Joint Bone Spine 90 (2023) 105619

Contents lists available at ScienceDirect

Joint Bone Spine

journal homepage: www.elsevier.com

Review

T cells in the pathogenesis of axial spondyloarthritis

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ARTICLE INFO

Article history:
Accepted 20 June 2023
Available online 22 July 2023

Keywords:
Axial Spondyloarthritis
T cells
IL-17A
Tissue resident memory T cells
SNP

ABSTRACT

Axial spondyloarthritis (axSpA) is the prototype of the spondyloarthritis spectrum. The involvement of T cells in its pathogenesis has long been suspected on the basis of the association with the major histocompatibility complex I molecule HLA-B27 and the pivotal role of interleukin 17 in the inflammatory mechanisms associated with the disease. Moreover, the presence of unconventional or "innate-like" T cells within the axial enthesis suggests an important role for these cells in the pathophysiology of the disease. In this review, we describe the characteristics and the interleukin 17 secretion capacity of the T-cell subsets identified in axSpA. We discuss the genetic and epigenetic mechanisms that support the alteration of T-cell functions and promote their activation in axSpA. We also discuss recent data on T cells that could explain the extra-articular manifestations of the SpA spectrum.

1. Introduction

Axial spondyloarthritis (axSpA) is a chronic rheumatic disease belonging to the immune-mediated inflammatory diseases (IMIDs). It is characterized by the presence of spinal inflammation resulting in both limited mobility of the spine and radiological evidence of structural changes in the sacroiliac joints and spine [1]. The disease course is highly variable and often characterized by ongoing axial inflammation mainly mediated by the cytokines TNF and interleukin 17 (IL-17) and radiographic progression associated with reduced spinal mobility and decreased functional ability.

In 2006, McGonagle and McDermott [2] proposed a new classification of these IMIDs. Redrawing the opposition of auto-immunity and auto-inflammation, the pathologies were classified in a continuum between auto-immunity and auto-inflammation (and vice versa) according to the genetic and immunological characteristics they presented. The diseases classified as SpA are in the middle of this continuum. Indeed, the characteristics of axSpA combine elements belonging to both adaptive immunity with the presence of the major histocompatibility complex class I (MHC I) molecule HLA-B27 in patients and to innate immunity according to the cells and molecules present at inflammatory sites. The presence of the MHC I molecule HLA-B27, owing to the expected interaction with CD8+ T lymphocytes, historically defined ankylosing spondylitis (AS) as a T-cell dependent pathology. In addition, Breban et al. suggested the role of CD4+ T cells by using the HLA-B27 transgenic rat model [3]. With recent data regarding the role of "innate-like" T cells, T cells remain the common thread when considering the inflammatory pathways associated with axSpA.

The past few years have witnessed major advances in our understanding of the involvement of T cells in the pathogenesis of axSpA. This review provides an update concerning the characteristics and roles of the T-cell subsets in axSpA pathophysiology. First, we discuss the involvement of conventional and unconventional T cells as a source of IL-17, a pivotal cytokine in SpA. Then, we describe advances in our understanding of the link between genetic data and T cells. Finally, we describe characteristics and potential functions of T resident memory cells, a cell population that could be central to the pathophysiological mechanisms involved in axSpA but also in the appearance of the extra-skeletal manifestations associated with it.

2. Conventional versus unconventional T-cells in axSpA

HLA-B27, a class I surface antigen encoded by the B locus in the MHC, is present in 74% to 89% of patients with non-radiographic axSpA or AS (odds ratio for allele > 50) [4]. This extremely strong

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https://doi.org/10.1016/j.jbspin.2023.105619
1297-319X/

association with HLA-B27 resulted in 3 theories concerning the pathophysiology of the disease and directly involving T cells. The arthritogenic peptide theory suggests that as an MHC I molecule, the HLA-B27 molecule should be able to present an arthritogenic self-antigen via a mechanism of molecular mimicry following a previous encounter with an infectious antigen. The interaction with an autoreactive CD8T lymphocyte would then trigger the inflammatory mechanisms leading to the disease [5]. Genetic deletion or depletion of cytotoxic CD8T cells in a mouse model overexpressing HLA-B27 and presenting an "SpA-like" phenotype did not prevent the onset of the disease or its progression. Moreover, in humans, no arthritogenic peptide has been identified [6]. Misfolding of HLA-B27 in the endoplasmic reticulum may induce stress in the latter and the unfolded protein response. In the HLA-B27tg rat model, this unfolded protein response leads to increased secretion of IL-23 and thus IL-17 by T helper 17 (Th17) lymphocytes [7]. The B27 heavy chain homodimer theory is based on the formation of HLA-B27 homodimers at the cell membrane leading to an interaction with receptors (KIR3DL1, KIR3DL2, LILIRB2) found on CD4+ and CD8+ T cells and natural killer (NK) cells. Bowness et al. showed that this interaction favored the survival and proliferation of Th17 cells [8], which has not been confirmed in humans. Thus, the direct link between HLA-B27 and T cells remains difficult to establish, at least in humans. Recently, the quest for the "famous" arthritogenic peptide(s) has been revived with the identification of T-cell receptors expressing a disease-associated public β chain variable-region complementary-determining region 3β (BV9-CDR3β) motif in HLA-B27–positive patients with AS [9–11]. Yang et al. isolated the chain variable region (AV21) chain pairing in joints and eyes of patients with HLA-B27+ AS and acute anterior uveitis. This discovery allowed the authors to screen a panel of peptides that could represent arthritogenic microbial and/or autoantigens [12]. In parallel, posttranslational modification (cysteine carboxyethylation) of proteins have been shown to create neoantigens inducing autoimmune response in AS [13].

CD4+ and CD8+ T cell subpopulations have been extensively studied in axSpA, but recent attention has shifted to the "innate-like" T cells or unconventional T cells. Here we briefly describe the immunological characteristics of these two cell types.

2.1. Conventional T cells

CD4+ and CD8+ T cells are involved in the adaptive arm of the immune system. Naïve CD4+ Th cells differentiate into functionally different subsets: Th1 cells, secreting interferon γ (IFN-γ), IL-2 and tumor necrosis factor β (TNF-β), Th2, secreting interleukins IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13 and Th17, which secrete IL-17. Th1, Th2, Th17 lymphocytes also differ in the panel of chemokines they produce and thus the immune response they induce. An additional CD4+ T cell population, expressing the transcription factor FOXP3, has regulatory function and is involved in the control of the immune response (natural and induced regulatory T cells, or Tregs). Th17 lymphocytes are implicated in orchestrating the IL-17–mediated inflammation observed in axSpA. An increased frequency of this cell subpopulation was demonstrated in SpA more than 15 years ago [14]. Th17 differentiation inhibits Treg differentiation [15]. Guo et al. showed that SpA was characterized by a decrease in IL-2 signaling and in number and functional capacities of peripheral blood Treg cells [16], whereas elevated Treg cell numbers in synovial fluid were related to disease remission [17]. Many teams have studied Tregs with discordant results concerning the proportion of these cells in axSpA (see for example [18–21]). A recent meta-analysis illustrated these results by an important heterogeneity of the gating strategy identifying Tregs [22]. Nevertheless, in studies where the transcription factor Foxp3 was used, a decrease in Tregs in patients compared to control populations was observed.

