Type 1 diabetes (T1D) is a chronic disorder in which the cells of the immune system mediate selective destruction of the insulin-producing beta-cells in the islets of Langerhans in the pancreas. CD4+ effector T cells, including Th1 and Th17 cells, are crucial mediators during disease development. Therefore, therapeutic strategies against T1D should target both T cell subtypes. We analyzed mechanisms of tolerance in plastic Th17 cells, and found that convertible (Th17 to Th1) cells displayed downregulation of the chemokine receptor CXCR3 that was associated with diminished T-bet expression and impaired trafficking to the pancreas. In contrast, stable Th17 cells downregulated RORgammat but increased FasL expression and died by apoptosis. Thus, the final signature transcription factor shapes the mechanism of tolerance in plastic Th17 cells.

Reversal of overt T1D requires restoration of beta-cell mass. It has been established that the diabetic state is tightly associated with a striking decrease of the islet endothelial cells, leading to poor beta-cell survival and function. Given that the endothelial progenitor cells (EPCs) reside in the bone marrow, we coupled bone marrow transfer with an antigen-specific therapy, and tested it against overt T1D. Indeed, transfer of whole bone marrow or fractioned EPCs gave rise to islet endothelial cells, which facilitated regeneration of endogenous beta-cells and normalization of glucose levels. Therefore, this work provides a new avenue in design of future therapies against T1D by emphasizing the importance of re-establishing a functional microvascular network and the symbiotic relationship between endothelial and beta-cells in the islet of Langerhans.