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Functional and phenotypic heterogeneity of Th17 cells in health and disease

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Abstract

Th17 cells have non-redundant roles in maintaining immunity, particularly at mucosal surfaces. These roles are achieved principally through the production of cytokines and the recruitment of other immune cells to maintain the integrity of mucosal barriers and prevent the dissemination of microorganisms. Th17 cells are heterogeneous and exhibit a considerable degree of plasticity. This allows these cells to respond to changing environmental challenges. In addition to their protective role in immunity, studies involving animal models, patient data, genome wide association studies and clinical trials targeting IL-17 for treatment of patients have provided evidence that Th17 cells also play pro-inflammatory roles in chronic autoimmune diseases. Less clear, however, are triggers that initiate or perpetuate Th17 responses to promote chronic inflammation and autoimmunity, and the divergent effects of tumour necrosis factor alpha blockade on Th17 cells in patient subgroups. Th17 cells also stimulate B lymphocytes and enhance humoral immunity by inducing polyclonal activation of autoreactive B lymphocytes, leading to autoantibody production. In addition, some pathogenic bacterial species can change Th17 cell phenotype and responses. These effects are implicated in promoting pathogenic roles for Th17 cells in autoimmune diseases. This article provides an overview of the distinct roles Th17 cells can play in maintaining immunity at mucosal surfaces and in skin mucosa and how this is linked to chronic inflammation in autoimmune rheumatic diseases.

Introduction

Th17 cells are effector T cells characterised primarily by the production of IL-17, principally IL-17A and IL-17F but also IL-22, IL-21 and GM-CSF.[1] The cells play an important role in maintaining immunity, particularly at mucosal surfaces but also contribute to chronic inflammation in autoimmune diseases. [1-3] Although many studies have explored the role of Th17 cells in the pathogenesis of autoimmune diseases using animal models, clinical samples from patients, clinical trials targeting IL-17 therapeutically and genome wide association studies (GWAS), there is still a lack of understanding of how Th17 cells are transformed from non-pathogenic protective lymphocytes to a major mediator of chronic and sometimes fatal inflammation. Evidence from studies of animal models and clinical trials suggest that TNFα is a suppressor of pro-inflammatory activities mediated by Th17 cells.[4-6] In this review we will provide an overview of current knowledge of the functional heterogeneity and phenotypic plasticity of Th17 cells. We will highlight factors thought to drive the protective functions versus pathogenic roles of Th17 cells in autoimmunity, with an emphasis on rheumatic diseases.

Differentiation of Th17 cells

Th17 differentiation and function in health: the gut and skin

In healthy humans, most Th17 cells are found in the intestinal lamina propria with some also being part of the cutaneous antigen positive resident memory T cell population (T_{RM}) in the skin (Figure 1).[7, 8] Steady-state Th17 cell differentiation is dependent on IL-1β, IL-6, IL-23 and TGFβ.[1] Low levels of IL-1β from macrophages, induced by intestinal commensal bacteria, maintains Th17 protective functions.[9] TGFβ, produced during the turnover of epithelial cells, is also abundant in the gut mucosa.[10] Furthermore, exogenous tryptophan and

other metabolites activate the transcription factor aryl hydrocarbon receptor (AhR) and augment Th17 cell differentiation.[1] Sodium chloride and hypoxia can also influence Th17 cells, with the former promoting Th17 differentiation whilst the latter modulate IL-17 production.[1] In the skin, the commensal bacterial species *Staphylococcus epidermidis* induces IL-1α and IL-1β production, which favour Th17 differentiation.[8]

In the intestine, Th17 cells produce IL-22 and IL-17. These two cytokines protect mucosal membranes by inducing the production of antimicrobial proteins, RegIIIβ and RegIIIγ.[11] They also help maintain tight epithelial cell junctions and promote epithelial cell re-generation.[1, 12] Th17 cells play comparable roles in the skin and in the airways of the lung.[13] The importance of Th17 cells in maintaining anti-microbial immunity is underscored by the fact that patients with loss-of-function mutations in genes coding for IL-17, IL-17 receptor or RORγt experience recurrent infections (e.g. *Candida albicans* and *Staphylococcus aureus*) of the skin, nails and oral and genital mucosae.[14]

The IL-17 receptor is expressed on several cell types including epithelial and endothelial cells, fibroblasts, keratinocytes and monocytes.[1] IL-17 binding to its receptor triggers the production of chemokines CXCL1, 5, 8, 9 and 10, CCL2 and 20 and cytokines such as IL-6.[1, 15] The chemokines attract neutrophils, T cells and NK cells which, in response to IL-17, produce IFNγ and GM-CSF leading to further neutrophil influx to eradicate fungi (Figure 1).[16] CCL20, by binding CCR6, which is highly expressed by Th17, recruits more cells to sites of infection.[15] IL-17 signalling also leads to β-defensin and S100 production that act on invading micro-organisms (Figure 1).[1] In addition, IL-17 induces the production of matrix metalloproteinases (MMPs) which facilitate the cleavage and activation of anti-microbial proteins and mediate tissue remodelling and the production of VEGFA to promote angiogenesis. [17,18]

Th17-derived IL-21 promotes humoral immunity by activating follicular T helper cells (Tfh) and B cells. By promoting B cell proliferation, antibody affinity maturation, class switching and differentiation to plasma cells, Tfh cells promotes humoral immunity in secondary lymphoid organs and germinal centres.[1, 19, 20] Studies of gut inflammation and vaccine development for respiratory infections have revealed that Th17 cells facilitate IgA production by B cells.[21, 22]

