



Much More Than IL-17A: Cytokines of the IL-17 Family Between Microbiota and Cancer

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The interleukin-(IL-)17 family of cytokines is composed of six members named IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F. IL-17A is the prototype of this family, and it was the first to be discovered and targeted in the clinic. IL-17A is essential for modulating the interplay between commensal microbes and epithelial cells at our borders (i.e., skin and mucosae), and yet, for protecting us from microbial invaders, thus preserving mucosal and skin integrity. Interactions between the microbiota and cells producing IL-17A have also been implicated in the pathogenesis of immune mediated inflammatory diseases and cancer. While interactions between microbiota and IL-17B-to-F have only partially been investigated, they are by no means less relevant. The cellular source of IL-17B-to-F, their main targets, and their function in homeostasis and disease distinguish IL-17B-to-F from IL-17A. Here, we intentionally overlook IL-17A, and we focus instead on the role of the other cytokines of the IL-17 family in the interplay between microbiota and epithelial cells that may contribute to cancer pathogenesis and immune surveillance. We also underscore differences and similarities between IL-17A and IL-17B-to-F in the microbiota-immunity-cancer axis, and we highlight therapeutic strategies that directly or indirectly target IL-17 cytokines in diseases.

Keywords: microbiota, Th17, autoimmunity, microbiome, gut, immunotherapy, arthritis, cancer

INTRODUCTION

Fine tuning of the interactions between eukaryotic and prokaryotic cells that literally share our body is essential for maintenance of health (1). In humans, the number of commensal, symbiont, and mutualistic microbes (i.e., microbiota) inhabiting the gut, skin, mucosae, and even some visceral organs, at least equals the number of eukaryotic cells (2). Nonetheless, the microbiome (i.e., the microbiota genomic repertoire) outnumbers the host's genome by 10 folds (3), and this may help explaining why the microbiota is so relevant for the correct functioning of our organs and tissues (4). The development of individual microbiota starts soon after birth (5), and it stabilizes within the first three years (6). Within the same time frame, the developing immune system has to deal with, and it is shaped by the microbiota (7). Indeed, the immune system adapts to antigens expressed by eukaryotic cells, through the mechanisms of central and peripheral immune tolerance, thus avoiding autoimmunity (8). The immune system also has to progressively cope with antigens

expressed by the microbiota (9), a phenomenon we originally defined as adaptation to the “extended self” (10). Tolerance to the extended self is likely enforced by the perfect balancing between regulatory T cells (Tregs), which block excessive immune reactions (11), and T helper (Th) cells, rapidly intervening when a commensal species has overtly grown, or a new species appears within the microbiota. Indeed, antigens and metabolites generated in the presence of a defined microbiota modulate the expansion or contraction of Tregs and effector Th cells (12–14). For example, microbiota-immune system interactions skew mouse Th cells to produce interleukin-17 (IL-17) (15), and together with IL-22 (16), Th17 cells producing these cytokines protect the integrity of the gut mucosa, and stimulate the local maturation of immunoglobulin (Ig) A-producing plasma cells, thus restraining dwelling bacteria (17). Additionally, fibroblasts, endothelial cells, chondrocytes, and adipocytes respond to IL-17A by expressing antimicrobial proteins and peptides, and proinflammatory cytokines and chemokines involved in acute-phase responses and tissue remodeling (18, 19). As a consequence, skin and mucosae of organisms lacking IL-17A are more susceptible to fungal and bacterial infection (20).

An alteration or imbalance of the normal microbiota composition (i.e., dysbiosis) is a common characteristic of many human diseases, albeit it remains to be clarified if dysbiosis is cause or consequence of the disease. Obesity, type 2 diabetes, nonalcoholic fatty liver disease, periodontitis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, and systemic lupus erythematosus are examples of diseases exacerbated or worsened by an altered gut flora (1, 4, 10, 14, 21). Interestingly, IL-17A has a relevant pathogenic role in all these diseases (10). For example, it is well known that the IL-12-IL-17 axis exerts an essential role both in the onset phase and at the time of bone destruction in autoimmune arthritis (22).

Microbiome analysis in rheumatoid arthritis patients showed dysbiosis and a relative abundance of *Prevotella copri*, Gram negative bacteria that appear to favor the induction of Th17 cells (23) (Table 1). In mice, transfer of Th17 cells polarized by *P. copri*-stimulated dendritic cells induced arthritis (38). Both in humans (39) and in mice (40), cross-reactivity between bacteria and myelin antigens seems to activate Th17 cells that induce autoimmune demyelination. In experimental autoimmune encephalomyelitis (EAE), microbiota-induced Th17 lymphocytes migrated from the gut into the central nervous system, where they exacerbated the disease (41). Thus, control of pathogenic Th17 cells occurs in the gut. The mechanisms by which commensals modulate the immune response, and Th17 cells in particular, has only been partially defined. Very recently, Duscha et al. (42) showed that the availability of propionic acid in feces and blood of multiple sclerosis patients depends on intestinal microbiota composition, and 14-day supplementation of propionic acid in the diet correlated with Treg expansion in the intestine, and neurologic symptom amelioration. Interestingly, monoclonal antibodies blocking either IL-17 or IL-23 are already in the clinic or under investigation for the treatment of rheumatoid arthritis patients (43). Thus, IL-17A is a master regulator of host-microbiota interactions both in physiologic conditions and in immune-mediated inflammatory diseases (44, 45).

More recently, a microbiome has also been found in the blood and tumor of cancer patients (46), and microbiota-induced IL-17A has also been implicated in the pathogenesis of colon cancer, breast, pancreatic and ovarian carcinomas, and multiple myeloma (MM) (10, 47). The role of IL-17A in cancer has not been fully elucidated, and data are controversial. While in melanoma and ovarian cancer, Th17 cells activate anti-neoplastic cytotoxic T cell responses (48–50), they are

TABLE 1 | Microbes driving the production of IL-17 cytokines in inflammation and cancer.

	Microbes	Site	Cytokine produced	Producer cells	Outcome	Ref.
Physiological inflammatory response	<i>Tritrichomonas</i> , <i>Heligmosomoides polygyrus</i>	Intestine	IL-17E	Tuft cells	Activation of ILC2 and type-2 immunity in mice	(24)
	<i>Citrobacter rodentium</i>	Intestine	IL-17C IL-17B IL-17F	Epithelial cells	Induction of inflammation, promotion of epithelial barrier integrity in mice	(25–27),
	<i>Listeria monocytogenes</i> , <i>Influenza virus</i>	Intestine	IL-17D	Non-hematopoietic cells	Increased susceptibility to infection	(28)
Inflammatory diseases	<i>Pseudomonas aeruginosa</i>	Lungs	IL-17C	Epithelial cells	Induction of inflammation	(29)
	<i>Bacteroides stercoris</i> , <i>Bacteroides ovatus</i> , <i>Prevotella melaninogenica</i>	Lungs	IL-17B	Macrophages	Induction of pulmonary fibrosis in mice	(30)
	<i>Fusobacterium nucleatum</i>	Intestine	IL-17F	Epithelial cells	Correlates with progression of ulcerative colitis in humans and mice	(31)
	<i>Prevotella copri</i> , <i>Prevotella nigrescens</i>	Intestine	IL-17A	Th17	Correlates with enhanced rheumatoid arthritis in humans and mice	(32)
Cancer	<i>Proteobacteria</i> , <i>Verrucomicrobia</i>	Intestine	IL-17E	Macrophages	Correlates with progression of hepatocellular carcinoma in humans and mice	(33)
	<i>Escherichia coli</i>	Intestine	IL-17C	Epithelial cells	Colorectal cancer progression in mice	(34)
	Nontypeable <i>Haemophilus influenzae</i>	Lungs	IL-17C	Epithelial cells	Progression of lung cancer in mice	(35)
	<i>Bacteroides fragilis</i>	Intestine	IL-17A	Th17 cells	Colorectal cancer progression in mice	(36)
	<i>Prevotella heparinolytica</i>	Intestine	IL-17A	Th17 cells	Multiple myeloma progression in mice	(37)

tumorigenic in a variety of mouse models of colon cancer (51), hepatocellular carcinoma (52), MM (37), and pancreatic cancer (53). The function of IL-17 may also vary depending on the disease phase, and in pancreatic cancer it has been proposed that IL-17-producing cells support tumor growth in the initial phases of the disease, while in advanced phases, IL-17A potentiates antitumor immunity (47). IL-17A can favor tumor growth either in a direct or in indirect manner. In mouse tumor cell lines expressing the IL-17R, IL-17A induced IL-6 production, which in turn activated signal transducer and activator of transcription (Stat) 3, eventually upregulating pro-survival and proangiogenic signals (54). On the other hand, IL-17A also recruits mouse innate immune cells like neutrophils and immature myeloid cells within the tumor, supporting the development of an immunosuppressive microenvironment, eventually favoring tumor growth (55–57).

Of relevance, modulation of the gut microbiota reduces expansion of Th17 cells and tumor progression both in solid and hematopoietic tumors (37, 58). For example, in mice affected by MM (59), a neoplasia of plasma cells accumulating primarily in the bone marrow together with an immune infiltrate (60), the gut microbiota enriched in *P. heparinolytica* induced Th17 cells locally, which migrated to the bone marrow and promoted aggressiveness of MM (Table 1). Indeed, both in humans and in mice neoplastic plasma cells express the IL-17 receptor (IL-17R) (37, 61), and IL-17 supports plasma cells survival and proliferation likely by inducing the autocrine release of IL-6 (54).

