The progress of immunosuppressive therapy has dramatically improved the short-term results of organ transplantation. However, no immunosuppressive drug is devoid of side-effects, and despite multiple therapeutic strategies to use immunosuppressive drugs in a less toxic manner, no alternative regimen has seriously challenged the universal use of these drugs in transplantation until recently. Immune cells with suppressive function have newly emerged as potential therapeutic approaches for the induction of prolonged allograft survival in a mature immune system that is free from immune suppression and chronic rejection. In this respect, manipulation of myeloid cells with potent inhibitory activity represents an innovative therapeutic methodology to achieve this goal, and the term MDSC has been proposed recently to define cells of myeloid origin with suppressor function [1].

As negative regulators of the immune response, MDSC includes a morphologically and functionally heterogeneous population of myeloid progenitor cells, which consist of monocytes, macrophages, granulocytes, DCs, and immature myeloid cells at different stages of differentiation. Given the wide range of cell types that may be included in this category, finding a phenotypic profile that characterizes all of them has been a difficult task. In mice, all MDSCs express the cell-surface markers CD11b+Gr1+ [2]. CD11b is a subunit of the β2 integrin macrophage receptor 1, which is expressed in granulocytes, DCs, monocytes, and macrophages and regulates leukocyte adhesion and cell migration. The Gr1 antigen is expressed predominantly on the surface of monocytes/macrophages and granulocytes and is recognized by the RB6-8C5 antibody, which binds to the cell-surface molecules Ly6C and Ly6G.

The most important function of MDSC is to inhibit the cytotoxic response mediated by T lymphocytes and NK cells. However, as a result of their heterogeneous phenotype, MDSCs can use diverse mechanisms to control immune responses. Tumor-derived MDSCs inhibit T cell responses through reactive oxygen species. In addition, MDSC-mediated depletion of nutrients required by T cell growth and differentiation, such as of L-arginine and L-cysteine, has been reported to inhibit T cell responses via iNOS [2].

Although described initially in cancer patients, MDSCs are also present in other inflammatory settings, including solid organ transplantation. MDSCs accumulate in the allografts of tolerant recipients and mediate the induction of indefinite allograft survival by inhibiting T cell proliferation and expanding the numbers of graft-infiltrating regulatory T cells [3]. As a result of their ability to manipulate the immune response effectively, several culture conditions for the generation of MDSCs in vitro have been developed. Whereas most methods use a combination of cytokines (IL-4, IL-6, IL-13, and IL-33), growth factors (vascular endothelial growth factor), and inflammatory mediators (PGE2, cyclooxygenase, and hypoxia-inducible factor 1α) [2], the effects of common immunosuppressive drugs in MDSC development, such as glucocorticoids, are largely unknown. Glucocorticoids are steroid drugs with anti-inflammatory and immunosuppressant effects that are given routinely to transplant recipient patients. Whereas the beneficial effects of glucocorticoids have been long demonstrated, the mechanisms of action by which steroid hormones mediate their suppressive function in transplant recipients are not fully understood.

In this issue of the Journal of Leukocyte Biology, Liao et al. [4], report that the glucocorticoid Dex significantly prolongs skin-graft survival to fully mismatched allografts. Mechanistically, the authors show that in vivo Dex treatment in transplant recipients results in a significant increase in the number of CD11b+Gr1+ MDSCs systemically (allograft, draining lymph node, spleen, blood, and bone marrow). Interestingly, Dex treatment induces the expression of the chemokine receptor CXCR2 in MDSCs, which is necessary for their migration into the allograft. Interestingly, the interference with CXCR2, using an in vivo blocking mAb, prevents graft-survival prolongation despite Dex treatment. This finding unmasks a previously unrecognized mechanism of action of glucocorticoids and is consistent with an

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**Abbreviations:** DC=dendritic cell, Dex=dexamethasone, Gr1=glucocorticoid receptor, Gr1=granulocyte differentiation antigen 1, L-NMMA=NOS inhibitor Nω-monomethyl-L-arginine, MDSC=myeloid-derived suppressor cell
earlier report, which demonstrated that MDSC migration to the allografts was required for the induction of indefinite allograft survival [3]. It also extends the findings from the Bernard Vanhove laboratory [5], which described the critical role for chemokine and chemokine receptor expression by MDSCs (CCL5/CCR5) in the control of kidney transplantation tolerance. Interestingly, Liao et al. [4] associate the up-regulation of CXCR2 expression with GR expression, as blocking GR with RU486 diminishes CXCR2 expression, reduces MDSC recruitment to the allografts, and diminishes graft survival.

