ANNUAL REVIEWS

Annual Review of Immunology

IL-17 in the Pathogenesis of Disease: Good Intentions Gone Awry

Saikat Majumder and Mandy J. McGeachy

Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh, Pennsylvania 15261, USA; email: sam353@pitt.edu, mandymcgeachy@pitt.edu

Annu. Rev. Immunol. 2021. 39:537–56

First published as a Review in Advance on February 12, 2021

The *Annual Review of Immunology* is online at immunol.annualreviews.org

https://doi.org/10.1146/annurev-immunol-101819-092536

Keywords

IL-17, autoimmunity, microbiota, wound healing, fibrosis, cancer, stromal cells

Abstract

The IL-17 family is an evolutionarily old cytokine family consisting of six members (IL-17A through IL-17F). IL-17 family cytokines signal through heterodimeric receptors that include the shared IL-17RA subunit, which is widely expressed throughout the body on both hematopoietic and non-hematopoietic cells. The founding family member, IL-17A, is usually referred to as IL-17 and has received the most attention for proinflammatory roles in autoimmune diseases like psoriasis. However, IL-17 is associated with a wide array of diseases with perhaps surprisingly variable pathologies. This review focuses on recent advances in the roles of IL-17 during health and in disease pathogenesis. To decipher the functions of IL-17 in diverse disease processes it is useful to first consider the physiological functions that IL-17 contributes to health. We then discuss how these beneficial functions can be diverted toward pathogenic amplification of deleterious pathways driving chronic disease.

INTRODUCTION: IL-17 PROTECTS BARRIER SURFACES

In healthy humans and mice, IL-17 expression is limited to barrier surface tissues: intestine, gingiva, conjunctiva, vaginal mucosa, and skin. At these surfaces, IL-17 is produced at low amounts in response to the beneficial resident microbiota, and it induces production of antimicrobial peptides by the epithelium to maintain a healthy bacterial and fungal population. IL-17 also stimulates epithelial cells to produce G-CSF (granulocyte colony-stimulating factor), chemokines that recruit neutrophils, and proinflammatory cytokines such as IL-6 (**Figure 1**). By inducing subclinical levels of these acute-phase responses in local tissue, and by supporting antibody production, homeostatic IL-17 not only helps to maintain healthy populations of microbiota but raises the epithelial antimicrobial threshold to protect against infection (1, 2). Although much emphasis has been placed on bacterial microbiota roles in barrier surfaces, it is likely that fungal residents of the mycobiome also contribute to IL-17 homeostatic roles, as demonstrated recently in mice (2–4).

If pathogens breach epithelial barriers, then tissue damage along with increased immune activation increases the magnitude of the IL-17 response to control and clear the invasion, with accompanying signs of inflammation. Mice or humans deficient in IL-17 signaling take longer to clear infections by pathogens such as *Candida albicans* and *Staphylococcus aureus* and develop

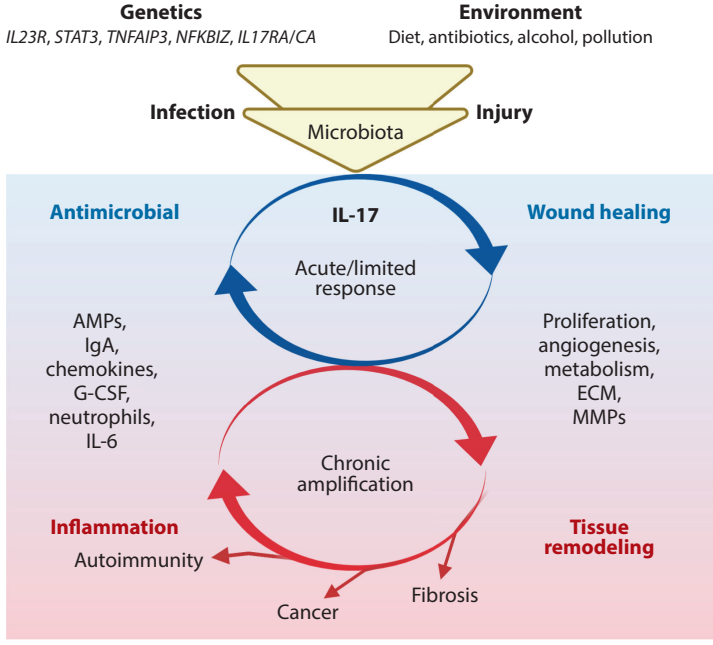


Figure 1

Overview of IL-17 in health and disease. IL-17 production and signaling are multifactorially regulated by an interplay between genetics, environment, and microbiota populations at barrier surfaces, leading to homeostatic maintenance in healthy individuals. Injury or infection increases the IL-17 effector functions that drive antimicrobial effector response and promote repair of the tissue. If the IL-17 response is inappropriately amplified due to altered input from genetic and environmental factors or due to chronic stimulation that occurs during autoimmunity, persistent infection, or cancer, then the antimicrobial and repair functions convert to pathologic inflammation and tissue remodeling that promote fibrosis, tumorigenesis, or autoimmune disease. Abbreviations: AMP, antimicrobial peptide; ECM, extracellular matrix; G-CSF, granulocyte colony-stimulating factor; MMP, matrix metalloproteinase. Figure adapted from image created with BioRender.com.

infections that spread across a wider surface area as well as penetrate underlying tissues (5, 6). Interestingly, the Kaplan lab recently demonstrated that local IL-17 responses are activated in the noninfected tissues adjacent to *Candida* infection, in a process termed anticipatory immunity that acts to contain the infection and protect surrounding tissues (7). Naik et al. (8) reported heterologous protection against skin invasion by newly encountered pathogens due to IL-17 signaling in epithelium in response to microbial colonization by a noninvasive pathogen.

The delicate balance between IL-17 and microbiota is most elegantly demonstrated in mice lacking IL-17 receptor specifically on intestinal epithelium: They develop intestinal dysbiosis due to outgrowth of normally IL-17-regulated bacterial strains. In turn, dysbiosis drives enhanced T helper 17 (Th17) activation and IL-17 production in an attempt to restore balance. The consequence for the host of this enhanced mucosal IL-17 response is increased autoimmune disease severity in a model of multiple sclerosis (MS) (9). Indeed, it is now widely thought that dysregulation of healthy microbiota populations contributes to autoimmune disease susceptibility in humans, in part by disrupting the balance of type 17 responses in the gut and thereby influencing systemic Th17 activation. The use of photoconvertible cell tracking in mice has shown that in some instances, Th17 cells that originate in the gut are found in inflamed peripheral tissues including kidney and joints, further supporting a role for microbiota-regulated Th17 cells in autoimmune disease (10, 11). Autoimmunity could thus be considered collateral damage from mucosal surface immunity.

IL-17 AND LYMPHOID ORGANS

A feature of chronically inflamed tissues is the generation of tertiary lymphoid organs (TLOs), which are semiorganized structures resembling lymph nodes (LNs) containing B and T cells. The role of TLOs in autoimmune disease and cancer remains unclear, but it is thought that they help to sustain local activation of adaptive immunity that might contribute to the ongoing disease process. Both TLOs and secondary lymphoid organs (lymph node and spleen) are maintained and architecturally zoned by specialized fibroblast-like stromal cells broadly termed fibroblastic reticular cells (FRCs) and follicular dendritic cells (FDCs). FRCs produce CCL19 and IL-7 to sustain T cell zones, and FDCs produce CXCL13 to recruit B cells and T follicular helper cells to form germinal centers (12). Chronic lung inflammation due to infection or repeated lipopolysaccharide (LPS) stimulation drives formation of TLOs called inducible bronchus-associated lymphoid tissue (iBALT) in an IL-17-dependent manner (13, 14). IL-17 induces chemokines CXCL13 and CCL19 to recruit lymphocytes to iBALT, implicating FRC involvement in establishing these structures (13, 14). IL-17 is also required for formation of TLOs in meninges in a mouse model of MS because it drives the expansion and differentiation of meningeal myofibroblasts into FRC-like cells (15, 16) (**Figure 2**).

Lymphoid tissue inducer (LTi) cells are similar to group 3 innate lymphoid cells (ILC3s) and require RORγt to establish secondary lymphoid organs during fetal development. However, LTi cells produce lymphotoxin for this function, and mice deficient in IL-17 do not have obvious structural defects in their LNs and spleens, which are of normal size compared to those of congenic wild-type mice. However, during adaptive immune responses, the size of the LN increases, with an accompanying increase in numbers of supporting FRCs. It was recently established that this expansion of the existing FRC population does require IL-17 signaling, at least during type 17 driving inflammatory responses. When IL-17 receptor was specifically deleted in FRCs, the cells failed to expand following immunization or colitis despite hypercellularity of the inflamed LN occurring as normal. While IL-17 is known to drive proliferation of epithelial cells, this study indicated that IL-17 supports proliferation and survival of activated stromal cells by increasing their

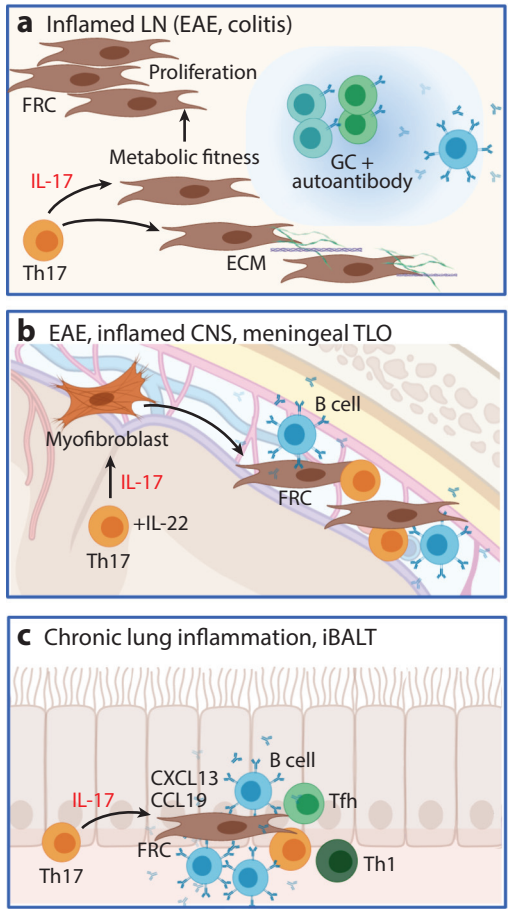


Figure 2

IL-17 activates lymphoid structural stromal cells. (*a*) During Th17-driving immune responses, FRCs proliferate in inflamed draining LNs, and IL-17 is required for increased metabolic fitness that promotes FRC survival and ECM production and optimizes B cell germinal center activation. (*b*) During experimental autoimmune encephalomyelitis, IL-17 promotes development of TLO structures by activating meningeal myofibroblast differentiation to FRC-like stromal cells. (*c*) IL-17 promotes iBALT, a form of TLO, in chronically inflamed lung tissue by inducing chemokines that recruit T and B cells to support antibacterial Th1 responses and antibody production. Abbreviations: CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; ECM, extracellular matrix; FRC, fibroblastic reticular cell; GC, germinal center; iBALT, inducible bronchus-associated lymphoid tissue; LN, lymph node; Tfh, T follicular helper cell; Th1, T helper 1; TLO, tertiary lymphoid organ. Figure adapted from image created with BioRender.com.

metabolic fitness, a role that was not previously known for IL-17 but has interesting connotations in terms of regulating IL-17-driven inflammatory outcomes in other organs. On a related note, IL-17 has been shown to regulate metabolic thermogenesis in adipose tissues (17).

