

Mesenchymal Stem Cells: A Potential Border Patrol for Transplanted Islets?

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Type 1 diabetes is a disorder caused by the autoimmune-mediated destruction of insulin-producing β -cells in the pancreas (1). Many promising intervention trials are currently underway or in development to prevent β -cell loss in patients with recent-onset type 1 diabetes and in individuals at increased risk for type 1 diabetes due to the presence of autoantibodies or elevated genetic risk (2). Despite this hope for future interventions, islet transplantation remains the only therapeutic option currently available for individuals with established type 1 diabetes when insulin therapy fails to maintain adequate metabolic control (3). Islet allograft transplantation has demonstrated great success in terms of restoring normoglycemia (4). Unfortunately, the long-term efficacy following transplantation has been limited due to chronic graft rejection (5). Thus, an optimal approach would involve an islet transplantation protocol that would prevent graft rejection without the need for potentially dangerous long-term and nonspecific immune suppression.

Mesenchymal stem cells (MSCs) have been proposed to be one possible means to enhance current islet transplantation protocols (6). MSCs represent a population of nonhematopoietic precursor cells that have generated marked interest and attention for their capacity to elicit tissue regeneration (7–9). For the treatment of type 1 diabetes, the therapeutic potential of MSCs is potentially twofold. First, these cells are reported to provide critical growth factors for tissue regeneration (8). Second, these cells possess potent immunoregulatory properties that could be exploited to suppress allograft rejection following transplantation (6).

In this issue of *Diabetes*, Ding et al. (10) provide evidence that MSCs possess the capacity to impede T-cell activation both in the context of a delayed-type hypersensitivity reaction and following an islet allotransplantation protocol. The authors essentially accomplished this through a series of in vitro and in vivo studies suggesting that MSCs exert potent immunosuppressive properties by blocking the interleukin (IL)-2 cytokine signaling pathway required for T-lymphocyte activation, expansion, and differentiation (11,12).

Given the potent immunosuppressive properties of MSCs, the authors of this article sought to interrogate the

potential mechanism(s) of suppression. A prior study had implicated various immunomodulatory pathways in the ability of MSCs to suppress T-cell responses. These include production of the immunomodulatory cytokines TGF- β and IL-10 (13) as well as enzymatic pathways involving indolamine 2,3-dioxygenase (12), nitric oxide synthase (14), and heme oxygenase-1 (15). Adding to the existing literature, Ding et al. demonstrate the potent immunosuppressive properties of MSCs in vitro either when cocultured with polyclonal T-cells that are activated with microbeads coated with anti-CD3 and anti-CD28 or during allogeneic antigen stimulation. The authors noted little influence on T-cell activation when the pathways described previously were specifically targeted. On the other hand, these authors did observe that production of the enzymes matrix metalloproteinase (MMP)-2 and -9 by MSCs had a potent immunosuppressive effect on T-cell activation. This finding is analogous to that described previously by Sheu et al. (16), who showed that MMP-2 and -9 production by tumors is capable of creating an immunosuppressive microenvironment. The authors also showed that the mechanism of suppression of T-cell activation involved the specific cleavage of CD25 (the α -chain of the IL-2 receptor) from the surface of responding CD4⁺ T-cells (see Fig. 1).

How can the findings by Ding et al. be translated into the clinic to benefit patients with type 1 diabetes? Whereas the authors demonstrated the efficacy of MSCs in suppressing a delayed-type hypersensitivity response and in preventing rejection of an islet allograft, additional studies are clearly warranted in animal models that more closely approximate clinical treatments in humans. Specifically, it will be helpful for future studies to test the capacity of MSCs to prevent allograft rejection in nonimmunodeficient recipient hosts (i.e., the authors reconstituted immunodeficient BALB/c Rag^{-/-} γ ^{-/-} mice with naive BALB/c CD4⁺CD25⁻ T-cells and transplanted B6 islets in the presence or absence of BALB/c MSCs). Moreover, it will be informative to assess the site of action for MSCs. Are MSCs simply guarding the border of the transplanted tissue to create a local immunosuppressive milieu, or is there a long-term tolerogenic effect of MSCs in the draining lymph nodes of the target organ, presumably the site where the majority of antigen priming occurs? Finally, it is of interest whether MSCs will show efficacy in blocking recurrent autoimmunity and preventing allograft rejection, with the former presumably a more difficult response to impede because memory T-cell responses may be less dependent on IL-2 signaling for effector function (16). One could also speculate that the cleavage of CD25 from the surface of regulatory T-cells (a population of cells characterized as IL-2 dependent and constitutively CD25⁺) might be detrimental in some settings (17,18). These questions are critical for understanding the mechanism(s) of action of MSCs and in the future design of translational therapies.

