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Preview

Bone marrow chimerism breaks the barrier to pancreatic islet transplantation

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In their recent *Cell Reports* paper, Chang and colleagues report on a successful strategy to achieve durable mixed hematopoietic chimerism that promotes the engraftment and long-term function of pancreatic islet allotransplants in fully immunocompetent mice without immunosuppression.

Transplantation of whole pancreas or isolated pancreatic islets has long been sought as an ideal alternative to daily injections of insulin for the treatment of type 1 diabetes (T1D). Yet, after more than five decades of intense research both with animal models and human clinical trials, the requirement of lifelong immune suppression to prevent graft rejection remains a major challenge due to significant short- and long-term complications. These include the occurrence of malignancies; lymphoproliferative disorders; corticosteroid-associated endocrine, cardiovascular, and kidney dysfunctions; metabolic and neural syndromes; and increased risk of infections.[1]

In their recent *Cell Reports* paper, Chang and colleagues[2] devised a strategy for immune conditioning of transplant hosts based on the treatment with anti-CD117 antibodies (Abs), a procedure adapted from bone marrow transplantation protocols applied to the treatment of hematologic malignancies.[3,4] The authors show that blockade of CD117 expressed by the hosts' bone marrow hemopoietic cells prior to infusion of an allogeneic donor bone marrow results in a robust hemopoietic chimerism. This pre-conditioning allows for allogeneic islets, major histocompatibility complex (MHC)-matched to the allogenic bone marrow, to successfully engraft and cure diabetes in immunocompetent mice. Further conditioning with anti-CD4 and CD8 Abs and low levels of radiation helped achieve and sustain the hemopoietic chimerism over time.

In considering the translational value of this approach, it could be argued that although the irradiation regimen used in the study is relatively mild, there are potential drawbacks and health risks associated with total body radiation exposure. Yet, a 200-cGy irradiation corresponds to roughly 20 medical X-rays, whereas one routine X-ray exposes the subject to about 100 mGy.[5] Ultimately, based on the notion that the anti-CD117 Ab treatment itself can target organs other than the hemopoietic system (e.g., kidney tubular epithelium and reproductive organs), it will be important to carefully evaluate risks versus benefits associated with this approach on a case-by-case basis, particularly if prospective transplant recipients are very young and/or with pre-existent disfunction of other organs. It should also be noted that anti-CD117 Ab treatment in association with far less toxic immune conditioning regimens, such as anti-CD47 Ab, are currently being sought after for tissue transplantation.[6,7] These approaches have shown promising results in animal models of allogeneic bone marrow transplantation and are currently under intense investigation in clinical trials.[8] In light of the robust bone marrow chimerism achieved in the present study, adoption of those safer conditioning approaches in place of irradiation may have a great potential for translation to the clinic in a wide range of cell replacement therapies, from the transplantation of allogeneic pancreatic islet tissue to the transplantation of solid organs, ultimately doing away with lifelong regimens of immunosuppression.

Of great significance is the fact that the bone marrow cell infusion was made with enriched hematopoietic stem/progenitor cells (HSPCs) depleted of mature effector immune cells. Currently, in the clinical setting, the transplantation of purified $CD34^+$ HSPCs while reducing the risks of graft versus host disease (GVHD) can pose the challenge of low levels of engraftment due to deficits of the host bone marrow niche caused by the myeloablative regimens prior to HSPC infusion. The protocol developed by Chang and colleagues yields robust levels of $CD34^+$ cell engraftment, a result likely linked to the relatively mild and non-myeloablative preconditioning regimen with the anti-CD117 Abs. This approach may spare critical cellular components of the bone marrow niche, thus facilitating HSPC engraftment. These are important aspects of the study that likely explain the absence of GVHD.

Finally, the authors show that long-term transplant engraftment can be achieved regardless of whether the islet transplant is performed at the same time as or after the hemopoietic chimerism is established. This is an important result indicating that there is translational potential of this protocol in the setting of allogenic islet transplantation, where islet tissue and bone marrow will need to be harvested simultaneously from the same cadaveric donors. In the future, since successful reversal of glycemia in diabetic transplant recipients requires islet tissue from multiple donors, it will be important to assess whether grafts mismatched at several MHC loci will still be accepted long term post-transplant. Alternatively, this conditioning approach could be applied to the induction of transplant tolerance to other sources of islet tissue, such as stem cell-derived pancreatic beta cells.

Lastly, one additional question raised by this study is whether this regimen could be successfully applied to support graft acceptance of islet tissue transplants in the context of an autoimmune genetic background. The pathophysiology of T1D includes defective function of both antigen-presenting cells and regulatory T cells (Tregs), with T effector cells that may be refractory to Treg suppression.[9] Therefore, islet transplantation and immunomodulation in such genetic contexts is expected to be challenging. Hence, before the approach described by Chang and colleagues can be applied to an autoimmune milieu, a more detailed functional characterization of central versus peripheral mechanisms of tolerance of both bone marrow donor and host's origin is warranted. Nevertheless, it is worth noting that in previous clinical trials, non-myeloablative autologous bone marrow transplantation could transiently keep autoimmunity against pancreatic islets at bay and delay full-blown disease.[10,11] Therefore, one can be guardedly optimistic that non-myeloablative regimens similar to the one used here could one day be effectively used to control and/or overcome recurrent autoimmune destruction of islet transplants in T1D.

Thus far, CD117 Ab-based immune conditioning has largely been applied to hemopoietic stem cell transplantation for cancer treatment. Aside from a careful consideration of possible side effects and the need for further validation in preclinical models, the results presented by Chang and colleagues suggest a wider therapeutic application for CD117 blockade that could extend to the induction of islet transplant tolerance. As such, the study by Chang and colleagues represents an important stepping stone toward the development of successful cell transplantation therapies that can restore lost pancreatic islet cell function in T1D and in select cohorts of patients with type 2 diabetes (T2D).

DECLARATION OF INTERESTS

The authors declare no competing interests.

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