

known for decades that IL-12 induces Th1 cells [interferon- γ (IFN- γ) producers] and IL-4 induces Th2 cells (IL-4, IL-5 and IL-13 producers), it was only recently demonstrated that Th17 cells differentiate upon exposure to combinations of IL-1, IL-6 and transforming growth factor- β (TGF- β). Interleukin-23, although not critical for the induction of the Th17 lineage, is required *in vivo* for the stabilization and proliferation of Th17 cells.^{4,8} In addition to IL-17, Th17 cells and most 'Th17-like' innate cells produce IL-17F, tumour necrosis factor- α (TNF- α), IL-22 and IL-21; accordingly, in this review we will discuss the involvement of these related Th17 cytokines as they pertain to co-operative target gene regulation. We refer the reader to numerous reviews outlining mechanisms underlying Th17 differentiation.^{8–12}

Interleukin-17 and other Th17 cytokines are linked to the pathogenesis of diverse autoimmune and inflammatory diseases (Table 1, Fig. 1). Conversely, IL-17 is essential for host defence against many microbes, particularly extracellular bacteria and fungi.¹³ The IL-17 receptor is expressed ubiquitously, and hence most cells can potentially respond to this cytokine.¹⁴ The target cell types best analysed are of non-immune origin, particularly epithelial and mesenchymal cells within diseased or inflamed tissues.¹⁵ Studies have revealed IL-17-dependent activities in immune cells, particularly B lymphocytes and antigen-presenting cells (APC). Here, we aim to describe how IL-17 exerts its beneficial and its harmful properties via specific target gene regulation in the context of disease (Fig. 1).

IL-17-mediated pathogenesis in autoimmune disease

Interleukin-17 mediates adverse effects in many autoimmune diseases. Before the discovery of the Th17 subset as a distinct CD4⁺ effector population, it was considered that Th1, Th2 and B cells were the main mediators of pathology in autoimmunity. For example rheumatoid arthritis (RA) was widely accepted to be Th1-mediated, supported by the presence of IFN- γ and TNF- α (then thought to be a Th1 cytokine) in synovial lesions and peripheral blood.¹⁶ Similarly, inflammatory bowel disease (IBD) was described as a 'mixed' Th1 and Th2 pathology, with both IL-4 and IFN- γ implicated.¹⁷ However, during the late 1990s, studies pointed to IL-17 as a possible effector in RA and other diseases, despite the prevailing confusion as to whether IL-17 was a Th1 or 'Th0' cytokine.^{18,19} The discovery of the Th17 cell as a bona fide T-cell subset led to a re-kindling of interest in this cytokine in the context of autoimmunity. Indeed, pre-clinical studies supporting a role for IL-17 in disease (outlined herein) led to current clinical trials designed to block IL-17, the IL-17 receptor (IL-17R) or its inducers (i.e. IL-23, IL-6) in autoimmunity.^{20–22}

