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Review Article

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IL-17 and IL-21: Their Immunobiology and Therapeutic Potentials

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ABSTRACT

Studies over the last 2 decades have identified IL-17 and IL-21 as key cytokines in the modulation of a wide range of immune responses. IL-17 serves as a critical defender against bacterial and fungal pathogens, while maintaining symbiotic relationships with commensal microbiota. However, alterations in its levels can lead to chronic inflammation and autoimmunity. IL-21, on the other hand, bridges the adaptive and innate immune responses, and its imbalance is implicated in autoimmune diseases and cancer, highlighting its important role in both health and disease. Delving into the intricacies of these cytokines not only opens new avenues for understanding the immune system, but also promises innovative advances in the development of therapeutic strategies for numerous diseases. In this review, we will discuss an updated view of the immunobiology and therapeutic potential of IL-17 and IL-21.

Keywords: Interleukin-21; Interleukin-17; Autoimmune; Cancer; Inflammation

INTRODUCTION

Cytokines are essential components of the body that determine the nature and magnitude of immune responses. They facilitate cellular interactions that enable a sophisticated and effective immune response to various biological challenges, such as inflammation and cancer (1). By influencing cell growth, differentiation, movement, and inflammatory responses, they play a critical role in maintaining the body's equilibrium and enhancing its defenses against pathogens. However, alterations in their activities can lead to various pathological conditions, from inflammatory and autoimmune diseases to increased susceptibility to infection, highlighting their complex role in health and disease (2).

IL-17 and IL-21 are key players in the body's immunological orchestra, each providing unique and vital elements to the overall functionality of our defense mechanisms—host defense immunity. IL-17 is a versatile cytokine that is essential for shaping inflammatory responses and acting as the first line of defense against bacterial and fungal invasion (3). It's key in mediating inflammation and maintaining the integrity of the body's barriers against environmental and microbial threats. Derived from diverse cells such as Th17 cells, γδ T

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Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
DC, dendritic cell; EAE, experimental autoimmune encephalomyelitis; GITR, glucocorticoid-induced tumor necrosis factor receptor; IL-17R, IL-17 receptor; IKK, inhibitor of NF-κB kinase; ISG, interferon-stimulated gene; IRF4, interferon regulatory factor 4; MDSC, myeloid-derived suppressor cell; MS, multiple sclerosis; RSV, respiratory syncytial virus; SEFIR, SEF/IL-17R; SLE, systemic lupus erythematosus; SOCS, suppressor of cytokine signaling; Tfh, follicular helper T; TRAF6, TNF-receptor associated factor 6; TAK1, TGF-β-activated kinase 1; uPA, urokinase type plasminogen activator.

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cells and innate lymphoid cells, IL-17 is a versatile entity in immune regulation. While it acts as a stabilizer between the host and commensal microbiota, ensuring barrier integrity and microbial balance, its activity is a double-edged sword (4). Any imbalance in its functions can lead to chronic inflammation and autoimmunity and has been implicated in several inflammatory and autoimmune diseases. The balance of IL-17 activity is therefore critical for maintaining health.

IL-21, mainly synthesized by CD4+ T cells, particularly follicular helper T (Tfh) cells, is a key orchestrator of adaptive immune responses (5). It controls the differentiation, proliferation and functions of B, T and NK cells, which are essential for optimal antibody production and B cell function (6). In addition, the influence of IL-21 extends to the innate immune response, affecting cells such as dendritic cells (DCs) and macrophages, and acting as a bridge between innate and adaptive immunity (7). However, its imbalance is associated with several pathological conditions, including autoimmune diseases and cancer, highlighting its delicate and multifaceted role in health and disease.

The important roles of IL-17 and IL-21 have attracted considerable scientific attention and have become focal points in the development of novel immunotherapies. Understanding their intricate mechanisms and regulatory networks is crucial to harnessing their potential for therapeutic innovation, offering hope for the effective treatment of immune-mediated diseases. The study of IL-17 and IL-21 highlights the complexity of the immune system and provides invaluable insights and potential therapeutic avenues. In this review, we aim to outline the current understanding of the biology of IL-17 and IL-21 and present the latest advances in research into the therapeutic use of these cytokines.

IMMUNOBIOLOGY OF IL-17

Cells producing IL-17

IL-17 is primarily produced by conventional Th17 cells, a distinct subset of Th cells characterized by the expression of the master transcription factor RORγt and the induction of IL-17 production by IL-23 (8). However, aside from Th17 cells, various other immune cell types can also generate IL-17 in response to diverse stimuli. These include γδT cells (γδT17), NKT cells (NKT17), innate lymphoid cells (ILC3), mucosa-associated invariant T cells (MAIT17), Foxp3+ Tregs (Tr17), and CD8 T cells (Tc17) (**Fig. 1**) (9-11). These IL-17-producing "type 17" cells commonly express RORγt, which is pivotal for their development and IL-17 production (12). However, environmental cues driving IL-17 production by each type 17 cells may vary. Additionally, there have been reports suggesting that myeloid cells, such as neutrophils, may possess the capacity to produce IL-17 in response to inflammatory signals (13-15). Nevertheless, the extent and significance of IL-17 production by these myeloid cell types remain the subject of ongoing research (9).

Signaling pathways

The IL-17 cytokine family consists of a group of cytokines that share both structural and functional similarities with the prototypical member, IL-17A (commonly known as IL-17). In addition to IL-17A, this family includes several related cytokines, including IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25), and IL-17F. Conversely, the IL-17 receptor (IL-17R) family consists of 5 members sharing structural similarities, which are IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE (9). Each cytokine within the IL-17 family interacts with its