CD8+ T cells differentiate into effector subsets with different degrees of cytotoxic activity. Effector CD8+ T cells secrete pro-inflammatory cytokines such as TNF-α, IFN-γ and IL-17. Cytotoxic activity is another pathogenic mechanism for CD8+ T cells in axSpA. The cytotoxic activity of CD8+ T cells is mediated by perforins and granzymes and the activation of the Fas/FasL pathway. The role of CD4+ T cells in SpA pathogenesis seems to be associated with the production of IL-17, while the role of CD8+ T cells in this disease is less clear. Genetic evidence supports the implication of CD8+ T cells activation through antigen recognition. Polymorphisms identified in the aminopeptidase genes involved in MHC I peptide trimming (ERAP1 and ERAP2), and in RUNX3, a central transcription factor for CD8+ T cell differentiation, have been all associated with psoriatic arthritis (PsA), AS as well as the strong association with the MHC I molecule, HLA-B27, which suggests a potential impact of genetics on CD8+ T-cell function [23]. IL-17-producing CD8+ T cells have also been described. These cells are present in various IMIDs such as PsA [24,25]. Skin lesions of patients with psoriasis featured IL-17 mRNA expression by human CD8+ T cell clones, and anti-CD8 monoclonal antibody treatment used on xenotransplanted mice with human psoriatic skin resulted in complete neutralization of psoriasis development [26].

In psoriasis, another cell type has been shown to contribute to IL-17A secretion: regulatory T-cells [27]. The authors showed that under pro-inflammatory conditions (such as IL-1β, IL-21, IL-23), CD4+CD25^{high}FoxP3+ cells from healthy controls could differentiate into IL-17A producing Treg. In patients with severe psoriasis, peripheral blood derived Treg differentiated into IL-17 producing T-reg in an IL-23 dependent process. FoxP3 expression was down regulated, while high expression of ROR-γt was maintained.

2.2. Unconventional T cells/"innate-like" T cells

Unconventional T cells share some biological characteristics with cells belonging to innate immunity. These cells have a restricted TCR repertoire that recognizes only very conserved antigens, as opposed to "conventional" CD4+ or CD8+ T cells, whose TCR are selected by specific MHC-peptide complexes. They can also react to the cytokine environment and produce a large panel of pro-inflammatory cytokines. In the case of axSpA, the scientific community focused on γδT cells, mucosal-associated invariant T (MAIT) cells, invariant NK T (iNKT) cells (detailed description reviewed elsewhere [28]) (Fig. 1).

γδT cells express heterodimeric TCRs composed of γ and δ chains. These cells are mainly found in tissues but are also present in peripheral blood in smaller proportions (0.5–5%). γδT cells expressing IL-17 were detected in patients with psoriasis. This study observed a decreased frequency in peripheral blood of (Vγ)9Vδ2 T cells, which produced inflammatory cytokines, including IL-17A. The decrease in the periphery was correlated with an increase of this population in lesional skin, compatible with an increased migration to the inflamed tissue [29]. The enthesis resident T cells observed in the SpA mouse model based on systemic IL-23 overexpression were also identified as γδT cells [30].

MAIT cells are characterized by expression of an invariant TCR α-chain (Vα7.2–Jα33 in humans) [31]. MAIT cells also show high expression of CD161 and MHC I-related gene protein (MR1) restriction [32]. MAIT cells can express pro-inflammatory cytokines such as IL-17, IFN-γ, TNF and also granzyme B upon stimulation with phorbol myristate acetate and ionomycin [33]. IL-17+CD8+ MAIT cells have been detected in skin and blood samples of patients with psoriasis [34]. These studies provided insights into the variability in MAIT cell frequency in blood and target tissues.

iNKT cells have a Va24-Jα18-Vβ11 invariant TCR (recognizing lipids or glycolipids) and are CD1d-restricted. Upon stimulation, they can release a large variety of pro- and anti-inflammatory

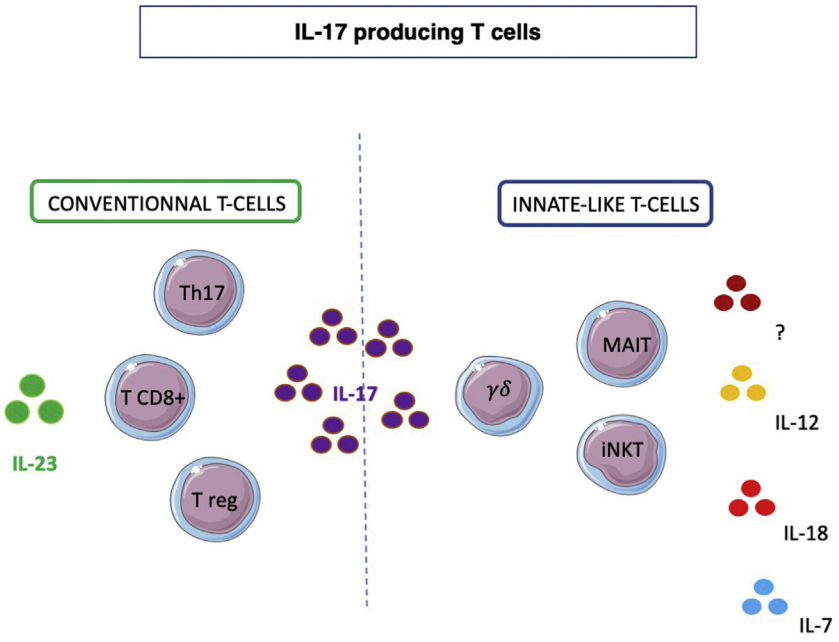

Fig. 1. T cells that may contribute to IL-23 – dependant and – independent IL-17 production in spondyloarthritis. Left: Th17, IL-17+CD8+ T and CD4+CD25^{high}FoxP3+ regulatory T cells contribute to the production of IL-17 through an IL-23 dependent pathway, in spondyloarthritis with entheseal and peripheral involvement. Right: unconventional T cells may contribute to the production of IL-17 following IL-23 stimulation but also independently of IL-23, through different pro-inflammatory cytokines.

cytokines. A subpopulation of IL-17A–producing iNKT cells was described in mice, but in the SpA TNF$^{\Delta ARE}$ mouse model, iNKT cells acted as regulatory cells by limiting symptom severity via the production of immunomodulatory cytokines.

2.3. IL-17producing T-cells: Who is the culprit in AxSpA?

The success of anti-IL-17A (secukinumab and ixekizumab) and then anti-IL-17A/F (bimekizumab) in treating both axial and/or peripheral forms of SpA in phase 3 trials has convinced the rheumatology community of the importance of the IL-23–IL-17 axis in SpA [35–37]. Therefore, efforts turned to the identification of the cellular source of IL-17 both to better decipher the inflammatory mechanisms involved and to propose new therapeutic targets. Attention initially focused on CD4+ and CD8+ T cells. In particular, CD4+ Th17 T cells were strong candidates because of their already well-described ability to produce IL-17A.

