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Immune Privilege Signatures of Embryonic and Adult Stem Cells

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Abstract

Tissues homeostasis depends on the presence of healthy adult stem cells present in bone marrow, blood or organs. Failure of this homeostasis due to pathological insults results in tissue dysfunction and diseases. Given the pluripotent and multi-potent features of embryonic and adult stem cells, respectively, they have been utilized for replacement and regenerative medicine. Additionally, the immune regulatory features possessed by adult stem cells including Hematopoietic Stem Cells (HSCs) and Mesenchymal Stem Cells (MSCs) make them a potential therapeutic approach for several diseases. However, stem cells in their own niche and upon their mobilization or transplantation need to create an immune privilege niche to protect them from the de facto defense mechanisms of the immune system for destruction. In this review article, we shed a light on both the intrinsic and extrinsic mechanisms that shape the overall immune privilege signature of embryonic and adult stem cells. Understanding the individual and combinatorial roles of these mechanisms would allow for a better application of stem cell biology in different clinical settings.

Keywords: Antigen presentation; Hematopoietic stem cells; Embryonic stem cells; Immune privilege niche; Mesenchymal stem cells; PD-1; TLR.

Introduction

Immune cells are educated to discriminate self from non-self, certain compartments in the body such as the testis, hair follicle and placenta developed additional mechanisms including physical, cellular and molecular barriers to protect themselves from the attack of immune cells through creation of immune-suppressive environments called immune-privileged sites [1]. Human and Mouse Stem Cells (hESCs and mESC, respectively) are capable of unlimited division, renewal, proliferation and specialization to specific cell types [2,3]. As such, they also need to possess an immune privilege features to protect themselves from the attack by immune cells [4,5]. This immune privilege feature of stem cells is controlled by cellular and molecular intrinsic mechanisms instructed in stem cells and extrinsic ones by the surrounded microenvironment in which they reside in.

The overall immune privilege signature of stem cells is critical not only for their homeostatic renewal and mobilization but also for their successful transplantation into syngenic, allogenic or xenogenic hosts for terminal differentiation without the risk of rejection. This-immune privilege feature has been suggested to be relative not absolute [4], so that under certain condition stem cells can acquire or fail immune privilege feature in their niche [6]. Therefore, any failure in this protection due to accidental or pathological dysfunction will impact the regenerative capacity of stem cells [7] and lead to diseases. In this chapter, we highlight the potential intrinsic and extrinsic mechanisms developed to give rise to immune privilege signature to stem cells. We will focus on embryonic and adult stem cells.

Embryonic stem cells (ESCs)

The pluripotent and self-renewing capacity of ESCs makes them an ideal source to generate multiple tissues for regenerative therapies [8]. Because ESCs are derived from the inner cell mass of pre-implantation-stage blastocysts, they may resemble the early embryo in terms of their intrinsic capacity for immune privilege. However, they have no in vivo counterpart in an adult organism, and hence they have no niche to which they could naturally home when transplanted into an adult recipient [9]. As such, ESCs are suggested to possess immune privileged signature in their native location but with the possibility to be recognized by the host immune cells. Therefore, the dilemma in ESC-based therapy is that lower immunogenicity of ESCs will lead to uncontrolled teratoma growth, while their immunogenicity will prevent teratoma formation but will lead to graft rejection. How to reach a balance between immunogenicity and teratoma formation is a challenge.

The phenotype of ESCs makes their immune privileged state controversial. For instance, injection of undifferentiated and differentiated hESCs into immune-competent mice did not induce an immune response and failed to stimulate proliferation of allo-reactive T cells and allogeneic DC-mediated T-cell proliferation [10]. By contrast, other studies showed that hESCs are rapidly rejected following injection into immune competent mice [11,12], where subsequent transplantation of additional hESC accelerated the rejection. This ESC rejection, however, were delayed when immunosuppressive therapies were used or when upon transplantation into immune deficient hosts [13]. Indeed, detailed studies revealed that rather than being ignored or not recognized ESCs actively inhibit T-cell responses and evade the effector functions of CTLs via suppression of the maturation of DCs and T-cell proliferation [14]. Although the precise mechanisms by which ESCs inhibit immune activation remain mostly unknown, several potential mechanisms can be postulated.

Intrinsic factors

Antigen presentation molecules

ESCs possess certain features that make them weak Antigen Presenting Cells (APCs). hESCs and mouse Embryonic Stem Cells (mESCs) express low levels of MHC class I molecules and almost no MHC class II, indicated that they have limited direct presentation of antigen to the recipient immune cells [15]. Also, ESCs are derived from pre-implantation embryos, which are usually not rejected by the maternal immune system despite being true semi-allogeneic implants with half of their proteins being foreign paternal antigens [16]. Mohib et al. (2012) suggested that ESC-derived factors can inhibit activation and antigen presentation of dendritic cells [17] which can explain why mESCs and hESCs are not lysed by peptide-specific CD8 CTLs even after their up-regulation of MHC class I by IFN- γ [18].

On the other hand, when professional APCs, in particular DCs, in the recipients pick up antigens from ESC-derived tissues and present it to T cells they are recognized as foreign and rejected. Further, ESCs are very likely to express minor histocompatibility and mitochondrial antigens, both of which can induce immune rejection, albeit on a somewhat delayed timeline [19]. Earlier in vitro studies showed that ESCs express lymphocyte B7-1 co-stimulatory molecules with negligible expression level of B7-2 and CTLA-4 and CD28. However, upon their differentiation into embryoid bodies they expressed B7-1, B7-2, and CD28 with undetectable level of CTLA-4 [20], indicating that ESCs might offer antigen presentation to T cells. In addition, lacking MHC-I expression by ESCs render them susceptible to NK cell killing [4], explaining why Hematopoietic Progenitor Cells (HPCs) derived from mESCs fail to engraft in the presence of NK cells. This would suggest that NK form a formidable barrier to the privilege state of ESC-derived cells [21]. Although these data indicate that ESCs expressing no or low levels of MHC class I molecules are ideal targets for NK cells, both hESCs and mESC linesare not killed by NK cells in vitro, indicating that the susceptibility of ESCs and their derived cells and tissues to NK cells might be different [22].