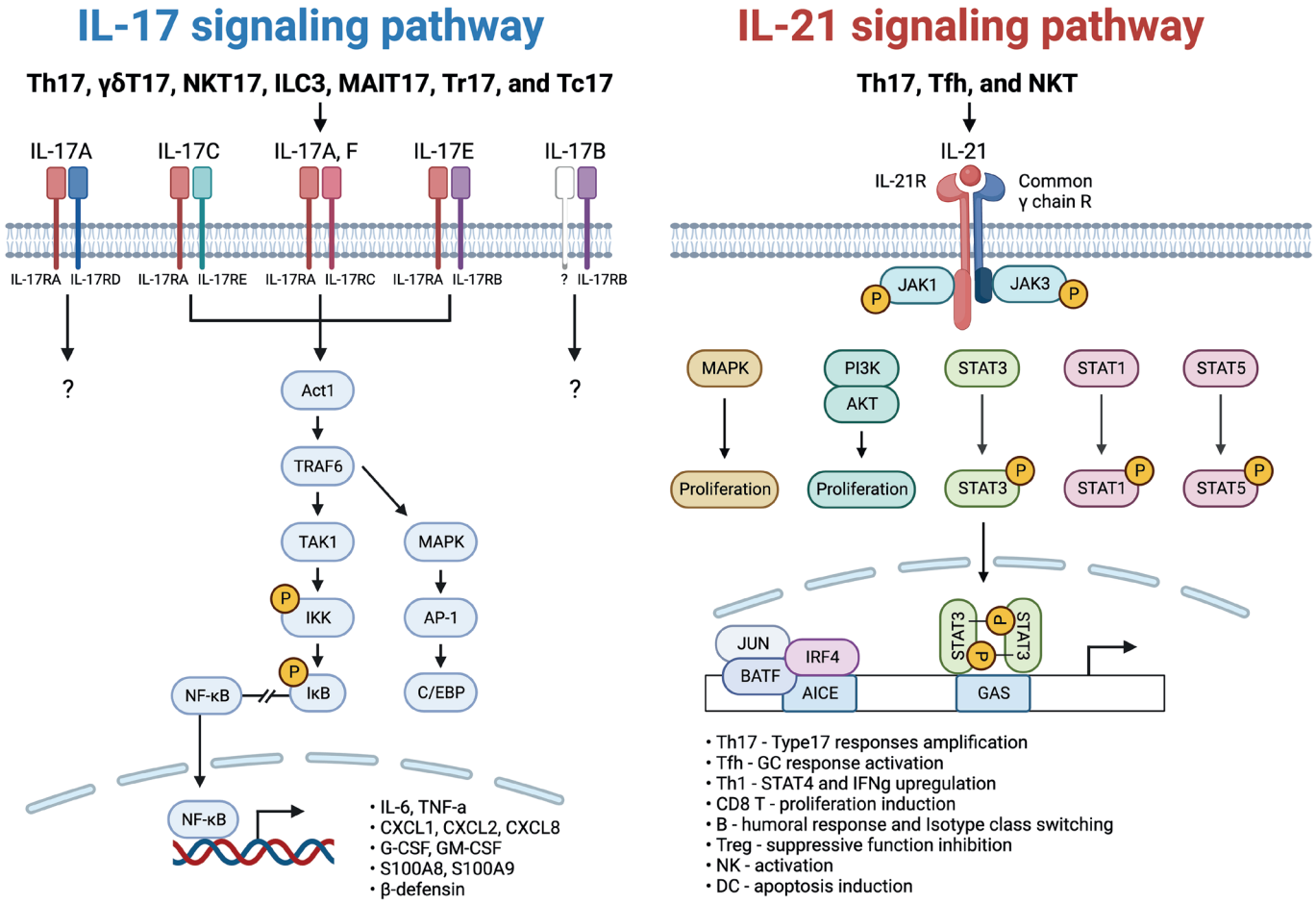

Figure 1. Comparison in the producers, receptors and signaling pathway between IL-17 and IL-21.
IL-17 is produced by Th17, γδT17, NKT17, ILC3, MAIT17, Tr17, and Tc17 cells. IL-17 family cytokines, including IL-17A, B, C, D, E, and F, bind and transduce signals through the hetero-dimeric combination of IL-17 receptors, such as IL-17RA, RB, RC, RD, and RE. IL-17R signaling involves the recruitment of Act1, which in turn recruits and ubiquitinates TRAF6. TRAF6 activates TAK1, which phosphorylates and activates the IKK. The activated IKK degrades IκB, leading to the translocation of NF-κB to the nucleus. TRAF6 also promotes the activation of MAPK and AP-1 pathways, along with the activation of the C/EBP transcription factors. IL-21 is produced by Th17, Tfh, and NKT cells. The IL-21 receptor heterodimerizes with the common gamma chain receptor and subsequently transduces signals through the activation of the JAK-STAT signaling pathway. JAK phosphorylate STAT3 and STAT1, and STAT5. IL-21 receptor also activates the MAPK and the PI3K pathway. The IL-21 response elements, IRF4 and STAT3, play global role in the regulating IL-21-responsive genes.
C/EBP, CCAAT/enhancer binding protein.

specific receptor, and most of these receptors belong to the IL-17 cytokine receptor family. For instance, IL-17A, either as a homodimer or in conjunction with IL-17F, primarily engages with the IL-17RA/IL-17RC receptor complex (**Fig. 1**). IL-17C interacts with the IL-17RA/IL-17RE receptor combination. IL-17E binds to the IL-17RA/IL-17RB receptors, while IL-17B competes with IL-17E for binding to the IL-17RB receptor. IL-17RD was previously considered an orphan receptor until a recent study revealed that IL-17A functions as a ligand for IL-17RD, forming a receptor-ligand pair (16). Additionally, there is emerging evidence suggesting that CD93 may serve as a receptor for the orphan ligand IL-17D (17). These interactions between cytokines and their respective receptors are critical for initiating downstream signaling events within cells (18,19).

The IL-17R subunits share a conserved cytoplasmic motif known as a SEF/IL-17R (SEFIR) domain, which is analogous to the TLR and IL-1 receptor domain (9). The initial step in IL-17R signaling involves the recruitment of Act1, a signaling protein that also contains a SEFIR

domain, which is crucial for its association with IL-17R (20,21). Act1 plays a pivotal role as a non-redundant activator of signals dependent on IL-17RA (**Fig. 1**). Notably, mice lacking Act1 exhibit similar characteristics to those lacking IL-17RA, and individuals with rare null mutations in Act1 display comparable traits, particularly susceptibility to fungal infections (9).

Upon stimulation by IL-17, Act1, acting as an E3 ubiquitin ligase, recruits and ubiquitinates TNF-receptor associated factor 6 (TRAF6) (22-24). TRAF6 catalyzes the formation of K63-linked polyubiquitin chains, which serve as a signal to activate a protein kinase called TGF-β-activated kinase 1 (TAK1). TAK1, in turn, phosphorylates and activates the inhibitor of NF-κB kinase (IKK) complex, and the activated IKK phosphorylates IκB, leading to the degradation of IκB. Degradation of IκB allows the translocation of NF-κB, which is usually sequestered in the cytoplasm when bound to IkB, to the nucleus. In the nucleus, NF-κB binds to specific DNA motifs and regulates the expression of various genes, including those involved in inflammation and anti-microbial immune responses. Additionally, TRAF6 also promotes the activation of MAPK and AP-1 pathways, along with the activation of the CCAAT/enhancer binding protein transcription factors (25). In contrast, IL-17-NF-κB signaling triggers the initiation of several negative feedback mechanisms that help regulate NF-κB activation. These mechanisms involve deubiquitinating enzymes, including A20 and ubiquitin-specific peptidase 25 and immunomodulatory cytokines (24,26,27). These feedback circuits play a crucial role in fine-tuning the inflammatory response (**Fig. 1**).

Functions of IL-17

IL-17 stands as a central orchestrator in the immune system, asserting profound effects on tissue physiology and homeostasis. This cytokine's influence spans beyond mere defense mechanisms, modulating a complex array of cellular processes that are crucial in maintaining the body's equilibrium. IL-17 not only induces acute inflammatory responses which are essential for immediate defense against pathogens but also modulates chronic inflammatory pathways that can influence the course of several autoimmune diseases. It's also recognized for its role in maintaining the integrity of epithelial barriers, fundamental structures that protect against environmental assaults and prevent pathogen invasion. IL-17's ability to induce the expression of tight junction proteins ensures that these barriers remain intact and functional.

Additionally, IL-17 is implicated in the recruitment and activation of fibroblasts, contributing to tissue remodeling and repair. Its regulatory actions extend to the orchestration of adaptive immune responses, where it can influence the activity and function of various cell types, including T cells, which are instrumental in shaping the immune response. Thus, IL-17 emerges not just as a participant in pathogen defense but as a key regulator of immune system homeostasis and an influential factor in the pathology of inflammatory and autoimmune conditions.

