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# Fine-tuning immunity: ubiquitin-dependent regulation of interleukin-17A expression by Th17 cells

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Interleukin-17A (IL-17A) is a pro-inflammatory cytokine that plays a pivotal role in immune responses, particularly in the pathogenesis of various autoimmune diseases and infections. Recent advances have highlighted the significance of post-translational modifications, particularly ubiquitination, in regulating IL-17A expression and IL-17A receptor signaling pathways. Here, we summarize the intricate relationship between IL-17A and ubiquitination, exploring how ubiquitin-mediated processes influence IL-17A production, receptor signaling, and downstream effector functions. We provide insights into the potential therapeutic implications of targeting IL-17A and its ubiquitination pathways in inflammatory diseases and autoimmune disorders. A clear understanding of this relationship could pave the way for novel strategies in immune modulation, potentially enhancing management and treatment efficacy in various human diseases.

## KEYWORDS

IL-17A, ubiquitination, deubiquitination, ROR $\gamma$ t, E3 ligases

## Introduction

Interleukin 17A (IL-17A) is critical in the host immune response against bacterial and fungal infections, especially at the mucosal surface (1, 2). However, dysregulated IL-17A expression is strongly linked to several human diseases, such as multiple sclerosis (MS), psoriasis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and asthma (2). Its biological effects are mediated by activating various signaling pathways that regulate the transcription of target genes involved in inflammation, tissue remodeling, and the recruitment of immune cells (2).

Ubiquitination, a post-translational modification whereby ubiquitin moieties are covalently attached to target proteins, regulates numerous cellular processes, including protein degradation, signal transduction, and cellular localization (3). It involves a multi-enzymatic biochemical reaction in which the Ub-activating (E1) enzyme activates Ub,

which is then transferred to the Ub-conjugating (E2) enzyme. The Ub-ligating (E3) enzymes facilitate the formation of the isopeptide bond between the Ub (C-terminus) and specific substrate lysine residues (3). The human genome is estimated to encode 2 E1s, nearly 50 E2s, and over 600 E3s. Each E3 recognizes a set of substrates that share one or more ubiquitination signals, and an individual E3 cooperates with one or a few E2s. The E3 ligases are divided into two different groups based on their functional domains: the homology to the E6-associated protein carboxyl terminus (HECT) type E3s and the fascinating new gene (RING) type E3s (3). The ubiquitin molecules in a polyubiquitin chain are generally linked through the K48 or K63-linked polyubiquitin chains; however, other lysine residues in a ubiquitin molecule have been shown to participate in linkage (3). Interestingly, the different types of polyubiquitin chains have different effects on the substrate. The function of E3 ubiquitin ligases is reversed by the action of deubiquitinating enzymes (DUBs) (4). They specifically cleave the isopeptide bonds between ubiquitin and the Lys residue within the ubiquitinated substrate (4). The dynamic interplay between ubiquitination and the signaling pathways that lead to IL-17 expression is an area of growing interest, offering insights into the fine-tuning of immune responses. Ubiquitin ligases and deubiquitinases modulate the expression of IL-17A and the stability and activity of IL-17A signaling components, thereby influencing the intensity and duration of IL-17A-mediated cellular responses.

Here, we summarize the current knowledge regarding the relationship between IL-17A and ubiquitination, highlighting how this axis regulates immune responses and the implications for therapeutic interventions in inflammatory diseases.

## IL-17 and inflammation

The IL-17 family of cytokines consists of six members (IL-17A to IL-17F) which binds to IL-17 receptors (IL-17RA to IL-17RE) and implement their physiological functions (5). Among the IL-17 family members, IL-17A is the most studied and highly significant cytokine. The human IL-17A is synthesized as a 155-amino-acid precursor which is then posttranscriptional modified by cleave of 23-amino-acid signal peptide at the N-terminus which is followed by dimerization via disulfide bonds to generate mature homodimer of 35 kDa (6). Among the members of the IL-17 family, IL-17F is most similar to IL-17A, with 55% sequence homology (7). IL-17F forms homodimers or heterodimers with IL-17A and binds to IL-17 receptors for signal transduction.

IL-17A is predominantly expressed by CD4<sup>+</sup> T helper cells (Th17); however, natural killer T cells, CD8<sup>+</sup> T cells,  $\gamma\delta$  T cells, innate lymphoid cells (ILCs), dendritic cells, macrophages, and other cells also produce this cytokine (8). The differentiation of Th17 cells depends on the presence of proinflammatory Interleukin-6 (IL-6), Transforming growth factor-beta (TGF- $\beta$ ), and Interleukin 1 $\beta$  (IL-1 $\beta$ ) (8, 9). Th17 differentiation requires the activation of the transcription factors signal transducer and activator of transcription 3 (STAT3) and retinoic acid-related

orphan receptor gamma t (ROR $\gamma$ t) (10). After the initial differentiation, Th17 expresses the IL-23 receptor (IL-23R) and requires IL-23 for their proliferation and survival. Although T-cell receptor (TCR) activation is necessary for CD4<sup>+</sup> and CD8<sup>+</sup> T-cell IL-17A synthesis, innate immune cells primarily produce IL-17A in the presence of IL-6 and IL-23 (11).

