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Delayed rejection of allogeneic transplants of pancreatic islet in NOD mice with streptozotocin-induced diabetes

Abstract

Transplantation of pancreatic islets emerged as an attractive alternative to standard insulin therapy in type 1 diabetes (T1D). Unfortunately, immune rejection of transplanted allogeneic islets is one of the major factors limiting its application to larger number of T1D patients and new strategies for tolerance induction are being searched for. Streptozotocin (STZ)-induced, acute hyperglycemia has been shown to induce long-term tolerance to transplanted allogeneic islets in healthy recipients, when islets were transplanted shortly after hyperglycemia induction. Considering importance of genetic background in the development and function of immune system, the aim of this work was to determine the effect of STZ-induced acute hyperglycemia on immune system and immune rejection of allogeneic pancreatic islets in autoimmune-prone NOD mice model. The main focus is on the balance between effector (Teff) and regulatory T cells (Treg).

Obtained results demonstrate that STZ-induced acute hyperglycemia delays but doesn't abrogate rejection of pancreatic islets in NOD mice, when islets are transplanted on second but not ninth day after STZ treatment. Acute hyperglycemia causes also drop of the cell numbers in lymphoid organs, accompanied by increased ratio of Tregs. Staining for marker of proliferation marker along with adoptive cell transfer to lymphopenic host revealed higher homeostatic expansion of Tregs over Teffs. Moreover, adoptive co-transfers of cells from hyper- and normoglycemic donors showed that Teffs are stronger affected by acute hyperglycemia in their potential to expand. Analysis of gene expression by RT-qPCR showed overexpression of pro-apoptotic protein PUMA in T effs but not Tregs, on second but not on ninth day after STZ administration. Analysis of TCR repertoire revealed that expansion of T cells after acute hyperglycemia induction is not clonal and doesn't reshape TCR repertoire of Teffs and Tregs. Moreover, acute hyperglycemia does not affect specificity of the response to alloantigens.

Taken together, presented results suggest that STZ-induced acute hyperglycemia causes apoptosis of effector T cells during first days after hyperglycemia induction which, together with increased ratio of regulatory T cells, creates tolerance-favoring environment leading to delayed rejection of allogeneic pancreatic islets.