Several teams found an increase in Th17 population in the peripheral blood of axSpA patients [38–41], which was associated with disease activity. In parallel, CD8+ T cells were described as another cellular source of IL-17 (reviewed elsewhere [42]). However, in axSpA, data regarding their involvement in IL-17 production remain limited. A recent publication reported reduced expression of cytotoxicity-associated genes in whole blood samples of AS patients [43]. The reduced levels of granzyme and perforin were associated with reduced CD8+ T-cell frequency in blood and increased CD8+ T-cell frequency in the synovial fluid from AS patients. This study suggested the enrichment of cytotoxic CD8+ T cells in the site of inflammation and underlined their importance in the joint inflammation observed in AS [43].

In 2018, the hypothesis of a dominant role for the IL-23–IL-17 axis and Th17 lymphocytes was questioned following the failure of the anti-IL-23 antibody risankizumab in a phase 2 trial in axSpA [44]. The cause of the failure of anti-IL-23 are still debated, but a number of reasons have been proposed: (1) the moderate relative risk of *IL23R* variants associated with ankylosing spondylitis, (2) that IL-23 is important in the preclinical phase as suggested by Baeten and colleagues in the HLA-B27tg rat model [45], (3) the main results concerning IL-23 were demonstrated in mouse models and may not be immediately extrapolated to humans, (4) the bioavailability of the drug at the sites of axial inflammation and insufficient dosage. An additional explanation could be the presence of pathogenic cells in axSpA that produce IL-17 independently of IL-23 stimulation. IL-17A production has been described in three unconventional T-cell populations: MAIT, γδT and iNKT cells. All these populations express the IL-23 receptor on their surface, but may not require IL-23 to produce IL-17 [46].

Kenna et al. suggested that γδT cells were the dominant IL-17 producers in AS. They showed a three-fold higher frequency of circulating γδT cells and five-fold higher frequency of IL-23R–expressing γδT cells in AS patients versus healthy controls and versus rheumatoid arthritis patients, respectively [47]. The IL-17A production capacity of MAIT cells in axSpA was demonstrated by Inman's team [48]. We recently confirmed this result by demonstrating that MAIT cells can produce IL-17F independent of IL-23 [49]. IL17+ iNKT cells have also been described in humans: Venken et al. reported a RORγT+ iNKT cell population that accounted for 2.1% of T cells in axSpA and was able to produce IL-17A and IL-22 [50]. Comparison of PMA-ionomycin stimulated MAIT and γδT cells to CD4+ and CD8+ T lymphocytes suggested that in axSpA, MAIT cells represent the major source of IL-17A on a per-cell basis [49].

Taken together, these data reinforce the importance of investigating further IL-23–independent IL-17A production in axSpA, and open the door to new hypotheses on the mechanisms of IL-17–mediated inflammation related to unconventional T cells (Fig. 1).

3. How to link genotype to T-cell phenotype?

3.1. The post-genome-wide association study (post-GWAS) era

The results of GWAS performed in recent years [51,52] have allowed the identification of non-MHC genes associated with AS and have confirmed the major involvement of the immune system, in particular the role of T cells, in the pathophysiology of this dis-

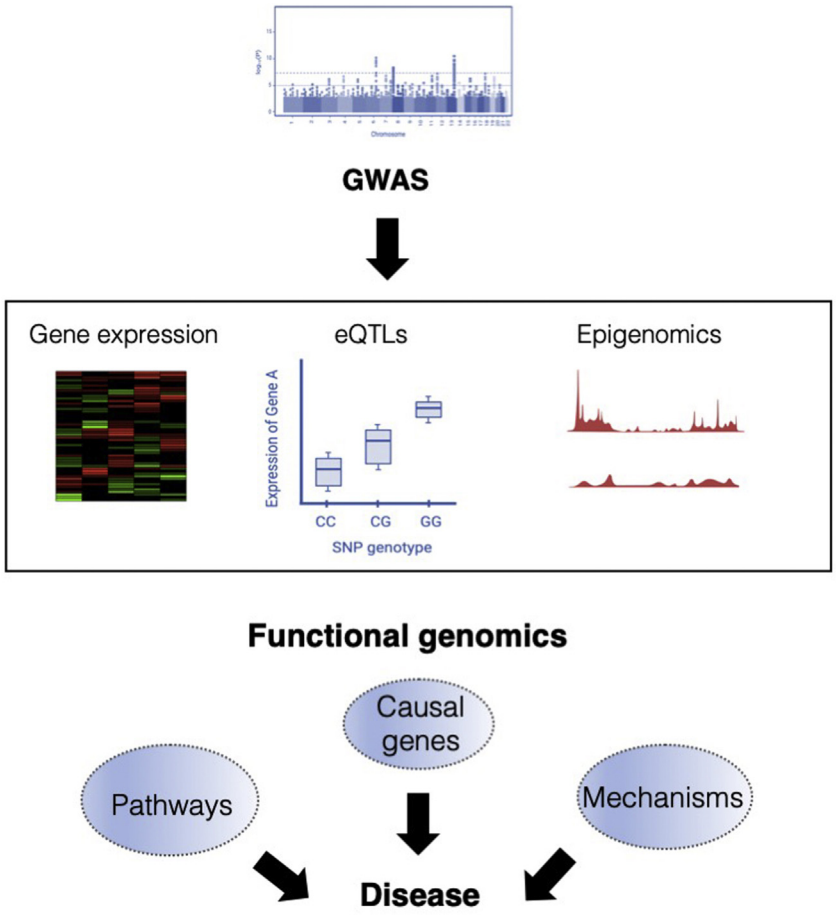

Fig. 2. Post-GWAS approaches to link GWAS variants to T-cell function. There is a need to consider new integrative approaches to assess the functional consequences of GWAS variants using in silico analysis with functional genomics data. New analytical methods now provide the first steps of functional in silico follow-up by exploiting the availability of resource datasets detailing gene expression, epigenetic marks, 3D chromatin contacts or other genomic annotations, including drug targets.

ease. To date, 48 loci associated with AS have been reported [53]. Specifically, genes involved in T-cell activation/proliferation (*IL7R*, *SH2B3*, *BACH2*, *ICOSL*, *ZMIZ1*, *EOMES*, *TBX21*) and 6 genes belonging to the IL-23/IL-17 axis (*RUNX3*, *IL23R*, *IL6R*, *IL1R2*, *IL12B*, *TYK2*) were identified. These results combined pointed further investigations toward this axis and toward Th17 lymphocytes, which at the time were the main cells described as IL-17 producers. Nevertheless, the failure of anti-IL-23 drugs in axial SpA reminded us of the polygenic and multifactorial character of this disease. An additional difficulty is that the disease-associated single nucleotide polymorphisms (SNPs) might have context-specific activity or may be of relevance only in a specific cell type or tissue [49,54]. The challenge of the post-GWAS era continues to be to understand the effect of these genetic variants on cell function, and to identify the cell type this effect applies to (Fig. 2).

