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Stem Cell Transplantation for Hematological Malignancies: Prospects for Personalized Medicine and Co-therapy with Mesenchymal Stem Cells

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Abstract

Bone marrow transplantation is a form of cell therapy that has been in practice for decades for the treatment of hematological disorders and solid tumors. Immunosuppressive therapy has been a mainstay for treatment, but the severity of the adverse effects has made it an undesirable choice. Mesenchymal stem cells (MSCs), which reside in the vascular regions of the bone marrow, have been shown to serve as cellular support for the hematopoietic stem cell (HSC) niche. Furthermore, the immune suppressive properties of MSCs have been explored in the treatment of inflammatory and autoimmune disorders. Thus, co-therapy with MSCs has been shown to facilitate engraftment of hematopoietic cells by suppressive graft versus host disease (GvHD). Although the mechanism by which MSCs suppress GvHD is unclear, the experimental evidence suggests that this partly occurs by modulation of immune response such as the induction of regulatory T cells. This paper discusses the role of MSCs as co-therapy for the future of stem cell transplantation, with the overarching theme of personalized medicine for cell-based health interventions.

Keywords

Bone marrow; CXCR4; graft-versus-host disease; hematopoietic niche; mesenchymal stem cells; micro-environment; personalized cell-based therapy; personalized medicine

1. INTRODUCTION

A major treatment modality for hematological disorders and malignancies is bone marrow transplantation, which allows for the restoration of the cellular components of the blood, including monocytes, lymphocytes, basophils, eosinophils, neutrophils, erythrocytes, and thrombocytes [1]. However, a major problem with the use of bone marrow transplant for treatment of hematological disorders is the development of immunological phenomena such as transplant rejection and graft-versus-host disease (GvHD) [2]. GvHD is a reaction in which host-reactive donor T lymphocytes mount a cellular attack against the recipient tissue based on major histocompatibility complex (MHC) mismatch [2]. This leads to potentially severe clinical manifestations involving the skin, liver, and gastrointestinal tract [3].

Typically, this disease is treated with immunosuppressive agents, such as anti-T-cell globulin, tacrolimus, cyclosporine, and methotrexate. The limitation to the use of immunosuppressive agents is evident in that these drugs can be toxic and have significant adverse effects, predisposing patients to infections.

Throughout the past decade, there has been a strong upsurge of interest in the basic biology of mesenchymal stem cells (MSCs). The seminal observations regarding the immunosuppressive properties of MSCs were made in 2002 and 2003, in which these cells were shown to suppress lymphocyte proliferation and act as third-party cells that suppress mixed lymphocyte reactions [4, 5]. Since then, the literature has expanded extensively, and clinical trials involving MSCs have been underway.

In this article, we explore the idea of employing MSC co-therapy along with hematopoietic stem cell (HSC) therapy for bone marrow transplantation and immune reconstitution for hematological disorders. MSC co-therapy may facilitate graft survival of HSC transplant through a variety of immunomodulatory mechanisms, such as induction of regulatory T cells, inhibition of T cell proliferation and dendritic cell maturation, and provision of a supportive niche for HSC engraftment through MSC-derived cellular progeny such as osteoblasts [6]. This idea is highly relevant to personalized medicine because allogeneic and autologous MSC therapy can have patient-specific responses, since cellular therapy varies based on genomic factors from donors and recipients. The host microenvironment is another major determinant of successful therapy, and tailored therapy must be considered based on the varied immune status of different patients. The strengths and drawbacks of MSC co-therapy will be discussed in detail with an emphasis on personalized medicine.

2. BONE MARROW ANATOMY

2.1. Overview

The bone marrow is the sites of hematopoietic activity, forming immune cells, platelets and erythrocytes [7]. The bone marrow exists predominantly in two forms known as red marrow and yellow marrow, based on the color of appearance [8]. Patient age and bone type are two major factors that determine the consistency of the bone marrow. At the time of birth, bone marrow consists mainly of red marrow, but as one ages, the red marrow is replaced by yellow marrow in the long bones, such as the humerus and femur [8] (Fig. 1).

In the case of yellow marrow and red marrow, the former can be identified within the central region of the cavity whereas the latter can be found at the epiphysis of the long bones [8]. The majority of adult red marrow is located within the flat and short bones such as the ribs, pelvic bones, vertebrae and skull. Red marrow consists of connective tissue, blood vessels and numerous cell types [9]. The majority of cells in red marrow are round nucleated cells known as the true marrow cells. Some specific types of cells found in red marrow include erythrocytes, platelets, fibroblasts, and a variety of leukocytes [10]. Yellow marrow also consists of connective tissue and blood vessels. However, unlike in red bone marrow, the cells found in yellow marrow are mostly adipocytes [8]. This suggests that the aging process, which is associated with accumulation of adipose tissue, leads to functional decline in marrow function.

