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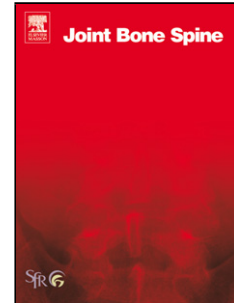
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T cells in the pathogenesis of axial spondyloarthritis

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Highlights

- Genetic polymorphisms associated with ankylosing spondylitis influence T cell function and activity.
- Unconventional T cells are an important source of IL-17 in axial Spondyloarthritis.
- The presence of resident memory T cells in the axial enthesis could be crucial in triggering the inflammation observed in axial Spondyloarthritis.

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.

Key words: Axial Spondyloarthritis, T cells, IL-17A, Tissue resident memory T cells, SNP

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 colleagues [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.

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 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 CD8 T lymphocyte would then trigger the inflammatory mechanisms leading to the disease [5]. Genetic deletion or depletion of cytotoxic CD8 T 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 3 β (BV9-CDR3 β) motif in HLA-B27-positive patients with AS [9–11]. Yang *et al.* isolated the α 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, post translational 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.

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, HLAB27, 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-1 β , 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 γ t was maintained.

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 $\gamma\delta$ T cells, mucosal-associated invariant T (MAIT) cells, invariant NK T (iNKT) cells (detailed description reviewed elsewhere [28]) (Figure 1).

$\gamma\delta$ T 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%). $\gamma\delta$ T cells expressing IL-17 were detected in patients with psoriasis. This study observed a decreased frequency in peripheral blood of (V γ)9V δ 2 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 enthesitis resident T cells observed in the SpA mouse model based on systemic IL-23 overexpression were also identified as $\gamma\delta$ T cells [30].

MAIT cells are characterized by expression of an invariant TCR α -chain (V α 7.2–J α 33 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 V α 24–J α 18–V β 11 invariant TCR (recognizing lipids or glycolipids) and are CD1d-restricted. Upon stimulation, they can release a large variety of pro- and anti-inflammatory cytokines. A subpopulation of IL-17A–producing iNKT cells was described in

mice, but in the SpA TNF^{ΔARE} mouse model, iNKT cells acted as regulatory cells by limiting symptom severity via the production of immunomodulatory cytokines.

IL-17-producing 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, $\gamma\delta$ T 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 $\gamma\delta$ T cells were the dominant IL-17 producers in AS. They showed a three-fold higher frequency of circulating $\gamma\delta$ T cells and five-fold higher frequency of IL-23R-expressing $\gamma\delta$ T 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 ROR γ T+ 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 $\gamma\delta$ T 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 (Figure 1).

How to link genotype to T-cell phenotype?

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 disease. 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 (Figure 2).

To address this last question, Fahr *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 $\gamma\delta$ T 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 $\gamma\delta$ T 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.

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 IFN γ upon stimulation, suggests an influence of the genetic polymorphism on CD8⁺ T cell function [56].

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].

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.

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- κ B 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.

How could T cell activity explain the axSpA spectrum?

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 α E integrin. However, the expression of these surface markers depends largely on their microenvironment. Some of the markers are site-specific, for example, α 4 β 7 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, $\gamma\delta$ T, 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 entheses of SpA patients would undoubtedly be an interesting advancement in the understanding of the pathophysiology 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 entheses. All this work is based on study of the axial entheses 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: $\gamma\delta$ T, 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 V δ 1 subtype of $\gamma\delta$ T 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 $\gamma\delta$ T, 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 pre-osteoblast 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 (figure 3).

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 $\alpha 4\beta 7$ marker; the $\alpha 4\beta 7$ –MAdCAM1 interaction constitutes the homing signal to the gut [73]. MAdCAM1 has been identified on ILC3s. AxSpA patients exhibited increased expression of $\alpha 4\beta 7$ 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 $\gamma\delta$ T 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, $\beta 7$, CD29, CD49 α) 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^{AARE} 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].

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–entheses axis. However, the main roadblock to a better understanding of SpA pathogenesis is still access to the axial entheses.

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–entheses–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 entheses characteristic of axSpA.

AUTHOR’S NOTE

Servier medical art was used for the realization of the figures

AUTHOR CONTRIBUTIONS

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

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Figure legends:**Figure 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 enthesal and peripheral involvement. Right: Unconventional T cells may contribute to the production of IL17 following IL-23 stimulation but also independently of IL-23, through different pro-inflammatory cytokines.

