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Takayasu Arteritis –A Geographically Distant but Immunologically Proximal MHC-I-Opathy

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Personal View

Takayasu Arteritis –A Geographically Distant but Immunologically Proximal MHC-I-Opathy

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Abstract

Here we describe how Takayasu Arteritis (TA), a granulomatosis vasculitis whose pathogenesis is poorly defined but is known to be associated with HLA-B*52, shares many features with other MHC-I-opathies. In addition to shared clinical features of inflammatory bowel diseases (IBD) and cutaneous inflammation, other than HLA-B*52, is an IL12B single nucleotide polymorphism (SNP) association encoding the common IL-12 and IL-23 p40 subunit and thus may affect not only type 17 cytokine responses but also IFNγ and TNFα production- the cardinal type 1 cytokines in granuloma formation. Considering the translational context of TA responses to TNFα inhibition, we propose TA as a "type 1 MHC-I-opathy." Also type 1 and type 17 T cell immune responses demonstrate immune plasticity, which further connects the overlapping features of TA and SpA spectrum disorders and points to p40 and IFNγ cytokine antagonism as well as potential selective CD8 T cell repertoire ablation.

Key Points

- The concept of the clinicopathological overlaps and segregation of seronegative spondyloarthropathies including ankylosing spondylitis and Behcet's Disease was described 50 years ago but was controversial at that time.

- Had Takayasu arteritis been more common in the UK at the time of the spondyloarthropathies concept inception, we argue that it would have been already included on clinical grounds alone, but now can be included based on shared and overlapping immunopathology.

- Collectively, it is now clear that a convergent "MHC-1-opathy" immunopathology exists in these entities with population level links to CD8 T-cell dysregulation especially in the IL-23/17 cytokine axis that underscores the neutrophilic pathophysiological phenotypes.

- Takayasu arteritis shares many overlapping features with SpA including a link to aortic root inflammation and Inflammatory bowel disease and an HLA-B*52 association, but the pathophysiological hallmark is granulomatous inflammation.

- The immunogenetics of TA incriminates IL-12B gene that encodes for the p40 subunit of both IL-23 and of IL-12- the latter of which is responsible for type 1 cytokines production including IFNγ and TNF, both of which are key to "type-1 cytokine responses that drive granulomata.

- It is argued that the well-established T-cell plasticity in the IL23/17 and type-1 cytokine responses in different tissues underscores the distinct phenotypes between SpA and TA but also overlapping features such as response to TNF inhibition across both.

- Recognition of shared pathophysiology could open up common T-cell targeting strategies in this inter-related family of diseases where the phenotype is strongly related to MHC-1 antigen presentation to CD8 T-cells.

Search strategy and selection criteria

We searched PubMed for articles that were published in English between Jan 1, 1973, and June 28, 2024 using the search terms “Takayasu arteritis”, “Genetics of Takayasu arteritis”, “Aortitis”, “Vasculitis”, “MHC-1 antigen presentation”, “HLA class I”, “Spondyloarthritis”, “Behcet’s disease”, “Psoriasis”, “Inflammatory bowel disease”, “IL-12”, “IL-23”, “IL-17”, “IFN gamma”, and reviewed publications that reported data on these variables. We also searched for articles on “IL-23/17 cytokine axis”, “MHC-1-opathy”, “therapeutic approaches in Takayasu arteritis”, “immunodeficiency in IL-12 and IFN gamma pathways” and “Th1/Th17 plasticity”.

Introduction

The seronegative spondyloarthropathy (SpA) concept was formulated in Leeds in 1974 and heralded the description of clinically interlinked inflammatory disorders that lacked autoantibody associations but remained poorly classified in the following decades (Figure 1).(1) Once it was recognised that "pure autoimmunity" mediated by aberrant B and T-cells responses and "pure autoinflammation" linked to innate immunity were at opposite ends of an immunological disease continuum of inflammation against self, later it became apparent that intermediate inflammatory diseases between autoinflammatory and autoimmunity existed.(2) The SpA umbrella diseases including ankylosing spondylitis (AS), acute anterior uveitis (AAU), psoriasis, and sometimes inflammatory bowel disease (IBD) and Behcet's disease (BD) that encompassed a unique blend of barrier dysfunction and also disease localization to physically stressed sites neatly fitted into this intermediate space.(3) Collectively, these disorders are also linked to MHC-I associations and multiple genetic polymorphisms incriminating T-cells, especially CD8 T-cells and also the IL-23/17 pathway. Given the link between these disorders and MHC class-I associations, they were collectively designated as MHC-I-opathies to highlight the putative roles of CD8 T-cells in these intermediate pathologies between innate and adaptive immunity.(4, 5)

Historically, diseases related to excessive production of IL-17 were dubbed as Th17 disorders indicative of CD4 helper T-cells IL-17 production.(6) However, recognising that aforementioned disorders were linked to CD8 T-cell IL-17 production, in addition to innate lymphocyte IL-17 production, these disorders can be immunogenetically and therapeutically designated as **"type 17 MHC-I-opathies",** although it is recognised that differential responses to both IL-23 and IL-17 blockade may exist. In such MHC-I-opathies, T-cell involvement especially CD8 T-cells and IL-17A as "the key dysregulated cytokine" has revealed the route by which MHC-I-mediated peptide recognition triggers inflammatory disorders at structural and antigenically diverse sites.(7) With the identification of the arthritogenic peptide and CD8 T-cell clonality that may be therapeutically tractable in AS and anterior uveitis, and IL-17A producing CD8 T-cells in psoriatic arthritis and psoriasis, the MHC-I-opathy concept appears to be increasingly relevant for novel SpA family therapy development. (8, 9)

At the birth of the SpA concept in 1974, the Leeds investigators included BD as this disorder was occasionally reported in the UK (Figure 1).(1) However, the fathers of the SpA concept would have been relatively unfamiliar with Takayasu arteritis (TA)- a rare to them, ill-understood large vessel vasculitis that, like BD is common in the Eastern Mediterranean region extending to Japan (Figure 1). It is against this backdrop of the ***"type 17 MHC-I-opathy"*** clinicopathological concept that we offer a perspective of "***type 1 MHC-I-opathy***" for TA- an HLA-B*52 associated large vessel vasculitis. We describe how many aspects of TA overlap with SpA including clinical involvement of aortic root and colitis, shared immunogenetics, the key role of TNF as determined by reverse translational immunotherapeutics. We synthesise clinical observations about TA and SpA overlaps and emergent knowledge of T-cell plasticity in vivo in humans to suggest the basis for the TA immune classification with therapy implications (Table 1).

Common Biomechanical Features between SpA and TA

A collective feature of the MHC-I-opathies is disease localisation to sites of barrier dysfunction (skin, mouth, genital mucosa, and gut) and/or localisation to sites of biomechanical physical stressing including entheses and bone, anterior uvea and importantly the aortic root in HLA-B27+ AS and reactive arthritis.(4) Although there are structural and histological differences among different vessels in terms of their size it has been firmly established that hemodynamic force through various mechanisms may play a role in diverse vascular pathologies especially atherosclerosis.(10) The major sites are affected in TA is aorta and its branches where the shear stress is the maximum, and each cardiac cycle is a biomechanical stress over the aorta.(11) The extensive biomechanical stress over the vessel walls might potentially put the aorta in the target of the disease and it is thought that unique structure of large vessels may also contribute. The biomechanical basis for the non-uniform nature of atherosclerotic disease throughout the vascular tree, points to how mechanical factors can determine plaque development and growth with wall shear stress linked to the plaque vessel wall anatomical location related to pre-existing arterial geometry and flow.(12, 13) At the same time, wall shear stress has effects on the inflammatory activity of endothelial cells.(14) Quintessentially, dysregulated or exaggerated inflammatory response in in the aortic root in SpA spectrum disease but more limited than in TA points to common biomechanical site-specific stress-induced inflammation, rather than primary B or T-cells dysregulation determining disease topography.

Overlap with HLA-B*27 positive SpA and TA beyond the aortic root

In addition to the ischemic and inflammatory TA large vessel vasculitis hallmarks, TA has "extravascular findings" including gut, joint and skin involvement that are also shared with SpA disease spectrum. This association may be considered an overlap rather than a coincidence and has been shown in many cohort studies. Considering the largest cohorts in the literature, in a single center from Turkey, out of 69 TA patients, SpA was detected in 14 (20.3%), psoriasis in 3 (4.3%), and uveitis in 4 (5.8%) patients.(15) In another cohort from Turkey, 15 (8%) of 198 TA patients had SpA, 2 (1%) had psoriasis, and 6 (4%) had uveitis.(16) In a 268 patients cohort, Kwon et al. detected SpA in 19 (7.1%) but psoriasis in only 2 (0.7%) patients.(17) Additionally, in the recently published study conducted in 350 TA patients, we noted that 31 (8.8%) patients had at least one SpA spectrum disease. Of these, 20 had axSpA, 8 had IBD, and 8 had psoriasis. In the TAK with SpA group, TAK had significantly earlier disease onset, compared to TAK without SpA in the same study.(18) On the other hand, the rarity of the relationship of TA to autoimmune (systemic lupus erythematosus, rheumatoid arthritis etc) and autoinflammatory disorders (Familial Mediterranean fever etc) may be assumed from the evidence limited to case reports.

MHC-I Immunogenetic Associations of TA

The MHC-I genetic associations of the SpA family of disorders have been well described elsewhere.(4) The HLA-B*52 genetic association in TA has been demonstrated in many different ethnic populations including Turkey, Japan, India, Korea, Mexico and Greece, incriminating antigen presentation to CD8 T-cells.(19) The HLA-B*52 frequency of the Turkish and Greek TA cohorts (20.9% and 37% respectively) is higher compared to healthy controls. (6.7% and 2.4% respectively).(20, 21) Additionally,

in a study from Mexico, the frequency of HLA-B*52 (OR=5.16) and HLA-B*15 (OR=3.24) was increased and HLA-A*24 was decreased in TA patients compared to healthy controls.(22) Kimura et al. detected the association HLA-B*52 and also HLA-B*39 with susceptibility to TA.(23) Moreover, akin to type-17 MHC-I-opathies, where different class-1 associations can exist within individual diseases, Terao et al. found HLA-B*67:01 (OR=3.44) to be associated with TA independently of HLA-B*52:01. In the same study, two amino acids in the HLA-B protein were shown to increase TA susceptibility.(24) Interestingly, despite the marked structural molecular similarity, HLA-B*51, the most important genetic predisposing factor for BD, is unrelated to TA.(20)

Immunogenetics of TA and SpA/IBD outside the MHC.

The strongest TA genetic association is with IL-12B which encodes IL-12p40, a subunit of both IL-12 and IL-23, and was shown in several different cohorts (rs56167332, OR = 1.54, p = 2.18 × 10(-8), rs6871626, p = 1.7 × 10(-13), OR = 1.75, 95% CI 1.42-2.16 and rs4379175, p value = 3.13 × 10(−9), OR = 1.36) (Figure 2).(25-27) IL12B rs6871626 A allele was found to be more associated with TA.(26) IL12B rs6871626, has recently been demonstrated to be also associated with vascular damage and disease severity. Aortic regurgitation was significantly associated with the A allele (risk allele) of IL12B rs6871626 (p = 0.0052; odds ratio [OR] 2.45), as well as the proportion of patients who underwent aortic valve replacement (p = 0.023; OR 3.64). (28) In the TA patient group carrying the IL12B AA allele, IL-12p40 and IL-12p70 expression was increased compared to those without, but IL-23 expression did not change. Additionally, more IFNγ production was detected in this group.(29) The ratio of CD4+IFNγ+ cells was significantly higher in patients with the risk allele, whereas CD4+IL-17A+ cells showed no differences.(29) These HLA-B*52 and IL12B SNP associations with TA support the idea of T-cell and IL-12 driven IFNγ and TNF or so called type-1 T-cells responses in TA disease severity (Figure 3).

IL-12B gene SNPs have also been identified in AS (IL-12B CC [matched relative risk (RR(m)) 1.93, 95% CI 1.23-3.03] and IL-12B AC (RR(m) 1.73, 95% CI 1.21-2.46) genotypes with greater risk of developing AS than subjects with the IL-12B AA genotype).(30) In addition to AS, the IL-12B gene rs6556412 polymorphism was associated with IBD and the rs4379175 polymorphism with psoriasis. The direction of this genetic effect is parallel between TA and IBD, nonetheless the risk allele in rs4379175-IL-12B appears to be protective against psoriasis.(31-33) Of course, out of IL-12B, the immunogenetics of SpA spectrum disorders also strongly incriminates IL-23R and IL-23A SNPs encoding respectively for the IL-23 receptor and the p19 subunit of IL-23 cytokine (Figure 2).(34-36) In addition, SNPs in downstream cytokines, especially TRAF3IP2 linked to IL-17RA signalling are well described in SpA spectrum diseases.(37) The IL-17F rs763780 G allele, which has been found to be associated with high disease activity and poor response to treatment in AS, is protective against TA (p=0.014), and the AG genotype of rs763780 is also associated with susceptibility to syncope and tuberculosis in TA (Figure 2).(38, 39) The fact that IL12B variants associated with TA affect UBLCP1 mRNA expression and that UBLCP1 is a genetic factor that may increase the risk of psoriasis is an indication that functional similarities intersect at certain points.(40) What is noteworthy is that another type of large-vessel vasculitis, namely giant cell arteritis (GCA), that is not linked to MHC-I, but MHC-II exhibits a

pathologically identical granulomatosis vasculitis and also shares common IL-12B SNPs but has a different immunological profile as revealed by reverse translational immunology insights where TNF blockade was not effective in GCA (Table 3). (41, 42)

A Closer look at TA and IBD Overlaps-Shared Genetics

An overarching concept in SpA is the presence of either overt or covert intestinal inflammation, especially at the ileocecal region.(43) Evidence of clinical overlaps between TA and IBD has also accumulated but is less well explored than in SpA. In a study conducted in 470 TA patients, a UC prevalence of (6.4%) was observed. In this study, HLA–B*52.01 carrier rate was higher in TA patients with UC than in without UC.(44) In another study where 142 TA patients were examined in terms of IBD overlap, the IBD/TA concurrence rate was 9.2% and HLA-B*52.01 carriage was detected in all TA with UC patients and was significantly higher than TA without UC group ($p = 0.001$).(45)

Although the immunopathogenesis of IBD is heterogeneous there is evidence for MHC-I links in UC.(46) In a Japanese study, HLA B*5201 had a highly significant OR of 2.62(2.13−3.22) for UC compared to healthy controls. Also, this meta-analysis detected that HLA-B*52.01 is protective for CD.(46) In another small Japanese 45 UC patients cohort, HLA-B*52 was detected with a remarkable frequency of 62.2%.(47) Outside the MHC, a recent meta-analysis showed strong evidence that PLCG2 (rs79773175, rs7204834, rs12596533, rs146948024) and ZMIZ1(rs1250573, rs1892497, rs1250566) SNPs which were associated with IBD (UC and CD, respectively) may also be associated with TA further supports the complexity of the TA-IBD relationship.(27) Moreover, hierarchical clustering of TA with other immune-mediated diseases GWAS and self-reported disease traits in UK Biobank considered significantly different from control, demonstrated that TA clusters with IBD and SpA.(27) Besides, IL12B SNP rs6887695, which has been shown to be associated with TA, an association with susceptibility to IBD ($p=0.035$; OR 1.15 [95% CI 1.01–1.31] including a trend for rs6887695 for association with CD (OR 1.41; [0.99–1.31], $p=0.066$) and UC (OR 1.18 [0.97–1.43], $p=0.092$) has been reported.(48) The genetic overlaps between TA and IBD, frames the shared clinical manifestations of these diseases and fit with the wider link of subclinical intestinal inflammation in SpA. (Table 2).

