\section{Introduction}

\subsection{The relevance of cell type and tissue specificity in the study of PsA}

Consideration of cell and type specificity in the study of complex diseases is fundamental for the understanding of the disease pathophysiology. As previously reviewed (\ref{ch:Intro}), the dysregulated immune response in PsA is the results of the interaction between cellular components of the innate and adaptive immune response. Consequently, the molecular characterisation of the different immune cell types is pivotal not only for the understanding of the immune response but also to define disease state, comprehend the impact of genetic variants increasing disease risk and identify drugs with optimal efficacy and specificity.

\subsubsection{Differences in the PsA inflammatory response between blood and the synovium}

PsA is considered a systemic disease where studies in PBMCs have demonstrated changes in cell type composition and cytokine production when compared to healthy individuals. For example, increased frequencies of circulating IL-17$^+$ and IL-22$^+$ CD4$^+$ T cells have been reported in PB from PsA patients compared to control individuals \parencite{Benham2013}. Moreover, reduced percentage of pDCs and NK in PB have also been observed in PB from PsA compared to controls \parencite{Jongbloed2008, Spadaro2004}. In terms of cytokine production, stimulated PBMCs from PsA patiens released greater levels of IL-17 and IL-22 than the healthy control counterparts \parencite{Benham2013}.

Nevertheless, PsA is characterised by affection of the joints, where the local inflammatory response leads eventually to joint destruction. Oligoarticular PsA (involving four or fewer joints) is commonly managed by joint aspiration prior intra-articular steroid injection to relieve pain, facilitating the sample collection for research purposes \parencite{Kavanaugh2006}. The importance of studying the synovium in PsA have been highlighted by differences in cell composition and cytokine production, amongst others, between PB and SF in PsA patients. For example, expansion mCD8$^+$ but not mCD4$^$ T cells was observed in SF when compared to PB in PsA paired samples \parencite{Ross2000}. Additionally, elevated proportion of T cells expressing the cytokine receptors CCR6$^+$ and IL-23R$^+$ were found in SF compared to PB in patients \parencite{Benham2013}.

\subsubsection{Bulk transcriptomic studies and their limitations}

Genome-wide transcriptomic studies in PsA have been mainly focused in characterising gene expression in bulk PBMCs and SFMCs samples. Several studies have been conducted to better understand gene expression differences in blood between PsA and controls and also specific differences between PB and SF from the same PsA patients or differences with other arthritic diseases \parencite{Stoeckman2006, Batiwalla2005, Gu2002, Dolcino2015}. Amongst the most comprehensives of thesestudies, that conducted by Dolcino and colleagues revealed genes from the Th-17 axis and type-I IFN signalling to be differentially expressed between PsA and healthy controls in synovial membranes. Moreover, the overlapof genes that were differentially expressed betweenpatients and controls in each of the compartments, highlighted differences and commonalities in the systemic and synovial immune response in PsA. %Other studies have also focused in the understanding the transcriptional changes in PBMCs from PsA patients following MTX and TNFi therapies \parencite{Cuchacovich2014}.

Cytokines production measurements have also been conducted in serum and SF, revealing increased levels of TNF-$\alpha$, for example, in both tissues \parencite{Ritchlin1999,Li2017}.

Studies using mixed cell populations can be influenced by the relative proportion of the different cell populations within the sample \parencite{Whitney2003}. For instance, the importance of considering cell types to understand the impact of genetic variants in transcriptional regulation has been explored in a number of immune cells \parencite{Fairfax2012, Fairfax2014, Raj2014, Peters2016, Kasela2017}. These studies have highlighted the regulatory role of some genetic variants only in particular cell types and conditions, previously masked when considering mixed population of cells such as PBMCs. In this respect, expression analysis for a limited number of genes have been performed in specific cell type populations such as stimulated macrophages and Th-17 \textit{in vitro} differentiated cells from na\"{i}ve CD4$^+$ isolated from PB and SF of PsA patients \parencite{Antoniv2006, Leipe2010}. Overall, achieving a detailed and precise understanding of complex diseases requires the study of sorted cell populations and when possible isolated from the affected tissue.

\subsubsection{Transcriptomics and proteomics at the single cell resolution}

In addition to the study of specific cell types, evidence for heterogeneity in the transcriptome across individual cells from the same population has accelerated the development of strategies providing single cell resolution. The establishment of scRNA-seq and mass-cytometry techniques represent an unbiased way to characterise and identify cell subpopulations within the samples, avoiding the pre-selection of particular cell types and thus providing a global overview of cell composition and interactions in the tissue of interest.

