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REVIEW

Interleukin-17 family members in health and disease

Soo-Hyun Chung, **Xiao-Qi Ye** and **Yoichiro Iwakura**

Research Institute for Biomedical Sciences, Tokyo University of Science, 2669 Yamazaki, Noda, Chiba 278-0022, Japan

Correspondence to: Y. Iwakura; E-mail: iwakura@rs.tus.ac.jp

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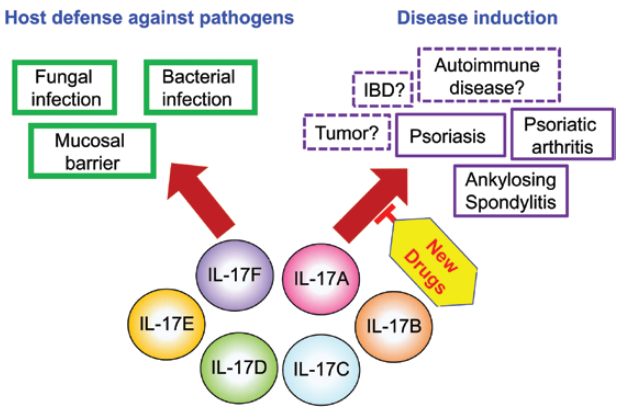
Abstract

The interleukin-17 (IL-17) family consists of six family members (IL-17A–IL-17F) and all the corresponding receptors have been identified recently. This family is mainly involved in the host defense mechanisms against bacteria, fungi and helminth infection by inducing cytokines and chemokines, recruiting neutrophils, inducing anti-microbial proteins and modifying T-helper cell differentiation. IL-17A and some other family cytokines are also involved in the development of psoriasis, psoriatic arthritis and ankylosing spondylitis by inducing inflammatory cytokines and chemokines, and antibodies against IL-17A as well as the receptor IL-17RA are being successfully used for the treatment of these diseases. Involvement in the development of inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis and tumors has also been suggested in animal disease models. In this review, we will briefly review the mechanisms by which IL-17 cytokines are involved in the development of these diseases and discuss possible treatment of inflammatory diseases by targeting IL-17 family members.

Graphical Abstract



Keywords: antibodies against IL-17 and the receptors, autoimmune disease, IL-17 family, IL-17 receptor, psoriasis

Introduction

The cytokine now called interleukin-17A (IL-17A) was first cloned in 1993, and five structurally related family members (IL-17B–IL-17F; IL-17E is also called IL-25) were identified later (1, 2) (Fig. 1). The pro-inflammatory nature of IL-17A was suggested in the initial studies *in vitro*, and its role in the host defense against bacterial infection was first shown using IL-17 receptor-deficient (*Il17r*$^{-/-}$) mice (1). After that, its roles in the development of allergic and autoimmune diseases were shown using *Il17a*$^{-/-}$ mice (1). Now, anti-IL-17A antibodies as well as anti-IL-17 receptor A (anti-IL-17RA) antibodies are being effectively used for the treatment of psoriasis, psoriatic arthritis and ankylosing spondylitis, showing that IL-17A plays crucial roles in the development of these diseases. However, the roles of other family members in health and disease remain largely obscure.

A decade ago, we reviewed the roles of IL-17 family members in health and disease (1). After that, studies of these family members, especially other than IL-17A, have greatly progressed and therapy targeting these molecules has been developed. In this review, we would like to introduce the recent progress of IL-17 research, especially targeting IL-17 for clinical use.