To address this last question, Farh et al. developed an algorithm (probabilistic identification of causal SNPs) to identify causal variants based on a statistical analysis of GWAS data. Comparative analysis between the location of these SNPs and accessible chromatin mapping showed that disease-associated SNPs were enriched in regions of open chromatin only in selected cell populations, suggesting that these genetic variants are active in specific cell types that may contribute to the disease. For example, for SpA, SNP enrichment was observed only in open regions of CD4+ Th0, Th1, Th17 T cells and monocytes [55]. This result supported the link between causal variants and these cell populations and therefore the role of CD4+ T cells in the inflammatory mechanisms associated with SpA. However, the study was limited to only few cell types (CD4+ and CD8+ T cells, B cells and monocytes). We recently analyzed the expression of genes encoded by 48 loci with genetic polymorphisms associated with axSpA in 4 lymphocyte populations: CD4+ and CD8+T cells, as well as γδT and MAIT cells [49]. Of note, we observed a cellular specificity in the expression of these genes suggesting a different impact of the SNPs on the different immune cell populations, and a distinct role for each of the studied T-cell subpopulations studied. Moreover, these data supported the involvement of unconventional T cells in the pathophysiology of the disease, and in particular in the production of IL-17 because the *IL23R*, *IL17A* and *IL17F* genes were more strongly expressed by MAIT and γδT cells than by CD4+ and CD8+ T cells [49]. These results extended the previous observations by Farh et al. to unconventional T cells, and underlined the need for a cell-specific approach to study the consequences of the polymorphisms associated with axSpA, and more generally with IMIDs.

Candidate gene approaches based on GWAS results have specifically studied the effect of a variant in relation to the nearest gene. Of particular interest for SpA have been studies of genes that are critical for T-cell differentiation or function.

3.1.1. TBX21

TBX21 encodes the transcription factor *T-bet*, which promotes the differentiation of Th1 cells and of effector CD8 T, cells and cooperates with eomesodermin to induce IFN-γ production by CD8 T cells. T-bet expression was found increased in AS patients compared to healthy individuals, and patients homozygous for the risk allele of the *TBX21* associated polymorphism rs11657479 had the

highest levels of *TBX21* expression in peripheral blood. This increase was observed mainly in natural killer cells and CD8+ T cells. T-bet+ CD8+ T cells produced high levels of IL-17 and IFNγ upon stimulation, suggests an influence of the genetic polymorphism on CD8+ T cell function [56].

3.1.2. RUNX3

Reporter gene assays are useful in determining the functional consequence of SNPs by testing allele-specific expression. This approach was used by Vecellio et al. to validate a possible role for a variant associated with AS located in a regulatory region of the *RUNX3* locus. In this study, the risk allele was found to be associated with decreased binding of the transcription factor IRF4 leading to decreased RUNX3 expression in CD8+ T cells, therefore suggesting a potential role for these cells in AS pathology [57].

3.1.3. IL23R

Coffre et al. focused on *IL-23R* variants. The authors showed that CD4+ T cells from SpA patients carrying *IL23R* risk alleles showed higher expression of genes involved in the differentiation and function of Th17 and Th1 lymphocytes, including *IL17A*, *IL17F*, *RORC*, *IFNG*, *TNF* and *TBX21*. In addition, this study showed that immune cell function in axSpA patients was determined by a combined action of several SNPs at distinct loci rather than a single variant [58].

This latter result reflects the complexity of functional genomics studies. Moreover, these targeted studies highlighted an effect of these variants on T-cell function without describing their pathogenetic consequences, in particular regarding their participation in inflammatory mechanisms. The remaining challenge is to integrate these molecular findings into the pathophysiology of the disease. New approaches allowing to clearly identify the causal variant could allow for better understanding the biological effect of these variants on the cellular function. The next challenge would be to integrate genetic information from all the different SNPs with environmental information.

3.2. Epigenetics influences T-cell activity in axSpA

The term "epigenetics" refers to mechanisms that modulate gene expression without altering the DNA sequence, and includes DNA methylation, histone modifications that modulate chromatin structure or non-coding RNAs. This is a rapidly growing field of research in rheumatology, but little concrete data are available for axSpA. Data concerning methylation and histone modifications are still fragmentary and often do not make the link with a specific cell type, at least in SpA. To date, the most relevant studies concern the analysis of microRNA (miR) expression. For example, Fogel et al. described a specific miR signature present in CD4+ T lymphocytes of SpA patients. Several miRs affecting T-cell function were overexpressed as compared with a control population. Bioinformatic analysis of the mRNA targeted by these miRs showed enrichment of genes involved in the control of inflammation (NF-κB pathway), in the polarization of the immune response (M1/M2 macrophages and Th1/Th2/Th17 cells) and in autophagy and apoptosis [59]. Another interesting study was from Chen's team, who analyzed miR expression in Th17 cells and showed that miR-10b-5p levels were significantly increased in Th17 cells in AS, compared with cells from healthy controls. miR-10p overexpression inhibited IL-17A secretion in CD4+ T cells differentiating towards the Th17 pathway. The authors suggested that the increase in miR-10b-5p level served as a feedback loop to regulate IL-17 secretion [60].

The above data indicate that the deregulation of miRs likely plays a role in the activation of lymphocytes responsible for the inflammatory phenomena present in SpA. However, the degree of influence on biological processes and the number of miRs involved remain to be determined. Furthermore, targeted studies of cell populations are necessary. As epigenetics modifications are tissue-specific, the absence of target tissue studies is one of the main limitations to this type of approach, at least in the axial form of SpA.

4. How could T cell activity explain the axSpA spectrum?

4.1. Tissue-resident memory T cells: "the missing link"?

Another unresolved question is what is the role of lymphocytes in the development of extra-articular manifestations in SpA.

Among the T lymphocytes that have encountered an antigen, we classically oppose the central memory T cells characterized by high proliferation capacity and the effector memory T cells characterized by migratory and secretory roles. Tissue-resident memory T cells (Trm) were described about 10 years ago [61]. This population is distinguished from peripheral blood T cells by its preferential retention in tissues. Within the tissue they inhabit, Trms represent an immune sensor responsible for monitoring local perturbations in homeostasis as a part of the tissue surveillance network. Such cells have been described in the skin, intestine and lung. Trm cells express adhesion and migration molecules, the most-described being CD69, CD103, and αE integrin. However, the expression of these surface markers depends largely on their microenvironment. Some of the markers are site-specific, for example, a4β7 for intestinal Trm and CXCR3 for skin or pulmonary epithelium resident T cells. Therefore, they are difficult to study in axSpA because of no unique phenotype for these cells, in addition to their absence in the blood. This resident cell function was originally described in memory CD8+ T cells, but we now know that CD4+ Trm cells also exist. Unconventional lymphocytes (iNKT, γδT, MAIT cells and ILC3s) have also been described as Trm cells. Indeed, these cells are also recruited for tissue homeostasis and repair and for immune defense. Trm cells express CD69 so they are either constitutively activated or recently activated. Gaide et al. showed from TCR sequencing that each effector T cell clone differentiated *in situ* into Trm [62]. But it is not excluded that the tissue environment plays also a key role in the development of Trm depending on whether it is permissive or restrictive. This suggests a critical role for chemokines on which lymphocytes depend for migration to the target tissue. In recent years, data concerning the role of Trm cells in immune-mediated diseases have accumulated for certain pathologies, such as Crohn's disease, psoriasis, or PsA [42], in which access to inflammatory tissue is relatively non-invasive.

