their clinical application remains under investigation. The mechanisms of immune modulation in cancer therapy using iPSCs are still being investigated, but their potential to generate personalized immune cell therapies holds great promise [96].

4.4 Cancer Stem Cells

CSCs are a subpopulation of tumor cells with stem-like properties that contribute to tumor initiation, progression, and therapeutic resistance, making them a critical target for cancer therapy [99]. CSCs can evade immune detection and elimination, contributing to tumor recurrence and metastasis, highlighting the need for strategies to overcome their immune evasion mechanisms [100].

The role of CSCs in immune evasion and therapeutic resistance has garnered significant attention, improving investigations into their interactions with the immune system and the mechanisms by which they escape immune surveillance [101]. CSCs can express high levels of immune checkpoint molecules, such as PD-L1, which inhibit T cell activation, preventing T cells from effectively targeting and killing cancer cells [102]. They can also secrete factors that suppress immune cell function and promote immune tolerance, creating an immunosuppressive environment that protects them from immune attack [103]. Additional mechanisms include reduced antigen presentation, expression of anti-phagocytic molecules such as CD47, and recruitment or activation of immunosuppressive populations including Tregs, MDSCs, and TAMs. These mechanisms can contribute to persistence of CSCs after treatment and thereby promote recurrence and therapeutic resistance [23].

Targeting CSCs has emerged as a promising strategy for cancer therapy, aiming to eliminate the root of the tumor and prevent recurrence and metastasis [6]. Strategies include developing drugs that specifically target CSCs, using immunotherapies to target CSC-associated antigens, blocking immune-evasion pathways such as PD-1/PD-L1 and CD47 signaling where appropriate, and modulating the TME to reduce CSC-mediated immune suppression. For instance, 4Mu decreases CD47 expression on hepatic cancer stem cells and primes a potent antitumor T cell response induced by IL-12, demonstrating the potential of targeting CSCs to enhance anti-tumor immunity (Figure 2) [104].

