Functional genomics of psoriasis

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A thesis submitted in partial
fulfilment of the requirements for the degree of
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Abstract

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This is my abstract...

Acknowledgements

Thank you, thank you, thank you.

Declarations

I declare that unless otherwise stated, all work presented in this thesis is my own. Several aspects of each project relied upon collaboration where part of the work was conducted by others.

Submitted Abstracts

Title **Year**
Authors

Associated Publications

Title
Journal
Authors

Other Publications

Title
Journal
Authors

Contents

List of Figures

List of Tables

Abbreviations

Abbreviation	Definition
Ab	Antibody
ATAC-seq	
Atopic dermatitis	AD
ChIPm	
CLE	cutaneous lupus erythematosus
DMARDs	disease-modifying antirheumatic drugs
Fast-ATAC	
IDR	
GWAS	Genome-wide association studies
KC	Keratinocytes
NSAID	nonsteroidal antiinflammatory drug
Omni-ATAC	
PCA	
PI	Protein inhibitor
PsA	
QC	
qPCR	quantitative polymerase chain reaction
RA	Rheumatoid arthritis
SDS	Sodium dodecyl sulfate
SF	Synovial fluid

Chapter 1

Introduction

1.1 Psoriasis and psoriatic arthritis

Psoriasis and psoriatic arthritis (PsA) have been progressively identified as two different common complex disease entities. Psoriasis is a chronic inflammatory dermatose disease with episodes of relapse and remitance (Nestle et al. 2009). On the other hand, PsA is a seronegative chronic inflammatory disease within the family of spondyloarthritis (Moll et al. 1973; Coates et al. 2016) that usually develops after the psoriasis skin manifestations(**Villanova2016**). Psoriasis and PsA have shared and distinct clinical features, which are likely a reflection of the commonalities and differences in genetic loci contributing to disease development. It is important to understand those commonalities and differences at the physiological and genetic level in order to better understand the relevance of the genetic variability in the risk to develop psoriasis and PsA.

1.1.1 Epidemiology and global impact

Psoriasis represents a serious global health problem that currently affects about 100 million people worldwide, including children and adults with no sex bias (Organization 2016). Although there is a very weak correlation with geographic latitude (Jacobson et al. 2011), it has been reported to vary upon ethnicity. For example, psoriasis prevalence in adults is lower among African,

African American and Asian (0.4-0.7%) compared to American and Canadian (4.6 and 4.7%, respectively) populations. In the UK, psoriasis prevalence ranges between 2-3% and it affects approximately 1.8 million people (Perera et al. 2012).

PsA prevalence in the general population ranges between 0.04-1.2% (Perera et al. 2012)but it dramatically increases to 10-30% within psoriasis cases (**Reich2008**; Gelfand et al. 2005) and evidences the association between the two diseases. Particularly, in the UK, 14% of the psoriasis patients develop chronic inflammatory arthritis in the form of PsA at some point of the disease course (Ibrahim et al. 2009).

Although psoriasis can be developed at any age, onset of disease seems to have a bimodal distribution strongly influenced by the Human Leukocyte Antigen (HLA) Cw*06:02 (HLA-Cw6:02), an allele for one of the genes in the Major Histocompatibility Complex (MHC) I, involved in antigen presentation (Henseler and Christophers 1985) and the strongest genetic association with psoriasis and PsA risk (()Ellinghaus2010, Strange2010, Stuart2010; Sun2010). The early-onset or Type I is characterised by development of disease around 16-22 and 30-39 years and a prevalence for HLA-C*06:02 (85.4% of the cases). In contrasts, the late-onset or Type II group manifests disease between 50-60 years old and presents positive HLA-C*06:02 only in 14.6% of the cases.

Psoriasis and PsA also represent an economical burden for the countries' economies due to treatment and associated morbidity. For example, in the UK treatment and management of psoriasis in 2015 ranged between 4,000 to 14,000, before and after requirements of biological therapy, respectively (Burgos-Pol and Dermo 2016) and the costs are even greater for PsA (Poole et al. 2010).

1.1.2 Psoriasis and inflammatory dermatoses

The group of inflammatory dermatoses affects up to 70% of the population, regardless age and geographic location (**ICD-10**), and it represents the 4^{th} leading

cause of nonfatal burden (**Roderick2014**). The skin is the biggest organ in the human body constituting an effective barrier between the environment and the internal organs. The most external layer, the epidermis, plays a relevant role in the innate and adaptive immunity (Proksch et al. 2008) and its alterations due to exogenous or endogenous factors can lead to development of inflammatory dermatose conditions, such as psoriasis, atopic dermatitis (AD) or cutaneous lupus erythematosus (CLE) (**Johnson-Huang**; **2009**). Lesions in psoriasis can be non-pustular and pustular which reflects the heterogeneity in the type, location and severity of the disease and impairs the clinical classification (Perera et al. 2012). As a result, several phenotypes of psoriasis including vulgaris, guttate, pustular, erythroderma and nail pitting have been defined and it is under debate whether some of those should be considered a different disease entity (Marrakchi et al. 2011).

1.1.3 PsA and spondyloarthropaties

PsA belong to the family known as spondylarthropaties (SpA) which also includes other subtypes such as ankylosing spondylitis (AS), reactive arthritis (ReA), idiopathic inflammatory bowel disease (IBD) and undifferentiated SpA (Baeten et al. 2013). All SpA subtypes are characterised by structural damage (bone formation and erosion) as well as inflammation of joints and extraarticular sites such as eyes, gut and skin. Additional SpA criteria have led to a reduced classification of SpA into axial and peripheral SpA based on the affected joint (spine/sacroilicac or peripheral) and the presence of extraarticular features (**Runwaleit2001**; **Runwaleit2001**). Studies in human families and rat models with HLA-B27 positive status have shown manifestation of different SpA forms, such as psoriasis and IBD, within a single family or individual (**Said-Nahal2000 "parencite** ; Hammer et al. 1990). These observations support the hypothesis that SpA subtypes may be a single multifaceted condition

with shared genetic, immunophatological and structural features and dynamic phenotypes (Baeten et al. 2013). Conversely, some studies suggest that multiple genetic factors may be involved in the determination of the axial and peripheral arthritis and partially explain the immunopathological differences between the two (Porcher et al. 2005; Appel et al. 2011; Noordenbos et al. 2012).

As a phenotype, PsA can be further subdivided in five clinical groups based on Moll and Wright criteria: distal, destructive, symmetric, asymmetric and spinal (Moll et al. 1973). These subclasses mainly differed upon the location, number and distribution of the affected joints. Later studies have questioned this method of classification due overlapping of the different subsets and lack of inclusion of dactylitis (diffuse swelling of a digit) a distinctive feature of PsA (Reich et al. 2009). This phenotypic heterogeneity increases the difficulty in the design and achievement of meaningful outcomes from clinical studies.

1.2 Pathophysiology of psoriasis and psoriatic arthritis

1.2.1 Clinical presentation and diagnosis

Approximately 90% of all psoriasis cases are plaque psoriasis vulgaris that manifests with raising well demarcated plaques, erythema and scaling. The thickening (acanthosis) and vascularisation of the epidermis leads to the plaques formation (Perera et al. 2012) that can vary in size and distribution, being the most common the elbows, knees and scalp (Griffiths and Lancet 2007). The second most common type is psoriasis guttate (10% of all cases) characterised by acute onset of small droplike papules usually in the trunk and proximal extremities (Vence et al. 2015). Type I psoriasis commonly appears in the form of guttate lesions after bacterial infection whilst type II involves spontaneous chronic plaques (Perera et al. 2012).