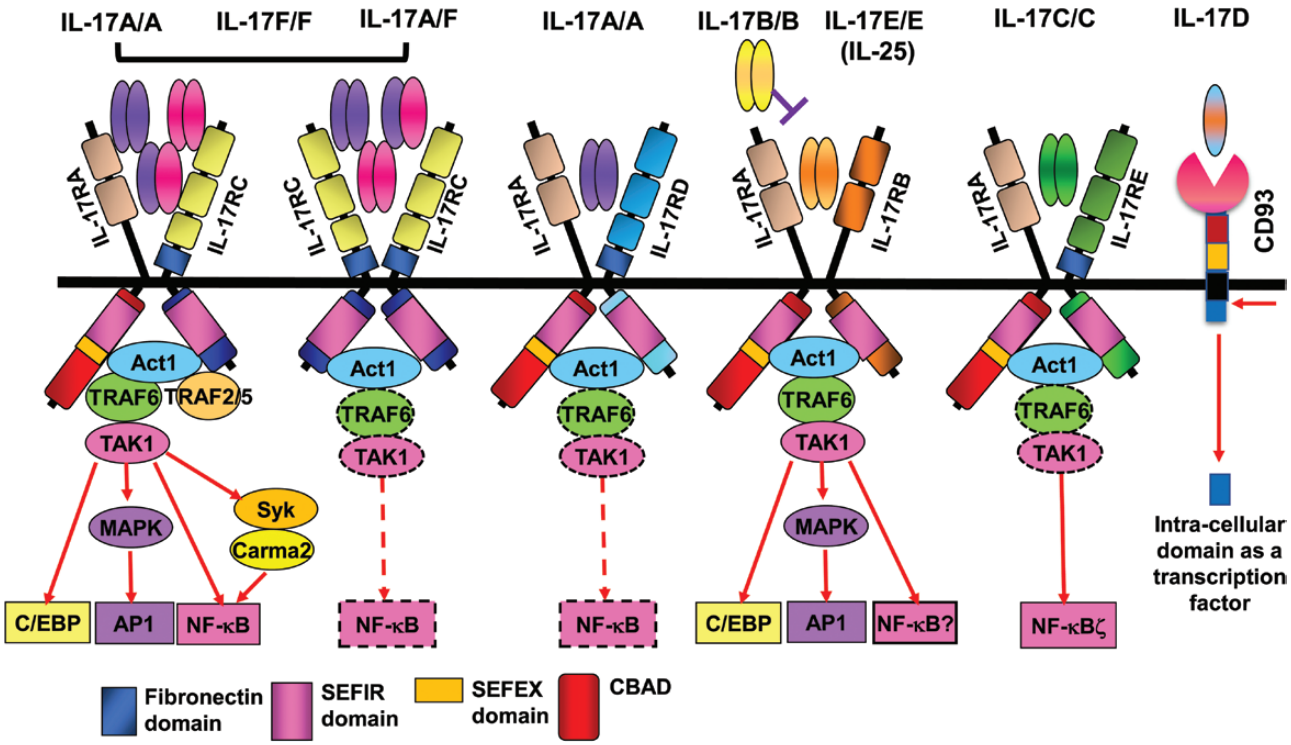


Fig. 1. The IL-17 family, its receptors and the downstream signaling pathways (1, 3, 4, 6). The IL-17 family consists of six family members. IL-17A and IL-17F form homodimers and heterodimers, whereas IL-17B, IL-17C and IL-17E form homodimers. Upon ligand binding, IL-17 receptors form dimers except for the IL-17D receptor CD93. IL-17A/A, IL-17A/F and IL-17F/F can induce the formation of IL-17RA/RC and IL-17RC/RC. In addition, IL-17A/A binds IL-17RA/RD. Dimer formation of receptors induces signal transduction by recruiting the ubiquitin ligase Act1 to the SEFIR domain and activates the TRAF6–TAK1–NF-κB pathway downstream. Activation of the C/EBP and MAPK pathways also occurs. The intracellular domain of CD93 is cleaved upon stimulation and functions as a transcription factor. The dotted lines show unconfirmed pathways.

The IL-17 family and its receptors

The IL-17 family consists of six family members (Fig. 1). All the family members except IL-17D are functional as homodimers, but IL-17A and IL-17F also form a heterodimer. The first receptor identified for the IL-17A homodimer (IL-17A/A) consists of IL-17RA and IL-17RC (IL-17RA/RC). The IL-17F/F homodimer and IL-17A/F heterodimer also bind the IL-17RA/RC heterodimer and transduce signals. Recently, IL-17RC/RC was identified as another receptor for IL-17A/A, IL-17F/F and IL-17A/F (3). IL-17A/A has high affinity to IL-17RA, but IL-17F/F has very low affinity, whereas IL-17F/F has at least 40 times higher affinity to IL-17RC compared with IL-17RA. IL-17RA/RD is another alternative receptor for IL-17A/A, but not for IL-17F/F or IL-17A/F (4). IL-17E/E binds the IL-17RA/RB complex, and IL-17B/B also binds the same receptor and antagonizes IL-17E/E function (5). IL-17C/C binds IL-17RA/RE, which is preferentially expressed on epithelial cells. IL-17D was recently reported to bind CD93 (6).

