Title etc

Psoriasis and psoriatic arthritis are chronic inflammatory diseases characterised by a dysregulated immune and inflammatory response. The functional basis of observed genetic associations and relationship with environmental factors remains unresolved. This thesis aims to establish genome-wide epigenetic and gene expression profiles for immune cells isolated from blood and disease-relevant tissues to inform understanding of pathogenesis and genome-wide association study (GWAS) results.

The first results chapter establishes methodological and analytical pipelines for novel chromatin profiling techniques in challenging clinical samples. It shows that Omni-ATAC, a variant of Assay for Transposase-Accessible Chromatin using sequencing (ATAC-seq), performs best for skin biopsies. Blood cell cryopreservation and fixation are critical steps for enabling larger-scale analysis but have not been explored systematically. I present results which indicate that sample processing conditions have cell-type specific impact and must be carefully designed and controlled for.

The second results chapter compares chromatin accessibility, histone acetylation and gene expression between psoriasis patients (n=8) and controls (n=10) in fresh blood monocytes, B cells, CD4+ and CD8+ T cells. Despite limitations in power, CD8+ T cells showed a significant number of differentially accessible regions (DARs) (n=55, FDR < 0.05) although intersection with differential H3K27ac-associated regions was only seen at *DTD1*. Monocytes and CD8+ T cells showed the highest numbers of differentially expressed genes (n=671 and 651 respectively, FDR <0.05, fold-change range XX) with background-corrected enrichment of ﻿MAPK and IL-12 signalling (both cell types) and NF-kappaB, TNF and chemokine signalling pathways (CD8+ T cells). Overall 702 (FDR<0.01, fold-change range XX) genes were differentially expressed between uninvolved and lesional psoriasis epidermis (n=3) with enrichment of metabolic and immune-related pathways. Integration of epigenetic and gene expression profiles implicated a likely functional variant in the 2p15 GWAS locus modulating *B3GNT2*, a polylactosamine synthase with T and B cell immune regulatory effects.

The third results chapter analyses differences in chromatin accessibility, gene and protein expression of immune cells between synovial fluid and peripheral blood of patients suffering psoriatic arthritis (n=3). The highest number of DARs were found in monocytes for both tissues with synovial fluid monocytes specifically enriched for interleukin and NF-kB signaling pathways. Single-cell RNA-seq identified two functionally relevant synovial fluid monocyte subpopulations characterised by up-regulation of IFN signalling and IL7R. Statistical fine-mapping based on GWAS lead variants identified seven loci with 292 unique SNPs which significantly overlapped with extended (10 kb) DAR windows as well as with known eQTL loci. Further refinement suggested rs11249213 as a possible regulator of *RUNX3* in CD8+ cells in the inflamed synovium.

Overall this thesis highlights the context-specificity of the epigenomic landscape in psoriasis and psoriatic arthritis and the potential of a multi-omics approach to provide new insights into pathophysiology and interpretation of GWAS.