Neutrophil recruitment and tissue inflammation

IL-17 plays a crucial role in immune defense by orchestrating the recruitment of neutrophils to sites of infection. This process is mediated by the induction of chemokines like CCL2 (also known as MCP-1), CXCL1, CXCL2 (also known as MIP-2), and CXCL8 (also known as IL-8) from non-hematopoietic cells, which serve as signals to direct neutrophils to the affected tissues (19). Beyond its role in chemokine-mediated recruitment of neutrophils, IL-17 enhances myeloid cell-mediated inflammation by stimulating the release of pro-inflammatory cytokines such as G-CSF (**Fig. 1**) (9). G-CSF is a key cytokine that stimulates the differentiation of hematopoietic stem cells into neutrophils in the bone marrow.

Furthermore, IL-17 can directly activate neutrophils and macrophages to enhance bacterial killing (3).

Barrier function and antimicrobial defense

IL-17 contributes significantly to the maintenance of structural integrity of barrier tissues (28). Particularly in the intestinal epithelium, IL-17 induces proteins that fortify the mucosal barrier, a frontline defense against invading pathogens (29,30). IL-17's influence extends to the skin and mucosal surfaces where it boosts the production of antimicrobial peptides, including β-defensins and S100A9. These peptides are essential for the body's innate immunity, providing a robust defense against a spectrum of extracellular pathogens like Staphylococcus, Klebsiella, and fungal organisms such as Candida and Blastomyces (9,25). The significance of IL-17 in antimicrobial defense is underscored by genetic studies linking IL-17R signaling defects to increased susceptibility to mucocutaneous infections (31,32).

Tissue repair and wound healing

Emerging evidence highlights IL-17's role in tissue regeneration and repair (25). During wound healing, IL-17 directly influences Lrig1+ stem cells located in the hair follicle, leading to the generation of progeny that actively contributes to wound closure (33). Furthermore, IL-17 promotes the induction of key factors in tissue repair and wound healing, such as REG3A (34) and urokinase type plasminogen activator (uPA) (35). The anti-microbial peptide REG3A, produced by keratinocyte in response to IL-17, promotes the proliferation and differentiation of keratinocytes themselves, playing a pivotal role in skin repair processes following normal wound repair as well as pathological conditions like psoriasis (34). Additionally, IL-17-mediated induction of uPA enhances the migration of peripheral blood mesenchymal stem cells to wounded skin, which is critical in tissue regeneration (35).

IMMUNOBIOLOGY OF IL-21

Cells producing IL-21

IL-21 and its receptor were discovered in 2000 (36). IL-21 is a cytokine that plays a crucial role in the regulation of the immune system, and it has been the subject of extensive research in the fields of immunology. IL-21 is a member of the γ-chain cytokine family, which includes several other cytokines. This family of cytokines shares a common γ-chain (gamma chain) receptor subunit, which is essential for their signaling. The cytokines in the γ-chain family include IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, and IL-21 (36).

IL-21 cytokine is mainly produced by Th17, Tfh and NKT cells (**Fig. 1**). In bulk cell analysis, the production of IL-21 in CD4 T cells was initially identified in Th17 polarizing condition, where naïve CD4 T cells are stimulated with IL-6 and TGF-β (37). However, single cell level cytometric analysis revealed that majority of CD4 T cells producing IL-21 under Th17 polarizing condition do not produce IL-17A or IL-17F (38). Further studies have demonstrated that *in vitro* stimulation of naïve CD4 T cells with IL-6 induces IL-21 production in STAT3 dependent manner while TGF-β inhibits IL-21 production in SMAD3 dependent manner (37-39).

NKT cells have been shown to produce IL-21 when stimulated with anti-CD3/CD28 and this production is synergistically increased in the presence of IL-12 (40,41). Subsequent studies have identified that Tfh cells, a specialized subset of CD4 T cells crucial for orchestrating B cell responses and antibody production, also produce IL-21 within the germinal center,

underscoring their pivotal role in regulating humoral responses (42-45). Recently, multiple studies have demonstrated that glucocorticoid-induced tumor necrosis factor receptor (GITR) agonism triggers the differentiation of IL-21 producing Tfh cells in the tumor microenvironment and the infectious tissue (46-48).

Signaling pathway of IL-21/IL-21R

The expression of IL-21 receptor was initially discovered on various immune cell types, including T, B, and NK cells (36,49). The IL-21 receptor heterodimerizes with the common gamma chain receptor and subsequently transduces signals through the activation of the JAK-STAT signaling pathway. Upon binding of IL-21 to its receptor, Jak1 and Jak3 kinases, which interact with IL-21 receptor and common gamma chain receptor respectively, become activated. These kinases phosphorylate STAT3 and STAT1, and to a weaker extent of STAT5 (**Fig. 1**). This phosphorylation leads to the dimerization of STAT proteins and their translocation into the cell nucleus, where they bind to regulatory elements of target genes (50). Interestingly, the activation of STAT1 and STAT3 by IL-21 receptor signaling have opposing effects on the expression Th1 related genes including *Tbx21* and *Ifng* (51). IL-21 has been observed to synergize with IFN-γ to induce the optimal expression of interferon-stimulated genes (ISGs) in both human and mice (51,52). Notably, the expression of ISGs appears to be independent of STAT3 signaling (53). Moreover, IL-21 receptor engagement can also activate the MAPK and the PI3K pathways (50). IL-21 induces the transcription of the suppressor of cytokine signaling 1 (SOCS1) and SOCS3 proteins, which subsequently function to downregulate the JAK-STAT signaling pathway, representing an important feedback mechanism in immune regulation (54). The IL-21 response element has been demonstrated to consist of a dual-component element capable of binding to 2 key transcription factors interferon regulatory factor 4 (IRF4) and STAT3. These dual-component response elements were discovered in a genome-wide analysis and were found to be globally implicated in the regulation of numerous IL-21-responsive genes (55). Hence, within T cells, numerous target genes of IL-21 are controlled through the transcription factors BATF, JUN, IRF4, and STAT3 (**Fig. 1**) (54,56-59).

Function of IL-21

The IL-21 receptor is expressed in various immune cell types, including T cells, B cells, DCs, and NK cells and extensive research has been conducted to understand their responses to IL-21 (60-62).

Th17 cells

IL-21 functions as an autocrine factor secreted by Th17 cells, playing a pivotal role in promoting and sustaining Th17 lineage commitment (37). In mice, TGF-β has been observed to inhibit IL-21 production from naïve CD4 T cells, whereas in humans, IL-21 has been implicated in collaboration with TGF-β in the differentiation of naïve CD4 T cells into Th17 cells (63-65). IL-21 expression and Th17 differentiation depend on the presence of the transcription factor IRF4. IRF4 not only regulates the expression of RORγt and RORα, key factors in Th17 differentiation, but also directly binds to the IL-21 promoters (66,67) (**Fig. 1**). Furthermore, IL-21 has the ability to induce its own expression through an autocrine loop and also upregulates the expression of IL-23 receptor. IL-23 is recognized as essential for amplifying Th17 cell programs, and notably, cells lacking IL-21 also fail to express the IL-23 receptor (64). IL-21 exerts its effects by enhancing the expression of IL-23 receptor, which subsequently enables heightened cellular responsiveness to IL-23. Additionally, IL-21 induces the expression of RORγt, further contributing to the differentiation and maintenance of Th17 cells (18).