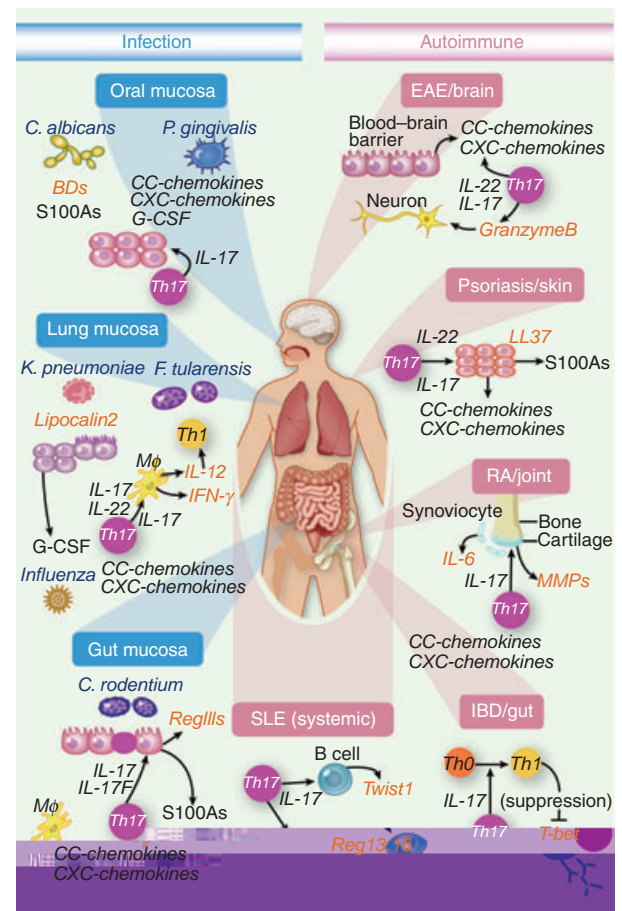


Figure 1. IL-17 signaling and target genes in various disease settings. In blue are representative mucosal infections where IL-17 plays a key role, along with key target genes involved in each. In pink are autoimmune diseases and the role of IL-17 and particular target genes therein.

Rheumatoid arthritis

Many, if not most, autoimmune diseases are now connected in some manner to IL-17 or the Th17 pathway. In particular, RA has been intensively studied, starting even before the recognition of the Th17 subset. The key features of inflamed arthritic joints are proliferating synovial fibroblasts, joint and cartilage erosion, infiltrating CD4⁺ T cells and autoantibody-producing plasma cells. In addition, increased numbers of innate immune cells (DC, granulocytes and macrophages), in some cases ectopic germinal centres (GC) are found within joints. Early studies showed that high levels of IL-17 were found in the rheumatoid synovium of patients with RA but not of controls or of patients with osteoarthritis. Consistently, adding IL-17 to an *in vitro* culture system stimulated bone resorption and collagen destruction.²³ Furthermore, neutralizing IL-17 or its receptor in collagen-induced arthritis mouse models resolved RA symptoms, IL-17A-deficient mice are protected from collagen-induced

which appears to promote spontaneous generation of autoreactive GC and hence elevated autoantibody production.⁴⁵

Another animal model with lupus-like features is the *Ets-1*^{-/-} mouse, characterized by increased high-titre

expressed.⁴³ Interleukin-17 synergizes with TNF- α to promote induction of nearly all its target genes, and in many cases synergy has also been observed with IFN- γ and IL-1 β (reviewed in ref. ²⁷). As a consequence, IL-17 alone or together with other inflammatory cytokines in the inflamed joint mediates adverse events in RA.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multi-organ systemic autoimmune disease characterized by autoantibody production. Although traditionally considered mainly a B-cell disease, recent reports indicate that there is likely to be a role for IL-17 in lupus (reviewed in ref.⁴⁴). Interleukin-17 is elevated in the serum of many SLE patients.^{45,46} The BXD2 mouse strain develops SLE-like features and spontaneous erosive arthritis with age.⁴⁵ These mice produce pathogenic autoantibodies because of increased somatic hypermutation and enhanced class-switch recombination, mediated by over-expressed activation-induced cytidine deaminase in GC.⁴⁷ In studies to elucidate the underlying mechanism of this phenotype, Hsu *et al.*⁴⁵ unexpectedly discovered IL-17-dependent signalling in BXD2 B cells that led to enhanced autoantibody production and increased numbers of GCs. CD4 T cells from BXD2 mice were also more prone to differentiate into Th17 cells. The IL-17 functions in this setting by inducing genes encoding Regulator of G-protein signalling 13 and 16 (Rgs13 and Rgs16), which inhibit G-coupled protein receptors such as CXCR4. Hence, IL-17 disrupts trafficking of B cells within lymph nodes,

