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Myeloid-Derived Suppressor Cells and their Potential Application in Transplantation

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Abstract

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immunosuppressive cells of the myeloid lineage upregulated by mediators of inflammation such as IL-2, GCSF, and S100A8/A9. These cells have been studied extensively by tumor biologists. Because of their robust immunosuppressive potential, MDSCs have stirred recent interest among transplant immunologists as well. MDSCs inhibit T cell responses through, among other mechanisms, the activity of arginase-1 and iNOS, and the expansion of T regulatory (Treg) cells. In the context of transplantation, MDSCs have been studied in several animal models, and to a lesser degree in humans. Here, we will review the immunosuppressive qualities of this important cell type and discuss the relevant studies of MDSCs in transplantation. It may be possible to exploit the immunosuppressive capacity of MDSCs for the benefit of transplant patients.

1. Characteristics of MDSCs:

MDSCs have been investigated extensively by tumor biologists seeking to determine factors which suppress a host's immune response to cancer.[1–4] A brief review of this important literature is important in order to understand the potential value of MDSCs in transplantation.[4]

Hematopoietic stem cells (HSC)s in the bone marrow differentiate into common myeloid precursors (CMPs) (figure 1), a developmental stage marked by DNA demethylation. [5,6] CMPs give rise to immature myeloid cells (IMCs). In nonpathologic conditions IMCs migrate to lymphoid organs where they can differentiate into dendritic cells, macrophages, and neutrophils.[7] In pathological conditions, however, such as tumor, stress, or infection, IMCs become activated and differentiate into MDSCs with an immunosuppressive phenotype. MDSC development appears to be associated with downregulation of IRF7 and IRF8 and upregulation of IRF1.[8–10] Recent data have illustrated that MDSCs can develop

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from monocytes, and that this transition occurs in response to GM-CSF (produced by T cells endogenously or administered exogenously). Importantly, it appears that GM-CSF exposure must preempt exposure to inflammatory mediators, such as IFN-gamma.[10]

Endogenous and/or exogenous signals generated by chronic inflammation, including auto-immunity, cancer, and infection[11,12] among others are the stimuli for MDSCs' activation and expansion (table 1).[1,5,13–15] The drivers of MDSC activation have been reviewed elsewhere, but include G-CSF, GM-CSF, IL-2, TGF-beta, CXCL1/2, S100A8/A9, and PGE2.[16–18] This MDSC expansion is observed clinically in healthy human bone marrow transplant donors with G-CSF mobilization. After G-CSF administration, donors demonstrate a 3-fold increase in peripheral blood MDSCs.[19] Once developed within the bone marrow, MDSCs can be sustained by T cells through the release of IL-10.[20]

Upon exiting the bone marrow, MDSCs migrate to sites of inflammation, and this migration is associated with (among others) CCR2 as well as and L and E-selectin expression.[21–25] For example, in a mouse islet transplantation model, MDSCs homed to the allograft in a CCR2-dependent fashion and MDSC homing was enhanced by the presence of proinflammatory IFN-gamma.[26] Further, MDSCs generated in mice which did not express CCR2 failed to exit the bone marrow.[25] In other models, MDSC migration was dependent on expression of CXCL-1 and CD62L (L-selectin).[27–29]

There are 2 primary sub-populations of MDSCs: monocytic MDSCs (M-MDSCs) and polymorphonuclear MDSCs (PMN-MDSCs).[30] While M-MDSCs are similar phenotypically and morphologically to monocytes, PMN-MDSCs are more similar to polymorphonuclear cells (PMN)s.[3,31] A third, very small group (<3%) of MDSCs are characterized as "early" or having myeloid colony-forming activity.[30,32–34] Complicating their identification, MDSCs are a heterogeneous group of cells and expression of MDSC cell surface markers may change depending on the environment.[35] As an example, tumor-derived MDSCs in environments devoid of tumor-derived growth factors may differentiate into macrophages or dendritic cells.[35,36] Further, it has been hypothesized that M-MDSC and PMN-MDSC may represent sequential developmental stages in the life of an individual MDSC. This potential MDSC plasticity may have important implications for transplantation.