In psoriasis, Trm have been characterized as expressing CD103 and CD69, which contribute both to retaining Trm in the skin. CD49, which binds collagen IV, is not consistently expressed on Trm, but allows the localization of these cells close to the epidermidis. CD8+ Trm have been observed in psoriatic lesions [63] and contribute to IL-17 expression [64]. Of interest, the subset of CD8+CD103+CD43+ cells decreased after Guselkumab treatment (at week 24), but remained unchanged after Secukinumab treatment [64]. These results may explain why IL-23 inhibitors can be associated with long-term remission, as observed following drug withdrawal [65]. In psoriatic arthritis, synovial Trm have been identified as IL-17A secreting cells in the CD8+CD69+CD103+ T-cell subset [66]. CD8+ Trm were shown to express CXCR6, which may contribute to the retention of these cells in the joint, in the context of increased levels of CXCL16 (the CXCR6 ligand) observed in the corresponding synovial fluid.

Confirming the presence and determining the characteristics of Trm cells in the axial enthesis of SpA patients would undoubtedly be an interesting advancement in the understanding of the pathophys-

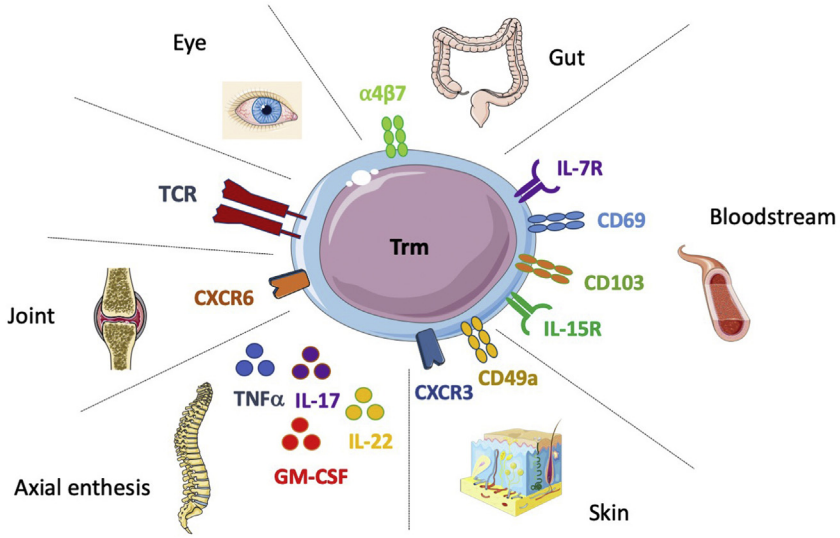

Fig. 3. Hypothetical Trm model for axial spondyloarthritis: dysregulated Trm subsets could be the missing link in explaining the extra-articular manifestations of the spondyloarthritis spectrum. CD4+ and CD8+ Trm can be distinguished from their circulating counterparts by the expression of CD103 (the αE subunit of the αEβ7 integrin that binds E-cadherin) and CD69 (a marker of activation and of retention). α4β7 and CXCR3 are homing markers for gut and skin, respectively. In the skin, the possible expression of CD49, an integrin receptor that binds collagen IV, allows recruitment of these cells close to the epidermis. In the joint, CD8+CD69+CD103+ Trm cells express IL-17A. Synovial Trm also express CXCR6, which contributes to the retention of the cells in the joint. Identifying homing markers for the spine and the eyes could be a major breakthrough.

iology of this disease. However, access to the pathological tissue remains a challenge.

The enthesis is a structure that transmits mechanical forces from the muscle to the bone to provide "stability". The axial enthesis described by Dennis McGonagle is divided into 2 zones [67]: Zone 1 is peripheral enthesis bone and Zone 2 is enthesis soft tissue. McGonagle provides a large body of work about axial enthesis. All this work is based on study of the axial enthesis of patients undergoing spinal surgery in the context of scoliosis. Although the data have not been collected in SpA patients, this work has provided useful information about enthesis physiology. Histological studies showed that resident mesenchymal cells and immune cells are present in both zones of the enthesis. Both Trm cells and conventional CD4+ and CD8+ T cells were found in the axial enthesis, which displayed a CD69+ phenotype characteristic of Trm cells. Transcriptomic analysis CD4+ and CD8+ T cells showed high expression of growth factors and molecules involved in tissue repair, which could suggest their role in bone remodeling mechanisms [68]. The authors also found unconventional T cells: γδT, MAIT cells [49,69]. These latter populations have been shown to produce IL-17 and TNF and are an important source of IL-17A and IL-17F in axSpA. Of major importance, the Vδ1 subtype of γδT cells, as well as MAIT cells, were found to produce IL-17 in response to PMA/ionomycin stimulation, but not in response to IL-23. Other teams have also confirmed the IL-17 production capacity of γδT, iNKT and MAIT cells in the joint of patients with SpA [48,50,70].

The presence of these resident IL-17–producing T cells in the axial enthesis is particularly important to explain the inflammatory and ossification mechanisms observed in SpA. Indeed, the ossification phenomenon could be directly related to IL-17–mediated inflammation. The main support for this model comes from data from *in vitro* studies, showing that mesenchymal stem cells proliferated and differentiated into osteoblasts after stimulation with IL-17A [71]. A similar phenomenon was observed in mouse preosteoblast cells using IL-17F [72]. The potential interaction of mesenchymal stem cells and IL-17–producing T cells in the enthesis, associated with the absence of osteoclasts, could explain why IL-17A and TNF lead to bone formation in SpA.

However, linking all these elements will require access to the inflamed tissue (Fig. 3).

4.2. Trm cells: migratory and resident in AxSpA?

The molecular mechanisms leading to Trm cell differentiation are not fully elucidated. These cells may differentiate in situ from an effector T phenotype in response to different signals present in the colonized tissue (reviewed elsewhere [73,74]). Once differentiated, the cells lose their ability to migrate via the bloodstream and thus become resident. The signals inducing this differentiation are likely tissue-specific.

Data from digestive tissue also support the previous hypothesis. Intra-epithelial CD8+ T cells represent the Trm cells of the digestive tissue. These cells have the hallmarks of Trm cells, namely expression of CD69 and CD103. Regner et al. showed a negative correlation between the peripheral lymphocyte count and intra-epithelial lymphocyte (IEL) number in patients with axSpA. This result could suggest a potential trafficking of these normally resident cells. As compared with healthy control cells, axSpA patient IEL cells secreted significantly more TNF. Another interesting point of this study was that these changes in cell profile were associated with alterations in the microbiota of these patients. Together, these data suggested both quantitative and qualitative modulation of IEL cells by the microbiota of SpA patients with the possibility that dysbiosis could affect the migratory abilities of these normally resident cells [75]. IEL cells also possess the α4β7 marker; the a4β7–MAdCAM1 interaction constitutes the homing signal to the gut [73]. MAdCAM1 has been identified on ILC3s. AxSpA patients exhibited increased expression of a4β7 on ILC3s, a population expanded in the intestine and in the bone marrow of the patients. The expression of the MadCAM1 ligand was also increased in the high endothelial venules of the gut and in the bone marrow. These data suggested the possibility that ILC3s could migrate from one site to another to create an inflammatory environment [76]. However, the circulatory capacity of these cells, and its possible role in pathogenesis was not demonstrated, and Blijdrop et al. subsequently demonstrated that in axSpA, ILC3s are IL-22–producing rather than