A possible clue as to how protective Th17 responses can "spill-over" into inflammation has been provided by studies of a mouse model of intestinal infection in which commensal segmented filamentous bacteria (SFB) induced an inflammatory Th17 cell response in the gut.[3] SFB and *Citrobacter rodentium* are more effective at inducing intestinal Th17 responses than other microbial species due to their ability to penetrate the protective mucus and adhere to intestinal epithelial cells and, thus, resist removal by epithelial turnover and digestive processes.[22]

Intracellular signalling and Th17 differentiation

T cell receptor (TCR) engagement in the presence of IL-1β activates nuclear factor kappa B (NF-κB) and interferon regulatory factor 4 (IRF4).[23] Together with the basic leucine zipper transcription factor, ATF-like (BATF), NF-κB and IRF4 translocate to the nucleus to reorganize chromatin sites relevant to Th17 cell differentiation.[23] Exposure to IL-6 and IL-23 phosphorylates signal transducer and activator of transcription 3 (STAT3) and causes it to dissociate from the receptor-bound Janus kinase 2 (JAK2).[24] STAT3 in Th17 cells can be phosphorylated on the amino acids tyrosine 705 and serine 727.[25] Phosphorylated STAT3 (pSTAT3) translocates to the nucleus to populate permissive chromatin sites, made accessible

by TGFβ, to stabilize BATF/IRF4 interactions.[1] The IRF4/BATF/STAT3 interaction induces the expression of Th17-associated genes such as *Il17a, Il17f, IL23r, Ccr6, Rora* and *Hif1a*.[23] Genes coding for IL-17A and IL-17F are located in close proximity to each other on human chromosome 6 (murine chromosome 1) and are co-regulated. In mice, IL-23 induces runt-related transcription factor 1 (RUNX1) gene expression to enhance expression of RORγt, an important cell lineage-specific transcription factor which, together with pSTAT3, binds promoters for *Il17a* and other Th17-related genes.[23] The transcription factor, Blimp-1, induced by IL-23 in Th17 cells, co-localizes with RORγt and STAT3.[26]

Super-enhancers are important regulatory elements characterized by a high density of both non-specific and lineage-specific transcription factors in multiple enhancer elements found in untranscribed chromatin. In cells destined to become Th17 cells, these regulatory elements are themselves regulated by multiple factors, including cytokines, TCR-engagement and environmental factors. STAT3 and RORγt are co-localized in such regions in the neighbourhood of genes involved in Th17 cell regulation and effector functions. These genes include *Rorc, Il17a, Il17f, Il23r, Il1r1, Runx1* and *Batf*.[27]

Heterogeneity and stability of Th17 cells

High-dimensional phenotyping by mass-cytometry (CyToF) has shown that human Th17 cells have a heterogeneous phenotype.[7] This concept is supported by single-cell RNA-sequencing (RNAseq) of murine Th17 cells which revealed considerable heterogeneity due to the existence of distinct Th17 cell subsets and different maturational states.[28] Immature Th17 cells have a stem cell-like gene-signature and are generally confined to lymph nodes. A more mature Th17 cell subset was identified as having high *Stat3* and *Rankl* mRNA levels while a further subset was shown to mainly produce IFNγ.[28] Hence, although Th17 cells are categorised by IL-17 production and by their presence in the skin, colon, lungs and tonsils, some Th17 cells also

produce IL-10, IL-22 and IFNγ.[7] Furthermore, different pathogens induce different cytokine responses in Th17 cells (Figure 1). For example, Th17 cells induced by *C. albicans* tend to produce IFNγ, while Th17 cells induced by *S aureus* produce IL-10.[29]

Exposure to pathogens in the presence of different cytokines alters the transcriptional profile of Th17 cells. For example, IL-23 induces RUNX1 expression that promotes Th17 differentiation while IL-12 induces T-bet expression with a Th1-like cells that produce IFNγ.[30] In patients with multiple sclerosis and experimental autoimmune encephalomyelitis in mice, Th17 cells become pathogenic when they are induced to produce IFNγ.[31, 32]

Further studies have shown that murine Th17 cells in the gut mucosa can transdifferentiate to IL-10-producing regulatory T cells (Tr-1 cells), a process apparently dependent on the AhR and TGFβ (Figure 1).[1] The ability of Th17 cells to produce IL-10 is also noted following treatment with TNFα inhibitors.[33] The production of IL-10 by Th17 cells is regulated by the transcription factors c-Maf and Aiolos.[1, 33] Early studies suggested that Th17 cells and Tregs were mutually exclusive. These studies indicated that Th17 cell development was inhibited by IL-2 and STAT5 activation. Recent studies, however, have shown that Th17 cells can transdifferentiate to Tregs and vice versa under the influence of the inflammatory milieu.[34-36]

In mice, Th17 cells in Peyer's patches can transdifferentiate to Tfh cells and facilitate IgA production by B cells.[21] In contrast, in an inflammatory milieu containing IL-23, Blimp-1 is induced and this, in turn, promotes the emergence of a pathogenic Th17 phenotype in which Blimp-1 binds to and supresses the *Bcl6* gene which is required for Tfh development.[26]

Th17 cells as drivers of autoimmunity

Autoimmune diseases are often associated with autoreactive T cell oligoclonality and the recognition of disease-related auto-antigens (Table 2).[37, 38] Small numbers of autoreactive T

cells can also be detected in healthy individuals but these are generally anergic and do not promote chronic inflammation and disease.[39] Changes in the balance between Tregs and Th17 cells have been implicated in shifting the balance between limiting and sustained autoimmunity.[40] Studies in animal models and in patients have indicated that the plasticity of Th17 cells contributes to disease in a permissive inflammatory milieu.[2, 31, 41] For example, IL-23-mediated inflammation in EAE mice induced Th17 cells to produce IFNγ.[31] Further, a study of peripheral blood cells from SLE patients revealed a subgroup of patients with a proportion of their Th17 cells likely transdifferentiated to Tregs.[41] Several genes identified by GWAS to be associated with TCR and cytokine signalling influence the activity and plasticity of Th17 cells. Furthermore, various SNPs associated with changes in gene expression levels or disruption of TCR and cytokine signalling proteins have been directly implicated in Th17 cell functions (summarised in Table 1).