TLR signaling pathways

TLRs are one of a family of pattern recognition receptors that can recognize and respond to ligands from damaged cells, Damage-Associated Molecular Patterns (DAMPs) or pathogen-associated molecular patterns. Triggering of TLR signaling pathways after binding to specific agonists can induce inflammatory responses [23]. ESCs express low levels of TLRs while differentiated ESCs express higher levels which increase over time in culture. However, both did not respond to a range of PAMPs, with the exception of TLR5 [24].

Similar to ESCs, the mESC lines R1, CGR8, and E14 showed mRNA expression of TLRs 1,2,3,5, and 6, but not TLRs 4, 7, 8, and 9, and high level of the protein expression of TLR2. When TLR2 was ligated by its specific agonist Pam (3) Cys, it enhanced proliferation and survival of the three cell lines coincided with induced NF-kappa B translocation, enhanced phosphorylation of IKK-α/β, and enhanced expression of TNF- α, IFN-γ, and IL-6. These effects were abrogated after blocking of TLR2 [25]. Other studies reported that both ESCs and ESC derivatives can sense and respond to microbial stimulation through both TLR3 and TLR4 [26].

Given that ESC-derived progenitors used in replacement therapy are possible to be exposed to PAMPs or inherent danger signals associated with tissue damage/injury, failure of ESCs to respond to TLR agonist may limit their rejection mediated by innate and adaptive immune mechanisms. Therefore, it is of great importance to understand the full expression and signaling pathways of all known TLRs in both ESCs and ESC-derived progenitors and tissues.

micRNAs pathways

micRNAs are small non-coding RNAs, usually 21-25 nucleotides long, present in a wide variety of organisms and able to regulate gene expression by targeting messenger RNAs (mRNAs), resulting in repression of translation and/or degradation of the targeted molecule, either of which leads eventually to gene silencing [27]. Recent studies elucidated the role of miRNAs in the modulation of the biological function of ESCs. Overall, the transcriptional regulation of ESC differentiation has been associated with changes in the miRNA expression profile [28], where deletion of the gene encoding for Dicer (Dicer1) in ESCs resulted in morphological abnormalities in the early stages of development and embryonic lethality [29].

These Dicer1-deficinet ESCs failed to generate detectable teratomas upon subcutaneous injection into nude mice, and did not express any of the most common differentiation markers such as T-Brachyury, Gata1, Bmp4 and Hnf4 [30]. These ESCs also showed reduction in DNA methylation [30], which was rescued by transfection of the miR-290 cluster, indicating to the importance of the epigenetic mechanisms in the impact

of micRNA on ESCs. Moreover, ESCs deficient for DGCR8, which encodes for an essential component of the nuclear microprocessor complex [31], lacked micRNA expression and showed impairment in their ability to express differentiation markers, in particular Fgf5, and a block in the G1-S transition and developed into undifferentiated teratoma after their injection it into immune compromised mice [31].

These studies indicate that miRNAs are critical for the programmed differentiation of ESCs. As such, alteration in the micRNA profiling in ESCs would bring about significant changes in their intrinsic properties and the immune privilege niche.

Soluble factors

ESCs have the capacity to produce cytokines and enzymes known to be involved in immune suppression that can turn immunogenic ESC-derived tissues into immune privilege microenvironment and the induction of tolerance. ESC-derived factors directly affect T cell activation and proliferation by markedly increasing the levels of IL-10, TGF-β while decreasing the expression levels IL-2 and IFN-γ [17]. In this regard, ESC differentiation into embyroid bodies in vitro induced them to express TGF-β2 which was further up-regulated after their long-term survival in vivo [32].

Similar to ESCs, MSCs derived from human ESCs inhibited T-cell proliferation and NK-cell-mediated cytotoxicity [33] through secreting soluble factors which also suppressed T cells proliferation and expression of IL-6, IFN-γ and TNF-α. The ESC-derived tissues have also express high levels of the anti-inflammatory cytokines IL-10 and TGFβ1 and β2 [34]. Further, rejection of ESCs when injected into mouse muscle [5,13] was due to the failure of ESCs to express classic immune-privileged factors such as TGF-β, FasL or IL-10 [35]. Besides, ESCs also express specific inhibitors of both perforin and granzyme B, i.e., cathepsin B and serine protease inhibitor (serpin or SPI-6), respectively, where knockdown of SPI-6 by shRNA fully restored the susceptibility of mESC to lysis by CD8 CTLs [7]. Thus, ESCs can counteract the cytotoxic effector molecules of both CD8+ CTL and NK cells. Production of these suppressor factors by ESCs and ESC-derived progenitors/tissues under certain conditions would explain some mechanisms contributing to the immune privilege of these cells.

Indoleamine-pyrrole 2,3-Dioxygenase (IDO) is an intracellular enzyme that catabolizes the essential amino acid tryptophan. Its role in establishment of immune privilege was first described in pregnancy of mouse models, where inhibition of its enzymatic activity resulted in loss of allogeneic embryos [36]. Interestingly, the ESC-derived tissues showed high expression levels of IDO and arginase 1 and 2, all of which are known to foster immune privilege by virtue of their capacity to deplete the essential amino acids tryptophan and arginine from the local microenvironment [37].