2.2. Hematopoietic Stem Cell Niche

Hematopoiesis is generated from the HSCs, which are self-renewing multipotent cells [11]. HSCs are located in the adult bone marrow of healthy individuals in a specific niche. The idea of a niche was first proposed by Schofield [12]. Niches provide facilitative microenvironments that support HSC self-renewal and differentiation [13]. HSCs are generally located in relatively hypoxic areas of the bone marrow in a region near the

endosteum. The bone marrow is also home to mesenchymal stem cells (MSCs). Although MSCs can also reside within the area of the endosteum, the majority of these stem cells appear to be located at the abluminal side of the central sinus in a relatively hyperoxic area [12]. The co-inhabitation of MSCs and HSCs in the marrow cavity is important because the MSCs give rise to osteoblasts and stroma, which seek residence near the endosteum, where they support the function of HSCs (Fig. 2). Thus, the HSC microenvironment depends in part on the cellular progeny of MSCs.

Two distinct niches have been suggested to support transplanted HSCs in the bone marrow: the perivascular niche, which contains MSCs, and the endosteal niche, which contains osteoblasts [14, 15]. The perivascular niche functions partly through CXCL12 signaling and consists of bone marrow endothelial cells and reticular cells [11]. The HSCs in the perivascular niche are generally active with regards to cell cycling. Within the perivascular niche, endothelial cells support the self-renewal of HSCs and to support hematopoiesis [16]. The osteoblastic niche, on the other hand, acts through cellular adhesion and soluble factors, such as angiopoietin and osteopontin, to regulate HSC functions [17, 18]. The HSCs in the osteoblastic niche are generally quiescent due to physical interactions with osteoblasts [12]. These niches provide critical cues to determine if the HSCs should self-renew to retain pluripotency or to differentiate into progenitors [18]. The niches are not mutually exclusive, as there may be redundant cellular properties in each niche for the regulation of HSC function [15]. For example, CXCL12 expression in osteoblasts could be important in retaining HSCs within the osteoblastic niche and its signaling could be important for regulating HSC functions [19, 20].

HSC functions can be regulated by calcium-dependent cell adhesion molecules known as cadherins. Although it is still unclear how the cadherins support HSC niche, N-cadherin has been shown to be vital to HSC quiescence, maintenance of pluripotency, and self-renewal ability. It also functions in anchoring HSCs and their progenitors in the endosteal region [12]. N-cadherin is involved in bidirectional intercellular interaction between hematopoietic progenitor cells and bone marrow stromal cells [12]. In addition to its role in the lodging of hematopoietic cells, N-cadherin appears to be important in cellular homing to the marrow cavity [12]. The wide array of roles played by N-cadherin places this molecule as an invaluable member of the hematopoietic niche. The marrow microenvironment has been studied in three-dimensional models to understand the migration, differentiation, and self-renewal of HSCs [12, 17]. Myelopoiesis in the bone marrow can also be examined in these models [21]. Currently, there are attempts to study the molecular regulation of these niches [21].

2.3. CXCL12/CXCR4 in Homing and Mobilization

Regulation of the HSC niches involves diverse signaling mechanisms that govern homing and mobilization. Homing refers to the process of entry of peripheral cells into the bone marrow, and mobilization refers to the process of cellular exit from the marrow cavity [17]. Upon leaving bone marrow niches, HSCs can become transient amplifying cells and committed progenitors. The processes of homing and mobilization are tightly controlled in the bone marrow [17]. Injury or stress to the hematopoietic environment can lead to loss of dormancy [22]. Approximately 1-5% of HSCs enter the periphery per day [23]. An important regulatory mechanism of the HSC niche is the interaction between stromal cell-derived factor-1 (SDF-1, CXCL12) and chemokine receptor 4 (CXCR4). This signaling axis elicits intracellular signal transduction pathways involved in cell survival, proliferation, homeostasis, and lymphocyte trafficking [24]. CXCL12 expression is high in the endosteal area, and its interaction with CXCR4 allows for the maintenance of quiescence of HSCs and the recruitment of other inflammatory cells to the bone marrow.