IL-17RA and IL-17RC have a SEFIR domain, which can bind the ubiquitin ligase Act1, in the cytoplasmic portion, and activate the TRAF6–TAK1–NF-κB pathway, the TRAF6–TAK1–MAPK–AP1 pathway and the C/EBP pathway downstream (Fig. 1) (2). Because IL-17RB, IL-17RD and IL-17RE also contain a SEFIR domain, a similar signaling mechanism is expected. In the case of the IL-17D receptor CD93, its intracellular domain cleavage products are thought to regulate gene expression by acting as a transcription factor (7).

Expression and functions of the IL-17 family

Although initially, T-helper 17 (Th17) cells attracted great attention as a new Th subset producing IL-17A and IL-17F, now various types of cells including γδT cells, type 3 innate lymphoid cells (ILC3s), NKT cells, NK cells, neutrophils and mast cells have been reported to produce these cytokines. Th17 cell differentiation from naive $CD4^+$ T cells is induced by the collaboration of TCR signaling and signaling by TGF-β+IL-6 or TGF-β+IL-21, which activates Stat3-dependent and IRF4-dependent expression of RORγt, a signature transcription factor of IL-17-producing cells (1). Both IL-1 (IL-1α or IL-1β) and IL-23 are also important for Th17 cell differentiation, growth, survival and effector functions.

In contrast, induction of IL-17A and IL-17F production in γδT cells and ILC3s does not require TCR stimulation, and collaborative stimulation with both IL-1β and IL-23 stimulation directly induces these cytokines (8–10). Because γδT cells and ILC3s rapidly produce IL-17A and IL-17F in response to IL-1β and IL-23 stimulation without further differentiation, this is an innate immune response in nature and may provide an essential initial source of these cytokines. NKT cells, neutrophils, monocytes, and NK cells are also capable of rapidly producing IL-17A and IL-17F. Interestingly, *Il17f*, but not *Il17a*, is expressed in colonic epithelial cells, suggesting that *Il17a* and *Il17f* expression are differently regulated in non-lymphoid cells (11). Actually, *Il17f* is expressed in most cells in the intestine including NK cells, dendritic cells (DCs)

and epithelial cells in a RORα-independent manner, whereas *Il17a* is expressed in CD4+ cells, γδT cells and ILC3s in a RORα-dependent manner (12). However, the detailed regulatory mechanisms for *Il17a* and *Il17f* expression remain to be elucidated.

The expression of IL-17 receptors is also different among different cell types; IL-17RA is predominantly expressed in lymphoid tissues, whereas IL-17RC is mainly expressed in non-lymphoid cells such as intestinal and lung epithelial cells (11). Thus, different types of receptors, IL-17RA/RC or IL-17RC/RC, will be formed upon stimulation with IL-17A/A, IL-17A/F or IL-17F/F depending on the cell types. This may explain the functional difference between IL-17A and IL-17F; mostly IL-17A regulates autoimmune responses, whereas IL-17F mainly regulates commensals and pathogens at mucoepithelial surfaces (11). Clearly, further studies are necessary to elucidate the gene expression regulatory mechanisms and their differential roles in the immune system.

IL-17C is produced mainly in epithelial cells of the gastrointestinal and respiratory tracts and keratinocytes of skin, but not in leukocytes, and binds IL-17RA/RE on epithelial cells (13). IL-17C is induced by Toll-like receptor (TLR) signaling and cytokines such as TNF-α, IL-1β and IL-17A (14). IL-17RE is expressed on Th17 cells and promotes Th17 cell responses through activation of the Act1–IkBζ pathway (15).

IL-17D is primarily expressed by colonic epithelial cells and specifically regulates ILC3s in the gut through its receptor CD93 (6). IL-17D regulates ILC3 maturation and promotes IL-22 production, which is important for microbial homeostasis and tissue repair under colitis conditions. CD93 is expressed in leukemia stem cells in addition to the expression in endothelial cells, myeloid cells and B cells, and promotes self-renewal and proliferation (7).

IL-17E is expressed in DCs, macrophages, T cells, neutrophils, mast cells, Paneth cells and mucosal epithelial cells in the intestine and lungs, and is involved in host defense against fungal and helminth infection and development of asthma (5). IL-17B is expressed in epithelial cells, neuronal cells and chondrocytes, and plays an anti-inflammatory role by antagonizing IL-17E signaling. IL-17B is also suggested to promote tumor development. However, the physiological roles of IL-17B and IL-17E and roles in disease largely remain to be elucidated.

