**ChIPm**

~~%Conversely, this region harbours SNPs that have been identified as \textit{cis}-eQTL in whole blood and total unstimulated and stimulated CD14$^+$ monocytes for the calmodulin-binding motif-containing protein \textit{IQCB1} gene, which is 186.4Kb up-stream of this peak \parencite{GTeX,Fairfax2014}. MS risk LD SNPs (rs34543553, rs73855480 and rs73855480) in this peak are also \textit{cis}-eQTLs in unstimulated total CD4$^+$ and CD8$^+$ cells for \textit{IQCB1} \parencite{Kasela2017}.~~

~~Potentially could move here:~~

~~Overall, restricting the differential analysis to enhancer annotated regions did not show a great increase in the number of significant differentially modified H3K27ac sites when compared to the genome-wide analysis in any of the four cell types. The results in this pilot cohort did not show relevant global epigenetic changes in H3K27ac sites between psoriasis patients and controls for these cell types and sample size.~~

**~~ATAC~~**

~~Both genes are relevant in driving and maintaining the inflammatory response. \textit{TNFSF11} is a cytokine from the TNF family involved in the regulation of the T cell-dependent immune response and osteoclast differentiation in RA and PsA \parencite{Miranda‐Car\'ús2006,Ritchlin2003}. \textit{TNFSF11} is also downstream of the lead SNPs for a CD risk locus \parencite{ImmunoBase}. Interestingly, the \textit{TNFSF11} protein, RANKL was found to be overexpressed in epidermis from psoriasis patients compared to controls and cutaneous lupus erythematosus, highlighting the role of this gene in the pathophysiology of psoriasis \parencite{Toberer2011}. On the other hand \textit{IL7R} is a proximal gene to SLE and MS GWAS SNPs?, and the IL-7/IL-7R axis has been found to drive IL7 independent TNF-$\alpha$ inflammation in RA patients presenting iTNF resistence \parencite{van Roon2017}.~~

~~http://www.jimmunol.org/content/198/1\_Supplement/124.6~~

~~Integration ATAC-ChIP~~

~~%This gene has been described to play a role in the initiation of DNA replication and has been associated with aspirine-intolerance in asthmatics \parencite{Pasaje2011}. However, no studies have yet highlighted a direct link of this gene with the pathophysiology of chronic inflammatory diseases.~~

~~%Altogether, these results suggest that differences in H3K27ac are not driving the genome-wide changes in chromatin accessibility between psoriasis patients and healthy controls in total CD8$^+$ cells in this data.~~

**~~RNA-seq in circulating immune cells~~**

~~The more dysregulated gene expression response between patients and controls found in circulating psoriasis CD8$^+$ when compared to the CD4$^+$ may suggest the same hypothesis as in skin, where CD8$^+$ are considered the main effector cells undergoing activation upon the inflammatory stimuli \parencite(Nickoloff1999).~~

~~To comment on the relative limited implication s of B cells in disease or not% Interestingly, CD19$^+$ presented a greater number of differentially expressed mRNAs than CD4$^+$, regardless of their not yet having been implicated in disease (confirm).~~

~~Paper:~~ [~~https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4991840/~~](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4991840/)

~~Overlap with other studies~~

~~%For example, CDC like kinase 1 (\textit{CLK1}) involved in protein splicing was downregulated in this CD8$^+$ data set and in the Lee PBMCs in patients when compared to controls and its deficiency has been shown to lead to neuro-inflammation in mice \parencite{Gu2017}. Similarly, only one overlap was found with the psoriasis DEGs in a study comparing PBMC transcriptional profiles of three inflammatory diseases (IBD, RA and psoriasis)\parencite{Mesko2010}. This was for the nicotinamide pPhosphoribosyltransferase (\textit{NAMPT}) gene involved in metabolism and stress response, which was up-regulated in our CD14$^+$ monocytes as well as in PBMCs from psoriasis, IBD and RA patients, suggesting its role as a marker of inflammation rather than marker for psoriasis.~~