antigens.⁵² Recognition of gut microbes is mediated by Toll-like receptors (TLR) and also intracellular pattern recognition receptors of the nucleotide oligomerization domain (NOD) family. Strikingly, genome-wide association studies (GWAS) identified NOD2 (CARD15) as an IBD-associated gene,^{53,54} leading to the current paradigm that IBD results from unregulated immune responses against commensal bacteria. In addition to NOD2, additional genes identified in GWAS studies have implicated the Th17 pathway, most notably the IL-23R,⁵⁵ which is expressed primarily on IL-17-producing cells. Other Th17-associated genes implicated in GWAS studies of IBD include

mune disease of the central nervous system. It is elicited by immunization of neuroantigens, such as myelin basic protein and proteolipid protein. As with many other autoimmune conditions, Th1 cells were long thought to be responsible for EAE pathology, despite the fact that IFN γ ^{-/-}, IFN γ R^{-/-} and IL-12p35^{-/-} mice were susceptible.⁷⁷⁻⁷⁹ Landmark studies comparing the IL-12p35^{-/-} and IL-23p19^{-/-} mice showed clearly that the Th17 pathway was responsible for pathology.⁸⁰ Further evidence for the role of Th17 cells in driving EAE was shown in STAT6^{-/-}/T-bet^{-/-} doubly deficient mice, lacking Th1 and Th2 cells.⁸¹ Furthermore, EAE in these mice could be ameliorated by treatment with anti-IL-17 antibodies. An elegant study noted that regulation of IL-17 pathogenic activity can be controlled by IL-10. Specifically, Th17 cells derived *ex vivo* following treatment with TGF- β and IL-6 do not cause EAE upon adoptive transfer, whereas Th17 cells derived *ex vivo* with TGF- β , IL-6 and IL-23 develop EAE.⁸² Interleukin-23 suppresses IL-10, correlating with elevated expression of IL-17 target genes such as CXCL10 (IP10), CCL2, CXCL2 and CCL20.⁸² Both IL-17 and IL-22 also disrupt the tight junctions that form the blood-brain barrier, enabling Th17 cells to migrate into the central nervous system and cause neuronal damage.⁸³

In summary, increasing numbers of autoimmune conditions implicate the Th17 pathway. Although the specific genes and mechanisms exhibit some variation depending on the location, chronicity and type of disease, there are many common threads in terms of IL-17-mediated gene expression. These findings have made blocking the IL-17 pathway an attractive target for anti-cytokine therapy.²² On the flip side, the same pathways that promote disease in autoimmunity are beneficial in many infection settings, which will be considered in the following sections.

Infection

In contrast to its adverse effects in autoimmunity, IL-17 plays a vital role in protecting the host from infection.¹³ This is particularly evident at mucosal sites such as lung, gut and the oral cavity. Interleukin-17-producing cells are enriched at mucosal surfaces, and Th17 cells express the CCR6 receptor that targets them to mucosal areas.^{84,85} Pro-inflammatory cytokines such as, IL-6, IL-1 β and TNF- α , which mediate defensive responses are induced by IL-17. In particular, IL-6, acts in a positive feedback loop to further amplify Th17 differentiation and activate acute-phase responses and complement.²⁸ Interleukin-17 modulates neutrophils via cytokines that promote polymorphonuclear cell expansion and survival (G-CSF, granulocyte-macrophage CSF)⁸⁶ as well as neutrophil chemoattractants (CXCL1, CXCL2 and CXCL5). Additionally, CXCL9, CXCL10 and CCL20 are target genes of IL-17, which have chemotactic activity for lymphocytes, DC and other immune cells, targeting them to mucosal

surfaces; IL-17 induces CCL2 and CCL7, monocyte-recruiting chemokines. Interestingly, IL-17 suppresses CCL5/RANTES, although the significance of this with respect to infection has not been determined.^{29,87} Antimicrobial peptides, which contribute to host defence by direct killing of invading organisms, are strongly up-regulated by IL-17. Notably, some of the chemokines regulated by IL-17 also exhibit antimicrobial activity (e.g. CCL20, which binds the CCR6 receptor found on DC and Th17 cells).^{88,89} In the following sections, we will discuss IL-17-induced genes in representative infectious models at various mucosal sites. Not surprisingly, most of the genes identified in the context of infection are the same as those identified from autoimmune studies or cell lines, but some appear to be somewhat specific to a particular pathogen or infected tissue.