Similar to its activity in peripheral inflamed tissues, IL-17 recruits neutrophils to the LNs during Th17 responses (18), which can provide an additional source of IL-1β for Th17 differentiation (19). However, it appears that FRCs are not the predominant cell type that recruits neutrophils, suggesting that other stromal cells also respond to IL-17 and influence the LN response (18). The

consequence of failed FRC expansion in the absence of IL-17 was instead found to be reduced numbers of germinal center B cells and impaired autoantibody production (18). IL-17-producing cells have previously been shown to support antibody production in autoimmunity and infection and proposed to act directly on B cells (20–23). It has also been suggested that Th17 cells convert to T follicular helper cells in Peyer patches to support IgA production against commensals and following oral immunization (22). These new FRC data provide an alternative explanation by demonstrating that IL-17 can promote antibody responses via signaling to LN stromal cells to act as an intermediary between Th17 and B cells recognizing autoantigen. Whether the same principle applies to infections that require antibody and to Th1- or Th2-dominated immune responses has yet to be determined. However, as most autoimmune diseases are associated with both IL-17 and autoantibody (as either diagnostic or pathogenic markers), this link between IL-17 responses and enhanced autoantibody responses is intriguing.

PATHOGENIC VERSUS HOMEOSTATIC FUNCTIONS OF IL-17: CONSIDER THE SOURCE

IL-17 is predominantly produced by immune cells of the adaptive and innate lymphocytic lineages, including $CD4^+$ Th17 cells, $CD8^+$ Tc17 cells, γδ T17 cells, mucosa-associated invariant T (MAIT) cells, and ILC3s. Collectively, the cells producing IL-17 are called type 17 cells hereafter. Commensal-driven type 17 immune responses tend to regulate microbiota without causing classical signs of inflammation and instead promote healing of skin wounds and enhanced defense against invading pathogens (1). This is in contrast to now well-known inflammatory roles of IL-17-producing cells in autoimmune disease pathogenesis and the proposed roles in cancer and fibrosis discussed below. How are these pleiotropic functions of IL-17 achieved to cause different outcomes? Here we describe three main mechanisms: synergy at the responder cell level, feed-forward loops, and finally regulation of coexpressed cytokines at the producing cell level. The common theme is that IL-17 is rarely a lone driver but rather acts to modulate and amplify signals in a local and context-dependent fashion.

One important aspect of IL-17 signaling is that it heavily relies on synergy with other cytokines for output. In fact, IL-17 by itself is a rather weak activator of signaling proteins and downstream gene expression. Instead, IL-17 synergizes with many cytokines, from obvious proinflammatory cytokines such as tumor necrosis factor (TNF) and interferon gamma (IFN-γ) to seemingly anti-inflammatory transforming growth factor beta (TGF-β), and can also promote LPS signaling through Toll-like receptor 4 (TLR4). In many instances, the mechanisms through which this synergy is achieved have not been established. IL-17 signaling has been recently reviewed in detail (24), so we only briefly discuss mechanisms of synergy here. IL-17 and TNF synergy has been most intensively studied and includes induction and/or activation of RNA-binding proteins that stabilize and promote translation of target mRNA transcripts and induction of transcriptional regulators that further enhance cytokine receptor signaling outputs (24). For example, Iκbζ coactivates NF-κb for gene transcription of IL-6. Iκbζ expression is induced by IL-17 but not TNF (25), whereas TNF is a strong activator of NF-κb compared to IL-17; hence, the result of both is a synergistic increase in Iκbζ -regulated targets (25–27). IL-17 also enhances expression of cytokines that can then act on the responder cells in a feed-forward loop. An example is the induction of leukemia inhibitory factor (LIF) in synovial fibroblasts that then acts to enhance and sustain IL-6 expression (28).

Another mechanism that has emerged as a key modulator of IL-17 effects is at the level of the cells that produce IL-17. Skin-resident Tc17 cells induced by the commensal *Staphylococcus epidermidis* produce IL-17 along with immunoregulatory and tissue repair factors, including

IL-10, TGF-β, fibroblast growth factor (FGF), amphiregulin, and vascular endothelial growth factor (VEGF) (1). In addition, they are poised for coproduction of type 2 cytokines depending on the tissue cytokine milieu, with IL-18 identified as a switch towards type 2 (29). In this context, it is interesting that γδ T17 and Th17 cells express IL-18R, but whether IL-18 alters the proinflammatory versus reparative bias of these cells is unknown. However, the balance of cytokines that activate Th17 cells is thought to be one factor driving a more proinflammatory (IL-23- and IL-1β-driven) versus nonpathogenic Th17 (TGF-β-driven) phenotype (30, 31). Human Th17 cells can be induced in vitro against *Candida albicans* or *Staphylococcus aureus*, both opportunistic pathogens known to elicit protective Th17 responses. IL-23, IL-6, and IL-1β were all required, but concentration of IL-1β was identified as a switch that could inhibit IL-10 production while promoting IFN-γ (32). A recent study compared gene expression signatures of intestinal Th17 cells induced in response to colonization with the commensal segmented filamentous bacteria or infection with the pathogen *Citrobacter rodentium*, both attaching-effacing bacteria but with different inflammatory outcomes (33). Commensal-induced Th17 cells coexpressed IL-10 and IL-22 along with IL-17, while pathogen-induced Th17 cells showed an increased propensity for plasticity toward a Th1 phenotype, an increased pathogenic Th17 signature, and metabolic activity suggesting greater activation and proliferation (33). An independent study has verified that commensal-driven gut Th17 cells express IL-17, IL-22, and IL-10 and further found that they are uniquely dependent on dendritic cell (DC) expression of the C-type lectin receptor Mincle, which induces IL-6 and IL-23 expression (34).

Reliance on Mincle highlights a common and interesting theme of type 17 cell activation at barrier surfaces: There is typically a limited reliance on DC stimulation through classical TLR pathways for IL-17 promoting cytokine production (**Figure 3**). IL-6 is produced by nonhematopoietic cells in response to mechanical stress and to cytokines including IL-17 itself (35). Epithelial cells detect the pathogenic determinant *Candidalysin* and produce IL-1β in response to oral *Candida* infection (36). In the skin, cutaneous sensory neurons detect *C. albicans* hyphal invasion and promote DC production of IL-23 through release of the neuropeptide CGRP (calcitonin gene–related peptide) (7). Attaching-effacing bacteria in the gut induce epithelial serum amyloid A production that then drives IL-23 and IL-1β production in DCs (37).

For ILCs and γδ T cells, major producers of IL-17 that do not express classical T cell receptors, cytokines are the critical drivers of proliferation and effector functions in tissues (38–40). Tc17 cells responding to skin commensals are activated through nonclassical MHC-Ib as well as cytokines (1). We recently described how STAT3 activation, downstream of IL-6 and IL-23 signaling, licenses effector Th17 cells to respond to antigen by maintaining mitochondrial membrane potential (41). This again suggests that the cytokine milieu is a strong regulator of IL-17 production even in antigen-specific Th17 cells. In addition, human Th17 cells do not require and in fact are inhibited by CD28 costimulation, unlike Th1 cells (42). Instead, IL-23 and IL-1β provide activation signals including metabolic reprogramming normally associated with CD28, albeit at a lower magnitude with correspondingly reduced proliferation (42). Hence, we propose that the cytokine conditions present in healthy barrier tissues promote the preferential induction of small populations of metabolically inert Th17 cells that in turn regulate barrier surface immunity without inducing overt inflammation. However, type 17 cells are poised to rapidly expand and increase their proinflammatory functions in case of tissue injury or pathogen invasion by sensing changes in cytokine composition.

IL-17 GOES VIRAL?

IL-17 is most critical for control of extracellular bacteria and fungi, as evidenced by the high susceptibility to these pathogens in humans with genetic mutations affecting the IL-17 pathway (6).

