Dynamic changes in pancreatic endocrine cell abundance, distribution, and function in antigen-induced and spontaneous autoimmune diabetes.

OBJECTIVE: Insulin deficiency in type 1 diabetes and in rodent autoimmune diabetes models is caused by beta-cell-specific killing by autoreactive T-cells. Less is known about beta-cell numbers and phenotype remaining at diabetes onset and the fate of other pancreatic endocrine cellular constituents.

RESEARCH DESIGN AND METHODS: We applied multicolor flow cytometry, confocal microscopy, and immunohistochemistry, supported by quantitative RT-PCR, to simultaneously track pancreatic endocrine cell frequencies and phenotypes during a T-cell-mediated beta-cell-destructive process using two independent autoimmune diabetes models, an inducible autoantigen-specific model and the spontaneously diabetic NOD mouse.

RESULTS: The proportion of pancreatic insulin-positive beta-cells to glucagon-positive alpha-cells was about 4:1 in nondiabetic mice. Islets isolated from newly diabetic mice exhibited the expected severe beta-cell depletion accompanied by phenotypic beta-cell changes (i.e., hypertrophy and degranulation), but they also revealed a substantial loss of alpha-cells, which was further confirmed by quantitative immunohistochemistry. While maintaining normal randomly timed serum glucagon levels, newly diabetic mice displayed an impaired glucagon secretory response to
non-insulin-induced hypoglycemia. CONCLUSIONS: Systematically applying multicolor flow
cytometry and immunohistochemistry to track declining beta-cell numbers in recently diabetic mice
revealed an altered endocrine cell composition that is consistent with a prominent and unexpected
islet alpha-cell loss. These alterations were observed in induced and spontaneous autoimmune
diabetes models, became apparent at diabetes onset, and differed markedly within islets compared
with sub-islet-sized endocrine cell clusters and among pancreatic lobes. We propose that these
changes are adaptive in nature, possibly fueled by worsening glycemia and regenerative processes.