The role of HLA-B*52:01 on TA disease severity.

The MHC-I associations in AS, uveitis and psoriasis are linked with disease onset at an earlier age and more severe or extensive involvement which points to the role of CD8 T-cells in magnifying immune responses in these entities.(4) Regarding of MHC class I, a high HLA-B*52 frequency was reported in UC in Japan.(49) In keeping with the MHC-I-opathy concept, where relevant class-1 genes are linked to earlier disease onset, TA also occurs at a younger age in HLA-B*52:01 positive subjects. (early vs late onset 24.2% vs 12%; $p=0.024$).(20) Japanese TA patients who were HLA*B52:01 positive are also more prone to hypertension, acute phase response and corticosteroid requirement in two studies as a severity marker.(50) In addition, aortic regurgitation was the most important cause of death in the Japanese TA patient group, where its relationship with HLA-B*52 was shown.(51)

From a different angle, in the series from Turkey where patients were subgrouped according to the angiographic subtype, it was demonstrated that only type 1 disease (branches from the aortic arch) according to the Hata's angiographic classification of TA(52) had a lower HLA-B*52:01 positivity where the vessel involvement is limited to the branches of the aorta, whereas HLA-B*52:01 was more frequently positive if the aorta is more extensively involved.(20) Another study also showed that HLA-B*52 allele carriage is associated with TA disease severity.(53) These data support that the disease tends to be more extensive and aggressive if the patient carries HLA-B*52:01 which akin to MHC-I-opathy incriminates T-cell responses driving earlier onset, more extensive and more severe pathology.

Pathology of TA from the MHC-I-opathy Perspective

The pathophysiological hallmark of the IL-23/17 axis MHC-1-opathy linked diseases is early neutrophilic inflammation.(54, 55) However, the pathological hallmark of TA is granulomatous infiltrates with multinucleated giant cells, T cell and histiocyte (tissue macrophages) accumulations in large arteries and of course such inflammation is strongly linked to IL-12, IFNγ and TNF (Figure 3). Compared to GCA, the CD4/CD8 ratio shifts towards CD8 in TA and CD4 in GCA that is in keeping with the fundamental MHC-I-opathy nature of TA versus the GCA MHC-II associations.(56) Conventionally CD4 T cells producing IFNγ or so-called **"Th1 cells"** were considered as driving granulomatous inflammation.(57) However, it is now well established that IFNγ producing CD8 cells are also equally capable of driving the same pathology.(58) In a study, CD8 T-lymphocytes were the main source of IFNγ, which is the key cytokine in granuloma formation in TA.(58) Generally speaking, IL-12 signalling drives IFNγ responses against intracellular pathogens whereas IL23/17 axis signalling drives immunity against extracellular pathogen such as fungi.(59)

Granulomatous arterial inflammation in the key feature of TA and such a pattern of intestinal transmural granulomatosis inflammation is also typical of CD. However, the pattern of mucosal inflammation of bowel in TA is more similar to UC than CD, together with some distinctive TA related findings (Figure 4). (45) The MHC-I-opathies are characterised by neutrophilic inflammation including hypopyon in the eye, Munro's abscess in the skin, sterile neutrophilic inflammation in the skeleton and also neutrophil rich crypt abscesses in UC and CD, in addition to granulomatosis inflammation in CD (Figure 3). (54) Immunogenetics studies and anti-IL-23 pathway antagonism incriminate the IL-23/17 axis in IBD and anti-TNF therapies and immunogenetics also incriminates TNF- the pivotal type 1 cytokine, that points towards involvement of both type 1 and IL-23 axis in the intestine.

Historically fungal immunity has been viewed as type 17 in nature. However, in mice with paracoccidioidomycosis, a chronic fungal mediated granulomatous disease, macrophage derived IL-6 and IL-23 positively regulated the expression of TNFα, IFNγ, and inducible nitric oxide synthase, promoting a Th17 immune profile that contributed to mature granuloma formation.(60) Accordingly, we would highlight potential Th1/Th17 plasticity in the TA intestinal environment that may be sculpted by the intestinal environment towards a non-granulomatous state.

Associations with Infectious Origins in the Concept of MHC-I-opathy

Infectious triggers, especially reactive arthritis, were integral features of the original SpA concept description. The potential role of tuberculosis, a granuloma triggering microbe, in the etiopathogenesis of TA has been well discussed.(61) Purified protein derivative (PPD) intradermal reaction was positive at a higher rate in patients with TA than in those without. Even further, PPD with induration over 10 mm might be as frequent (92.5% versus 89%) in TA as in patients with extra-pulmonary tuberculosis. In contrast, conflicting results were obtained between TA and healthy controls in the frequency of latent tuberculosis detected by QuantiFERON-TB Gold test positivity.(62, 63) Also in Japan, one of the countries where TA is common, TB incidence and mortality are higher in men than in women. However, a higher rate of latent TB was commoner in women, may also suggest that the manifestations of TB exposure may depend on some gender-related genetic/inflammatory factors.(64) Given the link between both TA and TB with granulomatosis inflammation, an immune hypersensitivity reaction to TB in females would represent a simple concept for the link between infection and TA.

A role for microbiota in the pathogenesis of AS is well supported by a wide array of self- and cross-reactive microbial peptides capable of engagement of clonally expanded BV9–CDR3β TCRs.(65) Additionally, case reports of deletion of TCR BV9 T-cells and good responses in AS support the MHC-I-opathy concept in AS.(8) These findings in AS underpin the realisation that robust immunity to infection requires widely cross-reactive T-cells where one T-cell can react with up to a million different MHC-associated peptides.(66) Additional factors including the inflammatory milieu including TLR pathway activation on DCs could also be major determinants in driving T-cell activation where low level antigen presentation is taking place. (67)

Secondary Humoral Autoimmune Responses in TA and SpA

What about the role of humoral autoimmunity driving the pathology of TA and SpA as an alternative or related scenario since autoimmune mechanisms have been reported in SpA and TA? In TA, autoantibodies against endothelial protein C receptor (EPCR) and scavenger receptor class B type 1 (SR-BI), another endothelial autoantigen, were reported. In 52 TA patients, the positivity rates for anti-EPCR and anti-SR-BI Abs were 34.6% and 36.5%, respectively. Additionally, anti-EPCR and anti-SR-BI Abs were detected at higher rates in TA patients complicated with UC. However, evidence that γδ T cells can recognize EPCRs of CMV-infected endothelial cells can be attributed to the fact that the main reason underlying the formation of EPCR-targeted secondary autoantibodies may be increased EPCR recognition of the cellular components of the immune system, which also represents the pathogenesis of TA.(68) Similarly, antiphospholipid antibodies have been reported in TA patients.(69) However, such autoimmunity may be secondary to tissue damage akin to ANCA and ASCA in IBD being linked to severity of gut inflammation rather than an IBD driver.(70)

Additionally, TA patients developed a humoral immune response against both human 60 kDa HSP (84% versus 22%, $p < 0.001$) and mycobacterial 65 kDa HSP (92% versus 11%, $p < 0.0001$) compared to the

healthy control group. Also, a strongly positive correlation between anti-human 60 kDa HSP IgG and anti-mycobacterial 65 kDa HSP IgG antibodies was found in TA patients.(71) In another study, serum HSP 65kDA antibodies were higher in patients with active arteritis compared to inactive arteritis.(72) Conceivably, this autoantibody formation may also be attributed to increased exposure due to vascular damage.(73)

Therapy Implications for TA

Therapies not only treat patients but dissect human immune disease mechanism. Some MHC-I-opathies may respond to both T cell directed therapies and to anti-cytokine approaches reflecting the impression that adaptive CD8 T-cell response exaggerates cytokine mediated inflammatory reactions at specific sites of barrier or biophysical stress. In that vein, therapies that work in part or predominantly via T-cell antagonisms have been used in TA, including methotrexate (MTX), azathioprine (AZA), cyclophosphamide (CYC), cyclosporine A (CSA), leflunomide (LEF) and mycophenolate mofetil (MMF) with a randomized, placebo-controlled trial with LEF currently ongoing.(74, 75) Within biologic therapies, anti-TNF agents, that are very effective across the SpA spectrum, were first tried in TA in 2004.(76) The last meta-analysis published about biologic agents in TA presented that the remission rates and relapse rates were: 0.65 (95% CI: 0.56-0.73; I2=49%) and 0.28 (95% CI: 0.16-0.40; I2=68%) for anti-TNF agents.(77)

In contrast to TA, the TNF agents were not efficacious in GCA with two negative phase 3 trials which is somewhat paradoxical given the IL-12B SNPs shared between GCA and TA that points towards type 1 immune responses.(42, 78) The efficacy of tocilizumab was demonstrated in RCTs in GCA.(79, 80) This apparent difference in responses to anti-TNFα treatment between GCA and TA provides reverse translational immunology support for the type 1 MHC-I-opathy for TA. Also, the value of TNF antagonism in the IL-23/17 axis SpA spectrum disorders links Th1 and Th17 plasticity in pathogenesis. This may partially underpin the positive effects of TNF blockade in SpA and psoriasis. (Figure 3)

With respect to IL-6 antagonism, a randomised-controlled study of tocilizumab in TA (TAKT study) failed to meet its primary end-point on an intention-to-treat analysis (hazard ratio 0.41, 95%CI 0.15-1.10) but successfully met the secondary end-point of superiority on per-protocol analysis (hazard ratio 0.34, 95%CI 0.11-1.00).(81) Positive clinical and imaging results along with significant reductions in daily glucocorticoid doses in 28 patients who received tocilizumab for 96 weeks in the open-label extension period of 36 patients enrolled in the double-blind period of the TAKT study, exhibited that tocilizumab may be an important option in the long term follow-up period.(82) In a multi-center retrospective study comparing subcutaneous and intravenous forms of tocilizumab, tocilizumab achieved complete remission at 6 months in 70% of patients with TA refractory to disease-modifying anti-rheumatic drugs.(83) There are no head-to-head randomized controlled trials between anti-TNFα agents and tocilizumab, but a meta-analysis of studies in the literature detected similar rates of clinical remission [risk ratio (RR) tocilizumab vs anti-TNFα agents 1.03, 95%CI 0.91-1.17)], angiographic stabilization (RR 1.00, 95%CI 0.72-1.40) or adverse events (RR 0.84, 95%CI 0.54-1.31) with either tocilizumab or

anti-TNFα agents.(84) Beyond therapeutic antagonism of IL-6, GWAS studies revealed an IL6 SNP (rs2069837) (odds ratio [OR] 2.07, P = 6.70 × 10(-9)) as an important non-HLA locus in the pathogenesis of TA.(85) IL-6 has been shown in biopsy specimens of the aorta with TA and correlated with disease activity.(86) Whilst IL-6 pathway SNPs are linked to AS, it is noteworthy that anti IL-6 therapy is not efficacious.(87, 88)

There are strong evidence points that IL-6 is indispensable for the lineage specification of Th17 cells via STAT3. In addition to IL-23, IL-6 is also essential for the maintenance of Th17 cells with highly plasticity characteristics (Figure 5).(89)Additionally, increased production of IFNγ induced neutrophil IL-6 secretion.(90) Given the IL-12B SNP and granulomata in GCA underpins type 1 immunity in GCA also but further studies are needed to confirm the efficacy of IL-17 blockade in both GCA and TA.(41) Both, IL-12/IFNγ and the role of IL-6 on IL-17 induction in GCA has been proposed.(91) As discussed earlier, IL-6 has a role in experimental fungal granulomatosis inflammation and further studies are needed in human TA to evaluate impact of its blockade.

Based on IL-12B as a susceptibility gene for TA, case reports of ustekinumab (a monoclonal antibody against IL-12/23p40, the IL12B protein product) efficacy in patients with TA are not surprising.(92) Whether this is an effect on IL-12, or IL-23 or both awaits clarification as IL-12B is shared between these type 1 and type 17 pathways. Additionally, in an open-label study comparing secukinumab with TNFα inhibitor in TA, both therapies showed similar effectiveness however randomized controlled double-blind studies with a larger number of patients are needed.(93)

JAK inhibition can directly antagonise some of the key cytokines proposed in our TA model including IL-12, IL-23 and IFNγ in addition to T-cell functional antagonism. Ruxolitinib which selectively inhibits JAK1 and JAK2 in vitro reduced global T cells activation, Th1/Th17 polarisation and promote increase of Tregs in TA.(94) In the same study, a good clinical response was obtained in three TA patients with JAK inhibitors.(94) In a recently published 10-patient case series, a significant decrease in disease activity and glucocorticoid requirement was detected in TA patients treated with Tofacitinib.(95) A randomized, double-blind, controlled trial with upadacitinib is also under way.

A Model for TA

Based on a synthesis of the available data, we propose a model for TA as a type 1 MHC-I-opathy in contra distinction to a type 17 MHC-I-opathy. This has immunotherapeutic applications and suggests that IFNγ blocking directly or its indirect blockade via JAK1/2 pathway inhibition could be an effective strategy for TA. Given the plasticity of T-cell responses in vivo, this model also accounts for overlapping features of TA and SpA that could simply represent different degrees of type 1 and type 17 immunity in different target organs (Figure 5). Although we suggest *type 1 MHC-I-opathy* for the TA classification, it is recognised that T-cell polyfunctionality and plasticity in SpA spectrum disease is also linked to aberrant TNF production.

