Functional deficiencies of granulocyte-macrophage colony stimulating factor and interleukin-3 contribute to insulitis and destruction of beta cells

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The pathogenesis of type 1 diabetes (T1D) involves the immune-mediated destruction of insulin-producing beta cells in the pancreatic islets of Langerhans. Genetic analysis of families with a high incidence of T1D and nonobese diabetic (NOD) mice, a prototypical model of the disorder, uncovered multiple susceptibility loci, although most of the underlying immune defects remain to be delineated. Here we report that aged mice doubly deficient in granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-3 (IL-3) manifest insulitis, destruction of insulin-producing beta cells, and compromised glucose homeostasis. Macrophages from mutant mice produce increased levels of p40 after LPS stimulation, whereas concurrent ablation of interferon-gamma (IFN-gamma) ameliorates the disease. The administration of antibodies that block cytotoxic T lymphocyte associated antigen-4 (CTLA-4) to young mutant mice precipitates the onset of insulitis and hyperglycemia. These results, together with previous reports of impaired hematopoietic responses to GM-CSF and IL-3 in patients with T1D and in NOD mice, indicate that functional deficiencies of these cytokines contribute to diabetes.

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