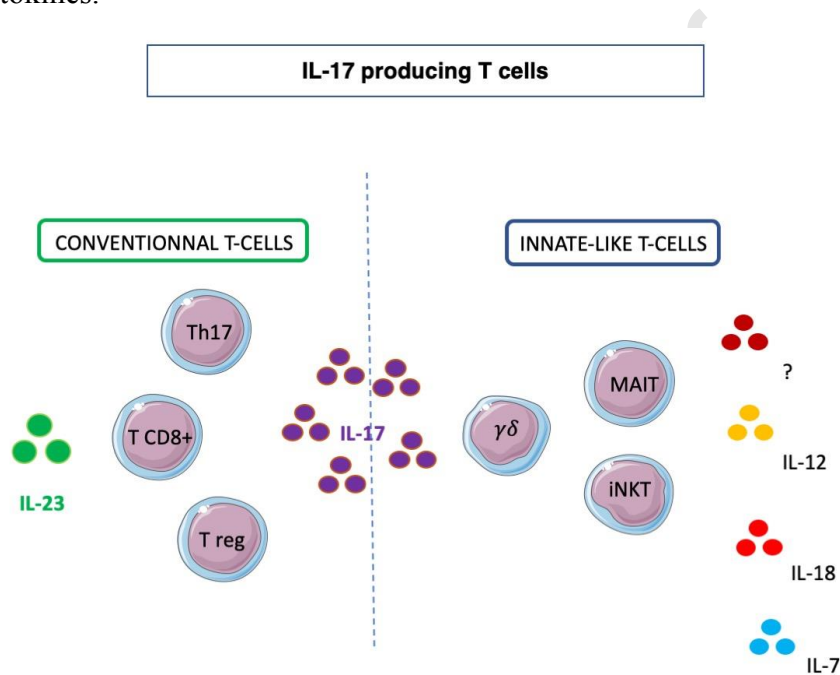


Figure 2: Post-GWAS approaches to link GWAS variants to T-cell function. There is a need to consider new integrative approaches to assess the functional consequences of GWAS variants using in silico analysis with functional genomics data. New analytical methods now provide the first steps of functional 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.

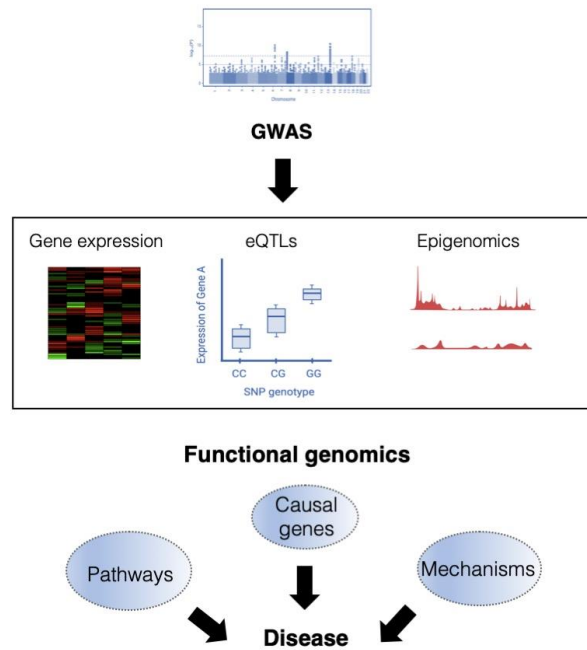
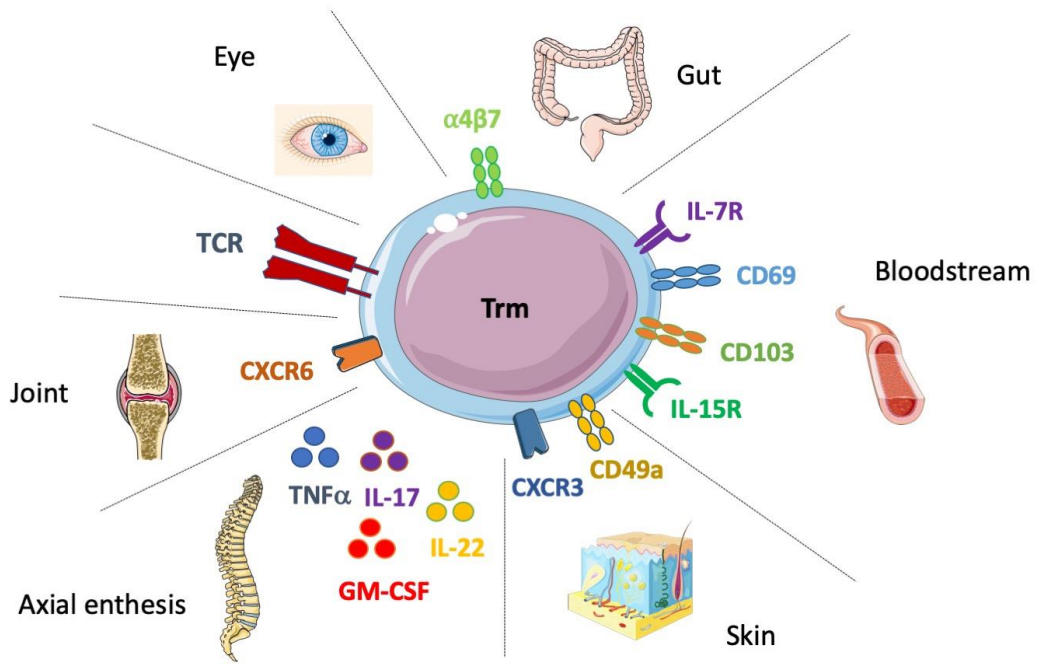


Figure 3: *Hypothetical Trm model for axial spondyloarthritis*: Dysregulated Trm subsets could be the missing link in explaining the extra-articular manifestations of the spondyloarthritis spectrum. CD4⁺ and CD8⁺ Trm can be distinguished from their circulating counterparts by the expression of CD103 (the αE subunit of the $\alpha E\beta 7$ integrin that binds E-cadherin) and CD69 (a marker of activation and of retention). $\alpha 4\beta 7$ 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.



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