lncRNAs

The negative regulator of antiviral response \textit{DYNLL1-AS1} (or \textit{NAV}), which has been shown to affect the histone modifications of some critical IFN-stimulated genes (ISGs), such as \textit{IFITM3} and \textit{MxA} leading to down-regulation of their expression \parencite{Ouyang2014}. In this data, \textit{DYNLL1-AS1} was down-regulated indicating lack of one of the negative regulators of the IFN response, notwithstanding the reverse IFN-$\gamma$ signature observed in the pathway enrichment analysis. Another interesting dysregulated lncRNA in CD14$^+$ monocytes was the HOXA transcript antisense RNA myeloid-specific 1\textit{HOTAIRM1}. In a study using PsA PBMCs \textit{HOTAIRM1} was found to be down-regulated and connected to the expression of the RNA helicase and ATPase \textit{UPF1} \parencite{Dolcino2018}. \textit{UPF1} is involved in nonsense-mediated decay and in partnership with the monocyte chemotactic protein-1-induced protein-1 (\textit{MCPIP1}) gene drives degradation of inflammation-related mRNAs to ensure maintenance of homeostasis \parencite{Mino2015}. In this present study, \textit{HOTAIRM1} appeared to be up-regulated in the CD14$+$ monocytes from psoriasis patients (Figure \ref{figure:RNAseq\_PS\_CTL\_CD14\_expression\_HOTAIRM\_UPF1} a) and this was consistent with significant down-regulation of \textit{UPF1} in the same cell type (Figure \ref{figure:RNAseq\_PS\_CTL\_CD14\_expression\_HOTAIRM\_UPF1} b), suggesting impairment of this homeostatic mechanisms in the psoriasis patients.

The last relevant lncRNA differentially expressed in monocytes was \textit{NEAT1}, which was up-regulated in the patients compared to the controls. \textit{NEAT1} has been reported to also be up-regulated in SLE CD14$^+$ monocytes and knocking it down has revealed impairment of the TLR-4 signalling and down-regulation of inflammatory genes including IL-6 and CXCL10 \parencite{Zhang2016}.

**Pathway enrichment analysis**

MAPK

%Enrichment was shared between CD14$^+$ monocytes and CD8$^+$ cells. Some of the DEGs contributing to the enrichment of this pathway in both cell types included MAPK gene members such as \textit{MAP3K4} and \textit{MAPK14}, both down-regulated in psoriasis when compared to controls. Interestingly, MAP3K4 is a member of the MAPKKK family, for which expression is down-regulated in LPS-stimulated PBMCs from CD patients, leading to reduced expression of the cytokine \textit{IL-1A} and a relative immune deficiency in TLR-mediated cytokine production. Moreover, DGE of members of the dual-specificity phosphatases (DUSP) family involved in fine-tuning the immune response \parencite{Qian2009} contribute to the enrichment of the MAPK pathway in CD14$^+$ monocytes and CD8$^+$ cells. \textit{DUSP10} was down-regulated in the psoriasis CD14$^+$ monocytes and could be modulating reactive oxygen species production according to a knock-out mice phenotype presenting enhanced inflammation \parencite{Qian2009}. Conversely, \textit{DUSP4} presented up-regulation in tCD8$^+$ patients when compared to healthy controls and it could represent a pro-inflammatory feature as this gene has been demonstrated to have a role in driving inflammation in a sepsis mice model \parencite{Cornell2010}.

IL-12

~~%Other interesting pathways enriched for both cell types included IL-12 mediated signalling (Table \ref{tab:RNAseq\_PS\_CTL\_pathway\_enrichment}). IL-12 signalling leads to T cell proliferation and IFN-$\gamma$ production through activation of TFs from the STAT family. Importantly STAT4 is a well-known drug target for psoriasis treatment. Interestingly, CD14$^+$ monocytes from psoriasis presented down-regulation of \textit{STAT4} and \textit{STAT5A} in patients compared to controls. Likewise, \textit{IFNG} expression in psoriasis patients was lower than in healthy controls in CD8$^+$ cells. This phenomenon has been previously observed in macrophages derived from AS patients as well as in an SpA rat model \parencite{Smith2008,Fert2014}. Additionally, \textit{IL2RA} was up-regulated in CD8$^+$ from psoriasis patients when compared to controls, which may enhance formation of the IL2-R$\alpha$ and the signalling by this cytokine involved in effector and regulatory T cell differentiation \parencite{Malek2010}.~~