The roles of IL-17 family members in host defense against pathogens

IL-17A and IL-17F play important roles in host defense against bacterial and fungal infection, by recruiting neutrophils through the induction of CXC chemokines and inducing anti-microbial proteins in infected sites (11, 16–18). Th17 cells are one of the main sources of IL-17A in anti-fungal immunity. Upon infection with fungi, Th17 cell differentiation is induced by the cytokines produced by DCs and macrophages through recognition of fungal cell-wall components via C-type lectins (CLRs), such as Dectin-1, Dectin-2 and the mannose receptor (MR) (19–23).

ILC3s play even more important roles than Th17 cells in oropharyngeal candida infection, because genetic deletion of the RAG1 gene (deleting T and B cells) did not change the fungal burden or IL-17A production but anti-CD90 treatment, which depleted ILC3s, strongly reduced IL-17A and IL-17F mRNA induction (24). In another report, however, both αβT cells and γδT cells were suggested to produce IL-17A in infected oral tissues (25). γδT cells are important in systemic candidiasis as early producers of IL-17A in lungs (26). In a *Malassezia sympodialis* skin infection model, both γδTCR deficiency and αβTCR deficiency caused increased susceptibility to the fungal infection (27). Finally, neutrophils are also reported to produce IL-17A in lungs of *Aspergillus fumigatus*-infected mice (28). IL-17A production from neutrophils depends on IL-23 secreted from Dectin-1-expressing myeloid cells.

IL-17C is important for the induction of anti-microbial proteins and pro-inflammatory molecules in the intestine, and IL-17RE-deficient mice show increased susceptibility to *Citrobacter rodentium* infection (29). However, upon systemic infection with candida, IL-17C is highly induced in kidney epithelial cells and causes tissue injury due to excessive production of inflammatory cytokines such as TNF-α, IL-6 and IL-1β (30). In another report, IL-17C and IL-17RE are dispensable for protection against candida in an oropharyngeal candidiasis model, although high levels of IL-17C were detected in infected oral tissues (31). Thus, the importance of IL-17C in anti-fungal/bacterial immunity may be different among different systems.

IL-17E is a unique cytokine in the IL-17 family, because it induces type 2 cytokines such as IL-4, IL-5 and IL-13 in Th2 cells and ILC2s to eradicate parasites such as *Trichuris muris* (32, 33) and the helminth *Nippostrongylus brasiliensis* (34). IL-17E also plays an important role in pulmonary infection by *Cryptococcus neoformans*, by inducing type 2 response to inhibit an excessive type 1 response in other tissues including the brain (35). IL-17E is also one of the highly induced cytokines in kidneys during systemic candidiasis (30).

The roles of IL-17 family members in the development of psoriasis

Psoriasis is a chronic inflammatory skin disease characterized by thickening and redness of the skin associated with keratinocyte hyperproliferation (36). Cytokines such as IL-23, IL-17A and TNF-α play important roles in the disease pathogenesis, and neutralizing-antibodies against these cytokines are being successfully used for the treatment of the disease (1, 37, 38).

The importance of the IL-23–IL-17 axis is suggested because the expression of IL-23 and Th17 cytokines such as IL-17A, IL-17F and IL-22 is enhanced in cutaneous lesions, and polymorphisms in IL-23R can control the susceptibility to psoriasis in humans (20, 39, 40). Psoriasis-like epidermal hyperplasia can be induced in mouse ears by injecting IL-23 (41). Imiquimod (IMQ), a TLR7 ligand, causes psoriasiform dermatitis in mice by inducing IL-23 from conventional DCs (cDCs) and Langerhans cells (LCs), followed by downstream induction of IL-17A (42, 43). IL-17A is mainly produced by innate immune cells such as γδT cells and ILC3s, but not by Th17 cells, after stimulation with IL-23 or IMQ (10, 44). IL-17-producing CD8+ T (Tc17) and Tc22 cells have also been suggested to be sources of these cytokines (45).

The involvement of IL-17F in psoriasis has been suggested in animal models (44). Antibodies targeting only IL-17F have not been tried yet, but antibodies targeting both IL-17A and IL-17F are more effective than antibodies against IL-17A only to treat psoriasis (46). However, the candida infection rate was increased (approximately 10%) after inhibition of both IL-17A and IL-17F, although the severities were mild to moderate (11, 46). Although anti-IL-17RA inhibits both IL-17A and IL-17F function, the susceptibility to candida was comparable to that in patients treated with anti-IL-17A (47), probably because the IL-17RA-independent IL-17RC homodimer still remains as a functional receptor for IL-17A and IL-17F.