Liao et al. [4] also demonstrate that Dex-induced MDSCs produce lower levels of TNF-α and higher levels of the immune modulatory cytokine IL-10. This is consistent with a previous report, which showed that LPS-induced MDSCs produce large amounts of IL-10 that were able to prolong graft survival in a skin-transplant model. In their study, Le Moine and colleagues [6] demonstrated that blocking IL-10 inhibited the suppressive function of MDSC, which resulted in early skin-graft rejection. This is consistent with a previous study, which demonstrated that Dex induces an anti-inflammatory monocyte that resembles MDSC. In their study, Sunderkoetter and colleagues [7] demonstrated that CD11b+Gr1+ myeloid cells up-regulate the expression of anti-inflammatory cytokine IL-10 and down-regulate the expression of the inflammatory cytokine IL-6 following 48 h of Dex treatment. In addition, Dex-treated monocytes were shown to increase motility and transmigration capacity, indicating that glucocorticoid-induced monocytes not only have an anti-inflammatory activity, but they can also migrate more rapidly to the inflammation site in vivo. On the contrary, the ability of glucocorticoid-treated CD11b+Gr1+ myeloid cells to suppress T cell proliferation was not investigated by Sunderkoetter and colleagues [7].

The main finding of Liao and colleagues [4] is that Dex-induced MDSCs produce large amounts of NO in the recipient allografts. Treatment with L-NMMA, which competitively inhibits the generation of NO from arginine and is a useful tool for inhibition of NO-mediated effects, results in MDSC loss of suppression function and abrogation of prolonged allograft survival. Furthermore, the authors demonstrated the critical role for NO in Dex-induced MDSC in a very elegant experiment. Adoptive transfer of Dex-treated MDSC but not Dex + L-NMMA-treated MDSCs was able to prolong allograft survival in MDSC-depleted recipients. These results are in agreement with previous literature described, which demonstrated that MDSCs, required for the induction of indefinite allograft survival, express high levels of iNOS. The critical role of NO in transplantation was demonstrated by blocking iNOS with aminoguanidine in vivo, which results in rapid rejection of all kidney donor allografts in long-term, tolerant recipients (>120 days post-transplant) [8]. The reported allograft protection mediated by iNOS may be a result of direct inhibitory effects of NO or through its reaction with the superoxide anion to form peroxynitrite, which is highly toxic [2] (Fig. 1).

In summary, the findings by Liao et al. [4] (in this issue) provide novel, mechanistic insights linking the necessary role of MDSCs in transplantation and Dex. The present study unveils a novel protocol to induce MDSCs in vivo, which compliments previous studies aiming at preventing MDSC function. As MDSCs were described initially in cancer patients and tumor-bearing mice and are, in part, responsible for the inhibition of the cell-mediated immune response against the tumor, most therapeutic application with MDSCs proposes to reduce their expansion and inhibit their activation [2]. However, MDSCs have considerable relevance to the crucial problem as to why a growing tumor

![Figure 1](image-url)  
**Figure 1.** Dex-induced MDSCs mediate T cell suppression and prolong skin allograft survival. In vivo-induced CD11b+Gr1+ MDSCs secrete IL-4 and IL-10 in transplant recipients following Dex treatment. Dex-induced CD11b+Gr1+ MDSCs inhibit T cell proliferation and prolong fully allogeneic skin-graft survival through NO-dependent mechanisms.
Editorial: The intricacy of choice: can bacteria decide what type of myeloid cells to stimulate?

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Sepsis is a major cause of death in the Western world with high mortality rates in ICUs. The disease is characterized by an excessive and dysregulated immune response to microbial infections, coagulation abnormalities leading to capillary leakage, lung damage, and finally, multiple organ failure [1]. It is known that most septic patients in ICUs, in addition to hyperinflammatory response, suffer from a hypoinflammatory state, which often leads to sepsis-induced multiorgan dysfunction and death. This suggests that sepsis-induced immunosuppression is a significant factor contributing to these deaths. MDS Cs may be a critical element in the development of such a hypoinflammatory state and thus, in the outcome of the disease.

Although MDSCs were described originally in cancer [2], it has now become increasingly clear that MDSCs play an important role in the regulation of immune responses in many pathological conditions not directly associated with infections.

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**KEY WORDS:** transplantation tolerance · immune regulation

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**DISCLOSURES**

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Editorial: Dexamethasone and MDSC in transplantation: yes to NO

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