The shared target tissue and granulomatosis inflammation shared by TA and GCA and the differing role of TNFα inhibition in both permits a reappraisal of immunopathology, especially if more confirmatory trials emerge (Table 3). IL-12/IFNγ pathway which is inducing the granuloma formation, was suggested to be leading the resistant and chronic disease along with the evidence of Th1 derived cytokines especially IFNγ in the post-treatment specimens of animal models.(96) Given the uniqueness of human TA, then ultimately reverse translational immunology insights from clinical trials will elucidate the field and will show whether TNFα inhibition is superior to IL-6 pathway inhibition. Given the type 1 MHC-I-opathy concept then monotherapy antagonisms of IFNγ would appear to be a promising option just as IL-23/17 axis antagonism has proven so successful in some MHC-I-opathy related diseases. To summarise, further trials are needed to fully decipher the role of cytokine blockade and relevant pathways in TA vs GCA.

Conclusions

In this perspective, we make the case that TA fits into the MHC-I-opathy spectrum of disorders but represents a novel "type I MHC-I-opathy" disorder. Thus, AS and psoriasis form more of a type 17-MHC-I-opathy class whilst TA has more IL12-driven pathogenic mechanisms and can be categorized more as a type I MHC-I-opathy. (Figure 2). We describe how overlapping clinical phenotypes could be related to convergent IL-12 and IL-23 pathway immunology that is influenced by the different TA target tissues and microbiota ecology, for example in the gut and the skin. We recognise that less than 50% of TA cases express HLA-B52 and that other class-1 antigens may be involved, so it is acknowledged that the disease is potentially heterogeneous, and that a "one size fits all" model may not cover the entire disease spectrum.

Given the uniqueness of human TA, then ultimately reverse translational immunology insights from clinical trials will elucidate the field and will show whether TNFα inhibition is superior to IL-6 pathway and the potential role of IFNγ antagonism. Also, the MHC-I-opathies are linked to subclinical intestinal inflammation as major drivers; this has been overlooked in TA to date. The emerging insights from type 17 MHC-I-opathies points towards an antigenic basis for MHC-I antigen presentation and activation of CD8 T-cells in psoriasis, uveitis and AS. This suggests that direct targeting of clonally expanded T-cells could be pursued in TA, towards novel therapy strategies. Overall, TA is geographically distant from the original SpA disease concepts but is in fact closely linked from the immunological perspective and a "half-sister" of the MHC-1-opathy diseases linked to the IL-23/17 axis.

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Personal View

Takayasu Arteritis –A Geographically Distant but Immunologically Proximal MHC-I-Opathy

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Abstract

Here we describe how Takayasu Arteritis (TA), a granulomatosis vasculitis whose pathogenesis is poorly defined but is known to be associated with HLA-B*52, shares many features with other MHC-I-opathies. In addition to shared clinical features of inflammatory bowel diseases (IBD) and cutaneous inflammation, other than HLA-B*52, is an IL12B single nucleotide polymorphism (SNP) association encoding the common IL-12 and IL-23 p40 subunit and thus may affect not only type 17 cytokine responses but also IFNγ and TNFα production- the cardinal type 1 cytokines in granuloma formation. Considering the translational context of TA responses to TNFα inhibition, we propose TA as a "type 1 MHC-I-opathy." Also type 1 and type 17 T cell immune responses demonstrate immune plasticity, which further connects the overlapping features of TA and SpA spectrum disorders and points to p40 and IFNγ cytokine antagonism as well as potential selective CD8 T cell repertoire ablation.

Key Points

- The concept of the clinicopathological overlaps and segregation of seronegative spondyloarthropathies including ankylosing spondylitis and Behcet's Disease was described 50 years ago but was controversial at that time.

- Had Takayasu arteritis been more common in the UK at the time of the spondyloarthropathies concept inception, we argue that it would have been already included on clinical grounds alone, but now can be included based on shared and overlapping immunopathology.

- Collectively, it is now clear that a convergent "MHC-1-opathy" immunopathology exists in these entities with population level links to CD8 T-cell dysregulation especially in the IL-23/17 cytokine axis that underscores the neutrophilic pathophysiological phenotypes.

- Takayasu arteritis shares many overlapping features with SpA including a link to aortic root inflammation and Inflammatory bowel disease and an HLA-B*52 association, but the pathophysiological hallmark is granulomatous inflammation.

- The immunogenetics of TA incriminates IL-12B gene that encodes for the p40 subunit of both IL-23 and of IL-12- the latter of which is responsible for type 1 cytokines production including IFNγ and TNF, both of which are key to "type-1 cytokine responses that drive granulomata.

- It is argued that the well-established T-cell plasticity in the IL23/17 and type-1 cytokine responses in different tissues underscores the distinct phenotypes between SpA and TA but also overlapping features such as response to TNF inhibition across both.

- Recognition of shared pathophysiology could open up common T-cell targeting strategies in this inter-related family of diseases where the phenotype is strongly related to MHC-1 antigen presentation to CD8 T-cells.

Search strategy and selection criteria

We searched PubMed for articles that were published in English between Jan 1, 1973, and June 28, 2024 using the search terms “Takayasu arteritis”, “Genetics of Takayasu arteritis”, “Aortitis”, “Vasculitis”, “MHC-1 antigen presentation”, “HLA class I”, “Spondyloarthritis”, “Behcet’s disease”, “Psoriasis”, “Inflammatory bowel disease”, “IL-12”, “IL-23”, “IL-17”, “IFN gamma”, and reviewed publications that reported data on these variables. We also searched for articles on “IL-23/17 cytokine axis”, “MHC-1-opathy”, “therapeutic approaches in Takayasu arteritis”, “immunodeficiency in IL-12 and IFN gamma pathways” and “Th1/Th17 plasticity”.

Introduction

The seronegative spondyloarthropathy (SpA) concept was formulated in Leeds in 1974 and heralded the description of clinically interlinked inflammatory disorders that lacked autoantibody associations but remained poorly classified in the following decades (Figure 1).(1) Once it was recognised that "pure autoimmunity" mediated by aberrant B and T-cells responses and "pure autoinflammation" linked to innate immunity were at opposite ends of an immunological disease continuum of inflammation against self, later it became apparent that intermediate inflammatory diseases between autoinflammatory and autoimmunity existed.(2) The SpA umbrella diseases including ankylosing spondylitis (AS), acute anterior uveitis (AAU), psoriasis, and sometimes inflammatory bowel disease (IBD) and Behcet's disease (BD) that encompassed a unique blend of barrier dysfunction and also disease localization to physically stressed sites neatly fitted into this intermediate space.(3) Collectively, these disorders are also linked to MHC-I associations and multiple genetic polymorphisms incriminating T-cells, especially CD8 T-cells and also the IL-23/17 pathway. Given the link between these disorders and MHC class-I associations, they were collectively designated as MHC-I-opathies to highlight the putative roles of CD8 T-cells in these intermediate pathologies between innate and adaptive immunity.(4, 5)

Historically, diseases related to excessive production of IL-17 were dubbed as Th17 disorders indicative of CD4 helper T-cells IL-17 production.(6) However, recognising that aforementioned disorders were linked to CD8 T-cell IL-17 production, in addition to innate lymphocyte IL-17 production, these disorders can be immunogenetically and therapeutically designated as **"type 17 MHC-I-opathies",** although it is recognised that differential responses to both IL-23 and IL-17 blockade may exist. In such MHC-I-opathies, T-cell involvement especially CD8 T-cells and IL-17A as "the key dysregulated cytokine" has revealed the route by which MHC-I-mediated peptide recognition triggers inflammatory disorders at structural and antigenically diverse sites.(7) With the identification of the arthritogenic peptide and CD8 T-cell clonality that may be therapeutically tractable in AS and anterior uveitis, and IL-17A producing CD8 T-cells in psoriatic arthritis and psoriasis, the MHC-I-opathy concept appears to be increasingly relevant for novel SpA family therapy development. (8, 9)

At the birth of the SpA concept in 1974, the Leeds investigators included BD as this disorder was occasionally reported in the UK (Figure 1).(1) However, the fathers of the SpA concept would have been relatively unfamiliar with Takayasu arteritis (TA)- a rare to them, ill-understood large vessel vasculitis that, like BD is common in the Eastern Mediterranean region extending to Japan (Figure 1). It is against this backdrop of the ***"type 17 MHC-I-opathy"*** clinicopathological concept that we offer a perspective of "***type 1 MHC-I-opathy***" for TA- an HLA-B*52 associated large vessel vasculitis. We describe how many aspects of TA overlap with SpA including clinical involvement of aortic root and colitis, shared immunogenetics, the key role of TNF as determined by reverse translational immunotherapeutics. We synthesise clinical observations about TA and SpA overlaps and emergent knowledge of T-cell plasticity in vivo in humans to suggest the basis for the TA immune classification with therapy implications (Table 1).

Common Biomechanical Features between SpA and TA

A collective feature of the MHC-I-opathies is disease localisation to sites of barrier dysfunction (skin, mouth, genital mucosa, and gut) and/or localisation to sites of biomechanical physical stressing including entheses and bone, anterior uvea and importantly the aortic root in HLA-B27+ AS and reactive arthritis.(4) Although there are structural and histological differences among different vessels in terms of their size it has been firmly established that hemodynamic force through various mechanisms may play a role in diverse vascular pathologies especially atherosclerosis.(10) The major sites are affected in TA is aorta and its branches where the shear stress is the maximum, and each cardiac cycle is a biomechanical stress over the aorta.(11) The extensive biomechanical stress over the vessel walls might potentially put the aorta in the target of the disease and it is thought that unique structure of large vessels may also contribute. The biomechanical basis for the non-uniform nature of atherosclerotic disease throughout the vascular tree, points to how mechanical factors can determine plaque development and growth with wall shear stress linked to the plaque vessel wall anatomical location related to pre-existing arterial geometry and flow.(12, 13) At the same time, wall shear stress has effects on the inflammatory activity of endothelial cells.(14) Quintessentially, dysregulated or exaggerated inflammatory response in in the aortic root in SpA spectrum disease but more limited than in TA points to common biomechanical site-specific stress-induced inflammation, rather than primary B or T-cells dysregulation determining disease topography.

Overlap with HLA-B*27 positive SpA and TA beyond the aortic root

In addition to the ischemic and inflammatory TA large vessel vasculitis hallmarks, TA has "extravascular findings" including gut, joint and skin involvement that are also shared with SpA disease spectrum. This association may be considered an overlap rather than a coincidence and has been shown in many cohort studies. Considering the largest cohorts in the literature, in a single center from Turkey, out of 69 TA patients, SpA was detected in 14 (20.3%), psoriasis in 3 (4.3%), and uveitis in 4 (5.8%) patients.(15) In another cohort from Turkey, 15 (8%) of 198 TA patients had SpA, 2 (1%) had psoriasis, and 6 (4%) had uveitis.(16) In a 268 patients cohort, Kwon et al. detected SpA in 19 (7.1%) but psoriasis in only 2 (0.7%) patients.(17) Additionally, in the recently published study conducted in 350 TA patients, we noted that 31 (8.8%) patients had at least one SpA spectrum disease. Of these, 20 had axSpA, 8 had IBD, and 8 had psoriasis. In the TAK with SpA group, TAK had significantly earlier disease onset, compared to TAK without SpA in the same study.(18) On the other hand, the rarity of the relationship of TA to autoimmune (systemic lupus erythematosus, rheumatoid arthritis etc) and autoinflammatory disorders (Familial Mediterranean fever etc) may be assumed from the evidence limited to case reports.

MHC-I Immunogenetic Associations of TA

The MHC-I genetic associations of the SpA family of disorders have been well described elsewhere.(4) The HLA-B*52 genetic association in TA has been demonstrated in many different ethnic populations including Turkey, Japan, India, Korea, Mexico and Greece, incriminating antigen presentation to CD8 T-cells.(19) The HLA-B*52 frequency of the Turkish and Greek TA cohorts (20.9% and 37% respectively) is higher compared to healthy controls. (6.7% and 2.4% respectively).(20, 21) Additionally,

in a study from Mexico, the frequency of HLA-B*52 (OR=5.16) and HLA-B*15 (OR=3.24) was increased and HLA-A*24 was decreased in TA patients compared to healthy controls.(22) Kimura et al. detected the association HLA-B*52 and also HLA-B*39 with susceptibility to TA.(23) Moreover, akin to type-17 MHC-I-opathies, where different class-1 associations can exist within individual diseases, Terao et al. found HLA-B*67:01 (OR=3.44) to be associated with TA independently of HLA-B*52:01. In the same study, two amino acids in the HLA-B protein were shown to increase TA susceptibility.(24) Interestingly, despite the marked structural molecular similarity, HLA-B*51, the most important genetic predisposing factor for BD, is unrelated to TA.(20)

Immunogenetics of TA and SpA/IBD outside the MHC.

The strongest TA genetic association is with IL-12B which encodes IL-12p40, a subunit of both IL-12 and IL-23, and was shown in several different cohorts (rs56167332, OR = 1.54, p = 2.18 × 10(-8), rs6871626, p = 1.7 × 10(-13), OR = 1.75, 95% CI 1.42-2.16 and rs4379175, p value = 3.13 × 10(−9), OR = 1.36) (Figure 2).(25-27) IL12B rs6871626 A allele was found to be more associated with TA.(26) IL12B rs6871626, has recently been demonstrated to be also associated with vascular damage and disease severity. Aortic regurgitation was significantly associated with the A allele (risk allele) of IL12B rs6871626 (p = 0.0052; odds ratio [OR] 2.45), as well as the proportion of patients who underwent aortic valve replacement (p = 0.023; OR 3.64). (28) In the TA patient group carrying the IL12B AA allele, IL-12p40 and IL-12p70 expression was increased compared to those without, but IL-23 expression did not change. Additionally, more IFNγ production was detected in this group.(29) The ratio of CD4+IFNγ+ cells was significantly higher in patients with the risk allele, whereas CD4+IL-17A+ cells showed no differences.(29) These HLA-B*52 and IL12B SNP associations with TA support the idea of T-cell and IL-12 driven IFNγ and TNF or so called type-1 T-cells responses in TA disease severity (Figure 3).

