

# Pancreatic Islet Transplants and IDO: When Starving the Enemy Does You Good

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**C**ompetition for essential nutrients and/or release of toxic metabolites are mechanisms highly conserved in both bacteria and higher organisms as innate defense systems from external pathogens. One such mechanism is based on the activation of indoleamine 2,3-dioxygenase (IDO), an enzyme that catalyzes the catabolism of the essential amino acid tryptophan (rev. in 1). By depleting tryptophan, IDO limits the ability of many pathogens to synthesize proteins. In addition, activation of the enzyme results in the accumulation of tryptophan breakdown products, collectively known as kynurenines, some of which are toxic to bacteria and parasites.

Consistent with the enzyme effects on the containment of pathogens' replication and invasion, constitutive IDO expression in higher organisms is found at mucosal interfaces, such as the mucosa of the intestine and the lung, which are barriers to external microorganisms (2). However, chronic inflammatory processes, particularly those sustained by interferon-driven immune responses, can induce high levels of IDO in many cell types including epithelial, endothelial, and myeloid cells (3–7). Intriguingly, under these conditions, active IDO appears to mute lymphocyte immune responses by “starving” actively proliferating leukocytes, thereby limiting the uncontrolled spread of inflammation. Both high levels of IDO as well as activation of the enzyme by redox active compounds present in the inflammatory microenvironment are required for the immunosuppressive effect (8).

The ability of IDO to regulate lymphocyte functions has prompted many investigators to test the effect of IDO overexpression at transplantation sites as a mean to avert destructive allogeneic immune responses against heart, skin, lung, cornea, and bone marrow grafts (9–13). Along these lines of studies, the article by Jalili et al. (14), published in this issue of *Diabetes*, demonstrates that local overexpression of IDO by fibroblasts cotransplanted with pancreatic islets can, by a bystander effect, significantly delay immune rejection of the graft in the absence of immunosuppressive treatment of the host. The authors show that IDO overexpression induces Th2 immune responses, downregulates the production of alloantigen-specific antibodies, and induces the transient appearance of T-cells with a regulatory phenotype in draining lymph

nodes. These findings reinforce the concept put forward in other transplantation settings that local overexpression of IDO may be a powerful tool to foster transplant tolerance and shed light into mechanisms of immunoregulation driven by this enzyme.

An intriguing finding reported by Jalili et al. is the containment of leukocyte infiltration in the grafts expressing IDO. This effect correlated with decreased expression of chemokines involved in T-cell recruitment. Although previous studies have reported a decreased lymphocyte infiltration in tissues overexpressing IDO, evidence was lacking that this effect may be related to a role played by this enzymatic pathway in controlling T-cell homing. This possibility is consistent with the observation that certain tryptophan metabolites downregulate the expression of lymphocyte adhesion receptors as well as monocyte chemoattractants in endothelial cells (15). Presently it remains unclear to what extent the phenomenon described by Jalili et al. is accounted for by the unique cellular composition of the grafts (i.e., IDO-expressing dermal fibroblasts and islets). IDO transduction in keratinocytes and fibroblasts was reported to alter expression of genes relevant to inflammatory processes (16,17). Hence, it will be important to determine in future studies whether IDO overexpression in skin fibroblasts also results in a unique chemokine or cytokine profile capable of influencing immune cell migration. Furthermore, it will be critical to show through the use of enzymatic inhibitors (e.g., 1-methyltryptophan) that the effect on graft infiltration by immune cells is truly dependent on the activation of the IDO transgene. Finally, IDO expression may induce other mechanisms of immune privilege independent of chemotactic factors as reported (18). Nevertheless, although clearly not elucidated yet, the observation by Jalili et al. remains noteworthy, as it suggests that, at least in the selected cellular context, control of leukocyte trafficking may be an additional mechanism by which IDO averts immune responses.

The induction of Th2 immune responses described by Jalili et al. is consistent with reported effects of IDO expressed by stromal cells and professional antigen-presenting cells, such as dendritic cells (DCs), on T-cell immune responses in vitro (rev. in 19). A role of IDO in maintaining a Th2 bias was also shown in other pathological conditions in vivo such as in animal models of asthma (19). This Th2 bias may be functionally linked to the observed concomitant downregulation of alloantibody production since Th1 immune responses are required for cognate help to B-cells and antibody responses. Hence, local overexpression of IDO may impact on both T- and B-cell arms of immune responses in islet transplantation settings. Further, the evidence that T-cells with a regulatory phenotype accumulate in draining lymph nodes indicates the potential for IDO to affect not only local immune responses, but also to systemically facilitate immunoregulatory networks. This latter observation is intriguing as it