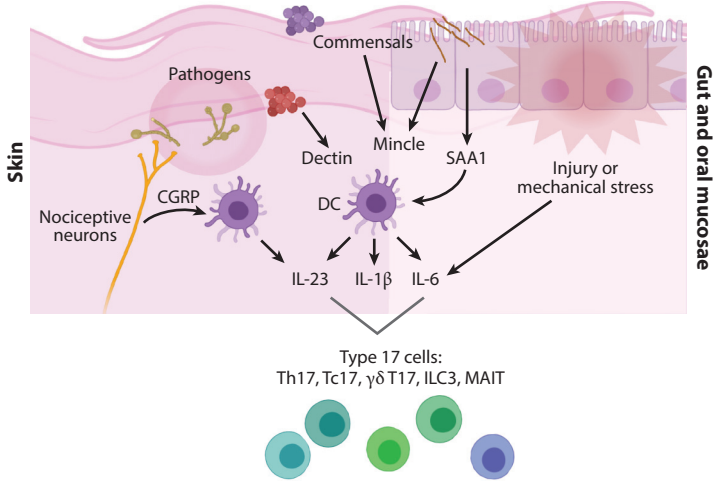


Figure 3

Atypical signals induce IL-17-promoting cytokines IL-23, IL-1β, and IL-6 at barrier surfaces. *Candida albicans* hyphal invasion is detected by cutaneous sensory neurons that release CGRP to promote DC production of IL-23. Both commensals and pathogens that activate type 17 responses preferentially activate DCs through C-type lectin receptors, including Mincle. Attaching-effacing commensal bacteria drive production of the acute-phase protein serum amyloid A by gut epithelia to activate DCs. IL-6 is produced by nonhematopoietic cells in response to mechanical stress, such as chewing hard food, and in response to cytokines including IL-17 itself in a positive-feedback loop, and damaged and dying cells release IL-1β. Abbreviations: CGRP, calcitonin gene–related peptide; DC, dendritic cell; ILC3, group 3 innate lymphoid cell; MAIT, mucosa-associated invariant T; SAA1, serum amyloid A1. Figure adapted from image created with BioRender.com.

Indeed, the well-established roles of IL-17 in promoting production of antimicrobial peptides and recruiting neutrophils are well-suited to controlling these types of infections. However, important contributions of IL-17 signaling have been found during infections with various viruses and intracellular bacteria. In mouse models, IL-17 has been reported to promote cytotoxic T cell function against West Nile virus and to promote recruitment of $CD8^+$ cytotoxic T cells to the liver during acute hepatitis (43, 44). During lung infection with *Mycobacterium tuberculosis*, early IL-17 supports the Th1 response by inducing chemokines that enhance recruitment to the site of infection (45). IL-17 has also been reported to promote the antibody response during H5N1 influenza infection by recruiting B cells to the lungs (46, 47). Similarly, $CD4^+$ tissue-resident memory Th1 cells are recruited and maintained in the vaginal mucosa after herpes simplex virus 2 infection in an IL-17-dependent manner, and $IL\text{-}17^{-/-}$ mice are highly susceptible to reinfection (48). Hence, induction of chemokines to aid in positioning of the antiviral immune response at the site of infection could be a beneficial function of IL-17 that is likely induced by viral tissue damage.

On the other hand, recruitment of immune cells and induction of proinflammatory cytokines, particularly neutrophils and IL-6, can have detrimental effects in an already-injured tissue (49). In a recent study with pediatric patients, the authors found that IL-17 production is significantly increased in the bronchoalveolar lavage (BAL) fluids of children with community-acquired pneumonia (CAP) (50). Profiling of immune cells identifies MAIT cells to be the major producers of IL-17 in BAL fluids. Along with levels of IL-22, IL-23, and IL-6, levels of IL-17 correlated with CAP severity (50). IL-17 levels were found to increase in patients with severe pandemic influenza A H5N1–associated disease, and neutralizing IL-17 in a mouse model of H1N1 reduced lung injury (51). Similarly, infants with severe respiratory syncytial virus infection had increased IL-17

and IL-6 in their BAL fluid, and mouse models show that IL-17-mediated CXCL1 and matrix metalloproteinase (MMP) expression in the airways leads to increased neutrophil accumulation and amplified lung tissue destruction (52, 53). Overall then, increased IL-17 appears to have negative consequences in viral lung disease, contributing to increased pathology in damaged lungs.

The most extreme version of inflammatory lung damage results in acute respiratory distress syndrome (ARDS), where the lungs fill with debris, immune cells, and mucus that impede oxygen exchange. The coronavirus disease 2019 (COVID-19) pandemic has dramatically illustrated the life-or-death consequences of an overactive cytokine response, as approximately 10–20% of confirmed cases require hospitalization and oxygen support in the second phase of the disease if the virus triggers ARDS. Another clinical feature of COVID-19-induced lung damage has been the extensive fibrotic changes that further compromise respiration and may have long-term consequences for surviving patients. Although we are still in the preliminary stages of understanding the pathology associated with COVID-19-induced ARDS, IL-17 and its downstream intermediary IL-6 have been proposed as drivers of immunopathology, and at least one of the ongoing clinical trials in China is testing the potential role of ixekizumab (a neutralizing IL-17A antibody used for psoriasis) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (54–56).

WHEN TISSUE REPAIR GOES WRONG: CANCER, FIBROSIS, AND AUTOIMMUNITY

Following injury, IL-17 plays dual roles in protecting the host, both protecting against microbes that invade the breached barrier and promoting healing. Chronic injury, for example in persistent infection or autoimmune attack, can lead to prolonged attempts at repair that become pathologic (**Figure 4**). There is now a multitude of evidence pointing toward a protumorigenic role for IL-17 in human cancer and murine cancer models (**Table 1**), although a few studies point toward protective effects (**Table 2**). Similarly, IL-17 is clearly associated with pathologic processes in autoimmune diseases and fibrotic disease. Here we discuss the role of IL-17 in beneficial reparative processes and how those become pathogenic during chronic stimulation and tissue injury.

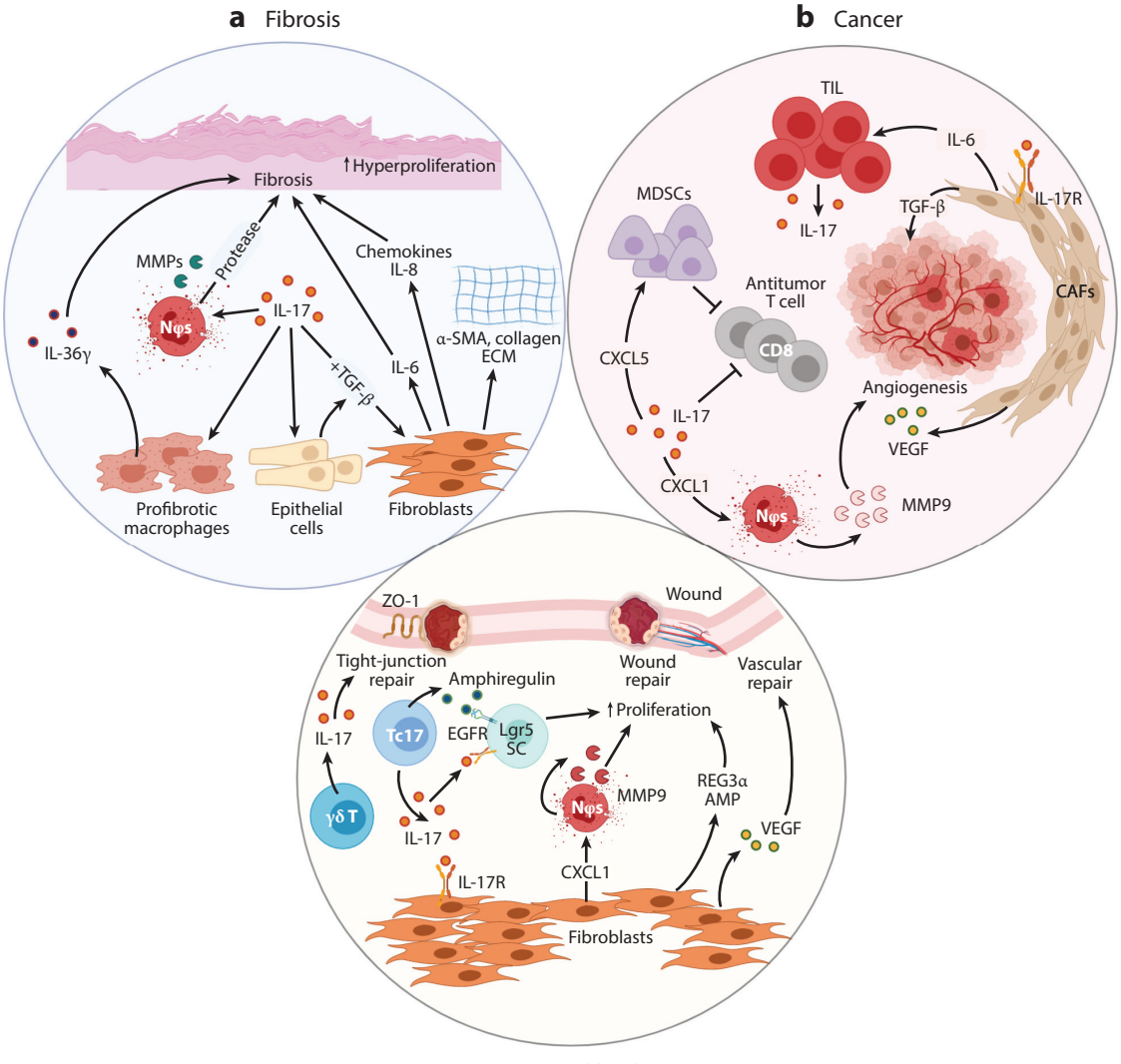
Following skin wounding, mice that are deficient in IL-17 have delayed wound closure (57–59). In the gut, IL-17 promotes epithelial repair following injury by promoting increased proliferation of epithelial stem cells to replace the damaged cells and enhancing the restoration of an effective barrier with expression of tight-junction proteins that prevent microbial translocation from the gut (60, 61). IL-17-neutralizing biologics are highly effective in treating psoriasis, supporting the proinflammatory and proliferative roles of IL-17 in the skin. However, the same drugs were disappointingly ineffective in Crohn disease and exacerbated disease in some patients, suggesting that on balance the beneficial roles of IL-17 in microbial homeostasis and repair of the gut outweigh the contributions to pathologic inflammation.

Pathologic proliferation of synovial fibroblasts also contributes to rheumatoid arthritis, where it is thought that IL-17 may contribute in the earlier phases of disease, because IL-17-targeting biologic therapy was only effective in a subset of patients with established rheumatoid arthritis (62). Another potential pathology that can result from excess proliferation is the depletion of precursor stem cells that ultimately contributes to failed repair of inflamed tissue. In a model of MS, hyperproliferation of oligodendrocyte precursors responding to IL-17 has been proposed to increase their death and thus contribute to oligodendrocyte decline and increased demyelination in the central nervous system (CNS) (63, 64).