Lack of IL-17A in MM mice, or treatment with antibiotics or monoclonal antibodies blocking IL-17/IL-17R interactions delayed disease progression (37). Thus, the microbiota-IL-17A axis is also relevant in cancer patients.

The gut microbiota may also influence response to therapy in cancer patients, and this is the focus of intense clinical investigation. For instance, the composition of the gut microbiota *per se* is sufficient to discriminate cancer patients who will or will not respond to antibodies blocking inhibitory immune checkpoints (62–64). Prospective clinical trials will better define the impact of microbiota modulation on cancer therapy.

IL-17A has been cloned in 1993 (65). At the beginning of this century, other molecules with sequence homology to IL-17A entered the IL-17 family, including IL-17B, IL-17C, IL-17D, IL-17E or IL-25, and IL-17F (66, 67). Each cytokine of the family acts as homodimer or heterodimer, and they interact with specific dimeric receptors (named IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE; Figure 1), with the exception of IL-17D, which remains orphan of its ligand (44). Binding of IL-17 cytokines to cognate IL-17Rs activates the shared SEFIR (SEF/IL-17R) cytoplasmic motif (68), which mediates the recruitment of Act1 (69). As detailed below, these steps are crucial for downstream recruitment and ubiquitination of TNF-receptor associated factor 6 (TRAF6), activation of nuclear factor κ B (NF- κ B), and expression of pro-inflammatory and anti-microbial molecules (70).

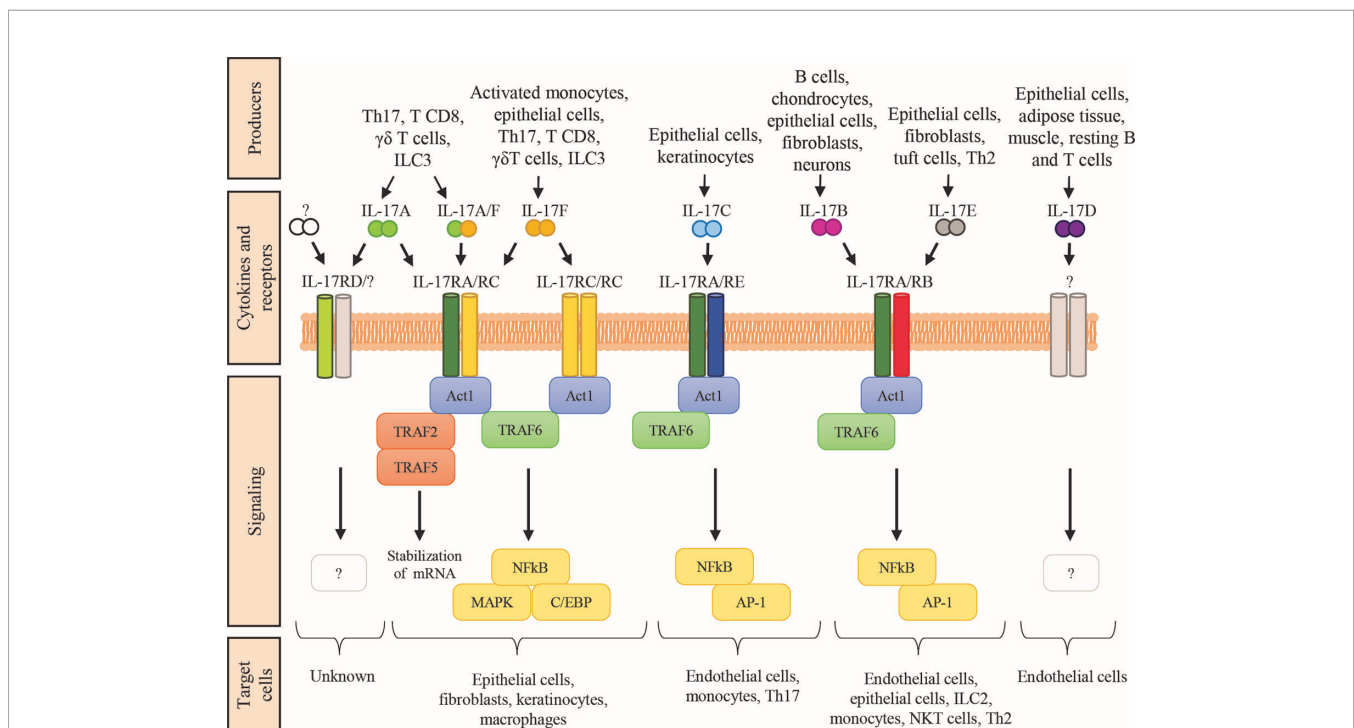


FIGURE 1 | The IL-17 family of cytokines. Schematic representation of the cytokines belonging to the IL-17 family, their respective receptor complexes coupled with intracellular signaling, and their target cells. Cytokines are reported in a mechanistic rather than alphabetic order. Producers each cytokine are also shown. AP-1, activator protein-1; C/EBP, CCAAT enhancer-binding protein; ILC, innate lymphoid cells; MAPK, mitogen-activated protein kinase; NKT, natural killer T cells; Th2, T helper-2 cells; Th17, T helper-17 cells; TRAF, TNF-receptor associated factor; NF- κ B, nuclear factor κ B.

While the role of microbiota-driven IL-17A and Th17 cells in cancer have been extensively reviewed [e.g. (10, 20, 47)], a review dedicated to the role of the other cytokines of the IL-17 family in the microbiota-immunity-cancer axis is lacking. Thus, we intentionally overlooked the IL-17A/IL-17RA-RC pathway, and we have focused on IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F.

IL-17 SIGNALING

Cytokines of the IL-17 family are pleiotropic and exert potent and diverse *in vivo* functions through both canonical and noncanonical signaling pathways (68). Canonical signaling induces both transcriptional and post-transcriptional mechanisms involved in autoimmunity, hypersensitivity, and metabolic reprogramming of lymphoid tissues. Noncanonical signaling acts in synergy with other receptor systems, and it is mainly responsible for tissue repair and regeneration. Both mechanisms participate to host defenses, and tumor progression.

The IL-17Rs belong to a new subfamily of receptors consisting of 5 members: IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE which are single-pass transmembrane receptors with conserved domains (71) (**Figure 1**). Indeed, all members of the IL-17R family encode two extracellular fibronectin II-like domains and the conserved region SEFIR, which mediates the recruitment of the multifunctional adaptor Act1 (69). SEFIR is structurally related to the domain found in the toll-like receptor (TLR)/IL-1R (72). Functionally, the IL-17R is a heterodimeric complex composed of the IL-17RA in combination with other subunits that confer ligand or signaling specificity. IL-17A signals through IL-17RA in combination with IL-17RC. Whereas the IL-17RA subunit is ubiquitously expressed, IL17RC is mainly present on non-hematopoietic epithelial and mesenchymal cells. Interestingly, IL-17A interacts with its receptor as a homodimer or as a heterodimer with IL-17F (73). IL-17F could also bind this receptor complex as a homodimer. The difference between these three ligands is mainly in the potency of interaction: IL-17A>IL-17A-IL-17F> IL-17F (74). Also the IL-17RD has been proposed as an alternative receptor subunit for IL-17A, but not for IL-17F, and appears to favor the IL-17A-mediated recruitment of neutrophils (75). Finally, IL-17RA is also used by IL-17B, IL-17C, and IL-17E (also known as IL-25) (66). The detailed function of IL-17 receptors and their ligands remains partially elusive and requires further investigation.

Canonical Signaling

The canonical IL-17 signaling pathway is initiated by SEFIR (**Figure 1**), which mediates Act1 recruitment (69). Act1 is crucial for IL-17 signaling, and it acts as adaptor and as RNA-binding protein (RBP) by forming several ribonucleoprotein particles (RNPs) (69, 76, 77). As adaptor, Act1 triggers multiple signaling cascades *via* the tumor TRAF-binding motif, which recruits different TRAF protein to initiate separate downstream pathways. The TRAF-binding motif is a distinct C-terminal region present only in IL-17RA. An analogous domain in other

IL-17R family members is not found (68). Downstream recruitment and ubiquitination of TRAF6 leads to the activation of nuclear factor- κ B (NF- κ B), the CCAAT enhancer-binding proteins (C/EBPs) family, and the mitogen-activated protein kinase (MAPK) pathways (p38, ERK, and JNK) responsible for transcriptional regulation (44, 70). The TRAF6-mediated signaling is controlled by several regulatory mechanisms to hamper IL-17-induced inflammation. For instance, upregulation of IL-17 signaling *via* NF κ B is associated with susceptibility to autoimmune syndromes, including psoriasis and experimental autoimmune encephalomyelitis (78, 79). Additionally, TRAF3 or TRAF4 compete with TRAF6 for the TRAF-binding motif on Act1, leading to reduced IL-17-induced expression of pro-inflammatory mediators, and Act1 is degraded by the proteasome in the presence of prolonged IL-17 stimulation (80). Thus, NF- κ B and MAPK pathways downregulate IL-17 signaling. Conversely, C/EBP family activation potentiates the IL-17-inflammatory response through a feed-forward mechanism with other transcription factors like I κ B ζ . I κ B ζ modulation is crucial to control the IL-17-dependent responses, and it is one of the few targeted genes so far investigated. Indeed, most of the C/EBP-dependent genes involved in the IL-17 pathway remain elusive.

Act1 also acts as RBP upon TRAF2-TRAF5 complex engagement to control the stability and translation of mRNA from IL-17-target genes in response to IL-17 stimulation. IL-17 signaling results in the formation of multiple RNPs, associated with mRNA-stabilizing or mRNA-destabilizing factors, for post-transcriptional regulation of gene expression (81). Interestingly, IL-17 increases the half-life of mRNA to induce the efficient production of effector proteins.