Tfh cells

IL-21 is not only produced by Tfh cells, but also is required for generation of Tfh cells. CD4 T cell intrinsic IL-21 is essential for the efficient development and germinal center responses of Tfh cells (44). IL-21 plays a role in upregulating the transcription factors BCL-6 and Maf, both of which are central to the transcriptional program of Tfh cells, contributing to their proper differentiation and function (68,69). In dextran sodium sulfate induced colitis model, IL-21 deficiency decreased the frequency of Tfh cells in the colon tissue, resulting in amelioration of colitis (70). IL-21 increases Tfh cells and reduces follicular regulatory T cells in lungs upon respiratory syncytial virus (RSV) infection. In this model, IL-21 induces the formation of tertiary lymphoid structures and the production of neutralizing antibody against RSV, thereby reducing severity of infection (71).

Th1 cells

Studies in human cells have demonstrated that IL-21 can also promote Th1 differentiation, leading to enhanced expression of Th1-associated transcription factors such as STAT4 and T-bet, along with increased IFN-γ production (72). IL-21 is highly detected in lamina propria of Crohn's disease patients, and neutralization of IL-21 decreased the phosphorylated STAT4 and T-bet expression, resulting in inhibition of IFN-γ production (73). In viral infection, IL-21 signaling has opposing effects on IFN-γ production in CD4 T cells. While STAT3 signaling suppresses IL-21 mediated T-bet and IFN-γ expression in CD4 T cells, IL-21 enhanced STAT1 signaling is required for the production of IFN-γ in CD4 T cells (51).

CD8 T cells

While IL-21 alone has limited effects on CD8 T cell proliferation, it exhibits strong synergy with either IL-7 or IL-15, resulting in the induction of both proliferation and IFN-γ production (74). In the presence of IL-2, IL-21 optimally enhance the clonal expansion and effector function of naïve CD8 T cells in STAT4-independent manner (75). After the transfer of IL-21 primed CD8 T cells into tumor-bearing mice, these cells display the characteristics of memory T cells and enhanced persistence *in vivo* (76). In the tumor microenvironment, GITR stimulation has been shown to enhance the antitumor function of CD8 T cells, and this is mediated through the IL-21 produced by Tfh cells (47). A recent study has identified single cell level transcriptomic profiles of IL-21 producing CD4 T cells in the LCMV infection model and found that Tfh cell-derived IL-21 was crucial for sustaining CD8 T cell responses and viral control (77).

B cells

It has been demonstrated that antigen-specific memory B cells and plasma cells failed to expand in IL-21 receptor deficient mice, highlighting the critical role of IL-21 signaling in humoral responses (78). IL-21 receptor knockout mice exhibit a normal distribution of B cell subsets but impaired B cell function, characterized by elevated IgE production and reduced levels of IgG (79). The increased levels of IgE are contingent on IL-4, as demonstrate by Il4 and Il21r double knockout mice, which exhibit markedly reduced level of all immunoglobulin isotypes, including IgE. This pattern resembles the pan-hypogammaglobulinemia observed in individuals with X-linked severe combined immunodeficiency and underscores the importance of both IL-4 and IL-21 in normal B cell response (6). IL-21 receptor signaling serves as a key regulator that triggers the secretion of all IgG subclasses, with a particular emphasis of IgG1 and IgG3 (80,81). Additionally, IL-21 plays a critical role in the regulation of B cell proliferation and is essential for the proper formation of germinal centers, differentiation into plasma cells, immunoglobulin production, and facilitating isotype

switching towards IgG, IgM, and IgA (82-84). IL-21R signaling in B cells promotes Bcl6 expression by B cells (85,86). B cell intrinsic IL-21 signaling, along with downstream STAT3 signaling, has been attributed to the generation and development of long-lived antibody responses (87,88). In line with their elevated immunoglobulin levels, IL-21 transgenic mice exhibit an increased abundance of plasma cells, indicating a positive correlation between IL-21 expression and plasma cell differentiation (83).

Treg cells

The role of IL-21 in suppressive T cells have been elucidated through numerous studies. The numbers of Treg cells are elevated in both *Il21* and *Il6* knockout mice. This is attributed to TGF-β signaling favoring the generation of Treg cells over Th17 cells in the absence of either IL-21 or IL-6 (89,90). This phenomenon appears to be mediated by IRF4, as IL-21 failed to reduce the differentiation of Treg cells in IRF4-deficient T cells (91). Conversely, other data suggest that IL-21 may enhance the suppressive function of Treg cells (92). Certain data indicate that IL-21 plays a role in the development of IL-10 producing Tregs type 1 (Tr1), which exhibit suppressive properties on effector T cells (93). This aligns with a study demonstrating that IL-21 induces IL-10 production in naïve CD4 T cells, CD8 T cells, and B cells (94).

NK cells

IL-21 exerts a dual role as it limits NK cell responses while simultaneously promoting antigen-specific T cell activation (95). IL-21 activates human NK cells and influences the expression of their surface receptor (96). During the tumor progression, exhausted NK cells have been identified in the tumor microenvironment and IL-21 reinvigorated the exhausted NK cells, restoring their functionality (97). The expansion of NK cells through IL-21 has been explored as a potential autologous cell therapy for chronic lymphocytic leukemia (98).

DCs

IL-21 may also have negative regulatory effect on the maturation and function of DCs (7,99). IL-21 exhibits potent inhibitory activity against the activation and maturation of DCs induced by GM-CSF (7). Following study has demonstrated that IL-21 can strongly induce the apoptosis of conventional DCs through a mechanism dependent on STAT3 and BIM while it has a modest effect on plasmacytoid DCs (100).

ROLES IN DISEASES

A number of studies on the genetic association or murine models have suggested a crucial role of IL-17 and IL-21 in diverse autoimmune diseases as well as in cancer immunity (101-106).

Autoimmune diseases

IL-17

The role of IL-17 has been demonstrated in several types of autoimmune diseases, including systemic lupus erythematosus (SLE), multiple sclerosis (MS), rheumatoid arthritis and psoriasis. In 1999, IL-17 producing cells were found to be increased in the cerebrospinal fluid of MS patients. (107). Using the experimental autoimmune encephalomyelitis (EAE) model, a rodent model of MS, IL-17 deficiency has been shown to improve the development of EAE (108). IL-17 is produced not only by T cells but also by glial cells in inflamed central nervous system tissue, as shown by immunohistochemical analysis of MS patients (109).

High concentration of IL-17 has been found in the synovial fluid of rheumatoid arthritis patients and most of them were produced by CD4 T cells (110,111). IL-17 deficiency significantly reduced the severity of diseases in both collagen-induced arthritis and LPS-induced bone destructive model (**Fig. 2**) (112,113).

Lupus-prone BXD2 mice express high levels of IL-17 and spontaneously develop germinal centers. In these mice, blocking IL-17 signaling significantly reduced germinal center formation and autoantibody production through regulation of the Rgs13 and Rg16 genes. Plasma IL-17 levels are elevated in SLE patients and correlate positively with disease severity in SLE patients (114).

It has also been shown that IL-17A, IL-17 and IL-17F are increased in lesional skin samples from psoriasis patients (115). Recent studies have shown that blocking of IL-17 signaling reduces the skin inflammation in psoriasis (116).

This evidence underscores IL-17's broad impact in autoimmune pathology and its potential as a therapeutic target in various autoimmune diseases (**Fig. 2**).