IL-12B gene SNPs have also been identified in AS (IL-12B CC [matched relative risk (RR(m)) 1.93, 95% CI 1.23-3.03] and IL-12B AC (RR(m) 1.73, 95% CI 1.21-2.46) genotypes with greater risk of developing AS than subjects with the IL-12B AA genotype).(30) In addition to AS, the IL-12B gene rs6556412 polymorphism was associated with IBD and the rs4379175 polymorphism with psoriasis. The direction of this genetic effect is parallel between TA and IBD, nonetheless the risk allele in rs4379175-IL-12B appears to be protective against psoriasis.(31-33) Of course, out of IL-12B, the immunogenetics of SpA spectrum disorders also strongly incriminates IL-23R and IL-23A SNPs encoding respectively for the IL-23 receptor and the p19 subunit of IL-23 cytokine (Figure 2).(34-36) In addition, SNPs in downstream cytokines, especially TRAF3IP2 linked to IL-17RA signalling are well described in SpA spectrum diseases.(37) The IL-17F rs763780 G allele, which has been found to be associated with high disease activity and poor response to treatment in AS, is protective against TA (p=0.014), and the AG genotype of rs763780 is also associated with susceptibility to syncope and tuberculosis in TA (Figure 2).(38, 39) The fact that IL12B variants associated with TA affect UBLCP1 mRNA expression and that UBLCP1 is a genetic factor that may increase the risk of psoriasis is an indication that functional similarities intersect at certain points.(40) What is noteworthy is that another type of large-vessel vasculitis, namely giant cell arteritis (GCA), that is not linked to MHC-I, but MHC-II exhibits a

pathologically identical granulomatosis vasculitis and also shares common IL-12B SNPs but has a different immunological profile as revealed by reverse translational immunology insights where TNF blockade was not effective in GCA (Table 3). (41, 42)

A Closer look at TA and IBD Overlaps-Shared Genetics

An overarching concept in SpA is the presence of either overt or covert intestinal inflammation, especially at the ileocecal region.(43) Evidence of clinical overlaps between TA and IBD has also accumulated but is less well explored than in SpA. In a study conducted in 470 TA patients, a UC prevalence of (6.4%) was observed. In this study, HLA–B*52.01 carrier rate was higher in TA patients with UC than in without UC.(44) In another study where 142 TA patients were examined in terms of IBD overlap, the IBD/TA concurrence rate was 9.2% and HLA-B*52.01 carriage was detected in all TA with UC patients and was significantly higher than TA without UC group ($p = 0.001$).(45)

Although the immunopathogenesis of IBD is heterogeneous there is evidence for MHC-I links in UC.(46) In a Japanese study, HLA B*5201 had a highly significant OR of 2.62(2.13−3.22) for UC compared to healthy controls. Also, this meta-analysis detected that HLA-B*52.01 is protective for CD.(46) In another small Japanese 45 UC patients cohort, HLA-B*52 was detected with a remarkable frequency of 62.2%.(47) Outside the MHC, a recent meta-analysis showed strong evidence that PLCG2 (rs79773175, rs7204834, rs12596533, rs146948024) and ZMIZ1(rs1250573, rs1892497, rs1250566) SNPs which were associated with IBD (UC and CD, respectively) may also be associated with TA further supports the complexity of the TA-IBD relationship.(27) Moreover, hierarchical clustering of TA with other immune-mediated diseases GWAS and self-reported disease traits in UK Biobank considered significantly different from control, demonstrated that TA clusters with IBD and SpA.(27) Besides, IL12B SNP rs6887695, which has been shown to be associated with TA, an association with susceptibility to IBD ($p=0.035$; OR 1.15 [95% CI 1.01–1.31] including a trend for rs6887695 for association with CD (OR 1.41; [0.99–1.31], $p=0.066$) and UC (OR 1.18 [0.97–1.43], $p=0.092$) has been reported.(48) The genetic overlaps between TA and IBD, frames the shared clinical manifestations of these diseases and fit with the wider link of subclinical intestinal inflammation in SpA. (Table 2).

The role of HLA-B*52:01 on TA disease severity.

The MHC-I associations in AS, uveitis and psoriasis are linked with disease onset at an earlier age and more severe or extensive involvement which points to the role of CD8 T-cells in magnifying immune responses in these entities.(4) Regarding of MHC class I, a high HLA-B*52 frequency was reported in UC in Japan.(49) In keeping with the MHC-I-opathy concept, where relevant class-1 genes are linked to earlier disease onset, TA also occurs at a younger age in HLA-B*52:01 positive subjects. (early vs late onset 24.2% vs 12%; $p=0.024$).(20) Japanese TA patients who were HLA*B52:01 positive are also more prone to hypertension, acute phase response and corticosteroid requirement in two studies as a severity marker.(50) In addition, aortic regurgitation was the most important cause of death in the Japanese TA patient group, where its relationship with HLA-B*52 was shown.(51)

From a different angle, in the series from Turkey where patients were subgrouped according to the angiographic subtype, it was demonstrated that only type 1 disease (branches from the aortic arch) according to the Hata's angiographic classification of TA(52) had a lower HLA-B*52:01 positivity where the vessel involvement is limited to the branches of the aorta, whereas HLA-B*52:01 was more frequently positive if the aorta is more extensively involved.(20) Another study also showed that HLA-B*52 allele carriage is associated with TA disease severity.(53) These data support that the disease tends to be more extensive and aggressive if the patient carries HLA-B*52:01 which akin to MHC-I-opathy incriminates T-cell responses driving earlier onset, more extensive and more severe pathology.

Pathology of TA from the MHC-I-opathy Perspective

The pathophysiological hallmark of the IL-23/17 axis MHC-1-opathy linked diseases is early neutrophilic inflammation.(54, 55) However, the pathological hallmark of TA is granulomatous infiltrates with multinucleated giant cells, T cell and histiocyte (tissue macrophages) accumulations in large arteries and of course such inflammation is strongly linked to IL-12, IFNγ and TNF (Figure 3). Compared to GCA, the CD4/CD8 ratio shifts towards CD8 in TA and CD4 in GCA that is in keeping with the fundamental MHC-I-opathy nature of TA versus the GCA MHC-II associations.(56) Conventionally CD4 T cells producing IFNγ or so-called **"Th1 cells"** were considered as driving granulomatous inflammation.(57) However, it is now well established that IFNγ producing CD8 cells are also equally capable of driving the same pathology.(58) In a study, CD8 T-lymphocytes were the main source of IFNγ, which is the key cytokine in granuloma formation in TA.(58) Generally speaking, IL-12 signalling drives IFNγ responses against intracellular pathogens whereas IL23/17 axis signalling drives immunity against extracellular pathogen such as fungi.(59)

Granulomatous arterial inflammation in the key feature of TA and such a pattern of intestinal transmural granulomatosis inflammation is also typical of CD. However, the pattern of mucosal inflammation of bowel in TA is more similar to UC than CD, together with some distinctive TA related findings (Figure 4). (45) The MHC-I-opathies are characterised by neutrophilic inflammation including hypopyon in the eye, Munro's abscess in the skin, sterile neutrophilic inflammation in the skeleton and also neutrophil rich crypt abscesses in UC and CD, in addition to granulomatosis inflammation in CD (Figure 3). (54) Immunogenetics studies and anti-IL-23 pathway antagonism incriminate the IL-23/17 axis in IBD and anti-TNF therapies and immunogenetics also incriminates TNF- the pivotal type 1 cytokine, that points towards involvement of both type 1 and IL-23 axis in the intestine.

Historically fungal immunity has been viewed as type 17 in nature. However, in mice with paracoccidioidomycosis, a chronic fungal mediated granulomatous disease, macrophage derived IL-6 and IL-23 positively regulated the expression of TNFα, IFNγ, and inducible nitric oxide synthase, promoting a Th17 immune profile that contributed to mature granuloma formation.(60) Accordingly, we would highlight potential Th1/Th17 plasticity in the TA intestinal environment that may be sculpted by the intestinal environment towards a non-granulomatous state.

Associations with Infectious Origins in the Concept of MHC-I-opathy

Infectious triggers, especially reactive arthritis, were integral features of the original SpA concept description. The potential role of tuberculosis, a granuloma triggering microbe, in the etiopathogenesis of TA has been well discussed.(61) Purified protein derivative (PPD) intradermal reaction was positive at a higher rate in patients with TA than in those without. Even further, PPD with induration over 10 mm might be as frequent (92.5% versus 89%) in TA as in patients with extra-pulmonary tuberculosis. In contrast, conflicting results were obtained between TA and healthy controls in the frequency of latent tuberculosis detected by QuantiFERON-TB Gold test positivity.(62, 63) Also in Japan, one of the countries where TA is common, TB incidence and mortality are higher in men than in women. However, a higher rate of latent TB was commoner in women, may also suggest that the manifestations of TB exposure may depend on some gender-related genetic/inflammatory factors.(64) Given the link between both TA and TB with granulomatosis inflammation, an immune hypersensitivity reaction to TB in females would represent a simple concept for the link between infection and TA.

A role for microbiota in the pathogenesis of AS is well supported by a wide array of self- and cross-reactive microbial peptides capable of engagement of clonally expanded BV9–CDR3β TCRs.(65) Additionally, case reports of deletion of TCR BV9 T-cells and good responses in AS support the MHC-I-opathy concept in AS.(8) These findings in AS underpin the realisation that robust immunity to infection requires widely cross-reactive T-cells where one T-cell can react with up to a million different MHC-associated peptides.(66) Additional factors including the inflammatory milieu including TLR pathway activation on DCs could also be major determinants in driving T-cell activation where low level antigen presentation is taking place. (67)

Secondary Humoral Autoimmune Responses in TA and SpA

What about the role of humoral autoimmunity driving the pathology of TA and SpA as an alternative or related scenario since autoimmune mechanisms have been reported in SpA and TA? In TA, autoantibodies against endothelial protein C receptor (EPCR) and scavenger receptor class B type 1 (SR-BI), another endothelial autoantigen, were reported. In 52 TA patients, the positivity rates for anti-EPCR and anti-SR-BI Abs were 34.6% and 36.5%, respectively. Additionally, anti-EPCR and anti-SR-BI Abs were detected at higher rates in TA patients complicated with UC. However, evidence that γδ T cells can recognize EPCRs of CMV-infected endothelial cells can be attributed to the fact that the main reason underlying the formation of EPCR-targeted secondary autoantibodies may be increased EPCR recognition of the cellular components of the immune system, which also represents the pathogenesis of TA.(68) Similarly, antiphospholipid antibodies have been reported in TA patients.(69) However, such autoimmunity may be secondary to tissue damage akin to ANCA and ASCA in IBD being linked to severity of gut inflammation rather than an IBD driver.(70)

Additionally, TA patients developed a humoral immune response against both human 60 kDa HSP (84% versus 22%, $p < 0.001$) and mycobacterial 65 kDa HSP (92% versus 11%, $p < 0.0001$) compared to the

healthy control group. Also, a strongly positive correlation between anti-human 60 kDa HSP IgG and anti-mycobacterial 65 kDa HSP IgG antibodies was found in TA patients.(71) In another study, serum HSP 65kDA antibodies were higher in patients with active arteritis compared to inactive arteritis.(72) Conceivably, this autoantibody formation may also be attributed to increased exposure due to vascular damage.(73)

Therapy Implications for TA

Therapies not only treat patients but dissect human immune disease mechanism. Some MHC-I-opathies may respond to both T cell directed therapies and to anti-cytokine approaches reflecting the impression that adaptive CD8 T-cell response exaggerates cytokine mediated inflammatory reactions at specific sites of barrier or biophysical stress. In that vein, therapies that work in part or predominantly via T-cell antagonisms have been used in TA, including methotrexate (MTX), azathioprine (AZA), cyclophosphamide (CYC), cyclosporine A (CSA), leflunomide (LEF) and mycophenolate mofetil (MMF) with a randomized, placebo-controlled trial with LEF currently ongoing.(74, 75) Within biologic therapies, anti-TNF agents, that are very effective across the SpA spectrum, were first tried in TA in 2004.(76) The last meta-analysis published about biologic agents in TA presented that the remission rates and relapse rates were: 0.65 (95% CI: 0.56-0.73; I2=49%) and 0.28 (95% CI: 0.16-0.40; I2=68%) for anti-TNF agents.(77)

In contrast to TA, the TNF agents were not efficacious in GCA with two negative phase 3 trials which is somewhat paradoxical given the IL-12B SNPs shared between GCA and TA that points towards type 1 immune responses.(42, 78) The efficacy of tocilizumab was demonstrated in RCTs in GCA.(79, 80) This apparent difference in responses to anti-TNFα treatment between GCA and TA provides reverse translational immunology support for the type 1 MHC-I-opathy for TA. Also, the value of TNF antagonism in the IL-23/17 axis SpA spectrum disorders links Th1 and Th17 plasticity in pathogenesis. This may partially underpin the positive effects of TNF blockade in SpA and psoriasis. (Figure 3)

With respect to IL-6 antagonism, a randomised-controlled study of tocilizumab in TA (TAKT study) failed to meet its primary end-point on an intention-to-treat analysis (hazard ratio 0.41, 95%CI 0.15-1.10) but successfully met the secondary end-point of superiority on per-protocol analysis (hazard ratio 0.34, 95%CI 0.11-1.00).(81) Positive clinical and imaging results along with significant reductions in daily glucocorticoid doses in 28 patients who received tocilizumab for 96 weeks in the open-label extension period of 36 patients enrolled in the double-blind period of the TAKT study, exhibited that tocilizumab may be an important option in the long term follow-up period.(82) In a multi-center retrospective study comparing subcutaneous and intravenous forms of tocilizumab, tocilizumab achieved complete remission at 6 months in 70% of patients with TA refractory to disease-modifying anti-rheumatic drugs.(83) There are no head-to-head randomized controlled trials between anti-TNFα agents and tocilizumab, but a meta-analysis of studies in the literature detected similar rates of clinical remission [risk ratio (RR) tocilizumab vs anti-TNFα agents 1.03, 95%CI 0.91-1.17)], angiographic stabilization (RR 1.00, 95%CI 0.72-1.40) or adverse events (RR 0.84, 95%CI 0.54-1.31) with either tocilizumab or

anti-TNFα agents.(84) Beyond therapeutic antagonism of IL-6, GWAS studies revealed an IL6 SNP (rs2069837) (odds ratio [OR] 2.07, P = 6.70 × 10(-9)) as an important non-HLA locus in the pathogenesis of TA.(85) IL-6 has been shown in biopsy specimens of the aorta with TA and correlated with disease activity.(86) Whilst IL-6 pathway SNPs are linked to AS, it is noteworthy that anti IL-6 therapy is not efficacious.(87, 88)

There are strong evidence points that IL-6 is indispensable for the lineage specification of Th17 cells via STAT3. In addition to IL-23, IL-6 is also essential for the maintenance of Th17 cells with highly plasticity characteristics (Figure 5).(89)Additionally, increased production of IFNγ induced neutrophil IL-6 secretion.(90) Given the IL-12B SNP and granulomata in GCA underpins type 1 immunity in GCA also but further studies are needed to confirm the efficacy of IL-17 blockade in both GCA and TA.(41) Both, IL-12/IFNγ and the role of IL-6 on IL-17 induction in GCA has been proposed.(91) As discussed earlier, IL-6 has a role in experimental fungal granulomatosis inflammation and further studies are needed in human TA to evaluate impact of its blockade.

