Antigen-Encoding Bone Marrow Terminates Islet-Directed Memory CD8+ T-Cell Responses to Alleviate Islet Transplant Rejection - DTU Orbit (08/11/2017)

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Islet-specific memory T cells arise early in type 1 diabetes (T1D), persist for long periods, perpetuate disease, and are rapidly reactivated by islet transplantation. As memory T cells are poorly controlled by “conventional” therapies, memory T cell–mediated attack is a substantial challenge in islet transplantation, and this will extend to application of personalized approaches using stem cell–derived replacement β-cells. New approaches are required to limit memory autoimmune attack of transplanted islets or replacement β-cells. Here, we show that transfer of bone marrow encoding cognate antigen directed to dendritic cells, under mild, immune-preserving conditions, inactivates established memory CD8+ T-cell populations and generates a long-lived, antigen-specific tolerogenic environment. Consequently, CD8+ memory T cell–mediated targeting of islet-expressed antigens is prevented and islet graft rejection alleviated. The immunological mechanisms of protection are mediated through deletion and induction of unresponsiveness in targeted memory T-cell populations. The data demonstrate that hematopoietic stem cell–mediated gene therapy effectively terminates antigen-specific memory T-cell responses, and this can alleviate destruction of antigen-expressing islets. This addresses a key challenge facing islet transplantation and, importantly, the clinical application of personalized β-cell replacement therapies using patient-derived stem cells.

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