Psoriasis and psoriatic arthritis (PsA) are chronic inflammatory diseases characterised by a dysregulated immune 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 studies (GWAS).

The first results chapter establishes methodological and analytical pipelines for a new technique, Assay for Transposase-Accessible Chromatin using sequencing (ATAC-seq). Omni-ATAC demonstrated the best performance for skin biopsies and the impact of cryopreservation and fixation of blood-isolated primary immune cells in the chromatin landscape was also assessed.

The second results chapter compares chromatin accessibility, histone acetylation and gene expression between psoriasis patients (n=8) and controls (n=10) for blood monocytes, B cells, CD4$^+$ and CD8$^+$ T cells. Only CD8$^+$ T cells showed a significant number of differentially accessible regions (DARs) (n=55, FDR$<$ 0.05), which intersection with differential H3K27ac was only seen at an intron of \textit{*DTD1}*. Monocytes and CD8$^+$ T cells showed highest numbers of differentially expressed genes (n=671 and 651 respectively, FDR$<$0.05) with enrichment of ﻿MAPK and IL-12 signalling (both cell types) and NF-$\kappa$B, TNF and chemokine signalling (CD8$^+$ T cells). Overall 702 (FDR$<$0.01) 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 potentially functional variant in the 2p15 GWAS locus modulating \textit{*B3GNT2}*.

The third results chapter analyses differences in chromatin accessibility, gene and protein expression of immune cells between synovial fluid and peripheral blood of PsA patients (n=3). The highest number of DARs were found in monocytes (5,285 FDR$<$0.01) for both tissues with synovial fluid monocytes specifically enriched for interleukin and NF-\kappa$B signalling. Single-cell RNA-seq identified two functionally relevant synovial fluid monocyte subpopulations characterised by up-regulation of IFN signalling and \textit{IL7R} genes, respectively. Mass-cytometry analysis (n=10) confirmed increased \textit{CCL2} and \textit{CXCL10} protein levels in monocytes from synovial fluid. Furthermore, intersection with fine mapped GWAS SNPs was conducted.

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

﻿﻿\noindent Psoriasis and psoriatic arthritis (PsA) are chronic inflammatory diseases characterised by a dysregulated immune 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.

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\noindent The second results chapter compares chromatin accessibility, histone acetylation and gene expression between psoriasis patients (n=8) and controls (n=10) in fresh blood-isolated monocytes, B cells, CD4$^+$ and CD8$^+$ T cells. Only CD8$^+$ T cells showed a significant number of differentially accessible regions (DARs) (n=55, FDR$<$ 0.05), which intersection with differential H3K27ac was only seen at an intron of \textit{DTD1}. Monocytes and CD8$^+$ T cells showed the highest numbers of differentially expressed genes (n=671 and 651 respectively, FDR$<$0.05) with enrichment of MAPK and IL-12 signalling (both cell types) and NF-$\kappa$B, TNF and chemokine signalling (CD8$^+$ T cells). Overall 702 (FDR$<$0.01) 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 potentially functional variant in the 2p15 GWAS locus modulating \textit{B3GNT2}.

\noindent The third results chapter analyses differences in chromatin accessibility, gene and protein expression of immune cells between synovial fluid and peripheral blood of PsA patients (n=3). The highest number of DARs were found in monocytes (5,285 FDR$<$0.01) for both tissues with synovial fluid monocytes specifically enriched for interleukin and NF-$\kappa$B signalling. Single-cell RNA-seq identified two functionally relevant synovial fluid monocyte subpopulations characterised by up-regulation of IFN signalling and \textit{IL7R} genes, respectively. Mass-cytometry analysis (n=10) confirmed increased \textit{CCL2} and \textit{CXCL10} protein levels in monocytes from synovial fluid. Furthermore, intersection with fine mapped GWAS SNPs was conducted .

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

-----------------------Antonio suggestions

\noindent Psoriasis and psoriatic arthritis (PsA) are chronic inflammatory diseases affecting mainly the skin and joints that result from the interaction of genetic and environmental factors. Currently, the functional basis of observed genetic associations still remain largely 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 studies (GWAS) results.

\noindent 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. The use of cryopreservation and fixation in blood-isolated immune cells revealed a cell type specific impact in the chromatin landscape that should be considered in the experimental design.

\noindent The second results chapter compares chromatin accessibility, histone acetylation and gene expression between psoriasis patients (n=8) and controls (n=10) for blood monocytes, B cells, CD4$^+$ and CD8$^+$ T cells. Only CD8$^+$ T cells showed a significant number of differentially accessible regions (DARs) (n=55, FDR$<$ 0.05), which intersection with differential H3K27ac was only seen at an intron of \textit{DTD1}. Monocytes and CD8$^+$ T cells showed highest numbers of differentially expressed genes (n=671 and 651 respectively, FDR$<$0.05) with enrichment of MAPK and IL-12 signalling (both cell types) and NF-$\kappa$B, TNF and chemokine signalling (CD8$^+$ T cells). Overall 1,227 genes (FDR$<$0.05) were differentially expressed between uninvolved and lesional psoriasis epidermis (n=3) with enrichment of metabolic and immune-related pathways. Integration of GWAS fine-mapping data with epigenetic and gene expression profiles implicated a potentially functional variant in the 2p15 GWAS locus modulating \textit{B3GNT2}.

\noindent The third results chapter analyses differences in chromatin accessibility, gene and protein expression of immune cells between synovial fluid and peripheral blood of PsA patients (n=3). The highest number of DARs were found in monocytes (5,285 FDR$<$0.01) for both tissues with synovial fluid monocytes specifically enriched for interleukin and NF-$\kappa$B signalling pathways. Single-cell RNA-seq identified two functionally relevant synovial fluid monocyte subpopulations characterised by up-regulation of IFN signalling and \textit{IL7R} genes, respectively. Mass-cytometry analysis (n=10) confirmed increased \textit{CCL2} and \textit{CXCL10} protein levels in monocytes from synovial fluid. Furthermore, statistical fine-mapping of PsA GWAS loci and integration with ATAC data suggested rs11249213 as a possible regulator of \textit{RUNX3} in CD8$^+$ cells in the inflamed synovium.

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