The distinction between M-MDSCs and PMN-MDSCs is phenotypically, functionally, and anatomically important.[29] In cancers, the ratio of PMN-MDSCs to M-MDSCs in each compartment of the tumor microenvironment depends on the type of cancer.[37] In human bone marrow transplant recipients, MDSC subtype is also important as it may predict risk of graft versus host disease.[19] Little is known about the MDSC subtypes which develop after organ transplantation, but a single study in humans suggested that M-MDSCs were the predominant MDSC subtype to develop in the peripheral blood of kidney transplant recipients.[38]

Table 2 shows some of the accepted phenotypes for mouse and human M-MDSCs and PMN-MDSCs.[30,39] In mice, the accepted phenotype of total MDSCs is defined as the dual expression of CD11b, also known as alpha_m-integrin, and the myeloid lineage marker Gr1.[36] CD11b is expressed on myeloid cells, as well as small subpopulations of natural killer (NK)

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cells, T cells, and B cells.[40,41] CD11b binds noncovalently with CD18 to form the leukocyte integrin Mac-1 complex which regulates inflammatory cell recruitment.[42] MDSC sub-classification is determined by expression of either Ly6G (PMN-MDSCs) or Ly6C (M-MDSCs). Mouse M-MDSCs also express CD49d, whereas PMN-MDSCs do not.[43] This is important because CD49d is a subunit of the alpha-4 integrin receptor which is critical for lymphocyte homing to sites of inflammation.[44,45]

Human PMN-MDSCs express CD15 with or without the expression of CD66b, but they do not express CD14.[29,30,32] CD33, a cell surface marker for myeloid cells, can be used in place of CD11b. CD15 is an adhesion molecule important for chemotaxis, phagocytosis, and cell-cell contact expressed on (but not restricted to) immature myeloid cells.[46,47] CD15 is upregulated during development of granulocytes and is highly expressed by human neutrophils and eosinophils. CD66b is also known as carcinoembryonic antigen-related cell adhesion molecule 8 (CEACAM8), and is an activation marker for human granulocytes. Under nonpathologic conditions myeloid cells express minimal CD66b.[48] Human M-MDSCs are defined as CD11b+CD14+HLA-DR$^{low/-}$, but they do not express CD15. CD14 is a co-receptor of Toll Like Receptor 4 (TLR4), and TLR4 (as well as CD14) binds cytosolic calcium binding proteins S100A8 and S100A9, leading to NF-kB upregulation and subsequent proinflammatory cytokine release.[17] Importantly, classic human monocytes are CD33+CD11b+CD14+CD15- and HLA-DR− expression in monocytes is likely influenced by immunosuppression. Thus, the cell surface markers for MDSCs in the context of transplantation require further investigation.

Despite the importance of MDSC subtype, distinguishing human M-MDSCs from PMN-MDSCs by flow cytometry remains challenging. Recent data suggest that MDSC expression of S100A9, may be useful in making this distinction.[23,49,50] Human flow cytometry studies comparing PMBC from healthy controls and patients with malignancies have helped to clarify gating strategies which can help differentiate between MDSC subtypes.[51] This was shown nicely by Bronte et al.[30] Specifically, expression of CD14+HLA-DR−/lo on human PBMC can identify the M-MDSC population while CD14−CD15+CD11b+ appear to distinguish PMN-MDSC.[30] Differentiating between PMN-MDSCs and non-MDSC PMNs is also challenging and controversial.[33] This difficulty is due, in part, to the heterogeneous nature of this immature cell type (eg not all MDSCs express the same cell surface markers). PMN-MDSCs and non-MDSC PMNs have similar morphology and are difficult to distinguish with Wright-Giemsa staining.[2,52] In mice, cell surface expression of Ly6C and CD11 are slightly lower for PMN-MDSC than non-MDSC PMNs.[2,3] Further, CD115 and CD224 are expressed at much higher levels in mouse MDSCs versus non-MDSC PMNs.[2,33] In humans, density gradient centrifugation is used to separate PMN-MDSCs from non-MDSC PMNs. However, this technique is suboptimal because it precludes the separation of PMN-MDSC from other myeloid cells and it inconsistently separates activated, nonsuppressive PMNs, from immunosuppressive PMN-MDSCs.[33] New data, however, suggests that, lectin-type oxidized LDL receptor 1 (LOX-1), may reliably distinguish human PMN-MDSC from non-MDSC PMNs by flow cytometry, allowing for cellular separation.[33]