Th17 cells have lower activation thresholds than Th1 cells and are, therefore, more prone to become self-reactive effector cells.[2, 42] Indeed, environmental pollutants and bacteria that are better at penetrating mucosa and persist in the gut can promote self-reactive Th17 responses.[22, 43] Furthermore, a study of an animal model of intestinal infection has shown that a milieu containing IL-23 and apoptotic epithelial cells preferentially promoted self-reactive Th17 cells and autoantibody production.[2]

Many autoimmune diseases are associated with the production of autoantibodies and several studies have identified links between Th17 cells, B cell activation and autoantibody production (Table 2). For example, the B cell activating factor (BAFF), which is important for B cell activation, also augments Th17 differentiation by facilitating upregulation of the IL-6 receptor on $CD4^+$ T cells, suggesting that the proliferation of the two cell types could occur

concurrently.[44] Furthermore, experimental SFB infection promotes Th17 cell differentiation, germinal centre formation, autoantibody production and autoimmune disease.[3, 45, 46]

Th17 cells and rheumatoid arthritis (RA) pathogenesis

RA is a debilitating disease affecting 0.5-1% of the population worldwide. The synovial lining of RA joints is targeted by an immune response that induces juxta-articular bone loss.[47] T cells in the synovium of RA patients manifest a relatively restricted, or oligoclonal, receptor (TCR) repertoire. The cause of this restricted repertoire is suggested to be the exhaustion and death of T cell clones due to persistent stimulation by pro-inflammatory cytokines and/or self-antigens.[38]

High blood levels of IL-17 are evident in patients with RA several years before the development of clinical disease.[48] Furthermore, Th17 cells are enriched in arthritic joints[49] and these cells promote arthritis by inducing the production of pro-inflammatory cytokines while inhibiting apoptosis in synoviocytes.[50] In addition, IL-17 induces MMP-1 and MMP-3 production from synovial fibroblasts, leading to collagen degradation.[51] Th17 cells also cause bone resorption by enhancing RANK-L expression leading to osteoclastogenesis.[52]

Studies in animal models of arthritis have indicated that self-reactive T cells differentiate to Th17 cells due to the inflammatory synovial milieu.[53] However, in RA no single self-antigen target for T cells has been identified. A number of GWAS have identified genetic associations between susceptibility to RA and chemokine receptors, cytokines- and TCR signalling (Table 1).[47] These findings imply that the risk for developing RA is increased by the combined effects of RA-permissive HLA alleles and dysregulated inflammatory signalling pathways, in which Th17-associated genes are over-represented.

Other studies of Th17 cells in RA have suggested the existence of a reciprocal relationship between Tregs and Th17 cells. For example, the ratio of Th17 to Treg is significantly greater in RA patients compared with healthy individuals.[40] Moreover, the Th17:Treg ratio decreases in response to treatment with the anti-IL6 receptor antibody Tocilizumab.[54] Such a relationship has been suggested to be primarily due to the plasticity of Th17 cells and studies in mice have confirmed that Tregs can transdifferentiate to Th17 cells in arthritic joints.[35] In patients with RA, IL-17^{+}FoxP3^{+} T cells can be identified in RA synovia and offer further evidence of Treg/Th17 transdifferentiation.[35] Although some clinical trials has not shown efficacy when using anti-IL-17 therapy for RA, there is evidence of increased Th17 cells following anti-TNFα therapy.[4, 55, 56] Moreover, evidence from phase two clinical trials with methotrexate or anti-TNFα non-responsive patients indicate that disease in some RA patients is driven by Th17 cells and that treatment with anti-IL-17 antibody could be therapeutically beneficial (Table 2).[57]

RA is traditionally associated with the presence of rheumatoid factors (RFs) and anti-cyclic citrullinated peptide (anti-CCP) auto-antibodies.[47] Interestingly, Th17 cells have been identified in germinal centres of ectopic lymphoid structures (ELS) in joints of RA patients.[58] In mice, Th17 cells induce ELS in joints while germinal centre-resident Th17 cells reduce sialylation of IgG, thus, promoting pathogenic auto-antibody production.[46] Relevant to the link between Th17 cells and autoantibody production is that BAFF activates both plasma cells and Th17 cells and exacerbates joint pathology.[59]

Given the potential of Th17 cells to modulate B cell responses, it is of potential significance that anti-TNFα non-responder patients tend to produce anti-nucleic acid antibodies[60] and that anti-TNFα therapy may interfere with cellular clearance mechanisms leading to lupus-like

symptoms.[61] Future research will determine whether such responses are driven by Th17 cells and whether these could be targets for the efficacious anti-IL17 therapy in these patients.

Th17 cells and the pathogenesis of Psoriasis

Psoriasis is manifested by uncontrolled proliferation of dermal keratinocytes. The disease affects 2-3% of populations worldwide, with a similar prevalence in both genders. The most common form of the disease is psoriasis vulgaris, in which the disease causes the appearance of itchy, red and scaly plaques all over the body.[62] Psoriatic lesions are reduced by anti-inflammatory therapy but often reoccur at the same location. Immune system involvement is indicated by association with HL-A class I haplotypes and by the therapeutic response of patients to immunosuppressive agents.[62] GWAS have identified several candidate genes that provide evidence for an association between Th17 cells and susceptibility to the disease (Table 1).