In PsA the most common manifestation is the symmetric/polyarticular (more than 50%) followed by the asymmetric/oligoarticular (around 30%) PsA, that affects single or few distal interphalangeal or phalangeal joints (Reich et al. 2009; McGonagle et al. 2011). The psoriatic lesions precede joint inflammation in approximately 60-70% of the cases(**McGonagle**; **2011**; Gladman et al. 2005). Particularly, nail, scalp and intergluteal lesions constitute a predictive biomarker for development of joint inflammation (**Moll1976**; **McGonagle**; **2011**; Griffiths and Lancet 2007). This reinforces the need of appropriate coordination between dermatologists and rheumatologists for an early diagnostic and treatment that could prevent functional joint disability.

Several comorbidities have been associated with psoriasis and PsA, with comparatively greater prevalence in PsA. For example, intraocular inflammation known as uveitis affects 8% of PsA patients compared to 2% of the psoriasis ones (Husted et al. 2011; Oliveira et al. 2015). Other comorbidities include inflammatory bowel disease(IBD), cardiovascular disease (CVD) (Gelfand et al. 2006), type II diabetes (T2D) (**Saphiro2007**) and metabolic syndrome (**Cohrn20017**).

The diagnosis of psoriasis and PsA is mainly based in clinical assessment since there is a lack of appropriate biomarkers at early stages of disease (Villanova et al. 2013). Evaluating the severity of psoriasis skin lesions remains challenging and different measures have been implemented. The Psoriasis Area and Severity Index (PASI) (Fredriksson and Dermatology 1978) is the most widely used in research and drug trials (Finlay 2005). This test quantifies lesional burden weighted by body part based on the amount of affected body surface area and the degree of severity of erythema, induration and scale (Table 1.1). Disease is considered mild for PASI¡7 and it is classified as moderate-to-severe for PASI¿7-12, depending on the study (**Schmitt2005**; **add ref from cell types**; Finlay 2005).

To evaluate PsA, analysis of performance of the previously mentioned Moll and Wright criteria together with additional ones led to the configuration of the Classification Criteria for Psoriatic Arthritis (CASPAR) (**Taylor2006**), the most widely used. It requires the patient displaying inflammatory arthritis, enthesitis, and/or spondylitis and three points from a list of associated elements (Table 1.2) . Another composite measure commonly used to evaluate treatment efficacy for PsA is the PsA Response Criteria (PsARC) based on the number of tender joints (TJC) and swollen joints (SJC) over 68 and 66, respectively, as well as a physician global assessment based on a short questionnaire (**Philipp2011**; Clegg et al. 1996).

PASI	description
Body location	Head and neck, upper limbs, trunk and lower limbs
Feature	Redness, thickness and scaling
Severity scale	Absent, mild, moderate, severe or very severe
Affected area (%)	0, 1-9, 10-29, 30-49, 50-69, 70-89 or 90-100

Table 1.1: For each of the four body locations the test quantifies the percentage of affected area and the severity of three intensity features: redness, thickness and scaling.

CASPAR: a patient must have inflammatory articular disease (joint, spine, or enthesial) with three points from five categories	
Psoriasis	a. Current skin or scalp disease b. History of psoriasis c. Family history of psoriasis
Psoriatic nail involvement	Typical psoriatic nail distrophy
A negative test for RF	Using preferrably by enzyme-linked immunosorbent assay (EMSA)
Dactylitis	a. Swelling of an entire finger b. History of dactylitis
Radiologic evidence of juxtaarticular new bone formation	Ossification near joint margins

Table 1.2: xxxx

1.2.2 Aetiology of psoriasis and PsA

Psoriasis and PsA are complex chronic inflammatory diseases where a dysregulated immune response initiates as result of genetic predisposition and exposure to a particular environmental trigger (Figure**??**). One of the greater controversies has been characterising the origin of the pathologies as well as the connection between skin and joint inflammation. Particularly, for psoriasis it remains unclear whether disruption of the skin triggers activation of the immune response or viceversa.

Histopathological alterations in skin and joints

The epidermis is the most external structure of the skin and it is formed by approximately 90% keratinocytes (KC) organised in a layer structure that self-renews in a time dependent manner from the bottom to the surface (Wikramanayake et al. 2014). As the KC differentiate they undergo changes in morphology, replication ability and keratin composition of their intracellular matrix. In the context of psoriasis impaired epidermis cell renewal leads histological alterations and development of the psoriatic lesions. KC undergo upregulation in the proliferation rate (hyperplasia) that causes aberrant cell differentiation (parakeratosis) (ref) thickening of the epidermis and the subsequent scale formation (ref). Concomitantly, inflammation causes immune cell infiltration and hypervascularisation of the lesion driven by upregulation in the expression of angiogenic factors and activation of the endothelium (Perera et al. 2012).

In PsA, joint affection usually follows skin lesions and it involves a wide range of histological changes in the joints, particularly bone remodeling (Haddad and Chandran 2013). One of the most common structural changes is the arthritis caused by the swelling and inflammation of the joints (**Schett2011**). As result of this inflammation, alterations in bone remodeling leads to osteolysis with

subsequent bone resorption and erosion at the affected joints (**Mensah2017**). This phenomenon is particularly relevant in arthritis mutilans or chronic absortive arthritis, one of the most severe forms of PsA (Haddad and Chandran 2013). Bone erosion is also the main histopathological process driving dactylatis, where bone lysis resolves in shortening of the digits (Gladman et al. 2005). On the other hand, 35% of the PsA patients undergo inflammation of the connective tissue at the insertion of tendons or ligaments, phenomenon known as enthesitis (McGonagle et al. 2011; Polachek et al. 2017). Overtime, this causes debilitating structural changes due to formation of bony spurs along the insertion sites(**Schett2011**).

Dysregulation of the innate and adaptive immune response

The dysregulated immune response in psoriasis and PSA is the result of the interaction between innate and adaptive immune cells (ref section) resulting in feedback loops involving a complex cytokine milieu. Among the most relevant cytokines of the innate immunity involved in disease initiation are IFN-α and IFN-γ (**Leanne2009**). They are mainly produced by circulating plasmacytoid DC (pDC) and myeloid DC (mDC), respectively, upon activation by KC proinflammatory cytokines (Perera et al. 2012). Both are upregulated at the mRNA level in the lesional skin and contribute to lymphocyte recruitment and maintenance of DC activation (**Schmid1994**).

Another key cytokine in this dysregulated inflammatory response is TNF-α which has a prominent role in bone turnover and bone remodeling in PsA (Mensah et al. 2008). It is produced by activated KC, mast cells but also by adaptive immune cells types, including infiltrated T helper(Th) 1 and Th-17 cells infiltrated in the psoriatic lesion and PsA inflamed joints (Perera et al. 2012) and it induces activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-B) signaling pathways (ref). It also activates several kinase signaling pathways as well as cell death programs (ref). In the context of inflammation,

NF-B represents a master transcriptional regulator of both, the innate and adaptive immune system that induces expression of proinflammatory cytokines, antiapoptotic genes and genes involved in chronic inflammation maintenance (ref). The importance of this transcription factor (TF) in psoriasis and PsA pathogenesis is reflected by the association with disease of several genetic variants in some of the negative regulators of its proinflammatory activity, including NF-B inhibitor alpha *NFKBIA* and TNF receptor-associated factor 3 interacting protein 2 *TRAF3IP2* (ref).