IL-36α may be important upstream of the induction of IL-17A and IL-17F, because IMQ directly induces IL-36α in LCs and cDCs (43). IL-36α induces chemokines in LCs and keratinocytes to recruit γδ T cells and ILC3s, and also induces IL-1α/β and IL-23 in LCs to induce IL-17A, IL-17F and IL-22 in these γδT cells and ILC3s (43). IL-17A, IL-17F and IL-22 recruit neutrophils and induce various inflammatory cytokines and chemokines including TNF-α, G-CSF, IL-1β, CXCL1 and CXCL2 from keratinocytes and fibroblasts, causing inflammation and keratinocyte proliferation. Because IL-36α is induced not only by IMQ but also by fungal cell wall-derived β-glucans and bacterial lipopolysaccharide (LPS), the involvement of these innate immune responses against commensal fungi and bacteria is suggested in the development of psoriasis (20, 43). Thus, although psoriasis was initially supposed to be induced by an autoimmune mechanism, accumulating evidence suggests that innate immune responses play central roles in the development of psoriasis. After the initiation of inflammation, however, various inflammatory cytokines may also activate cells of the acquired immune system by forming an amplification loop (43).

Interestingly, IL-17C is the most abundant IL-17 isoform in the psoriasis skin (15). IL-17C promotes inflammation in an IMQ-induced psoriasis model, and transgenic mice expressing *Il17c* in keratinocytes develop dermatitis closely resembling psoriasis in humans (15, 48). The development of IMQ-induced dermatitis is suppressed in *Il17c*$^{-/-}$ mice and *Il17re*$^{-/-}$ mice (13). Thus, it is highly likely that IL-17C is also involved in the pathogenesis of psoriasis.

The roles of IL-17 family members in the development of inflammatory bowel disease and colorectal cancer

The role of IL-17A in inflammatory bowel disease (IBD) remains controversial. IL-17 expression is elevated in the mucosa of patients with IBD (49). Genetic polymorphisms of IL-17A and IL-23R that are associated with elevated expression of IL-17A are suggested to be associated with IBD pathogenesis (50). Anti-IL-23 antibody is effective to treat IBD, whereas both anti-IL-17A antibody and anti-IL-17RA antibody failed in alleviating patients with Crohn's disease, with an even higher rate of adverse events compared with placebo (49, 51). This is probably because IL-17A plays a protective role in maintaining epithelial barriers of the intestine by regulating the expression and localization of tight-junction components (2, 52). New-onset and worsening of Crohn's disease were reported at low rates (approximately 1% of patients) by the treatment of psoriasis with anti-IL-17A or anti-IL-17RA (37, 38, 47).

Interestingly, inhibition of IL-17F, but not IL-17A, ameliorates dextran sodium sulfate (DSS)-induced colitis in mice through modification of the microbiota in the intestine; IL-17F induces anti-microbial proteins and hinders T-regulatory (Treg) cell differentiation by suppressing the growth of bacteria such as *Clostridium* cluster XIVa and *Lactobacillus murinus*, which can induce Treg cell differentiation (12).

IL-17B, IL-17C, IL-17D and IL-17E are dominantly expressed in the intestinal epithelium and play protective roles in mouse colitis models. IL-17B protects against DSS-induced colitis by antagonizing IL-17E-mediated IL-6 production. However, supplementation of recombinant IL-17E suppressed DSS-induced colitis by inducing IL-23 and TGF-β1 in another study (53). IL-17C expression in inflamed lesions is correlated with increased inflammatory activity of IBD. Interestingly, DSS-induced colitis was aggravated in *Il17c*$^{-/-}$ mice and *Il17re*$^{-/-}$ mice, associated with decreased expression of tight-junction molecule occludin in colon epithelial cells (53). Therefore, IL-17C may also have an intestinal-barrier protection function like IL-17A. *Il17d*$^{-/-}$ mice or *Cd93*$^{-/-}$ mice were highly susceptible to DSS-induced colitis, associated with a reduction of IL-22 and the downstream anti-microbial proteins, which are important for tissue repair and immune homeostasis of the intestine (6). Although dysbiosis was induced in *Il17d*$^{-/-}$ mice, it still remains to be elucidated whether the intestinal microbiota is involved in the increased susceptibility to colitis.

