Psoriasis is an inflammatory skin disease most commonly manifested as well-demarcated erythematous plaques (psoriasis vulgaris) that in 10 to 30\% of the cases is followed by one or more joint inflammation in the form of psoriatic arthritis (PsA). Both are complex phenotypes resulting from the interaction of environmental factors and genetic associations identified through GWAS studies. Genetic variation has been demonstrated to have a cell type and context specific effect in the transcriptional and epigenetic profiles. The latest technical advances in functional genomics, importantly in epigenetics, are opening the door to characterise changes in chromatin accessibility, histones modifications, transcriptomic and proteomic landscape using clinical samples, and to further dissect the functional impact of genetic variability in a tissue and cell type specific manner. In this thesis, complementary functional genomics approaches were used to interrogate disease, tissue and cell type specific changes in the regulatory genetic landscape of psoriasis and PsA, and to inform the interpretation of genetic associations arising from GWAS.

This first required the establishment in the group of the methodology and analytical tools to perform chromatin accessibility profiling through Assay for Transposase Accessible Chromatin with high-throughput sequencing (ATAC-seq) in clinical samples. Following this, ATAC, H3K27ac ChIPm and RNA-seq data were generated from psoriasis patients (10) and healthy controls (10) in CD14$^+$ monocytes, total CD4$^+$ and CD8$^+$ T cells and CD14$^+$ B cells to identify disease-relevant features. Amongst the moderate number of differentially accessible and H3K27ac modified regions, ﻿only one overlap was found at an intron of the \textit{DTD1}, a D-Tyr-tRNA deacylase not previously reported in psoriasis. RNA-seq analysis revealed differentially expressed mRNAs and long non-coding RNAs, including up-regulation in CD14$^+$ monocytes of \textit{HOTAIRM1} and down-regulation of its target \textit{UPF1}. CD14$^+$ monocytes and CD8$^+$ showed the largest number of dysregulated targets and common enriched pathways including ﻿MAPK and IL-12 signalling, Additionally, NF-$\kappa$B, TNF and chemokine signalling pathways were also enriched in CD8$^+$ DEGs only, highlighting the role of this cell type in the systemic psoriasis footprint. The differential gene expression analysis between lesional and uninvolved epidermis sheets from psoriasis skin biopsies revealed larger fold changes in the DEGs and highlighted enrichment for metabolic and immune-related pathways, importantly the NOD-like receptor signalling, showing up-regulation of \textit{NOD2}, \textit{CARD6} and \textit{IFI16}, a pathway not identified by other studies using whole skin biopsies.

ATAC data form synovial fluid (SF) and peripheral blood (PB) CD4^+$ monocytes, memory CD4$^+$ (mCD4$^+$), mCD8$^+$ and natural killer (NK) cells in 3 PsA patients with oligoarthritis revealed the larger number of DARs in CD14$^+$ monocytes (5,285) and distinct enrichment of functionally relevant pathways for SF and PB open DARs in all four cell types. In CD14$^+$ monocytes immune-relevant DEGs between the two tissues were enriched for DARs in the proximity (p-value=0.028) and highlighted dysregulation of chemokine and NOD-like signalling pathways. Further exploration of SF and PB CD14$^+$ monocytes by single-cell RNA-seq (scRNA-seq) revealed additional pathways enriched in genome-wide DEGs between SF and PB and identified two functionally relevant SF CD14$^+$ monocytes subpopulations characterised by up-regulation of genes IFN signalling genes and the \textit{IL7R}, respectively. Additionally, mass-cytometry analysis confirmed increased production of \textit{CCL2} and \textit{CXCL10} protein products CD14$^+$ monocytes at the inflamed joints, consistent with the transcriptional up-regulation and proximity to SF open DARs of these two chemokines.

Lastly, integration of fine-mapping of psoriasis and PsA Immunochip GWAS with in-house and publicly available functional data showed cell type allele-specific ATAC chromatin accessibility for the top fine-mapped SNP (rs4672505) at the chr2p15 locus in CD8$^+$ cells, which may be related to distal gene regulation of the polylactosamine synthase \textit{B3GNT2}. Moreover, the fine-mapped SNP rs11249213 at the RUNX3/SYF2 locus overlapped a CD8$^+$ SF open DAR (significant for FDR$<$0.05) which may suggest a functional role of this SNP importantly under inflammatory conditions.