In spontaneous tumorigenesis models that combine tissue damage with a carcinogenic stimulus, IL-17 promotes increased proliferation of epithelial stem cells in response to tissue injury. Recently, a novel IL-17A-activated epidermal growth factor receptor (EGFR) signaling pathway

was discovered that drives the expansion and migration of Lrig1$^+$ stem cells during skin injury, leading to skin tumorigenesis and suggesting that repeated injuries can promote dysregulated IL-17-dependent wound repair leading to neoplastic growth (59). Similarly, another study from the same group found that inhibition of IL-17 in a mouse gut-injury model of colitis resulted in restricted tumor growth (61).

Tissue injury rapidly recruits neutrophils for microbial control and debris clearance (65), and as already discussed, IL-17 is a major recruiter of these cells during sustained inflammation. Myeloid-derived suppressor cells (MDSCs) and neutrophils are two important myeloid cell types often found in the tumor microenvironment. IL-17 can recruit suppressive MDSCs and neutrophils that inhibit cytotoxic T cells and produce MMPs to enhance metastasis of cancer cells (66–72). While IL-17 is primarily considered to act through nonhematopoietic cells, it is worth noting that



(*Caption appears on following page*)

Figure 4 (*Figure appears on preceding page*)

Pleiotropic IL-17 regulates fibrosis, cancer development, and wound healing. (*a*) IL-17 promotes fibrosis by acting on fibroblasts, epithelial cells, and profibrotic macrophages. IL-17 signals on epithelial cells promote secretion of TGF-β. TGF-β and IL-17 act on fibroblasts to promote production of IL-6. Other than IL-6, fibroblasts in the presence of IL-17 signaling also produce α-SMA, collagen, and ECM proteins as well as chemokines such as IL-8 and CXCL1 to recruit neutrophils, which can synthesize MMPs. Similarly, profibrotic macrophages respond to IL-17 and produce IL-36γ. (*b*) Protumorigenic roles of IL-17. Besides directly promoting tumor formation through pro-proliferative signaling, IL-17 acts on stromal cells to manifest its protumor functions. IL-17 signaling in CAFs generates VEGF, IL-6, and chemokines, all of which have critical protumor roles. VEGF drives angiogenesis, one of the hallmarks of cancer. IL-6 can directly act on tumor-infiltrating lymphocytes to produce more IL-17. CXCL1, on the other hand, recruits neutrophils to synthesize MMP9, which is important for angiogenesis. Moreover, IL-17 can block antitumor CD8 T cells, critical for fighting cancers, either directly or through CXCL5-driven MDSCs. (*c*) IL-17 function is indispensable for wound healing. IL-17 derived from conventional CD4 T cells, γδ T cells, or Tc17 cells plays a critical role in repairing wounds. IL-17 promotes vascular repair, neutrophil recruitment, restoration of gut epithelial tight junctions, and proliferation of $Lgr5^+$ stem cells through synergistic signaling of IL-17R and EGFR. Besides secreting IL-17, Tc17 cells also produce amphiregulin, an important protein for wound repair. Abbreviations: α-SMA, alpha smooth muscle actin; AMP, antimicrobial peptide; CAF, cancer-associated fibroblast; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; MDSC, myeloid-derived suppressor cell; MMP, matrix metalloproteinase; Nφ, neutrophil; REG3α, regenerating islet-derived 3α; SC, stem cell; TGF-β, transforming growth factor beta; TIL, tumor-infiltrating lymphocyte; VEGF, vascular endothelial growth factor, ZO-1, zonula occludens 1. Figure adapted from image created with BioRender.com.

a recent single-cell analysis of foreign-body-induced fibrosis identified a profibrotic macrophage subtype that both expresses IL-17 receptor subunits and responds to IL-17 by producing IL-36γ, an IL-1 family member also highly expressed by psoriatic keratinocytes (73, 74). This suggests that tissue-resident macrophages could be subverted along with stromal cells toward an IL-17-responsive profibrotic phenotype under chronic stimulation.

Tissue growth and repair are energy-intensive processes. A recent immune-profiling study of more than 1,000 breast cancer patients in the Cancer Genome Atlas demonstrated that the cohort with highly glycolytic breast cancers was linked with lower infiltration of tumor-killing cells, higher expression of checkpoint inhibitors such as PD-L1, and poor prognosis (75). Interestingly, the most strongly upregulated pathway in this group of patients is the IL-17 signaling pathway, further linking IL-17 with protumorigenic functions (75). We recently demonstrated that IL-17 signaling has profound effects on LN stromal cell metabolism, boosting glucose uptake, glycolysis, and oxidative phosphorylation (18). FRCs deficient in IL-17 receptor had very low spare respiratory capacity, displayed signs of nutrient stress, and underwent increased apoptosis in vivo (18). We speculate that metabolic changes driven by IL-17 signaling through IκBζ and NF-κB could also enhance the proliferation and survival of cancer-associated fibroblasts (CAFs), or indeed tumor cells, though this has yet to be tested.

In addition to replacement of damaged cells, one of the critical aspects of wound healing is vascular repair to provide nutrients to the recovering organ, and this often requires angiogenesis (formation of new blood vessels). IL-17 drives the production of VEGF by epithelial and fibroblastic cells to stimulate angiogenesis, as observed in the highly vascularized red areas underlying psoriasis lesions. Fast-growing tumors require rapid vascularization in order to avoid necrosis, and one of the major protumorigenic roles of IL-17 likely depends on these proangiogenic properties (76–81).

Stromal cells, or fibroblast-like cells, produce and organize extracellular matrix (ECM) components to provide structural support of organs. In addition, stromal cells produce growth factors to promote the function of adjacent cells that are tissue specific, and it is increasingly appreciated that they exist as heterogeneous and specialized functional subsets within a tissue and between organs. During wound healing, local fibroblasts provide a scaffold for epithelial migration to help close the wound and produce ECM with a balance of proteases to produce an organized scar that is as close to the original tissue as possible. Extensive or inappropriate production of ECM and

Table 1 Protumorigenic roles of IL-17

Species	Cancer type	Major findings/mechanisms
Mouse	Colorectal	Barrier disruption by microbial products triggers tumor-elicited inflammation, which in turn drives tumor growth (118).
Human	Advanced-stage colorectal	Metastatic disease was associated with elevated Th17-associated cytokines such as IL-23 and IL-17F in both colonic tissue and circulation (119).
Mouse	Colorectal	IL-17RA signals directly within transformed colonic epithelial cells (enterocytes) to promote early tumor development via an ERK, p38 MAPK, and NF-κB signaling pathway (120).
Human	Advanced-stage colorectal	Th17 cells inhibit $CD8^+$ T cell migration by downregulating CXCR3 expression via the IL-17A/STAT3 axis (121).
Human	Colorectal	Patients with lower IL-17 levels have increased five-year survival rates (122).
Mouse	Sporadic colorectal	Tumor-prone mice colonized with oncotoxin-producing bacteria showed increased IL-17 in the colon and DNA damage in the colonic epithelium with faster tumor onset and greater mortality (123).
Mouse	Colon	Damage to the intestinal epithelium activates IL-17A signaling in PLET1 cells, leading to aberrant wound healing favoring tumor growth (61).
Mouse	Colon	IL-17 targets colonic epithelial cells to promote ETBF-mediated carcinogenesis via NF-κB signaling, triggering CXC chemokines to drive protumoral neutrophil infiltration to the distal colon (72).
Mouse	Multiple myeloma	Gavaging tumor-prone mice with *Prevotella heparinolytica* promotes differentiation of Th17 cells in the gut and migration to the bone marrow, favoring multiple myeloma growth (124).
Mouse	Skin	IL-23 is required for spontaneous skin tumors (125). Damage to the skin activates IL-17A signaling in $Lrig1^+$ stem cells, leading to aberrant wound healing favoring tumor growth (59).
Mouse	Liver	IL-17A-induced CXCL5 production by tumor cells enhances the infiltration of MDSCs, thereby reducing antitumor immunity (66).
Mouse	Lung	IL-17A weakens antitumor immunity by inhibiting apoptosis of MDSCs (67).
Human	Gastric	IL-17A from $CD8^+$ T cells regulates the influx of MDSCs to the tumor site via a CXCL12-CXCR4 axis to mitigate antitumor $CD8^+$ T cell functions (70).
Human	Gastric	Both IL-17A (rs2275913) and IL-17F (rs763780) polymorphisms significantly increase gastric cancer risk (126, 127).
Mouse	Breast	IL-17A from γδ T cells induces the infiltration of neutrophils to suppress $CD8^+$ T cell function and promote metastasis (69).
Mouse	Lung	Commensal bacteria drive IL-17 production from γδ T cells to promote neutrophil infiltration and tumor cell proliferation (71).
Mouse	Non-small cell lung	lL-17 drives angiogenesis by stimulating VEGF production of cancer cells via STAT3/GIV signaling (76).
Human	Gall bladder	IL-17-producing γδ T cells drive VEGF production to promote blood vessel formation (78).
Human	Gastric	IL-17-producing neutrophils drive MMP9 production to promote angiogenesis and tumor growth (128).
Mouse	Liver, pancreatic	IL-17 promotes chemokine-signaling-driven angiogenesis (80, 81).

Abbreviations: ERK, extracellular signal-regulated kinase; ETBF, enterotoxigenic *Bacteroides fragilis*; GIV, Gα-interacting vesicle-associated protein; MAPK, mitogen-activated protein kinase; MDSC, myeloid-derived suppressor cell; MMP9, matrix metalloproteinase 9; STAT3, signal transducer and activator of transcription 3; VEGF, vascular endothelial growth factor.

Table 2 Antitumor roles of IL-17

Species	Cancer type	Major findings/mechanism(s)
Human	Cervical adenocarcinoma	An increased number of IL-17$^+$ cells in patients was significantly correlated with the absence of vasoinvasion, shallower infiltration, and less tumor growth (129).
Mouse	Fibrosarcoma	IL-17 overexpression drives upregulation of MHC-I and MHC-II, thereby making fibrosarcoma cells increasingly susceptible to antitumor T cells (130).
Human	Esophageal	IL-17 promotes chemokine production by tumors, leading to the infiltration of cytotoxic neutrophils, CD8$^+$ cytotoxic T lymphocytes, and dendritic cells and resulting in better tumor control and patient survival (131, 132).
Mouse	Lung	IL-17 controls tumor growth and metastasis by enhancing the cytotoxic potential of antitumor CD8$^+$ T cells (133) and by increasing IFN-γ production by antitumor T cells and natural killer cells (134).
Mouse	Breast	IL-17 inhibits the accumulation of myeloid-derived suppressor cells in the tumor microenvironment by suppressing their proliferation and triggering apoptosis (135).
Human	Colorectal	Individuals with higher IL-17 expression exhibited better disease control and survival, which are linked to increased infiltration of cytotoxic CD15$^+$ neutrophils (136).