Additionally, ESCs suppressed cytokine production by T cells and their proliferation through an arginase I-dependent mechanism [38], which in turn might limit T-cell infiltration and subsequent graft destruction. Given that ESCs may require high amount of arginine and tryptophan for their proliferation and differentiation, the intrinsic up-regulation of IDO by these cells may also impact their differentiation.

Extrinsic factors

Treg cells

The mechanisms of the tendency of ESCs and its derivatives to immune tolerance have been suggested to involve interplay between ESCs and DCs and Treg cells to induce antigen-specific tolerance [39]. For instance, ESCs and ESC-derived factors directly affect T cell activation and proliferation by promotion of Treg cells (Foxp3+CD4+ CD25+) [17].

Further, fully allogeneic ESC-derived tissues were accepted across a class I MHC disparity by applying with a regimen of co-receptor blockade. In this setting, TGF-β-mediated expansion of Treg cells appeared to be essential for this natural "privileged" state as their ablation with an anti-CD25 mAb results in rejection of ESC-derived tissue [40]. Moreover, ESC tolerance can be established by blocking of CD4 [41] and CD154 [42] through induction of antigen-specific expansion of Tregs with coincided increased levels of TGF-β. Under this setting, approximately 10% of infiltrating T cells in the surviving embryonic bodies was found to be FoxP3+ cells, where depletion of Treg cells abrogated the survival of embryonic bodies [42].

Further, adoptive transfer of genetically modified ESC-derived DCs induced protection from myeline-induced experimental autoimmune encephalomyelitis associated with increased numbers of Foxp3+ cells in the spinal cords; the effect diminished when Treg cells were depleted [43]. Taken together, these studies suggest that infiltrating T cells become polarized towards a regulatory phenotype within this privileged microenvironment.

Macrophages

The role of macrophages in ESC growth and teratoma development is not clear. On study showed that interaction between transplanted ESCs and macrophages creates a microenvironment that facilitates the initiation and progression of teratomas [44]. The infiltrated macrophages deliver macrophage Migration Inhibitory Factor (MIF) and other angiogenic factors to stimulate endothelial cell proliferation and pericyte differentiation [44]. In a recent study, ESCs were found to promote survival and function of host macrophage [45].

Specifically, this study showed that implantation of syngenic ESCs induced rapid recruitment of BM-derived macrophages with more phagocytic activity and prolonged survival but reduced apoptosis. These effects were associated with high secreted levels of IL-34 and involved activation of ERK1/2 and PI3K/Akt pathways. Most importantly, ESCs induced polarization of macrophages into M2-type with production of high levels of arginase-1, Tie-2, and TNF-α, which participated in angiogenesis and teratoma progression. Not only ESCs but also their conditioned medium, which contained several cytokines, chemokines and growth factors, enhanced survival of normal murine BM myeloid progenitors [46]. Besides ESCs, co-culture of hESC-derived neural stem cells with monocyte during HC-CSF/IL-4-induced their differentiation into DCs resulted in down-regulation of CD14 and the maturation marker CD83 as well as the functional capacity of DCs to stimulate alloreactive T cells [47].

Similarly, injection of embryoid bodies from hESCs after cecal ligation and puncture significantly induced reduction in the lung

inflammation as well as TNF- α and IFN-γ production by the inflamed lungs through inhibition of lung resident cells to express inducible macrophage-type NO synthase activation in CD11b+ cells [48]. Taken together, these studies indicate the critical role of M2 phenotype in teratoma formation. As such, strategies that can target these cells would inhibit teratoma development and increase the safety of ESC-based therapies. This is likely possible since M2 macrophages have been found to promote tumorigenesis and that the tumor microenvironment polarizes macrophages toward an M2 type [49].

Adult stem cell

Bone Marrow (BM) is a unique microenvironment which harbors two subsets of adult stem cells, including Hematopoietic Stem Cells (HSCs) and Mesenchymal Stem Cells (MSCs). HSCs differentiate into all lymphoid and myeloid lineages while MSCs differentiate into other types of tissue specific cells. HSCs, which give rise to all blood cells and their progenies, including immune cells are controlled by special microenvironments, termed niches in the BM during homeostasis and infection [50].

HSCs

HSCs express high levels of the cell surface glycoprotein CD34, which is often downregulated upon their differentiation. $CD34^+$ cells are capable of initiating long-term hematopoiesis both in vitro and in vivo and have the unique ability to self-renew, differentiate into multiple lineages, and withstand stress signals to survive and function [51]. In the BM, HSCs are maintained in a quiescent state by their surrounding microenvironment (extrinsic factors) as well as by their built-in (intrinsic) regulatory molecules [3,52,53].

This niche provides the appropriate support for maintaining self-renewal and multi-lineage differentiation capacity of HSCs and protects them from environmental insults such as cytotoxic chemotherapy and pathogenic immunity [54]. As such, induced dysfunction in this niche would contribute to pathological environment such as inflammation and cancer [55]. Indeed, recent evidence suggests that HSCs are immune privileged within the in vivo BM niche through different intrinsic and extrinsic factors.

Intrinsic factors governing the immune privilege of HSC

Antigen presentation molecules

Earlier studies showed that CD34+ HSCs co-expressed HLA-DR and HLA-DP and HLA-DQ. In the presence of IL-3, the expression of CD34 and class II MHC antigens was found to be gradually lost in culture. Interestingly, these cells became CD34-, HLA-DR+ blast cells after 8 days of culture and expressed low levels of HLA-DR (HLA-DRlo) after ten days of culture in IL-3, indicating that HSCs are elastic for MHC expression which can be up- or down-regulated based on their microenvironment [56].