The interaction between CXCL12 and CXCR4 is important because current therapy involving HSCs employs either cell from the bone marrow or from the peripheral blood, in which mobilization first must be achieved [25]. Granulocyte colony stimulating factor (G-CSF) has traditionally been used to mobilize cells into the periphery, but it sometimes fail to induce mobilization in patients [24]. Antagonists to the CXCL12/CXCR4 axis results in stem and progenitor cell mobilization [26]. Pharmacological inhibition with the CXCR4 receptor antagonist, AMD3100, for example, can lead to mobilization of stem cells that can be used in allogeneic and autologous transplants [26]. Small molecule inhibitors of CXCR4, such as BKT140 and plerixafor, have been suggested to be valuable in treatment of cancers [26].

The role of this signaling axis in cancer is significant because many epithelial cancer cells express CXCR4, allowing for homing of malignancies to target organs expressing CXCL12, such as the bone marrow [27, 28]. In cancer cells, CXCL12/CXCR4 signaling resulted in tumor progression, metastasis, angiogenesis and cell survival [24]. Breast cancer cells expressing high levels of CXCR4 have an increased tendency for metastasis to bone [29] (Fig. 2). Preliminary studies from our laboratory have shown that AMD3100 disrupts the interaction between MSCs and breast cancer cells, which has significant implications in breast cancer resurgence from the bone marrow many years after the establishment of dormancy (unpublished data). Personalized genomics comes into play when considering that different patients may have varied levels of CXCL12 production in the bone marrow. Breast cancer cells from patients with high levels of CXCL12 may have high likelihood of distant metastasis to the endosteal region of the bone. CXCL12 secretion by hepatic stellate cells (discussed later) has been shown to facilitate the initiation of colon cancer to the liver [30]. The CXCL12/CXCR4 axis is clinical important because pharmacological antagonism using AMD3100 has been shown to reduce the metastatic tendency of colorectal carcinoma cells [30].

3. CLINICAL CORRELATIONS

3.1. Hematopoietic Stem Cell (HSC) Transplantation

Hematopoietic stem cell transplant (HSCT) is used to replace the immune system of patients with immune dysfunctions, such as hemophagocytic disorders, auto-immune disease, severe combined immune deficiency, and other innate immune defects [31]. Allogeneic stem cell transplant (allo-SCT) involves the transplantation of donor bone marrow from a genetically non-identical human. This type of treatment has been used as a curative therapy for patients with hematological malignancies [31]. The advantage to the use of allo-SCT as compared to conventional chemotherapy is that there is a lower risk for resurgence and increased probability of survival [32]. Allo-SCTs are frequently used to maintain a durable remission of the cancer [32]. It is thought to be the most important therapy for patients with acute lymphocytic leukemia, especially those that are positive for the Philadelphia chromosome, since the rate of relapse is relatively high with chemotherapy [33]. Similarly, allogeneic transplantation is frequently administered in an attempt to cure patients with acute myeloid leukemia, myelodysplastic syndrome, cutaneous T cell lymphoma, Sezary syndrome, and myelofibrosis [32, 34-36]. The allo-SCT can serve to replace host's hematopoietic system, including those with dysplastic cells with healthy HSCs [37]. The outcome of using human leukocyte antigen (HLA)-matched siblings as donors is superior in efficacy as compared to HLA-matched unrelated donors [37]. HLA matching is one of the most important personalized factors that must be considered in order to achieve the best engraftment. However, some degree of mismatch may be beneficial in the graft-versus-tumor phenomenon, which will be discussed later.

Despite the advantages to allo-SCT, there are numerous drawbacks that must be considered. Allo-SCTs have been associated with high morbidity and mortality rates when performed in conjunction with the administration of standard doses of total body irradiation and chemotherapeutic drugs [31]. For example, mortality is approximately 20% to 60% within the first year of treatment [38]. This may be due to the fact that transplant procedures are generally invasive. Co-administration of reduced-dose conditioning with agents such as melphalan, fludarabine, or busulfan has been shown to promote tolerance [35]. Invasive fungal infections can complicate HSC transplantation, resulting in high mortality [36, 39]. Graft-versus-host response in allo-SCTs is generally treated with immunosuppressive agents, which can lead to diverse complications, associated with immune suppression [40]. Since allo-SCT carries significant risks, the decision of whether or not to administer this type of transplant should be carefully considered, based on a patient's remission status, presence or absence of minimal residual disease, patient age, availability of donors, co-morbidities and immune phenotype [32, 33]. Thus, pharmacogenomic compatibility can determine the outcome of bone marrow transplant between individuals.