Pathogenic T cells in psoriasis are not commonly detected in blood but reside in the skin.[63] Blockade of E-selectin prevents the egress of leukocytes from the circulation into the dermal tissue compartment but this does not improve disease.[64] The importance of skin-resident T cells for psoriasis pathology is indicated by studies showing that engraftment of patient's skin into immune deficient mice lead to a reaction to keratinocyte-derived proteins. Autoreactive T cells present in the graft were found to be responsible for the response (Figure 2).[65] Such autoreactive T cells in psoriatic skin lesions are generally oligoclonal, produce IL-17 and IL-22 and persist despite disease resolution.[37, 63]

The role of Th17 cell in psoriasis was initially suggested by studies in animal models. For example, mice deficient in IL-17 did not develop experimental psoriasis[66] and administration of IL-23 or IL-21 into mouse skin induced psoriasis-like symptoms.[66, 67] The role of Th17 cells in

psoriatic patients was thereafter verified by the effective therapeutic effect of human IgG1κ monoclonal antibodies targeting IL-17A and IL-17RA (Table 2).[68] As cited earlier, at least in mice, some tissue resident T cells recognize *C. albicans* and respond by producing IL-17.[8] Although *C. albicans* can exacerbate psoriasis via activation of T cells there is currently no evidence that the fungus is responsible for the pathogenic Th17 response.[69] Instead, various keratinocyte proteins, such as ezrin, maspin, peroxiredoxin 2, heat shock protein 27 and LL-37 are recognized by T cells and this appears to induce IL-17 production (Table 2).[70, 71]

The available evidence indicates that the activity of pathogenic Th17 cells is augmented indirectly by plasmacytoid dendritic cells (pDCs). pDCs produce type 1 interferons and TNFα that activate myeloid DCs (mDCs).[62] mDCs, in turn, produce IL-23 and present self-antigens to activate tissue-resident Th17 cells. In this respect, there is evidence that blood IL-21 levels are increased in psoriasis and correlate with Psoriasis Area and Severity Index (PASI) scores.[62] In addition, IL-21 is found in plaques of a murine model of psoriasis and is both produced by and augments Th17 cell activity in psoriatic patients.[72] IL-17 produced in the plaques activates keratinocytes to produce IL-8, CCL-1, -3, -5, and -6, and 20. These chemokines help recruit neutrophils.[62] CCL20 recruits further Th17 cells and DCs. IL-17 also increases the production of β-defensin and VEGF by fibroblasts which leads to angiogenesis and plaque formation.[17, 73] Interestingly, blockade of TNFα in murine psoriasis increases the number of Th17 cells.[5]

Th17 cells in the pathogenesis of and autoantibody production in systemic lupus erythematosus (SLE)

SLE affects 20-70 individuals per 100,000 of the population in the UK and has a 9:1 female:male ratio.[74] The aetiopathogenesis of SLE is thought to be driven by a combination of environmental and genetic factors. A feature of SLE is defective removal of apoptotic bodies leading to the accumulation of cell debris of nuclear, cytosolic and membrane origin. This

debris activates autoreactive B cells to proliferate and stimulate autoreactive T cells leading to the production of anti-nuclear autoantibodies production.[74] Although association of SLE with HLA is not as strong as in RA, a number of other immune-related gene candidates have been linked to SLE. Several of these genes are involved in Th17 cell regulation (Table 1).[75] Reduced global DNA methylation is a feature of SLE.[76] In this context, it may be relevant that reduced levels of the transcription factor, regulatory factor X1 (RFX1), was recently shown to result in reduced histone and DNA methylation. This leads to an increase in Th17 cell differentiation in patients and experimental lupus mice.[77]

Effector Th17 cells found in the blood and tissues of patients with SLE are implicated in the pathogenesis of the disease.[36] Imbalance in the intestinal microbiome, characterized by reduced Firmicutes:Bacteroidetes ratios, has been reported in SLE and shown to promote Th17 differentiation (Table 2).[36] Furthermore, stimulation with bacterial species resulted in the development of $FoxP3^{+}IL\text{-}17^{+}$ T cells suggestive of trans-differentiation (Figure 2).[36] Interestingly, the frequency of Th17 cells in SLE correlates with autoantibody levels, disease activity and high blood levels of IL-17.[36] There is also evidence for increased Th17 cells co-expressing IL-17 and IFNγ.[78]

There is an association between defective TNFα signalling and SLE disease pathogenesis. This has been demonstrated in several contexts. For example, lupus mice deficient in TNFα receptors have higher numbers of Th17 cells and show accelerated pathology.[6] This is consistent with the observation cited earlier in this review that blockade of TNFα leads to an increase in the frequency of Th17 cells and high levels of IL-17 production by T cells. Thus, there is an increase in the frequency of Th17 cells in RA and psoriatic patients treated with biologic anti-TNFα agents.[4, 5] It not entirely clear how deficient TNFα signalling promote lupus pathology. However, it is interesting to note that the TNFα-induced, ubiquitin editing enzyme

A20/TNFAIP3 that acts downstream of TNFR1 has been linked in GWAS to RA, Psoriasis and lupus (Table 1). Although there is no compelling experimental evidence yet that TNFα exacerbates lupus in humans, the disease is, nonetheless, associated with an augmented Th17 cell response mediated, at least partly by reduced expression *TNFAIP3* in T cells. This reduced expression *TNFAIP3* in known to enhance Th17 cell differentiation.[79, 80]