A wide range of approaches to study single-cell transcriptomics have been developed in the last few years, including Drop-seq, SmartSeq2 and 10X Chromium amongst the most widely used \parencite{Picelli2014,Ziegenhain2017}. 10X Chromium technology is based on microfluidics where cells in suspension get directly encapsulated into nanoL droplets that incorporate cell and transcript barcode identifiers (see \ref{ch:Mat}). As a result, 10X Chromium technology does not require pre-sorting of single-cells into plates and enables higher throughput than other with less manipulation and variability than other scRNA-seq methods such as SmartSeq2 \parencite{Baran-Gale2017}

Mass cytometry represents the next generation of fluorescence based flow-cytometry analysis to interrogate expression of cell surface and intracellular molecules. Mass cytometry is a hybrid technique between mass spectrometry and flow cytometry, where the Abs recognising the molecular markers have been labelled with stable isotopes instead of fluorophores \parencite{Bandura2009}. The use of isotopes enables incorporating up to 45 Abs to profile cellular populations and assess molecular functions.

\subsection{Using a multi-omics approach in the study of complex diseases}

The interaction between genetics and environmental factors in the risk to develop complex diseases, such as PsA, results in shaping the epigenetic landscape of the cells. This dynamism of the epigenome involves cell and context specific features, reinforcing the importance of studying purified cell types instead of mixed populations. Moreover, the importance of the epigenomic landscape in understanding disease state and also contextualizing the role of putative genetic risk variants has made necessary the implementation of multi-omics approaches to study complex diseases. This involves the study of chromatin accessibility, gene expression including further resolution using scRNA-seq and immunophenotypes of the relevant cell involved in disease pathophysiology.

Recent technical advances such as ATAC-seq are enabling the characterisation of the regulatory landcape in a wide range of cell types and tissues obtained from valuable clinical samples minimising the amount of material required. Profiling the chromatin accessibility in the cell populations isolated from the tissues of interest provides details about the molecular programming of cells and can also inform about the location and status of \text{cis}-regulatory elements. For example differential analysis in B cells isolated from SLE and healthy controls has revealed changes in chromatin accessibility for loci nearby genes involved in B cells activation and enrichment for TFBS potentially regulating pathogenic processes \parencite{Scharer2016}. Similarly a study in age-related macular degeneration (AMD) has identified the retina epithelium as the main tissue driving disease onset though global loss of chromatin accessibility compared to healthy tissue \parencite{Wang2018}. Transcriptional profiling of discrete cell populations have also been performed in monocytes and Th-17 cells in AS, intestinal epithelial cells in CD and fibroblast-like synoviocytes in RA \parencite{Al-Mossawi2017,Smith2008, Howell2018, Ai2016}. Moreover, recent advances have yielded the possibility to study the transcriptomic and proteomic profiles at the single-cell resolution and account for the variability at the single-cell level in gene expression and protein translation.

Incorporation of scRNA-seq and mass cytometry in addition to bulk RNA-seq and flow cytometry have led to a more detailed understanding of the immune system \parencite{Jaitin2014, Villani2017,Bengsch2018}. In complex diseases such as RA, scRNA-seq has discovered heterogeneity in the synovial fibroblast population and identified a potentially pathogenic cluster highly proliferative and active in pro-inflammatory cytokine secretion \parencite{Mizoguchi2018}. Similarly, mass cytometry analysis performed in RA identified an expanded CD4$^+$ T cell population promoting B cell response \parencite{Rao2017}.

\subsubsection{Data integration}

One of the most challenging aspects of using a multi-omics approach is the appropriate integration of the data in order to maximise the amount of information extracted and also the reliability of the findings. The power of this integration is increased by generating paired data for all the omics across all the individuals in the cohort, which cannot always be achieved due to sample availability and cost.

Integrating chromatin accessibility and gene expression data has allowed to better understand the correlation and specificity between open chromatin and transcription. In terms of identifying cell populations, chromatin accessibility has appeared to be more cell type specific than bulk RNA-seq \parencite{Corces2016}. In pancreatic islets, the overlap of ATAC-seq and RNA-seq has shown chromatin accessibility to be a better proxy for gene expression in $\alpha$ than in $\beta$ cells. Moreover, integration of both data sets reinforced the functional specificity of AMD DEGs nearby differentially accessible regions across tissues \parencite{Ackermann2016, Wang2018}.

The most comprehensive available study integrating multi-omics (bulk RNA-seq, scRNA-seq and mass cytometry) has been performed in RA \parencite{Zhang2018}. This recent study has identified eighteen unique subpopulations amongst the the main cell types involved in RA pathophysiology by systematic correlation between transcriptional profiles and mass cytometry.

Regarding PsA, no such a comprehensive multi-omic study has been conducted to date. Characterisation of chromatin accessibility and transcriptomic landcape of the most relevant cell types in SF and PB would improve the understanding of differences across tissues as well as the relationship between chromatin accessibility and gene expression in PsA. Furthermore, implementation of single-cell transcriptomic and mass cytometry would help to ......

\subsection{Genetic fine-mapping in the context of functional data}

General comments about integration and also explaining the use of genotyping data to perform fine-mapping (brief)

\subsection{Aims}