IL-17–producing cells [77]. Recently, Mortier et al. showed that in non-radiographic axSpA patients with microscopic intestinal inflammation, an increase in intraepithelial γδT cells involved in IL-17A production was observed in the ileum [78]. In contrast, the frequency of MAIT cells remained unchanged. This subset of cells had previously been identified by the same team in the joints and peripheral blood of axSpA patients [50]. Until now, no cell directly linking the gut with the enthesis could be clearly identified. The seminal work of Qaiyum et al. identified a resident CD8+ T-cell population present in the blood and joints of patients with axSpA. This cell population had characteristic markers of intestinal homing (CD103, β7, CD29, CD49a) and produced IL-17A even under resting conditions. It would be interesting to know whether these cells were also present in the digestive tract but the authors did not analyze intestinal biopsies [79]. The most concrete data on the trafficking of lymphocytes from the intestine to the enthesis were obtained by crossing the transgenic mouse kikGR (used for its ability to photoconvert a protein so it is detectable on cytometry and fluorescent microscopy) and the $TNF^{\Delta ARE}$ mouse model (an SpA mouse model presenting enthesitis and colitis). The crossing of these 2 mouse lines allowed for following the trafficking dynamics of colon IEL cells. The authors showed that after 72 h, IEL cells were found in the enthesis of the Achilles tendon. These cells were also able to produce IL-17 and exacerbated inflammation in the joint [80]. Another argument, albeit indirect, suggesting a major role for immune-cell trafficking in the onset of the disease, is given by the analysis of the impact of treatments on the immune response. Indeed, one of the modes of action of anti-TNF in SpA is to decrease the expression of chemokines and leukocyte recruitment signals [81].

5. Conclusion and perspectives

T cells undeniably have a central place in the pathophysiology of axSpA. The OMICS era has and will allow for better identifying the phenotypic characteristics of the T cells involved. In the axial form of the disease, T cells with innate characteristics are probably as important as conventional adaptive immune cells. The study of these unconventional T cells has revealed their capacity to produce IL-17. The "rediscovery" of conventional T lymphocytes through multi-omics approaches suggests the importance of migration and differentiation into resident cells, reinforcing the hypothesis of a gut–enthesis axis. However, the main roadblock to a better understanding of SpA pathogenesis is still access to the axial enthesis.

Thus, determining to what extent these cells interact with each other and behave in situ is difficult. Our current knowledge does not allow for defining precisely the characteristics of a hypothetical continuum of intestine – enthesis – ossification.

Future directions in the post-omics era need to be directed to investigate the tissue-residency of these T cells and their participation in signaling pathways and deregulation mechanisms responsible for the inflammation and ossification of the axial enthesis characteristic of axSpA.

Author's note

Servier medical art was used for the realization of the figures.

Disclosure of interest

The authors declare that they have no competing interest.

Authors' contributions

All authors contributed to the article and approved the submitted version.

References

[1] Dougados M, Baeten D. Spondyloarthritis. Lancet 2011;377:2127–37.
[2] McGonagle D, McDermott MF. A proposed classification of the immunological diseases. PLoS Med 2006;3:e297.
[3] Breban M, Fernández-Sueiro JL, Richardson JA, et al. T cells, but not thymic exposure to HLA-B27, are required for the inflammatory disease of HLA-B27 transgenic rats. J Immunol Baltim Md 1950 1996;156:794–803.
[4] Poddubnyy D, Conrad K, Haibel H, et al. Elevated serum level of the vascular endothelial growth factor predicts radiographic spinal progression in patients with axial spondyloarthritis. Ann Rheum Dis 2014;73:2137–43.
[5] Hermann E, Yu DT, Meyer zum Büschenfelde KH, et al. HLA-B27-restricted CD8T cells derived from synovial fluids of patients with reactive arthritis and ankylosing spondylitis. Lancet 1993;342:646–50.
[6] Taurog JD, Dorris ML, Satumtira N, et al. Spondylarthritis in HLA-B27/human beta2-microglobulin-transgenic rats is not prevented by lack of CD8. Arthritis Rheum 2009;60:1977–84.
[7] DeLay ML, Turner MJ, Klenk EI, et al. HLA-B27 misfolding and the unfolded protein response augment interleukin-23 production and are associated with Th17 activation in transgenic rats. Arthritis Rheum 2009;60:2633–43.
[8] Bowness P, Ridley A, Shaw J, et al. Th17 cells expressing KIR3DL2+ and responsive to HLA-B27 homodimers are increased in ankylosing spondylitis. J Immunol 2011;186:2672–80.
[9] Komech EA, Pogorelyy MV, Egorov ES, et al. CD8+ T cells with characteristic T cell receptor beta motif are detected in blood and expanded in synovial fluid of ankylosing spondylitis patients. Rheumatology (Oxford) 2018;57:1097–104.
[10] Hanson AL, Nel HJ, Bradbury L, et al. Altered repertoire diversity and disease-associated clonal expansions revealed by T cell receptor immunosequencing in ankylosing spondylitis patients. Arthritis Rheumatol 2020;72:1289–302.
[11] Faham M, Carlton V, Moorhead M, et al. Discovery of T Cell receptor β motifs specific to HLA-B27-positive ankylosing spondylitis by deep repertoire sequence analysis. Arthritis Rheumatol 2017;69:774–84.
[12] Yang X, Garner LI, Zvyagin IV, et al. Autoimmunity-associated T cell receptors recognize HLA-B*27-bound peptides. Nature 2022;612:771–7.
[13] Zhai Y, Chen L, Zhao Q, et al. Cysteine carboxyethylation generates neoantigens to induce HLA-restricted autoimmunity. Science 2023;379 [eabg2482].
[14] Jandus C, Bioley G, Rivals J-P, et al. Increased numbers of circulating polyfunctional Th17 memory cells in patients with seronegative spondylarthritides. Arthritis Rheum 2008;58:2307–17.
[15] Zhang W, Liu X, Zhu Y, et al. Transcriptional and posttranslational regulation of Th17/Treg balance in health and disease. Eur J Immunol 2021;51:2137–50.
[16] Guo H, Zheng M, Zhang K, et al. Functional defects in CD4+ CD25high FoxP3+ regulatory cells in ankylosing spondylitis. Sci Rep 2016;6:37559, http://dx.doi.org/10.1038/srep37559.
[17] Appel H, Wu P, Scheer R, et al. Synovial and peripheral blood CD4+FoxP3+T cells in spondyloarthritis. J Rheumatol 2011;38:2445–51.
[18] Appel H, Wu P, Scheer R, et al. Synovial and peripheral blood CD4+FoxP3+T cells in spondyloarthritis. J Rheumatol 2011;38:2445–51.
[19] Guo H, Zheng M, Zhang K, et al. Functional defects in CD4+ CD25high FoxP3+ regulatory cells in ankylosing spondylitis. Sci Rep 2016;6:37559.
[20] Xueyi L, Lina C, Zhenbiao W, et al. Levels of circulating Th17 cells and regulatory T cells in ankylosing spondylitis patients with an inadequate response to anti-TNF-α therapy. J Clin Immunol 2013;33:151–61.
[21] Ciccia F, Accardo-Palumbo A, Giardina A, et al. Expansion of intestinal CD4+CD25(high) Treg cells in patients with ankylosing spondylitis: a putative role for interleukin-10 in preventing intestinal Th17 response. Arthritis Rheum 2010;62:3625–34.
[22] Lai N-L, Zhang S-X, Wang J, et al. The proportion of regulatory T cells in patients with ankylosing spondylitis: a meta-analysis. J Immunol Res 2019;2019:1058738.
[23] International Genetics of Ankylosing Spondylitis Consortium (IGAS)Cortes A, Hadler J, Pointon JP, et al. Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. Nat Genet 2013;45:730–8.
[24] Ortega C, Carrillo Fernández-AS, Romero JM, et al. IL-17-producing CD8+ T lymphocytes from psoriasis skin plaques are cytotoxic effector cells that secrete Th17-related cytokines. J Leukoc Biol 2009;86:435–43.
[25] Res PCM, Piskin G, de Boer OJ, et al. Overrepresentation of IL-17A and IL-22 producing CD8T cells in lesional skin suggests their involvement in the pathogenesis of psoriasis. PLoS One 2010;5:e14108.
[26] Di Meglio P, Villanova F, Navarini AA, et al. Targeting CD8(+) T cells prevents psoriasis development. J Allergy Clin Immunol 2016;138:274–6.e6.
[27] Bovenschen HJ, van de Kerkhof PC, van Erp PE, et al. Foxp3+ regulatory T cells of psoriasis patients easily differentiate into IL-17A-producing cells and are found in lesional skin. J Invest Dermatol 2011;131:1853–60.
[28] Rosine N, Miceli-Richard C. Innate Cells: the alternative source of IL-17 in axial and peripheral spondyloarthritis? Front Immunol 2020;11:553742.