Based on IL-12B as a susceptibility gene for TA, case reports of ustekinumab (a monoclonal antibody against IL-12/23p40, the IL12B protein product) efficacy in patients with TA are not surprising.(92) Whether this is an effect on IL-12, or IL-23 or both awaits clarification as IL-12B is shared between these type 1 and type 17 pathways. Additionally, in an open-label study comparing secukinumab with TNFα inhibitor in TA, both therapies showed similar effectiveness however randomized controlled double-blind studies with a larger number of patients are needed.(93)

JAK inhibition can directly antagonise some of the key cytokines proposed in our TA model including IL-12, IL-23 and IFNγ in addition to T-cell functional antagonism. Ruxolitinib which selectively inhibits JAK1 and JAK2 in vitro reduced global T cells activation, Th1/Th17 polarisation and promote increase of Tregs in TA.(94) In the same study, a good clinical response was obtained in three TA patients with JAK inhibitors.(94) In a recently published 10-patient case series, a significant decrease in disease activity and glucocorticoid requirement was detected in TA patients treated with Tofacitinib.(95) A randomized, double-blind, controlled trial with upadacitinib is also under way.

A Model for TA

Based on a synthesis of the available data, we propose a model for TA as a type 1 MHC-I-opathy in contra distinction to a type 17 MHC-I-opathy. This has immunotherapeutic applications and suggests that IFNγ blocking directly or its indirect blockade via JAK1/2 pathway inhibition could be an effective strategy for TA. Given the plasticity of T-cell responses in vivo, this model also accounts for overlapping features of TA and SpA that could simply represent different degrees of type 1 and type 17 immunity in different target organs (Figure 5). Although we suggest *type 1 MHC-I-opathy* for the TA classification, it is recognised that T-cell polyfunctionality and plasticity in SpA spectrum disease is also linked to aberrant TNF production.

The shared target tissue and granulomatosis inflammation shared by TA and GCA and the differing role of TNFα inhibition in both permits a reappraisal of immunopathology, especially if more confirmatory trials emerge (Table 3). IL-12/IFNγ pathway which is inducing the granuloma formation, was suggested to be leading the resistant and chronic disease along with the evidence of Th1 derived cytokines especially IFNγ in the post-treatment specimens of animal models.(96) Given the uniqueness of human TA, then ultimately reverse translational immunology insights from clinical trials will elucidate the field and will show whether TNFα inhibition is superior to IL-6 pathway inhibition. Given the type 1 MHC-I-opathy concept then monotherapy antagonisms of IFNγ would appear to be a promising option just as IL-23/17 axis antagonism has proven so successful in some MHC-I-opathy related diseases. To summarise, further trials are needed to fully decipher the role of cytokine blockade and relevant pathways in TA vs GCA.

Conclusions

In this perspective, we make the case that TA fits into the MHC-I-opathy spectrum of disorders but represents a novel "type I MHC-I-opathy" disorder. Thus, AS and psoriasis form more of a type 17-MHC-I-opathy class whilst TA has more IL12-driven pathogenic mechanisms and can be categorized more as a type I MHC-I-opathy. (Figure 2). We describe how overlapping clinical phenotypes could be related to convergent IL-12 and IL-23 pathway immunology that is influenced by the different TA target tissues and microbiota ecology, for example in the gut and the skin. We recognise that less than 50% of TA cases express HLA-B52 and that other class-1 antigens may be involved, so it is acknowledged that the disease is potentially heterogeneous, and that a "one size fits all" model may not cover the entire disease spectrum.

Given the uniqueness of human TA, then ultimately reverse translational immunology insights from clinical trials will elucidate the field and will show whether TNFα inhibition is superior to IL-6 pathway and the potential role of IFNγ antagonism. Also, the MHC-I-opathies are linked to subclinical intestinal inflammation as major drivers; this has been overlooked in TA to date. The emerging insights from type 17 MHC-I-opathies points towards an antigenic basis for MHC-I antigen presentation and activation of CD8 T-cells in psoriasis, uveitis and AS. This suggests that direct targeting of clonally expanded T-cells could be pursued in TA, towards novel therapy strategies. Overall, TA is geographically distant from the original SpA disease concepts but is in fact closely linked from the immunological perspective and a "half-sister" of the MHC-1-opathy diseases linked to the IL-23/17 axis.

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01.10.2024

Dr Anna Clark
Editor
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Dear Anna,

Re: TLRHEU-D-24-00175 entitled "Takayasu Arteritis –A Geographically Distant but Immunologically Proximal MHC-I-Opathy"

Thanks for considering our paper and we are really pleased with the process. Please find below our detailed responses to the comments. We hope the manuscript will now be suitable for publication.

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Dennis

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1. Please supply a section entitled "Search strategy and selection criteria". This should state clearly the sources (databases, journals, or book reference lists, etc) of the material covered and the criteria used to include or exclude studies. Please state which search terms, languages and date ranges were used.

Author's response: We have already a section entitled "Search strategy and selection criteria"

1. If your paper is a systematic review, please check our Systematic reviews and meta-analyses formatting guidelines here to ensure that your paper is formatted correctly. Please note that you will need to provide a PRISMA flowchart if so.

Author's response: Our paper is not a systemic review.

1. *The Lancet Rheumatology* endorses the SAGER guidelines for reporting of sex and gender information in study design, data analyses, results and interpretation of findings: https://www.equator-network.org/reporting-guidelines/sager-guidelines/. For all study types, we encourage correct use of the terms sex (when reporting biological factors) and gender (when reporting identity, psychosocial, or cultural factors). Where possible, please report the sex and/or gender of study participants, and describe the methods used to determine sex and gender. Separate reporting of data by demographic variables, such as age and sex, facilitates pooling of data for subgroups across studies and should be routine, unless

inappropriate. Please also discuss the influence or association of variables, such as sex and/or gender, on your findings, where appropriate, and the limitations of the data.

Author's response: This is not a clinical study, so we did not use such terminology.

1. When discussing findings in relation to race or ethnicity, please mention how the original data defined these categories. Race and ethnicity are sociocultural constructs, not biologic traits. Thus we ask that, instead of making race-based statements about disease ("disease X is more common in Y race"), you could instead mention the original observations (eg "disease X has been observed to be more common in Y race") and the limitations of the original data eg possible role of unmeasured socioeconomic confounders, wider structural drivers for which race or ethnicity may be surrogate measures. Consider a strengths-based approach to writing rather than a deficit discourse eg how findings might promote health and wellbeing, instead of focusing on problems (https://www.lowitja.org.au/wp-content/uploads/2023/05/deficit-discourse-strengths-based.pdf).

Author's response: This is not a clinical study, so we did not use such terminology.

1. Please supply tables as separate Word files (not excel or fdf/pdf). Each row of data should be in a separate line. Please ensure that rows and columns are not tabbed; data should be entered in cell form.

Author's response: We supplied tables as separate Word files.

1. Please supply the web appendix as a single PDF file, with the pages paginated - when you refer to an item in the appendix, please refer to the page number on which it appears, not the table or section. Please note that we will be unable to correct any errors in the web appendix, including errors or omissions in author names or affiliations, following publication; as such, please check carefully when submitting.

Author's response: We don't have any web appendix.

1. Please ensure ICMJE and author statement forms have been submitted for all authors.

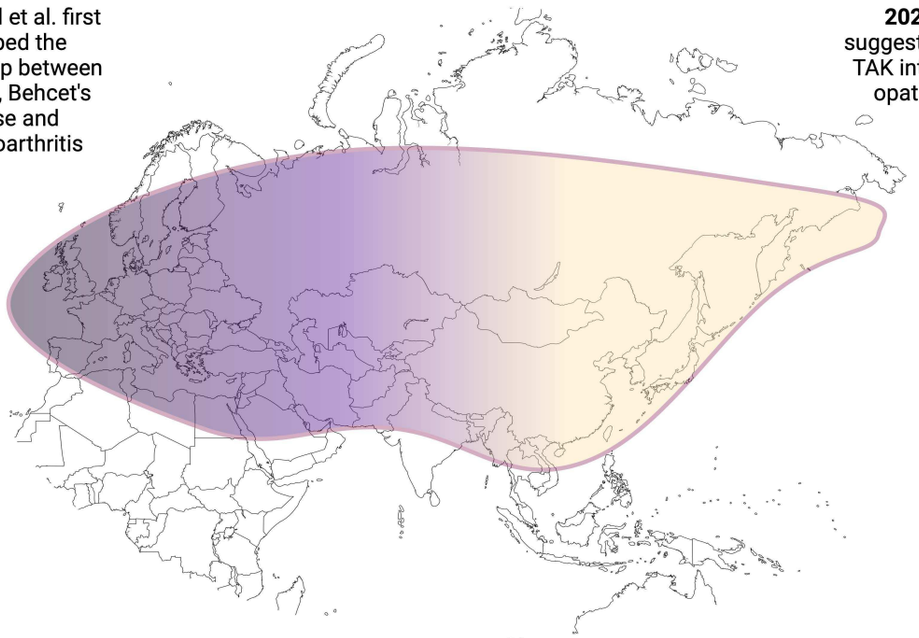
Author's response: We have submitted these forms.

Figure 1 pdf

1974: Moll et al. first described the relationship between psoriasis, Behcet's disease and spondyloarthritis

2024: We are suggesting to include TAK into the MHC-I-opathy consept

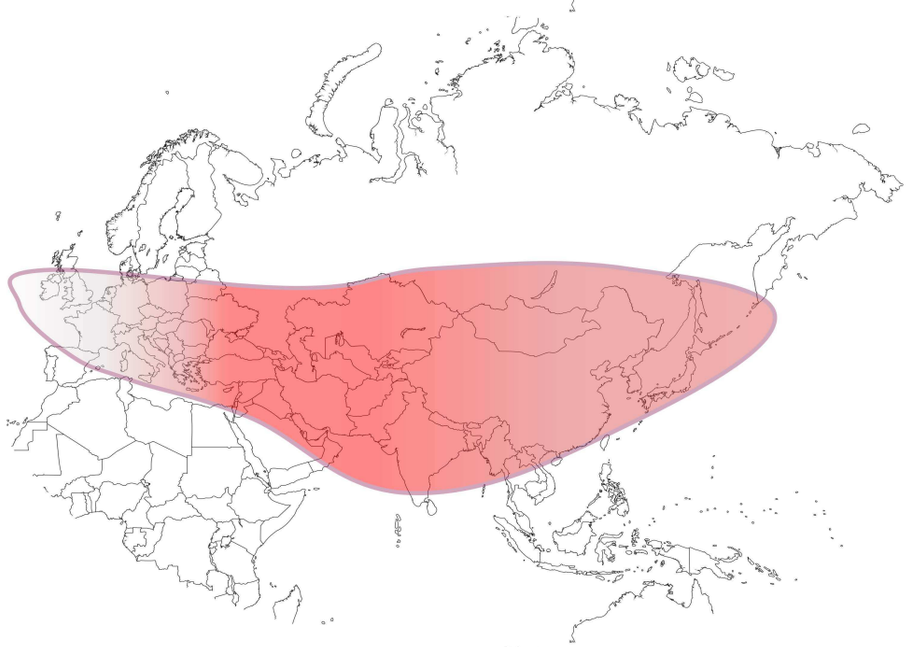
A



Spondyloarthritis
(HLA-B*27, ERAP1, IL23R...)

- **Axial disease**
- Enthesitis (13-60%)
- Aculte anterior uveitis (40%)
- Inflammatory bowel disease (6-14%)
- Psoriasis (3.1-18.9%)
- Aortic root involvement (14-18%)

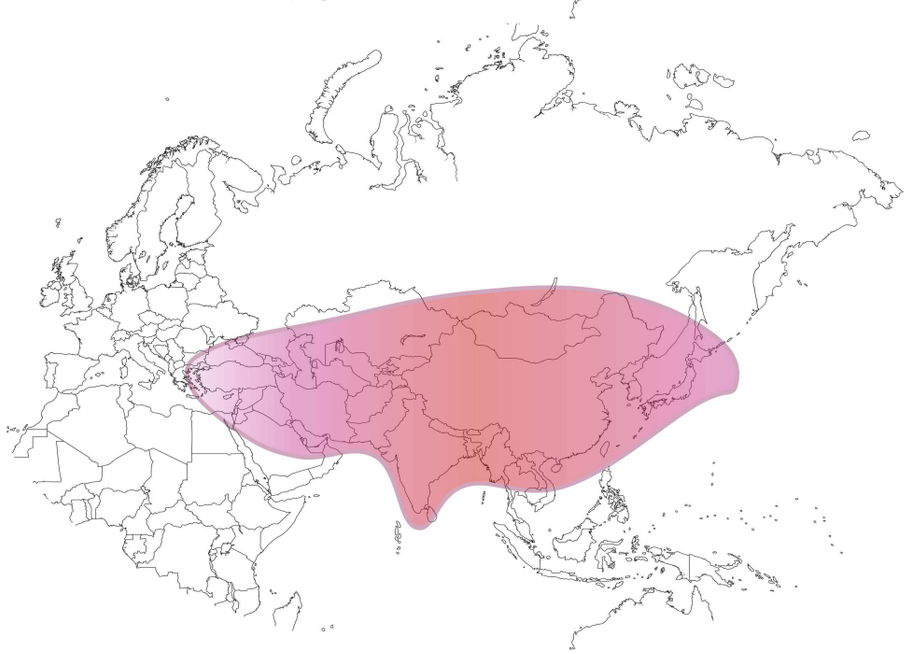
B



Behcet's disease
(HLA-B*51, ERAP1, IL23R, IL12B...)

- **Oral aphtous stomatitis**
- Erythema nodosum-like lesions (15-78%)
- Uveitis (40%)
- Venous vascular involvement (20%)
- Aortic involvement (1.5%)
- Intestinal Behcet (2.8-50%)

C



Takayasu arteritis
(HLA-B*52, IL12B...)