Interleukin-23 (IL23) and Th17 axis represents a key loop for the maintenance of psoriasis and PsA inflammatory response and a very important link between innate and adaptive immunity. IL-23 is an innate regulatory cytokine, mainly produced by mDC and macrophages homing the inflamed skin and it binds to the IL-23 receptor (IL-23R), which expression is upregulated in the DC and T cells of the lesion and in circulating Th cells (ref). In psoriasis, IL-23 is the mediator for the pathogenic loop between activated KC and T cells (ref). Both IL-23 and IL-23R present protective and pathogenic genetic variants associated with psoriasis and PsA risk (ref). The activation of the IL-23 pathway leads importantly to increased IL-17 production through NF-activation by *TRAF3IP2* (ref). IL17 favors maintenance of the adaptive immune mediated Th17 response through recruitment and activation of neutrophils, induction of proinflammatory cytokines including IL-1β*andIL* − 6*andalsoperpetuationofKCactivation*(*ref*)(*https* : *//www.ncbi.nlm.nih.gov/pmc/articles/PMC*3580541/).*Morerecently*,*interleukin*22(*IL*− 22)*hasarisenasanotherofthekeycytokinesinmediatingthedysregulatedcrosstalkbetweentheinna* cells known as Th22 (ref). It mediates some of the histological changes in skin as well as AMP production by KC (ref).

Environmental factors and disease

Several environmental triggers are known to be associated with increased risk and worsening of psoriasis and PsA development. A wide range of drugs including antidepressant, antihypertensive and anticytokine therapies have been clinically associated with initiation, exacerbation and worsening of psoriasis (Kim et al. 2010). Infectious agents such streptococcal throat infection have likewise been associated with development of type I psoriasis (**Valdimarsson2009**; Gudjonsson and of 2003; Diluvio et al. 2006). Consistently with other chronic inflammatory disease such as IBD and AS, recent studies have also observed perturbation in the composition of the gut and skin microbiota in psoriasis and PsA patients. On the other hand, physical trauma, including tattoos, surgical incisions and mechanical stress can trigger the appearance of lesions in psoriatic uninvolved skin as well as joint inflammation in digits (**Weiss2002**; Nestle et al. 2009). Lastly, as for most of the complex diseases, behavioral factors including smoking, alcohol and stress have been linked to psoriasis and PsA without a clear conclusion of their involvement in triggering disease (Meglio et al. 2014).

1.2.3 Cell types involved in psoriasis and PsA pathogenesis

Identifying the most relevant cell types contributing to psoriasis and PsA pathogenesis remains challenging. There has been a reinterpretation of both phenotypes that understands them as dynamic and continuous processes where different cell types became predominantly important at different stages of the pathology.

KC are one of the most relevant cell type at early stages of psoriasis pathogenesis, which is reinforced by the genetic association between skin specific genes from the late cornified envelope (LCE) family and psoriasis (Tsoi et al. 2012). Several studies have shown the role of KC as immune sentinels through

MHC-II antigen presentation and production of antimicrobial peptides (AMP), cytokines and chemokines (Black and of 2007). There is evidence of complex formation between the cationic AMP LL-37 and self-DNA/RNA released by KC upon damaged triggered by environmental factors (Lande et al. 2007). This complex acts as an antigen for activation of the skin-resident DC (Nestle et al. 2005) and that initiate and perpetuates the skin inflammatory response through secretion of pro-inflammatory cytokines, importantly IL-1, IL-6 and TNF-α (**Feldmeyer2007**; Arend et al. 2008; Nestle et al. 2009). Studies in mouse models have also shown development of psoriatic lesions in immunodeficient mice upon human xenotransplant of psoriasis skin(Boyman et al. 2004). Overall, these findings would support the hypothesis attributing the initiation of the chronic inflammatory response in psoriasis as the consequence of the epidermis dysfunction Proskch2008.

mDC and pDC are professional APC also considered important innate immune cells in disease initiation through T cell activation and subsequent triggering of the adaptive immune response (Mahil et al. 2016). pDC are circulating cells absent in healthy skin that infiltrate into the lesional and uninvolved dermis of psoriasis patients and get activated by the aforementioned KC self-DNA and LL-37 complex through Toll-like Receptor (TLR)-9 (Nestle et al. 2005; Lande et al. 2007). In contrast, quiescent mDC are epidermal resident cells and upon secretion of IFN-α by pDC a 30-fold increase of mature mDC is observed in lesional skin but not in uninvolved or healthy tissue (ref). Different mDC subpopulation mediate the Th1 and Th17 response as well perpetuation of KC activation through IL-23 production (ref). Studies in immunodeficient psoriasis mice models have shown that blockage of downstream IFN-α signaling or its production by pDC failed to induce T cell activation and onset of psoriasis (Nestle et al. 2005).

Neutrophils are also though to be closely involved in disease initiation through their ability to form neutrophil extracellular traps (NET)that contain host DNA and LL-37 (Hu et al. 2016). There is evidence of increased NET formation in peripheral blood and lesional skin of psoriasis patients and they seem to be contributing to pDC and $CD4^+$ T activation (Hu et al. 2016). Neutrophils have also been identified in recent studies as one of the main sources of IL-17 production in the skin lesions (Lin et al. 2011) and they also release a wide range of proteases which some induce KC proliferation (**Mahil2006**).

In the context of the innate immunity, the involvement of monocytes and macrophages in psoriasis and PsA has not been extensively studied. Resident macrophages in the healthy dermis undergo a 3-fold increase upon skin lesion and they are involved in disease development through TNFα production (Perera et al. 2012; Mahil et al. 2016). Similarly, mice models for chronic psoriasiform skin inflammation have shown macrophage migration into the affected skin and TNF-α production for maintenance of the skin lesions (**Stratis2006**; **Wang2006**). Some studies using isolated monocytes from psoriasis patients PBMC have shown greater phagocytic and bactericidal activity compare to those from healthy individuals (**Bar-Eli1979**). Later studies have also shown increased circulating intermediate monocytes ($CD14^+$ high $CD16^+$ high) and monocyte aggregation in psoriasis patients causing enhanced platelet activation and angiogenesis (**Golden2015**). In PsA, synovial membranes levels of monocytes/macrophage metalloproteinases which mediate bone erosion through differentiation into osteoclasts are comparable to those found in RA joints (Hitchon et al. 2002). Overall, these observations highlight the systemic aspects of both pathologies.

Historically, T lymphocytes have been considered one of the most relevant cell types in initiation and maintenance of psoriasis and PsA and its role is also supported by genetic findings. Report cases in humans have demonstrated that bone marrow transplantation can initiate or terminate

psoriasis (**Gardembas1990**; Eedy et al. 1990). The percentage of circulating T cells in psoriasis have shown reduced number of T cells in moderate-to-severe and severe psoriasis patients but increased percentage of the memory populations $CD4^+CD45RO^+$ and $CD8^+CD45RO^+$ when compared to milder phenotypes and healthy controls (**Lecewicz-Toru2001**; Langewouters et al. 2008). There is still controversy regarding the total $CD4^+$ and $CD8^+$ abundance and $CD4^+/CD8^+$ ratios in PBMC, which may be due to the phenotype heterogeneity of psoriasis patients in the different studies (**Lecewicz-Toru2001**; Cameron and of 2003; Langewouters et al. 2008). In PsA, no differences abundance of circulating T cells have been identified compared to healthy individuals (Costello et al. 1999).

