The Impact of Microbiome Alterations in the NOD Mouse Model of Type 1 Diabetes

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Abstract

Type 1 Diabetes (T1D) is an autoimmune disease characterized by the T cell mediated destruction of insulin producing β cells in the pancreatic islets. Although more than 40 genetic risk loci have been identified, much of the total heritable T1D risk remains unaccounted for. Epidemiological and experimental data suggest that environmental factors, such as the composition of the gut microbiome, may play a role in the disease. The non-obese diabetic (NOD) mouse model of T1D recapitulates many aspects of the immunopathogenesis of the human disease. The non-obese resistant (NOR) mouse is a strain closely related to the NOD, but is protected by the genetic contributions from the C57BLKS/J strain. The T1D incidence in the NOD mouse exhibits a noted sex bias, with T1D incidence in females at ~80%, and ~30% in males, which is dependent on microbial colonization status; germ-free female NOD mice display a T1D incidence similar to that of males. Recent work from our group and others demonstrate that alterations in commensal microbes can alter disease incidence. Specifically, our lab found that male-derived microbiome transplant into female NOD mice produced durable alterations in the gut microbiome of treated mice and protected them from T1D in a hormone-dependent mechanism.
The first goal of my work was to investigate the possible protective effects of NOR-derived microbiome transplant in the NOD model of T1D. We hypothesized that the T1D protection afforded by genetic contributions from the C57BLKS/J strain in the NOR strain might also be linked to microbiome composition. Previous work in our lab found 5 bacterial taxa which were differentially abundant between NOD and NOR animals. We report the design and validation of qPCR-based quantification assays for these 5 bacterial taxa. Quantification of these taxa in adult NOD and NOR mice confirms 16S pyrosequencing in our lab showing differential abundance between NOD and NOR animals. We further report these 5 taxa show major shifts between weaning and adulthood in NOD mice, specifically between 25d and 41d of age. Furthermore, quantification of these taxa in NOD, NOR and NOD recipients of NOR-derived microbiome transplant (NOR→NOD) found that the microbiome of NOD→NOR mice were neither identical to the NOR donor microbiome, nor a simple mix of NOD and NOR contributions. Finally, we report that, despite quantifiable, durable changes in the gut microbiome of NOR→NOD mice, these mice were not protected from T1D, which is in contrast to previous results in our lab showing male→female microbiome transfers were protective against T1D.

The second part of this thesis aimed to investigate the possible protective effects of treatment with probiotic microbes in the NOD model of T1D. T1D and gut inflammatory disorders have been found to share genetic risk factors, and can occur as co-morbidities suggesting shared genetic and environmental factors in T1D and autoimmune diseases of the gut. Studies in ulcerative colitis, inflammatory bowel syndrome and T1D have suggested that probiotic bacteria can have protective effects in these diseases. We hypothesized that continuous treatment with Protecflor probiotic would impact the gut microbial composition of diabetes-prone NOD mice, and consequently, have an effect on the progression of islet autoimmunity. We report oral gavage
and subsequent drinking water treatment with Protecflor protected treated mice from autoimmune infiltration of the islets (insulitis) in the NOD mouse model of T1D. We further report treated mice differed in gut microbiome composition in multiple taxonomical groups, as determined by high-throughput 16S sequencing. Multivariate analysis of 16S sequencing results revealed correlations between differing bacterial taxa and insulitis severity in Protecflor and vehicle-treated mice. Further analysis suggested correlations between ecological community indices for richness and diversity and insulitis severity. Thus, probiotic treatment with Protecflor alters the gut microbial community and is protective against insulitis in the NOD model.