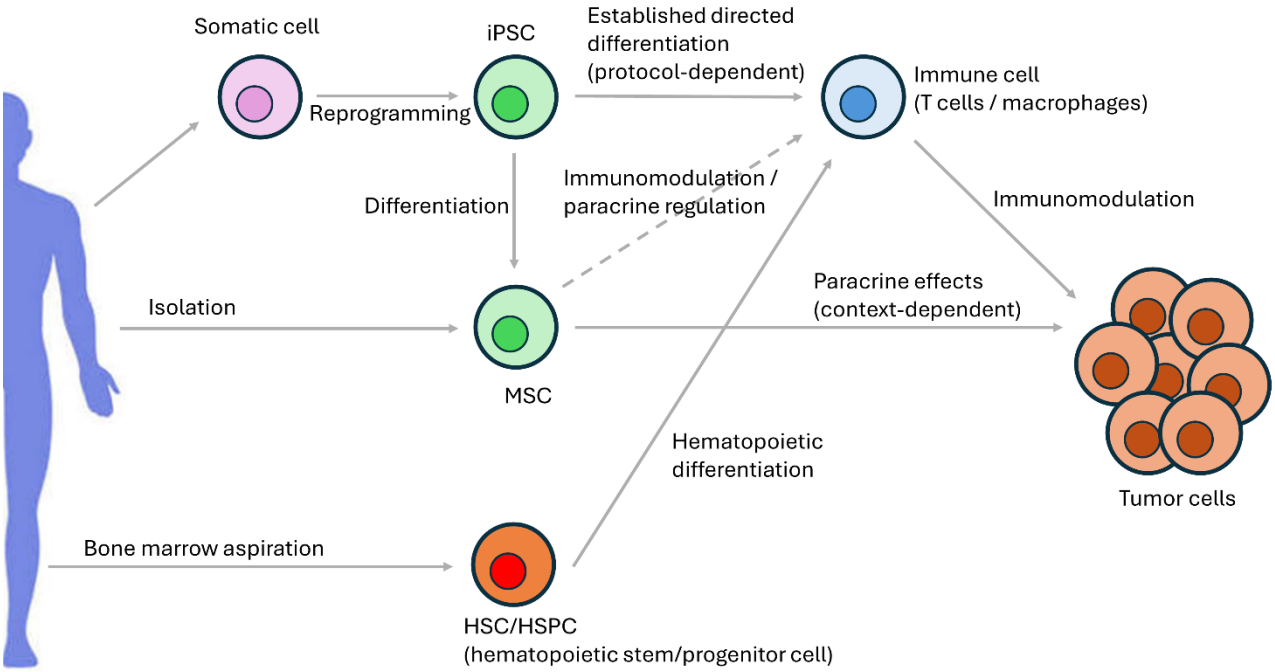

Figure 2 Cellular sources and pathways relevant to cancer immunomodulation. Somatic cells can be isolated and reprogrammed into induced pluripotent stem cells (iPSCs). Through established, protocol-dependent directed differentiation, iPSCs can generate immune cells, including T cells and macrophages, or differentiate into mesenchymal stem cells (MSCs). MSCs can also be isolated directly for potential therapeutic applications. Hematopoietic stem cells (HSCs) and hematopoietic stem/progenitor cells (HSPCs), obtained through bone marrow aspiration, give rise to immune cells through hematopoietic differentiation. MSCs regulate immune cells through immunomodulation and paracrine signaling rather than direct differentiation into T cells or macrophages. MSC-derived paracrine effects on tumor cells are context-dependent, while immune cells influence tumor cells through immune-mediated mechanisms. Solid arrows indicate activation or differentiation, inhibitory lines indicate suppression, and dashed arrows indicate indirect or context-dependent immunomodulatory effects. Solid arrows labeled "Isolation," "Bone marrow aspiration," or "Reprogramming" denote the corresponding procedures; the MSC-to-tumor-cell arrow represents the explicitly labeled context-dependent paracrine effects. Abbreviations: iPSC, induced pluripotent stem cell; MSC, mesenchymal stem cell; HSC, hematopoietic stem cell; HSPC, hematopoietic stem/progenitor cell.

5. Challenges and Limitations

5.1 Tumor Microenvironment and Immune Evasion

The TME critically influences the effectiveness of stem cell-based immunomodulation [105]. The TME is a complex network of cells, including immune cells, fibroblasts, and endothelial cells,along with extracellular matrix components and soluble factors. The TME can promote tumor growth and metastasis by suppressing anti-tumor immune responses and promoting angiogenesis [106]. Immune evasion is a major challenge in cancer therapy. Cancer cells can evade immune detection

and elimination through various mechanisms, including the expression of immune checkpoint molecules, the secretion of immunosuppressive factors, and the recruitment of immunosuppressive cells [107]. The TME can also contribute to immune evasion by creating a physical barrier that prevents stem cells and stem cell-derived immune cells from reaching tumor cells [108].

5.2 Safety and Ethical Concerns

The safety of stem cell-based immunotherapies is a major concern [109]. Potential risks include tumorigenicity or teratoma formation from residual undifferentiated pluripotent cells, unwanted differentiation, immune rejection, transmission of infectious agents, genomic instability after prolonged culture or genetic manipulation, and potential enhancement of tumor growth by some MSC populations. Immune rejection can occur with allogeneic cells, while infectious-agent transmission remains a risk if cells are not properly screened and handled [110]. Long-term safety also remains incompletely defined for many genetically modified or stem-cell-derived therapeutic products.

Ethical issues surrounding stem cell use in cancer therapy include informed consent, patient selection, and the potential for commercial exploitation. Patients must be fully informed about the potential risks and benefits of stem cell therapy before undergoing treatment. Patient selection criteria must be carefully considered to ensure that patients are likely to benefit from stem cell therapy. The commercialization of stem cell therapy must be carefully regulated to prevent exploitation of vulnerable patients [111].

Recent preclinical and clinical development has attempted to reduce these risks through stringent cell characterization, elimination of residual undifferentiated cells, genomic-stability testing, standardized differentiation and purification procedures, sterility testing, controlled dosing, and long-term follow-up. Gene-engineered cell products may also incorporate safety switches to permit elimination of the administered cells if severe toxicity develops [112].