In healthy skin, $CD4^+$ and $CD8^+$ are found in the dermis and epidermis, respectively (Clark et al. 2006; Perera et al. 2012) and an increase in activated memory $CD4^+CD45RO^+$and $CD8^+CD45RO^+$ can be detected as soon as 3 days after lesion appearance (Clark et al. 2006), highlighting the importance of the memory population. *In vivo* studies conducted in mice by Boyman and colleagues showed that development of psoriasis following engrafted human pre-lesional skin was dependent of local T cell proliferation without injection of additional factors (**Boyle2013**), supporting that recruitment of circulating T cells may be restricted to the priming event and it is minimal afterward (Perera et al. 2012). The relative importance of $CD4^+$versus $CD8^+$ in psoriasis initiation has been tested immunodeficient mice with pre-lesional skin xenografts suggesting a model where $CD4^+$ but not $CD8^+$ T cells where required for the progression of uninvolved to lesional skin in mice (Nickoloff and Wrone-Smith 1999). Interestingly, injection of $CD4^+$ activated cells was followed by an increase in activated resident $CD8^+$ T cells expressing the acute activation marker CD69 which suggests that skin $CD4^+$ cells drive activation of resident T cells and that the activated $CD8^+$ resident population would act as the main effector cells. In

PsA, $CD4^+$ are significantly more abundant than $CD8^+$ cells in synovial tissues (Diani et al. 2015). However, among the $CD8^+$ population the memory cells are prevalent in the SF and they are significantly increased when compared to controls (Costello et al. 1999). The contribution of regulatory T (Treg) cells have also been investigated with controversial outcomes regarding relative abundance and impaired function in both pathologies (Perera et al. 2012).

Based on the T cells cytokine profile, psoriasis and PsA has been demonstrated to be a type 1 Th/Tc disease, where activation of naive $CD4^+$ and $CD8^+$ cells is driven by IL-12 and IFN-γ (Austin et al. 1999; Perera et al. 2012). Later studies have also identified additional T cells subsets including Th-17/Tc-17 and Th-22/Tc-22, characterised for the high production of IL-17 and IL-22, respectively, two cytokines very relevant for perpetuation of the inflammatory response (Mahil et al. 2016). The importance of Th17 cells and IL-17 production has been assessed in skin, joints and blood, where elevated IL-17 and also IL-23 mRNA and protein levels have been found in psoriasis and PsA patients compared to controls (**Cai2012**; **Dolcino2015**). It has been shown that the predominant $CD8^+$ populations in the SF are also IL-17 producers and their abundance correlates with markers of inflammation and structural changes in the joint (Menon et al. 2014). This finding is in line with observations in skin and it suggests a prominent role of $CD8^+$ IL-17 producing cells in the different stages of both pathologies. Understanding the importance of IL-17 has also led to the discovery of other immune cells producing this pivotal cytokine, including innate immune lymphoid (ILC) cells and $\gamma\delta$ T cells which have also started to be investigated in the context of psoriasis and PsA pathophysiology and treatment (Meglio et al. 2014; Leijten et al. 2015). IL-17 producing cell have also been hypothesised to be responsible for the link between skin and joint lesions. Although the precise mechanisms for transition between psoriasis and

PsA is unknown, studies using psoriasis and RA mice models have shown that skin lesions facilitate arthritis and joint inflammation

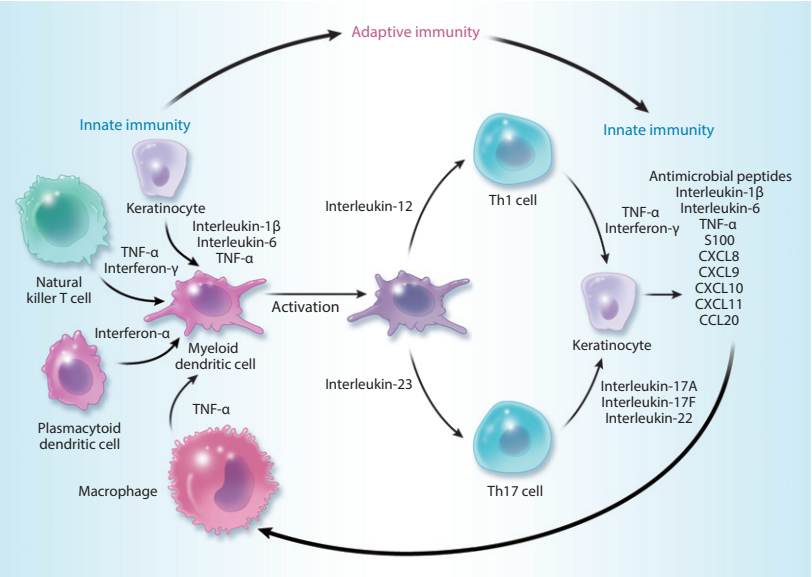

Figure 1.1: Figure adapted from (Nestle et al. 2009)

1.2.4 Therapeutic intervention and prognosis

Currently, there is no cure for either psoriasis or PsA and the different treatments available are focused in managing symptoms. The approach to treat them are usually dependent on the disease severity. Cases of mild-to-moderate psoriasis are usually managed with topical therapies for which corticosteroids and emollients are the most commonly used and affordable ones (Menter et al. 2009). In psoriasis, other topical treatments are used in combination with corticosteroids such ultra violet (UV) light therapy and vitamin D analogues, which inhibit KC proliferation, stimulate KC differentiation and inhibits T cell proliferation (**Rizova2001**). For PsA patients presenting swelling of two or less joints, intra-articular injection of glucocorticosteroids together with joint aspiration have shown to reduce pain and inflammation as a short-time measure (Coates et al. 2016).

Treatment of most forms of PsA and more moderate-to-severe psoriasis require the use of a broad range of systemic therapies. For mild cases of PsA nonsteroidal anti-inflammatory drug (NSAID) are the most commonly used to help controlling the mild inflammatory symptoms (Coates et al. 2016). For more severe forms of PsA, disease-modifying antirheumatic drugs (DMARDs) including the an antagonist of folic acid methotrexate (MTX) and the phosphodiesterase 4 inhibitor apremilast are used with immunosupressive effects on activated T cells and cytokine production, respectively (**Schmitt2014**; **Keating2017**; Gossec et al. 2016; Polachek et al. 2017). Biologic systemic agents are the most specific for the treatment of severe psoriasis and PsA. They are cell-based molecular species that modulate the immune response in a physiological manner (Perera et al. 2012). Among the biologic agents targeting cytokines, TNFα inhibitors (TNFi) have been broadly used for the past five decades to treat both, psoriasis and PsA due to the relevance of TNFα in disease. Three TNFi have been approved for the treatment of psoriasis: etanercept, infliximab

and adalimumab (**Ahil2016**). In addition to those, certolizumab pegol and golimumab are also used in the management of PsA and other rheumatoid diseases (**Coates2016b**). All the TNFi are antibody-based agents but etanercep, which is a soluble receptor, and they show differences in the frequency and via of administration (Mease et al. 2000). Although TNF-α blockade is one of the most effective treatments, some patients experience common side effects such as increased risk of infection, reactivation of latent infections, demyelinating disease and induced pustular psoriasis have been identified (Nickoloff and Nestle 2004). Between 20 to 50% of the patients fail to respond to the first TNFi, due to side-effects or tolerance, and they require switching to a second or third one (Abramson and and 2016). New biologic therapies have been developed to target other key cytokines in the pathogenesis of PsA and psoriasis, such as IL-12, IL-23 (ustekinumab) or IL-17 (secukinumab and ixekizumab) (Mahil et al. 2016). These new biologics represent a substantial benefit for treating patients and they are routenely administered to individuals failing to respond after a switch to a second TNFi (**Coates2016b**).