Noncanonical Signaling

Noncanonical IL-17 signaling is characterized by synergistic interactions of IL-17 signals with other ligands, like cytokines or microbial products, that lead to activation of diverse signaling pathways (82–84). As few examples, NF- κ B is activated upon interaction of IL-17 with tumor necrosis factor- α (TNF- α) or lymphotoxin, and the signal transducer and activator of transcription 1 (STAT1) when IL-17 interacts with interferon- γ (IFN- γ). Interaction between IL-17 and IL-13 activates STAT6, whereas the SMADs family is triggered by the interaction with tumor growth factor- β (TGF- β). Finally, IL-17 interactions with bacterial lipopolysaccharide or fungal products, like candidalysin, activates c-Fos (82–84).

IL-17 also controls tissue homeostasis by integrating signals from the IL-17R and growth factor receptors in a high cell type- and context-specific manner. In particular, an integration of IL-17 receptor signaling has been described with the epidermal growth factor receptor (EGFR), the fibroblast growth factor receptor (FGFR), NOTCH1, and with components of the C-type lectin receptors. The EGFR cascade is mainly identified in skin stem cells, and it is involved in wound healing and tumorigenesis (85, 86). Interactions between IL-17 and FGFR have been described in mouse colonic epithelial cells during tissue repair caused by colon inflammation (87). In mice, IL-17 signaling also engages the NOTCH1 receptor to promote

neuroinflammation through expansion and differentiation of oligodendrocyte progenitor cells (88, 89). Finally, signaling integrations between IL-17 and components of C-type lectin receptors have been reported in keratinocytes during psoriasis (90).

Altogether, these findings support the existence of a complex and yet partially explored net of signaling pathways downstream IL-17 cytokine secretion and interaction with their receptors.

CYTOKINES OF THE IL-17 FAMILY OTHER THAN IL-17A IN HEALTH AND DISEASE

Cytokines of the IL-17 family are crucial components of the inflammatory response, and they are essential for normal host immune responses. Both in humans and in mice, IL-17 cytokines are produced by a vast array of cell types, and act on a multitude of cellular targets (44, 66, 67, 91–93), eventually inducing production of pro-inflammatory cytokines, chemokines, and prostaglandins (94) (**Figure 1**). Cytokines of the IL17 family exert non-redundant, and even opposing functions to promote elimination of intruders, and tissue reconstitution. They are also involved in many human pathologies including inflammatory immune mediated diseases and cancer.

Cytokines within the IL-17 family share 16–50% amino acid identity with IL-17A, with IL-17F being the most similar (50%) and IL-17E the most divergent (16%). The similarity between IL-17 cytokines is higher in the C terminus and in five spatially conserved cysteine residues. N terminus sequences of IL-17B, IL-17C, and IL-17E are substantially different from those found in IL-17A and IL-17F because of a longer extension of the former three proteins (95), suggesting that the N terminus is involved in receptor specificity (96).

Because IL17F has the highest homology with IL-17A, binds to the same complex IL17RA-RC, and activated Th17 cells to produce both IL-17A and IL-17F (97), we followed a mechanistic rather than an alphabetic order to describe cytokines of the IL-17 family, and we started from IL-17F. As we will see, not all these cytokines are produced by immune cells, but all of them either directly or indirectly impact the immune system. We refer the interested reader to excellent reviews for a comprehensive description of these cytokines (44, 66, 67, 91–93).

IL-17F

The *Il17f* gene is closely located to the *Il17a* gene both in humans (chromosome 6) and mice (chromosome 1), whereas genes encoding the other members of the IL-17 family are located in different chromosomes (18). The protein has a molecular mass of 18045 Da and is composed of 163 amino acids. IL-17F can form homodimer or heterodimer with IL17A (<https://www.genecards.org/cgi-bin/carddisp.pl?gene=IL17F#summaries>). Many genetic variants have been identified for the *Il17f* gene: most of them are missense mutations and some of them are pathogenetic (https://gnomad.broadinstitute.org/gene/ENSG00000112116?dataset=gnomad_r2_1). For example, the heterozygous missense mutation S95L (c.284C>T) in the *Il17f* gene has been found in

patients with chronic mucocutaneous candidiasis, an infection caused by *Candida albicans* that affects nails, skin, and oral and genital mucosae. The S95L IL-17F mutant (IL-17FS95L) is normally expressed and forms homo- and heterodimers with IL-17F, IL-17FS95L, and IL-17A. However, IL-17FS95L is severely hypomorphic and exerts a dominant-negative effect by impairing the binding of its complexes to the receptor (98).

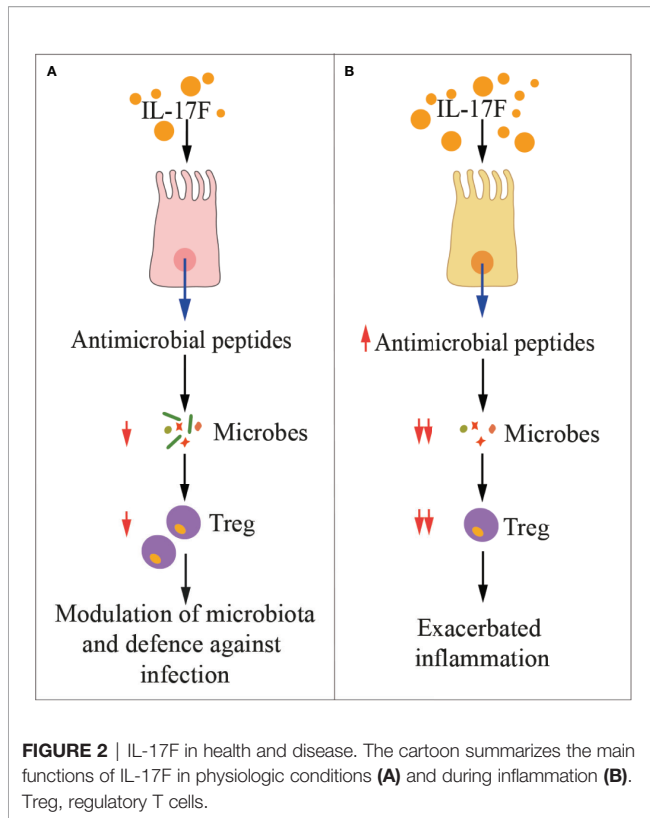
IL-17A and IL-17F are mainly produced by activated CD4⁺ T cells leading to the definition of a distinct T cell subset named Th17 (66). The differentiation of Th17 cells in humans is induced by several cytokines including IL-1 β , IL-21, IL-23 and TGF- β that activate the Stat3- and the IRF4-dependent expression of retinoic acid receptor-related orphan receptor- γ t (ROR- γ t). Th17 cells comprise IL-17A and IL-17F double positive cells, but also populations that are only positive for IL-17A or IL-17F have been identified, suggesting that the mechanisms regulating IL-17A and IL-17F production are different. Interestingly, in mice the expression of *Il17a* but not *Il17f* is strictly coupled to the T cell receptor (TCR) signaling through the inducible T cell kinase (Itk)-mediated nuclear factor of activated T cells (NFAT) recruitment (99). These data demonstrate that in mice Itk specifically links TCR signaling to *Il17a* expression, thus regulating Th17 cell cytokines through NFATc1.

As for IL-17A, IL-17F is also expressed in innate lymphoid cells (ILCs), $\gamma\delta$ T cells, natural killer T (NKT) cells and CD8⁺ T cells, but IL-17F is exclusively produced by activated monocytes and epithelial cells (25, 100, 101). Both IL-17A and IL-17F bind to the IL-17RA-RC heterodimer, and they induce a qualitatively but not quantitatively similar signal, being IL-17A far more potent than IL-17F. Both IL-17A and IL-17F can be secreted as disulfide-linked homodimers or heterodimers (18). Heterodimers exhibit intermediate levels of potency in inducing IL-6 and CXCL1 when compared to homodimeric cytokines (102).

Both cytokines act in synergy with TNF- α (103), and in mice contribute to inflammation and protection at barrier surfaces, with overlapping yet distinct roles (**Figure 2**) (25). *In vitro*, IL-17F preferentially associates with IL-17RC homodimers, leading to IL-17RA-independent signaling (104). The expression profiles of IL-17RA and IL-17RC are different among tissues and cell types, with IL-17RC preferentially expressed in non-immune cells (25). In mouse models, the constitutive expression of IL-17RC in intestinal epithelial cells (25) explains the more pathogenic effects of IL-17F than IL-17A on microbiota during colitis (**Figure 2**) (105, 106).