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2. Function:

A key function of MDSCs is T cell suppression.[3,36,53–55] MDSC mediated T cell suppression has been shown nicely in co-culture models. For example, when Gr1+ MDSCs isolated from C57Bl/6 mice bearing Lung Lewis carcinoma were co-cultured with CD3+ stimulated T cells, T cell proliferation was markedly suppressed. This effect was most pronounced when the MDSC:T cell ratio was 1:1. In this model, PMN-MDSCs were more potent suppressors than M-MDSCs.[53,54]

One of the primary mechanisms by which MDCSs mediate their immunosuppressive effects is through the action of arginase-1.[32,56,57] Arginase-1 reduces local levels of L-arginine, starving lymphocytes of this critical amino-acid and inhibiting their ability to proliferate.[57–61] MDSCs also deplete local levels of cysteine through sequestration. MDSC depletion of cysteine also leads to T cell suppression because T cells cannot produce cysteine independently and because cysteine is required for T cell activation. [60,62]

MDSC mediated immunosuppression also occurs through oxidative stress. MDSCs express both inducible nitric oxide synthase (iNOS) as well as well as NADPH oxidase-2 (Nox2) which lead to the production of nitric oxide (NO) and reactive oxygen species (ROS), respectively.[29] NO and ROS suppress proliferating cells.[29,63] MDSCs also inhibit lymphocyte trafficking through the downregulation of L-selectin, as well as through the production of peroxynitrite (PNT). PNT-associated nitrosylation of the T cell receptor inhibits binding to the antigen-MHC complex. [31,32,43,58]

Additionally, MDSCs inhibit T cell responses through the expansion of T regs.[38,43] MDSCs express programmed death ligand-1 (PDL-1) and bind PD-1 expressed by Treg, upregulating Treg responses.[25,64,65] Indeed, MDSCs enhance PDL-1 mediated T cell suppression and blockade of PDL-1 inhibits MDSC-mediated suppression.[25,64–66]

Both cell-cell contact in addition to soluble factors are important for MDSC effector function. Isolation and analysis of MDSCs generated in animals with hepatocellular carcinoma revealed expression of membrane-bound TGF-beta. Transwell assays showed that soluble factors (ie soluble TGF-beta, other factors) produced by MDSCs could inhibit T cells responses (CD4 and NKT).[13] In an investigation of human umbilical cord blood-derived MDSCs (largely PMN-MDSCs), inhibition of Th1 responses was dependent on cell-cell interaction. In subsequent transwell assays, MDSC-mediated control of Th2 responses was mediated by soluble factors including ROS.[67,68] Taken together, the effector function of MDSCs involves both cell-cell contact and the release of soluble inhibitory factors. However, MDSC effector function may vary depending on the stimulus for MDSC activation, the MDSC sub-type, and target cell type.[68] This important topic requires further investigation.

Early reports in the tumor biology literature suggested that MDSC-mediated CD8 T cell suppression was antigen specific.[69] CD8 T cell antigen specificity was restricted to MHC class I and required cell-cell contact.[70] In contrast, more recent work showed that MDSC-mediated CD4 T cell regulation could also be achieved, however this was only possible when MDSCs expressed substantial MHC class II.[71] MDSCs which develop after

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transplantation do not appear to demonstrate the same degree of antigen specificity, however limited work has been done to address this important topic (for caveats see evidence for a role of MDSCs in transplantation).[69,72]

While MDSCs' immunosuppressive effects are typically described as "local" MDSCs also downregulate CD62L on T and B cells.[73] This is important because MDSC-mediated loss of CD62L expression on naïve T cells allows for more far-reaching MDSC-dependent immunosuppressive effects. [73]

3. Evidence for MDSC control of semi-allogeneic responses at the maternal fetal interface:

MDSCs can control immune responses at the maternal-fetal interface.[74] An immunologic environment supportive of the semi-allogeneic fetus is provided by the mother at the level of the placenta.[58] MDSCs within the placenta sustain pregnancy by preventing T cell influx into the uterus and reducing T cell activation. Loss or disruption of this tolerogenic interface may lead to spontaneous abortion or miscarriage.[58,75]