1.3 Genetics of psoriasis and psoriatic arthritis

As complex diseases, the risk to develop psoriasis and PsA is not only influenced by the surrounding environmental conditions but also by the genetic background of each individual. Determining the magnitude of contribution of the genetic factors in the development of these disease and identifying the exact genes or regions involved in the predisposition to psoriasis and PsA remains challenging.

1.3.1 Heritability

Several studies have shown a trend towrads the increase of psoriasis and PsA prevalence over the last 30 years in different countries (Organization 2016).

This importantly reflects changes in life style habits and it highlights the need to better understand the genetic factors that predispose to disease upon interaction with environmental stresses.

The contribution of genetics in the development of psoriasis has also been demonstrated in several twins studies. The concordance of psoriasis has been shown to be greater in monozygotic (33-55%) compared to dizyogtic (13-21%) twins with some variation between studies and populations, estimating an 80% of heritability in this condition (**Faber1974**; **Pendersen2008**; Duffy et al. 1993). For PsA, similar concordance between mono- and di- zygotic twins has been shown, probably due to lack of statistical power and appropriate diagnosis (**Pendersen2008**). In the general population, approximately 40% of the patients with psoriasis or PsA have family history in first degree relatives (Gladman et al. 1986). Interestingly, the recurrence in first-degree relatives ha been shown to be greater in PsA (40) compared to psoriasis (8) in a study in Icelandic population (Chandran et al. 2009). This could suggest differences in the heritability between the two phenotypes and maybe an stronger genetic contribution in PsA.

1.3.2 Non-GWAS and linkage studies

Different approaches have been undertaken to uncover the genetic variability contributing to the predisposition to psoriasis and PsA. The appearance of next generation sequencing (NGS) techniques and the progressive reduction of cost has allowed to move from candidate genes studies looking at the genetic variability at particular locus to a genome-wide approach.

The study of psoriasis and PsA genetics architecture started with linkage analysis in family pedigrees with autosomal dominant condition to try to . The use of this approach yielded nine psoriasis susceptibility loci (PSORS1-9) (Capon 2017) with the strongest association in PSORS1 (**International2003**). PSORS1 lies within chromosome 6p21.3 and its identification by linkage

analysis confirmed the association previously identified in serological studies between psoriasis susceptibility and the MHC I (**Rusell1972**; **Tiilikainen1980**). Importantly, Mendelian forms of disease with rare highly penetrant mutations have been identified in family studies for two genes within PSORS2 (17q25): zinc finger protein 750 (*ZNF750*) (**Tomfohrde1994**) and caspase domain family member 14 (*CARD14*) (Jordan et al. 2012). Rare gain of function and *de novo* mutations and also common variants in *CARD14* have been identified in psoriasis and PsA patients, suggesting an important role of the genetic variation in this gene for Mendelian and multi-factorial forms of disease (Jordan et al. 2012; Tsoi et al. 2012). In PsA, a region close to the psoriasis PSORS8 was also identified (Karason et al. 2003). Nevertheless, the ability of independent studies to only reproduce PSOR1, 2 and 4, highlighted the limitations of the linkage studies to understand the genetics of complex diseases (Capon 2017). Gene based studies in psoriasis and PsA have also identified the relevance of genetic variability in the activating killer immunoglobulin receptors 2DS1 (KIR2DS1) (**uszczek2004**; **Williams2005**), similarly to AS and RA (**Yen2001**; Carter et al. 2007). This receptor is expressed on NK and NK T cells and mainly triggered by HLA-Cw*06:02. Similarly, specific association with PsA but not psoriasis was found for microsatellites and promoter polymorphisms in TNF-α (**H""–o˝hler2002**).

1.3.3 Genome-wide association studies

The technological advances experienced in sequencing and genotyping has allowed to implement association studies at a genome-wide scale. The genome-wide association studies (GWAS) have benefit from the understanding of common (frequency >1%) single base-pair changes know as single nucleotide polymorphisms (SNPs) in different populations through whole genome sequencing (WGS) projects such as HapMap (**The international HapMaP Consortium**) project and the 1000 Genomes project (**The 1000 Genomes**). GWAS have

focused in the association to a particular phenotype of single-nucleotide bi-allelic substitutions with minor allele frequency (MAF) >5% in a case-control design (Ku et al. 2010). This followed the hypothesis driving the field of complex diseases where common diseases are more likely to be caused by common variants (Schork et al. 2009). Due to the organisation of the genome into segments of strong linkage desiquilibrium (LD) where genetic variants are strongly correlated with each other (measured as a squared correlation r^2), the genotyped SNPs in GWAS are used a proxy for the disease causative variant. In the context of complex diseases, GWAS have greater power than the previous linkage studies when looking at the influence of many loci with low penetrance and small effects in disease risk and they have identified common alleles conferring effect sizes (Cui et al. 2010). Disease causal variants can be non-genotyped SNPs or other type of genetic variability such as copy number variants (CNVs), also highly frequent in the genome, which are less widely studies by GWAS (Hirschhorn 2005; Ku et al. 2010).

Since the improvement of genotyping technologies, several GWAS studies have been performed in psoriasis and PsA (Table). Since the first psoriasis GWAS analysis in 2007 more the number of risk loci associated with psoriasis and PsA have increased. Currently, there are a total of 63 associations to psoriasis and PsA susceptibility at a genome-wide significance (pval¿5x10¯8) which explain 28% of the heritability (**Tsoi2017**). Most of the studies have been performed in Caucasian European or North American cohorts but lately few GWAS studies Chinese populations have also been published (Zhang et al. 2009; Sun et al. 2010; Yin et al. 2015). The earlier studies were performed in discrete cohort sizes with moderate power that confirmed association with loci overlapping the PSOR1, PSOR2 and PSOR4 regions from the linkage studies (). HLA-C has consistently been identified in all the GWAS studies as the most significant locus with the greatest effect size which account for approximately 50% of psoriasis heritability.

Additional MHC-I and MHC-II associations were identified doing step-wise conditional analysis for the HLA-C association and revealed contribution of HLA-A, HLA-B and HLA-DQA1 to disease risk (Okada et al. 2014)

One of the most informative GWAS studies was the one performed using the Immunochip genotyping platform, which includes greater genotyping density only at 186 immune relevant loci identified in previous GWAS studies across different inflammatory diseases (Tsoi et al. 2012). This study uncovered 15 new associations and it also included meta-analysis analysis with the largest available psoriasis cohorts (Tsoi et al. 2012). This meta-analysis has later been expanded, being the largest one the Tsoi and colleagues in 2017 (**Tsoi205**; **Tsoi2017**). This latest study has revealed additional 16 associations reinforcing NFκB and cytotoxicity pathways in disease.

Meta-analysis of GWAS across Caucasian and Chinese populations have showed the value of this trans-ethnic approach to identify new association and understand the genetic differences between populations contributing to disease (Yin et al. 2015). In this study four new loci including *LOC144817*, *COG6*, *RUNX1* and *TP63* were associated with psoriasis and PsA in both populations at non-coding gene regions. Genetic heterogeneity was also observed for 10 of the GWAS reported loci such as *ELMO1* and *TYK2* among others, when looking at the association in Caucasian and Chinese cohorts independently.