Cord blood-stem cells also expressed a very low level of MHC antigens and fail to stimulate the proliferation of allogeneic lymphocytes [57]. mESC- derived HSC poorly express MHC class I antigens but are responsive to stimulation by IFN-γ and other cytokines. However, despite up-regulating MHC class I antigens after stimulation, they do not express class II molecules, a consequence of their lack of expression of the critical class II transcription factor CIITA [58]. Additionally, however, ex vivo expanded mHSCs were found to be efficient to overcome the MHC barrier and as a result repopulated allogeneic-recipient mice [59]. In vivo studies, however, showed that transplantation of purified allogeneic HSCs, although there was diminished risk of Graft-Versus-Host Disease (GVHD), result in decreased engraftment. The underlying reason may be because of their expression of MHC molecules.Thus, although HSCs express low levels of MHC molecules they have the tendency to up-regulate it under inflammatory conditions.

TLR3 signaling pathways

Recent studies have implicated TLR signaling in the proliferation and differentiation of hematopoietic CD34+ cells [60]. With this regard, human and mouse BM HSCs expressed functional TLRs, including TLR1, TLR2, TLR3, TLR4, TLR7, TLR8, TLR9, as well as associated signaling adaptor molecules MyD88 and Toll/IL-1R domain-containing adaptor-inducing IFN-β adaptor molecules [61-63] TLR 7/8 and TLR9 signaling pathways in human BM HSCs stimulated these cells to produce inflammatory cytokines including IL1-β, IL6, IL8,TNF-α, GM-CSF (and induced their differentiation into macrophages and monocytic DC precursors characterized by the expression of CD13, CD14 and/or CD11c markers [64-66].

In vivo studies showed that endotoxin treatment, infection by Staphylococcus aureus or cecal ligation and puncture induced TLR4, MyD88, and Toll/IL-1 coincided with expansion of BM HSPCs [67]. Interestingly, the G-CSF-mediated expansion of HSCs is reduced in mice lacking TLR or TLR signaling adaptor MyD88, indicating that TLR agonist production by commensal flora contributes to the regulation of HSC function and that G-CSF negatively regulates HSCs, in part, by enhancing TLR signaling [68]. Therefore, HSCs may sense pathogen or pathogen-derived products directly during infection, inducing a rapid generation of cells of the innate immune system. More studies, however, are required to explore the role of different TLR specific pathway in modulation of HSC phenotypes and function.

PD-1/PDL-1 pathway

Programmed Death-1 (PD-1; CD279) receptor molecule is immune checkpoint pathway widely believed to be a negative regulator predominantly expressed by exhausted/activated T cells. Upon interaction with its ligands, PD-L1 (CD247, PDL-1 or B7-H) and PD-L2, PD-1 inhibits activation of T cells and cytokine production. The recent development of anti-PD-1 monoclonal antibodies has offered a targeted approach to cancer therapy [69,70]. Interestingly, HSCs in their niche were found to express low level of CD274. After in vitro culture, however, HSCs markedly up-regulate the expression levels of PD-1 and as a consequence suppress proliferation of host T cells after allograft transplantation [3]. Further, ex vivo expansion of mHSCs to about 40-fold associated with increases in the expression of CD274 (B7-H1) on the surface of HSCs [3]. These expanded HSCs efficiently overcome the MHC barrier and as a result were able of repopulating the allogeneic-recipient mice.

Based on the expression profile of CD247 on fresh and cultured HSCs, Zhang group [3] suggested a model of interaction of HSCs with their niche. In this model HSCs express surface immune molecules for “in” signaling and “out” signaling that directly dialog with the immune system. The “out” signaling” is mediated by surface molecules such as CD274. The stimulatory “in” signaling respond to inflammation induced by surface receptors including TLR, TNFR, IFNR, and others. This model present HSCs as a cellular machinery capable of interacting with the immune system as signal “providers” and signal “receivers”. The “in” signaling acts as the signal receivers, in which HSCs directly sense systematic immune signals through their surface recep-

tors and change their cell fates in response to the altered immune microenvironment.

Extrinsic factors governing the immune privilege of HSCs

Stromal network

Real-time visualization of cellular interactions in BM revealed that hematopoiesis depends not only on the biology of HSCs, but also on the nature of the niche they reside in [71,72]. The niche that form the 3-D platform in which stem cell reside in is formed mainly of stromal cells [71] which included endosteal niche composed of osteoblasts [73-75] and the vascular niche composed of sinusoidal endothelial cells surrounded by perivascular MSCs which interact directly with HSCs [76-78]. The endosteum, lined by bone cells such as osteoblasts and osteoclasts, is the inner surface of the BM cavity where hematopoiesis occurs actively [54]. Most of HSCs reside adjacent to sinusoidal endothelium, where a few show preference for the BM endosteum [50].

The endothelial cells express plethora of factors that are known to enhance haematopoiesis [54]. These factors included G-CSF, GM-CSF, macro M-CSF, Stem Cell Factor (SCF; also known as KIT ligand), IL-6 and FMS-related tyrosine kinase 3 ligand (FLT3L; also known as FLK2 ligand) [13]. In addition, these cells were shown to express the adhesion molecules E-selectin, P-selectin, Vascular Cell Adhesion Molecule 1 (VCAM1) and Intercellular Adhesion Molecule 1 (ICAM1). Similarly, BM adventitial cells (positive for CD146 in human and the cytoplasmic filament protein nestin in mice) which surround blood vessels both in the central and endosteal niche [79] also express several proteins such as CXCL12, angiopoietin 1 and SCF [80].

Other extrinsic factors that reside in the BM microenvironment close to HSCs are macrophages [81,82], MSCs [83], SDF-1 abundant reticular (CAR) cells [84], subendothelial stromal which express high level of CD146 [85], and the sympathetic nervous system [86]. These studies clearly indicate that BM niche not only provide the accessory infrastructure to stem cell function but also provide a unique cellular components for HSCs to acquire immune privilege signature.

