Psoriasis is an inflammatory skin disease that in 10-30\% of cases is followed by psoriatic arthritis (PsA). Both are complex phenotypes resulting from the interaction of environmental and genetic factors. Genetic variation has been demonstrated to have a cell type and context specific effects on transcription and epigenetic profiles. Recent technical advances enable characterisation of changes in chromatin accessibility, histone modifications, the transcriptome and proteome using clinical samples. In this thesis, complementary functional genomics approaches were used to interrogate tissue and cell type specific changes in the regulatory genetic landscape of psoriasis and PsA, to aid interpretation of genetic associations arising from GWAS.

Establishment of the methodological and analytical tools to profile chromatin accessibility using ATAC-seq in clinical samples was followed by generation of ATAC, H3K27ac, ChIPm and RNA-seq, for psoriasis patients (n=8) and healthy controls (n=10), in CD14$^+$ monocytes, total CD4$^+$ and CD8$^+$ T cells and CD19$^+$ B cells. Low number of differentially accessible regions (DARs) and H3K27ac modified sites were observed, with only one overlapping site in an intron of the D-Tyr-tRNA deacylase \textit{DTD1} in CD8$^+$. Paired RNA-seq analysis revealed differentially expressed genes (DEGs), including lncRNAs such \textit{HOTAIRM1}, which up-regulation was consistent with down-regulation of its target \textit{UPF1} in CD14$^+$ monocytes. CD14$^+$ monocytes and CD8$^+$ showed the largest number of DEGs with commonly enriched pathways including ﻿MAPK and IL-12 signalling. Furthermore, CD8$^+$ DEGs were also enriched for NF-$\kappa$B, TNF and chemokine signalling pathways, highlighting the relevance of this cell type in the systemic psoriasis footprint. Differential gene expression analysis between lesional and uninvolved epidermis sheets from psoriasis skin biopsies (n=3) revealed greater effect sizes than circulating cells and highlighted enrichment of metabolic and immune-related pathways. In PsA (n=3), DARs between synovial fluid (SF) vs peripheral blood in CD14^+$ monocytes, memory CD4$^+$ (mCD4$^+$), mCD8$^+$ and natural killer cells were enriched for pathophysiological relevant processes, with CD14$^+$ showing the most changes in chromatin accessibility. CD14$^+$ monocytes DEGs were enriched for proximal DARs and highlighted dysregulation of chemokine and NOD-like signalling pathways. Further exploration of SF and PB CD14$^+$ monocytes by single-cell RNA-seq revealed additional pathways enriched in DEGs between SF and PB and identified two functionally relevant SF CD14$^+$ monocyte subpopulations characterised by up-regulation of IFN signalling genes and \textit{IL7R}, respectively. Mass-cytometry analysis (n=10) confirmed increased \textit{CCL2} and \textit{CXCL10} protein levels in CD14$^+$ monocytes at the inflamed joints, consistent with their transcriptional up-regulation and proximity to SF open DARs.

Lastly, integration of fine-mapped GWAS outputs with in-house and publicly available functional data showed CD8$^+$ and allele-specific chromatin accessibility for a top fine-mapped SNP hypothesised to regulate the polylactosamine synthase \textit{B3GNT2}. Moreover, the fine-mapped SNP rs11249213 at the \textit{RUNX3/SYF2} locus overlapped a CD8$^+$ SF open DAR, which may suggest a functional role of this SNP under inflammatory conditions.

This thesis applied a multi-omics approach to interrogate cell and tissue-specific changes in patient epigenetic and transcriptomic profiles, showing utility for the interpretation of disease-associated regulatory variants that can be further investigated through functional studies.