Except for some circumstantial evidence for genetic associations from GWAS and reported changes in the gut microbiome, it remains unclear what is driving the generation of pathogenic Th17 cells in SLE. However, the inflammatory milieu in lupus underpins defective phagocytosis which, in turn, promotes IL-23 production leading to Th17 cell differentiation.[81] In addition, there are suggestions for a link between B cell differentiation and Th17 cells development. Thus, the transcription factor Blimp-1, which is the gene product of *PRDM1,* another gene identified by GWAS to be associated with lupus, plays a role in plasma cell and Th17 differentiation (Table 1). Thus, Blimp-1 regulates differentiation of B cells to plasma cells but is also reported to be involved in the development of murine Th17 cells in response to IL-23; in these cells, Blimp-1 represses transcription of Bcl6.[26] As Bcl6 is required for Tfh differentiation, and SLE is associated with auto-antibody production, one of the effects of disease associated *PRDM1* polymorphisms could be the augmentation of Th17 cell-driven autoantibody production (Figure 2).[21]

In addition to playing a role in autoantibody production in lupus, the Th17 axis has been implicated in accelerating organ damage and mortality.[82] IL-23 levels are increased in the blood and urine of SLE patients compared with healthy controls. In addition, urine levels of IL-23 correlate with renal SLE Disease Activity Index (rSLEDAI) score and proteinuria. After 6 months of treatment with immunosuppressive agents, a cohort of patients showed a high frequency of $CD4^+$ T cells, increased numbers of $CD3^+CD4^-CD8^-$ T cells that produced IL-

17.[78] Interestingly, the cells homed to the kidneys, produced copious amounts of IL-17 and IFNγ and recruited neutrophils. These findings suggest that Th17 cells could contribute to lupus nephritis through the recruitment of neutrophils. Other studies, however, focus on the link between Th17 cells and B cells. For example, lack of IL-17RA reduces while administration of IL-17 accelerates germinal centre formation in mice and enhance autoantibody production.[45] This role is also supported by increased BAFF production.[83] In this respect, it is noteworthy that in RA, a lack of response to anti-TNFα is associated with the generation of anti-dsDNA autoantibodies, increased Th17 cell numbers and lupus-like symptoms.[60]

Do Th17 cells contribute to the pathogenesis of systemic sclerosis (SSc)?

SSc is an autoimmune connective tissue disease in which activation of the immune system, inflammation, vasculopathy and uncontrolled fibrosis lead to organ-based complications. The disease is exemplified by progressive dermal fibrosis and vasculopathy. SSc affects 12,000 individuals in the UK with a female:male ratio of 9:1.[84] Its aetiopathogenesis involves genetic and environmental factors, such as exposure to organic solvents and silica.[84] The pattern of fibrotic disease is clinically classified to either limited or diffuse based on the extent of cutaneous involvement. The diffuse subtype, in particular, has an inflammatory phenotype with progressive fibrosis of lungs, kidneys, heart and the gastrointestinal tract in the first few years of disease onset.[84] SSc is characterized by damage to the micro- and macro-vasculature leading to tissue hypoxia with excessive accumulation of extracellular matrix. Pathology develops from an interplay between altered vasculature and immune-mediated inflammatory events.[84] Genes associated with SSc are involved in TCR and cytokine receptor signalling (Table 1).[85] A major feature of autoimmunity in SSc is high levels of autoantibodies to cellular proteins including topoisomerase I enzyme (Scl-70).[84] Sub-epithelial inflammation is reported years before disease symptoms.[86]

IL-17 level is elevated in the blood of SSc patients compared with healthy individuals.[87] Furthermore, several pro-inflammatory cytokines including IL-6 that promote Th17 cell differentiation are produced at high levels by immune cells including B cells.[88] The indirect effects of IL-17 on fibrosis are likely to be mediated by the effect of IL-6 on fibroblast proliferation and increased production of pro-fibrotic factors. Thus, in experimental models of SSc, IL-17 stimulates fibroblast proliferation and increases key pro-fibrotic mediators such as TGFβ, connective tissue growth factor and collagen.[87, 89] Notably, the frequency of topoisomerase-reactive Th17 cells was reported to predict disease prognosis in SSc patients with interstitial lung disease.[90] Interestingly, Th17 cells inhibit the ability of TGFβ to induce pro-fibrotic collagen production by fibroblasts from healthy individuals but not SSc patients'.[89]

Similar to psoriasis, SSc patients have skin-resident Th17 cells. However, in contrast to psoriasis, in SSc patients these cells react with nuclear antigens rather than keratinocyte-derived proteins. In addition, these Th17 cells are likely to promote autoantibody production by B cells at least in a subgroup of patients.[88] This is supported by high levels of IL-6 and BAFF in SSc.[59]

Conclusions

A number of factors are involved in changing Th17 cell responses from been involved in protective immunity to promoting inflammation and autoimmune diseases. The best link between Th17 homeostatic barrier functions and dysregulation leading to the failure of immunological tolerance, chronic inflammation and autoimmune disease mediation by Th17 cells is likely to result from responses to bacterial infections in the gut and, potentially, in the skin (Figure 1 and 2). Hence, an aberrant immune response to bacterial antigens leading to a propensity of self-antigen presentation and Th17 cell responses in genetically susceptible

individuals is a possible mechanism.[3, 36, 39, 91] The ability of Th17 cells to enhance B cell responses could be further evidence for a role for Th17 cells either directly, or through trans-differentiation to Tfh cells, in promoting the production of pathogenic autoantibodies (Table 2).[21, 46]

The lack of responsiveness to treatment with biologic anti-TNFα agents in some patients with RA, psoriasis and most SLE patients is associated with the production of anti-nuclear antibodies and an increased Th17 frequency and responses.[4, 6] As described in the section on SLE, altered expression of the GWAS-associated ubiquitin editing enzyme TNFAIP3/A20 down-stream of TNFR1 in the T cells/Th17 cells could be one factor contributing to altering Th17 cell responses (Table 1). Genetic susceptibility can also be a contributing factor to enhanced production of IL-12/23p40 when TNFα is inhibited/eliminated.[4] Further studies are, however, required to determine how associated polymorphisms contribute to Th17 cells expansion and their plasticity in chronic inflammatory autoimmune diseases. Such studies should also address the influence of patients' microbiome, availability of self-antigens and the mechanism by which Th17 cells promote auto-antibody production.