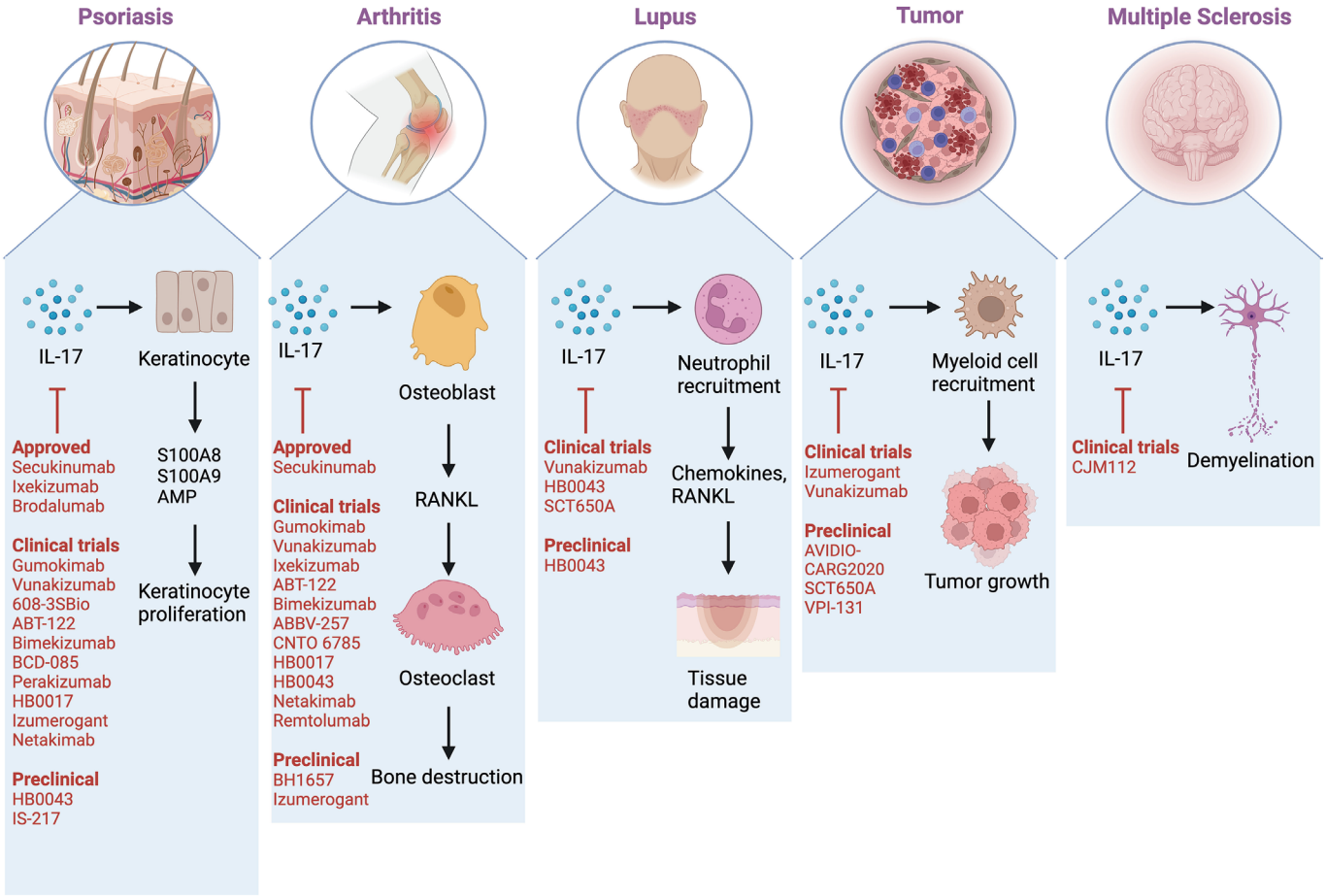

Figure 2. Role of IL-17 in diseases and potential therapeutics.
IL-17 play critical roles in many diseases, and drugs targeting IL-17 have been clinically used or are under investigation. In psoriasis, IL-17 stimulates keratinocytes to produce S100A8, S100A9, and AMP which in turn activate the proliferation of keratinocytes. In arthritis, IL-17 induces osteoblast to secrete RANKL, leading to osteoclast formation and subsequent bone destruction. In lupus, IL-17 recruits neutrophils and exacerbates tissue damage. In tumors, IL-17 recruits immune-suppressive myeloid cells contributing to tumor growth. In MS, IL-17 contributes to the degradation of myelin in the central nervous system.

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IL-21

Dysregulated IL-21 expression is associated with multiple inflammatory conditions, including Crohn's disease, celiac disease and arthritis (117-119). IL-21 is highly produced in human subjects with Crohn's disease and the blockade of the IL-21/IL-21R signaling axis in these patients resulted in reduced production of IFN-γ by mucosal lymphocytes (73). As such, the lack of an intact IL-21/IL-21R signaling axis in mice (*Il21r*−/−) resulted in attenuated inflammatory responses and reduced colitis in a murine model of human Inflammatory bowel disease (120). The activation of STAT3 in target cells has been proposed as a mechanism by which the IL-21/IL-21R signaling promotes tissue inflammation (117). These findings suggest that IL-21/IL-21R axis could be part of a positive feedback loop that amplifies an inflammatory response in the gut (**Fig. 3**) (73,121).

IL-21 expression is increased in skin of psoriasis patients and the intradermal treatment of IL-21 directly induces the hyperplasia of keratinocytes (122). Disease score of psoriasis patients is positively correlated with the frequency of IL-21 producing CD4 T cells and Th17 cells (123).

