Impact of *Parabacteroides distasonis* Colonization on Hosts' Microbiome, Immune Responses, and Diabetes Onset

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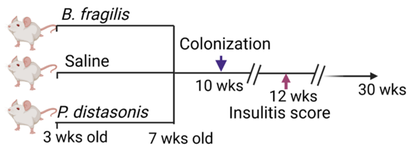
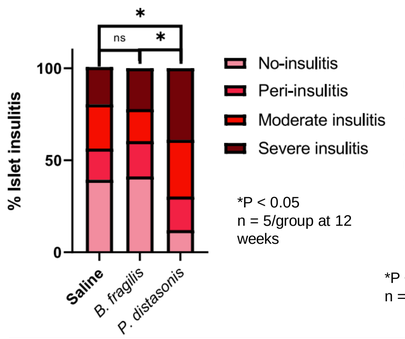
Abstract

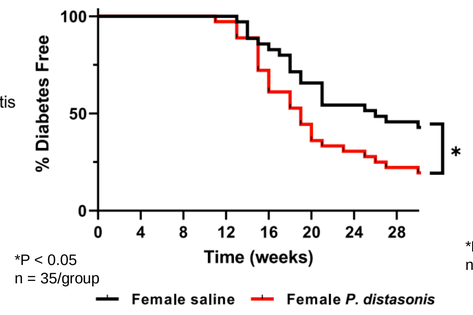
Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by the destruction of pancreatic, insulin-producing beta cells by autoreactive T-cells. Limited research is available on what activates autoreactive T-cells though T1D incidence is increasing worldwide. People with T1D have altered gut microbiome which is thought to be associated with T1D development. In T1D, amino acids 9-23 of the insulin B chain (insulin B:9-23) are a primary autoantigen. We previously showed *Parabacteroides distasonis* (*Pd*), a human gut commensal, has a peptide in HPRT that cross-reacts with human and mouse insulin B:9-23-specific T-cells in vitro. Orally gavaging 3-week non-obese diabetic (NOD) mice with *Pd* accelerated diabetes onset compared to the saline-treated mice. We hypothesize *Pd* is accelerating T1D onset via molecular mimicry of insulin B:9-23. *Pd* did not stimulate small intestinal epithelial lymphocytes and did not change small and large intestinal permeability. The abundance of only 28 amplicon sequence variants changed, indicating gut alpha diversity was minimally affected. Among the cytokines, *Pd* colonization lowered IL-15. Injecting mice with the metabolite most enriched in colonized mice, TMAO, did not significantly accelerate pancreatic insulitis. To assess the impact of *Pd* in the absence of gut microbes, germ-free NOD mice were orally gavaged with *Pd* once at 3 weeks of age. Germ-free NOD *Pd*-colonized mice had more severe insulitis but gut permeability and the serum metabolite composition did not change. Neonatal NOD mice gavaged with *Pd*, had fewer splenic CD4+ T-cells, more FOXP3+ regulatory T-cells, suggesting immune tolerance to *Pd*. Our findings further support our hypothesis that *Pd* accelerates T1D onset via insulin mimicry. Despite enhancing a specific autoimmune response, *Pd* causes similar effects as non-inflammatory commensals in NOD mice.

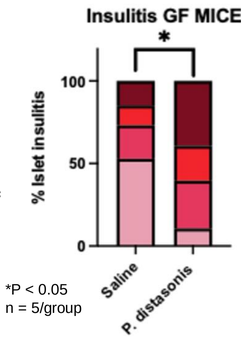
P. distasonis accelerates diabetes onset in SPF and GF NOD mice



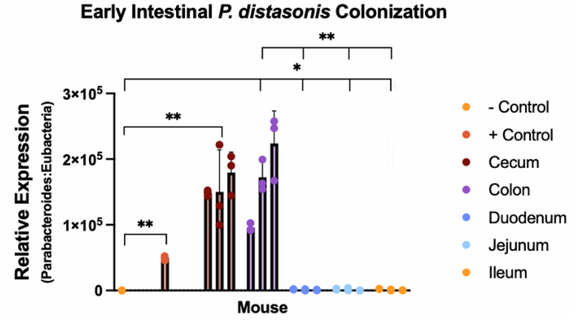
Human insulin B:9-23 peptide SHLVEALYLVCGERG
Hyperactive peptide SHLVEALYLVCGEEG
***Parabacteroides distasonis* 33B** RILVELLYLVCSEYL