- **Aorta and major branches involvement**
- Inflammatıry bowel disease (2.6-9.2%)
- Erythema nodosum (6%)

IL-23/17
TNFα/IL-1
(Spondyloarthritis)

IL-12/IFNɣ
TNFα/IL-6
(Takayasu arteritis)

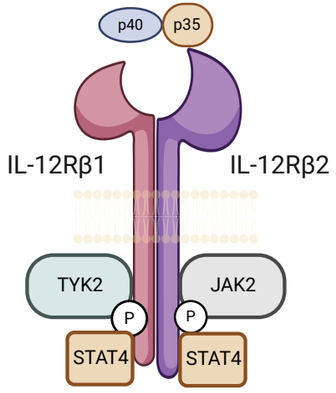
Figure 2 pdf

Autoimmunity

Takayasu Arteritis
- *IL12B*: rs56167332, rs6871626, rs4379175

MHC-I-opathies and IBD
- *IL12B* rs17860508, carriage of rs3212227 C allele in AS
- *IL12B* SNP rs6887695 in IBD (CD and UC)
- *IL12B* rs3212227, rs6887695 in psoriasis
- IL12A rs17810546 in BD

IL-12



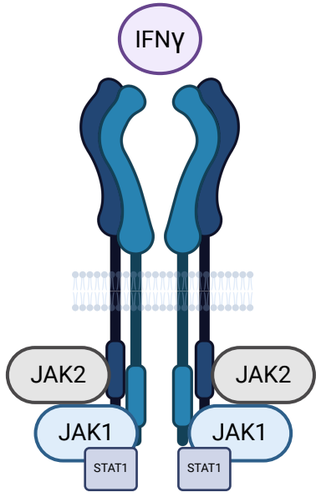
Immunodeficiency

Chronic Mucocutaneus Candidiasis
- IL-12 p40 deficiency
- IL-12Rβ1 deficiency
- TYK2 deficiency

Mycobacterial Infection
- IL-12 p40 deficiency
- IL-12Rβ1 deficiency
- TYK2 deficiency

IFNγ

MHC-I-opathies
- *IFNGR1* rs4896243 in BD



Immunodeficiency

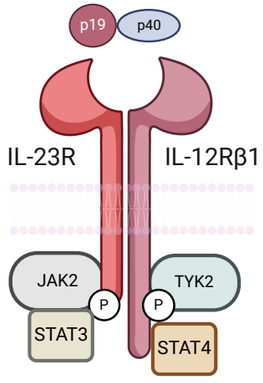
Mycobacterial Infection
- *IFNGR1* gene SNPs: rs2234711, rs1327474, and rs7749390
- *IFNG* rs1861494 tuberculosis resistance

Chronic Mucocutaneus Candidiasis
- GOF in STAT1

Autoimmunity

MHC-I-opathies and IBD
- IL23R rs11209026, rs11209032 in AS
- IL23R rs1004819: increases risk, rs7517847: decreases risk in CD
- IL23R rs7517847, rs1004819, rs10889677, rs2201841, rs11209032, rs1495965, rs1343151 and rs11465804 association with UC
- *IL23R* rs7530511, rs11209026 in psoriasis
- *IL23R*,*IL12RB2* rs1495965, rs924080 in BD
- STAT4 rs7574070, rs897200 in BD
- STAT3 activated in CD, psoriasis
- STAT4 activated in CD

IL-23



Immunodeficiency

Chronic Mucocutaneus Candidiasis
- IL-12 p40 deficiency
- IL-12Rβ1 deficiency
- TYK2 deficiency
- Dominant-negative mutations in STAT3 in HIES

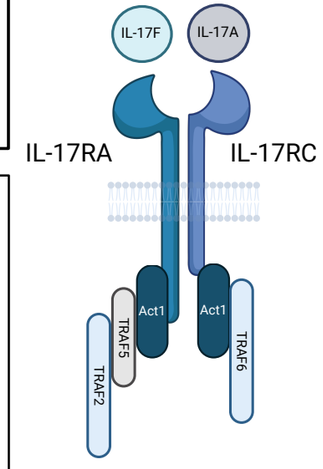
Mycobacterial Infection
- IL-12 p40 deficiency
- IL-12Rβ1 deficiency
- TYK2 deficiency
- IL-23R rs11209026, rs7518660, rs11465802 (drug resistance)
- Dominant-negative mutations in STAT3 in HIES

Autoimmunity

Takayasu Arteritis
- G allele of rs763780 in *IL17F*: protectively associated against susceptibility to TA
- *IL17F* re763780 AG phenotype: susceptibility to syncope and tuberculosis in TA

MHC-I-opathies
- *IL17RC* rs708567 AA: early onset of AS
- *IL17F* rs763780 G: high disease activity in AS
- *IL17RA* rs4819554 G: high disease activity in AS
- The TT genotype and T allele of *IL17A* rs10484879 and TC and TT genotypes of *IL17F* rs763780: associated with increased risk of psoriasis
- *TRAF3IP2* rs33980500 in psoriasis

IL-17



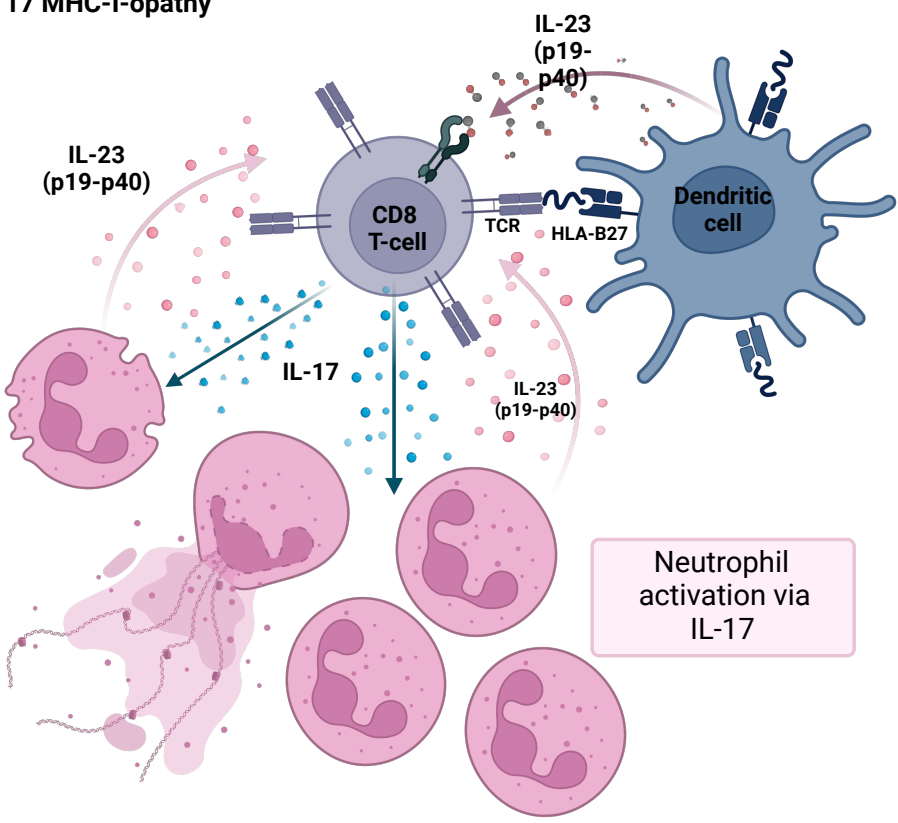
Immunodeficiency

Chronic Mucocutaneus Candidiasis
- IL-17A/F deficiency
- ACT1 deficiency
- Homozygous mutation in *IL17RA*, c.1696insAG: loss of IL-17RA expression

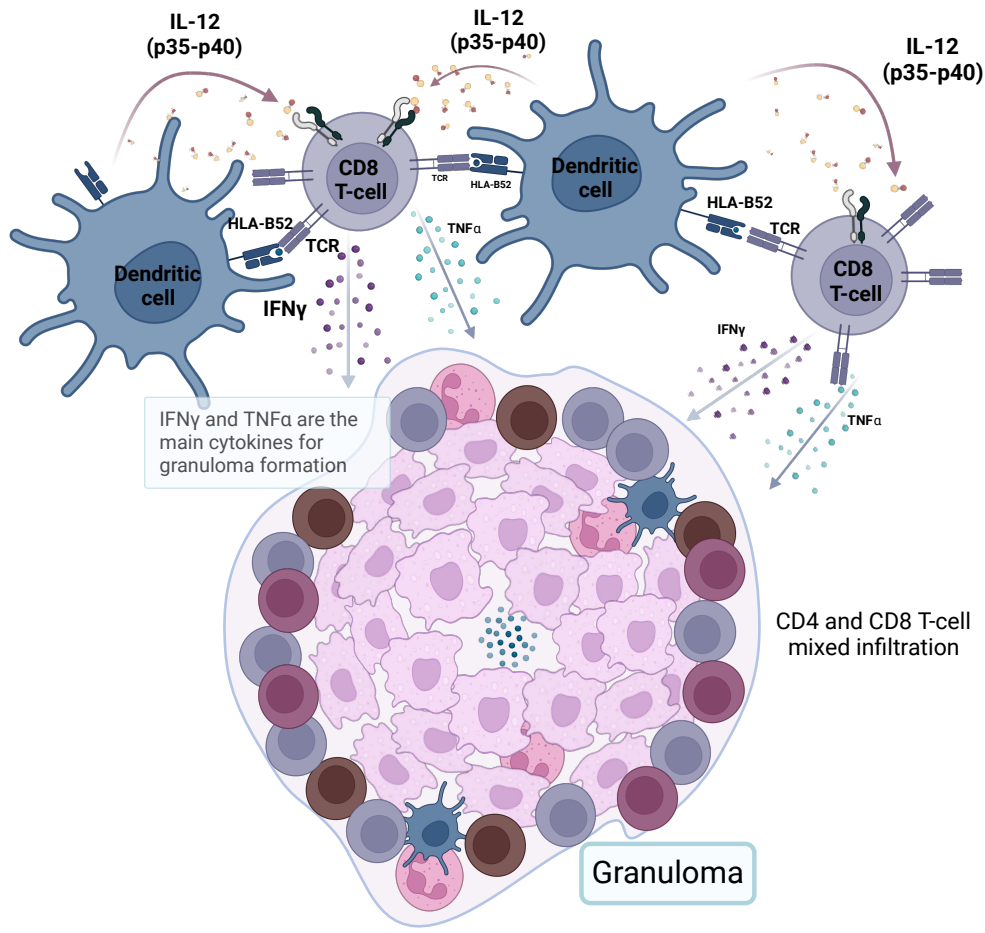
Mycobacterial Infection
- rs763780 in *IL17F*

Figure 3 pdf

A Type 17 MHC-I-opathy



B Type 1 MHC-I-opathy



C Giant cell arteritis

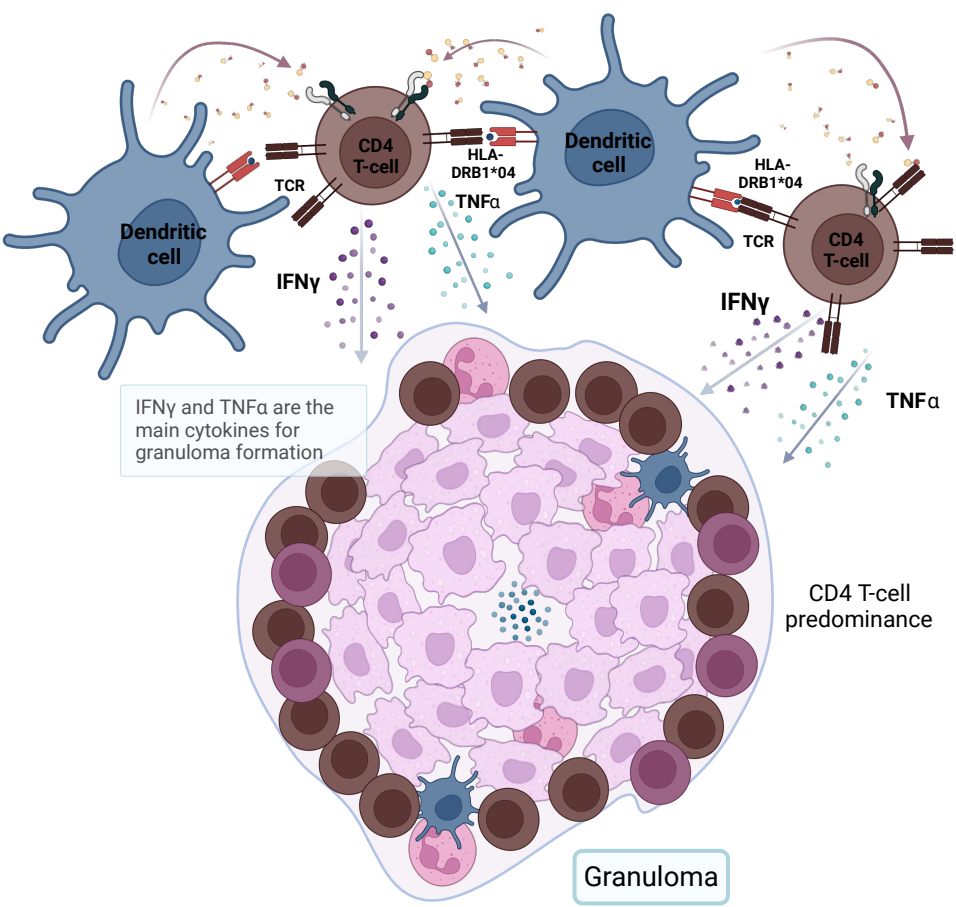
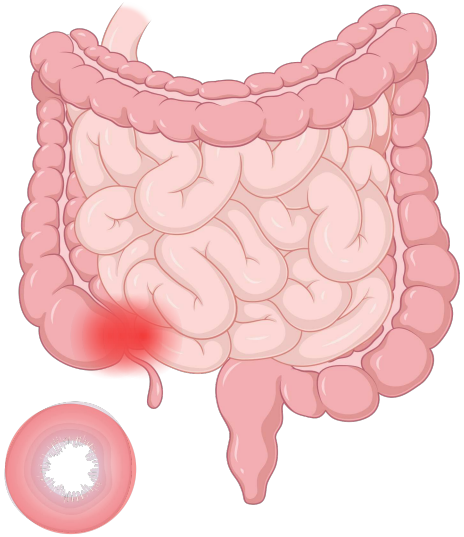


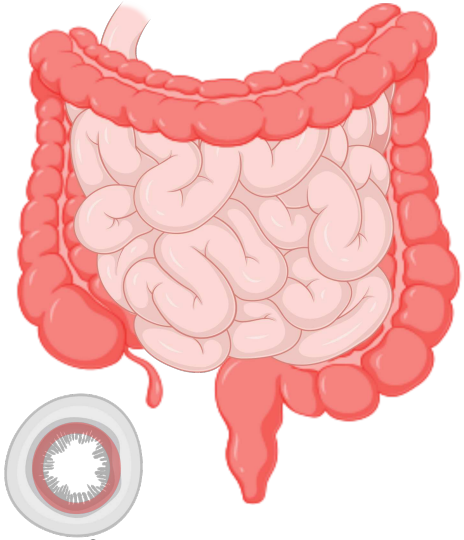
Figure 4 pdf

A-SpA pattern (Crohn's disease like ileocecal involvemet)