Abbreviation: IFN-γ, interferon gamma.

scar formation, particularly over an extended period, as occurs with chronic injury due to autoimmunity, infection, or cancer, ultimately results in dysfunction. During autoimmune attack of the CNS, astrocytes contribute to glial scarring in MS plaques. IL-17 certainly activates astrocytes to promote chemokine and inflammatory cytokine production in the mouse model of MS (82), but its roles in aberrant astrocyte scar formation have not been investigated.

Systemic sclerosis (SSc) is an autoimmune connective tissue disease in which excess fibroblast proliferation and activation cause fibrosis, most commonly in the skin, leading to decreased pliability and movement around joints that can be disabling. Even more severe morbidity and mortality occur in SSc patients experiencing fibrosis of internal organs, especially lungs, who ultimately require transplantation for survival. Fibrotic tissues have signatures of inflammatory cytokines including IL-6 and IL-17, but with high expression of TGF-β considered the major driver of ECM production (83). Mice deficient in IL-17 are resistant to bleomycin-induced lung fibrosis (84). IL-6 is a major target of IL-17 signaling in almost every cell type tested, and IL-17 has also been reported to enhance production of TGF-β in human lung alveolar epithelial cells (85). It is interesting to note that Th17 cells themselves express TGF-β, which has been verified to act in an autocrine manner in mice (86). In both healthy and SSc dermal fibroblasts, IL-17 synergized with TGF-β to increase IL-6 production by a factor of approximately 100 compared to either cytokine alone (87). The authors of this study made the important point that fibroblasts do not express IL-6R and so rely on IL-6 *trans*-signaling through soluble IL-6R produced by other cells in the tissue to display the profibrotic effects of IL-6: This is something that needs to be considered for the many in vitro studies of human fibroblasts in which IL-17 function is assessed. Nevertheless, this study also revealed a potentially interesting dichotomy in which IL-17 synergized with TGF-β for IL-6 production but inhibited TGF-β-induced ECM production (in the absence of IL-6 signaling), further emphasizing the complexity of cytokine interactions in fibrosis (87).

Patients with chronic viral hepatitis are at risk for developing fibrotic liver disease (cirrhosis) as well as liver cancer. Increased intrahepatic IL-17A and IL-22 at biopsy is considered a signature of advanced liver fibrosis with worse prognosis (88, 89). Hepatic stellate cells are the major driver of liver fibrosis, and IL-17 has been shown to drive collagen formation by stellate cells, in part by increasing the expression of receptor for TGF-β (90). Similarly, we found that IL-17 enhanced expression of genes encoding collagen and fibronectin in LN stromal cells that were

preactivated in vivo by immunization, and it promoted proliferation of these cells (18). During chronic inflammation of LNs, for example in HIV patients or those experiencing frequent infections due to suboptimal nutrition or living conditions, fibrosis of the LN itself leads to reduced T cell survival and reduced response to vaccination (91–93). We speculate that repeated infections or exposure to gut microbes, as occurs in leaky gut of HIV patients, could promote LN fibrosis through increased inflammation and locally induced IL-17 signaling. However, it is the loss of gut-resident IL-17-producing T cells that is thought to lead to increased leakiness due to reduced tight-junction proteins in HIV and the nonhuman primate model simian immunodeficiency virus (SIV) (94–96). As a side note, there is another interesting connection between HIV and IL-17: Human Th17 cells express receptors important for HIV entry and preferentially produce higher viral capsid proteins due to reduced expression of RNase A, an important enzyme that limits HIV replication (97). Hence, a fraction of Th17 cells act as a reservoir to allow HIV persistence despite antiretroviral therapy (98).

Tumor stromal architecture not only guides initial tumor growth but also controls all stages of cancer progression by dynamically interacting with tumor cells and the immune system (99). CAFs are increasingly appreciated for their roles in limiting access and function of cytotoxic T cells in tumors and providing architectural support to invading cancer cells. It is still unclear exactly how CAFs promote immune evasion by tumors. One mechanism could be production and organization of ECM, including collagen to wall off the tumor in a form of fibrosis. TGF-β is not only a major driver of fibrosis but also an inhibitor of cytotoxic T cell function. TGF-β-driven CAFs are a key indicator of nonresponsiveness to anti-PD-L1 therapy in cancer patients, and these tumors more frequently have T cells that are trapped in the surrounding collagen-rich fibroblast zones (100, 101). CAF-derived IL-6 can promote IL-17 production by tumor-infiltrating T cells (102). As IL-17 drives and enhances IL-6 and TGF-β production, it is highly probable that IL-17 can also act on CAFs in a feed-forward loop to modulate their proliferation and function during cancer progression, thereby controlling the disease outcome.

FUTURE HORIZONS

IL-17 has now been associated with immunopathologies beyond classic inflammatory autoimmune disease, and mouse models support a functional role, but in many cases a definitive test in clinical trials has not been done. From the experience of targeting IL-17 in autoimmune disease, it appears that two components may be critical to evaluate the likelihood of success of anti-IL-17 therapy: (*a*) understanding whether IL-17 is an initiator, driver, or amplifier of the disease, and (*b*) determining whether IL-17 is contributing any important benefit that may outweigh the pathological contribution, as is now thought for Crohn disease (103). In many cases, it seems that IL-17 as an adjunct therapy could improve the success of stand-alone therapies. An example would be in fibrosis where IL-17 appears to enhance the profibrotic effects of TGF-β. Evidence suggests that adjunct blockade of IL-17 could improve immunotherapy and reduce chemoresistance in cancer. Studies of anti-PD1 and anti-PD-L1 therapy response identified an increased IL-17 gene signature in colorectal cancer patient nonresponders and increased Th17 cell frequency in melanoma patient nonresponders (104, 105). The potential to improve the autoimmune disease that can occur as a side effect of checkpoint inhibitors is another attractive benefit of neutralizing IL-17 in these patients. It has also been suggested that IL-17 may promote development of cisplatin resistance in colorectal cancer (106). Given the mixed results of IL-17-neutralizing therapies in autoimmune diseases, determination of appropriate biomarkers to identify cancers in which IL-17 is a driver of disease progression is critical.

An exciting new frontier in IL-17 biology is neural-immune interactions. Several lines of evidence already demonstrate that IL-17 is involved in neural-immune circuits that can affect

inflammatory disease. Skin neurons promote local IL-17 production to increase psoriatic or pathogen-induced inflammation (107, 108). IL-17 and IL-17-inducing gut microbiota contribute to the degree of lesion severity following ischemic stroke (109). Conversely, by regulating gut microbiota, IL-17 can alter systemic microbial products that are increasingly thought to affect mental health, and Th17 cells were increased and promoted depression-like symptoms in mouse models (110). In this context, it is interesting to note that depression is a relatively common comorbidity in autoimmune patients, often attributed to effects of living with chronic disease but perhaps exacerbated by the underlying disease processes. Alcoholic humans have increased levels of IL-17 thought to be driven by liver injury, and in mice IL-17 was found to promote alcohol-seeking behavior, suggesting an important feedback loop in addiction (111). IL-17 is increased in lesions from pediatric patients with intractable epilepsy and causes neuron hyperexcitability in mouse models of epilepsy, MS, and pain (112–114). In a mouse model of autism induced by causing inflammation in the pregnant dam, IL-17 is required for autistic trait development in the offspring (115). However, boosting IL-17 in autistic mice provided temporary restoration of nonautistic social behaviors (116). This study was initiated because of the clinical observation that autistic children experiencing infection with fever sometimes show transient improvement in social behaviors, and the authors suggest that increased IL-17 during fetal development causes a heightened threshold for later IL-17 signaling that promotes typical social behaviors after birth (116). Although it is surprising that IL-17 could act in the brain to regulate behavior, there is precedent for cytokines acting this way: IFN-γ increases in response to social interactions in mice and conversely regulates social behavior (117). In the current age of social distancing, it seems timely to consider that our neural-immune circuits may be evolutionarily far ahead of us in linking pathogen-induced immune responses with change in social behavior.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

Funding provided by NIHAI137029 (M.J.M.) and an American Association of Immunology training fellowship (S.M.).

LITERATURE CITED

1. Linehan JL, Harrison OJ, Han SJ, Byrd AL, Vujkovic-Cvijin I, et al. 2018. Non-classical immunity controls microbiota impact on skin immunity and tissue repair. *Cell* 172:784–96.e18
2. Jiang TT, Shao TY, Ang WXG, Kinder JM, Turner LH, et al. 2017. Commensal fungi recapitulate the protective benefits of intestinal bacteria. *Cell Host Microbe* 22:809–16.e4
3. Wheeler ML, Limon JJ, Bar AS, Leal CA, Gargus M, et al. 2016. Immunological consequences of intestinal fungal dysbiosis. *Cell Host Microbe* 19:865–73
4. Limon JJ, Skalski JH, Underhill DM. 2017. Commensal fungi in health and disease. *Cell Host Microbe* 22:156–65
5. Cho JS, Pietras EM, Garcia NC, Ramos RI, Farzam DM, et al. 2010. IL-17 is essential for host defense against cutaneous *Staphylococcus aureus* infection in mice. *J. Clin. Investig.* 120:1762–73
6. Li J, Casanova JL, Puel A. 2018. Mucocutaneous IL-17 immunity in mice and humans: host defense versus excessive inflammation. *Mucosal Immunol.* 11:581–89
7. Cohen JA, Edwards TN, Liu AW, Hirai T, Jones MR, et al. 2019. Cutaneous TRPV1$^+$ neurons trigger protective innate type 17 anticipatory immunity. *Cell* 178:919–32.e14