Autologous stem cell transplant (auto-SCT) involves the re-implantation of the patient's own bone marrow. This form of stem cell therapy has been successful for the treatment of multiple myeloma [38]. The use of adjuvant chemotherapy after auto-SCT for multiple myeloma has been associated with increased in disease-free survival and increased probability of complete remission in comparison to chemotherapy alone [38]. A comparison between allo-SCT and auto-SCT in the treatment of multiple myeloma has revealed advantages and disadvantages of each therapy (Table 1). The use of allo-SCT allows for mounting of a graft-versus-tumor effect to eliminate minimal residual disease. Furthermore, allo-SCT bypasses the possibility of infusing a tumor-replete graft, which would be true for auto-SCT. For these reasons, auto-SCT has a higher relapse rate for disease dissemination [41]. However, the advantage to auto-SCT is that pharmacogenomic compatibility is 100%, since the recipient serves as his/her own source of cells for transplant.

3.2. Graft-versus-Host Disease (GvHD) and Graft-Versus-Tumor Phenomena

Close HLA matching between donor and recipient for allogeneic bone marrow transplantation is important for the prevention of GvHD response in allo-SCT. HLA mismatch causes the donor-derived immune cells to respond to the host's tissue where the host is perceived as foreign [42]. Donor-mediated attack of host tissue could involve multiple systems, such as the gastrointestinal tract, skin and liver [43]. These events are thought to be partly a result of minor histocompatibility antigen mismatch [44]. These minor histocompatibility antigens can be presented as peptides on donor MHC molecules to stimulate donor T lymphocytes [44].

Despite the advantage of close match between the host and donor MHC molecules, some mismatch is desired when the transplantation is indicated for tumors. The desire is to achieve stimulation of the donor immune cells against the tumor cells, *via* graft-versus-tumor effect [45]. Thus, allo-SCT has a therapeutic benefit over autologous transplant for some tumors such as lymphoma and leukemia. The graft-versus-leukemia effect has been shown to improve survival in patients with acute lymphoblastic leukemia [46]. Donor lymphocyte infusion has been given to patients post-transplant for chronic myelogenous leukemia in order to induce graft-versus-leukemia effect [47]. In T cell lymphoma and natural killer (NK) cell lymphoma, the clinical studies have supported the benefit of graft-versus-lymphoma effect [48]. The aforementioned benefits of graft-versus-tumor effect represent only a few examples and do not represent the exhaustive studies on this form of treatment.

Current investigations seek to optimize the balance between graft-versus-host and graft-versus-tumor effect. These studies will likely require an understanding of the basic science that underscores these events. These include but are not limited to an appreciation of the chemokine gradients and cytokine networks that mediate cytotoxicity [40]. Optimization of the balance may involve events at both the cellular and molecular levels, including the role of donor- and host-derived regulatory T cells (T_{regs}) and regulatory natural killer T (NKT) cells [49].

MSCs have been shown to influence the balance between these GvHD and graft-versus-tumor effect [50]. At the cellular level, co-therapy with MSCs may lead to preservation of the cytotoxicity in the graft-versus-tumor effect while diverting the graft-versus-host effect, but the studies are not definitive [50]. These cellular mechanisms involved in optimizing the balance between graft-versus-host disease may not be mutually exclusive, as MSCs have been shown to induce the production T_{regs} (Fig. 3) [51, 52]. These ideas are explored in detail in the next section.

Minimization of the GvHD response remains a continuing challenge in the clinic [44]. The alleviation of graft-versus-host disease may be possible by co-administration of MSCs or hepatic stellate cells, based on the immunomodulatory characteristics of both cell types [53-55]. MSCs have been shown to assist hematopoietic recovery after allogeneic transplant after myeloablation [55]. These cells, when co-cultured with hematopoietic progenitors, can lead to the expansion of hematopoietic colony forming units [56]. MSCs have been suggested for first-line therapy to prevent failure of engraftment after stem cell transplant [56]. Both MSCs and hepatic stellate cells have been shown to reduce T cell proliferation, a critical event in GvDH, while prolonging patient survival [52, 54]. Importantly, third-party MSCs have been shown to suppress acute GvDH after allo-SCT [57]. As third-party cells, the MSCs have exerted veto activity [5]. The veto property of MSCs is highly significant because this is an indication that allogeneic MSCs can be transplanted from off-the-shelf [5, 58]. This bypasses the need for autologous MSCs, which may be difficult to obtain in emergent situations.

MSCs are relatively easy to obtain from bone marrow aspirates and fat tissues, among other sources. However, MSCs can also be derived from inducible pluripotent stem (iPS) cells [5, 59]. This source of inducible cells shows similar instability as embryonic stem cells [59]. In addition, iPS cells appear to retain their memory from the initial differentiated cells thereby making it difficult to generate MSCs [5, 59]. However, if MSCs can be generated safely from iPS, this would be an advantage for autologous transplant. Since MSCs can be transplanted across allogeneic barriers, the expansion from iPS cells remains a question of costly redundancy. Since the field is still in the early stage and we have reported on the re-expression of MHC-II on differentiated MSCs, it cannot be assumed that MSCs cannot be allo-rejected.

