T lymphocytes have been considered the most relevant cell types in the initiation and maintenance of psoriasis and PsA. Skin-resident memory T cells have been demonstrated to have a key role in psoriatic lesion development in mice models \parencite{Boyle2004}. In human case reports, bone marrow transplantation has shown to cause initiation or termination of psoriasis \parencite{Gardembas1990; Eedy1990}. \textit{In vivo} studies demonstrated that transition to psoriatic lesions following engrafted human pre-lesional skin in immune-deficient mice was only dependent on T cells requiring injection of autologous activated CD4$^+$ not CD8$^+$ cells \parencite{Wrone-Smith1996}. Nevertheless, preferential migration into the epidermis and clonal populations T cells have only been isolated for CD8$^+$ cells \parencite{Wrone-Smith1996, Chang1994}. %Altogether, this may suggest that CD4$^+$ are drivers of T cell activation but resident CD8$^+$ are the main effector cells in the dysregulated psoriasis immune response.

In psoriasis and PsA, IL-23 together with other cytokines, including IL-1$\beta$ and IL6, induce activation and differentiation of na\”{i}ve CD4$^+$ and CD8$^+$ into pathogenic Th-17 and Tc17 cells producing IL-17 \parencite{Weaver2007}. IL-17$^+$ CD8$^+$ cells have been found in psoriatic skin and are enriched in PsA synovial fluid when compared to peripheral blood, showing correlation with markers of inflammation and structural changes in the joint \parencite{Menon2014,Ortega2009). Likewise, Th-17 infiltrated cells have been found in the epidermis of psoriatic lesions \parencite{Lowes2008, Pene2008}. Additionally, IL-12 and IFN-$\gamma$ lead *to* expansion ofTh-1 and Tc-1 cells, which contribute to perpetuation of the immune response through IFN$\gamma$ and IL-18 production in psoriasis and PsA \parencite{Austin1999, Perera2012, Cai2012, Dolcino2015}.

%Elevated IL-17 mRNA and protein levels have also been reported in psoriasis and PsA patients compared to controls \parencite{Cai2012; Dolcino2015).

NK

NK cells are lymphoid-derived innate immune cells identified as CD3$^-$ CD56$^+$. The majority of circulating NK cells (90\%) are CD56$^{dim}$ and show strong cytotoxicity driven by high content of perforin and granzymes \parencite{Mandal2014}. In contrast, CD56$^{bright}$ commonly infiltrate into second lymph organs and other tissues, where they are activated by DCs and produce immunoregulatory cytokines such as IFN-$\gamma$, promoting Th-1 expansion and the adaptive immune response \parencite{Martin-Fontecha2004,Ferlazzo2004}. In psoriasis, significant increase of cells expressing NK markers have been found in lesional compared to uninvolved skin \parencite{Cameron2002,Ottaviani2006}. %with NK CD56$^{bright}$ cells isolated from acute plaque lesions producing abundant IFN-$\gamma$ upon activating stimuli \parencite{Cameron2002,Ottaviani2006} . Expansion of NK CD3$^-$ CD56$^{bright}$ cells in inflamed joints was observed in a cohort including RA, PsA and AS patients \parencite{Dalbeth2002}. Moreover, NK cells in RA have shown to trigger osteoclastogenesis and bone destruction in vitro and in mice models \parencite{Soderstrom2010} . %Moreover, the cytokine IL-15, which is highly present in the the joint microenvironment can prime NK cells isolated from PsA peripheral blood to kill via activation of the receptor NKG2D and cPLA2.82 \parencite{Tang2013}.

Amongst the target cells receptors regulating NK cells function, the killer immunoglobulin-like receptor (KIR) family includes activating and inhibitory members. The inhibitory receptor KIR2DL1 and the activatory receptor KIR2DS1 recognise HLA- Cw\*06:02, strongly associated with psoriasis and PsA \parencite{Tobin2011}. Interestingly, gene based studies have shown genetic variability in \textit{KIR2DS1} gene, associated with psoriasis and PsA susceptibility and also reported for AS and RA \parencite{Luszczek 2004, Williams2005,Carter2007, Yen2001).

The role of B cells in the pathophysiology of psoriasis and PsA has remained unclear. B cells are mainly known as key players of the humoral adaptive immune response through antibody production. However, they also act as APCs, regulate CD4$^+$ activation and differentiation into Th effector cells by providing co-estimulatory signals and actively secrete cytokines \parencite{Bouaziz2007,Constant1995,Harris2000,Linton2003}. Recent studies in the imiquimod-induced psoriasis mice model have demonstrated more severe inflammation in CD19 knock-out mice a regulatory B cell subset producing IL-10 \parencite{Yanaba2013,Alrefai2016}. Furthermore, different B cell subsets have been found in PBMCs from psoriasis patients and in lesional skin and correlation with disease severity has been identified for some clinical subtypes \parencite{Lu2016}.

GWAS

GWAS represent a biologically unbiased approach to shed some light on pathophysiological relevant cell types and molecular pathways associated with disease. GWAS have underlined some of the most important cell types for which genetic variation may be functionally relevant by overlapping them with epigenetic features mapped in cell lines or primary cells isolated from healthy control \parencite{}. In psoriasis and PsA, enrichment of associated variants has been found for regulatory elements in several cell types and the majority of GWAS risk loci have been linked to genes that belong to a limited number of pathways, as detailed below (Capon 2017). These genes are selected by proximity to the associated variant and genes unknown to be regulated at a distance fail to be include, a limitation when interpreting GWAS results.

Systematic comparison of the genetic architecture across different conditions has revealed associated psoriasis and PsA risk loci shared, in the same or opposite directions, with AS, Crohn’s disease (CD), multiple sclerosis (MS), RA and type 1 diabetes (T1D) (ImmunoBase). This has supported the use of therapeutic interventions such as anti- IL-23 and anti- IL-17 antibodies to treat a number of immune-related phenotypes including psoriasis, PsA, AS and IBD, amongst others (Visscher et al. 2017).

GWAS have highlighted keratinocyte-specific genes such the *LCE* gene cluster and genes with a key role in skin biology such as *CARD14*. Further studies in the *PSORS4* region have revealed that association with disease is driven by a deletion in two of the genes within this family, *LCE3B* and *LCE3C* (*LCE3C LCE3B del*)(Cid et al. 2009). The lack of *LCE3B* and *LCE3C* expression in psoriasis patients has been hypothesised to impair the repair following skin disruption, potentially facilitating microorganism infection and triggering a dysregulated immune response (Bergboer et al. 2011). *C*ommon and rare pathogenic mutations of *CARD14* in keratinocyte cell lines leadk to increased activation of NF-kB as well as overexpression of psoriasis-associated genes including *IL6*, *TNFA* and *TNFAIP2*, among others (Jordan et al. 2012b).