Treg cells

$CD4^+$ Forkhead box protein 3 $(Foxp3)^+$ regulatory T cells (Tregs) are the major cell type express substantial heterogeneity to maintain tolerance and regulate immune responses [2]. Treg cells in BM milieu might also impact the privilege of HSCs in BM [87]. Similar to the survival profile of syngeneic HSCs, allogenic HSCs persisted in non-irradiated recipient mice for 30 days without the treatment with immunosuppressive protocols and co-localized with Treg ($FoxP3^+$) cells on the endosteal surface. Interestingly, IL-10 produced by these Treg cells mediated this immune protection and the allogenic HSCs were lost after depletion of Treg cells.

Macrophages

Earlier in vitro studies indicated the roles of macrophages in HSC proliferation, where successful proliferation of primitive hematopoietic cells in vitro for several months was dependent on the presence of adherent stromal cells in the culture, including osteoblasts, endothelial cells and macrophages [88]. Recent studies also suggest a role for monocytes /macrophages in HSC mobilization, where osteomacs, progenies of monocytic precursors are crucial for the integrity of the HSC endosteal niche. Depletion of these precursors resulted in disappearance of endosteal osteoblastic cells [89,90], reduction in SDF-1 and induction of HSPC mobilization without the involvement of neutrophils [82].

In vivo, trabecular and mesenchymal niche components also include macrophages which were found to play important roles in shaping the immune privilege of HSCs. Indeed, deletion of these cells in vivo led to HSC mobilization through a decrease in the expression of HSC retention factors by nestin-expressing cells and perhaps by osteoblasts [91]. Additionally, the mobilizing effects of G-CSF on HSCs and modulation of their localization were found to be mediated by exerting inhibitory effects on monocyte/macrophages in the BM niche [81,82,90].

Macrophages may also contribute the immunomodulatory effects of HSCs. CD47 is an integrin-associated protein, which is known to inhibit macrophage phagcytosis after binding to the signal regulatory protein alpha on these cells. HSCs in fresh BM were found to express CD47 but at low level, indicating to their limited interaction with innate immune cells such as macrophages [92].

This limited interaction would allow escape of HSCs from innate immunity and their long-term survival. Interestingly, however, HSCs express higher level of CD47 upon their mobilization from the niche into the circulation after treatment with inflammatory stimuli [92]. This high level of CD47 on mobilized HSCs is critical for their migration to the peripheral pool. Indeed, this role of macrophages in modulation of HSC localization and their egression from BM to circulation may also alter the immune privilege phenotype of HSCs through altering their phenotype.

MSCs

MSCs are unique stem cells with multi-lineage differentiation potential where they can be induced to differentiate into osteogenic, adipogenic and chondrogenic lineages, myogenic, hepatogenic and other lineages [93].

MSCs have the capability to secrete growth factors that stimulate formation and differentiation of other progenitor cells [94]. They are found mainly in BM but they can also be found in other organs such as skin [95], adipose tissues [96], spleen and heart [97]. MSCs can be characterized in vitro by their capability of plastic adherence, forming colony and their rapid proliferation. MSCs can be identified as CD45−, CD34−, CD13+, CD44+, $CD73^+$, $CD90^+$, $CD166^+$, $CD80^-$, $CD86^-$, HLA class-II^{ow}, HLA class II^- [98].

Taken this unique phenotype of MSCs with their capability for multiple differentiation and secretion of growth factors, MSCs are thought to weakly immunogenic which make them a potential attractive target for cell-based therapy in replacement and regenerative medicine [99,100].

Besides their regenerative feature, MSCs also possess immunosuppressive effects with enhancing and suppressive effects. For instance, MSCs induced immunosuppressive effects on T cell proliferation and cytokine production in vitro [101,102] may be through inhibition of cyclin-D2 expression and disruption of the cell cycle [100]. BM MSCs also can inhibit antibody production by B cells [103], and generation and function of APCs [104,105]. Similarly, both adipose tissue-derived MSCs and swine BM MSCs showed low immunogenicity and immunosuppressive effects on T cells [106]. These effects were found to be MHC-independent and cell dose-dependent. In contrast to the low numbers of MSCs which expressed stimulatory effects, high

numbers of MSCs inhibited the in vitro allogenic responses of T cells and their proliferation in responses to different mitogens [107].

Based on these immunosuppressive effects on lymphocytes and antigen presentation, MSCs were utilized to treat several inflammation-mediated diseases such as colitis [108], autoimmune enteropathy [109], GVHD [110] and bronchiolitis obliterans in a murine model [111]. This potent immunosuppressive effects of MSCs could explain why ESC-based therapy is more successful when MSCs are co-transferred with ESCs [112-114].

Intrinsic factors

Antigen presentation molecules

The immune privilege signature of MSCs might be strongly correlated with the magnitude of their immunosuppressive machinery which enables them to escape from immune attack. Although the precise cellular and molecular mechanisms mediating the immunosuppressive effects of MSCs are not fully understood, the expression profiles of MHC class I and II molecules are critical factors. Similar to mHSCs and mESCs, MSCs also express SPI-6 and SPI-CI, making them resistant to CTLs [115].