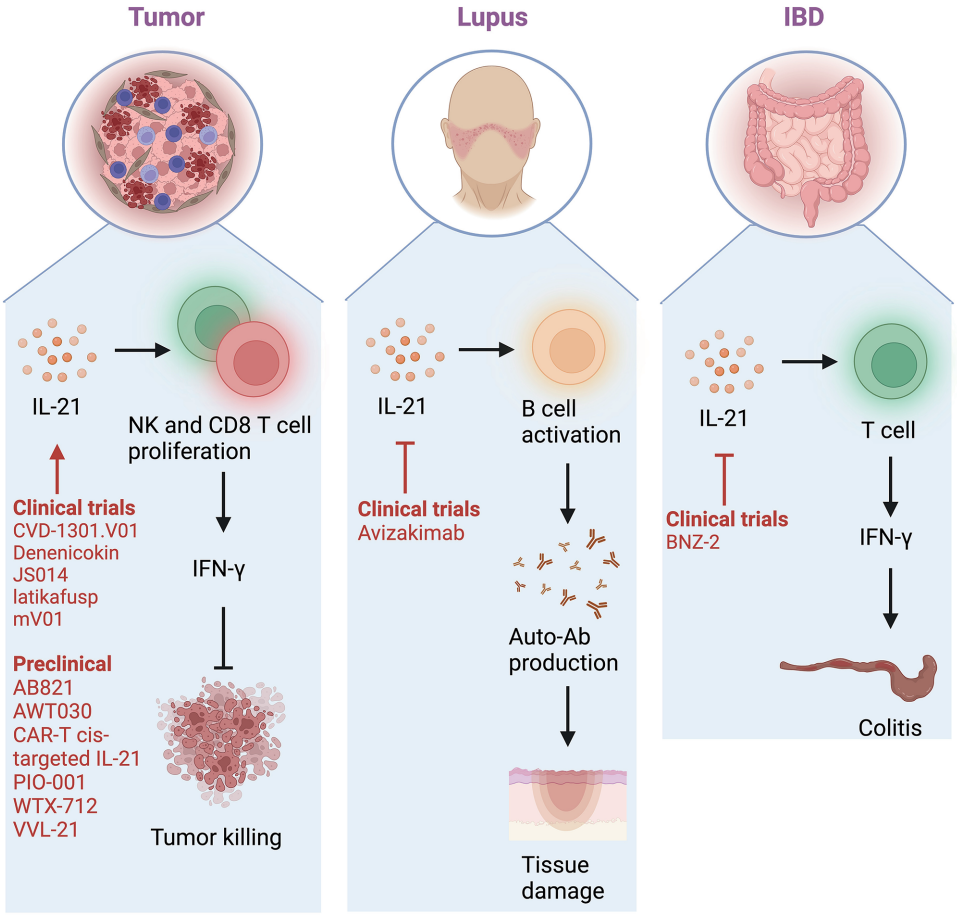

Figure 3. Role of IL-21 in diseases and potential therapeutics.
IL-21 plays crucial roles in both tumors and other autoimmune diseases, and the drugs targeting IL-21 are currently under investigation in clinical trials. In the context of tumors, IL-21 activates NK and CD8 T cells within the tumor microenvironment, while not stimulating Treg cells. IL-21-activated NK and CD8 T cells induce the destruction of tumor cells. In lupus, IL-21 activates B cells, promoting the production of autoantibodies, which further exacerbates tissue damage. In inflammatory bowel diseases, IL-21 stimulates T cells to secret IFN-γ, leading to severe inflammation in the affected tissues.

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In line with this context, recent study has demonstrated that IL-21 may promote psoriatic inflammation by inducing imbalance in Th17 and Treg populations (124).

Significantly increased percentages of IL-21 expressing CD4 T cells and CD8 T cells were found in SLE patients compared to healthy control. The frequency of IL-21 expressing T cells were positively correlated with the frequency of IL-17 expressing T cells in SLE patients, suggesting a crucial role of IL-21 in the pathogenesis of SLE (125). Recent finding suggests that IL-21 potently expand unique CD11c^{hi}T-bet^{+} B cells and differentiate these cells into autoreactive plasma cells in SLE patients (**Fig. 3**) (119).

Tumor immunology

IL-17

In the tumor microenvironment, IL-17 plays a role in recruiting neutrophilic myeloid cells, which are often referred to as either myeloid-derived suppressor cells (MDSCs) or tumor-induced neutrophils (**Fig. 2**) (126-128). In humans, it has been observed that the frequencies of intra-tumoral granulocytic polymorphonuclear MDSCs correlate with the presence of IL-17-producing cells in both gastric and colorectal cancers (127,129). The induction of pathogenic myeloid cells has been linked to tumor progression in various IL-17-dependent murine cancer models, encompassing lung, colon, liver, and breast cancer (126,128,130-132). The depletion of Gr1^{+}CD11b^{+} cells resulted in the suppression of tumor growth in lung adenocarcinoma model (131). Collectively, multiple studies have demonstrated that IL-17 mediates tumor progression by recruiting immune-suppressive myeloid cells. Nonetheless, in certain studies, IL-17 has been found to stimulate anti-tumor immunity by facilitating the recruitment of neutrophils that, in turn, mount effective anti-tumor immune responses, particularly in cases of squamous cell carcinoma and bladder cancer (133,134).

IL-21

Extensive research has been dedicated to understanding the role of IL-21 in anti-tumor immune responses. *In vitro* studies have demonstrated that IL-21, in synergy with IL-15, robustly enhances the proliferation of both memory and naïve phenotype CD8 T cells, along with an augmentation of IFN-ɣ production (**Fig. 3**). Consequently, *in vivo* administration of IL-21 in combination with IL-15 not only increased the numbers of antigen-specific CD8 T cells but also demonstrated a synergistic effect in promoting tumor regression in established B16 melanomas (74). The antitumor effect of IL-21 is enhanced in Erbitux-based IL-21 tumor-targeting fusion protein through the proliferation of tumor-infiltrating PD-1^{int}TIM-3^{-} CD8 T cells (135). A recent study has demonstrated that the protein BATF serves as a key molecule of IL-21 mediated antitumor effect of CD8 T cells (136). Additionally, in the MCA205 tumor model, it was observed that overexpression of the IL-21 cytokine inhibited tumor growth in a manner that depended on NK cells rather than T cells (137). The intraperitoneal injection of recombinant IL-21 protein elicited antitumor responses in NK cell dependent manner against 4T1 breast carcinoma, Lewis Lung carcinoma, and RM-1 tumors transfected with NKG2D ligand (138). Furthermore, IL-21 has been shown to directly induce the apoptosis of certain types of tumor cells *in vitro*. IL-21 induces BIM up-regulation and combination of IL-21 with fludarabine or rituximab enhances the direct cytotoxic effect in chronic B-type lymphocytic leukemia (139,140), follicular lymphoma (5,141), and diffuse large B cell lymphoma (142,143).

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THERAPEUTIC IMPLICATIONS

Therapeutic Implications of IL-17

IL-17 has emerged as an important target in immunotherapy due to its extensive and pivotal role in immune responses, particularly in inflammatory and autoimmune diseases. Therapeutic strategies are diverse, ranging from small molecule therapy to monoclonal and bispecific antibodies (144).

Clinical development and applications

A number of IL-17 inhibitors have not only entered clinical trials but have also received approval for clinical use, reflecting their significant therapeutic potential. Secukinumab and ixekizumab, both monoclonal antibodies targeting IL-17A, have been approved and are effectively used in the management of plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis. Their clinical success has been a testament to the importance of IL-17 in the pathophysiology of these autoimmune conditions (145). Additionally, gumokimab and vunakizumab are currently in Phase 3 clinical trials, showing promise particularly in the treatment of plaque psoriasis and other immune-mediated diseases. 608-3SBio (608 Q2W), another monoclonal antibody, is currently in Phase 3 and is being studied primarily for its role in the treatment of chronic plaque psoriasis. Its advancement to this stage indicates potential efficacy and applicability in alleviating symptoms associated with psoriasis (**Fig. 2**) (146).

Preclinical innovation

Several drugs targeting IL-17 are in the preclinical stage, investigating efficacy and safety in conditions such as cancer indications and autoimmune diseases. AVIDIO/CRC (CARG-2020), a combination of an immune checkpoint modulator, oncolytic virus and small hairpin RNA, is under preclinical investigation for use in colorectal and ovarian cancer, illustrating the broad scope of IL-17-targeted therapies beyond autoimmune diseases (147).

Discontinued and inactive therapeutics

Despite the promising therapeutic implications, some drugs, including remtolumab, have been discontinued or are not active, underscoring the challenges and complexities associated with the development of IL-17-targeted therapies. The discontinuation of these drugs highlights the complexity of developing effective and safe IL-17 inhibitors and underscores the importance of continued research and refinement in this area (148).

Bispecific antibodies and small molecule therapies

The development of bispecific antibodies such as BCD-121 and BH1657 (149), which are in early stages of development, provides a nuanced approach that allows simultaneous targeting of IL-17 and other cytokines such as TNF-alpha. Small molecule therapies such (150) and Novel Scaffold Program #1 & #2 are being investigated for their potential to modulate IL-17 activity in conditions such as psoriasis and other inflammatory diseases, offering a more targeted and specific approach to therapy (**Table 1**) (151).