Tregs also help to protect pregnancies against allogeneic responses, and proliferation of placental Tregs is driven, at least in part, by MDSCs.[58,74,76] Adoptive transfer of normal mouse T regulatory cells can prevent murine miscarriage.[77] At the maternal-fetal interface of successful pregnancies, CD4+ T cells are oriented towards the regulatory Th2 phenotype as suggested by the production of TGF-beta and IL-4 and IL-10.[58,78] In contrast, Th1 responses mediated pregnancy loss.[76] This Th2 regulatory response was reliant on the presence of MDSCs, and placental MDSCs readily polarized T cells towards the Th2 phenotype.[67]

Kostlin et al demonstrated that PMN-MDSCs were expanded in fetal cord blood. A similar population of MDSCs was expanded in the peripheral blood of healthy pregnant patients. These PMN-MDSCs demonstrated a regulatory phenotype as reflected by their expression of Arg1 and iNOS.[79] After delivery, the PMN-MDSC population was reduced to levels of nonpregnant controls.[79] Suppressive macrophages within the placenta were found to be important for fetal tolerance and successful gestation.[80] Further, these macrophages were induced by G-CSF, produced anti-inflammatory cytokines, and induced FoxP3+ T reg.[80] While these macrophages were not described as expressing the classical MDSC cell-surface markers, they appeared functionally similar. Given the heterogeneity of the MDSC population it is possible that these placental macrophages represented a unique group of MDSCs. The Tregs induced by maternal-fetal interface macrophages expressed CTLA-4, CD39 and IL-10. Further, placental-macrophage associated Tregs were inducible with IL-10 and TGF-beta and they were functionally suppressive.[80] Taken together, it appears that myeloid derived cells present at the maternal fetal interface are important for fetal success, largely through their ability to suppress T cell responses.

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4. Evidence for a role of MDSCs in transplantation:

There is important evidence to suggest that MDSCs are important in transplantation. The same proinflammatory factors which characterize the development and chemotaxis of MDSCs in cancer and infection also characterize anti-donor responses.[29,36,81–86] Accordingly, it may be possible to exploit the regulatory capacity of MDSCs following transplantation to either supplement or eliminate the need for immunosuppressive drugs.[38,85,87]

Corneal transplantation:

MDSCs can prolong graft survival in corneal transplantation models.[88] An exciting recent report published in *Transplantation* described a mouse model in which anti-donor T cell infiltration of corneal grafts could be inhibited through the adoptive transfer of MDSCs induced by either tumor or inflammation.[89] T cell inhibition led to a reduction in the histopathological changes in the corneal allograft. In vitro studies demonstrated suppression of allogeneic responses with both tumor derived and inflammation induced MDSCs. These data suggest that transplantation may lead to recipient derived MDSCs capable of suppressing anti-donor responses.[89,90]

Islet transplantation:

A recent study of mouse islet transplantation showed that peri-transplantation MDSC infusion prolonged allograft survival. Prolongation of islet survival was due to MDSC-mediated inhibition of T cell responses. Further, administration of MDSCs increased the number of Tregs within the graft.[26] These data corroborated findings by Marigo et al in which adoptive transfer of MDSCs, generated from treating BM cells in vitro with GM-CSF + IL-6, induced long-term acceptance of islet allografts in mice.[72] In Marigo's protocol, animals were given 4 weekly injections of syngeneic MDSCs beginning on the day of islet transplantation. At 200 days after transplantation, 75% of mice were euglycemic.[72] Importantly, these MDSCs were not globally suppressive, but rather they suppressed antigen-specific responses.[72] It is also important to note that various combinations of GM-CSF, G-CSF, and IL6 in this model yielded MDSCs with differing suppressive potentials.

Skin transplantation:

Skin grafts can readily promote the accumulation of MDSCs in recipient spleens.[91] In a separate model, investigators evaluated the ability of MDSCs from immunoglobulin-like transcript 2 (ILTR2) transgenic mice to prolong skin graft survival.[92] Uniquely, ILT2R mice MDSCs express higher levels of Arg-1 when compared with wild type mice. In a separate study, administration of 1 million syngeneic MDSCs significantly prolonged skin graft survival. The suppressive in vivo effects of the adoptively transferred MDSCs were dose-dependent, and graft survival was prolonged by 50% when the dose of MDSCs was increased to 3 million cells.[93] Other groups found that skin graft survivals were markedly prolonged with the adoptive transfer of syngeneic MDSCs.[94] MDSCs were given prior to transplantation and on posttransplantion day 6. Prolongation could be enhanced with weekly injections of syngeneic MDSCs.[94] When recipient skin grafts and spleens were analyzed 2 weeks after adoptive transfer, no MDSCs were identified, suggesting rapid elimination.