Changes in the frequencies of HLA-C and HLA-B alleles had already shown evince of genetic differences between psoriasis and PsA supporting the importance of independent GWAS studies(**Winchester2012**; Okada et al. 2014). Therefore, although most of the GWAS include mixed psoriasis and PsA cohorts some of them have performed stratified analysis between the two subcohorts. As result, a new association for a some of the loci such as *TRAF3IP*, *IFNLR1*, *IFIH1* and *NFKBIA* were confirmed to be associated when using only PsA cases (**Stuart2015**; Ellinghaus et al. 2010). When performing association analysis

of psoriasis versus PsA, a signal in chr18 overlapping the long non-coding RNA (lnc-RNA) *LOC100505817* was identified. Moreover, a PsA GWAS using the Immunochip platform revealed a PsA specific association in chromosome 5q31 (Bowes et al. 2015). Overall, GWAS studies have demonstrated shared genetic susceptibility between psoriasis and PsA, but have also highlighted some specificity that may support a difference in the genetic architecture of both diseases. It is important to take into account that these results are affected by imprecise phenotyping of cases, which entails one of the many challenges when trying to compare both diseases.

1.3.4 Relevance of non-coding versus coding variants in disease susceptibility

GWAS studies have revealed a large number of SNPs associated to different complex diseases. From all the GWAS associations, approximately 88% of the hits map within non-coding regions (**Welter2013**) and only the remaining are variants in coding regions that could be causing non-synonymous mutations with impact in proteins by truncation or alteration in folding or glycosylation (**Welter2013**).

Exome psoriasis association studies in Chinese and Caucasian populations have increased the number of coding variants with putative effect in protein coding (**Tang2014**; **Zuo2015**; Dand et al. 2017). These studies confirmed some of the previously identified missense associations in *CARD14*, *ERAP1* and *ZNF815A* (**Tang2014**), revealed new common ones at previously GWAS associated loci such as IL23R and identified protective rare missense changes at *TYK2* and *IFIH1* (Dand et al. 2017). Nevertheless, results from extenssive exome studies suggest that non-synonimous SNPs have a limited contribution to the overall genetic risk of psoriasis when compared to non-coding variants (**Tang2014**).

Non-coding variants associated with disease could become causal by altering the regulation of gene expression. These variants are usually found at

introns, intergenic regions or gene deserts. The functional mechanism by which they affect gene expression will depend on the type of regulatory element where the variants are located, including enhancer, silencers, promoters and the 5' and 3' untranslated region (UTR) of genes (**Ward2012**). It will also be influenced by the dynamic cell and context specific functional epigenome, which involves different DNA and DNA-protein bound modifications such as methylation and acetylation, as detailed later on and defines the accessibility of the surrounding chromatin (Knight and C 2014).

Non-coding variants at enhancers, silencers and promoter can dysregulate gene expression by altering affinity for transcription factor (TF) binding and drive alterations in histone modifications and chromatin accessibility (ref). For example, in thyroid autoimmunity the risk allele of an intronic SNP in the tyroid stimulating hormone receptor (TSHR) reduces *TSHR* expression by increasing the affinity of the repressor promyelocytic leukemia zinc finger protein (PLZF), which impairs tolerance to thyroid auto-antigens (Stefan et al. 2014). Alterations in TF binding can also affect looping and long-range chromatin interactions between enhancers and promoter, which for example in prostate cancer causes upregulated expression of the oncogene *SOX9* due to increased interaction and enhancer activity (**Zhang2012**). Non-coding SNP can regulate gene expression by creating a new promoter-like element, as it is the case in α- thalassemia leading to dysregulated downstream activation of all α-like globin genes (Gobbi et al. 2006). Non-coding variants at the 3' UTR SNP can affect binding of micro-RNA and lnc-RNA and therefore alter transcript stability and translation. For example there is a Crohns-disease-associated variant at the 3'UTR of the gene immunity related GTPase M *IRGM* that reduces binding of the miR-196 which increases stability of the transcript and enhancing mRNA transcript altering autophagy (Brest et al. 2011) In psoriasis and PsA some SNPs located at 3' UTR of genes such as *IL-23*, *TRAF3IP2* or *SOCS1* have been hypothesised to create or alter

miRNA binding sites but there is lack of experimental evidence (Pivarcsi et al. 2014). Lastly, transcriptional regulation can also be altered by intronic SNPs that lead to splicing alterations with a protective effect of the variant in TNF Receptor Superfamily Member 1A (*TNFRSF1A*) associated with multiple sclerosis (MS) (Gregory et al. 2012) or an increase of risk to migraine by exon skipping due to an intronic variant in acyl-coenzyme A synthetase 5 (*ASCL5*) (Matesanz et al. 2016).

One of the most informative approaches to connect the effect of a SNP allele with expression regulation of a particular gene are the expression quantitative trait loci (eQTL) analysis. This performs an association between gene expression and SNPs in *cis* (<1Mb) or *trans* of each gene (ref). Identification of *cis* and *trans* eQTLs could reveal gene networks, as in T2D where e a *cis*-eQTL for the TF Kruppel-like factor 14 (*KLF4*) is also associated with other genes in trans, highlighting downstream targets regulated by that TF (**Small2011**). Similarly, cis effect of a variant in cytokine coding genes could be accompanied by a trans association with downstream members in the same signaling pathway. For example, our group found that in monocytes a *cis*-eQTL in the gene coding for IFN-β is associated in trans with IFN modulated genes, among others IFN regulatory factor 9 (*IRF9*) (Fairfax et al. 2014). Nevertheless eQTLs are only one of the many available and necessary additional sources of functional information to convey when trying to understand the mechanisms behind non-coding variant GWAS associations, as it will be detailed in section xxxxx.

1.3.5 The role of GWAS studies in highlighting immune-relevant cell types and pathways

GWAS represent a biologically unbiased approach to shed some light into pathophysiological relevant cell types and molecular pathways associated with disease. In the field of common immune-mediated diseases, GWAS have

underscored some of the most important cell types for which genetic variation is functionally relevant. For example, in T2D the strongest GWAS associations showed to be enriched at pancreatic β cells and to affect genes involved in insulin secretion, consistently with the insulin resistance that characterises the disease pathology (**Visscher2017**).

Immune diseases have benefited from the use of the immune targeted genotyping array Immunochip to perform a systematic comparison of the genetic architecture across the different conditions. For example psoriasis and PsA share risk loci with AS, CD, MS, RA and T1D, among others (**ImmunoBase**). However, genetic overlap where the signal is the same across different diseases have not necessarily the same direction and a risk allele for one can be protective for another reflecting true differences in the pathophysiology of different immune mediated diseases. The better understanding of immune-related diseases has led to identification of shared susceptibility loci and the use of therapeutic interventions across diseases, such as anti IL-23 and anti IL-17 antibodies to treat psoriasis, PsA, AS and IBD (**Visscher2017**).Cross disease association studies have also been performed for the simultaneous analysis of AS, UC, primary sclerosing cholangilitis (PSO), CD and psoriasis (Ellinghaus et al. 2016). This study revealed the greatest genetic pleiotropy of psoriasis with AS and CD, this meaning same alleles predisposing to disease risk (**ImmunoBase**). Among the 206 multi-trait associated loci, enrichment was found for regulatory elements in bone marrow, NK and T cells as well as for immune response pathways, supporting the contribution of GWAS to the biological understanding of disease. In the case of psoriasis and PsA, most of the GWAS risk loci highlight genes that belong to a small number of pathways and they are enriched for regulatory elements of several cell types (Capon 2017). Nevertheless, it is important to bear in mind that in most of the cases non-coding variants from GWAS studies lack of functional characterisation and they tend to be associated arbitrarily to the nearest gene or

the closest gene which fits into current knowledge about pathophysiology. This bias to some extent the genes that contribute to enrichment of certain pathways and the efficacy of drugs developed to target some of those genes has helped to further confirm their truly involvement in disease.