IL-17A promotes colorectal cancer (CRC) development in multiple ways. *Il17a*$^{-/-}$ mice develop fewer polyps in both the (azoxymethane+DSS)-induced tumor model and the *Apc*^{Min} model (54, 55). Colorectal tumors exhibit defective expression of Mucin-2 and tight-junction components, resulting in the infiltration of microbial products and activation of the IL-23–IL-17 axis that drives inflammation and tumor growth (53, 56). IL-17RA signaling directly promotes the proliferation of transformed colonic epithelial cells (57). IL-17A promotes CRC metastasis by enhancing cancer cell motility and matrix digestion, and serum levels of IL-17A are negatively correlated with disease-free survival in CRC patients (58). IL-17A inhibits CD8$^+$ cytotoxic T-cell recruitment by down-regulating either CXCL9/CXCL10 or CXCR3 via the IL-17A–STAT3 axis (59, 60). IL-17A increases PD-L1 expression in CRC cells by activating the P65–NRF1–miR-15b-5p axis (61). IL-17A also promotes the recruitment of myeloid-derived suppressor cells and sustains their immunosuppressive activity (54).

Moreover, IL-17A contributes to angiogenesis to promote CRC growth (2, 54). Thus, targeting IL-17A is an attractive possibility for the treatment of CRC. Actually, combining chemotherapy, which induces IL-17A expression, and an IL-17A-neutralizing antibody enhanced the therapeutic responsiveness of colon tumors in a mouse model (57). Interestingly, however, another study found that Th17 cells recruit beneficial neutrophils and cytotoxic CD8$^+$ T cells, which indicates that IL-17A may have a dual role in inhibiting CRC tumorigenesis (62). Less is known about other IL-17 family members. IL-17C promotes tumorigenesis through increasing intestinal epithelial cell survival by inducing Bcl-2 and Bcl-xL expression (53). Depleting either IL-17D or

IL-17F promotes tumorigenesis but the mechanisms need to be elucidated (6, 53).

The roles of IL-17 family members in the development of autoimmune diseases and of other cancers

IL-17A and IL-23 are also involved in the pathogenesis of ankylosing spondylitis and psoriatic arthritis, because antibodies against IL-17A, IL-17RA or IL-23 are effective to treat the diseases. In the case of ankylosing spondylitis, endoplasmic reticulum (ER) stress induced by the accumulation of abnormal HLA-B27 proteins may induce IL-23 production (63). The involvement of IL-23 is also suggested in the pathogenesis of psoriatic arthritis, in which involvement of HLA-B27 is reported in 20–40% patients and a relationship between IL-23R change was suggested in genome-wide association studies (GWAS) analysis (63, 64). Thus, innate immune responses play important roles in the pathogenesis of these diseases.

Clinical trials to treat autoimmune diseases such as rheumatoid arthritis and multiple sclerosis using anti-IL-17A were carried out, because a critical involvement of IL-17A in the pathogenesis was suggested in animal disease models (1). However, the results of clinical trials were not as impressive as in animal models; anti-IL-17A treatment shows only moderate efficacy in reducing the signs and symptoms of rheumatoid arthritis compared with the placebo control in a phase 2 trial (65). Treatment of multiple sclerosis with anti-IL-17A significantly reduced the number of cumulative new gadolinium-enhancing T1 lesions, although the cumulative number of combined unique active lesions examined by magnetic resonance imaging (MRI) was not significantly reduced (66). Regarding these results, Chong *et al.* suggested an interesting possibility that inhibition of IL-17A may enhance the expression of other inflammatory cytokines, such as GM-CSF and IL-17F, from Th17 cells, because IL-17A limits its pathogenicity by inducing the anti-inflammatory cytokine IL-24 (67).

IL-17A also promotes tumorigenesis in other organs than the intestine by directly promoting cancer cell proliferation, producing inflammatory mediators to mobilize myeloid-derived suppressor cells and accelerating angiogenesis (68). IL-17RA-deficiency and pharmacological blocking of IL-17A with anti-IL-12/IL-23 antibody successfully suppressed the progression of alcohol-induced hepatocellular carcinoma in mice (69). IL-17A-neutralizing antibody increases the sensitivity to anti-angiogenic therapy in mouse lymphoma, lung tumor and colon tumor models (70). The results of these early clinical trials and results in mouse disease models seem promising, and further studies are awaited for the development of new therapies targeting IL-17 family members.

Conclusions

In the last decade, the treatment of psoriasis, psoriatic arthritis and ankylosing spondylitis has been greatly improved by using antibodies against IL-17A and its receptor. However, functional roles of other IL-17 family members than IL-17A and mechanisms by which their functions are regulated by related cytokines have not been elucidated completely. Elucidation of their roles and regulatory mechanisms will further expand the clinical use of drugs targeting IL-17 family member and related cytokines.

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