IL-17C

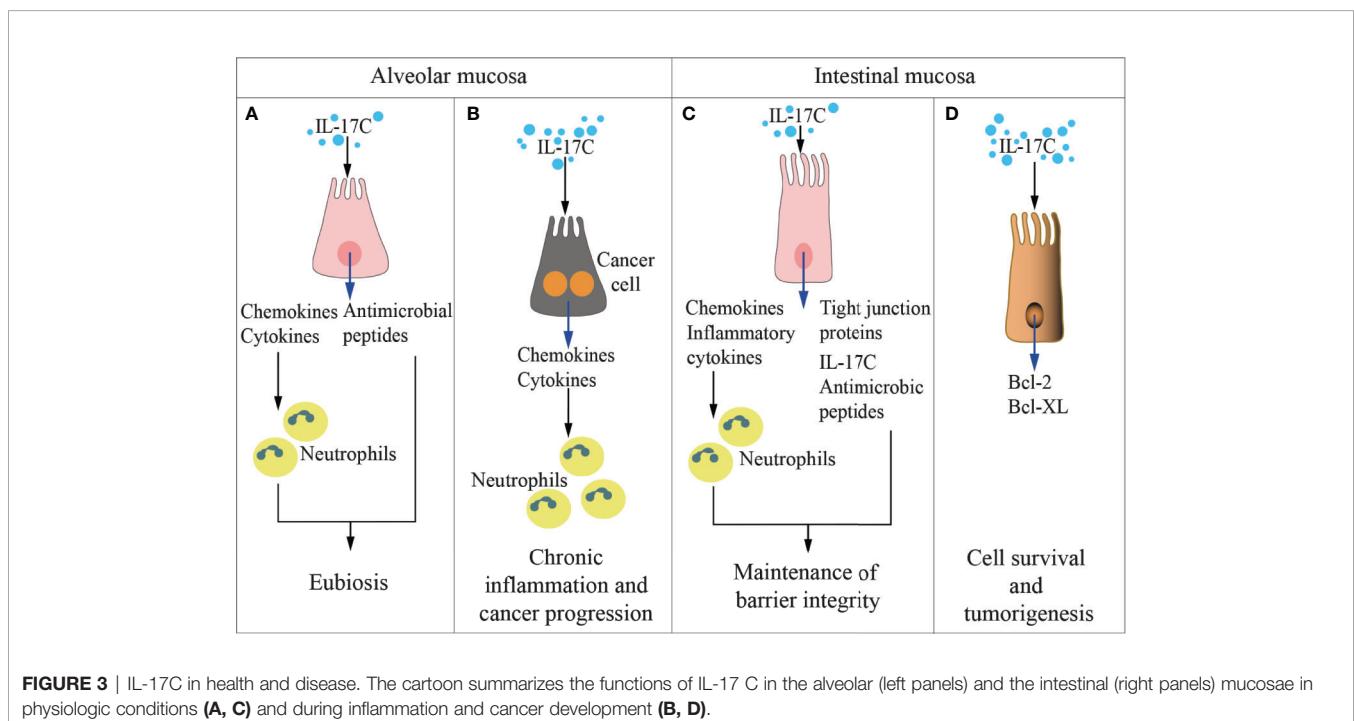
IL-17C is mainly known for its pro-inflammatory and antibacterial functions at epithelial sites in synergy with IL-17F (107). The *Il17c* gene is located in the long arm of human chromosome 16 (16q24.2). The IL-17C protein has a molecular mass of 21765 Da, and it is composed of 197 amino acids (<https://www.genecards.org/cgi-bin/carddisp.pl?gene=IL17C>). IL-17C share 23% amino acid homology with IL-17A (108), and while it binds a heterodimeric receptor formed by IL17RA and IL17RE, the IL-17RE subunit is the specific functional receptor for IL-17C (26). Most of the genetic variants of the *Il17c* gene are



missense mutations (https://gnomad.broadinstitute.org/gene/ENSG00000124391?dataset=gnomad_r2_1), and just few of them have clinical significance (<https://www.ncbi.nlm.nih.gov/clinvar/?term=il17c%5Bgene%5D>).

Both in humans and in mice, the IL-17C is produced by several cells, including intestinal, tracheal and lung epithelial cells and keratinocytes, which also express the IL-17RA-RE heterodimer (107). Thus, IL-17C acts locally in an autocrine manner to protect the mucosa or to induce epithelial inflammatory responses (Figure 3) similarly to IL-17A and IL-17F (107). For example, stimulation of mouse epithelial cells by *Escherichia coli* or pathogen-associated molecular patterns (PAMPs) activates a MyD88-dependent intracellular signaling, eventually inducing IL-17C production, which activates expression of chemokines, granulocyte-colony stimulating factor (GM-CSF), AMPs, and IL-1 β in an autocrine fashion (78). Additional target genes of IL-17C in epithelial cells encode antimicrobial peptides like S100A7/8/9, β -defensin2, immune-activating molecules CXCL1/2/3 and CCL20, and proinflammatory cytokines as well as occludin, claudin-1, and claudin-4, which are involved in the formation of epithelial tight junctions (107, 109). Interestingly, Wolf et al. showed that in mice, *Pseudomonas aeruginosa*-induced IL-17C expression in lung epithelial cells by a IL-17A-dependent mechanism, thus demonstrating a network within the family of IL-17 cytokines that regulates each other expression (29).

IL-17C induces the expression of IL-1 β and TNF- α in monocytes (67). IL-17RA-RE is also expressed on activated Th17 cells, and when triggered by IL-17C, it favors IL-17A, IL-17F, and IL-22 production by mouse Th17 cells, potentiating the adaptive immune response against pathogens and in autoimmunity (80, 110). Song et al. also identified the IL-17C/IL-17RE pathway as a pivotal regulator of innate immunity to intestinal bacterial pathogens in mice (26). Thus, IL-17C induces inflammation, but also promotes tissue healing.



IL-17C is involved in several human diseases. IL-17C levels are elevated in psoriatic lesions, and it significantly affects the abundance of F4/80⁺ macrophages within inflamed psoriatic plaques (107, 111, 112). Interestingly, IL-17C appears to also have a role in pathogenesis of atherosclerosis. Smith et al. reported that the mouse vasculature is an important source of IL-17C in atherosclerosis (113). Here, IL-17C exerts a pro-inflammatory role (114), by favoring the accumulation of pro-atherogenic Th17 cells within the aorta, which in turn affect the recruitment of monocytes and neutrophils to the plaque (115). Inflammatory glomerulonephritis also appears dependent on IL-17C, and Krohn et al. reported that patients affected by acute anti-neutrophil cytoplasmic antibody-associated crescentic glomerulonephritis had significantly elevated serum levels of IL-17C (but not IL-17A, F, or E) (116). Additionally, they showed that glomerulonephritis ameliorated in mice lacking IL-17C and/or its receptor IL-17RE, and associated with a reduced Th7 response (116). We expect that in the next years IL-17C will be found involved in many more human diseases.

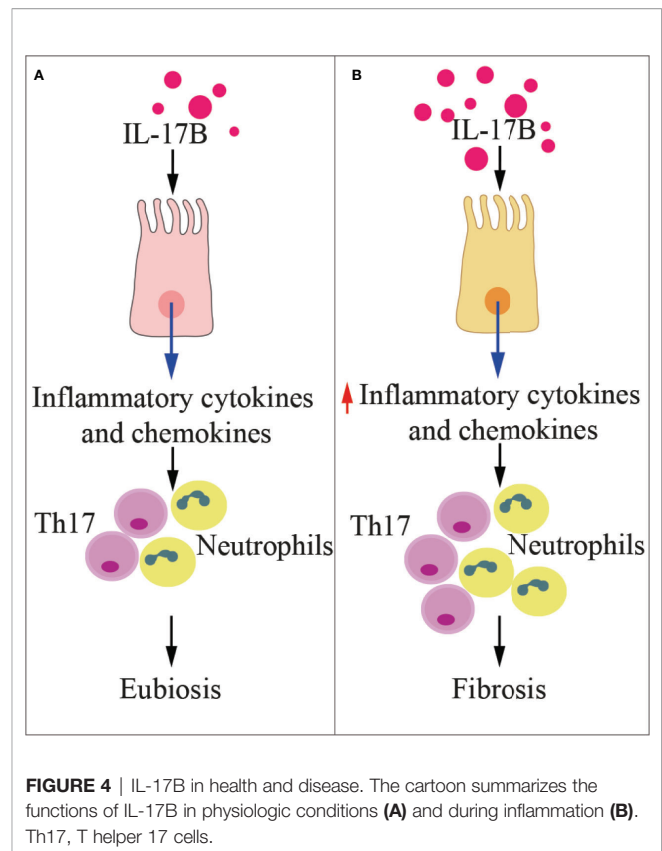
IL-17B

The human *Il17b* gene was cloned together with *Il17c* and is located on the long arm of human chromosome 5 (5q32). The translated protein has a molecular mass of 20437 Da and is composed of 180 amino acids (<https://www.genecards.org/cgi-bin/carddisp.pl?gene=IL17B>). At the N terminus, there is an 18–20-amino acid sequence containing a hydrophobic motif, which functions as secretory signal sequence (117). IL-17B is secreted as a noncovalent dimer (18). Among the IL-17 family members, IL-17B has 29% homology with IL-17A (108).

Also for *Il17b*, most of the genetic variants are missense mutations (https://gnomad.broadinstitute.org/gene/ENSG00000127743?dataset=gnomad_r2_1). Almost nothing is known about their consequences, except for three specific conditions: a neurodevelopmental disorder of clinical uncertain significance, an hereditary cancer-predisposing syndrome and keratoconus, an eye condition that affects the shape of the cornea (<https://www.disgenet.org/browser/1/1/2/27190/>), and it is due to C176Y, C124Y protein changes. (<https://www.ncbi.nlm.nih.gov/clinvar/?term=IL17b%5Bgene%5D>).

IL-17B was found to be originally expressed in adult pancreas, small intestine, and stomach, but not in T cells (118, 119). IL-17B is also highly expressed in chondrocytes and neurons, although low IL-17B mRNA has been detected in several organs (120). According to recent investigations, IL-17B is weakly expressed by the epithelium, whereas IL-17B is strongly expressed in a healthy colon by connective tissue cells (121). IL-17B expression, especially in the epithelial and stromal compartments, is increased in colorectal cancer (121).