% The platelet-derived growth factor (PDGF-$\beta$) signalling pathway was only enriched in CD14$^+$ monocytes

NFkB, TNF and chemokine

\*read inverse IFNg response and see if anything else in these lines

%Interestingly, \textit{NFKBIA} and \textit{TNFAIP3} were also up-regulated in CD14$^+$ monocytes and CD4$^+$ cells. \textit{NFKBIA} codes for the NF-$\kappa$B inhibitor alpha (I$\kappa$B$\alpha$) which binds to the NF-$\kappa$B subunits preventing them from translocation to the nucleus by masking a nuclear localisation signal (NLS). Similarly, \textit{TNFAIP3} codes for the zinc finger protein and ubiqitin-editing enzyme A20, that inhibits both NF-$\kappa$B signalling and TNF-mediated apoptosis. Unexpectedly, these two genes with an anti-inflammatory role appeared to be up-regulated in psoriasis patients when compared to controls in two of the studied cell types.

~~Other genes with a prominent pro-inflammatory role also appeared to be down-regulated in the NF-$\kappa$B or TNF signalling pathways, such as the activating transcription factor 2 (\textit{ATF2}) and 4 (\textit{ATF4}) members of the TNF signalling cascade and the protein kinase C beta\textit{PRKCB} from the NF-$\kappa$B and chemokine signalling pathways.~~ Notably, \textit{ATF4} was found to be up-regulated in CD noninflammed ileal biopsies causing activation of autophagy genes, whilst its expression was down-regulated in biopsies with active CD, pointing towards dysregulation of this pathway in disease onset \parencite{Bretin2016}. ~~In contrast, up-regulation of pro-inflammatory genes members of these two pathways were also found. For example JunB proto-oncogene (\textit{JUNB}) coding for one of the subunits of the TF AP-1 and three of the NF-$\kappa$B subunits including \textit{RELA}, \textit{RELB} and \textit{NFKB2}. Particularly, AP-1 undergoes activation following growth factors, cytokines, chemokines, hormones and multiple environmental stresses and acts as a negative regulator of cell proliferation and IL-6 production \parencite{Schonthaler2011}~~

Although in psoriasis lesional skin AP-1 protein levels have been found to be down-regulated, JunB was found to be increased both at the protein and mRNA levels, consistent with this observation in CD8$^+$ circulating cells \parencite{Johansen2004}.

%Some studies have demonstrated an increased of CCR10$^+$ infiltrated T lymphocytes in psoriasis \parencite{Homey2002}. In circulation, expression of CCR10 is restricted to the a subset of circulating mCD4$^+$ and mCD8$^+$ T cells expressing the cutaneous lymphocyte-associated antigen (CLA), which are preferentially recruited to cutaneous sites of inflammation where KCs express CCL27 \parencite{Hudak2002}. A study in psoriasis circulating cells revealed a correlation between the frequency of CTLA$^+$ CD8$^+$ cells and disease severity measured by PASI score \parencite{Sigmundsd\'{o}ttir2001}. Other up-regulated chemokine receptors in CD8$^+$ circulating psoriatic cells included \textit{CXCR4} gene (receptor for CXCL12) for which ?conflicting findings have been reported about its role in skin inflammation and psoriasis \parencite{Zgraggen2014,Takekoshi2013}.

RNA-seq skin

%\textit{IFIH1}, \textit{NOS2}, \textit{LCE3D} and \textit{STAT3} were also found to be up-regulated in lesional compared to uninvolved skin biopsies from psoriasis patients in \parencite{Tsoi2015}. In contrast, \textit{TFNAIP3} was found to be up-regulated in \parencite{Jabbari2011}, opposite to our finding.

LCE genes discrepancy between my data and Tsoi/Tervaniemi:

%Notably, qPCR quantification of \textit{LCE} genes from groups 1, 2, 5 and 6 demonstrated increased expression in psoriasis lesional skin \parencite{Bergboer2011}.