Extracellular bacterial infections

Klebsiella pneumoniae (lung mucosa)

The first report to describe the IL-17RA^{-/-} mouse assessed pulmonary infection by an extracellular pathogen, *Klebsiella pneumoniae*.⁹⁰ *Klebsiella pneumoniae* is a Gram-negative bacterium that causes intra-abdominal and urinary tract infections, as well as hospital and community-acquired pneumonia. Infection with *K. pneumoniae* in IL-17RA^{-/-} mice led to reduced survival and elevated bacterial burden. Neutrophil levels in lung were severely impaired, which was linked to reduction of CXC chemokines and G-CSF in bronchoalveolar lavage fluid. The same group demonstrated a requirement for IL-23 in defence against *K. pneumoniae*.⁹¹ Mice that were IL-23^{-/-} showed a significant reduction in CCL3, CXCL2, CXCL1, CXCL5 and IL-6. When it was recognized that IL-22 is also a Th17-derived cytokine, IL-22 was found to be an even more critical player than IL-17 in the setting of *K. pneumoniae*.⁹² Although blocking both IL-17 and IL-22 significantly lowered G-CSF and CXCL1 expression in bronchoalveolar lavage fluid, the addition of IL-22 alone did not serve to increase G-CSF and CXCL1 expression. Rather, IL-22 affected mainly production of IL-6 and CCL3. In addition to stimulating chemokine expression, IL-17 and IL-22 induce lipocalin 2 (Lcn2, 24p3) in tracheal epithelial cells. The Lcn2 blocks catecholate-type siderophores of Gram-negative bacteria, preventing them from scavenging free iron,^{93,94} and is potently regulated by IL-17.⁹⁵ Surprisingly, however, IL-17 and IL-22 are apparently not necessary for Lcn2 induction in *K. pneumoniae* infections, whereas TLR4 and Myd88 are essential.⁹⁶

Citrobacter rodentium (gut mucosa)

Interleukin-17-expressing cells are particularly abundant in the gut, including classic $\alpha\beta$ -T cells as well as more

innate cells such as $\gamma\delta$ -T and natural killer T cells. *Citrobacter rodentium* is a naturally occurring murine enteric pathogen, and is an extracellular Gram-negative organism considered a model for enteropathic attaching and effacing *Escherichia coli* infections. In model studies of *C. rodentium* infection, IL-17 did not play a significant protective role compared with IL-22 at early stages of disease.⁹⁷ Infection with *C. rodentium* induces a variety of antimicrobial peptides, such as S100A8, S100A9, RegIII β and RegIII γ . RegIII β and RegIII γ are C-type lectins originally thought to selectively kill Gram-positive bacteria. Not surprisingly, adding back RegIII γ protected mice significantly. In contrast, direct comparison of IL-17A^{-/-} versus IL-17F^{-/-} mice suggested that IL-17 and IL-17F do contribute to protection from *C. rodentium* in later stages.⁹⁸ Here, CXCL1, CXCL2, IFN- γ , IL-1 β , IL-6, TNF- α and inducible nitric oxide synthase were regulated normally in the colons of IL-17A^{-/-}, IL-17F^{-/-} and IL-17A/F^{-/-} mice following *C. rodentium* infection. Similarly, IL-17A^{-/-} and IL-17F^{-/-} mice showed increased expression of BD2, Lcn2, S100A8, S100A9, RegIII and RegIII γ compared with wild-type mice, yet these mice still had a higher bacterial burden. However, BD1, BD3 and BD4 were impaired in the knockout strains, implying that in this setting they may be the major IL-17 gene targets.