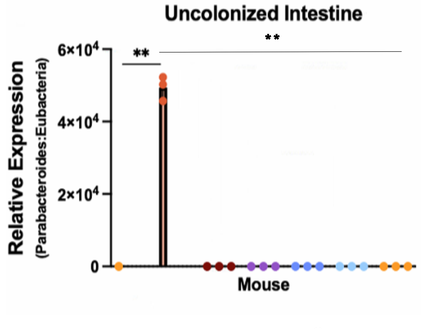


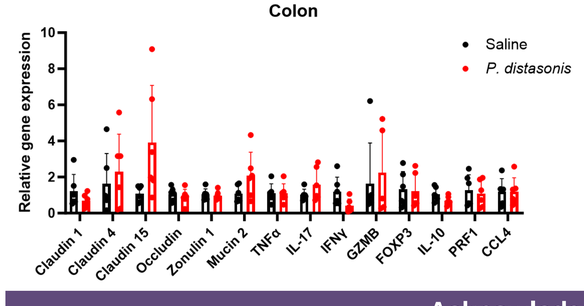


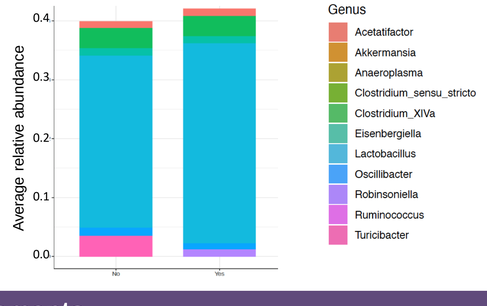


P. distasonis colonizes the cecum and colon and preserves gut integrity and microbial diversity

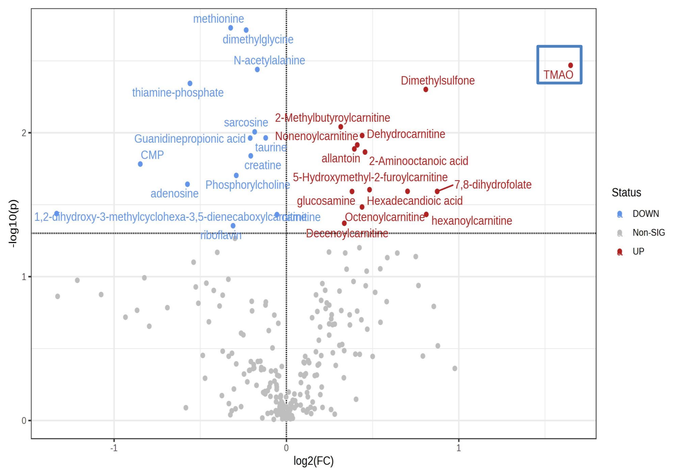


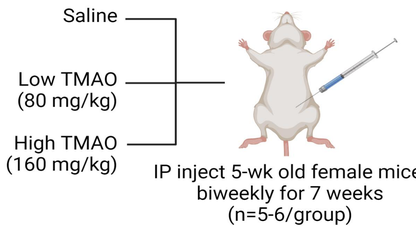


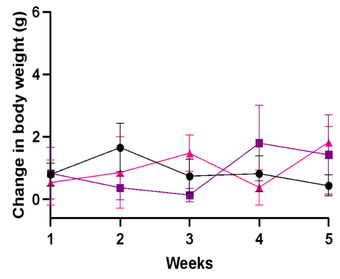




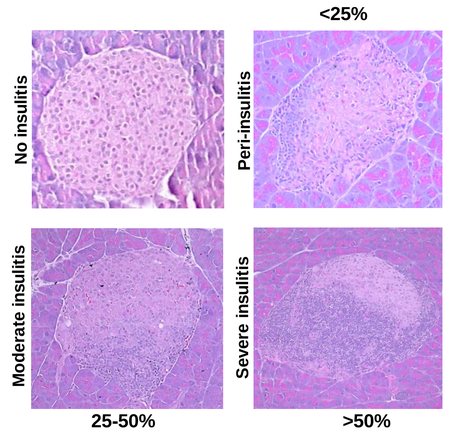
P. distasonis increases the pro-inflammatory metabolite TMAO in the serum