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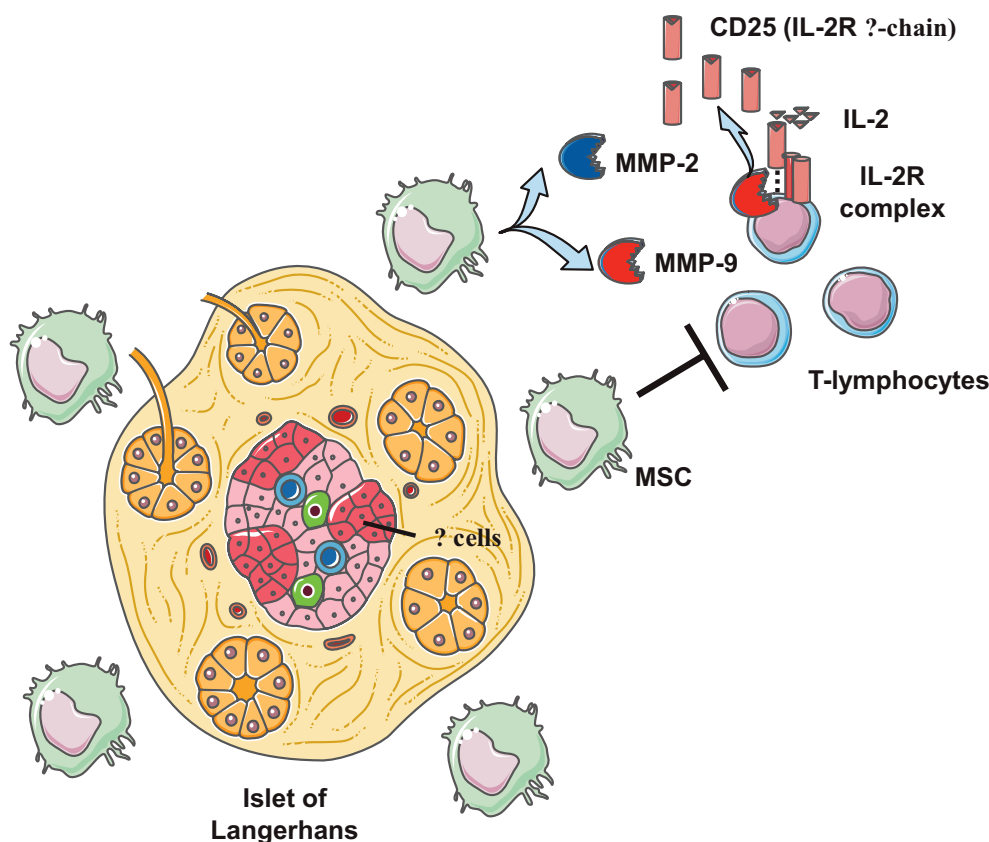


FIG. 1. MSCs protect transplanted allogeneic islets by creating an immunosuppressive microenvironment. MMP-2 and -9 produced by MSCs suppress T-cell responses by cleaving the high-affinity growth factor receptor CD25 (the α -chain of the IL-2 receptor) from the surface of infiltrating T-lymphocytes.

From a broader immune standpoint, questions remain regarding the immunomodulatory properties of MMP-2 and -9. These proteolytic enzymes are produced not only by MSCs (as highlighted in this issue) but also by innate antigen-presenting cells as well as in an autocrine fashion by T-cells following activation (reviewed in 19). Their role in modulating the normal immune response remains poorly defined and requires additional consideration.

This study brings to light a novel mechanism by which MSCs can protect transplanted tissues and raises the possibility that these cells could be added to current protocols to improve the long-term engraftment of transplanted islets. Clearly, more studies in animal models are required to validate these results and further describe the therapeutic mechanisms of MSCs.

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