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Authors suggested that techniques to improve the suppressive ability after adoptive transfer could decrease the frequency of MDSC injections.[94]

Kidney transplantation:

In rats, MDSCs accumulate in the peripheral blood and within grafts after kidney transplantation. However, these MDSCs were identified only after treatment with anti-CD28 antibodies. These MDSCs were suppressive in vitro of both donor-derived and recipient-derived CD3-stimulated recipient T cells.[95] The suppressive function of MDSCs relied on iNOS, and appeared to be cell contact dependent.[95] Importantly, MDSCs in this model were suppressive of anti-donor as well as 3rd party responses, suggesting a lack of antigen specificity.[95]

Cardiac transplantation:

Transcoronary adoptive transfer of MDSCs led to a 2-fold increased graft survival following cardiac transplantation in mice.[96] In this model, animals were treated with rapamycin as well. When MDSCs were depleted using anti-Gr1 antibodies, graft survival was reduced, suggesting a synergy in the mechanisms of action for rapamycin and MDSCs.[96] These rapamycin-induced MDSCs expressed high levels of iNOS and induced Tregs.[96] In a separate model of mouse cardiac transplantation, co-stimulatory blockade-induced MDSCs also suppressed anti-donor responses through the action of iNOS.[25] Unlike the above-cited islet cell models, heart transplants did not survive in the long term with MDSC infusion alone (ie without pharmacologic immunosuppression).[25,72] Co-stimulatory blockade-induced MDSCs accumulated in the blood, bone marrow, as well as in the transplanted cardiac allograft.[25]

Human experience:

There is a paucity of human data addressing the role of MDSCs in transplantation. In an important study of 29 kidney transplant patients, separation of peripheral blood mononuclear cells revealed an upregulation in M-MDSCs over the course of 1 year after transplantation.[38] Increases in MDSCs were observed as early as 3 months after transplantation. Further, CD11b+CD33+DR- MDSCs lead to a robust increase in FoxP3+ Treg cells in vitro. Notably, the MDSCs which accumulated in the peripheral blood of transplanted patients were largely M-MDSCs. It remains unknown if the M-MDSCs identified in the kidney transplant population home to the transplanted graft.[38] Further, the human MDSC response to other organs such as livers and lungs (which may themselves carry many donor-derived MDSCs), hearts, and pancreata is unstudied.[38]

In a report of 31 renal transplant recipients, investigators observed a higher percentage of CD14+ and CD14(−) MDSCs in the peripheral blood, when compared with healthy volunteers (*n*=34).[97] Nontransplanted patients with chronic kidney disease also demonstrated higher percentages of MDSCs, but only of the CD14(−) subset.[97] MDSCs from these human renal transplant recipients were suppressive of anti-donor T cell responses in vitro. This important study included patients on varied immunosuppressive protocols transplanted over a long period of time and MDSC profiles were measured at a single time point. Nonetheless, authors concluded that renal failure alone did not lead to MDSC

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mobilization, and that the combination of transplantation and immunosuppression influenced peripheral blood MDSC populations.[97]

Immunosuppression effects on MDSCs:

Regarding the use of immunosuppressive agents and their effects on MDSCs, there is also a paucity of data. In vitro, G-CSF + cyclosporine A (CyA) led to increased differentiation of MDSCs. MDSCs cultured with CyA demonstrated increased suppressive activity against T cells activated in an anti-CD3/anti-CD28 system, and this increased suppressive activity was attributed to expression of iNOS.[98] While there are no investigations of tacrolimus' effect on MDSCs there are data suggesting that FK binding protein (FKBP; target of tacrolimus) is upregulated in MDSCs, and that blocking FKBP reduces MDSCs' immunosuppressive capacity.[99,100] These data imply that tacrolimus negatively affects MDSC function, but this remains unclear.