Therapeutic implications of IL-21

IL-21, a cytokine with an extensive role in the immune response, especially in adaptive immunity, has become a target for therapeutic development in immunotherapy. Its importance is seen in various stages of drug development involving monoclonal antibodies, fusion proteins, peptides, immunocytokines, and oncolytic viruses, each of which aims to explore the potential of IL-21 in treating various diseases ranging from autoimmune diseases to cancer.

Table 1. Current and emerging therapies targeting the IL-17 pathway

Drug names	Therapeutic class	Drug developers	Targets	Disease indication	Highest phase of development
608-3SBio	Monoclonal antibody	3SBio, Inc.; Sunshine (Sansheng) Guojian Pharmaceuticals (Shanghai) Co., Ltd.	IL-17	Chronic plaque psoriasis; Plaque psoriasis (psoriasis vulgaris); Psoriasis	3
AVIDIO/CRC	Immune checkpoint modulator; Oncolytic virus; Small hairpin RNA	CaroGen Corporation; University of Connecticut Health Center	IL-17; IL-12; PD-1	Colorectal cancer; Ovarian cancer	Preclinical
BCD-121	Bispecific antibody; Monoclonal antibody	Biocad	IL-17; TNF-alpha	Healthy volunteers	1
BH1657	Bispecific antibody	Hanmi Pharma	IL-17; TNF-alpha	Autoimmune disease	Preclinical
E-36041	Small molecule therapy	Ensemble Therapeutics	IL-17	Inflammation	Preclinical
EBI-028	Cytokine	Sesen Bio	IL-17	Eye disorders	Preclinical
Gumokimab	Monoclonal antibody	Akeso Biopharma (Zhongshan Kangfang Biomedical Co., Ltd.)	IL-17	Ankylosing spondylitis; Plaque psoriasis (psoriasis vulgaris); Psoriasis; Psoriatic arthritis	3
HB0017	Monoclonal antibody humanized	Huabo Biopharm	IL-17	Ankylosing spondylitis; Chronic low back pain; Chronic plaque psoriasis; Healthy volunteers; Plaque psoriasis (psoriasis vulgaris); Psoriatic arthritis; Sacroiliitis	2
HB0043	Antibody	Huabo Biopharm	IL-17; IL-36	Pustular psoriasis; SLE; Ulcerative colitis	Preclinical
IS-217	Antineoplastic; Peptide	Issar Pharmaceuticals	IL-17; IL-23; p38 MAPK; VEGFR-2	Angiogenesis; Inflammatory bowel disease; Psoriasis	Preclinical
Izumerogant	Biological therapy	Immunic Therapeutics	IL-17	Castration resistant prostate cancer; Healthy volunteers; Metastatic prostate cancer; Psoriasis	1
JNJ-63823539	Bispecific antibody	Covagen; Janssen Pharmaceuticals	IL-17; TNFR	Rheumatoid arthritis	Preclinical
LY-3114062	Bispecific antibody	Eli Lilly and Company	IL-17; TNF-alpha	Inflammatory arthritis (arthritis)	1
Netakimab	Monoclonal antibody humanized	Biocad	IL-17	Ankylosing spondylitis; Healthy volunteers; Liver cirrhosis; Plaque psoriasis (psoriasis vulgaris); Primary biliary cholangitis; Psoriasis; Psoriatic arthritis	3
NVS451	Fusion protein; Small molecule therapy	Shulan (Hangzhou) Hospital; Changchun Institute of Biological Products Co., Ltd.	IL-17; Undisclosed	Healthy volunteers; Plaque psoriasis (psoriasis vulgaris)	1
Orega Biotech Anti-IL-17 antibody	Monoclonal antibody	Orega Biotech	IL-17	Cancer indications	Preclinical
P243876	E3 modulator; Small molecule therapy	Progenra Inc.	IL-17; ITCH	Immune mediated disease; Psoriasis	Preclinical
Remtolumab	Bispecific antibody	Abbott; Abbvie	IL-17; TNF-alpha	Psoriatic arthritis; Rheumatoid arthritis	2
RG7990	Bispecific antibody	Genentech, Inc.; Hoffmann-La Roche	IL-17; IL-13	Asthma; Healthy volunteers	1
SCT650A	Cytokine	Sinocelltech Ltd.	IL-17	Cancer indications	Preclinical
SO11806	Small molecule therapy	Eli Lilly and Company	IL-17	Healthy volunteers; Plaque psoriasis (psoriasis vulgaris); Psoriasis	2
VPI-131 (IL7-Vault)	Cytokine-nanobody	Vault Pharma	IL-17	Idiopathic pulmonary fibrosis; Lung cancer	Preclinical
Vunakizumab	Monoclonal antibody humanized	Jiangsu HengRui Pharmaceutical Co., Ltd.	IL-17; IL-17A/F	Ankylosing spondylitis; Cancer indications; Chronic plaque psoriasis; Graves' disease; Healthy volunteers; Lupus nephritis; Plaque psoriasis (psoriasis vulgaris); Psoriasis; Psoriatic arthritis	3
ZL1102	Antibody	Crescendo Biologics; Zai Lab (Shanghai) Co., Ltd.	IL-17	Chronic plaque psoriasis	1

This table provides a comprehensive overview of drugs targeting the IL-17 pathway and associated immunological processes. It includes specific drug names, their therapeutic classes (such as monoclonal antibody or bispecific antibody), the drug developers, targeted biological pathways (like IL-17, IL-12, PD-1), the diseases or conditions each drug aims to treat (e.g., chronic plaque psoriasis, colorectal cancer), and the current phase of development ranging from preclinical to advanced clinical trials.

Clinical development and applications

Several IL-21-targeting drugs are in various stages of clinical development to treat conditions such as SLE, various cancers and Crohn's disease. Avizakimab (BOS161721), a humanized monoclonal antibody targeted for SLE, has completed its Phase 1/2 clinical trials. Similarly, JS014 (AWT008, Exenokine-21), a cytokine nanobody, is in Phase 1 trials in advanced cancers, lymphomas and solid tumors (**Fig. 3**).

Preclinical innovations

The potential of IL-21 is also being explored at the preclinical level with various therapeutic strategies. AB821 is a preclinical immunocytokine being developed by Asher Bio for cancer indications. AWT030, a fusion protein being developed by Anwita Biosciences, is being investigated for its efficacy in solid tumors. PIO-001, a monoclonal antibody, and RBM-011, an aptamer, are in preclinical stages to explore their potential in cancer and pulmonary arterial hypertension, respectively (54).

Discontinued and inactive therapeutics

Not all developments have progressed, illustrating the challenges of IL-21-related therapeutic development. ATR-107 (PF-05230900) (152), developed by Pfizer and Wyeth, was discontinued after clinical trials in Crohn's disease. BITRAP, a protein targeting IL-21R and TNF-alpha for rheumatoid arthritis, is not active at the preclinical stage, underscoring the complexity and challenges of developing effective and safe IL-21 targeting therapeutics (153).

Oncolytic viruses and fusion proteins

IL-21 research also extends to oncolytic viruses, such as CVD-1301.V01 (hV01), which is clinically active and under investigation for advanced solid tumors and cancer indications (154). VVLΔTK-STCΔN1L-IL21 (VVL-21) is a preclinical stage oncolytic virus targeting diseases such as glioblastoma multiforme and pancreatic cancer (155).

