Low-grade mucosal inflammation in aged SAMP8 mice blunts recovery after DSS-induced colitis

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The intestinal barrier becomes compromised in various pathological conditions. Increasing evidence suggests a link between a disrupted gut microbiome, heightened intestinal permeability, and accelerated aging, although the underlying mechanisms remain poorly understood. To investigate the relationship between aging and gastrointestinal (GI) dysfunction, we used a mouse model that exhibits accelerated aging, the senescence-accelerated prone 8 (SAMP8) model and compared it to its naturally aging control, SAMR1. At baseline, SAMP8 mice demonstrated an age-related increase in colonic mucosal inflammation, characterised by a higher histological damage score, increased myeloperoxidase activity, and elevated levels of pro-inflammatory cytokines. Surprisingly, this low-grade intestinal inflammation did not correspond with changes in GI transit or epithelial barrier permeability when compared to SAMR1 mice at any of the tested ages (2, 5, 9, and 11 months). To determine whether this pro-inflammatory state would make SAMP8 mice more susceptible to pathological insults, we exposed them to dextran sodium sulphate (DSS) to mimic chronic colitis. This involved three cycles of 7 days of DSS treatment, followed by 7 days of normal drinking water. Daily observations revealed that SAMP8 mice exhibited a higher disease activity index than SAMR1 mice, especially during the first cycle of DSS treatment. Among the various molecular and physiological markers related to colitis that we assessed, only a significant increase in paracellular flux was observed in 11-month-old SAMP8 mice. Reasoning that this might indicate slower recovery, we quantified the proportion of Ki67-positive cells in the mucosa to measure epithelial cell turnover. SAMP8 mice showed a significantly lower abundance of Ki67 signal after DSS-induced colitis, suggesting a reduced cell proliferation rate. Additionally, SAMP8 mice did not show an upregulation of *IL-22* expression. IL-22 is a cytokine crucial for tissue repair as it promotes epithelial cell proliferation and regulates inflammation. We also observed up-regulation of the antimicrobial peptide-encoding genes *Reg3b* and *Reg3g*, which respond to infections and have been previously associated with aging. Based on these findings, we hypothesize that low-grade immune hyperactivity impairs intestinal barrier recovery in aged SAMP8 mice following DSS-induced colitis.