Regardless of current confounds, iPS-derived MSCs show promise in the clinic. The iPS-generated MSCs have shown success for limb ischemia [5, 59]. Since iPS cells show similar functions as embryonic stem cells and the latter can form tumor, the safety of iPS-generated MSCs needs to be studied. Based on the discussion in this section, it appears that both MSCs and hepatic stellate cell types may be able to be translated in transplantation medicine in the future, with rigorous experimental studies. A detailed discussion of co-therapy using MSCs in hematological disease follows.

3.3. Mesenchymal Stem Cell (MSC) Therapy in Transplantation for Hematological Malignancies

The delivery of MSCs in the clinical hematology has received attention because of their potential role in graft tolerance of allo-SCT [5, 56, 60]. Recent findings have reported on improved efficiency of hematopoietic engraftment when MSCs were co-transplanted [5, 61]. Although this success might be attributed to a complex mechanism, the following two reasons have been proposed: Firstly, MSCs are the source of osteoblasts, which comprise one of the major HSC niches in the bone marrow near the endosteum [12, 13, 17, 61]. Secondly, MSCs have been well documented to harbor immunosuppressive properties and would therefore facilitate the engraftment of HSCs [62].

Clinical studies on hematopoietic engraftment have followed years of rigorous basic science research demonstrating the immunomodulatory effects of MSCs. A large body of literature has demonstrated that MSCs can inhibit diverse aspects of the immune system, including innate and adaptive immune responses [51]. Among the seminal findings in the field of MSC immunology has been the *in vitro* demonstration of a third-party veto-like effect from allogeneic MSCs [5]. MSCs can inhibit T cell proliferation and induce hyporesponsiveness [63]. Both cellular contact and soluble factors have been proposed to mediate the immunosuppression, yet controversy regarding the mechanisms remains [63, 64].

MSCs have been repeatedly shown to promote graft tolerance and prevent immune-mediated tissue rejection [58, 62]. The mechanisms by which MSCs suppress graft rejection are now beginning to unravel, and current speculation holds that these cells downregulate proinflammatory cytokines while inducing the production of T_{regs} [51, 62, 64]. In an allogeneic heart transplant model, pre-infusion of MSCs *in vivo* resulted in increased semi-allogeneic graft tolerance through increased production of T_{regs} and decreased activation of the Th1 response [50]. Whether MSCs can induce tolerance through T_{regs} in fully allogeneic transplants remains to be determined. MSCs have been shown to reduce T cell proliferation through the production of T_{regs}, which are known sources of the immunosuppressive cytokines IL-10 and TGF- β . These findings have been correlated with reduction in the proinflammatory cytokines TNF- α [65].

Contrary to prior belief, the bone marrow is not the only tissue type whose MSCs have been shown to demonstrate immune-modifying properties. Gingival MSCs, for example, have been shown to induce the expression of immunosuppressive cytokines, such as IL-10, and increase production of the immunomodulatory enzymes indoleamine 2,3-dioxygenase and inducible nitric oxide synthase [66]. MSCs from adipose tissue have been shown to have beneficial anti-inflammatory effects in multiple sclerosis models partly through the induction of a Th2 phenotype [67, 68]. Adipose-derived MSCs have been shown to induce the production of T_{regs} and reduce the expansion of the Th1 subset, allowing for alleviation of inflammatory bowel disease [67, 68].

One of the major factors influencing MSC-mediated immunosuppression is the cytokine IFN- γ . At the molecular level, interferon- γ (IFN- γ) may play a bimodal role in the immunological effects of MSCs. It has been suggested to either suppress or induce graft-versus-host disease while enhancing the graft-versus-leukemia effect based on its anti-tumor properties [61, 68, 69]. The bimodal role of IFN- γ appears to be attributable to its effects on the expression of MHC-II on MSCs. Low levels of IFN- γ lead to upregulation of MHC-II while high levels downregulate MHC class II [70]. Thus, IFN- γ may license MSCs to exert immunosuppressive effects, as IFN- γ receptor I knockout MSCs mice fail to suppress graft-versus-host disease *in vivo* [71]. In gingival tissue, MSCs have been shown to respond to IFN- γ by inducing secretion of immunosuppressive cytokines and proteins [65].