Recombinant proteins and immune checkpoint modulators

The development of recombinant proteins such as Werewolf Therapeutics' WTX-712 (IL-21 INDUKINE) and immune checkpoint modulators such as Amgen's latikafusp (AMG 256) illustrate the diversity of approaches to harnessing the potential of IL-21 in immunotherapy (156,157). These developments illustrate the variety of strategies used to modulate IL-21 activity in immune responses (**Table 2**).

FUTURE DIRECTION AND CONCLUSION

The study of IL-17 and IL-21 has revealed a spectrum of opportunities and challenges in immunology and medicine. As we move forward, it's essential to carefully unravel the complexities and intricacies of these fascinating cytokines in order to realize their full therapeutic potential. The first steps in this journey should prioritize the advancement of current clinical trials and explore a broader range of disease indications, with a focus on the pathological conditions, such as various inflammatory and autoimmune diseases, in which these cytokines play a pivotal role (3,158). IL-17 and IL-21 are cornerstones of our body's defense mechanisms, and their diverse roles in immunological processes necessitate a broad exploration of their therapeutic applications. By broadening the scope of research, new dimensions of their implications in various pathological conditions, including infectious diseases, can be revealed. This diversified exploration is not only about better understanding

Table 2. Emerging treatments targeting IL-21 and associated receptors

Drug names	Therapeutic class	Drug developers	Targets	Disease indication	Highest phase of development
AB821	Immunocytokine	Asher Bio	IL-21	Cancer indications	Preclinical
ATR-107	Monoclonal antibody humanized	Pfizer; Wyeth (subsidiary of Pfizer)	IL-21R	Crohn's disease	
Avizakimab	Monoclonal antibody humanized	Boston Pharmaceuticals	IL-21	Healthy volunteers; SLE	1/2
AWT030	Fusion protein	Anwita Biosciences	IL-21	Solid tumors	Preclinical
BITRAP	Protein	Y-Biologics	IL-21R; TNF-alpha	Rheumatoid arthritis	Preclinical
BNZ-2	Peptide	Bioniz Therapeutics, Inc.; Equillium	IL-21; IL-15	Celiac disease; Healthy volunteers	1
CAR-T cis-targeted IL-21	Immunocytokine	Asher Bio	IL-21; EGFR	Cancer indications	Preclinical
CVD-1301.V01	Oncolytic virus	Hangzhou Converd Co. Ltd.	IL-21	Advanced solid tumors; Cancer indications	1
Denenicokin	Recombinant protein	Bristol-Myers Squibb	IL-21	Advanced melanoma; Advanced solid tumors; Melanoma; Metastatic melanoma; Metastatic solid tumors; Neoplasms; Solid tumors	1
Fred Hutchinson Cancer Research Center autologous IL-21 modulated CD8+ antigen-specific T cells	Non-Engineered CTLs (CD8+)	Fred Hutchinson Cancer Research Center	IL-21	Melanoma; Metastatic melanoma	1/2
JS014	Cytokine-nanobody	Shanghai Junshi Bioscience Co., Ltd.; Anwita Biosciences	IL-21R	Advanced cancers; Advanced malignant tumors; Advanced solid tumors; Lymphoma; Malignant neoplasm; Solid tumors	1
latikafusp	Bispecific antibody; Fusion protein; Immune checkpoint modulator	Amgen	IL-21R; PD-L1	Advanced solid tumors; Locally advanced solid tumor; Metastatic solid tumor	1
M.D. Anderson Cancer Center autologous IL-21-primed CD8+ tumor antigen-specific CTLs	Non-engineered CTLs (CD8+)	M.D. Anderson Cancer Center	IL-21	Advanced ovarian cancer; Platinum resistant ovarian cancer; Recurrent ovarian epithelial cancer	1/2
mV01	Oncolytic virus	Hangzhou Converd Co. Ltd.	IL-21	Hodgkin lymphoma; Non-Hodgkin lymphoma	1
NN-9828	Monoclonal antibody	Novo Nordisk	IL-21	Type 1 diabetes mellitus	
PIO-001	Monoclonal antibody	Monash University; Pio Therapeutics; BioCurate	IL-21	Cancer indications	Preclinical
RBM-011	Aptamer	Ribomic Inc; National Cerebral and Cardiovascular Center; Japan Agency for Medical Research and Development	IL-21	Pulmonary arterial hypertension	Preclinical
VVLΔTK-STCΔN1L-IL21	Oncolytic virus	Queen Mary University of London; Zhengzhou University	IL-21; B5R	Glioblastoma multiforme; Pancreatic cancer	Preclinical
VVLΔTKΔN1L-mIL-21	Guide RNA-mediated gene editing; Oncolytic virus	Zhengzhou University	IL-21	Colorectal cancer	Preclinical
WTX-712	Recombinant protein	Werewolf Therapeutics	IL-21	Solid tumors	Preclinical

This table details emerging treatments focusing on the IL-21 pathway and its receptors. It lists drugs by name, their therapeutic classification (including immunocytokine, monoclonal antibody humanized, etc.), the developers behind these drugs, their specific biological targets (such as IL-21, IL-21R), the medical conditions targeted (like cancer indications, Crohn's disease), and the highest phase of clinical development achieved, from preclinical stages to phase 1/2 trials.

their therapeutic implications, but also about exploring previously unexplored territories of intervention points and applications (1,151).

It is also imperative to delve deeper into the underlying mechanisms that contribute to resistance to therapies targeting IL-17 and IL-21. A nuanced understanding of these mechanisms will provide insights into why certain therapies either fail or are discontinued

in certain conditions, leading to the development of more effective and precisely targeted interventions. We should not overlook the importance of refining therapeutic strategies to increase specificity and selectivity. The development and refinement of small molecule inhibitors, bispecific antibodies and fusion proteins can further optimize therapeutic approaches and allow precise modulation of IL-17 and IL-21 activities in different physiological contexts (150,151). Advances in therapeutic strategies should be accompanied by innovations in drug delivery methods. By developing novel drug delivery systems, we can improve the bioavailability and therapeutic efficacy of interventions, potentially reducing adverse effects and improving patient outcomes. Such advances may include innovations in formulation technologies and delivery methods that could significantly optimize the therapeutic index of these interventions.

In the era of personalized medicine, the integration of sophisticated diagnostic tools and predictive analytics is essential. These tools will allow us to stratify patients based on their likelihood of responding to IL-17 and IL-21 targeted therapies, fostering the development of more personalized therapeutic strategies, and optimizing treatment outcomes. Advanced diagnostic methods coupled with predictive analytics can revolutionize patient management and allow for the tailoring of therapeutic regimens based on individual response profiles. In addition, a deeper understanding of the biological and molecular mechanisms underlying the actions of IL-17 and IL-21 is critical (25,159). Such exploration may reveal novel targets for therapeutic intervention and provide invaluable insight into their role in immune regulation and response. The quest to understand these complexities holds the promise of uncovering new therapeutic innovations and providing profound insights into immune-mediated diseases (155).

In summary, delving into the intricate worlds of IL-17 and IL-21 has emerged as a beacon of hope in immunological research, revealing potential pathways to unprecedented advances in both the study and development of therapeutic interventions. Unraveling the intricate mystery of IL-17 and IL-21 is not only a quest to understand the intricate workings of the immune system, but also a journey toward innovations that have the potential to alleviate human suffering by addressing a wide range of pathological conditions.

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