Neutrophils and autoantibodies in autoimmune rheumatic diseases

Background
Neutrophils and autoantibodies represent two sides of the inflammatory spectrum in autoimmune rheumatic diseases. Despite the adaptive immune system being responsible for the specific attacks towards self-antigens, the innate immune system is involved by intricate cell-cell crosstalk providing inflammatory or immunoregulatory signals guiding the adaptive response. Both abnormalities in neutrophil function and presence of autoantibodies targeting nuclear antigens (ANA) are associated with several rheumatic diseases, two of which being systemic lupus erythematosus (SLE) and juvenile idiopathic arthritis (JIA). This thesis will be an investigation of neutrophil function in relation to clinical disease in SLE and JIA as well as an in-depth analysis of autoantibodies in JIA.

Research question and methods
1. How does a SNP in the NCF1 gene regulating neutrophil function and affect clinical disease phenotype in SLE?
2. How are neutrophil phenotypes, functions and immunomodulatory effects altered in the inflamed joint in JIA?
3. Are ANA produced locally in the inflamed joint in JIA?
4. What are the antigens for autoantibodies in JIA, and how are these related to clinical outcome?
All questions will be answered using translational methods including clinical data, patient material and cellular/molecular assays.

Preliminary results
1. Neutrophils with NCF1-339 T-genotype have impaired oxidative burst and altered formation of neutrophil extracellular traps. The T-genotype is associated with serum interferon and antiphospholipid syndrome in SLE.
2. JIA synovial neutrophils are activated and “polarized”. Neutrophils from JIA blood and synovial fluid have impaired phagocytosis and oxidative burst.
3. ANA are enriched in synovial fluid compared to plasma. Tertiary lymphoid organs containing antibody-producing cells can be found in synovial tissue.
4. JIA autoantibodies bind previously unknown ANA targets, which might be associated with specific disease outcomes.

Significance
Altered neutrophil function is associated with both SLE and JIA but no current treatment specifically targets neutrophils. Knowledge about how neutrophil function is associated with pathology could open new venues for therapeutic intervention. Specific antibodies are often associated with certain clinical disease phenotypes. Identification of new autoantigens in JIA could be used as biomarkers for diagnostic or prognostic purposes in JIA.
Published papers that are part of the thesis