Understanding the interaction between MSCs and IFN- γ is critical because levels of IFN- γ

can fluctuate with varying stages of inflammation, thereby changing the behavior of MSCs on the immune system. Additional cytokines that appear to be involved in licensing, but for which the experimental data is limited, include interleukin-2 (IL-2), tumor necrosis factor- α (TNF- α), and IL-6 [72, 73]. Low doses of IL-10 have been shown to nullify the immunosuppressive effects of the MSCs [72]. Thus, the cytokine milieu is highly important in determining the effects of MSCs [72]. The salient features of MSCs are summarized in Table 2.

Clinical testing regarding MSC therapy has been attempted over the past few years based on the immunosuppressive properties of MSCs. In a study conducted from 2003-2007, MSCs from HLA-identical and haploidentical donors were administered to three patients to prevent transplant rejection and promote HSC engraftment [74]. MSC therapy resulted in rapid engraftment with recovery of neutrophils and platelets in three patients and recovery from aplastic anemia in one patient [74]. In a clinical trial assessing the effects of MSCs in GvHD, MSC infusion alleviated skin, hepatic, and gastrointestinal manifestations in six out of eight patients [75]. In a phase II/III clinical trial for GvHD involving 10 subjects, MSC therapy resulted in complete response in one patient, partial response in six patients, and no response in three patients [76]. Umbilical cord blood-derived MSCs have shown safety and efficacy in acute GvHD [77]. A limitation to these clinical trials involving the use of MSC therapy is the relatively low sample size. Currently, there are a limited number of clinical trials underway regarding MSC co-therapy for HSC transplant (www.clinicaltrials.gov). One trial is studying the safety and efficacy of MSCs derived from umbilical cord blood. These cells are speculated to promote engraftment of unrelated HSCs in patients with acute leukemia. Other trials include MSC infusion therapy for the treatment of steroid-resistant GvHD.

4. CONFOUNDS OF MSC THERAPY IN UNDIAGNOSED SOLID TUMORS

Although there are numerous benefits to the use of MSCs as co-therapy with bone marrow transplantation, MSCs have been shown to favor the progression of cancers [78-80]. Most of the reports on this role have been studied with solid tumors [81]. This role of MSCs is an important consideration when MSCs are planned as co-therapy in the clinic. It is possible that the transplanted MSCs may serve as a nidus for undiagnosed cancer or cancer in the remission phase. The evidence that MSCs can support cancer progression is two-fold: Firstly, MSCs can interact with and maintain solid tumors [78, 79]. Secondly, the MSCs can undergo cell transformation [82, 83]. However, transformation of MSCs is an unlikely scenario.

4.1. MSC-Cancer Cell Interactions

MSCs and breast cancer cells have been shown to migrate and interact with each other [52]. Tumor immunology studies have recently shown that MSCs could promote the dormancy of breast cancer by inducing an increase in T_{regs} and suppression of cytotoxic activity by immune cells [52, 84]. Since MSCs are in large part found in bone marrow, their oncoprotective role might explain why many solid tumors can remain latent in the bone marrow and evade clinical detection and serve as a source for future cancer resurgence. A major player in immune subversion by MSCs is linked to the functions of MSC-derived TGF- β [52]. This cytokine has been shown to significantly increase T_{regs} in the presence of breast cancer cells. This could lead to the decrease of pro-immune responses to target cancer cells [52]. TGF- β signaling is critical in the polarization of immune responses such that NK and other effector cell activity is diverted, allowing for tumor maintenance [85].

Aside from the role of bone marrow-derived MSC-mediated cancer maintenance *via* T_{reg} induction, MSCs have been shown to promote tumor growth by their conversion into

carcinoma-associated fibroblasts [81]. While normal fibroblasts have been implicated in the suppression of cancer progression, mutated fibroblasts that are presumably derived from MSCs have been shown to provide cellular support for cancer growth [86]. Secretion of CXCL12 by carcinoma-associated fibroblasts has been implicated in breast cancer progression, based on the idea that CXCL12 can recruit endothelial precursors and increase cancer cell proliferation [81]. These cells are one component of the heterogeneous population of cells found in the tumor microenvironment, which consists of endothelial cells, epithelial cells, adipocytes, monocytes, and macrophages [87, 88]. Fibroblasts of the tumor stroma have been shown to increase the proportion of a stem-like subset of breast cancer cells and enhance the formation of tumorsphere-like structure [89, 90]. Targeted therapy against carcinoma-associated fibroblasts and MSCs may be a valuable therapeutic avenue in cancer, based on their diverse roles in progression of cancer [90]. However, scientists should be cautioned considering the heterogeneity of fibroblast populations, since some elements of the stroma can promote cancer growth while others can suppress growth [86]. Taken together, the diversity of interactions between MSCs and solid tumors makes the behavior of solid tumors somewhat unpredictable.