Immunophenotypically, hMSCs either derived from BM or umbilical cord are $CD80^{-}$, $CD86^{-}$, HLA class-II^{ow}, HLA class II^{-} [116]. They are also negative for the co-stimulatory molecules CD40, CD80 and CD80 at rest. This unique phenotype renders MSCs low immunogenic. Swine and umbilical cord-derived and adipose tissue-derived MSCs also expressed low levels of MHC class II and failed to stimulate proliferative responses by human T cells in MLR and in response to mitogen stimulation [117,118]. Interestingly, even after their treatment in vitro with IFN- γ, MSCs showed higher expression of MHC class I and MHC class II with no expression of CD40, CD80 and CD86 [119,120]. Furthermore, they were still able to exert immunosuppressive effects [121]. These molecular features of MSCs with their expression of FasL allow these cells to have the immune tolerant phenotype. This would explain their incapability to physically contact with APCs and as a consequence their inhibitory effects on naïve and memory T cells [122].

MSCs can also impact the phenotype and function of DCs where co-culture of BM-derived hMSCs with monocyte during their differentiation into DCs with IL-4 and GM-CSF resulted in down-regulation of CD1, CD14, CD40, CD80, CD83, and CD86 and inhibited functional capacity of DCs to stimulate alloreactive T cells [47,104,120]. This would explain why umbilical cord-derived MSCs are capable of suppressing experimental arthritis [121], GVHD [122], inflammatory bowel disease [123], multiple sclerosis [124], systemic lupus erythromatosus [125], experimental biliary cirrhosis [126] and autoimmune myasthenia gravis [127].

TLR signaling pathways

Both hMSCs and mMSCs express several TLRs (e.g., TLR3 and TLR4). As such, the migration, invasion, and secretion of immune modulating factors of these cells are markedly modulated by the engagement of each TLR with its specific ligand [128,129]. To induce immunosuppressive effects, MSCs need to be modulated by mediators produced by inflammatory immune cells and tissues. The optimal setting in which these events occur under triggering of TLR signaling pathways [130] has been established by several studies [131,132]. However, the magnitude of the immunosuppressive effects of MSCs can increase or decrease [132,133].

In a recent study, a new aspect of hMSC biology was introduced which may solve this contradicting effects of TLRs. This aspect suggests that based on the type of TLR signaling pathway induced in MSCs, where they can be polarized into MSC1 and MSC2. This concept is based on the observations that TLR4-primed hMSCs (MSC1) produce pro-inflammatory mediators and induced T cell activation, while TLR3-primed hMSCs (MSC2) express mostly immunosuppressive mediators and suppressed T cell activation [132].

Interestingly, the self-renewal capabilities of MSCs can be altered by the type of TLR triggered. For instance, stimulation of MSCs by TLR3 ligand has no effect while the reverse occurs after stimulation with the TLR4 ligand. Further, improvement of the immunosuppressive abilities of MSCs in cecal ligation and puncture-induced sepsis after their treatment with the TLR3 ligand poly(I:C) confirm this aspect [134]. Furthermore, it was found that TLR3- but not TLR4-primed MSCs expressed higher suppressive functions against NK cells [135]. These studied confirm the notion that MSCs response to different TLR ligands lead to different immunomodulatory effects [136]. In line with this notion, TLR-primed adult BM and embryonic MSCs have been found to be more resistant to IL-2-activated NK-induced killing than TLR-unprimed MSCs [135]. Elucidating the effects of TLR activation on MSCs could identify new preconditioning strategies which might improve their immunomodulatory effects.

PD-1/PDL-1 pathway

Sheng and coworkers have focused on the role of PD-1 and PDL-1 in the immunomodulatory properties of MSCs. B7-H1, expressed by MSCs in response to increased IFN-γ production by T cells can down-modulate the effector functions of activated T cells through PDL-1 ligation [137]. Alternatively, MSCs can also induce PD-1 expression on T cells or Treg cells. For instance, in a co-culture system of MSCs and conventional CD4+CD25−T cells with and without transwell systems, MSCs suppressed the activation of T cells where PD-1/B7-H1 pathway was involved independent of IL-10 and TGF-β1 [138].

Further, MSC-exposed Tregs are capable of more immunosuppressive than Tregs without co-culturing with MSCs. This effect was coincided with IL-10-mediated marked increase in the expression of PD-1 on Tregs where PD-1/B7-H1 interactions mediated this effect [139]. These studies indicate that MSCs can also express PDL-1 to be able to interact with PD-1 on T and Treg cells. Indeed, hMSC-induced inhibition of $CD4^{+}$ T cell proliferation during their polarization into Th1 cells and Th17 cells required cell-cell contact and PD-L1 expression on MSCs where blocking PD-L1 or PD-1 abrogated this suppressive effects of MSCs [140]. In line with this, BM-MSCs-induced inhibition of antigen-dependent proliferation and differentiation of B cells to plasma cells [141] and T cells [142] also required cell-cell contact and PD-1/PDL-1 pathway. Further, stimulation of BM-derived mMSCs with IFN- γ and TNF-α associated with high expression level of PDL-1 on MSCs, which potently suppressed T cell proliferation [143,144]. Taken together, these studies highlight the complexity of the role PD-1/PDL-1 pathway in shaping the final signature of the immunomodulatory effects of MSCs.

Soluble factors

In a non-inflammatory environment, BM-derived murine MSCs constitutively expressed low levels of COX-2, PGE-2, but not IL-10, PD-1, PD-L1 or PD-L2. They can also secrete plethora

of cytokines and chemokines such as IFN-γ, TNF-α IL-6, IL-8, CCL2 and TIMP-2, TGF-β, hepatocyte growth factor (HGF) [145], nitric oxide [146], HLA-G [147], and IDO [148]. Under inflammatory condition, however, these MSCs showed higher expression levels of COX-2 and PGE-2, which have a non-redundant role in the effects of MSCs on T cells [149].