Antigen presentation

*HLA-Cw*0602*, the strongest GWAS association in psoriasis is also associated with other diseases such as Hepatitis C, PSO and Graves disease (Blais et al. 2011). *HLA-Cw*0602* is involved in antigen presentation and the absence of differences at the transcript level between normal and psoriatic individuals suggests the association is not explained by alteration in regulation of gene expression (Hundhausen et al. 2012). The relevance of antigen presentation in psoriasis and PsA has been reinforced by the GWAS association of the endoplasmic reticulum aminopeptidase 1 *ERAP-1* gene, which codes for an aminopeptidase involved in the trimming of peptide antigens. GWAS studies identified that *ERAP-1* was associated with psoriasis and PsA only in individuals carrying one copy of the rs10484554 *HLA-C* risk allele (Strange et al. 2010). Moreover, the same studied also found dependent association of an SNP nearby the zeta chain of T cell receptor associated protein kinase 70 *ZAP70* gene and *HLA-Cw*0602*. ZAP70 is a tyrosin kinase that binds the CD3-ζ of the TCR and it is involved in the $CD8^+$ cells auto-reactivity regulation (Picard et al. 2009), overall highlighting the role of HLA-dependent $CD8^+$ dysregulation in psoriasis and PsA. At the clinical level, *HLA-Cw*0602* and *ERAP-1* have also been associated with pediatric psoriasis onset together with other GWAS loci (Bergboer and of 2012). These epistatics phenomena, where association of one gene is dependent by the presence of another, has also been found between other HLA class I molecules such as *HLA-B*27* and *HLA-B40* and *ERAP1* in AS (**Cortes2015b**; Evans et al. 2011). The signal at chromosome 5q15 for *ERAP1*

allele is the same in psoriasis and AS and they also share the direction of the effect (**ImmunoBase**). Several studies have revealed that the disease associated polymorphisms in AS increased *ERAP-1* and *ERAP-2* gene expression and also altered splicing, resulting in ERAP-1 protein isoforms with increased activity (**Constatino2015**; Hanson et al. 2018). Regarding cell types, the role DC and macrophages involved in antigen presentation is reinforced by genetic evidence.

Skin barrier

GWAS have highlighted KC specific genes such the *LCE* gene cluster or genes with a very relevant role in the skin such as *CARD-14*, both previously mentioned. Further studies in the *PSORS4* have revealed that association with diseases is due to a deletion comprising two of the genes within this family, *LCE3B* and *LCE3C* ($LCE3C_LCE3B_del$)(*CidEt al.*2009).*Innormalskin,expressionofLCE3BandLCE3Cisverylowanditisinduceduponbarrierdi al.*2009).*Overall,thelackofLCE3BandLCE3Cexpressioninpsoriasispatientcouldleadtoanimpai al.*2005).*CARD14isprimarilyexpressedinepithelialtissueswhereitisinvolvedinrecruitmentand pathway (Blonska and research 2011). Common and rare pathogenic mutations of CARD14 in KC cell lines led to increased activation of NF-kB as well as overexpression of psoriasis-associated genes including IL-6, IL36, TNFA and TNFAIP2, among others (***Jordan2012b***).*

NF-κB and TNF pathways

The NF-κB pathway is involved in the regulation of the innate and adaptive immune response. Several psoriasis and PsA GWAS loci have been mapped to gene members of the NF-κB and TNF signaling pathway such as TNIP1, TNFAIP3, NFKBIA, REL, TRAF3IP2, among others NF-κB is a dimeric TF, formed by assembly of two of the five proteins from the NF-κB family, that translocates into the nuclei upon cytokine stimuli, importantly TNF-α. Dysregulation of a feedback loop between TNF-

*α and NF-κB contributes to the development of many chronic inflammatory diseases (***Liu2017***) and neutralisation of TNF-α is used for treatment of many immune-mediated diseases, as previously described. In psoriasis, elevated levels of NF-κB are found in lesional skin compared to uninvolved and normal skin (Lizzul et al. 2005). Psoriasis and PsA GWAS association with NFKBIAand REL, two of the genes coding for NF-κB subunits, are driven by SNPs at an intergenic region, not having yet directly evidence to their effect over regulation of these genes (***GWAS studies***). REL has been associated with other inflammatory diseases, including CD and RA (***ImmunoBase***) and, interestingly, the RA risk allele has a protective effect in PsA showing opposite direction effects (Bowes et al. 2012). The relevance of members downstream TNF-α signaling is highlighted by the GWAS association of TNIP1 and TNFAIP3, protein products interact with each other and participate in the regulation of NF-κB activation. SNP variants in these regions have also been identified for CD, UC and SLE, among other immune diseases, reinforcing the relationship between these two pathways in chronic inflammation (***ImmunoBase***). In mice, a chromosomic region including Tnfaip3 induces psoriasis in a TNF- dependent manner and it also increases atheroclerosis risk, one of the most prevalent co-morbidities in psoriasis and PsA (***Wang2008***; ***Idel2003***). The association with the interacting protein TRAF3IP2 is stronger in PsA than in psoriasis (***H“”–u˝ffmeier2010***) and a haplotype including two missense mutations and two intronic variants has been reported in two different studies (***H“”–u˝ffmeier2010***; Ellinghaus et al. 2010). The missense mutations rs33980500 located at a highly conserved region of the TRAF3IP2 protein has shown reduced affinity TRAF interacting proteins, which has a downstream effect in NF-κB activation and the IL-17/IL-23 axis(***H“”–u˝ffmeier2010***). Exome-sequencing studies have also lately implicated variants with predicted evidence on protein structure and function at TNFSF15, a TNF ligand family protein induced by TNF-α, mostly expressed in endothelial cells and with a role in regulating NF-κB and MAP kinases activation (***Wang2014***; Dand et al. 2017). The latest psoriasis and PsA meta-analysis*

*study of Tsoi and colleagues has identified three additional associations with genes belonging to the NF-κB pathway, reinforcing the implication of NF-κB activation in psoriasis and PsA development (***Tsoi2017***). Nevertheless, there is no currently approved drug for the treatment of psoriasis or PsA targeting directly any member of this pathway since some studies have shown that naturally occurring constitutive deficiency in NF-κB leads to immune related pathologies (***Orange2005***; ***Puel2004***)*

Type I IFN and innate host defense

*Psoriasis and PsA GWAS associations have highlighted genes involved in innate immunity including host response to virus and bacteria, which importantly involve genes from type I IFN signaling pathway. Mapping of several GWAS loci to genes from the type I IFN signaling pathway together with clinical and experimental data has reinforced the role of pathogen response psoriasis and PsA (***Nextle2005***). Some of the genes highlighted by GWAS studies include IL28RA, IFIH1, TYK2, RNF114, ELMO1 and DDX58. Some of these genes are also susceptibility loci for other immune-mediated diseases. GWAS lead SNPs causing a missense mutations in TYK2 have been identified in several immune-mediated diseases including CD, IBD, T1D, RA and MS, in addition to psoriasis and PsA (***ImmunoBase***). TYK2 codes one of the Janus kinases (JAK) protein family which phosphorylates the IFN-α and IFN-β receptor α chain and initiates the IFN type I downstream response (***Calamonici1994***). Exome-sequencing and GWAS studies have identified two independent missense mutations predicted to impair its catalytic activity to phosphorylate the receptor and initiate the downstream inflammatory cascade, overall having a protective effect for the risk to develop disease (Strange et al. 2010; Tsoi et al. 2012; Dand et al. 2017). Currently, tofacitinib is the only inhibitor of all the JAKs that is used for RA treatment (***van Vollenhoven2012***) and despite its side-effects it is currently under clinical trials for approval to treat other immune-related diseases together with more specific JAK inhibitors (Baker and diseases 2017). Moreover, several drugs targeting type I IFN pathway members are*

