Natural Killer (NK) cells and γδ T cells differentially modulate Th17-driven disease in ankylosing spondylitis.

Wythe, S.E., Freidin, A. Griseri, T., Demetriou, P, Freidin, A. *McCann, F.E. and *Horwood, N

Kennedy Institute of Rheumatology, University of Oxford, Old Road Campus, Roosevelt Drive, Headington, Oxford, OX3 7FY.

* equal contribution

Ankylosing spondylitis (AS) is characterised by chronic joint inflammation, associated inflammatory bowel disease, and inappropriate new bone formation at the entheses. However, the immunological factors linking gastrointestinal inflammation with joint pathology have not been delineated. Natural Killer (NK) cells are recruited to these inflammation sites and previous studies in our laboratory have shown that NK cells augment osteoblast differentiation of mesenchymal stem cells, stimulating new bone growth. As such we hypothesized that NK cells form a bridge linking gastrointestinal inflammation and joint pathology. To test this, we used the BALB/c ZAP-70^{W163C}-mutant (SKG) mouse model of AS, Curdlan treated SKG mice were depleted of NK cells (anti-asialo GM1) and paw swelling, enthesitis and weight scored weekly. Inflammation was observed in both the ileum and the joint following challenge, and significantly NK cell numbers were increased at both sites in control curdlan mice. NK-depletion exacerbated weight loss and ileitis inflammatory score, correlating with increased numbers of γδT cells, Th17 cells, and neutrophils there however in the joint, arthritis, enthesitis and new bone formation were ablated with a significant reduction in γδT cells and neutrophils. In contrast, γδ T cell depletion (clone GL3; 2x/wk; i.p) moderately increased disease in both ileum and joint. Thus, we suggest a conflicting role for NK cells and gd T cells in gut versus joint pathology, protective in the SI but disease promoting in the joint. and perhaps NK-γδT cell cross-regulation is an important factor in determining morbidity associated with this complex multifactorial disease. [247 words]