8. Naik S, Bouladoux N, Linehan JL, Han SJ, Harrison OJ, et al. 2015. Commensal-dendritic-cell interaction specifies a unique protective skin immune signature. *Nature* 520:104–8
9. Kumar P, Monin L, Castillo P, Elsegeiny W, Horne W, et al. 2016. Intestinal interleukin-17 receptor signaling mediates reciprocal control of the gut microbiota and autoimmune inflammation. *Immunity* 44:659–71
10. Krebs CF, Paust HJ, Krohn S, Koyro T, Brix SR, et al. 2016. Autoimmune renal disease is exacerbated by S1P-receptor-1-dependent intestinal Th17 cell migration to the kidney. *Immunity* 45:1078–92
11. Morton AM, Sefik E, Upadhyay R, Weissleder R, Benoist C, Mathis D. 2014. Endoscopic photoconversion reveals unexpectedly broad leukocyte trafficking to and from the gut. *PNAS* 111:6696–701
12. Krishnamurty AT, Turley SJ. 2020. Lymph node stromal cells: cartographers of the immune system. *Nat. Immunol.* 21:369–80
13. Eddens T, Elsegeiny W, de la Luz Garcia-Hernadez M, Castillo P, Trevejo-Nunez G, et al. 2017. *Pneumocystis*-driven inducible bronchus-associated lymphoid tissue formation requires Th2 and Th17 immunity. *Cell Rep*. 18:3078–90
14. Rangel-Moreno J, Carragher DM, de la Luz Garcia-Hernandez M, Hwang JY, Kusser K, et al. 2011. The development of inducible bronchus-associated lymphoid tissue depends on IL-17. *Nat. Immunol.* 12:639–46
15. Pikor NB, Astarita JL, Summers-Deluca L, Galicia G, Qu J, et al. 2015. Integration of Th17- and lymphotoxin-derived signals initiates meningeal-resident stromal cell remodeling to propagate neuroinflammation. *Immunity* 43:1160–73
16. Peters A, Pitcher LA, Sullivan JM, Mitsdoerffer M, Acton SE, et al. 2011. Th17 cells induce ectopic lymphoid follicles in central nervous system tissue inflammation. *Immunity* 35:986–96
17. Kohlgruber AC, Gal-Oz ST, LaMarche NM, Shimazaki M, Duquette D, et al. 2018. γδ T cells producing interleukin-17A regulate adipose regulatory T cell homeostasis and thermogenesis. *Nat. Immunol.* 19:464–74
18. Majumder S, Amatya N, Revu S, Jawale CV, Wu D, et al. 2019. IL-17 metabolically reprograms activated fibroblastic reticular cells for proliferation and survival. *Nat. Immunol.* 20:534–45
19. McGinley AM, Sutton CE, Edwards SC, Leane CM, DeCourcey J, et al. 2020. Interleukin-17A serves a priming role in autoimmunity by recruiting IL-1β-producing myeloid cells that promote pathogenic T cells. *Immunity* 52:342–56.e6
20. Xie S, Li J, Wang JH, Wu Q, Yang P, et al. 2010. IL-17 activates the canonical NF-κB signaling pathway in autoimmune B cells of BXD2 mice to upregulate the expression of regulators of G-protein signaling 16. *J. Immunol.* 184:2289–96
21. Mitsdoerffer M, Lee Y, Jager A, Kim HJ, Korn T, et al. 2010. Proinflammatory T helper type 17 cells are effective B-cell helpers. *PNAS* 107:14292–97
22. Hirota K, Turner JE, Villa M, Duarte JH, Demengeot J, et al. 2013. Plasticity of Th17 cells in Peyer's patches is responsible for the induction of T cell-dependent IgA responses. *Nat. Immunol.* 14:372–79
23. Solans L, Debrie AS, Borkner L, Aguilo N, Thiriard A, et al. 2018. IL-17-dependent SIgA-mediated protection against nasal *Bordetella pertussis* infection by live attenuated BPZE1 vaccine. *Mucosal Immunol.* 11:1753–62
24. Li X, Bechara R, Zhao J, McGeachy MJ, Gaffen SL. 2019. IL-17 receptor-based signaling and implications for disease. *Nat. Immunol.* 20:1594–602
25. Shen F, Ruddy MJ, Plamondon P, Gaffen SL. 2005. Cytokines link osteoblasts and inflammation: microarray analysis of interleukin-17- and TNF-α-induced genes in bone cells. *J. Leukoc. Biol.* 77:388–99
26. Slowikowski K, Nguyen HN, Noss EH, Simmons DP, Mizoguchi F, et al. 2020. CUX1 and IκBζ (NFKBIZ) mediate the synergistic inflammatory response to TNF and IL-17A in stromal fibroblasts. *PNAS* 117:5532–41
27. Sonder SU, Saret S, Tang W, Sturdevant DE, Porcella SF, Siebenlist U. 2011. IL-17-induced NF-κB activation via CIKS/Act1: physiologic significance and signaling mechanisms. *J. Biol. Chem.* 286:12881–90
28. Nguyen HN, Noss EH, Mizoguchi F, Huppertz C, Wei KS, et al. 2017. Autocrine loop involving IL-6 family member LIF, LIF receptor, and STAT4 drives sustained fibroblast production of inflammatory mediators. *Immunity* 46:220–32

29. Harrison OJ, Linehan JL, Shih H-Y, Bouladoux N, Han S-J, et al. 2019. Commensal-specific T cell plasticity promotes rapid tissue adaptation to injury. *Science* 363(6422):eaat6280
30. McGeachy MJ, Bak-Jensen KS, Chen Y, Tato CM, Blumenschein W, et al. 2007. TGF-β and IL-6 drive the production of IL-17 and IL-10 by T cells and restrain T_H-17 cell-mediated pathology. *Nat. Immunol.* 8:1390–97
31. Ghoreschi K, Laurence A, Yang XP, Tato CM, McGeachy MJ, et al. 2010. Generation of pathogenic T_H17 cells in the absence of TGF-β signalling. *Nature* 467:967–71
32. Zielinski CE, Mele F, Aschenbrenner D, Jarrossay D, Ronchi F, et al. 2012. Pathogen-induced human T_H17 cells produce IFN-γ or IL-10 and are regulated by IL-1β. *Nature* 484:514–18
33. Omenetti S, Bussi C, Metidji A, Iseppon A, Lee S, et al. 2019. The intestine harbors functionally distinct homeostatic tissue-resident and inflammatory Th17 cells. *Immunity* 51:77–89.e6
34. Martinez-Lopez M, Iborra S, Conde-Garrosa R, Mastrangelo A, Danne C, et al. 2019. Microbiota sensing by Mincle-Syk axis in dendritic cells regulates interleukin-17 and -22 production and promotes intestinal barrier integrity. *Immunity* 50:446–61.e9
35. Dutzan N, Abusleme L, Bridgeman H, Greenwell-Wild T, Zangerle-Murray T, et al. 2017. On-going mechanical damage from mastication drives homeostatic Th17 cell responses at the oral barrier. *Immunity* 46:133–47
36. Ho J, Yang X, Nikou SA, Kichik N, Donkin A, et al. 2019. Candidalysin activates innate epithelial immune responses via epidermal growth factor receptor. *Nat. Commun.* 10:2297
37. Sano T, Huang W, Hall JA, Yang Y, Chen A, et al. 2015. An IL-23R/IL-22 circuit regulates epithelial serum amyloid A to promote local effector Th17 responses. *Cell* 163:381–93
38. Martin B, Hirota K, Cua DJ, Stockinger B, Veldhoen M. 2009. Interleukin-17-producing γδ T cells selectively expand in response to pathogen products and environmental signals. *Immunity* 31:321–30
39. Sutton CE, Lalor SJ, Sweeney CM, Brereton CF, Lavelle EC, Mills KH. 2009. Interleukin-1 and IL-23 induce innate IL-17 production from γδ T cells, amplifying Th17 responses and autoimmunity. *Immunity* 31:331–41
40. Verma AH, Zafar H, Ponde NO, Hepworth OW, Sihra D, et al. 2018. IL-36 and IL-1/IL-17 drive immunity to oral candidiasis via parallel mechanisms. *J. Immunol.* 201:627–34
41. Poholek CH, Raphael I, Wu D, Revu S, Rittenhouse N, et al. 2020. Noncanonical STAT3 activity sustains pathogenic Th17 proliferation and cytokine response to antigen. *J. Exp. Med.* 217:e20191761
42. Revu S, Wu J, Henkel M, Rittenhouse N, Menk A, et al. 2018. IL-23 and IL-1β drive human Th17 cell differentiation and metabolic reprogramming in absence of CD28 costimulation. *Cell Rep.* 22:2642–53
43. Acharya D, Wang P, Paul AM, Dai J, Gate D, et al. 2017. Interleukin-17A promotes $CD8^+$ T cell cytotoxicity to facilitate West Nile virus clearance. *J. Virol.* 91:e01529-16
44. Hou L, Jie Z, Desai M, Liang Y, Soong L, et al. 2013. Early IL-17 production by intrahepatic T cells is important for adaptive immune responses in viral hepatitis. *J. Immunol.* 190:621–29
45. Khader SA, Bell GK, Pearl JE, Fountain JJ, Rangel-Moreno J, et al. 2007. IL-23 and IL-17 in the establishment of protective pulmonary $CD4^+$ T cell responses after vaccination and during *Mycobacterium tuberculosis* challenge. *Nat. Immunol.* 8:369–77
46. Wang X, Chan CC, Yang M, Deng J, Poon VK, et al. 2011. A critical role of IL-17 in modulating the B-cell response during H5N1 influenza virus infection. *Cell Mol. Immunol.* 8:462–68
47. Wang X, Ma K, Chen M, Ko KH, Zheng BJ, Lu L. 2016. IL-17A promotes pulmonary B-1a cell differentiation via induction of Blimp-1 expression during influenza virus infection. *PLOS Pathog.* 12:e1005367
48. Bagri P, Anipindi VC, Nguyen PV, Vitali D, Stampfli MR, Kaushic C. 2017. Novel role for interleukin-17 in enhancing type 1 helper T cell immunity in the female genital tract following mucosal herpes simplex virus 2 vaccination. *J. Virol.* 91(23):e01234-17
49. Muir R, Osbourn M, Dubois AV, Doran E, Small DM, et al. 2016. Innate lymphoid cells are the predominant source of IL-17A during the early pathogenesis of acute respiratory distress syndrome. *Am. J. Respir. Crit. Care Med.* 193:407–16
50. Lu B, Liu M, Wang J, Fan H, Yang D, et al. 2020. IL-17 production by tissue-resident MAIT cells is locally induced in children with pneumonia. *Mucosal Immunol.* 13:824–35
51. Li C, Yang P, Sun Y, Li T, Wang C, et al. 2012. IL-17 response mediates acute lung injury induced by the 2009 pandemic influenza A (H1N1) virus. *Cell Res.* 22:528–38