Conflict of interest

The authors declare no conflict of interest.

Table 1. Genes associated with autoimmune disease and Th17 cells

Gene	Chr	Protein Name	Disease linkage	SNPs	Study population (n)	MAF, Reported effect (5×10^{-8}, considered effect)	Reference
IL21	4	IL-21	SLE	rs907715[c]	5,549 SLE E/AA	2.17×10^{-8}	92
				rs6835457[b]	5,313 HC E/AA	*9.35×10^{-5}**	
IL12B	5	IL-12B	PSO	rs12188300[c]	10,588 SLE E/US	7.5×10^{-23}	93
					22,806 HC E/US		
IL23A/STAT2	12	IL-23A	PSO	rs2066819[c]	same as *IL12B*	7.5×10^{-12}	93
IL23R		IL-23R	PSO	rs9988642[d]	same as *IL12B*	2.5×10^{-13}	93
			SSc	rs11209026[a]	1402 SSC US	Missense, SSc: association with	94
					1038 HC US	anti-SCL70^{+}, *1×10^{-3}**	
TRAF3IP2	6	Act1	PSO	rs33980500[a]	6,487 PSO E/US	1.24×10^{-16}	95
					8,037 HC E/US	Missense, reduced binding of Act1 to TRAF6	
TNFAIP3	6	A20	PSO	rs582757[c]	same as *IL12B*	2.0×10^{-14}	93
			RA	rs10499194[c]	2,680 RA E	1×10^{-9}	96
					4,469 HC E		
			SLE	rs5029939	431 SLE E	2.89×10^{-12}	97
					2,155 HC E		
TNIP1	5	TNIP1	PSO	rs2233278[b]	same as *IL12B*	4.9×10^{-17}	93
			SLE	rs7708392[c]	1,963 SLE US/E	3.8×10^{-13}	75
					4,329 HC US/E		
			SSc	rs3792783[c]	4389 SSc E	9.11×10^{-16} SSc: reduced expression in skin	98
					7611 HC E		

PRDM1	6	Blimp-1	SLE,	rs6568431[c]	Same as *TNIP1*	7.1×10^{-10}	75
			SSc	rs4134466[d]	4436 SSc JP/E	6.6×10^{-10}	99
					14 751 HC JP/E		
RUNX1	21	RUNX1	PSO	rs8128234[c]	15,369 PSO CH/E	5.99×10^{-8}	100
					19,517 HC CH/E		
CCR6	6	CCR6	RA	rs3093024[c]	7,069 RA JP	7.7×10^{-19}	101
					20,727 HC JP	RA: changed expression level on Th17 cells	
			SSc	rs10946216	2,411 SSc E	SSC: association with	102
					7,084 HC E	anti-Scl70^{+}, *9.0×10^{-5}**	

SLE: systemic lupus erythematosus, PSO: psoriasis, RA: rheumatoid arthritis, SSc: Systemic sclerosis, MAF: minor allele frequency, 5'UTR: 5' upstream transcription region, a: SNP in protein coding part. b: SNP in 5' or 3'UTR; c: intronic; d: up-or down-stream of gene. Ethnicity: E: European, AA: African American, US: mixed USA, JP: Japanese, CH: Chinese.

* MAF below 5×10^{-8}

Table 2. Factors associated with Th17 cell response in auto immune diseases

	T cell oligo-clonality[1]	Self-antigens[2]	Microbiome[3]	T cell plasticity	Activity to stimulate B cells	Clinical trials targeting the IL-17 pathway
Rheumatoid arthritis	Yes[47]	Citrullinated proteins?*[47]	Yes[103]	Treg to Th17[35]	Germinal centre (A)[47] Reduced sialylation of auto-abs (A)[46]	Ixekizumab (antiIL17), response biologics naïve and anti-TNF non-responders [57]
Psoriasis	Yes[37]	Keratinocyte derived[70, 71] Ezrin*, Maspin*, LL37 Peroxiredoxin 2*, HSP27* (antiIL17R)[105]	?	?	?	Secukinumab (antiIL17) [68] Ixekizumab (antiIL17) [104] Brodalumab Guselkumab[106] (anti IL23p19) All: improvement of moderate to severe psoriasis
SLE	?	ds-DNA, histones*[107] Small nuclear ribonucleo-proteins*	Yes[36]	FoxP3$^+$, IL-17$^+$ T cells[36] IFNγ^+, IL-17$^+$ T cells[78]	Germinal centre (A)[40]	not done
Systemic sclerosis	Yes[89]	Topoisomerase-1[80] RNApol3*	?	?	?	not done

* Information not available for Th17 cell specificity

A, animal model

1) T cell oligo-clonality reported provide evidence for involvement and dysregulation of T cells in autoimmune diseases listed.
2) Reports of self-antigens associated with autoimmune diseases, although not proven to be causative, suggest a specific involvement of T cells. Some self-antigens have been specifically linked to a Th17cell response (LL37 and Topoisomerase-1).
3) The microbiome composition has been linked to certain autoimmune diseases and a specific Th17 response.
4) Reports providing evidence for role Th17 cells plasticity in autoimmune disease.
5) Reports supporting Th17 cells ability to support an auto-antibody response in autoimmune disease.