Porphyromonas gingivalis (oral mucosa)

The oral cavity is another important but often overlooked site of mucosal infection. Studies of a major human periodontal pathogen revealed a strongly protective role for IL-17 receptor signalling, at least in acute oral infections. *Porphyromonas gingivalis* is a Gram-negative anaerobic microbe that is one of the three major pathogens associated with periodontal disease, characterized by gingival tissue destruction, chronic infection and bone loss in the alveolar bone crest of the jaw. Despite the potential of IL-17 to promote bone destruction as it does in the context of RA, IL-17RA^{-/-} mice are more susceptible to infection than wild-type mice. The major IL-17 gene targets shown to be impaired were CXCL1, CXCL2 and CXCL5,^{99,100} which correlated with reduced neutrophil recruitment to the gingival area. Consistently, CXCR2^{-/-} mice (the receptor for CXCL1, CXCL2 and CXCL5) are exquisitely susceptible to *P. gingivalis*-induced periodontal disease. Interestingly, these studies also revealed a gender bias for IL-17R activity. Regardless of genetic background, female IL-17RA^{-/-} mice were more susceptible than males to *P. gingivalis*-induced bone loss. Although the female mice showed a more dramatic reduction in CXC chemokine expression, the male mice were mainly impaired in G-CSF. Consequently, although both genders had reduced neutrophil activity, this appeared to be directed through different mechanisms.⁹⁹

Intracellular bacterial infections

It is commonly considered that IL-17 is primarily important for protection against extracellular pathogens rather than intracellular bacteria. Indeed, in many cases, but not all, IL-17 is dispensable for host defence against intracellular bacteria.¹³ For example, *Listeria monocytogenes* induces IL-17 in liver $\gamma\delta$ -T cells, which is associated with enhanced neutrophil recruitment;¹⁰¹ however, IL-17RA^{-/-} mice have no defect in survival, arguing against a role for IL-17 in this disease.¹⁰¹ *Mycobacterium tuberculosis* infection studies also revealed critical roles of IFN- γ rather than IL-17 in primary infections, although IL-17 is induced during infection.^{102,103} Nonetheless, the picture is more complex than this because IL-17 is essential for an effective vaccine-induced response to *M. tuberculosis*.¹⁰⁴ Although the detailed mechanisms need to be defined more carefully, IL-17 may contribute more to the development of memory responses than to initial infections for some intracellular organisms.¹⁰⁴ In contrast, infection with *Francisella tularensis*, another intracellular organism, shows a requirement for IL-17.¹⁰⁵ Mechanistically, this is regulated via IL-17-mediated induction of IFN- γ and IL-12 in macrophages, linking Th17 and Th1 responses *in vivo*. Similarly, responses to *Chlamydia* infection also involve IL-17.¹⁰⁶ Therefore, the concept that IL-17 activity is exclusively linked to protection from extracellular pathogens is overly simplistic.

Fungal infections

In the setting of fungal infections, IL-17 plays both protective and destructive roles depending on route of infection and perhaps the morphological form of the organism. The primary organism where this has been examined is *Candida albicans*, a common commensal that colonizes human mucosal surfaces. *Candida albicans* causes both systemic and mucosal infections, but the immune responses at these sites are quite different.¹⁰⁷ The most severe form of candidiasis is a disseminated disease associated with hospital settings, which is modelled by intravenous injection of *C. albicans* into mice. The IL-17RA^{-/-} mice are highly susceptible to this form of disease. Although detailed analysis of relevant target genes was not performed, neutrophil recruitment was severely defective.¹⁰⁸ Consistent with this, two reports using mouse models of oropharyngeal candidiasis ('thrush') showed that IL-17 and IL-23 play a strongly protective role against mucosal *C. albicans*.^{109,110} Microarray analysis showed that immunocompetent wild-type mice infected with *C. albicans* up-regulate numerous classic IL-17 target genes in the oral mucosa, including BD3, S100A8/9, MMP-8, G-CSF, CCL20, IL-6, CXCL1 and CXCL5.¹⁰⁹ BD3 and S100A8/9, in particular, were strongly impaired in IL-17RA^{-/-} tongue tissue. In contrast, few IFN- γ signa-

