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Introduction Up to 40% of patients with inflammatory bowel disease (IBD) also suffer with osteoporosis.[1] Receptor activator of NF-kB ligand (RANKL) promotes the formation of bone resorbing osteoclasts and is linked to osteoporosis.[2] RANKL is controlled by decoy receptors, osteoprotegerin (OPG) and TNF-stimulated gene-6 (TSG6) that bind to it and block osteoclast bone resorption.[2] We have shown increased serum levels of RANKL in a mouse model of colitis and bone disease.[3] RANKL may also increase the lifespan and activity of dendritic cells (DCs), which accumulate in the colon in colitis.[3] We hypothesise that the RANKL pathway links the development of colitis with bone disease and aimed to determine the mechanism of action of RANKL, OPG and TSG6 on DC function.

Methods We used the validated *Trichuris muris*, mouse whipworm induced model of colitis.[4] After infection, wildtype C57BL/6 mice develop a resolving colitis while IL10-KO (knockout) mice develop a chronic colitis. Colitis was assessed histologically and expression of RANKL family members by immunofluorescence and quantitative real time PCR (qRT-PCR). Additionally, the effects of RANKL family members were assessed in cultured bone marrow derived DCs.

Results The colitis was severe in the IL10-KO mice, with statistically significant increases in colitis scores and crypt length from a mean of 80 to 147 μm, $p<0.001$ between uninfected and infected IL10-KO mice but not wildtype controls with resolving colitis. qRT-PCR of RANKL, OPG and TSG6 mRNA in colonic snips showed increased expression over the course of infection in wildtype mice but decreased expression in IL10-KO mice. Immunofluorescence staining of colonic sections showed expression of OPG and TSG6 in macrophages and epithelial cells. Finally, in vitro functional assays on bone marrow DCs from wildtype naïve mice surprisingly showed that RANKL had little effect on the expression of DC maturation markers (CD80, CD86, MHCII). In contrast, OPG and TSG6 promoted MHCII and CD86 expression but not CD80.

Conclusion The results suggest that increased expression of RANKL, OPG and TSG6 may be important in the resolution of colitis, in contrast to their decreased expression in persistent colitis. This finding supports our hypothesis that molecules which control bone homeostasis are involved in controlling colitis. The direct effects of RANKL members on DCs is unclear as the decoy receptors may partially activate DC function or promote activation of specific DC subsets.

Competing interests None.

Keywords Dendritic cell, Inflammatory Bowel Disease, Osteoprotegerin, Receptor activator of NF-κB ligand, TNF-stimulated gene-6.

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MECHANISMS UNDERLYING THE DEVELOPMENT OF INFLAMMATORY BOWEL DISEASE: THE ROLE OF RANKL IN DENDRITIC CELL ACTIVITY

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