52. Mebratu YA, Tesfaigzi Y. 2018. IL-17 plays a role in respiratory syncytial virus-induced lung inflammation and emphysema in elastase and LPS-injured mice. *Am. J. Respir. Cell Mol. Biol.* 58:717–26
53. Crowe CR, Chen K, Pociask DA, Alcorn JF, Krivich C, et al. 2009. Critical role of IL-17RA in immunopathology of influenza infection. *J. Immunol.* 183:5301–10
54. Megna M, Napolitano M, Fabbrocini G. 2020. May IL-17 have a role in COVID-19 infection? *Med. Hypotheses* 140:109749
55. Pacha O, Sallman MA, Evans SE. 2020. COVID-19: a case for inhibiting IL-17? *Nat. Rev. Immunol.* 20(6):345–46
56. Lythgoe MP, Middleton P. 2020. Ongoing clinical trials for the management of the COVID-19 pandemic. *Trends Pharmacol. Sci.* 41:363–82
57. Naik S, Larsen SB, Gomez NC, Alaverdyan K, Sendoel A, et al. 2017. Inflammatory memory sensitizes skin epithelial stem cells to tissue damage. *Nature* 550:475–80
58. Wu L, Chen X, Zhao J, Martin B, Zepp JA, et al. 2015. A novel IL-17 signaling pathway controlling keratinocyte proliferation and tumorigenesis via the TRAF4-ERK5 axis. *J. Exp. Med.* 212:1571–87
59. Chen X, Cai G, Liu C, Zhao J, Gu C, et al. 2019. IL-17R-EGFR axis links wound healing to tumorigenesis in Lrig1^{+} stem cells. *J. Exp. Med.* 216:195–214
60. Lee JS, Tato CM, Joyce-Shaikh B, Gulen MF, Cayatte C, et al. 2015. Interleukin-23-independent IL-17 production regulates intestinal epithelial permeability. *Immunity* 43:727–38
61. Zepp JA, Zhao J, Liu C, Bulek K, Wu L, et al. 2017. IL-17A-induced PLET1 expression contributes to tissue repair and colon tumorigenesis. *J. Immunol.* 199:3849–57
62. Lubberts E. 2015. The IL-23-IL-17 axis in inflammatory arthritis. *Nat. Rev. Rheumatol.* 11:562
63. Wang C, Zhang CJ, Martin BN, Bulek K, Kang Z, et al. 2017. IL-17 induced NOTCH1 activation in oligodendrocyte progenitor cells enhances proliferation and inflammatory gene expression. *Nat. Commun.* 8:15508
64. Kang Z, Wang C, Zepp J, Wu L, Sun K, et al. 2013. Act1 mediates IL-17-induced EAE pathogenesis selectively in NG2^{+} glial cells. *Nat. Neurosci.* 16:1401–8
65. Lammermann T, Afonso PV, Angermann BR, Wang JM, Kastenmuller W, et al. 2013. Neutrophil swarms require LTB4 and integrins at sites of cell death in vivo. *Nature* 498:371–75
66. Ma S, Cheng Q, Cai Y, Gong H, Wu Y, et al. 2014. IL-17A produced by γδ T cells promotes tumor growth in hepatocellular carcinoma. *Cancer Res.* 74:1969–82
67. Wang J, Zhang Y, Yin K, Xu P, Tian J, et al. 2017. IL-17A weakens the antitumor immuity by inhibiting apoptosis of MDSCs in Lewis lung carcinoma bearing mice. *Oncotarget* 8:4814–25
68. Veglia F, Perego M, Gabrilovich D. 2018. Myeloid-derived suppressor cells coming of age. *Nat. Immunol.* 19:108–19
69. Coffelt SB, Kersten K, Doornebal CW, Weiden J, Vrijland K, et al. 2015. IL-17-producing γδ T cells and neutrophils conspire to promote breast cancer metastasis. *Nature* 522:345–48
70. Zhuang Y, Peng LS, Zhao YL, Shi Y, Mao XH, et al. 2012. CD8^{+} T cells that produce interleukin-17 regulate myeloid-derived suppressor cells and are associated with survival time of patients with gastric cancer. *Gastroenterology* 143:951–62.e8
71. Jin C, Lagoudas GK, Zhao C, Bullman S, Bhutkar A, et al. 2019. Commensal microbiota promote lung cancer development via γδ T cells. *Cell* 176:998–1013.e16
72. Chung L, Thiele Orberg E, Geis AL, Chan JL, Fu K, et al. 2018. *Bacteroides fragilis* toxin coordinates a pro-carcinogenic inflammatory cascade via targeting of colonic epithelial cells. *Cell Host Microbe* 23:203–14.e5
73. Chung L, Maestas DR Jr., Lebid A, Mageau A, Rosson GD, et al. 2020. Interleukin 17 and senescent cells regulate the foreign body response to synthetic material implants in mice and humans. *Sci. Transl. Med.* 12(539):eaax3799
74. Sommerfeld SD, Cherry C, Schwab RM, Chung L, Maestas DR Jr., et al. 2019. Interleukin-36γ-producing macrophages drive IL-17-mediated fibrosis. *Sci. Immunol.* 4(40):eaax4783
75. Li W, Xu M, Li Y, Huang Z, Zhou J, et al. 2020. Comprehensive analysis of the association between tumor glycolysis and immune/inflammation function in breast cancer. *J. Transl. Med.* 18:92

76. Pan B, Shen J, Cao J, Zhou Y, Shang L, et al. 2015. Interleukin-17 promotes angiogenesis by stimulating VEGF production of cancer cells via the STAT3/GIV signaling pathway in non-small-cell lung cancer. *Sci. Rep.* 5:16053
77. Yang B, Kang H, Fung A, Zhao H, Wang T, Ma D. 2014. The role of interleukin 17 in tumour proliferation, angiogenesis, and metastasis. *Mediators Inflamm*. 2014:623759
78. Patil RS, Shah SU, Shrikhande SV, Goel M, Dikshit RP, Chiplunkar SV. 2016. IL17 producing γδ T cells induce angiogenesis and are associated with poor survival in gallbladder cancer patients. *Int. J. Cancer* 139:869–81
79. Kato T, Furumoto H, Ogura T, Onishi Y, Irahara M, et al. 2001. Expression of IL-17 mRNA in ovarian cancer. *Biochem. Biophys. Res. Commun.* 282:735–38
80. Liu L, Sun H, Wu S, Tan H, Sun Y, et al. 2019. IL-17A promotes CXCR2-dependent angiogenesis in a mouse model of liver cancer. *Mol. Med. Rep.* 20:1065–74
81. Wu HH, Hwang-Verslues WW, Lee WH, Huang CK, Wei PC, et al. 2015. Targeting IL-17B-IL-17RB signaling with an anti-IL-17RB antibody blocks pancreatic cancer metastasis by silencing multiple chemokines. *J. Exp. Med.* 212:333–49
82. Kang Z, Altuntas CZ, Gulen MF, Liu C, Giltiay N, et al. 2010. Astrocyte-restricted ablation of interleukin-17-induced Act1-mediated signaling ameliorates autoimmune encephalomyelitis. *Immunity* 32:414–25
83. Paquissi FC. 2017. Immunity and fibrogenesis: the role of Th17/IL-17 axis in HBV and HCV-induced chronic hepatitis and progression to cirrhosis. *Front. Immunol.* 8:1195
84. Wilson MS, Madala SK, Ramalingam TR, Gochuico BR, Rosas IO, et al. 2010. Bleomycin and IL-1β–mediated pulmonary fibrosis is IL-17A dependent. *J. Exp. Med.* 207:535–52
85. Wang T, Liu Y, Zou JF, Cheng ZS. 2017. Interleukin-17 induces human alveolar epithelial to mesenchymal cell transition via the TGF-β1 mediated Smad2/3 and ERK1/2 activation. *PLOS ONE* 12:e0183972
86. Gutcher I, Donkor MK, Ma Q, Rudensky AY, Flavell RA, Li MO. 2011. Autocrine transforming growth factor-β1 promotes in vivo Th17 cell differentiation. *Immunity* 34:396–408
87. Dufour AM, Alvarez M, Russo B, Chizzolini C. 2018. Interleukin-6 and type-I collagen production by systemic sclerosis fibroblasts are differentially regulated by interleukin-17A in the presence of transforming growth factor-beta 1. *Front. Immunol.* 9:1865
88. Fabre T, Molina MF, Soucy G, Goulet JP, Willems B, et al. 2018. Type 3 cytokines IL-17A and IL-22 drive TGF-β-dependent liver fibrosis. *Sci. Immunol.* 3:eaar7754
89. Wang Q, Zhou J, Zhang B, Tian Z, Tang J, et al. 2013. Hepatitis B virus induces IL-23 production in antigen presenting cells and causes liver damage via the IL-23/IL-17 axis. *PLOS Pathog.* 9:e1003410
90. Tan Z, Qian X, Jiang R, Liu Q, Wang Y, et al. 2013. IL-17A plays a critical role in the pathogenesis of liver fibrosis through hepatic stellate cell activation. *J. Immunol.* 191:1835–44
91. Zeng M, Smith AJ, Wietgrefe SW, Southern PJ, Schacker TW, et al. 2011. Cumulative mechanisms of lymphoid tissue fibrosis and T cell depletion in HIV-1 and SIV infections. *J. Clin. Investig.* 121:998–1008
92. Estes JD, Reilly C, Trubey CM, Fletcher CV, Cory TJ, et al. 2015. Antifibrotic therapy in simian immunodeficiency virus infection preserves $CD4^+$ T-cell populations and improves immune reconstitution with antiretroviral therapy. *J. Infect. Dis.* 211:744–54
93. Kityo C, Makamdop KN, Rothenberger M, Chipman JG, Hoskuldsson T, et al. 2018. Lymphoid tissue fibrosis is associated with impaired vaccine responses. *J. Clin. Investig.* 128(7):2763–73
94. Klatt NR, Estes JD, Sun X, Ortiz AM, Barber JS, et al. 2012. Loss of mucosal $CD103^+$ DCs and IL-17^+ and IL-22^+ lymphocytes is associated with mucosal damage in SIV infection. *Mucosal Immunol.* 5:646–57
95. Lee JS, Tato CM, Joyce-Shaikh B, Gulen MF, Cayatte C, et al. 2015. Interleukin-23-independent IL-17 production regulates intestinal epithelial permeability. *Immunity* 43:727–38
96. Ryan ES, Micci L, Fromentin R, Paganini S, McGary CS, et al. 2016. Loss of function of intestinal IL-17 and IL-22 producing cells contributes to inflammation and viral persistence in SIV-infected rhesus macaques. *PLOS Pathog.* 12:e1005412
97. Christensen-Quick A, Lafferty M, Sun L, Marchionni L, DeVico A, Garzino-Demo A. 2016. Human Th17 cells lack HIV-inhibitory RNases and are highly permissive to productive HIV infection. *J. Virol.* 90:7833–47