4.2. Transformation of MSCs

In addition to the role of MSCs in supporting cancer growth, MSCs themselves can become targets of transformation. For instance, MSCs can undergo sarcomatous transformation in the retroperitoneum and other regions of the body [91]. They have been suspected to serve as the cell of origin for malignant fibrous histiocytoma and for mesothelioma of the pleura [82, 83]. The clinical significance of these findings is that transplanted MSCs can directly lead to new cancers if they become targeted by oncogenic insults.

In summary, these findings point to the importance of the tumor microenvironment, especially bone marrow-derived MSCs, in the maintenance of solid malignancies. The local cytokine milieu, which can be a product of both the host microenvironment or of the malignant cells, serves to maintain cancer and eventually lead to its progression [88]. The cytokines that are frequently implicated in cancer progression include CXCL12, TGF- β , VEGF, and members of the matrix metalloproteinase family, and these may serve as targets for exploration [88]. The co-evolution of host stroma and the malignant epithelium is an area that is not well understood, but its significance merits further research.

CONCLUSIONS AND OUTLOOK

Personalized Medicine for Stem Cell Based Health Interventions

Since bone marrow transplant is an invasive procedure, alternatives to such transplant have been considered. *Ex vivo* correction of genetic deficiencies in autologous stem cells may hold the cure to diseases such as severe combined immune deficiency [92]. For example, retroviral vectors harboring a functional copy of adenosine deaminase may lead to functional improvement [92]. The use of *ex vivo* correction in HSCs may preclude the need for enzyme replacement therapy or allogeneic bone marrow transplant, which is the current modality of treatment and can be complicated by rejection [92, 93]. In summary, with regards to HSC transplantation, despite the clinical success for hematological disorders, this area of translational medicine requires research to improve and to optimize these procedures.

Co-therapy of HSC transplantation with MSCs offers a promising method to enhance the effectiveness of the transplant. The rationale is to use MSCs to suppress GvHD. The major problem with such indication with MSCs is the dual immune effects of MSCs: stimulator and suppressor effects.

The delivery of MSCs to patients will depend on the underlying condition of a patient. This section provides examples to demonstrate how personalized application of stem cells can be effective in cell therapy. MSCs express receptors for inflammatory mediators [94]. The functions of MSCs as immune suppressors must be a focus in cell therapy. The particular response of MSCs in a host will depend on the microenvironment. Therefore, it would be appropriate to first ask what is required from the transplanted MSCs and then 'adjust' the microenvironment to induce the MSCs to function as expected. This brings up a role for other drugs as adjuvant to stem cell therapy. Although there is several biotechnology companies involved in stem cell therapy, the translation of stem cell therapy to the clinic will be slow unless these companies partner with large pharmaceutical companies. The latter have a large library of compounds, perhaps those that failed for particular trials, and these compounds may be indicated for combined drug-cell therapy.

In order to circumvent the dual immune effects of MSCs, perhaps in-depth studies should evaluate the detailed hierarchy of MSCs. This would lead to the implantation of partially differentiated cells that harbor the immaturity of the stem cells. It is likely that this might also circumvent the fear of tumor formation by MSCs. Although rare, there are reports of transformation by MSCs [91]. This brings up the question of robust studies to understand transformation of MSCs in experimental models.

In addition to endogenous transformation of MSCs, these stem cells can also support tumor growth. Since HSC transplantation is generally indicated for older patients, it is difficult to determine if a potential recipient of MSCs could have an undiagnosed cancer. However, in cases where a patient might be in remission for a solid tumor, caution will have to be taken in decision of using MSCs for GvHD. As the science progress for biomarkers of tumors, this would make it safer to determine who could be a recipient of MSCs.

It is difficult to discuss MSCs in HSC transplantation without addressing the literature on MSCs in aging individuals. The literature suggests that MSCs might be dysfunctional in patients with hematological disorders. Since HSC transplantation is indicated for the same patients, the literature on MSCs, regardless if the outcome seems negative for GvHD, needs to be examined for benefit to the disorders. MSCs and/or HSCs treatment should be examined on a personalized basis, based on the patient's clinical history. The science is available for investigator initiative trials to personalized cell therapy for patients with hematological disorders. This might not require HSCs but perhaps MSCs alone and in combination with other drug treatment in a personalized method.