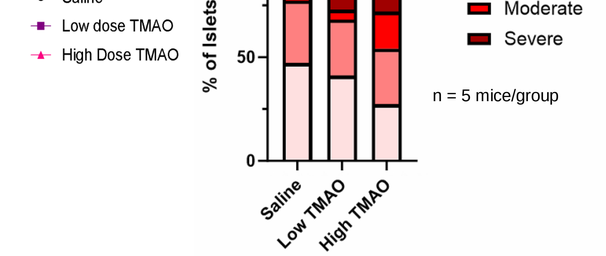




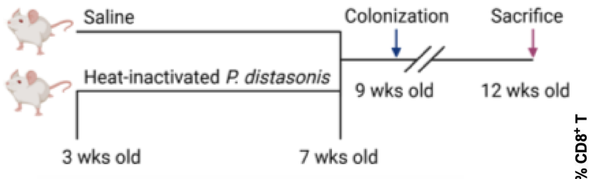


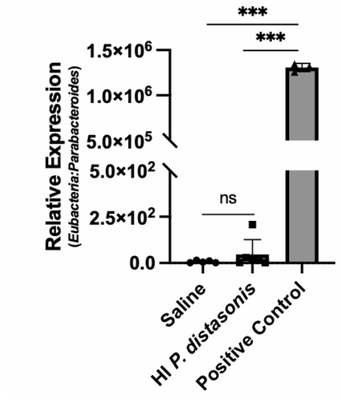
TMAO does not significantly accelerate insulitis

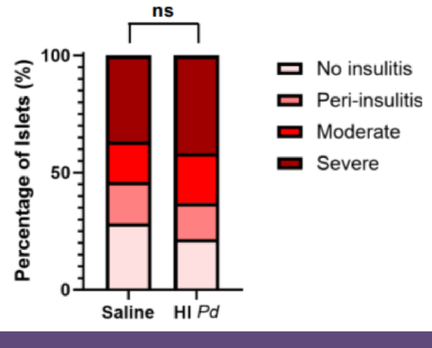


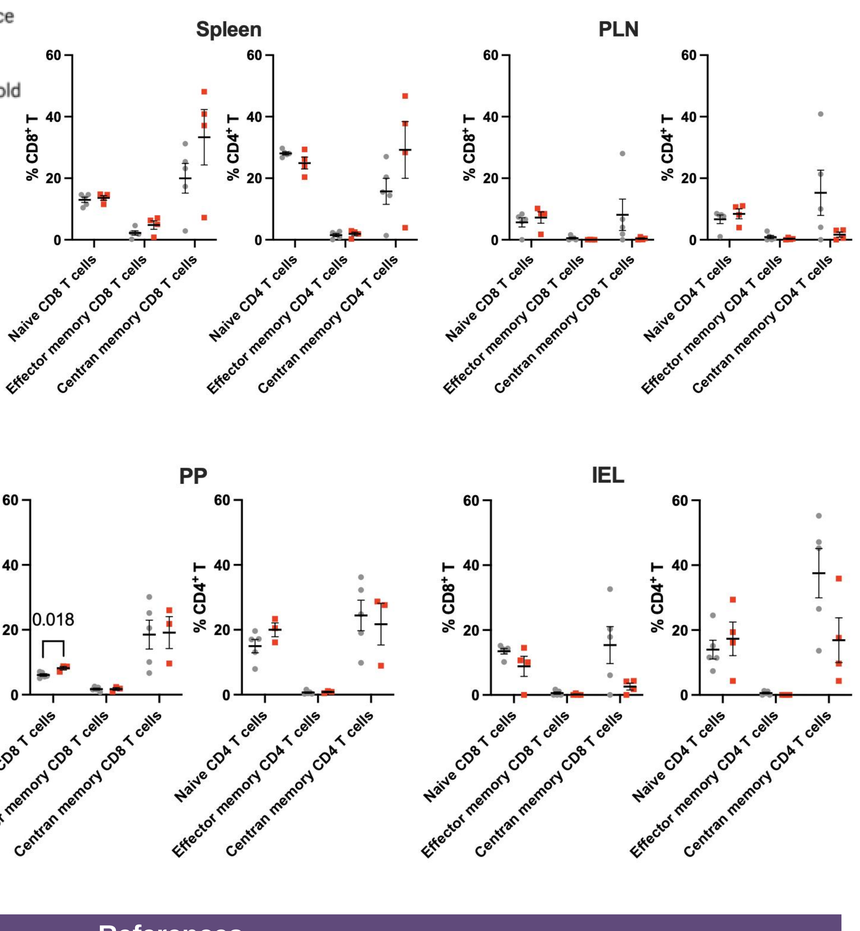


Heat-inactivated *P. distasonis* does not accelerate insulitis and does not stimulate intestinal inflammation









Acknowledgements

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References

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