[29] Laggner U, Di Meglio P, Perera GK, et al. Identification of a novel proinflammatory human skin-homing Vγ9Vδ2T cell subset with a potential role in psoriasis. J Immunol 2011;187:2783–93.
[30] Reinhardt A, Yevsa T, Worbs T, et al. Interleukin-23–dependent γ/δ T cells produce interleukin-17 and accumulate in the enthesis, aortic valve, and ciliary body in mice. Arthritis Rheumatol 2016;68:2476–86.
[31] Toubal A, Nel I, Lotersztajn S, et al. Mucosal-associated invariant T cells and disease. Nat Rev Immunol 2019, http://dx.doi.org/10.1038/s41577-019-0191-y.
[32] Treiner E, Duban L, Bahram S, et al. Selection of evolutionarily conserved mucosal-associated invariant T cells by MR1. Nature 2003;422:164–9.
[33] Dusseaux M, Martin E, Serriari N, et al. cells are xenobiotic-resistant, tissue-targeted, CD161hi IL-17 – secreting T cells. Blood 2011;117:1250–9.
[34] Teunissen MBM, Yeremenko NG, Baeten DLP, et al. The IL-17A-producing CD8+ T-cell population in psoriatic lesional skin comprises mucosa-associated invariant T cells and conventional T cells. J Invest Dermatol 2014;134:2898–907.
[35] van der Heijde D, Wei JC-C, Dougados M, et al. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. The Lancet 2018;392:2441–51.
[36] Baeten D, Sieper J, Braun J, et al. Secukinumab, an Interleukin-17A inhibitor, in ankylosing spondylitis. N Engl J Med 2015;373:2534–48.
[37] van der Heijde D, Gensler LS, Deodhar A, et al. Dual neutralisation of interleukin-17A and interleukin-17F with bimekizumab in patients with active ankylosing spondylitis: results from a 48-week phase IIb, randomised, double-blind, placebo-controlled, dose-ranging study. Ann Rheum Dis 2020, http://dx.doi.org/10.1136/annrheumdis-2020-216980.
[38] Jandus C, Bioley G, Rivals J-P, et al. Increased numbers of circulating polyfunctional Th17 memory cells in patients with seronegative spondylarthritides. Arthritis Rheum 2008;58:2307–17.
[39] Shen H, Goodall JC, Gaston JSH. Frequency and phenotype of T helper 17 cells in peripheral blood and synovial fluid of patients with reactive arthritis. J Rheumatol 2010;37:2096–9.
[40] Shen H, Goodall JC, Hill Gaston JS. Frequency and phenotype of peripheral blood Th17 cells in ankylosing spondylitis and rheumatoid arthritis. Arthritis Rheum 2009;60:1647–56.
[41] Benham H, Norris P, Goodall J, et al. Th17 and Th22 cells in psoriatic arthritis and psoriasis. Arthritis Res Ther 2013;15:R136.
[42] Steel KJA, Srenathan U, Ridley M, Durham LE, Wu S-Y, Ryan SE, et al. Synovial IL-17A+ CD8+ T cells display a polyfunctional, pro-inflammatory and tissue-resident memory phenotype and function in psoriatic arthritis. Arthritis Rheumatol.
[43] Gracey E, Yao Y, Qaiyum Z, et al. Altered cytotoxicity profile of CD8+ T cells in ankylosing spondylitis. Arthritis Rheumatol 2020;72:428–34.
[44] Baeten D, Østergaard M, Wei JC-C, et al. Tam L-S, et al. Risankizumab, an IL-23 inhibitor, for ankylosing spondylitis: results of a randomised, double-blind, placebo-controlled, proof-of-concept, dose-finding phase 2 study. Ann Rheum Dis 2018, http://dx.doi.org/10.1136/annrheumdis-2018-213328 [annrheumdis-2018-213328].
[45] van Tok MN, Na S, Lao CR, et al. The initiation, but not the persistence, of experimental spondyloarthritis Is dependent on interleukin-23 signaling. Front Immunol 2018;9:1550.
[46] Cole S, Murray J, Simpson C, et al. Interleukin (IL)-12 and IL-18 synergize to promote MAIT Cell IL-17A and IL-17F production independently of IL-23 signaling. Front Immunol 2020;11:585134.
[47] Kenna TJ, Davidson SI, Duan R, et al. Enrichment of circulating interleukin-17-secreting interleukin-23 receptor-positive γ/δ T cells in patients with active ankylosing spondylitis. Arthritis Rheum 2012;64:1420–9.
[48] Gracey E, Qaiyum Z, Almaghlouth I, et al. IL-7 primes IL-17 in mucosal-associated invariant T (MAIT) cells, which contribute to the Th17-axis in ankylosing spondylitis. Ann Rheum Dis 2016;75:2124–32.
[49] Rosine N, Rowe H, Koturan S, et al. Characterization of blood mucosal associated invariant T (MAIT) cells in axial spondyloarthritis and of resident MAITs from control axial enthesis. Arthritis Rheumatol 2022;74:1786–95.
[50] Venken K, Jacques P, Mortier C, et al. RORγt inhibition selectively targets IL-17 producing iNKT and γδ-T cells enriched in Spondyloarthritis patients. Nat Commun 2019;10:9.
[51] International Genetics of Ankylosing Spondylitis Consortium (IGAS)Cortes A, Hadler J, Pointon JP, et al. Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related, loci. Nat Genet 2013;45:730–8.
[52] Roberts AR, Vecellio M, Chen L, et al. An ankylosing spondylitis-associated genetic variant in the IL23R-IL12RB2 intergenic region modulates enhancer activity and is associated with increased Th1-cell differentiation. Ann Rheum Dis 2016, http://dx.doi.org/10.1136/annrheumdis-2015-208640 [annrheumdis-2015-208640].
[53] Ellinghaus D, Jostins L, Spain SL, et al. Analysis of five chronic inflammatory diseases identifies 27 new associations and highlights disease-specific patterns at shared loci. Nat Genet 2016;48:510–8.
[54] Farh KK-H, Marson A, Zhu J, et al. Genetic and epigenetic fine mapping of causal autoimmune disease variants. Nature 2015;518:337–43.
[55] Farh KK-H, Marson A, Zhu J, et al. Genetic and epigenetic fine mapping of causal autoimmune disease variants. Nature 2015;518:337–43.