IL-17B and IL-17E (also named IL-25) share the same heterodimeric receptor IL-17RA/RB, and may exert redundant or contraposed effects, depending on the tissue context, as detailed below. The signaling pathway downstream IL-17RA/RB receptor is poorly detailed, and mainly described upon IL-17E binding. Li et al. showed that *in vitro* IL-17B does not induce IL-6 expression, but induces monocytes to produce TNF- α and IL-1 β (118), and in mice it favors neutrophils recruitment



(Figure 4) (119). *In vitro*, IL-17B promotes chemotaxis of IL-17RB-positive B cells by downregulating RGS16, the negative controller of CXCR4 and CXCR5 chemokine receptors (122). *In vivo*, IL-17B promotes embryonic development, tissue regeneration, and chemotaxis of B cells through IL-17RB in an autocrine fashion (93).

IL-17B has been investigated in several inflammatory diseases. While Ryan et al. (123) found genetic variants at the IL-17B locus in a 409 cases of coeliac disease and 355 controls, they did not find evidence that this locus was associated with the disease. Patients affected by systemic lupus erythematosus in the active phase showed higher levels of serum IL-17B than patients in the inactive phase (124). In community-acquired pneumonia, patients also showed higher serum levels of IL-17B when compared to healthy controls (125). IL-17B induced the expression of IL-8 in human bronchial epithelial cells through the activation of Akt, p38 mitogen-activated protein kinase, extracellular signal-regulated kinase (ERK), and NF- κ B signaling pathways. Finally, in mice affected by pneumonia, high IL-17B levels significantly correlated with IL-8 concentrations (125). IL-17B also is the predominant cytokine of the IL-17 family in the rheumatoid synovia, it is locally produced by neutrophils, and it contributes to tissue destruction by enhancing TNF- α -induced production of G-CSF and IL-6 in fibroblasts (126). Interestingly, treatment with IL-17B neutralizing antibodies ameliorated collagen-induced arthritis in mice (127). Altogether, these findings demonstrate

that IL-17B is a proinflammatory cytokine involved in inflammation and autoimmunity.

High levels of IL-17B have also been associated with poor prognosis in patients with pancreatic, lung or breast cancer, suggesting that the same signaling is exploited by cancer cells for survival, proliferation, and migration (93). Moreover, a relationship between IL-17B and stemness has been found in gastric cancer (128). Conversely, high levels of IL-17B appear to exert antiangiogenic activities *in vitro* (129).

IL-17E

The *Il17e* gene is located on the long arm of human chromosome 14 (14q11.2). The molecular mass of the IL-17E protein, also named IL-25, is 20,330 Da, and it is composed of 177 amino acids. The IL-25 gene has two types of alternative spliced mRNA transcripts encoding two distinct subtypes (subtypes 1 and 2). Subtype 2 is different from subtype 1 for a shorter N end (130). To date, no studies have reported differences in the physiological role of the two subtypes. IL-17E shares only 17% homology with IL-17A, being the most distant among the cytokines of the IL-17 family (108). The human and mouse IL-17E genes share 80% homology (131). Genetic variants of *Il17e* gene are mostly missense mutations (https://gnomad.broadinstitute.org/gene/ENSG00000166090?dataset=gnomad_r2_1), and no specific clinical conditions have been associated to them ([https://www.ncbi.nlm.nih.gov/clinvar/?term=IL25\[gene\]](https://www.ncbi.nlm.nih.gov/clinvar/?term=IL25[gene])).

Intestinal tuft cells are the main producers of IL-25 (132). Additional sources of IL-17E exist, such as activated Th2 cells within the gastrointestinal tract and in other mucosal tissues (133), alveolar epithelial cells (134), alveolar macrophages (135), mesenchymal stem cells derived from the placenta and bone marrow (136), and mouse bone marrow-derived mast cells (137). IL-25 has been also found expressed in the murine central nervous system (138) as well as in the bronchial submucosa from asthmatic patients (139). In mice, IL-17E is also produced by brain capillary endothelial cells (140).

The receptor for IL-25 is composed of the IL-17RA and IL-17RB subunits (120). Thus IL-25 and IL-17B share the same receptor, and depending on tissue context, the two cytokines may exert redundant or contrasting effects. IL-17E stands among IL-17 family members for promoting the production of IL-4, IL-5 and IL-13 by innate type-2 immune cells (132, 141), nuocytes (142), T helper-2 cells, and NKT cells, thus contributing to the host defense against nematodes, but also to allergic reactions (133, 143). For example, after helminthic infection in mice, tuft cells-derived IL-17E induce ILC2 to produce IL-13, which activates epithelial cell progenitors resulting in the remodeling of the intestinal tissue and the induction of type-2 response (**Figure 5**) (132). Indeed, IL-17RA-RB triggering by IL-17E leads to TRAF6-mediated activation of NF- κ B (144) and to the nuclear recruitment of the Th2 master regulator, GATA-3, in T cells (145). Additionally, IL-25 production is triggered in bronchial epithelial cells by rhinovirus infection, which causes local recruitment of eosinophils, neutrophils, basophils, and T and non-T type 2 cells, thus exacerbating asthma (146). IL-17E also

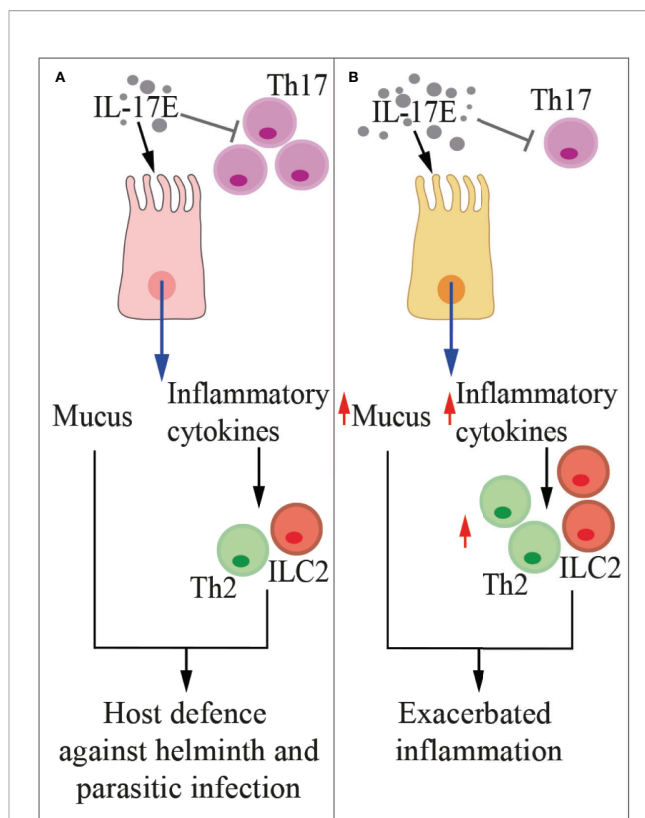


FIGURE 5 | IL-17E in health and disease. The cartoon summarizes the functions of IL-17E in physiologic conditions (**A**) and during inflammation (**B**). Th2, type-2 T helper cells, ILC2, type-2 innate lymphoid cells.

amplifies a Th2 cell-dependent pathway in mice, thus promoting allergy (147).

While *in vitro* IL-17B elicits type 2 cytokine secretion (148), in several inflammatory conditions it antagonizes the pro-inflammatory activity of IL-17E by competing for the same receptor (27). IL-13 induced by IL-17E also inhibits IL-23, IL-1 β , and IL-6 expression in activated DCs, thus blocking the induction of pathogenetic Th17 cells in autoimmune diseases (138). Interestingly, the IL-17E levels in the intestinal mucosa and serum of patients with active inflammatory bowel disease negatively correlated with endoscopic disease activity and C-reactive protein level (149), thus suggesting a protective role for IL-25 in this pathology. Indeed, IL-25 significantly inhibited the *in vitro* production of TNF- α , IFN- γ , and IL-17A by CD4⁺ T cells, but it promoted IL-10 secretion (149).

IL-17E appears to exert a dual role also in cancer. In a variety of human tumor xenograft models, including melanoma, breast, lung, colon, and pancreatic cancers IL-17E has an antitumor effect (150). However, IL-17E, likely released by epithelial tuft cells in the presence of intestinal dysbiosis, can promote the progression of hepatocellular carcinoma by favoring alternative activation of macrophages and their CXCL10 secretion in the tumor microenvironment (33). The role of IL-17E in tumors needs to be further investigated.

IL-17D

IL-17D is the least investigated member of the IL-17 family (66). The *Il17d* gene is located on the long arm of the human chromosome 13 (13q12.11). The translated protein has a molecular mass of 21893 Da and is composed of 202 amino acids, making it the largest IL-17 (<https://www.genecards.org/cgi-bin/carddisp.pl?gene=IL17D&keywords=il17d>). Like all IL-17 family members, IL-17D also has four cysteine residues that may allow homodimer formation through interchain disulfide linkages (96). Whether it forms heterodimer is not known. IL-17D, unlike other members of the IL-17 family, shows an extended C-terminal domain, which may mediate a unique receptor interaction. Most *Il17d* genetic variants are missense mutations, but little is known about their phenotypes (https://gnomad.broadinstitute.org/gene/ENSG00000172458?dataset=gnomad_r2_1).

IL-17D was originally found to be highly expressed in skeletal muscle, adipose tissue, brain, heart, lung and pancreas (96). Curiously, resting CD4⁺ T cells and resting CD19⁺ B cell, but not activated T cells, express low levels of the cytokine, which is orphan of its receptor (96), although hints are coming from the sea lamprey. Investigators have found that IL-17D, which is the most expressed IL-17 in this ancient fish, interacts with IL-17RA in B-like cells (151).