ture genes were induced in this setting, arguing against a role for Th1 cells.¹⁰⁹ Studies of the pattern recognition receptors involved in early activation events indicate that C-type lectin receptors such as Dectin 1, Dectin 2 and the Mannose receptor as well as the NLRP3 inflammasome induce IL-23 from macrophages and DC, hence promoting Th17 cell differentiation (reviewed in ref.¹¹¹). These findings are supported by studies in humans with mutations in STAT3 (who are selectively Th17-deficient), who are exquisitely susceptible to mucosal candidiasis and staphylococcal infections.¹¹²

In contrast, in a gastrointestinal model of *C. albicans* and *Aspergillus fumigatus* mucosal infection induced by injection of fungi into the gut, Romani and colleagues¹¹³ reported that IFN- γ plays a primary role in protection, whereas IL-23 and IL-17 exacerbate inflammation. However, when IFN- γ is absent, IL-23 plays a protective role via mechanisms involving cross-regulation of IL-12 and IL-23.¹¹³ A caveat of this model is that it does not have a true parallel human disease state, but may nonetheless reflect the complexity of immune responses that differ by anatomic location.

Viral infections

Viral host defence depends heavily on Type I IFNs that modulate viral replication, and so IL-17 is considered to be relatively less important. However, there is emerging evidence that IL-17 may participate in viral immune responses, which can be beneficial or detrimental to the host. It is also intriguing that a homologue of IL-17 is encoded in a Herpesvirus saimiri, a T-cell tropic γ herpesvirus.¹¹⁴ The significance of this is unknown, although viral IL-17 promotes positive signalling through IL-17RA.¹¹⁴ Nonetheless, this homologue presumably benefits the virus in some aspect of pathogenesis, by some as yet unknown mechanism.

In poxvirus infections, genetically engineered recombinant vaccinia viruses (VV) encoding IL-12, IL-23 or IL-17 were created to test the roles of these cytokines in viral host defence. Surprisingly, VV-IL-23 and VV-IL-17, but not VV-IL-12, caused reduced virulence in mice.¹¹⁵ Although the mechanism was not well defined, protection was not mediated by enhanced cytotoxic lymphocyte activity. Surprisingly, IL-23-induced viral resistance was also not primarily the result of IL-17, as IL-17^{-/-} mice infected with VV-IL-23 were not significantly compromised.¹¹⁵ Interleukin-22 and other Th17-hallmark cytokines were not evaluated in this study. In a contrasting report, an IL-17-expressing VV was found to be more virulent than its parental virus in mice, associated with altered immunoglobulin G isotype generation.¹¹⁶ The distinctions between these models is unclear, but may reflect the fine line between host defence and immunopathology mediated by IL-17.

Interleukin-17 signalling may be counterproductive in certain viral settings, by contributing to the 'cytokine

storm' that characterizes disease pathology. In an influenza infection model, IL-17 and IL-17F were induced as soon as 2 days post-infection. The survival rate of IL-17RA^{-/-} mice was higher than WT, associated with reduction in neutrophil chemokines and inflammatory cytokines (G-CSF, CXCL1, IL-6, TNF- α , IL-1 β and IFN- γ). Lung injury in this setting may be partly the result of IL-17-mediated oxidation of phospholipids by recruited neutrophils.¹¹⁷

Another report identified a function of IL-17 in maintaining virus persistence in a model using Theiler's murine encephalomyelitis virus (TMEV),¹¹⁸ which leads to a demyelinating disease. In a susceptible mouse strain, Th17 development was elevated during TMEV infection, and Th17 cells infiltrated into the central nervous system. Viral persistence in brain and spinal cord and production of IL-6, CXCL1 and MCP-1 correlated with the appearance of Th17 cells.¹¹⁸ Importantly, the mechanism by which the virus persists was because of the resistance to apoptosis of infected astrocytes. Interestingly, IL-17F did not mediate an anti-apoptotic effect. Collectively, these findings indicate that infection by viruses often induces Th17 differentiation and so its signature target genes, yet this is often ineffective in terms of host defence, and may even promote immunopathology.

