Role of inflammation in BPA induced ß-cell defects in offspring

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Abstract

Bisphenol A (BPA), is associated with increased risk of type 2 diabetes and obesity in humans and animals. We have previously shown that maternal BPA exposure in mice at comparable human exposure levels (10 µg/kg/day or 10 mg/kg/day) increases body fat, impairs glucose tolerance, and reduces insulin secretion in first (F1) and second generation (F2) adult male, but not female offspring. Expression of key immune response genes was also altered. Immunostaining of F1 pancreatic sections showed increased staining of CD3 for T-lymphocytes and F4/80 for macrophages in islets of BPA male mice. Luminex assays of pancreatic lysates also showed increased levels of the Type 2 (Th2) immune response cytokines in F1 and F2 BPA adult male mice. It is unclear what the underlying mechanisms are for this inflammatory response in BPA exposed mice, whether the inflammatory process is causal to the ß-cell phenotype, what the progression of the immune response is, and the mechanisms responsible for preventing the deleterious effects of BPA in female mice. Our preliminary data showing a significant reduction in ER□ expression in islets of F1 and F2 adult male offspring (no change in female mice), results of previous studies showing that estrogens and BPA mediate their action on ß-cell function via ER□□□and the finding that loss of ER□ leads to perturbed development of thymus and spleen and an altered immune response, lead us to hypothesize that the reduction in ER□□expression in the ß-cell mediated by maternal BPA exposure induces an exaggerated activation of Th2 immune cell populations in ß-cells leading to ß-cell dysfunction in the F1 and F2 offspring. In this pilot proposal we will determine: 1) whether islets, spleen and thymus of BPA exposed offspring have functionally distinct immune cell populations; 2) the progression of the immune cell dysfunction; and 3) whether the immune cell profile differs in male and female mice.