IL-17D does not stimulate the proliferation of immune cells of its own, but, in response to stress, it induces endothelial cells to produce IL-6, IL-8 and GM-CSF (96). Recent studies have shown that IL-17D expression is regulated by the transcription factor nuclear factor erythroid-derived 2-like 2 (Nrf2), sensor for oxidative and xenobiotic stress (152). The Nrf2-mediated expression of IL-17D in response to carcinogenic stimuli initiates antitumor immune responses in mice by activating natural killer (NK)-mediated immune surveillance (152). IL-17D is required for optimal antiviral immunity as well: also in this case, viral infection induces Nrf2 and IL-17D, causing local oxidative stress and antiviral responses (152). Thus, IL-17D should contribute to protecting us from viruses and cancer. Whether IL-17D participates in immunity against other pathogens, such as intracellular bacteria, remains to be defined (153).

As for the other members of the IL-17 family, also IL-17D is implicated in autoimmunity. IL-17D RNA has been detected in rheumatoid nodules, where IL-17A is absent, but not in peripheral blood mononuclear cells or in synovial fluid from patients with rheumatoid arthritis (154). Conversely, IL-17D lacks in psoriatic skin (155), thus suggesting that the pathogenic mechanisms downstream IL-17D are heterogenous.

All together, these findings demonstrate that cytokines of the IL17 family exert non-redundant, and even opposing functions spanning from elimination of intruders or neoplastic cells and tissue reconstitution with limited collateral damage at the inflammation site, to pro-inflammatory and pro-tumoral activities.

CYTOKINES OF THE IL-17 FAMILY OTHER THAN IL-17A AND THE MICROBIOTA

As for IL-17A, also other cytokines of the IL-17 family are involved in maintaining homeostasis at the interface between

microbiota and barrier epithelia (**Table 1**). In addition, overproduction of some of these cytokines may lead to immune mediated inflammatory diseases, and even propel cancer.

IL-17F is one of the major regulators of commensal microbiota in the intestine (**Figure 2**), where it is constitutively expressed and induces the production of antimicrobial peptides (i.e., defensins) (25). Whereas IL-17F appears to have a marginal pathogenic role in immune mediated inflammatory diseases, it exerts a crucial function in host defense against infections, as for example, against *Citrobacter rodentium* (25), a Gram negative enteropathogenic bacterium, which is equivalent of *E. coli* in humans. Defensins also extensively modulate the gut microbiota, and Tang et al. clearly showed that IL-17F-induced production of defensins constrained growth of commensal bacteria directly involved in the expansion of Tregs (105). As consequence, chemically-induced colitis was milder in mice deficient of IL-17F than that of IL-17A-deficient or wild type mice (105). Interestingly, in this experimental setting, IL-17A and IL-17F exerted opposing roles. Indeed, IL-17A was protective against colitis mainly by ensuring integrity of the gut mucosa, while IL-17F was proinflammatory. These experimental evidences have been validated in humans by showing that IL-17F RNA was elevated in colon biopsies from patients affected by ulcerative colitis, and together with IL-6 and TNF- α , they support the generation of a local inflammatory environment (31). Additionally, blockade of the IL-17A pathway in patients with bowel syndromes worsened the pathology (156). Thus, IL-17F may protect against pathogens, but also limit the local immunosuppressive activity of Tregs, eventually unleashing undesired inflammation.

Also the IL-17C is involved in maintenance of epithelial barrier integrity (**Figure 3**), where it is selectively induced by inflammatory or bacterial *noxae* (91). While IL-17C and IL-17A appear to exert overlapping functions (107), IL-17C is mostly produced by epithelial cells at very early time points, and acts both in autocrine and exocrine fashions by inducing the expression of tight junction proteins (109), proinflammatory cytokines and antimicrobial peptides (26, 107). On the contrary, IL-17A is also produced by immune cells like Th17 cells, $\gamma\delta$ T cells, iNK T cells, macrophages, and ILCs. As an example, during infection with *C. rodentium*, IL-17C is upregulated in colon epithelial cells, and protects the mucosa in synergy with IL-22 (26), IL-17B (27), and IL-17F (25). IL-17C also attenuated inflammatory diseases like colitis, but it increased inflammation in psoriasis (107) and EAE (110) underlying the dual role exerted by this family of cytokines. At odds with IL-17A that controls fungal proliferation and infection, and whose blockage has been associated with fungal overgrowth and candidiasis (157), IL-17C is dispensable for immunity against candidiasis (158).

IL-17B is produced by epithelial cells in response to the abnormal expansion of pathobionts (i.e., commensals that in particular circumstances become pathogenic) within the microbiota (**Figure 3**). Its function is to protect the tissue and favor healing (93). Also in the course of allergic asthma, chemically-induced colitis or infection with *C. rodentium*, IL-17B exerts protective anti-inflammatory functions by interfering with IL-17E-induced IL-4 and IL-13 from type 2 Th cells and IL-6 from colon epithelial cells (27).

On the other hand, IL-17E, which also targets IL-17RA-RB, is essential for protecting the intestinal mucosa from parasitic infections (**Figure 4**) (159, 160). IL-17E production by tuft cells is constitutive and increases upon infection with natural mouse parasites like *Tritrichomonas* and *Heligmosomoid polygyrus*, resulting in stimulation of lamina propria ILC2 and mucosal tissue remodeling (**Table 1**). Schneider et al. (24) showed that *Tritrichomonas* favors fiber fermentation and intestinal accumulation of the short-chain fatty acid succinate, eventually inducing mouse intestinal tuft cells to release IL-17E, which in turn boosts type-2 immunity. Additionally, IL-17E produced by mouse intestinal epithelial cells upon microbiota stimulation limits the expansion of local Th17 cells (161) and IL-22 production by ILCs (162), thus identifying a delicate equilibrium among microbiota, adaptive immunity, and ILCs.

The expression of both IL-17E and IL-17B is upregulated during acute colonic inflammation (**Figures 4 and 5**), suggesting a dwelling activity between the two cytokines (27). Whereas IL-17B inhibits signaling of IL-17E but not of IL-17A or IL-17F, IL-17E does not interact with the IL-17RB homodimer, which remains available for IL-17B binding (27). Thus, the balance between IL-17B and IL-17E has to be fine-tuned to limit local inflammation and preserve mucosal integrity from the aggression of pathogens and pathobionts.

Also a dysregulated lung microbiota can drive IL-17B production, as it has been shown in a mouse model of bleomycin-induced lung fibrosis (30). More in details, the authors elegantly showed that depletion of the lung microbiota by antibiotics blocked bleomycin-induced lung fibrosis and death in mice. They also demonstrated that outer membrane vesicles locally released by *Bacteroides stercoris*, *B. ovatus*, and *Prevotella melaninogenica*, which were found enriched in the lung microbiota of mice treated with bleomycin, induced IL-17B production in the lung, thus favoring local immune cell infiltration and activation of profibrotic genes. These effects eventually increased bleomycin-induced mouse mortality. IL-17A and IL-17B have also been found in the bronchoalveolar lavage fluid of patients affected by lung fibrosis, but antibiotic treatments did not appear to be beneficial in limiting acute exacerbation in these patients (163, 164).

The role of IL-17D in the crosstalk between microbes and the immune system is less defined. Whereas IL-17D appears redundant in the context of inflammation induced by lipopolysaccharide, allergic agents or in EAE, it suppresses the function of DCs in inducing CD8⁺ T cell responses, thus favoring infection by *Listeria monocytogenes* or influenza virus (28). However, IL-17D also activates NK-mediated immune surveillance (152), thus potentiating innate immunity. Further investigation is required to clarify how these IL-17D-mediated mechanisms impact microbiota-host interactions.

CYTOKINES OF THE IL-17 FAMILY OTHER THAN IL-17A, MICROBIOTA, AND CANCER

As for IL-17A, the role of IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F in cancer remain controversial. While IL-17D and IL-17E

appear to exert preponderant tumor-protective activities, IL-17B, IL-17C, and IL-17F are tumor promoting, either through a direct effect on tumor cells, or by modulating the tumor microenvironment.

Anti-Tumor Activities of IL-17D and IL-17E

While IL-17D is released by several epithelial cells in response to pathogenic noxae, IL-17D expression in tumors does not appear compatible with their growth. In an elegant study, O'Sullivan et al. (165) showed that IL-17D derived from non-immunoedited cancer cells induces endothelial cells to produce monocyte chemoattractant protein 1 (MCP1), which is responsible for NK cell recruitment, eventually leading to tumor rejection. The same group also showed that mice deficient for IL-17D are more susceptible to viral infections and tumors (152). Nrf2 was shown to be responsible for IL-17D dependent recruitment of NK cells, and induction of Nrf2 by agonists led to regression of already established tumors *in vivo* (152). Thus, IL-17D might be an essential mechanism of immunoediting, and loss of IL-17D production might select for more aggressive tumors. Taking into account the propensity of IL-17A to propel tumor growth either in an autocrine (61, 166) or paracrine fashion (37), findings on IL-17D suggest that this cytokine counterbalances the pro-tumor activity of Th17 cells and IL-17A, and strategies to increase IL-17D might find clinical application. Gene expression analyses on human samples will define potential correlates between tumor immune infiltrate and expression of both IL-17A and IL-17D.

The potent pro-inflammatory activity of IL-17E also appears to be exploited against cancer. Purified IL-17E has been shown to delay growth of a variety of tumor xenografts when given alone or in combination with several drugs (150). The authors also documented accrual of eosinophils and activation of B cells in IL-17E-treated mice (150), but these mechanisms require further investigation.