[56] Lau M.C., Keith P., Costello M.-E., et al. Genetic association of ankylosing spondylitis with TBX21 influences T-bet and pro-inflammatory cytokine expression in humans and SKG mice as a model of spondyloarthritis. Ann Rheum Dis. 2017;76:261–9. [annrheumdis-2015-208677].
[57] Vecellio M, Roberts AR, Cohen CJ, et al. The genetic association of RUNX3 with ankylosing spondylitis can be explained by allele-specific effects on IRF4 recruitment that alter gene expression. Ann Rheum Dis 2016;75:1534–40.
[58] Coffre M, Roumier M, Rybczynska M, et al. Combinatorial control of Th17 and Th1 cell functions by genetic variations in genes associated with the interleukin-23 signaling pathway in spondyloarthritis. Arthritis Rheum 2013;65:1510–21.
[59] Fogel O, Bugge Tinggaard A, Fagny M, et al. Deregulation of microRNA expression in monocytes and CD4+ T lymphocytes from patients with axial spondyloarthritis. Arthritis Res Ther 2019;21:51.
[60] Chen L, Al-Mossawi MH, Ridley A, et al. de, et al. miR-10b-5p is a novel Th17 regulator present in Th17 cells from ankylosing spondylitis. Ann Rheum Dis 2017;76:620–5.
[61] Mueller SN, Mackay LK. Tissue-resident memory T cells: local specialists in immune defence. Nat Rev Immunol 2016;16:79–89.
[62] Gaide O, Emerson RO, Jiang X, et al. Common clonal origin of central and resident memory T cells following skin immunization. Nat Med 2015;21:647–53.
[63] Fujiyama T, Umayahara T, Kurihara K, et al. Skin infiltration of pathogenic migratory and resident T cells is decreased by Secukinumab treatment in psoriasis. J Invest Dermatol 2020;140:2073–6.
[64] Mehta H, Mashiko S, Angsana J, et al. Differential changes in inflammatory mononuclear phagocyte and T-cell profiles within psoriatic skin during treatment with guselkumab vs. secukinumab. J Invest Dermatol 2021;141:1707–18.e9.
[65] Gordon KB, Armstrong AW, Foley P, et al. Guselkumab efficacy after withdrawal is associated with suppression of serum IL-23-regulated IL-17 and IL-22 in psoriasis: VOYAGE 2 study. J Invest Dermatol 2019;139:2437–46.
[66] Steel KJA, Srenathan U, Ridley M, et al. Polyfunctional, proinflammatory, tissue-resident memory phenotype and function of synovial interleukin-17A+CD8+T cells in psoriatic arthritis. Arthritis Rheumatol 2020;72:435–47.
[67] Benjamin M, McGonagle D. Histopathologic changes at "synovio-entheseal complexes" suggesting a novel mechanism for synovitis in osteoarthritis and spondylarthritis. Arthritis Rheum 2007;56:3601–9.
[68] Watad A, Rowe H, Russell T, et al. Normal human enthesis harbours conventional CD4+ and CD8+ T cells with regulatory features and inducible IL-17A and TNF expression. Ann Rheum Dis 2020;79:1044–54.
[69] Cuthbert RJ, Watad A, Fragkakis EM, et al. Evidence that tissue resident human enthesis γδT-cells can produce IL-17A independently of IL-23R transcript expression. Ann Rheum Dis 2019;78:1559–65.
[70] Kenna TJ, Davidson SI, Duan R, et al. Enrichment of circulating interleukin-17-secreting interleukin-23 receptor-positive γ/δ T cells in patients with active ankylosing spondylitis. Arthritis Rheum 2012;64:1420–9.
[71] Huang H, Kim HJ, Chang E-J, et al. IL-17 stimulates the proliferation and differentiation of human mesenchymal stem cells: implications for bone remodeling. Cell Death Differ 2009;16:1332–43.
[72] Nam D, Mau E, Wang Y, et al. T-lymphocytes enable osteoblast maturation via IL-17F during the early phase of fracture repair. PLoS One 2012;7:e40044.
[73] Masopust D, Soerens AG, Tissue-Resident T. Cells and other resident leukocytes. Annu Rev Immunol 2019;37:521–46.
[74] Sathaliyawala T, Kubota M, Yudanin N, et al. Distribution and compartmentalization of human circulating and tissue-resident memory T cell subsets. Immunity 2013;38:187–97.
[75] Regner EH, Ohri N, Stahly A, et al. Functional intraepithelial lymphocyte changes in inflammatory bowel disease and spondyloarthritis have disease specific correlations with intestinal microbiota. Arthritis Res Ther 2018;20:149.
[76] Ciccia F, Guggino G, Rizzo A, et al. Type 3 innate lymphoid cells producing IL-17 and IL-22 are expanded in the gut, in the peripheral blood, synovial fluid and bone marrow of patients with ankylosing spondylitis. Ann Rheum Dis 2015;74:1739–47.
[77] Blijdorp ICJ, Menegatti S, Mens LJJV, Sand MGH van de, Chen S, Hreggvidsdottir HS, et al. IL-22- and GM-CSF-expressing but not IL-17A-expressing group 3 innate lymphoid cells are expanded in the inflamed spondyloarthritis joint. Arthritis Rheumatol n.d.;0.
[78] Mortier C, Quintelier K, De Craemer A-S, et al. Gut Inflammation in axial Spondyloarthritis patients is characterized by a marked Type 17 skewed mucosal Innate-like T cell signature. Arthritis Rheumatol 2023, http://dx.doi.org/10.1002/art.42627.
[79] Qaiyum Z, Gracey E, Yao Y, et al. Integrin and transcriptomic profiles identify a distinctive synovial CD8+ T cell subpopulation in spondyloarthritis. Ann Rheum Dis 2019;78:1566–75.
[80] Lefferts AR, Norman E, Claypool DJ, et al. Cytokine competent gut-joint migratory T Cells contribute to inflammation in the joint. Front Immunol 2022;13:932393.
[81] Menegatti S, Guillemot V, Latis E, et al. Immune response profiling of patients with spondyloarthritis reveals signalling networks mediating TNF-blocker function in vivo. Ann Rheum Dis 2020, http://dx.doi.org/10.1136/annrheumdis-2020-218304 [annrheumdis-2020-218304].