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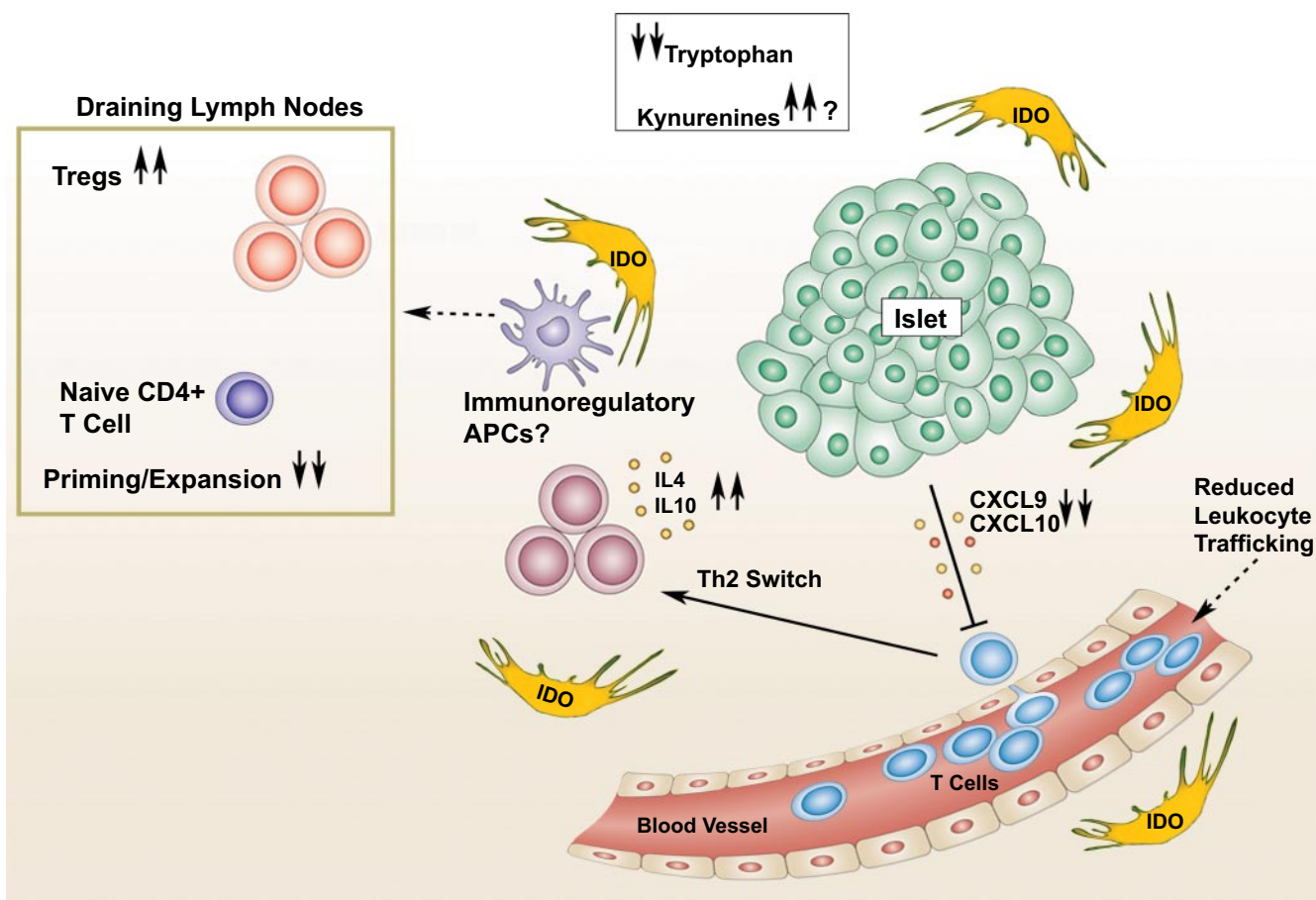


FIG. 1. Overview of the effects of IDO overexpression in composite fibroblasts/islet grafts as described by Jalili et al. (14). Dashed lines and question marks indicate possible mechanisms suggested by the authors' data.

implies that local expression of IDO may affect the emergence of migratory antigen-presenting cells (e.g., DCs) competent to expand regulatory T-cells (Tregs) in secondary lymphatic stations. A role of interferon and IDO activation in the generation of immature immunoregulatory DCs was demonstrated in previous *in vitro* studies (20). As Jalili et al. provide only a limited analysis of CD11c<sup>+</sup> cells populating the grafts, a more comprehensive characterization of myeloid cell populations is warranted to evaluate their role in the induction of Tregs in their experimental setting. On the other end, such increased frequency of Tregs appears to be transient. Further work is needed to determine whether this result is linked to the loss of IDO expression within the grafts over time or to the unique features of IDO-induced Tregs (e.g., short life span and/or reprogramming into other T-cell types).

Overall, the findings by Jalili et al. (14) are promising and suggest the potential for islets grafts positioned in an IDO-enriched transplant microenvironment to evade immune rejection, at least transiently, through multiple mechanisms (Fig. 1). Perhaps more effective gene transfer approaches, ensuring persistence of high levels of IDO expression, may improve this outcome in the future. However, long-term, potentially toxic effects of tryptophan metabolites on pancreatic islets are currently unknown. In addition, possible species-specific differences between mouse and human islets in their response to tryptophan metabolites will have to be carefully evaluated. It is also unknown whether, in a

transplantation setting, a chronic state of immunosuppression maintained by local IDO expression may select for pathogens that are resistant to tryptophan deprivation, thereby enhancing the risk of opportunistic infections postsurgery. Finally, overexpression of IDO may not necessarily result in enhanced tryptophan catabolism since enzyme activation depends upon posttranslational modifications influenced by the inflammatory microenvironment. Hence, paradoxically, a sustained inflammatory microenvironment may be required for persistent IDO activation and induction of immunoregulatory networks. Will it be possible to maintain the transplant microenvironment permissive to IDO activation without tilting the balance toward immune rejection? How would the autoimmune milieu of type 1 diabetic transplant recipients influence activation of IDO delivered locally? Promising work has begun to address some of these questions (21). However, a more in-depth knowledge of the molecular mechanisms triggering the activation of IDO—as well as a better understanding of how tryptophan deprivation and/or its metabolites functionally impact on select inflammatory cell subsets—will be critical to guide possible therapeutic strategies based on the use of IDO in clinical settings.

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