IL-17E, which is also produced by mammary epithelial cells, has been shown to engage the IL-17RB on human mammary cancer cells, and to induce their caspase-dependent apoptosis. Interestingly this effect was restricted to neoplastic cells, because they express much more IL-17RB than normal mammary cells, and IL-17RB *in vivo* is expressed in high amounts in tumors from patients with poor prognosis (167). The authors also showed that purified IL-17E inhibited the growth of human mammary cancer cells xenografted in the mammary fat pad of mice (167). Additionally, administration of a synthetic compound able to induce IL-25 production by tumor associated fibroblasts suppressed growth of mammary tumor metastases in mice (168).

The effects of IL-17E might be context-dependent. It has been reported that the addition of cisplatin to cervical cancer cell cultures induced IL-17E and IL-17RB down-regulation, eventually inhibiting *in vitro* growth, migration, and invasion (169). Thus, IL-17E might exert a tumor-promoting activity, unless the latter depends on IL-17B, which also interacts with IL-17RB. *In vivo* data in genetically modified mice will clarify the effect of the two cytokines in cervical cancer.

Pro-Tumor Activities of IL-17B, IL-17C, and IL-17F

IL-17B acts as tumor promoter in several solid and hematopoietic malignancies (Figure 4). Furuta et al. showed that the IL-17B/IL-17RB signaling is critical for breast tumorigenesis, and that IL-17RB expression correlates with poor prognosis in breast cancer patients (167). Engagement of IL-17B with its receptor induces Nf- κ B-mediated upregulation of Bcl-2 expression, and resistance of mammary cancer cells to etoposide (170). Because IL-17B and IL-17E share the same receptor heterodimer, and IL-17E induces apoptosis in mammary cancer cells (167), an opposing role for IL-17B and IL-17E can be hypothesized in breast cancer. It will be necessary to understand how two similar cytokines engaging the same receptor deliver anti- or pro-apoptotic signals.

Up-regulation of IL-17RB expression was also found in pancreatic cancer, where expression of IL-17RB associated with metastasis incidence and reduced progression free survival (171). IL-17RB triggering induced CCL20/CXCL1/IL-8/TFF1 chemokine expressions via the ERK1/2 pathway, thus promoting macrophage and endothelial cell recruitment at primary sites, cancer cell invasion and survival at distant sites. *In vivo*, anti-IL-17RB monoclonal antibodies inhibited tumor metastasis and prolonged survival in a mouse xenograft model (171). Others confirmed a direct tumor-promoting activity of IL-17B in gastric cancer (172), thyroid cancer (173), and in acute myeloid leukemia (174).

A direct connection between local microbiota, cytokine production and tumorigenesis has been reported for IL-17C (Figure 3). Song et al. found that IL-17C is upregulated in human colorectal cancers (34), and alterations in the microbiota (Table 1) drove IL-17C upregulation specifically in murine intestinal epithelial cells, eventually supporting their survival and neoplastic transformation (34). In line with these findings, it has been reported that both intra- and peri-tumoral expression of IL-17RE predict early and late recurrence in hepatocellular carcinoma (175).

IL-17C, which promotes neutrophilic inflammation (Figure 3), was also found abundant in human lung cancer samples, and IL-17C is a negative prognostic factor in patients with lymph node metastasis (35). Patients with chronic obstructive pulmonary disease are highly susceptible to non-small cell lung cancer, and often harbor IL-17C-inducing nontypeable *Haemophilus influenza* in their lungs (Table 1). In IL-17C-deficient mice, nontypeable *Haemophilus influenza* induced less neutrophil lung infiltrates and promoted less tumorigenesis (35), thus linking IL-17C to bacteria and lung cancer.

IL-17A and IL-17F share the same heterodimeric receptor (IL-17RA-RC). Tang et al. showed that mice deficient for IL-17F, and not mice deficient for IL-17A, resist chemically induced colitis, and this correlates with a different gut microbiota (105). *Fusobacterium nucleatum*, which has been linked to chronic inflammation and cancer (176), aggravates intestinal inflammation in mice by targeting caspase activation and recruitment domain 3 through NOD2, eventually activating the IL-17F/NF- κ B pathway (31). Because colitis often anticipates colon cancer, a microbiota-modulated, tumor

promoting role for IL-17F can be hypothesized, and it needs to be proven in *in vivo* experimental settings.

Strong correlations have been found between IL-17RA, microbiota, and cancer, and most of them have been attributed to IL-17A. As IL-17B, IL-17C, IL-17E, and IL-17F also exploit the subunit IL-17RA to deliver their intracellular signals, mice selectively deficient for either these cytokines or the IL-RC, IL-RB, and IL-RE will help in better understating the role of the different cytokines of the IL-17 family in the microbiota-immunity-cancer axis.

STRATEGIES TO TARGET CYTOKINES OF THE IL-17 FAMILY

Several strategies are being adopted in the clinic to impact the microbiota-IL-17 axis (Table 2). They include diets, prebiotics, probiotics or even fecal microbiota transplantation in effort to transiently or permanently modify the microbiota and eventually the immune response. Additionally, monoclonal antibodies directed against IL-17A or other cytokines and receptors of the

TABLE 2 | Therapeutic strategies under investigation to target cytokines of the IL-17 family.

Therapeutic Agent	Target Molecule	Impact on disease	Clinical Trial Number/Ref.
Brodalumab	IL-17RA	Reduced symptoms in rheumatoid arthritis and psoriatic arthritis patients	NCT00771030 NCT01059448 NCT00950989 NCT02024646 NCT02029495 NCT04183881 NCT01516957
Bimekizumab	IL-17A-IL-17F	Reduced symptoms in psoriatic arthritis patients Reduced chemical-induced colitis in mice	NCT02969525 (105)
Anti-IL-17RB	IL-17RB	Delayed pancreatic tumor growth and metastasis formation in mice	(171)
MOR106	IL-17C	Reduced atopic dermatitis in mice Ineffective against human atopic dermatitis	(177) NCT03864627 NCT03568071 NCT03689829 NCT02739009
Antibiotics	↓ IL-17B ↓ IL-17C ↓ IL-17F	Reduced bleomycin-induced lung fibrosis in mice Reduced colon cancer formation in mice Reduced chemical-induced colitis in mice	(30, 34, 105)
Q2-3	↑ IL-17E	Reduced breast cancer metastasis in mice	(168)
tBHQ	↑ IL-17D	Delayed growth of B16 melanoma, Burkitt's lymphoma and MCA-induced sarcoma in mice	(152)

Brodalumab, fully human IgG2 monoclonal antibody against IL-17RA; *Bimekizumab*, humanized IgG1 monoclonal antibody against both IL-17A and IL-17F; *MOR106*, fully human IgG1 monoclonal antibody against IL-17C; *Q2-3*, synthetic dihydrobenzofuran lignan; *tBHQ*, *Tert-butylhydroquinone*; *MCA*, *methylcholanthrene*.