PGE seems to be critical for the immunolmodulatroy effects of MSCs, which constitutively secrete significant amounts of PGE, including PGE1, PGE2, PGE3, PGI2, PGF2α and PGJ2 [150]. Fetal MSCs also express subtypes receptors for PGE, including EP1, EP2, EP4, FP and IP [99]. In MLR, addition of indomethacin, an inhibitor of PGE-synthesis, partially restored the inhibitory effects of MSCs on T cells [105]. Similarly, MSC inhibition of Th-17 cell-differentiation from naïve and memory T-cell precursors coincided with secretion of high levels of PGE2, which when blocked by indomethacin the inhibitory effect was reversed [151]. Further, PGE2 produced by MSCs was found to promote the release of IL-10 from macrophages and inhibited their production of IL-6 and TNF- α [152]. Umbilical cord-derived MSCs, which suppress the differentiation and proliferation of T cells from patients with primary Sjögren's syndrome, showed higher IDO mRNA expression and protein secretion when co-cultured with naive $CD4^+$ T cells under T cell-polarizing conditions [153].

In vivo studies also showed that upon their infusion, MSCs migrate to the injured tissues directed by their chemokine receptors such as CCR1, CCR4, CCR7, CXCR5 and CCR10 [100] and then secrete several factors including IL-10, TGF- β, IL-6, stem cell factor, leukemia inhibitory factor, Jagged and angiomotin-1, VEGF, soluble HLA-G, hepatocyte growth factor, IDO, NO, PGE2, epidermal growth factor, nerve growth factors and stromal cell-derived factor-1 [154]. These factors are known to exert anti-apoptotic and immunomodulatory effects that favor the tissue regeneration but also create immune privilege niche that lower the inflammatory response during regeneration.

As such, the net effect of the soluble factors produced by MSCs will affect the quality and the magnitude of the immunomodulatory effects of MSCs, where PGE, IDO and IFN-g play significant roles in shaping the signatures of immune privilege of MSCs.

Extrinsic factors

Treg cells

Yan and coworkers indicated that the immune privilege signature of MSCs might be mediated via their interaction with Treg cells, where MSC-exposed Tregs showed high immunosuppressive effects than Tregs without co-culturing with MSCs [139]. A direct evidence for the regulatory nature of MSCs was success to develop a Treg ($CD4^+CD25^+CD127^{lo}FoxP3^+$) cells that emerge in co-culture of cord blood CD34+ progenitors.These hematopoietic progenitor-derived Tregs have comparable suppressor function with cord blood natural Tregs in vitro, where the addition of IL-2 to the co-culture enhanced their expansion and survival [154-156].

Additional in vitro studies revealed that the emerged immunosuppressive effects of MSCs on Tregs increased greatly when Treg cells were pre-exposed to MSCs and that the inhibitory effects were coincided with production of IL-10 and TGF-β1 as well as an enhanced expression of PD-1 by Treg cells where blocking of PD-1 or IL-10 mediated these effects [157]. It was also found that MSC inhibition of Th-17 cell-differentiation from naïve and memory T-cell precursors depended on emergence of Treg cells [151]. Even under immunological quiescent settings where MSCs enhance survival, activation and proliferation of CD4+ T cells it was associated with an increased number of Treg cells [158,159].

Interestingly, the role of Treg cells in mediating the immunosuppressive effects of MSCs does not depend on the source of MSCs since the inhibitory effects of MSCs derived from umbilical cord matrix, from BM or from adipose tissue associated with promotion of FoxP3+ Treg cells [160] In vivo studies also showed that human umbilical cord-derived MSCs down regulate experimental colitis [161,162], arthritis [163], acute lung injury [164] and acute GVHD [165] and increased skin allograft survival [166] by enhanced expansion of CD4+CD25+Foxp3+ and CD8+Foxp3+ Tregs coinciding with increased IL-10 and TGF-β production, and reduced TNF-α and IFN-γ secretion. Taken together, these studies clearly indicate the marked role of Treg cells in shaping the immune privilege signature of MSCs.

Macrophages

Besides Treg cells, BM or other stroma in the body may also harbor other regulatory cells such as macrophages that can favor immune privilege niche. For instance, auricular chondrocytes in mice express Fas ligand (FasL) which contributes the establishment of immune privilege [167]. Specifically, interactions between these chondrocytes and macrophages increased G-CSF secretion in macrophages and induced FasL on chondrocytes, which in turn induced the apoptosis of macrophages and suppressed tissue reactions, and promoted the maturation of tissue-engineered cartilage [168]. This would explain the efficacy of BM MSCs to prevent the development of airway occlusion and increased IL-10 levels in trachea grafts and the elimination of this effect after the depletion of macrophages. PGE2 produced by MSCs promoted the release of IL-10 and inhibited the production of IL-6 and TNF-α by macrophages [169].

BM-derived MSCs were also found to reduce acute lung injury, and its more severe form, acute respiratory distress syndrome dependent on reduced TNF-α and macrophage inflammatory protein (MIP)-2 and MIP-2 with a corresponding increase in the anti-inflammatory cytokines IL-10, IL1RN, and IL-13, keratinocyte growth factor (KGF) and IL-1 receptor antagonist (IL1RN) [170]**.** These studies suggest that macrophages in MSC niche and under inflammatory condition can act as regulatory cells to decrease the innate inflammatory responses by down-regulating the levels of IL-6 and TNF-α and increasing IL-10 production [171].

Infusion of adipose tissue-derived MSCs was found to associates with a marked decrease in the infiltration of macrophages (CD11b+Gr-1+F4/80+) in ConA-inflammed liver [172]. Similar effects were observed for BM-derived MSCs which induced decreases in the numbers of neutrophils and activation of the hepatic macrophages (Kupffer cells) [171], and in BM and in the peripheral blood [173]. Interestingly, MSC infusion reduced the numbers of the M1-type pro-inflammatory and increased the activation of M2-type macrophages with immune regulatory effects in the circulation [174].