Figure legends

Figure 1. Role of Th17 cells in maintaining homeostasis. Th17 cells reside in mucosal membranes and in the skin. The gastrointestinal tract (GIT) microbiome, infections or a disrupted homeostasis can promote a surge in pro-inflammatory cytokine production, including high levels of IL-1β, IL-6 and IL-23. This induces resident T cells to differentiate to effector Th17 cells aided by antigen-presenting cells (APCs), such as dendritic cells (DCs). IL-17 and IL-22 production by these effector cells increases barrier functions, such as tighter junctions and the production of antimicrobial peptides. The production of IL-17 induces chemokine production and neutrophil recruitment. In the skin, *C. albicans* stimulates DCs and promotes IL-1β-dependent T_{RM} IL-17 production, leading to antimicrobial protein and chemokine production and the recruitment of neutrophils. GIT tryptophan (Trp) and TGFβ promote Th17 cell trans-differentiation to IL-10-producing T cells. M cells, that are part of Peyer's patches, transport intestinal antigens from the gut lumen for presentation by DCs to the immune system leading to B cell activation. In this environment, Th17 cells transdifferentiate to Tfh cells that produce IL-21, which promote B cell development and IgA production. Tfh promotes plasma cell development.

Figure 2. Th17 cells role in rheumatic diseases. Gut, left; Pathogenic (and certain commensal) bacterial species in the GIT can potentiate a Th17-mediated inflammatory responses. Self-antigens (red colour) can erroneously be presented by DCs to naïve T cells during GIT infections with pathogenic bacterial species resulting in autoreactive responses. In SLE, defective clearance of apoptotic cells leads to IL-23 production by DCs. IL-23 promotes Th17 cell differentiation and also facilitates Treg conversion to IL-17-producing cells. BAFF, which is also elevated in SLE, promotes further Th17 cell differentiation and B cell survival and proliferation leading to the production of autoantibodies with specificity for apoptotic cell debris. Skin, left; In the skin of patients with psoriasis, auto-antigens (red colour) are presented to T_{RM} cells by APCs. These APC produce IL-23 leading to the differentiation of T_{RM}s to Th17 cells. These cells, in turn, exacerbate skin pathology through the production of chemokines, neutrophil recruitment and the production of MMPs, and other mediators of inflammation. Synovium, right; In RA, Th17 cells augment synovial cartilage degradation and inflammation by stimulation of synoviocytes leading to production of MMPs, IL-6. IL-17 can also induce RANK-L release from synoviocytes and osteoblasts thereby promoting osteoclastogenesis. Furthermore, IL-22 production by Th17

cells accelerates ectopic germinal centre formation and B cell proliferation and differentiation in inflamed synovia. IL-17 produced in these ectopic germinal centres enhances the production of pathogenic autoantibodies.