Glucocorticoids' effect on MDSCs have been studied in a mouse trauma model.[101,102] When a glucocorticoid antagonist was administered, the MDSC response to trauma was abrogated. Glucocorticoids did not appear to affect expression of arginase-1, or other important MDSC regulatory mechanisms.[102]

Rapamycin has garnered interest among investigators of regulatory myeloid cells.[96,103,104] Rapamycin administration significantly decreased both MDSC number and suppressive activity in an allogeneic skin transplant model.[91] In vitro studies suggested that rapamycin directly inhibited MDSCs.[91] In a model of multi-organ inflammation, molecular target of rapamycin (mTOR) signaling pathway transcripts were upregulated, particularly in the PMN-MDSC sub-population, suggesting that mTOR inhibitors may suppress the regulatory function of MDSCs.[105,106] Paradoxically, after cardiac transplantation, rapamycin-treated mice produced MDSCs which were suppressive of T cell proliferation.[96] In the same cardiac transplant model, rapamycin administration enhanced MDSC recruitment and activity via iNOS.[96] An additional report addressing the murine MDSC response to acute kidney injury included an in vitro analysis of rapamycin on MDSC function.[107] Rapamycin upregulated the expression of Arg-1 and iNOS, as well as Treg populations.[107] Taken together, the evidence on mTOR inhibitors is mixed, and further work is needed to determine which MDSC populations demonstrate enhanced versus suppressed function in response to rapamycin.

MDSCs in transplantation tolerance:

MDSCs are important not only for self-tolerance[108] (and cancer), but also for transplantation tolerance.[109] The combination of M-CSF and TNF-alpha induced M-MDSCs and allograft tolerance of mouse skin transplants.[110] Further, the suppressive function of the induced MDSCs required iNOS expression.[110] Depletion of iNOS after tolerance induction in this model abrogated the tolerant state.[95]

An important study from Garcia et al (2010) showed in mice that suppressive monocytes (CD11b+ Gr1+CD115+), which were functionally and phenotypically similar to MDSCs, were required for the establishment of tolerance of cardiac allografts. The investigators used an established tolerance induction protocol of donor specific transfusion in combination with

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co-stimulatory blockade via anti CD40L. When animals were depleted of these suppressive monocytes, tolerance could not be induced.[25] Monocytes were suppressive in vitro and functioned through the production of iNOS, in a manner quite similar to classical MDSCs.[25] In a subsequent study using the same model, the authors showed that the suppressive monocytes which developed in tolerant animals homed to the cardiac allograft.[111]

Mixed chimerism has also been used to establish tolerance of heterotopic cardiac transplants.[109] Following cardiac transplantation, mice were given 5 days of anti-thymocyte serum (ATS) and 10 days of total lymphocyte irradiation.[109,112,113] This model, which is similar in design to human transplant tolerance protocols, yielded long-lasting chimerism and donor-specific tolerance to the transplanted heart.[109] However, when recipients were depleted of MDSCs using an antibody to Gr1, chimerism and subsequent tolerance were lost. Add back of MDSCs to the transplanted recipients increased cardiac graft survival.[109] MDSCs derived from the transplanted recipient were sufficient to control anti-donor T cell responses in vitro. It was hypothesized that tolerance was induced by MDSC-mediated T cell suppression via arginase-1 and Treg expansion via PD-L1 mediated pathways.[25,65,109] MDSCs played an important role in the establishment and maintenance of both chimerism and tolerance.

In a rat model of kidney transplantation, MDSCs were critical for tolerance establishment. When tolerance was induced using anti-CD28 antibodies, peripheral blood MDSCs were increased 2-fold and this increase was not due solely to the use of anti-CD28.[95] Adoptive transfer of MDSCs which were generated as a result of anti-CD28 administration was, however, not successful in tolerance establishment,[95] suggesting that anti-CD28 generated MDSCs may not be sufficient for controlling anti-donor responses in vivo.

Tregs are important in many studies of transplantation tolerance.[114–117] Recent evidence has suggested robust pathways of “crosstalk” between MDSC and Tregs.[70,118,119] As discussed above, Tregs are one of the primary mechanisms by which MDSCs mediate T cell suppression.[25,65,118] Depletion of MDSCs in cardiac tolerance models led to a failure of Treg development and tolerance.[25] This link between cell types is important because in many tolerance studies the stimulus for Treg upregulation remains unclear.[117,120–123] It is plausible that Treg responses in transplant tolerance models are at least partly driven by an “upstream” MDSC response.