Similar effects were also observed in the liver where MSC infusion favored decrease and increase in the numbers and

activation of CD68+ M1-type (and their gene expression of TNF-α and NO) and CD206+ M2-type (and their gene expression of arginine-1, and IL-10) Kupffer cells, respectively [154]. MSCs were also found to decrease the MMP-9 release from hepatic macrophages [174]. These data indicate to the role of marcophages in the immunomodulatory effects of MSCs regardless of their source.

IL-17

IL-17, a Th17 cell-derived pro-inflammatory molecule, which play an important role in hematopoiesis through stimulation of granulocyte and erythroid progenitors as well as MSCs [175]. The mechanisms involved in the capacity of MSCs to inhibit the proliferation of pro-inflammatory T lymphocytes mediated by generation Treg cells [140]. The impact of Th17 on MSCs showed both stimulatory and inhibitory effects. For instance, IL-17A induces expansion of hMSCs in vitro and in vivo. IL-17 stimulated the proliferation of hBM-derived MSCs as well as their migration, motility, and osteoblastic differentiation via generation of ROS [175] and activation of p38 MAPK [176]. IL-17 also stimulated hMSCs to produce leptin, which is known to promote osteogenesis of MSCs [177]. In contrast, in vitro and in vivo studies showed that IL-17 enhances immunosuppression by MSCs in an iNOS-dependent manner [178]. For instance, IL-17 inhibited osteoblast differentiation and bone regeneration in rat MSC cells [179] and adipocyte differentiation in hMSCs by upregulating the secretion of IL-6 and IL-8 as well as the COX-2 and PGE2 levels [180].

The impact of MSCs on Th17 cells also showed stimulatory and inhibitory effects. In vitro studies showed that MSCs inhibit the differentiation of CD4+ T cells into IL-17-secreting T cells [181] as wells as Th17 cell differentiation and function via the CCR6 chemokine ligand CCL20 induced adhesion of Th17 cells to MSCs [182]. Some of these suppressive effects of MSCs on Th17 cell differentiation were reversed by treatment with PGE2 and IDO [183,184]. In vivo studies also showed that MSCs can induce CCL2-mediated amelioration of experimental autoimmune encephalomyelitis by inhibiting CD4 Th17 T cells [185]. Further, injection of adipose tissue-derived MSCs increased skin allograft survival by inhibition of Th-17 cell functions through the suppression of PKA activity and SOX9 phosphorylation [166].

On the contrary, Guo et al. showed that MSCs augment Th-17 cells. In vitro, fetal BM-derived MSCs promoted the expansion of human Th17 cells through increasing the levels of IL-6 and IL-1 [186]. Early addition of MSCs in vitro during differentiation of $CD4^+$ T cells into Th1, Treg or Th17 cells by IL-12, TGF-β+IL-6 or TGF-β, respectively, decreased IFN-γ production by Th1 cells while markedly increased IL-17 production by Th17 cells in particular once T cell activation has occurred [187]. In vivo, MSC-induced prolonged allograft survival depended on the conversion of Th17 into IL-17anergic Treg cells [188]. Further, systemic transplantation of allogenic fetal membrane-derived MSCs suppressed Th1 and Th17 T cell responses in experimental autoimmune myocarditis [189].

Interestingly, Th17 cells were found to have stem cell-like features. Th17 stemness may be partially controlled by signaling pathways of hypoxia inducible factor HIF1a, Notch and Bcl. The stem cell-like character of Th17 cells is an important decisive factor in controlling the stem cell niche, in particular Th17 cells are polyfunctional and highly plastic in the chronic inflammatory environment and would be converted into Treg cells or effector T cells [190]. MSCs were also found to contain an IL-17+ subset capable of inhibiting Candida albicans growth via NFκB-mediated down-regulation of TGF-β. This subset of MSCs producing IL-17 is different from bulk MSC population in that it cannot up-regulate Tregs, down-regulate Th17 cells, or ameliorates disease phenotypes in a colitis mouse mode. Taken together, these studies suggest that the altered niche in tumor microenvironment by presence of inflammatory cytokines such as IL-17 significantly impact the self-renewal and proliferation of MSCs and accordingly the immune privilege signature.

Conclusion

Certain cellular and molecular factors, encoded in stem cells themselves or in the surrounding niches play remarkable roles in shaping the immune privilege signature of the stem cells. The list of these factors is increasing, making it difficult to understand the precise nature of the immune privilege niche of stem cells. Understanding the role of each factor as well as the synergistic and additive effects of the already explored factors will lead to better strategy to target normal stem cells as well as cancer stem cells which possess similar features. It is still undetermined, however, whether other cellular immune regulatory factors, other than Treg cells, DCs, and Th17 cells as well as molecular factors, others than PD-1/PDL-1, IDO, PGE, and IL-17 act as “inside” and “outside” signaling on HSCs and other stem cells, including ES cells, iPS cells, other tissue specific stem cells. It is also important to explore if these molecules and others are modulated upon stem cells mobilization from their niche and whether their expression profile is reversible and can be reprogrammed. It is also important to understand the expression profile of these molecules upon induction of differentiation of HSCs in vitro, in vivo, or ex vivo in particular under the effect of inflammatory stimuli or infection. Since most of these cellular and molecular factors play similar roles in cancer cell progression and metastasis, it is important to understand how cancer impacts the biology of stem cells niche and how chemotherapy interfere with these effects, if any. Finally, it is of paramount significance to explore the reciprocal interaction between stem cell niche and different forms of cancer immunotherapy particularly therapies that target PD-1/PDL-1, IDO, COX, and Treg cells. These studies might lead to new avenue of anticancer targeted therapy.

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