Cellular Cholesterol Homeostasis is Altered in Murine Models of Rheumatoid Arthritis and is Linked to Enhanced Myelopoiesis

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Rheumatoid arthritis (RA) is associated with a ~2-fold elevated risk of morbidity and mortality from atherosclerotic cardiovascular disease (CVD) compared with the general population. Atherosclerosis in RA patients tends to be more aggressive and therefore more challenging to treat. Identifying CVD in these patients is difficult as traditional CVD risk factors, such as changes in plasma lipid profiles (i.e. elevated LDL, decreased HDL) are not always observed, underscoring the need for better understanding of the reasons contributing to the enhanced atherosclerosis in RA patients. People with RA often have monocytosis and neutrophilia, which we hypothesize to plays causal roles in atherosclerosis. Two mouse models of RA were used, K/BxN serum transfer and collagen induced arthritis (CIA). Flow cytometry was used to quantify the abundance of leukocyte and stem cell subsets. BODIPY-cholesterol was employed to determine the membrane cholesterol status of the various cells. Prominent monocytosis and neutrophilia due to an expansion and increased proliferation of the haematopoietic stem and multipotential progenitor cells (HSPCs) in the bone marrow (BM) was observed in both models of RA. There was also an increase in the mobilisation of HSPCs into the circulation, which homed to the spleen, resulting in extramedullary haematopoiesis. Interestingly, key cholesterol efflux genes, Abca1, Abcg1 and Apoe were down regulated in the BM HSPCs isolated from the K/BxN mice, resulting in increased cell membrane cholesterol levels. We also observed an increase in the expression of the common beta subunit of the interleukin-3 receptor on the HSPCs and the M-CSF receptor in myeloid progenitor cells, likely explaining their increased proliferation and skewing to the myeloid lineage. Moreover, blood monocytes and neutrophils had increased membrane cholesterol content, independent of changes in plasma cholesterol levels. These data suggest that while plasma cholesterol levels may not be increased in RA, cellular cholesterol homeostasis might be increased. We hypothesize that this, together with enhanced monocyte production, underlies the increased risk of CVD in RA.