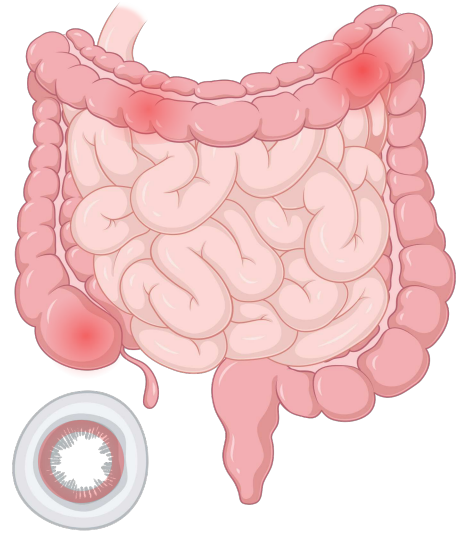
Transmural inflammation

B-Ulcerative colitis



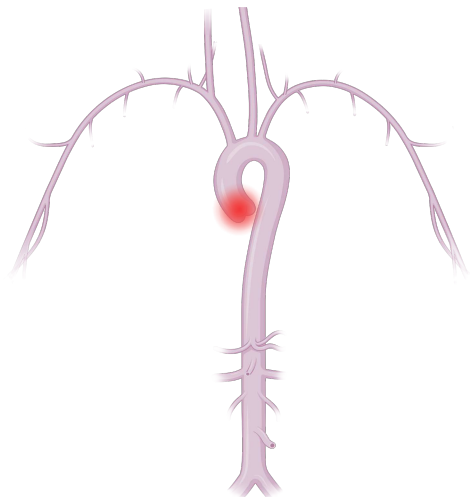
Superficial inflammation

C-Takayasu Arteritis associated colonic inflammation



Superficial inflammation

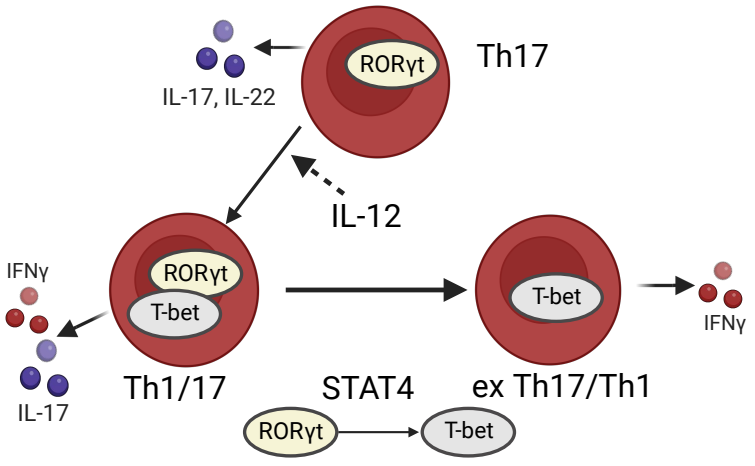
D-Aortic involvement in SpA



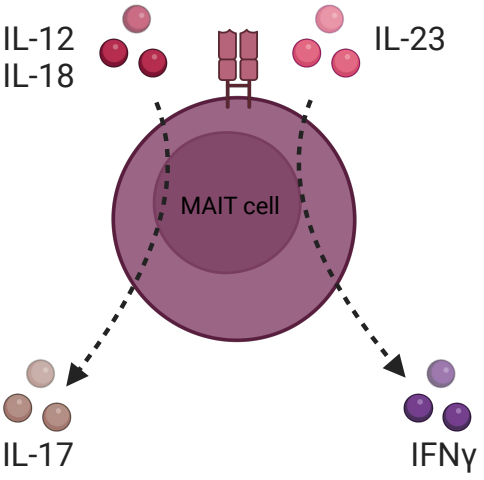
E-Takayasu Arteritis

Figure 5 pdf

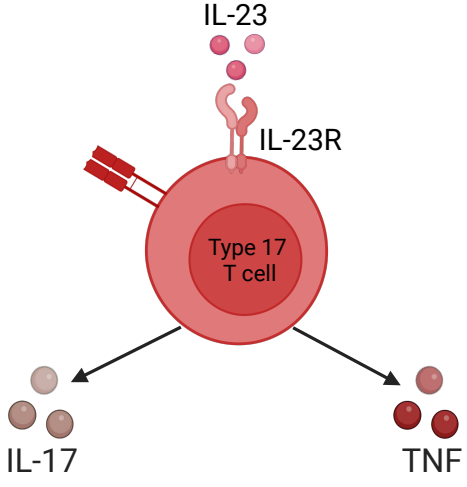
A-From Th17 to Th1 transition



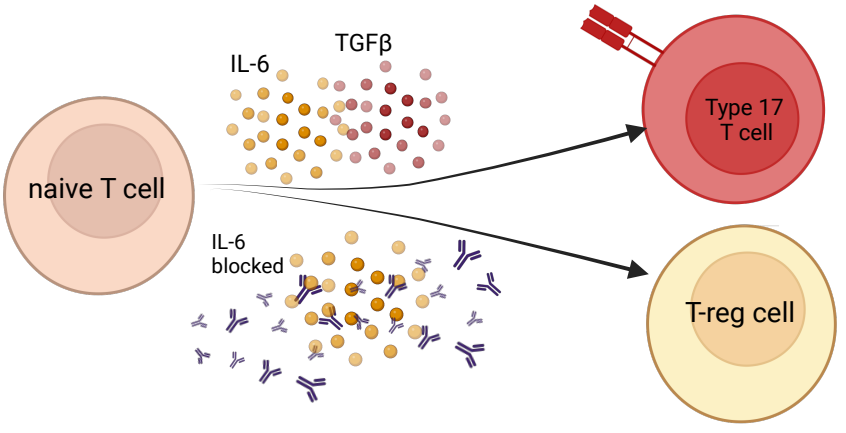
B- MAIT cell



C-Type 17 T cell



D-IL-6 and type 17 inflammation



E-Erythema nodosum

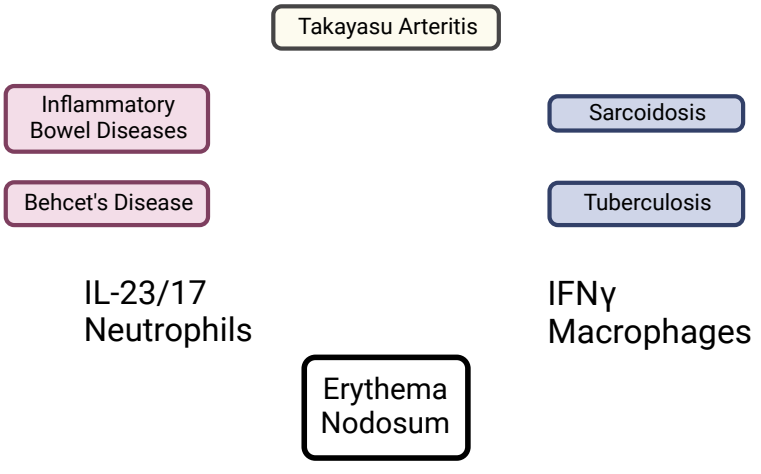


Figure 1 tiff

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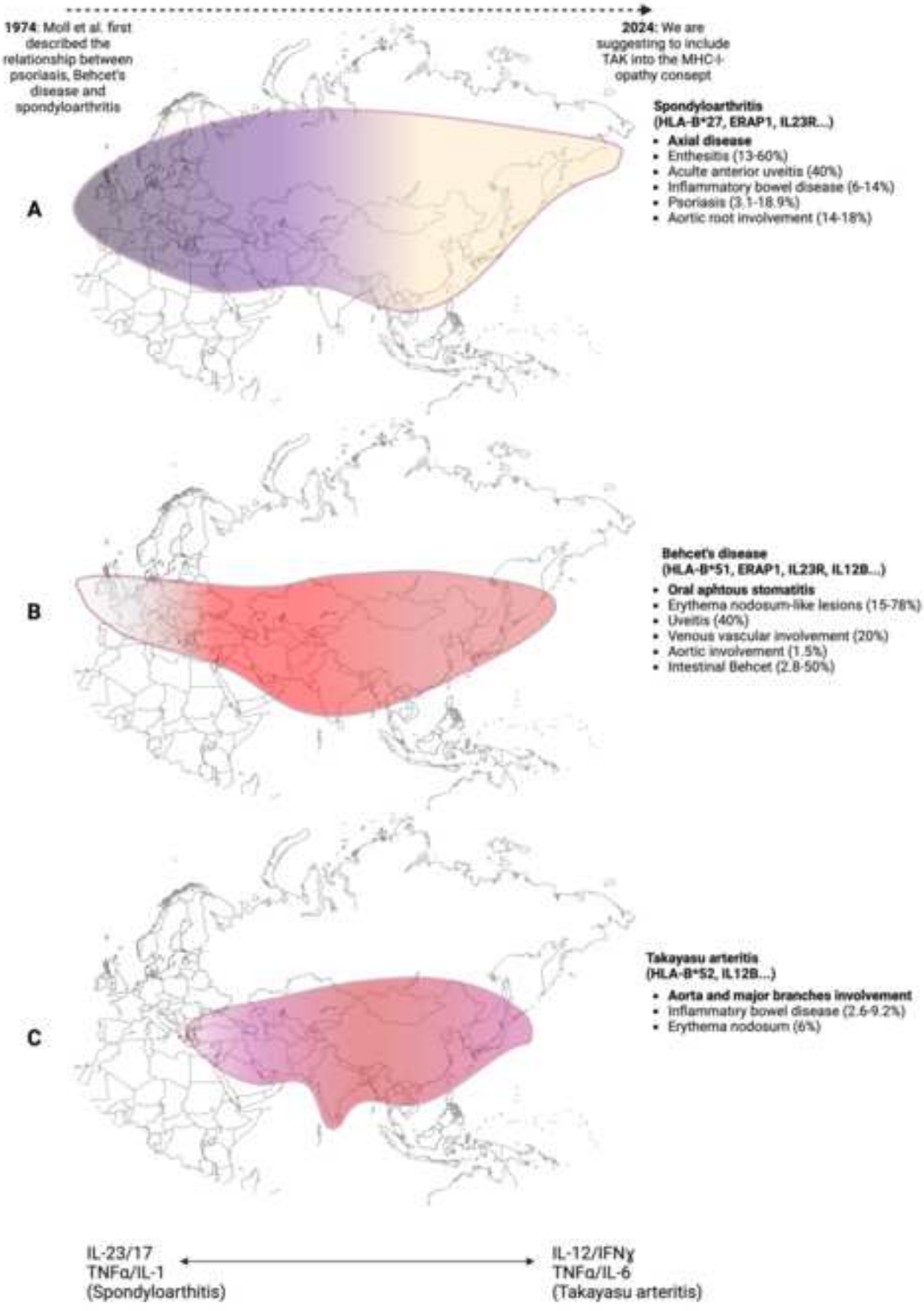

Figure 2 tiff

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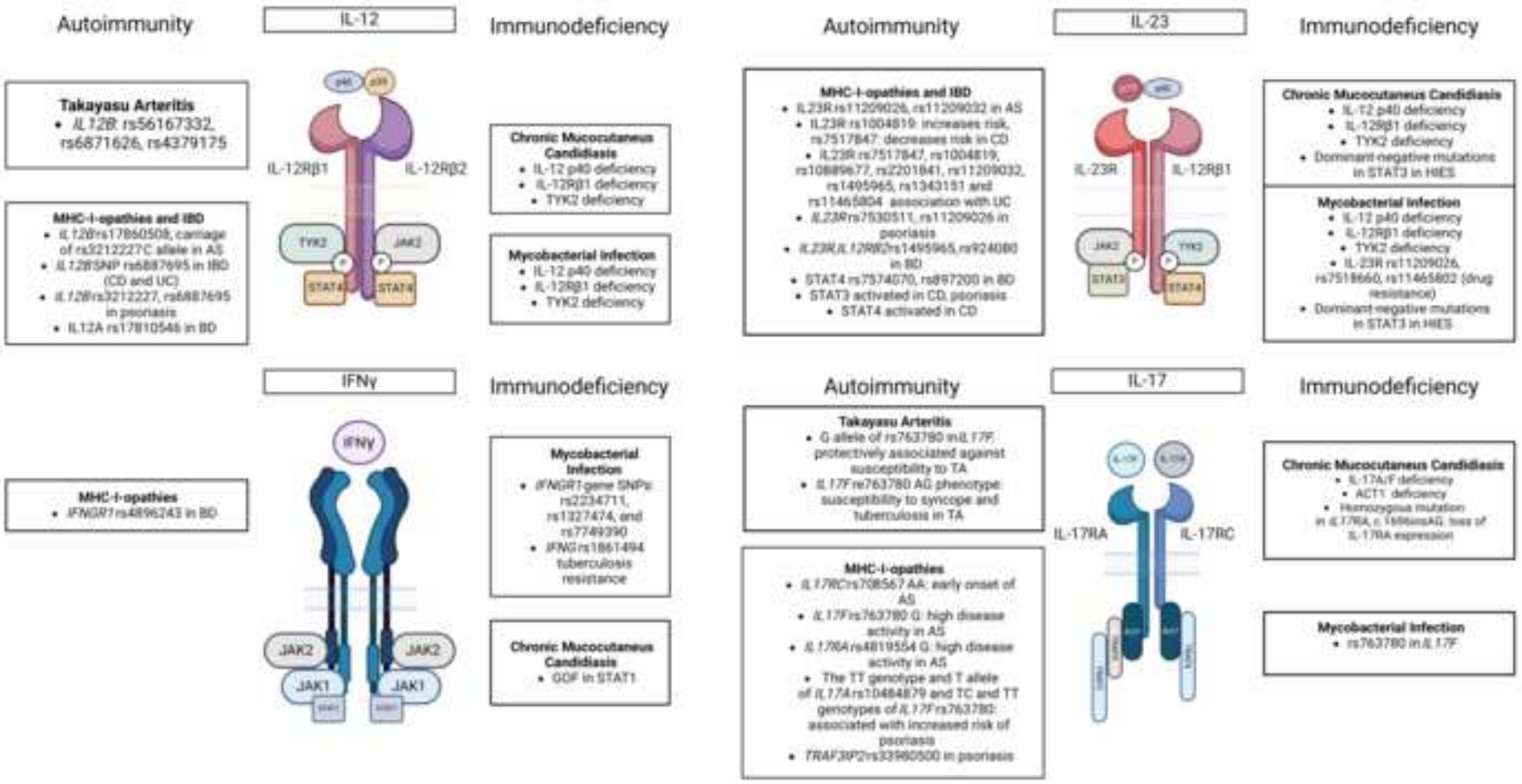

