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Loss of peripheral immune tolerance contributes to the progression of Type 1 Diabetes (T1D). Ectopic expression of self-products, normally confined to specific tissues, is required for particular tolerogenic cells outside these tissues to exert their antigen-specific tolerogenic effects. Thus, loss of tolerance may be due to a reduced ability of tolerogenic cells in peripheral lymphoid tissues (lymph nodes and spleen) to ectopically express and present the needed tissue-specific self-antigens, resulting in an insufficient elimination or inactivation of self-reactive T cells that escaped deletion in the thymus. As we previously demonstrated, this is particularly evident in the pancreatic lymph nodes of T1D-susceptible mice, prior to onset of hyperglycemia, and of T1D patients, where the function of DEAF1, a regulator of ectopic expression of self-antigens, becomes impaired. In this context, it may be difficult for tolerogenic cells with insufficient islet antigen expression to target and control diabetogenic T cells. The nature of the peripheral tolerogenic cells (ie. outside the thymus) capable of expressing islet antigens in healthy humans is presently unknown. In a collaborative effort between the Creusot and Farber groups, we propose to obtain lymph node and spleen tissues from control donors, isolate cells of tolerogenic potential (stromal and dendritic cells), characterize them and fractionate them into subsets, in which we can then detect the expression of tissue-specific antigens, with a particular focus on islet antigens and antigens known to be targeted by diabetogenic T cells in humans. This pilot project would greatly help future translational studies looking into the dysfunction of DEAF1 and of self-antigen expression and presentation in the relevant tolerogenic cell subsets. Such studies will lead the way to new therapeutic approaches aimed at repairing the defective tolerogenic mechanisms or administering functional and disease-targeting tolerogenic cells, with the ultimate goal of reinforcing tolerance, a prerequisite to a cure for this disease.