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Resistant starch supplementation limits kidney injury in an experimental model of anti-neutrophil cytoplasmic antibody associated vasculitis

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Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is a rare autoimmune disease of unknown aetiology. The characteristic feature of the disease is severe inflammation of the small blood vessels, causes severe kidney injury (glomerulonephritis).(1) Within 3 years of diagnosis 30% of patients either relapse and die or become dialysis dependent.(1) Neutrophils are the key mediator of injury in this disease, whereby autoimmunity to the major neutrophil enzyme myeloperoxidase (MPO) or proteinase 3 results in the generation of ANCA which binds to activated neutrophils and triggers a unique form of pathological cell death termed "neutrophil extracellular traps" (NETs) or NETosis. Neutrophil activity is highly influenced by microbial metabolites, including short chain fatty acids (SCFAs), produced from fermentation of non-digestible carbohydrates by the gut microbiota. We utilised a well-established mouse model of AAV, whereby autoimmunity is to MPO is generated via subcutaneous immunisation with recombinant murine MPO at Day 0 and Day 7. Mice were randomised to receive either a control diet or a diet supplemented with 15% resistant starch (RS) ($n = 8$ per group). These diets were isocaloric and matched for fat, protein and micronutrient content. At Day 20, mice were culled. Formalin-fixed kidneys were embedded in paraffin, stained with Periodic Acid-Schiff and glomerular injury was assessed blinded. Glomerular neutrophil and macrophage infiltration were assessed by immunohistochemistry. Cecal contents were collected, DNA extracted and the V1-V2 hypervariable region amplified using 27F and 338R universal primers. Raw sequence data were analysed using dada2 and taxonomy assigned using the SILVA 138.1 database, taxa with a prevalence threshold < 5% were removed. The resistant starch intervention significantly reduced segmental necrosis in glomeruli (77.63 ± 7.2% v. 25.59 ± 4.5%, $p < 0.0001$) and reduced both neutrophil (1.3 ± 0.37 per glomerular cross section [*p*/gcs] v. 0.4 ± 0.3 *p*/gcs, $p < 0.0001$) and macrophage (1.6 ± 0.3 *p*/gcs v. 0.4 ± 0.08 *p*/gcs, $p < 0.0001$) infiltration into glomeruli. The resistant starch diet significantly altered the gut microbiol consortium (Unweighted Unifrac PERMANOVA $p < 0.0001$) and was associated with a substantial expansion of *Bacteroidaceae* (3.9% ± 1.3% v. 10.3% ± 5.3%, $q < 0.0001$) and *Muribaculaceae* (17.2 ± 6.6% v. 35.5 ± 8.4%, $q < 0.0001$), both SCFA producing bacteria, primarily butyrate and propionate, respectively. This is the first report of the therapeutic efficacy of a resistant starch supplemented diet in experimental AAV. These findings suggest that the use of a gut targeted dietary intervention causing expansion of SCFA-producing bacteria represents a promising therapeutic avenue to limit autoimmune kidney injury in AAV.

Reference

1. Kitching AR, Anders HJ, Basu N, *et al.* (2020) *Nat Rev Dis Primers* **6**, 71.