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Immunopathology

CTLA-4 regulation of autoimmune thyroiditis: a role for IFN- γ induced indoleamine 2, 3 dioxygenase in disease

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Cytotoxic T-lymphocyte antigen-4 (CTLA-4) signals are known to play important role in immune tolerance by providing negative signals for T cells. The precise role of CTLA-4 remains unclear in autoimmune thyroiditis (AT). We investigated the role of CTLA-4 signals in the spontaneous mouse model of AT, the NOD.H2^{h4} mouse. The disease is enhanced after excess intake of dietary iodine in this mouse model, similar to humans. Administration of anti-CTLA-4 monoclonal antibody (mAb) to iodine fed NOD.H2^{h4} mice significantly enhanced AT as compared to mice receiving iodine alone. Increased serum levels of thyroglobulin (Tg)-specific IgG1 autoantibody were observed that characteristically represented the disease in treated mice. Anti-CTLA-4 mAb treated group of mice also showed an increased population of T-regulatory (T_{reg}) cells, and elevated levels of Th1 and Th2 type of cytokines. *In vitro* studies showed that recombinant IFN- γ induced strong expression of enzyme indoleamine 2, 3-dioxygenase (IDO) in the cultured peritoneal macrophages, and splenic dendritic cells from the anti-CTLA-4 mAb treated mice as compared to control mice on iodine. Furthermore, enhanced expression of IDO was also observed in the local thyroid macrophages of anti-CTLA-4 treated mice by immunohistochemical staining. We demonstrate that anti-CTLA-4 treatment of iodine fed NOD.H2^{h4} mice exacerbated AT by upregulation of cytokines that in turn induced the expression of enzyme IDO in local and lymphoid antigen presenting cells (APCs).