The role of MDSCs in models of transplantation tolerance induced by bone marrow transfusion is also unclear. While speculative, it is possible that intra-bone marrow MDSCs transplanted along with CD34+ HSCs may be important for tolerance establishment.[124,125] Further data to support this theory come from a nonhuman primate model of tolerance induction where, although chimerism was lost after bone marrow transfusion induced mixed chimerism, animals remained tolerant.[82,114] This result was puzzling. The mechanism for tolerance maintenance after loss of chimerism in this experiment was hypothesized to be the generation of peripheral Treg subsequent to a transient state of mixed chimerism. While unproven, it is reasonable to suggest that MDSCs which were present in the donor bone marrow, led to a Treg response in the recipient which aided in tolerance to donor antigens.[84,124,125]

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Future Directions:

MDSCs are an important group of immunosuppressive cells, which may have the potential to benefit transplanted patients.[126] Biologic therapies which act to harness the immunosuppressive capacity of a recipient's own immune system may be game-changing for the field of transplantation. Critical questions remain ahead of the attempted clinical use of MDSCs, but these questions are indeed answerable. Cell surface markers which more clearly define MDSC sub-populations will be important for our understanding of MDSC's in the blood, bone marrow, and allografts, following transplantation. Beyond the need for improved MDSC sub-population identification is the need for improved ability to distinguish PMNs from non-PMN MDSCs. The lifespan and migration patterns of MDSCs which develop after transplantation are poorly described. As an example, while MDSCs (particularly in cancer) are thought not to migrate to lymph nodes, it is possible that MDSCs which develop following transplantation do enter the lymphatic circulation. The effector function of MDSCs which develop after transplantation is largely unstudied. It may be that, analogous to cancer, different types of organ transplants (eg, kidneys versus hearts, etc.) induce different types of MDSCs, which have varied effector function.

Regarding transplantation, there are many unanswered questions from the standpoint of MDSCs. An important issue which requires clarification is that of antigen-specificity. Because MDSCs generated in tumor models can suppress anti-donor responses, and because limited data suggests that transplantation-induced MDSCs can suppress 3rd party T cell responses, it does not appear that MDSCs are antigen-specific. However, very little work has been done to address this question specifically. It is also not clear if tacrolimus affects MDSC function. Further, the data on rapamycin's effect on MDSCs requires clarification. Whether or not MDSCs generated as a result of transplantation function similarly to those MDSCs generated after various tumors is also not clear. In addition, it remains unknown if the type of organ transplanted (eg kidney versus liver) leads to MDSCs with different suppressive capacities. Regarding transplantation tolerance, different induction protocols (eg co-stimulatory blockade versus mixed-chimerism) likely lead to the development of phenotypically, anatomically, and functionally different MDSCs, but this too remains unclear.

Not all MDSCs have equal suppressive potential.[72] This may explain the varied approaches and outcomes associated with MDSCs and transplantation tolerance induction. For example, in some studies of transplantation, MDSC infusions are administered pretransplantation, and others are given posttransplantation. Some infusions are given one time, whereas others are given at multiple time points. Similarly, MDSC lifespan may differ depending on the sub-type of MDSC infused. An improved understanding of which treatments yield optimally suppressive MDSCs that remain in circulation (or in the transplanted graft) for the desired duration will be required for the adoption of clinical MDSC protocols. The authors' laboratory has begun investigations designed to address each of these important questions.

Additional MDSC studies in large animals and following human transplantation are important for our understanding of both tolerance induction and immunosuppression minimization. The effects of immunosuppression on MDSCs should be studied further as

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well, as this may partly explain why previous attempts at tolerance induction in humans have been inconsistent.[115,127–129] Indeed, it may be possible to augment naturally occurring recipient MDSCs after transplantation, such that immunosuppression dosing can be reduced or eliminated altogether.[130–133]

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Abbreviations:

CMP	Common myeloid precursor
IMC	Immature myeloid cell
HSC	Hematopoietic stem cell
IL	Interleukin
LOX-1	lectin-type oxidized LDL receptor 1
M	Monocyte
MDSC	Myeloid derived suppressor cell
PMN	polymorphonuclear cell
TGF-b	transforming growth factor beta
Treg	T Regulatory cell