IL-17 signalling: synergy and mechanisms

Mechanisms of IL-17 signalling are poorly described compared with other cytokine receptor subfamilies. Although reviewed in detail elsewhere,^{2,27,51} IL-17 binds to both the IL-17RA and IL-17RC subunits to mediate signalling.¹¹⁹ Both receptors encode a conserved signalling motif known as the SEFIR (SEF/IL17R) domain,¹²⁰ which engages the Act1 adaptor/ubiquitin ligase enzyme through its own SEFIR motif.^{121–123} Act1 in turn recruits TRAF6, which leads to activation of the nuclear factor- κ B (NF- κ B) pathway. Act1 is also upstream of the CCAAT/Enhancer Binding Protein (C/EBP)- β and C/EBP- δ and mitogen-activated protein kinase pathways, all of which act in concert to control target gene expression. Most IL-17 downstream genes have NF- κ B and C/EBP binding sites, and in many cases both are necessary for IL-17-mediated promoter activity.^{95,124}

As mentioned previously, a notable feature of IL-17 is its strong co-operative effect with other cytokines in regulating down-stream gene/protein expression. Interleukin-17 has been shown to synergize with IL-1 β , IL-22, IFN- γ , TNF- α , Oncostatin M, CD40, BAFF and Vitamin D3 (1,25-dihydroxyvitamin D3), and this list may grow^{29,73,75,125,126} (Table 2). This synergy is reflected in the fact that IL-17 alone is not a potent inducer of inflammatory pathways such as NF- κ B, despite the potent *in vivo* effects of an IL-17 deficiency (reviewed in ref. 2). The molecular mechanisms underlying synergistic signalling are not fully elucidated, although various pathways are implicated. Many IL-17 target genes are controlled

post-transcriptionally by messenger RNA stabilization. In particular, CXCL1, CXCL2, IL-6, I- κ B ζ and CXCL5 messenger RNAs are induced by IL-17 and/or TNF- α somewhat weakly and are subject to rapid degradation, but in the presence of both IL-17 and TNF- α their stability is significantly enhanced.¹²⁷ Mechanistically this is mediated by the mitogen-activated protein kinase pathway and Act1, but surprisingly not by TRAF6. At the promoter level, co-operative induction of C/EBP proteins but not NF- κ B by the combination of IL-17 and TNF- α contributes to co-operative induction of the IL-6 promoter.¹²⁴ The synergy between IL-17 and BAFF, however, is mediated by the NF- κ B pathway, where IL-17RA out-competes the BAFFR for Act1, leading to positive rather than suppressive signalling.⁴⁶ Interleukin-17 has also been shown to regulate the TNF receptor, which may account for enhanced TNF- α signalling capacity in the presence of IL-17.¹²⁸ Similarly, the synergy between IL-17 and IL-19, IL-20 and IL-24 was dependent on the expression of IL-22 receptor.¹²⁵ Finally, the mechanisms by which IL-17 and IL-22 synergize to regulate antimicrobial peptides such as S100A8/9 and IL-20 family members still need to be determined. In summary, although IL-17 is generally a weak inducer of target genes, this cytokine has a major impact *in vivo*. Therefore, the synergistic effects of IL-17 almost certainly play a significant role in dictating its physiological activities.

Conclusion and perspectives

As suggested by ubiquitous IL-17R expression,¹⁴ IL-17 plays a role in multiple cell types and conditions. Initial studies revealed the IL-17 target genes from mesenchymal and epithelial cells, but recent work has shown important IL-17 target genes in lymphocytes and other immune cells as well. Defining the complete range of IL-17 effects *in vivo* will probably never be fully achieved, but it is clear that this cytokine is a central player in numerous disease states.

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