*also being developed. For example Monoclonal Ab against IFN-α subtypes have failed to suppress the IFN gene signature in psoriasis patients and new approaches towards blocking the IFN-α receptor have shown greater efficacy in SLE (Furie et al. 2017). Regarding upstream targets of the IFN I pathway, the psoriasis and PsA GWAS intronic variant at ELMO1 is essential for activation of the pathogen-sensing receptors TLR7 and (***TLR9***) and the subsequent IFN-α production in pDC (Tsoi et al. 2012). Currently, clinical trials testing inhibitors of these TLR receptors are being conducted in SLE (Baker and diseases 2017).*

IL-17 and IL-23 pathways

IL12B, IL23A, IL23R TRAF3IP2 and NFKBIZ STAT in IL17 pathway IL28RA

Experiments undertaken in the uninvolved skin xenograft model suggest that the induction of myeloid DC maturation and/or activation is a key intermediary through which IFN-a produced by pDCs leads to T-cell activation by myeloid DC (Nestle et al., 2005). Again, variants in the IL12B, IL23A, IL23R, TNFAIP3, and/or TNP1 genes could all have plausible role(s) in this process.

Other pathways

Genome wide pathway analysis paper

Gene deserts

chromosome 2p15

Swindell Procedures outlined in Figures 7 and 8 were repeated with respect to six genes near intergenic risk loci (TNFRSF9, B3GNT2, IL12B, TAGAP, KLF4 and NFKBIA). Top: Expression of each gene was evaluated

1.3.6 Limitations and future of GWAS studies

Although GWAS have made a great contribution into the understanding of the genetic component of complex diseases, this approach has several limitations that need to be considered when interpreting the results.

One of the GWAS limitation is due to the LD block structure of the genome, as the disease associated loci are large and include hundreds or thousands of SNPs equally likely to be causal. Therefore, an association between a genetic locus and a disease does not reveal neither the causal variant, which could be any of the variants in high LD r^2 with the tag SNP, or the target gene and genetic mechanisms driving the association. Additional genotyping, statistical fine-mapping and epigenetic data are required in order to shed light towards the identification of the causal SNP.

*GWAS are very much dependent on the sample size, which will have great impact on the effect size of the associated variants to disease that can be uncovered (***Visscher2017***). In addition to the effect size, GWAS have a higher statistical power to identify association with common SNPs than with rare variants for any sample size. Since for two variants to be in high LD r^2 their allele frequencies need to be similar, arrays tagging common SNPs lack of power to detect associations due to rare variants (***Wray2005***). This has partly tried to be overcome by improving the design of the genotyping arrays. For example, the Immunochip incorporated SNPs with MAF<1%. However, it has failed to identify association driven by rare SNPs in loci already reported in GWAS for different immune diseases (***Visscher2017***). Although the sample size and adequate coverage of rare variants may be contributing, the role of rare variants in common diseases have also been largely discussed and opposing views are reflected in the common disease common variant and common disease rare variant hypothesis.*

Another concern is the heritability missed to be explained by the risk alleles associates with different complex diseases by GWAS. For example, in type 2 diabetes (T2D) or height only 5% and 10% of the total heritability could be explained,

*respectively, with the early GWAS associations (Ku et al. 2010; Yang et al. 2010). Later studies in height proposed a model with two main sources of missing heritability: SNPs association with small effect not passing the genome-wide statistical significant threshold and the rare variants not tagged by common SNPs due to low LD (Yang et al. 2010). Exome SNP arrays and greater sample size uncovered 83 height associations of SNPs with MAF<5% that individually accounted for the same amount of variation as previously detected common variants (Marouli et al. 2017). Similarly in psoriasis new associations such us the intronic signal at (***TNFSF15***) and rare alleles at already identified signals could suggest that some of the unexplained heritability would come from new associations and rare alleles at previously reported loci (***Dand2017.***). Moreover, heritability could have been overestimated assuming additive effect instead of epistatic interaction between different associated loci contributing to trait heritability (***Zuk2012***).*

*In addition to rare SNPs, other sources of common variation such as CNV, small (¡1Kb) insertions/deletions (indels) and inversions could contribute to the missing heritability. The 1000 Genome Project and HapMap have helped to better understand these other sources of variation and later genotyping platforms such as the Illumina Human 1M Beadchip, the Affymetrix 6.0 and the Immunochip have included probes for CNV and small indels (Ku et al. 2010). Incorporation of new genotyping platforms have allowed to identify genome-wide associations of CNV with autism and schizophrenia, among others (Glessner et al. 2009; Marshall et al. 2017). CNV in LCE has been proved to be the causal for the association to psoriasis and PsA, as previously mentioned (Cid et al. 2009). However, genome-wide studies have failed to yield reproducible results (***Uebe2017***).*

It is clear that as the whole-genome sequencing (WGS) technologies became more affordable they will naturally replace to the genotyping arrays in the GWAS. Currently, examples of some diseases whole genome sequencing

*In the case of translocations and inversions, neither arrays or widely-used short reads NGS technologies are appropriate to detect this type of variation. Although this type of variation has a role in several disease genotypes (***Feuk2010***), detection of translocations and inversions at a genome-wide scale is still very and their real frequency understimated (Ku et al. 2010). There are some statistical methods that use dense SNP genotyping to detect an unusual LD pattern among the SNPs as a read oy for chromosome rearrangements (Bansal et al. 2007). Nevertheless, implementation of WGS using long reads sequencing technologies are the best tool to accurately assess this genetic variability (***Visscher2017***).*

1.4 Functional interpretation of genome-wide association studies in complex diseases

1.4.1 Overcoming the limitations of GWAS: post-GWAS studies

-Could be how to integrate other datasets and the observations about enrichment of GWAS variants in enhancers, promoters and bla bla bla Approaches: -Fine mapping in the GWAS loci to identify the functional variants responsible for traits and dis- eases -Functional annotations using computational tools -In vivo/in vitro experimental assays in cells and model organisms

-Example about it

1.4.2 The use of fine-mapping to prioritise causal variants

1.4.3 The importance of context specificity in the regulation of gene expression

-Importance of cell type specificity: e.g eQTLs in Ben's paper

Epigenetics and gene expression

Ward and Kellis 2012 paper includes methodology to incorporate this data for the interpretation of genetic variation at a functional level ***Understanding the chromatin landscape Chromatin accessibility Histone modifications Transcription factor occupancy*** *Multiple variants in strong linkage disequilibrium (LD) identified by GWAS can exert functional effects through various different enhancers, resulting in cooperative effects on gene expression Stefan et al 2014* ***Chromatin interaction***

1.4.4 Approaches to establish disease mechanisms and causality of genetic variant

Wiley and sons 2010 Determining the function of these polymorphisms requires methods which do not necessarily lend themselves to high-throughput techniques, such as those which identied the variants in the rst place; and thus, at present, there is a bottle-neck between the polymorphisms with putative functional effects and with those proven effects in vitro.

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