5.3 Regulatory Issues and Standardization

Regulatory challenges in stem cell-based cancer therapies include unclear regulatory guidelines and the need for standardized protocols. Stem cell therapies are often classified as biologics, which require rigorous testing and approval processes. However, the regulatory pathways for stem cell therapies are not always clear, leading to delays in the development and approval of new therapies [113].

Standardization of protocols for stem cell isolation and therapy is essential to ensure the reproducibility and reliability of stem-cell-based approaches. Standardized protocols are needed for stem-cell isolation, culture, characterization, and delivery. Use predefined quality-control criteria to assess cell identity, purity, viability, potency, genomic stability, sterility, and batch-to-batch consistency. Manufacturing processes should also control donor or starting-material selection, culture conditions, passage number, cryopreservation, and, when applicable, genetic modification. These requirements are particularly important for clinical-grade products manufactured under Good Manufacturing Practice conditions [114].

6. Future Directions and Perspectives

Genetic modification of stem cells can enhance their immunomodulatory properties and improve therapeutic efficacy. Stem cells can be engineered to express anti-tumor cytokines, deliver oncolytic viruses, or target cancer stem cells [115]. For example, CAR T-cells can be engineered for adoptive cell therapy of cancer using long-term episomal gene transfer [116].

Combining stem-cell-based approaches with immune checkpoint inhibitors or CAR-based immune-cell therapies has been proposed as a strategy to improve anti-tumor activity. Potential mechanisms include modulating the immunosuppressive TME, improving delivery of therapeutic molecules, and generating stem-cell-derived immune effector cells. However, most evidence for these combinations remains preclinical, and major barriers include limited cell persistence and tumor infiltration, tumor heterogeneity, immunosuppressive cytokines, manufacturing complexity, and safety concerns [117, 118].

Recent developments have also expanded the field toward engineered NK-cell therapies and advanced stem-cell-derived experimental models. NK-cell expansion, activation, and genetic engineering are being investigated to improve persistence and tumor cytotoxicity [119], while stem-cell-derived organoid systems provide increasingly sophisticated models for studying tissue development, disease, and therapeutic responses [98, 120].

Tailoring stem-cell-based therapies to individual patient needs and tumor characteristics may improve therapeutic efficacy and reduce side effects. Personalized approaches may involve selecting the most appropriate cellular platform, genetically modifying cells to target specific tumor antigens, and optimizing their delivery to tumor sites [121]. However, such personalized strategies remain largely investigational and require validation in prospective clinical studies.

7. Conclusion

Stem cells and stem-cell-derived products can exert diverse immunomodulatory effects in cancer, influencing immune cells and the TME. These effects include cytokine secretion, modulation of macrophage polarization, and regulation of T-cell responses, particularly in the case of MSCs. However, these effects are highly context-dependent and may either suppress or promote tumor progression. Hematopoietic stem cell transplantation represents an established clinical application for selected hematological malignancies, whereas most MSC-, iPSC-, and engineered stem-cell-based immunotherapeutic approaches remain experimental or in early clinical development. Major challenges include tumorigenicity, unwanted differentiation, genomic instability, immune rejection, manufacturing variability, and uncertain long-term safety. Future studies should therefore focus on clarifying mechanisms, standardizing manufacturing, rigorously evaluating clinical benefit, and identifying patients most likely to benefit from these approaches.

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Author Contributions

Manal Hadi Ghaffoori Kanaan: conceptualization, supervision, writing – original draft, writing – review & editing; Beom-Jin Lee: conceptualization, investigation, writing – original draft, writing –

review & editing; Sura Saad Abdullah: writing – original draft, investigation; Chulhun Park: writing – review & editing; Abdolmajid Ghasemian: writing – review & editing; Marianne Marianne: writing – review & editing. All the authors critically revised and approved the final version of the manuscript.

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Data Availability Statement

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AI-Assisted Technologies Statement

Artificial intelligence (AI) tools were used solely for basic grammar correction and language refinement in the preparation of this manuscript. Specifically, ChatGPT6.1 was employed to improve the readability and linguistic clarity of the English text. All scientific content, data interpretation, and conclusions were developed independently by the author. The authors have thoroughly reviewed and edited the AI-assisted text to ensure its accuracy and accept full responsibility for the content of the manuscript.

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