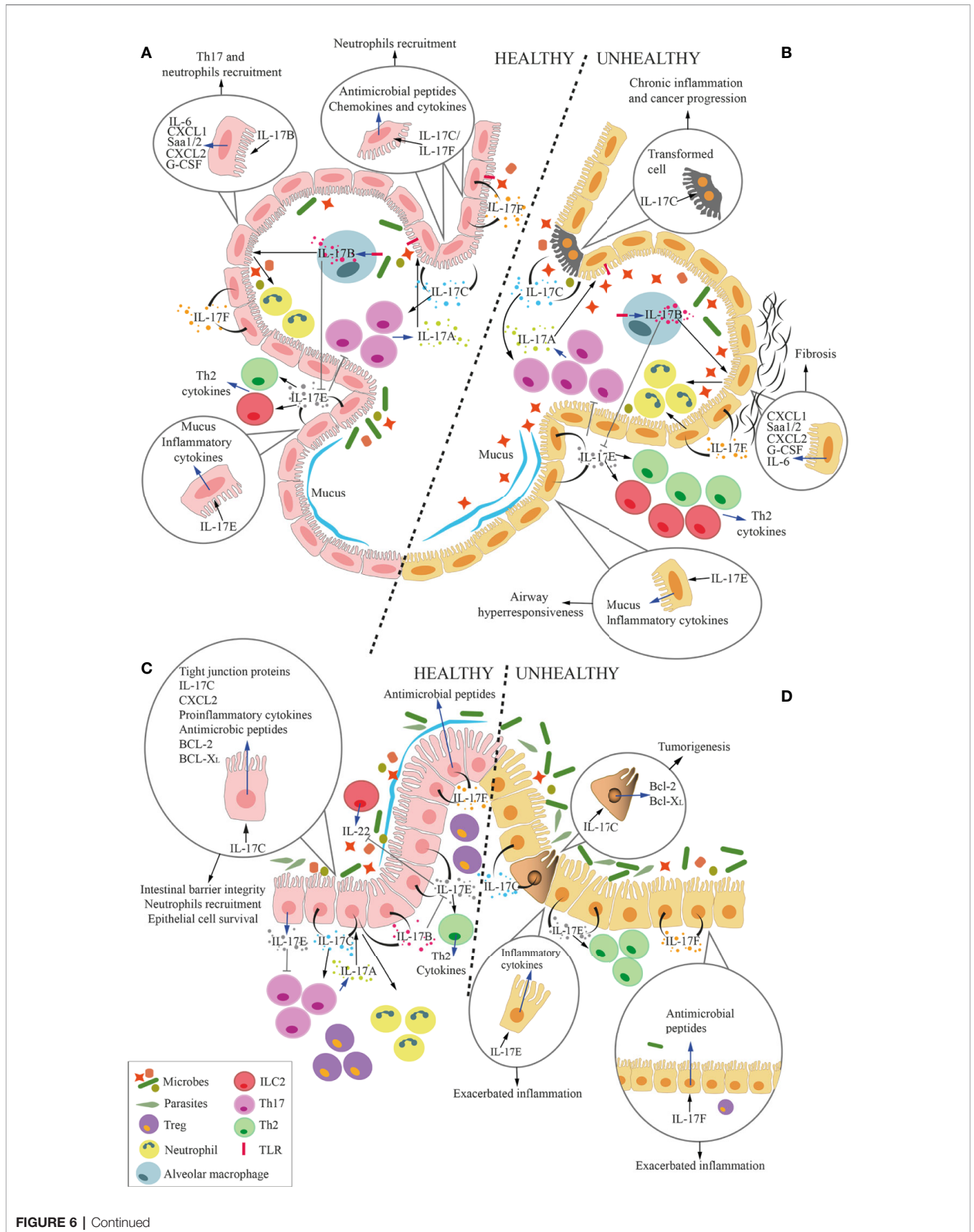


FIGURE 6 | Continued

FIGURE 6 | Overall function of IL-17 cytokines at the microbiota-host interface in the lung and the gut. Cartoon summarizing the overall role of IL-17 cytokines at the interface between microbiota and alveolar (**A, B**) and intestinal mucosa (**C, D**) in health (**A, C**) and disease (**B, D**). Circles within the panels enlarge and focus on several effects of IL-17 cytokines on epithelial cells. Blue arrows represent the secretion of cytokines or the expression of genes by cells, whereas black arrows represent the stimulation of the cell by the cytokines. (**A, C**) In physiologic conditions, IL-17A, which is mostly released by Th17 cells, keep growth of commensal microbes residing in the lumen of the respiratory tract or the intestine under control. Mucosal epithelial cells secrete IL-17B, IL-17C, IL-17E and IL-17F in response to stimuli coming from the local microbiota. More in details, IL-17B, produced by alveolar macrophages (MØs) under TLR4-mediated stimulation, act on epithelial cells inducing release of several factors, among which IL-6, serum amyloid A1 and A2 (Saa1/2), CXCL1, CXCL2, and G-CSF. Some of these factors favor local recruitment of Th17 cells and neutrophils, which also contribute to maintain an adequate balance in the microbiota composition. Additionally, IL-17B induces monocytes to release TNF- α and IL-1 β , which also favor neutrophil recruitment (not shown). IL-17C and IL-17F are released by epithelial cells, and act in autocrine and paracrine fashion inducing the production of antimicrobial peptides, but also chemokines and cytokines that favor neutrophil recruitment. IL-17C also promotes Th17 cell responses, and it supports barrier integrity through tight junction formation in epithelial cells. Also IL-17C induces expression of TNF- α and IL-1 β in monocytes (not shown). IL-17E favors the induction of type 2 responses by Th2 cells and ILC2, whereas IL-17B blocks this action, thus avoiding excessive type 2 immune responses. While IL-17D activates NK-mediated immune surveillance (not shown), its relationship with lung and gut microbiota remains unknown. Therefore, IL-17D is not depicted in the figure. IL-17E inhibits IL-23, IL-1 β and IL-6 expression in activated dendritic cells (not shown), thus blocking the induction of pathogenic Th17 cells. Healthy alveolar epithelial cells also secrete mucus in response to IL-17E to protect the epithelium from bacterial adhesion. (**B, D**) In pathologic conditions, excessive IL-17A causes local inflammation. In response to the expansion of pathobionts, MØs release more IL-17B, which acts on epithelial cells to induce pro-inflammatory signals (IL-6, Saa1/2, CXCL1, CXCL2, and G-CSF), which may induce lung fibrosis. Stimuli from pathogenic bacteria unleash IL-17C hyperproduction, leading to chronic inflammation and tumorigenesis, also through the upregulation of Bcl-2 and Bcl-XL. Excessive IL-17E signaling is associated with stronger Type 2 immune reaction (Th2 and ILC2) that exacerbate airways hyperresponsiveness and gut inflammation. Unbalanced IL-17F in the gut induces the release of excessive antimicrobial peptides, which constrains Treg-inducing bacteria, therefore promoting gut inflammation.

IL-17 family are used or are under investigation. These strategies are tested both in inflammatory diseases (21, 178–182) and cancer (183–185).

In the field of cancer, almost 200 clinical trials are ongoing that aim either at identifying the microbiota accompanying malignancies, or at testing microbiota-modulating strategies. The composition of the gut microbiome is being analyzed in breast cancer (NCT03885648), colorectal cancer (NCT03385213), lung cancer (NCT04333004), thyroid cancer (NCT03543891), hepatocellular carcinoma (NCT02599909), and glioblastoma (NCT03631823) among others. There is also interest for the microbiota of the lung in lung cancer (NCT03068663), of the oronasal cavities in hematopoietic malignancies (NCT02949427), or even the intratumor microbiota as for breast cancer (NCT03586297) and prostate cancer (NCT03947515). Several clinical trials are designed to modify the microbiota and increase susceptibility to chemotherapy (NCT04138979), radiotherapy (NCT02559349), or immunotherapy (NCT04116775). A more extensive list of clinical trials on this issue is out of the scope of this review, and can be found at (www.clinicaltrials.gov). Many of them interfere with the interplay between microbiota and the immune system, thus impacting all the cytokines of the IL-17 family.

Monoclonal antibodies against IL-17A or IL-17RA are already available to patients affected by psoriasis and arthritis (45), and might even find application in malignancies (10, 47). Results from one clinical trial with anti-IL17A monoclonal antibodies in MM patients are longed for (NCT03111992). Brodalumab, a monoclonal antibody against IL-17RA is also under investigation in patients affected by rheumatoid and psoriatic arthritis (**Table 2**), and it might also find application in cancer patients.

Few approaches have instead been proposed to target cytokines of the IL-17 family other than IL-17A. Because IL-17F can be tumor promoting (31), it will be interesting to investigate the anti-tumor activity of Bimekizumab especially in colorectal cancer (105) (**Table 2**). Bimekizumab is a monoclonal antibody against both IL17A and IL-17F, which is currently investigated in psoriatic arthritis patients

(186). Anti-IL17RB monoclonal antibodies might impact metastatic pancreatic cancer, has it has been shown in a mouse model (171). IL-17C is an interesting target in colorectal cancer because IL-17C has been found upregulated in these tumors, and in mice IL-17C was modulated by the gut microbiota (34). MOR106 is a humanized monoclonal IgG1 antibody against IL-17C, which has been developed to treat atopic dermatitis (177). Unfortunately, the clinical development program of MOR106 in atopic dermatitis was ended because of disappointing results. Because blocking IL-17C signaling significantly reduces the number and extension of colonic tumors in mice, MOR106 might be investigated in human colorectal and lung cancer (35). MOR106 would be of advantage in respect to anti-IL17A because IL-17C/IL-17RE signaling is dispensable for immunity to systemic, oral, and cutaneous candidiasis (158). Thus, either blocking the IL-17C/IL-17RE axis or acting on the gut microbiome might be beneficial to cancer patients (**Table 2**).

Q2-3, a synthetic dihydrobenzofuran lignan that stimulates production of IL-25, which competes with IL-17B for the IL-17RB receptor, reduces myeloid derived suppressor cell infiltration and metastasis appearance in a mouse model of breast cancer (168), suggesting its potential application to prevent breast cancer metastasis in humans (**Table 2**). Nonetheless, targeting the IL-17RB in cancer should be carefully investigated in breast cancer, because it could interfere with the anti-tumor activity of IL-17E (167).

Finally, Nrf2, a cellular checkpoint of xenobiotic and oxidative stress (187) is an interesting molecule, as it delays tumor growth by stimulating IL-17D production in tumor cells, which recruits NK cells within the tumor (**Table 2**) (152). An advantage of such compound is that it activates the tumor autocrine Nrf2/IL-17D signaling, by inducing cellular stress without producing reactive oxygen species. As an example, Tert-butylhydroquinone (tBHQ) has been tested in preclinical models of B16 melanoma, human Burkitt's lymphoma, and in the MCA-induced sarcoma, where activated Nrf2 and IL-17D production, resulting in delayed tumor progression (152). Nrf2 agonist are currently in clinical trials (e.g., NCT03182959, and NCT03934905).

CONCLUSIONS AND PERSPECTIVES

While characterized by a common genetic origin, cytokines from the IL-17 family demonstrate a wide heterogeneity in functions as well as in cellular source, and kinetic of production and secretion (Figure 6).

An intriguing evidence is that even if some of these cytokines share the same receptor, they may exert opposite downstream activities. For instance, blocking IL-17A is detrimental rather than curative in the murine model of chemically-induced colitis, and blockage of IL-17F either alone or with IL-17A resulted in disease amelioration (105). Thus, blocking IL-17RA impacts all IL-17 cytokines but IL-17D, and might exert unpredictable/undesired effects.

The same unpredictable/undesired effects might occur when attempting to modulate the microbiome. Examples are available of unexpected side effects of patients treated with probiotics (181).

All together these findings suggest that even if very fascinating and promising, the actual knowledge on the role of IL-17 cytokines in cancer is preliminary. A plethora of information about these cytokines in health and disease is waiting to be unveiled in next years.

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AUTHOR CONTRIBUTIONS

AB and MB developed the concept of the review. All authors participated to retrieve the relevant literature, wrote and prepared the manuscript. DM and LC prepared the figures. All authors contributed to the article and approved the submitted version.

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