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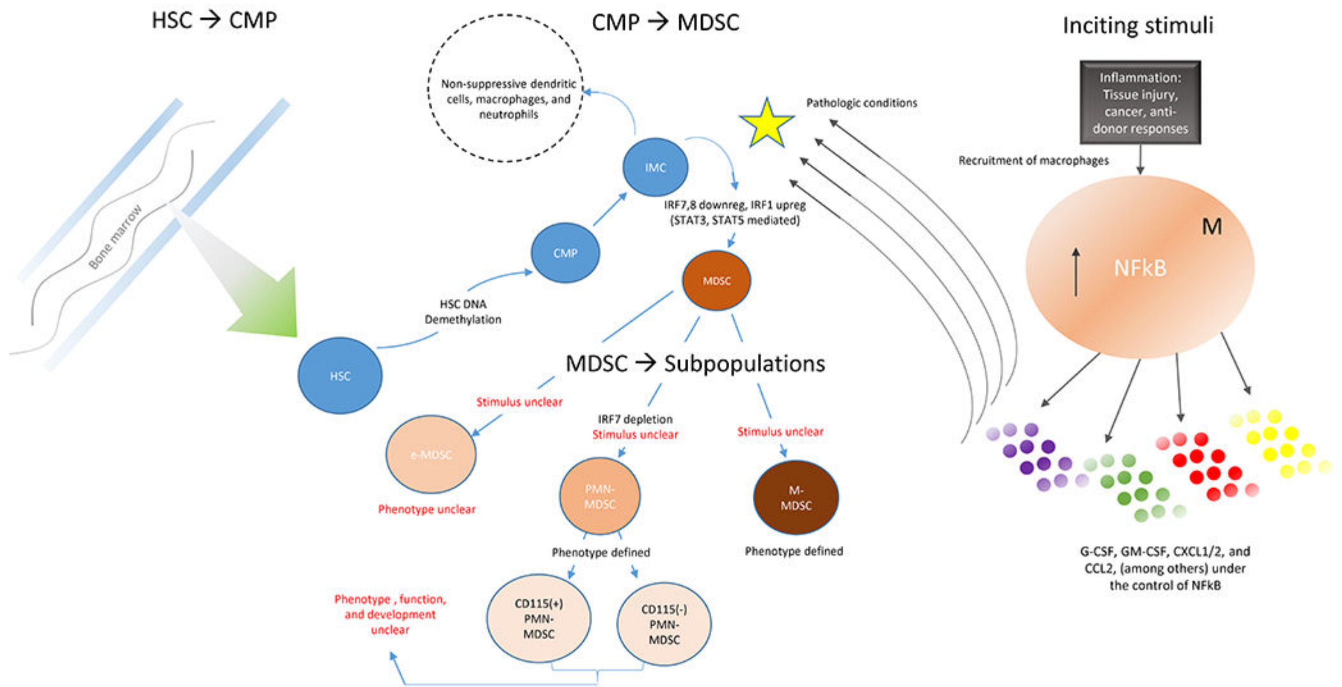

Figure 1.

Development of MDSCs based on a synthesis of the literature

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Table 1:

Phenotype of MDSCs for humans and mice

Molecules known to upregulate MDSC proliferation *and/or* lead to MDSC activation		
• IL-1B	• CXCL8	• S100A8/A9
• IL-2	• CXCL12	• HMGB1
• IL-4	• CXCR4	• PGE2
• IL-6	• SDF-1	
• CCL2	• TGF-beta	
• CCL5	• IFN-gamma	
• CXCL1/2	• G-CSF	
• CXCL6	• GM-CSF	

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Table 2:

Inflammatory signals which activate MDSCs and lead to their chemotaxis

Accepted phenotyping of MDSCs in mice and humans		
Mice		
M-MDCS	PMN-MDSC	e-MDSC
CD11b+Gr-1^{mid}Ly6C^{hi}Ly6G−CD49d+	CD11b+Gr-1hiLy6C^{low}Ly6G+CD49d−	poorly defined
Human		
M-MDCS	PMN-MDSC	e-MDSC
CD11b+CD14+HLA-DR$^{low/-}$CD15^{-}	CD11b+CD14−CD15+(or CD66b+)	Lin-(CD3/14/15/19/56)/HLA-DR−/CD33+