Figure 3 tiff

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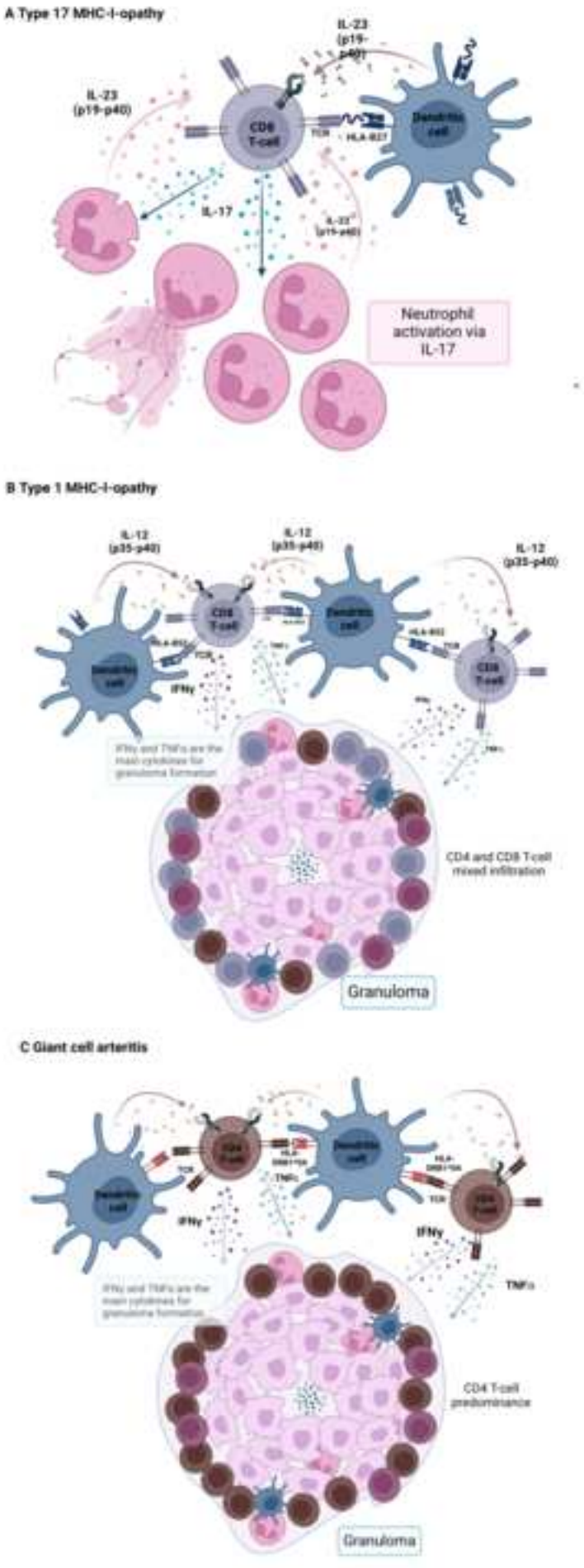

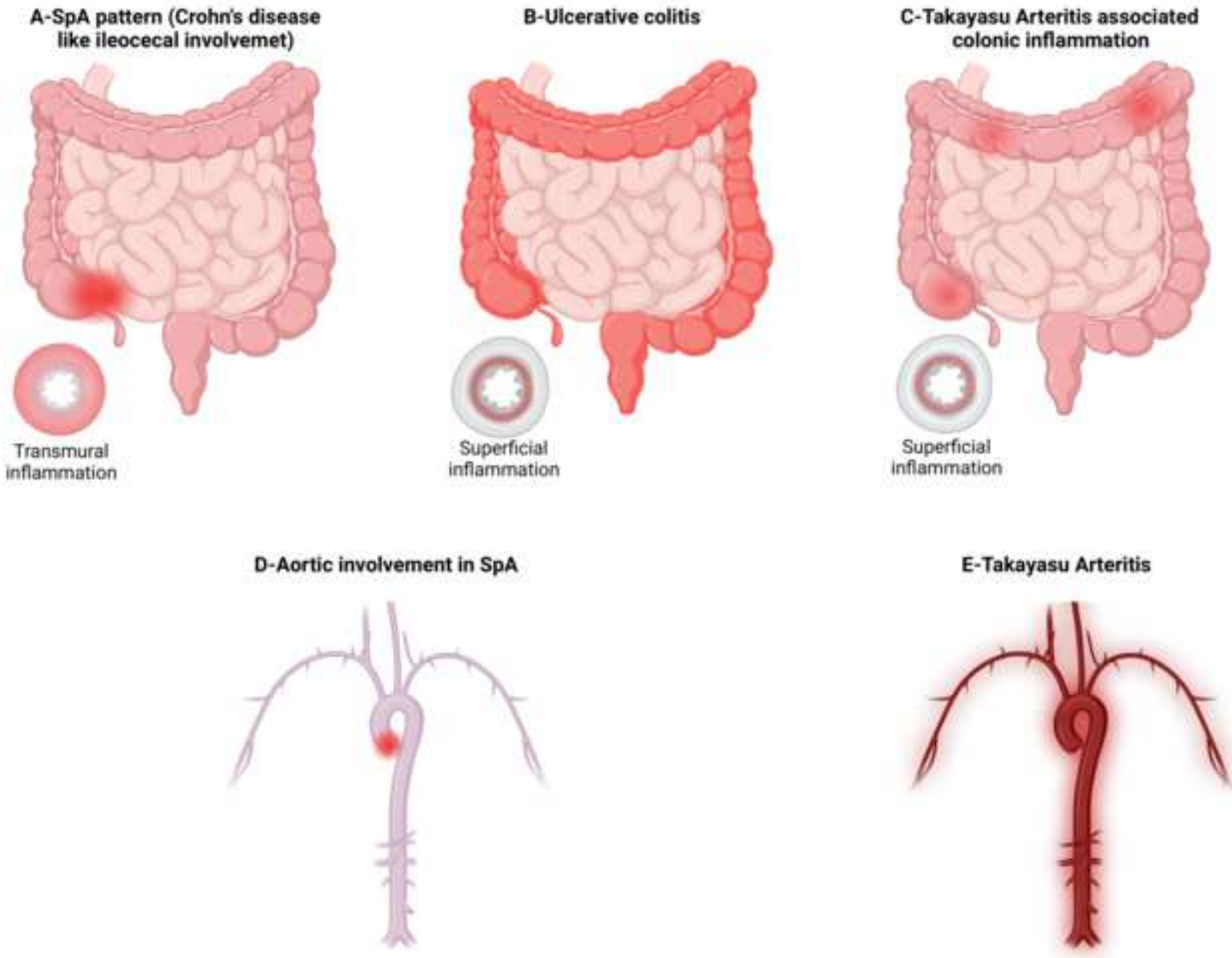

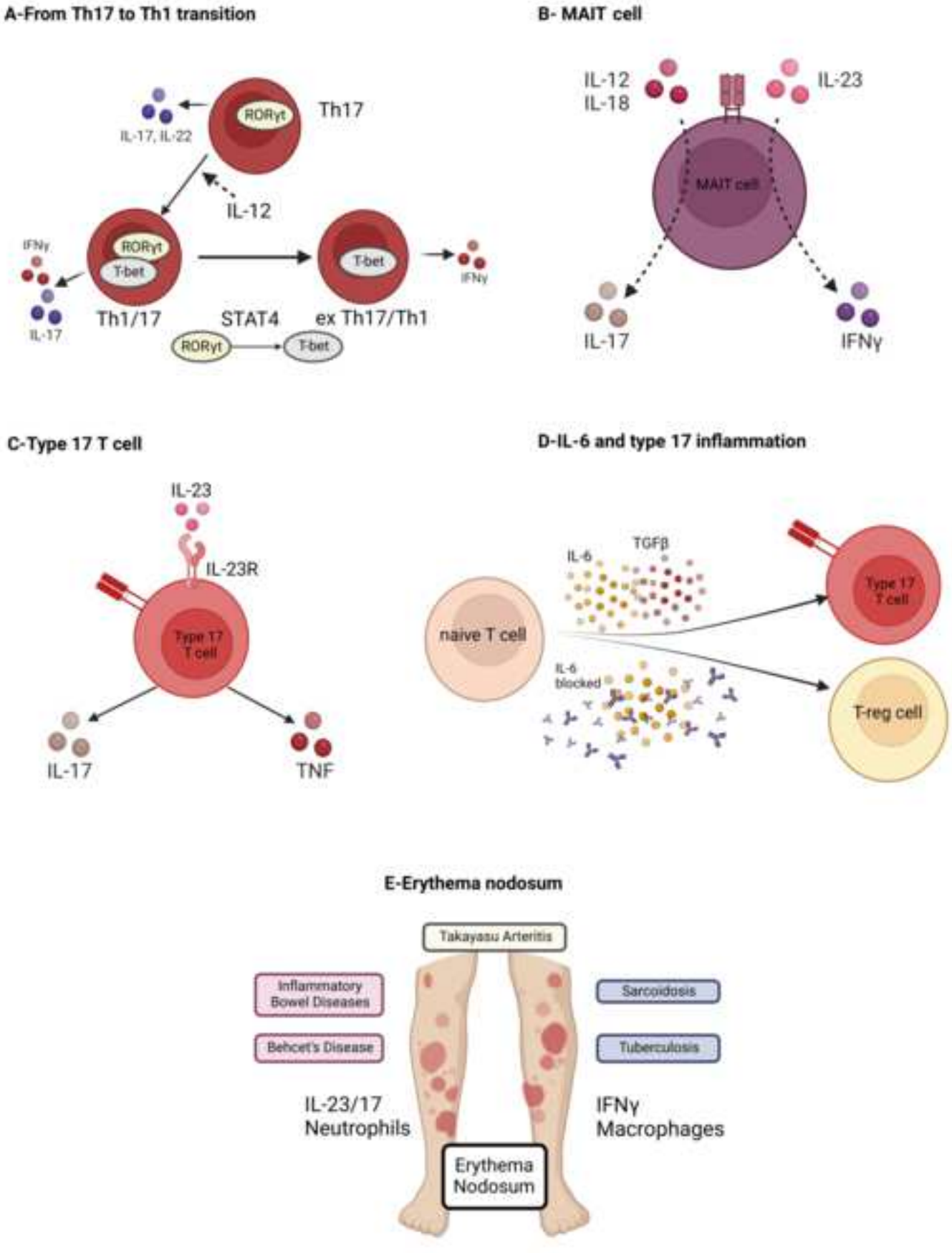

Table

Table 1. Phenotypic comparison between Type 1 and Type 17 MHC-I-opathies.

	Type 1 MHC-I-opathy	Takayasu Arteritis- Type 17 MHC-I-opathy
Age	Generally younger	Generally younger
Sex	No female predominance	Female predominance
Disease Course	Waxing and waning	Both waxing and waning and progressive
Ocular Involvement	Uveitis	Retinopathy (usually hypertensive) in 10-35% patients
Mechanical Stress	Koebner, Oral ulcers, Enthesitis	Shear stress (mainly aorta)
Barrier Perturbances	Skin, mouth, gut	Link to gut barrier disturbance
Underpinning Immunology Theory	Danger theory as driver	Authors impression is of mechanism similar to MHC-I-opathy
Skin involvement	Psoriasis, mucosal ulcers, erythema nodosum	Erythema nodosum
Joint Disease	Site of entheseal stress and lower limbs	Arthralgia (39%), arthritis (7.7%- mainly in large joints of the lower extremities resembling SpA disease spectrum)
Gut involvement	Clinical or subclinical gut disease common	Subclinical gut involvement
Gut Involvement Type	Inflammatory Bowel Disease	Patchy/mucosal
Large Vessel Involvement	Aortic root involvement (SpA), Arterial aneurisms including aorta (Behcet's disease)	Stenosis and/or aneurism of aorta and main branches
Therapy	IL-17, IL-23, TNFα and JAK targeted therapies	TNFα and IL-6 targeted therapies

(MHC: Major Histocompatibility Complex, SpA: Spondyloarthritis, IL: Interleukin, TNF: Tumour Necrosis Factor, JAK: Janus Kinase)

Table 2. Pathogenetic comparison between Type 1 and Type 17 MHC-I-opathies

	Type 17	Type 1
MHC-I Involvement	HLA-B*27, HLA-Cw*05, HLA-B*51	HLA-B*52
Subtype of MHC-I-Opathy	Type 17	Type 1
ERAP Association	Strong	Lack of evidence
Main non-HLA Gene	IL23R	IL12B
Main Cytokine Pathway	IL23/17	TNFα/IFNγ
CD8 T-cell Evidence	Strong	Potential IFNγ producer
Dominant Innate Immune Cells	Neutrophils (Munroe's abscess...)	Macrophages (granulomata)

(MHC: Major Histocompatibility Complex, HLA: Human Leukocyte Antigen, ERAP: Endoplasmic reticulum aminopeptidase IL: Interleukin, TNF: Tumour Necrosis Factor, IFN: Interferon)

Table 3. Comparison of the main features between Takayasu Arteritis and Giant Cell Arteritis

	Takayasu Arteritis	Giant Cell Arteritis
Age	Young	Old
Sex (F/M)	9/1	2/1
Geographic distribution	Asian, Indian and Middle Eastern countries	European countries
Most involved arteries	Main branches of the aorta	Extracranial branches of external carotid artery
Overlaps	Spondyloarthropathies and IBD	Polymyalgia Rheumatica
MHC	MHC-I (HLA-B*52)	MHC-II (HLA-DRB1*04)
Key adaptive cell	CD8 T-cells	CD4 T-cells
Emerging cytokine targets	IL-12/IFNγ	IL-12/IFNγ/IL-17?
Cytokines targets from reverse translational immunology	TNFα/IL-6?	IL-6
Histology	Granulomatous vasculitis	Granulomatous vasculitis

(F: Female, M: Male, IBD: Inflammatory bowel disease, MHC: Major Histocompatibility Complex, HLA: Human Leukocyte Antigen, TNF: Tumour Necrosis Factor, IFN: Interferon, IL: Interleukin)