
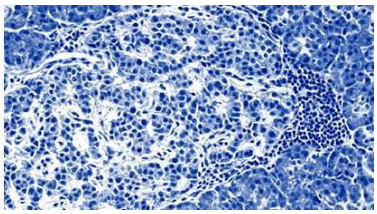

Virus-Mediated Dysbiosis Promotes Autoimmunity and Type 1 Diabetes Onset

AUTHORS

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PURPOSE

In combination with genetic determinants, susceptibility to autoimmune diseases such as Type 1 Diabetes (T1D) is established by various environmental factors including microbial dysbiosis, exposure to dietary antigens, antibiotic use, vitamin D deficiency, and infection. Compelling evidence indicates commensal bacteria and viruses are important cofactors in T1D development and pathogenesis. Clinical and epidemiological studies have implicated infection with certain viruses such as coxsackievirus B (CVB) to be a risk factor associated with diabetes onset. Infections may be an instigating factor to alter the microbiome and this microbial change may be sufficient to promote autoimmunity. As an enterovirus, CVB is spread via a fecal-oral route, yet little is known about how this virus affects the intestinal microbiome. Recently, mucosa-associated invariant T (MAIT) cell populations were shown to be altered leading up to diabetes onset in patients and in mice. These cells are activated by microbial products derived from riboflavin biosynthesis in the gut to promote intestinal integrity, but they can also take on a more inflammatory phenotype and participate in autoimmune responses in the pancreas. Ultimately, there exists a significant potential for cross-talk between CVB infection, the microbiome, and gut-resident immune cells impacting T1D susceptibility and we proposed to analyze this interrelationship.

METHODS

To address these questions, we modeled the interaction a non-obese diabetic (NOD) mice to examine how the commensal bacteria composition in the gut is altered by CVB4 infection. We used a number of techniques including NGS and FMT analysis to examine the interrelationship between virus infection, the microbiome and diabetes onset.

SUMMARY OF RESULTS

CVB4 not only promotes onset of T1D in these mice but also causes dysbiosis and loss of bacterial diversity which resembles that of a spontaneously diabetic NOD mouse. Introducing this new infection-induced microbial composition into naïve mice through the use of fecal microbiome transfers (FMTs) can accelerate T1D onset and alter immune profiles in the gut as well as the pancreas. We have found MAIT populations are altered by a “diabetogenic” microbiome and respond directly to CVB4 infection.

CONCLUSIONS

Together our data highlights the role of the gut microbiome and its ability to affect immune homeostasis and contribute to T1D development.