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Figure 1

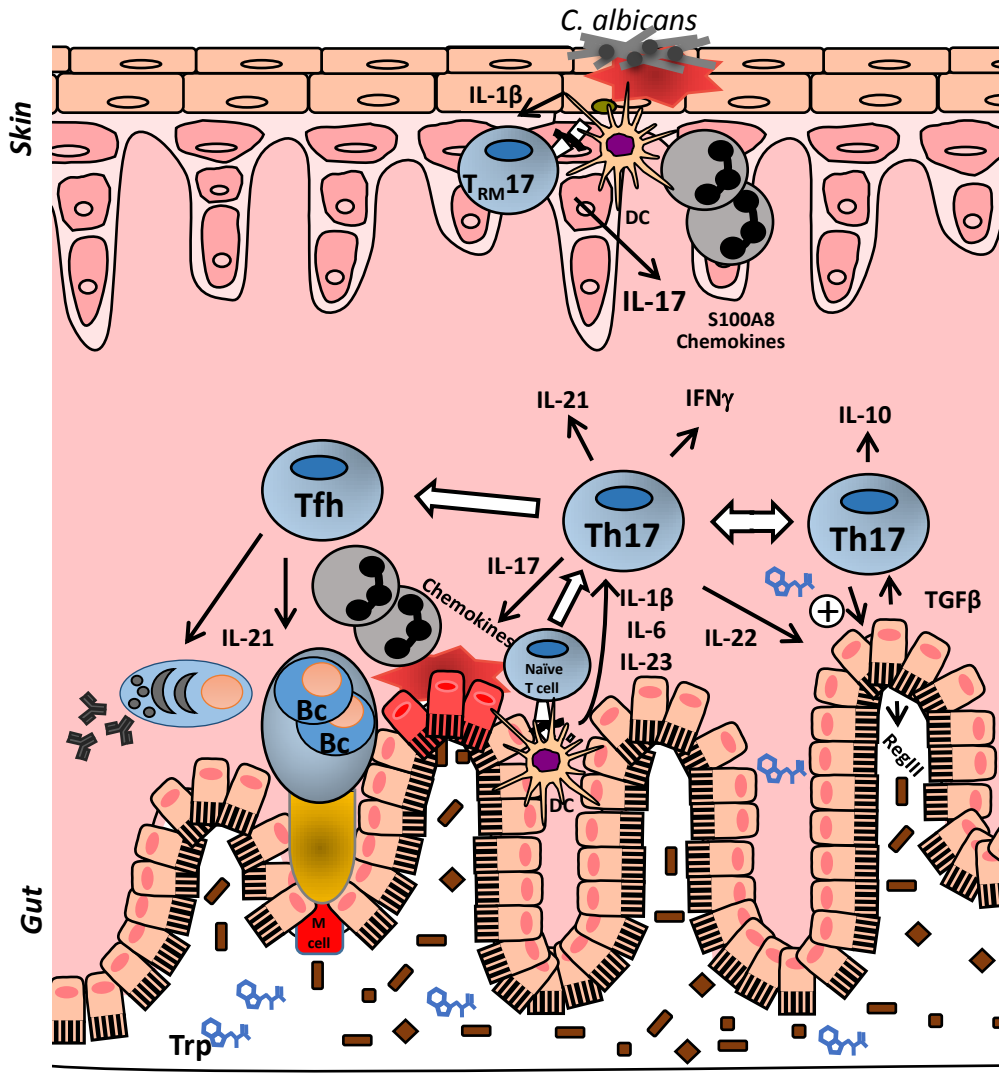
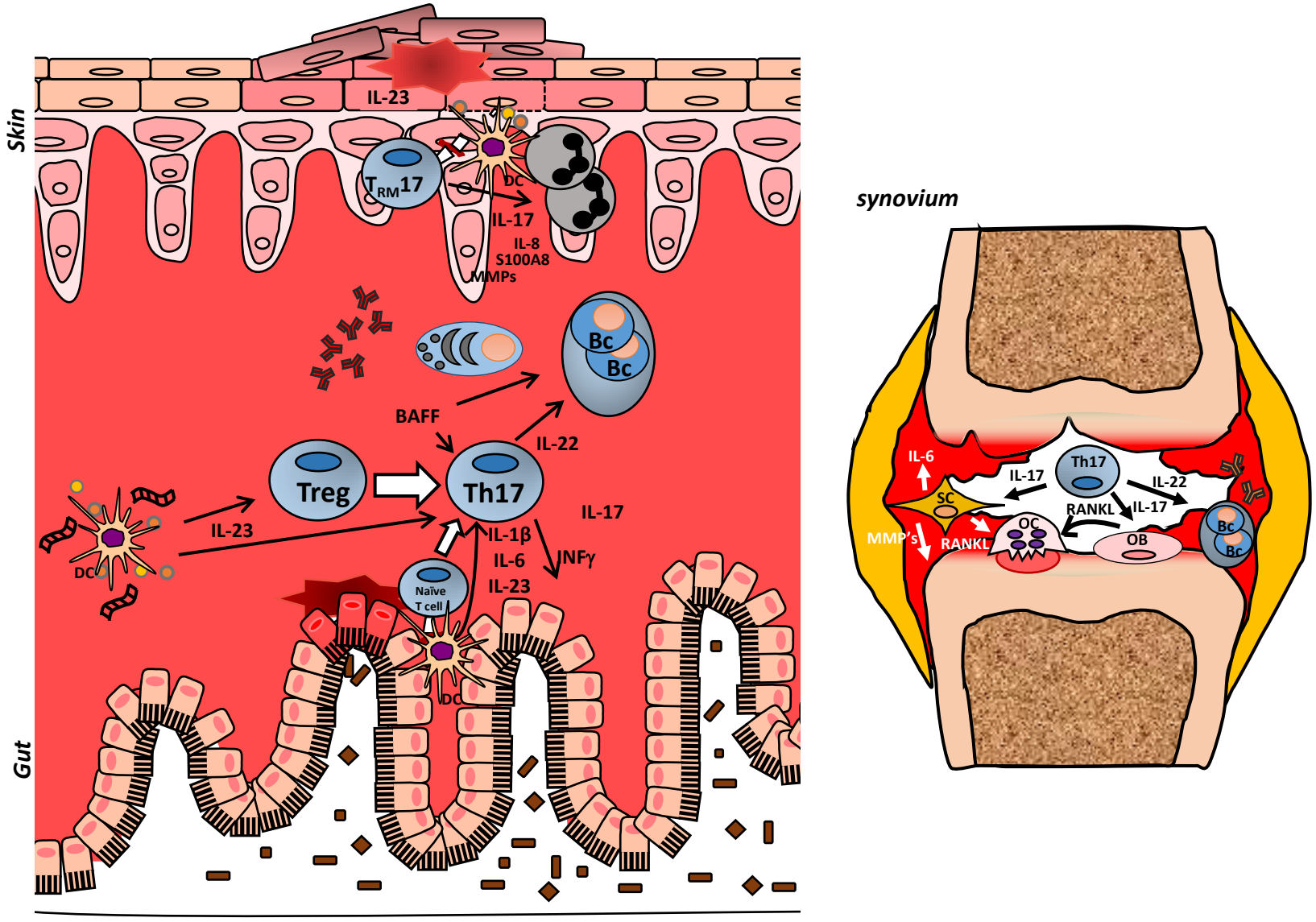

C. albicans
Skin
IL-1β
TRM17
DC
IL-17
S100A8
Chemokines
IL-21
IFNγ
IL-10
Tfh
Th17
Th17
IL-17
Chemokines
IL-1β
IL-6
IL-23
IL-22
TGFβ
IL-21
Naïve
T cell
Bc
Bc
DC
RegIII
M
cell
Gut
Trp

Figure 2


Skin
IL-23
$T_{RM}17$
DC
IL-17
IL-8
S100A8
MMPs
Bc
Bc
BAFF
IL-22
Treg
Th17
IL-17
IL-23
DC
IL-1β
IL-6
IL-23
INFγ
Naïve
T cell
DC
Gut

synovium
IL-6
Th17
IL-17
IL-22
SC
RANKL
IL-17
OC
MMP's
RANKL
OB
Bc
Bc