NLRP1 exacerbates colitis-associated cancer through IL-18, with effects on butyrate producing Clostridiales

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Inflammasomes are cytoplasmic protein complexes that cleave and activate the cytokines IL-1β and IL-18. Different innate immune sensors such as NLRP3 and NLRP6 can form inflammasomes, and regulate the host microbiome. In their absence, mice are more susceptible to dextran sodium sulphate (DSS)-induced colitis. In contrast, we studied mice that lack all alleles of NLRP1, and show that they are resistant to DSS-induced colitis and colitis-associated carcinogenesis. This protection can be transferred to co-housed wild-type mice. Microbiome analysis revealed that protective species from the Clostridiales order were increased in the absence of NLRP1 and that this was associated with increased butyrate production in the colon. Butyrate supplementation, or vancomycin treatment to deplete clostridiales, equilibrated the mice and resolved the phenotype. Humans with an activating mutation in NLRP1 suffer from an inflammatory skin disease associated with cancer. We found that mice with an activating mutation in NLRP1a were more susceptible to DSS-induced colitis, and colon cancer, due to increased IL-18 production. Increased NLRP1 expression was also observed in biopsies from the colon from patients with ulcerative colitis, and associated with decreased levels of Clostridiales. These data suggest a novel role for NLRP1 in irritable bowel disease and colitis-associated cancer, which could be targeted to increase the levels of protective butyrate producing commensals and treat disease.