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ABBREVIATIONS

BM	Bone marrow
CXCL12	Chemokine ligand 12
CXCR4	Chemokine receptor 4
G-CSF	Granulocyte colony stimulating factor
GvHD	Graft versus Host Disease
HLA	Human leukocyte antigen

HSC	Hematopoietic stem cell
HSCT	Hematopoietic stem cell transplant
HSPC	Hematopoietic stem/progenitor cells
IDO	Indoleamine 2,3-dioxygenase
IFN-γ	Interferon- γ
IL	Interleukin
iNOS	Inducible nitric oxide synthase
iPS	Inducible pluripotent stem
MHC	Major histocompatibility complex
MSC	Mesenchymal stem cell
NK	Natural killer
SCT	Stem cell transplant
SDF-1	Stromal cell-derived factor-1
TGF-β	Transforming growth factor- β
Th	T helper
TNF-α	Tumor necrosis factor- α
T_{regs}	Regulatory T cells
VEGF	Vascular endothelial growth factor

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Fig. (1).

Human bone marrow at birth consists predominantly of red marrow, with high numbers of cells of myeloid lineages. Throughout the aging process, yellow marrow accumulates in the hollow portion due to increased numbers of adipocytes. This leads to reduction in bone marrow function, perhaps accounting for the increased incidence of hematological disease with increasing age [8].

Fig. (2).

Cross section of the bone marrow to depict the relative location of mesenchymal stem cell (MSC) and hematopoietic stem cell (HSC) niche. MSCs are located in the perivascular region and differentiate into osteoblasts, which provide a supporting microenvironment for the HSC niche. The HSC niche is near the endosteal area in a region of high levels of CXCL12. After interacting with MSCs, breast cancer cells (BCCs) can migrate towards the endosteum and engage in CXCL12/CXCR4 signaling to potentially establish dormancy in the bone marrow [28-30].

Fig. (3).

Mesenchymal stem cells (MSCs) surround the bone marrow vasculature and have important implications in the alleviation of graft-versus-host disease. The proposed mechanisms for immunomodulation partly involve MSC-derived TGF- β , which leads to induction of regulatory T cells (T_{regs}), thereby promoting graft tolerance and protection of breast cancer cells (BCCs), indicated by the asterisk (*). Clinical trials involving MSC therapy for graft-versus-host disease are currently underway. GvHD, graft-versus-host disease [53, 70].

Table 1

Comparison and Contrast of Allogeneic and Autologous Bone Marrow Transplantation

Allogeneic stem cell transplant *		Autologous stem cell transplant *	
<i>Advantages</i>	<i>Disadvantages</i>	<i>Advantages</i>	<i>Disadvantages</i>
Graft-versus-tumor/leukemia effect	Graft-versus-host disease	Lack of graft-versus-host disease	No graft-versus-tumor/leukemia effect
Elimination of minimal residual disease	Potential rejection of transplanted cells	No rejection of transplanted cells	Healthy cells must be harvested prior to disease onset
	Limited availability of HLA-matched donors	No need to find donors	

* See also the following references [41-43, 53].

Table 2**Salient Features of MSCs When Considering Co-therapy with HSCs**

Feature	Relevance to Transplant	Reference
Third party veto-like effect in mixed lymphocyte reaction	Potential for “off-the-shelf” therapy during times of immediate necessity	[5]
Inhibition of T cell proliferation and induction of hyporesponsiveness	Inhibition of donor lymphocyte response against recipient's cells	[64]
Induction of regulatory T cells	Enhanced graft survival by preventing rejection	[52, 53]
Induction of iNOS and IDO	Increase local concentration of immunosuppressive soluble mediators	[67]
Induction of Th2 phenotype	Suppression of Th1 cytokines that could lead to rejection	[53, 68, 69]
Expression of low levels of MHC-II	Possibility of rejection due to recognition of foreign graft tissue	[71]
Differentiation into osteoblasts	Provision of microenvironmental and cellular support for HSC transplant	[13, 17]
IFN- γ -regulated MHC-II presentation	Precise tailoring of immunosuppressive vs. immunostimulatory potential based on local inflammatory milieu (high vs. low levels of IFN- γ)	[71]
Interaction with cancer cells	Facilitation of tumor growth and survival in the bone marrow	[82, 87]

Mesenchymal stem cells (MSCs) harbor a variety of salient characteristics that make them suitable for co-therapy with hematopoietic stem cells (HSCs). The most significant discoveries on MSC biology in the recent years concern their pan-suppressive effects on the immune system, facilitating engraftment and preventing immune-mediated rejection. However, MSCs can also serve as antigen presenting cells in the presence of low levels of IFN- γ . Additional features include the differentiation into osteoblasts, which are supportive cells for HSCs in the endosteal regions of the bone marrow. iNOS = inducible nitric oxide synthase; IDO = indoleamine 2,3-dioxygenase.