%Overall, the comparison of our results with these two studies suggested greater similarities with the full skin thickness biopsies from Tsoi \textit{et al.}, 2015 in terms of DEGs overlapping, due to different technical reasons as further detailed in the Discussion.

lncRNAs->An interesting example was \textit{H19} which was significantly down-regulated in the lesional skin when compared to uninvolved. H19 has been described as directly binding miR-130b-3p which down-regulates Desmoglein 1 (\textit{DSG1}), a gene promoting KC differentiation \parencite{Li2017}. Nevertheless, \textit{DSG1} did not appear as one of the DEGs between lesional and uninvolved skin. %This finding was consistent with Tsoi \textit{et al.}, 2015 and also with results from Li \textit{et al.}, 2014 and ?\textit{et al.}, 2016 where they compared lesional versus normal skin.

miR-146a <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1567904/>

%Moreover, a polymorphism in miR-146a has been associated with psoriasis in a small cohort study and a \textit{MIR146A} knock-out mice with chemical induced psoriasis led to earlier disease onset and amplified epidermal activation \parencite{Srivastava2017}.

MIR31HG

%Notably, a functional study using the KC immortal cell line HaCaT demonstrated that silencing miR-31hg induces cell cycle arrest and inhibits cell proliferation consistently with two characteristic functions dysregulated in psoriatic KCs \parencite{Gao2018}.

%also role in osteogenesis https://www.ncbi.nlm.nih.gov/pubmed/27334046

%HIF-1 up-regulation https://molecular-cancer.biomedcentral.com/articles/10.1186/s12943-018-0916-8

Pathway analysis

%Dysregulation of similar functions have previously also been reported in other studies comparing lesional and uninvolved skin and genome-wide pathway analysis\parencite{Coda2012, Aterido2016, Tervaniemi2016}.

HIF-I signalling has been found to be up-regulated in psoriasis skin likely through hypoxia caused by increased cell proliferation rates and epidermal thickening.In this data up-regulation of \textit{HIF1A}, \textit{VEGFA}, \textit{ENO1} and \textit{NOS2}, amongst others, contributed to the enrichment of this pathway (Figure \ref{figure:PS\_lesional\_vs\_uninvolved\_HIF\_pathway}).

%Up-regulated expression of the hypoxia-inducible TFs HIF-1$\alpha$ and HIF-2$\alpha$ has been found in lesional skin and co-related with the increase in \textit{VEGF} transcript levels, a target gene regulated by HIFs that mediates the pathological angiogenesis driving psoriasis \parencite{Rosenberg2007}.

NOD-I pathway %These findings highlight the failure of whole skin biopsies transcriptomics to identify additional NOD-I signalling genes differentially regulated between lesional and uninvolved skin and the value of studying epidermal biopsies to unveil exacerbated dysregulation of functional pathways in KCs.

IL-17 pathway: The production of IL-17 by Th-17 ?cells contributes to perpetuation of the innate host defense in the skin.

%BCL2 downregulation <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2080542/>

PPAR %PPARs are ligand-dependent TF that have been shown to induce the inhibition of pro-inflammatory genes including IL-1 and TNF-$\alpha$ \parencite{Ji2001}. In skin, PPARs have been demonstrated to contribute to homeostasis by inducing differentiation and preventing proliferation \parencite{Rivier1998}. Moreover, inhibition of genes regulated by PPAR-$\gamma$ has been described in studies comparing lesional versus healthy skin biopsies \parencite{Li2014}.

**Overlap blood and skin**

A similar or larger proportion of the total overlapping DEGs presented opposite direction of change in circulating immune cells and in skin from psoriasis patients. An examples was \textit{TNFAIP3} gene, which was up-regulated in psoriasis CD4$+$ and CD8$^+$ cells compared to controls and down-regulated in lesional epidermis when compared to uninvolved.

%In Tsoi \textit{et al.}, 2015 this gene did not change expression between lesional and uninvolved nor between lesional and healthy skin and Li \textit{et al.}, reported its up-regulation in lesional skin.

Moreover,some of the pro-inflammatory genes contributing to those pathways appeared down-regulated in psoriasis when compared to controls.% some of the genes in these circulating immune cells suggested certain immuno-supression features that could be characteristic of these cells before or/and after having been exposed to the skin inflammatory \textit{milieu}.

Conclusion about changes and overlap

**Fine-mapping**

B3GNT2 role in macrophages https://link.springer.com/content/pdf/10.1186%2F1755-8794-7-27.pdf