98. Planas D, Routy JP, Ancuta P. 2019. New Th17-specific therapeutic strategies for HIV remission. *Curr. Opin. HIV AIDS* 14:85–92
99. Hinshaw DC, Shevde LA. 2019. The tumor microenvironment innately modulates cancer progression. *Cancer Res.* 79:4557–66
100. Mariathasan S, Turley SJ, Nickles D, Castiglioni A, Yuen K, et al. 2018. TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. *Nature* 554:544–48
101. Dominguez CX, Muller S, Keerthivasan S, Koeppen H, Hung J, et al. 2020. Single-cell RNA sequencing reveals stromal evolution into LRRC15^{+} myofibroblasts as a determinant of patient response to cancer immunotherapy. *Cancer Discov.* 10:232–53
102. Barnas JL, Simpson-Abelson MR, Brooks SP, Kelleher RJ Jr., Bankert RB. 2010. Reciprocal functional modulation of the activation of T lymphocytes and fibroblasts derived from human solid tumors. *J. Immunol.* 185:2681–92
103. Ghilardi N, Pappu R, Arron JR, Chan AC. 2020. 30 years of biotherapeutics development—What have we learned? *Annu. Rev. Immunol.* 38:249–87
104. Llosa NJ, Luber B, Tam AJ, Smith KN, Siegel N, et al. 2019. Intratumoral adaptive immunosuppression and type 17 immunity in mismatch repair proficient colorectal tumors. *Clin. Cancer Res.* 25:5250–59
105. Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, et al. 2018. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science* 359:97–103
106. Sui G, Qiu Y, Yu H, Kong Q, Zhen B. 2019. Interleukin-17 promotes the development of cisplatin resistance in colorectal cancer. *Oncol. Lett.* 17:944–50
107. Kashem SW, Riedl MS, Yao C, Honda CN, Vulchanova L, Kaplan DH. 2015. Nociceptive sensory fibers drive interleukin-23 production from CD301b^{+} dermal dendritic cells and drive protective cutaneous immunity. *Immunity* 43:515–26
108. Riol-Blanco L, Ordovas-Montanes J, Perro M, Naval E, Thiriot A, et al. 2014. Nociceptive sensory neurons drive interleukin-23-mediated psoriasiform skin inflammation. *Nature* 510:157–61
109. Benakis C, Brea D, Caballero S, Faraco G, Moore J, et al. 2016. Commensal microbiota affects ischemic stroke outcome by regulating intestinal γδ T cells. *Nat. Med.* 22:516–23
110. Beurel E, Harrington LE, Jope RS. 2013. Inflammatory T helper 17 cells promote depression-like behavior in mice. *Biol. Psychiatry* 73:622–30
111. Xu J, Ma HY, Liu X, Rosenthal S, Baglieri J, et al. 2020. Blockade of IL-17 signaling reverses alcohol-induced liver injury and excessive alcohol drinking in mice. *JCI Insight* 5(3):e131277
112. Luo H, Liu HZ, Zhang WW, Matsuda M, Lv N, et al. 2019. Interleukin-17 regulates neuron-glial communications, synaptic transmission, and neuropathic pain after chemotherapy. *Cell Rep.* 29:2384–97.e5
113. Xu D, Robinson AP, Ishii T, Duncan DS, TD Alden, et al. 2018. Peripherally derived T regulatory and γδ T cells have opposing roles in the pathogenesis of intractable pediatric epilepsy. *J. Exp. Med.* 215:1169–86
114. Siffrin V, Radbruch H, Glumm R, Niesner R, Paterka M, et al. 2010. In vivo imaging of partially reversible Th17 cell-induced neuronal dysfunction in the course of encephalomyelitis. *Immunity* 33:424–36
115. Gumusoglu SB, Hing BWQ, Chilukuri ASS, Dewitt JJ, Scroggins SM, Stevens HE. 2020. Chronic maternal interleukin-17 and autism-related cortical gene expression, neurobiology, and behavior. *Neuropsychopharmacology* 45:1008–17
116. Reed MD, Yim YS, Wimmer RD, Kim H, Ryu C, et al. 2020. IL-17a promotes sociability in mouse models of neurodevelopmental disorders. *Nature* 577:249–53
117. Filiano AJ, Xu Y, Tustison NJ, Marsh RL, Baker W, et al. 2016. Unexpected role of interferon-γ in regulating neuronal connectivity and social behaviour. *Nature* 535:425–29
118. Grivennikov SI, Wang K, Mucida D, Stewart CA, Schnabl B, et al. 2012. Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. *Nature* 491:254–58
119. Sharp SP, Avram D, Stain SC, Lee EC. 2017. Local and systemic Th17 immune response associated with advanced stage colon cancer. *J. Surg. Res.* 208:180–86
120. Wang K, Kim MK, Di Caro G, Wong J, Shalapour S, et al. 2014. Interleukin-17 receptor A signaling in transformed enterocytes promotes early colorectal tumorigenesis. *Immunity* 41:1052–63

121. Wang D, Yu W, Lian J, Wu Q, Liu S, et al. 2020. Th17 cells inhibit $CD8^+$ T cell migration by systematically downregulating CXCR3 expression via IL-17A/STAT3 in advanced-stage colorectal cancer patients. *J. Hematol. Oncol.* 13:68
122. Tosolini M, Kirilovsky A, Mlecnik B, Fredriksen T, Mauger S, et al. 2011. Clinical impact of different classes of infiltrating T cytotoxic and helper cells (Th1, Th2, Treg, Th17) in patients with colorectal cancer. *Cancer Res.* 71:1263–71
123. Dejea CM, Fathi P, Craig JM, Boleij A, Taddese R, et al. 2018. Patients with familial adenomatous polyposis harbor colonic biofilms containing tumorigenic bacteria. *Science* 359:592–97
124. Calcinotto A, Brevi A, Chesi M, Ferrarese R, Garcia Perez L, et al. 2018. Microbiota-driven interleukin-17-producing cells and eosinophils synergize to accelerate multiple myeloma progression. *Nat. Commun.* 9:4832
125. Langowski JL, Zhang X, Wu L, Mattson JD, Chen T, et al. 2006. IL-23 promotes tumour incidence and growth. *Nature* 442:461–65
126. Dai ZM, Zhang TS, Lin S, Zhang WG, Liu J, et al. 2016. Role of IL-17A rs2275913 and IL-17F rs763780 polymorphisms in risk of cancer development: an updated meta-analysis. *Sci. Rep.* 6:20439
127. Wu X, Zeng Z, Chen B, Yu J, Xue L, et al. 2010. Association between polymorphisms in interleukin-17A and interleukin-17F genes and risks of gastric cancer. *Int. J. Cancer* 127:86–92
128. Li TJ, Jiang YM, Hu YF, Huang L, Yu J, et al. 2017. Interleukin-17-producing neutrophils link inflammatory stimuli to disease progression by promoting angiogenesis in gastric cancer. *Clin. Cancer Res.* 23:1575–85
129. Punt S, van Vliet ME, Spaans VM, de Kroon CD, Fleuren GJ, et al. 2015. $FoxP3^+$ and $IL\text{-}17^+$ cells are correlated with improved prognosis in cervical adenocarcinoma. *Cancer Immunol. Immunother.* 64:745–53
130. Hirahara N, Nio Y, Sasaki S, Minari Y, Takamura M, et al. 2001. Inoculation of human interleukin-17 gene-transfected Meth-A fibrosarcoma cells induces T cell-dependent tumor-specific immunity in mice. *Oncology* 61:79–89
131. Lu L, Pan K, Zheng HX, Li JJ, Qiu HJ, et al. 2013. IL-17A promotes immune cell recruitment in human esophageal cancers and the infiltrating dendritic cells represent a positive prognostic marker for patient survival. *J. Immunother.* 36:451–58
132. Chen CL, Wang Y, Huang CY, Zhou ZQ, Zhao JJ, et al. 2017. IL-17 induces antitumor immunity by promoting beneficial neutrophil recruitment and activation in esophageal squamous cell carcinoma. *Oncoimmunology* 7:e1373234
133. Martin-Orozco N, Muranski P, Chung Y, Yang XO, Yamazaki T, et al. 2009. T helper 17 cells promote cytotoxic T cell activation in tumor immunity. *Immunity* 31:787–98
134. Kryczek I, Wei S, Szeliga W, Vatan L, Zou W. 2009. Endogenous IL-17 contributes to reduced tumor growth and metastasis. *Blood* 114:357–59
135. Ma M, Huang W, Kong D. 2018. IL-17 inhibits the accumulation of myeloid-derived suppressor cells in breast cancer via activating STAT3. *Int. Immunopharmacol.* 59:148–56
136. Lin Y, Xu J, Su H, Zhong W, Yuan Y, et al. 2015. Interleukin-17 is a favorable prognostic marker for colorectal cancer. *Clin. Transl. Oncol.* 17:50–56