IL-17A is a potent proinflammatory cytokine that induces neutrophil and monocyte recruitment to the site of inflammation by inducing the expression of chemokine (C-X-C motif) ligand 1 (CXCL1), CXCL2, and CCL20 (8). IL-17A also promotes neutrophil differentiation via the production of granulocyte colony-stimulating factors (G-CSF) and monocyte chemoattractant protein-1 (MCP-1) by non-hematopoietic target cells (11). *Il17a* deficiencies in mice result in defective neutrophils, leading to increased susceptibility to extracellular pathogens, including the bacteria *Klebsiella pneumoniae*, *Candida albicans*, and *Toxoplasma gondii* (12). In addition, IL-17A regulates the expression of molecules with antimicrobial activity, such as  $\beta$ -defensins, calgranulins, and mucins. Defensins act as natural antibiotics in the lungs, skin, and gut. Another IL-17A target gene is Chemokine (C-C motif) ligand 20 (CCL20), a chemokine that recruits dendritic cells (DCs) and T cells, thereby providing a positive feedback loop for IL-17A amplification by recruiting Th17 cells to inflamed sites (12). However, IL-17A is not always protective against infections. In schistosomiasis, IL-17A stimulates a pathogenic inflammatory response that can be alleviated with antibodies to IL-17A (13). Elevated IL-17A levels are also associated with severe periodontal disease. Importantly, elevated IL-17A is strongly linked to autoimmune pathology. Increased IL-17A levels were found in RA, SLE, and psoriasis patients (11). Consistent results suggest a pathogenic role for IL-17A in various mouse models of autoimmune disease. Similarly, dysregulated IL-17A-mediated inflammation is linked to graft vs host disease and some cancers (14, 15).

## Intracellular events of IL-17A expression

The differentiation of Th17 cells requires coordinated activation of T cells in the presence of TGF- $\beta$ , IL-6, IL-1 $\beta$ , and IL-23 (8). TCR stimulation-induced phosphatidylinositol 3-kinase (PI3K), Nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B), Nuclear Factor of Activated T cells (NFAT), and Mitogen-activated protein (MAP) kinase pathways are involved in IL-17A production (10). RAR-related orphan receptor gamma t (ROR $\gamma$ t), a member of the nuclear receptor family of proteins, is a key transcriptional factor for IL-17A expression (16). It has been demonstrated that cholesterol derivatives, including desmosterol and oxysterols, serve as natural ligands and activate ROR $\gamma$ t (17, 18). Whereas 3-oxoLC, a bile acid synthesized from cholesterol, acts as an inhibitory ligand of ROR $\gamma$ t (19). Further, Raftlin1, a lipid raft protein, was shown to recruit specific phospholipids to ROR $\gamma$ t and promote the transcriptional activity of ROR $\gamma$ t and IL-17A expression (20). ROR $\gamma$ t binds to RORE sequences within the

CNS2 of the *Il17a* gene and mediates *Il17a* transcription by controlling the chromatin remodeling (10). In addition to ROR $\gamma$ t, p300 and JmJc domain-containing protein (JMJD)3 also bind to CNS2 and mediate permissive histone acetylation and remove repressive histone marker H3K27me3 (21). CNS2 interacts with the *Il17a* promoter to induce *Il17a* transcription (10, 22). Runt-related transcription factor (RUNX)1 also binds to the CNS2 region of *Il17a* promoter (23). RUNX1 binds to ROR $\gamma$ t to enhance expression of *Il17a* (10, 24).

STAT3 (another transcription factor), activated by IL-6, is involved in IL-17A expression by binding to the *Il17a* promoter (25). Additionally, JunB was found to colocalize with interferon regulatory factor (IRF)4, which is involved in IL17A expression (26, 27). IRF4 binds to the regulatory elements of the *Il17a* promoter, which are co-bound by BATF, an AP-1 factor (10, 27). KLF4, a Kruppel-like factor, is involved in IL-17A expression by directly binding to the *Il17a* promoter independently of ROR $\gamma$ t (28). A metabolic sensor, Hypoxia-inducible factor (HIF)-1 $\alpha$ , associates with ROR $\gamma$ t, and binds to hypoxia response element located in the proximal region of the *Rorc* promoter (29). This suggests a complex network of transcriptional regulators is involved in generating Th17 cells.

## Ubiquitination in IL-17A expression

Ubiquitin(Ub) conjugation was initially thought to be involved in proteasomal degradation of misfolded proteins (30). However, increasing evidence shows a broader implication in multiple subcellular processes, including the localization of proteins within the cytoplasm, nuclear translocation, protein-protein interactions, cell membrane receptor turnover, and gene expression. Predictably, IL-17A expression is also regulated by ubiquitin conjugation (Figure 1).

## E3 Ligases and IL-17A

The PDZ-LIM domain protein PDLIM2, a nuclear ubiquitin E3 ligase, has been shown to inhibit Th17 cells by targeting STAT3 for polyubiquitination and proteasomal degradation (31, 32). Deficiency in PDLIM2 resulted in the accumulation of STAT3 in the nucleus, enhanced Th17 cell differentiation, and exacerbated IL-17A-mediated granuloma formation (32). whereas the E3 ubiquitin ligase HECTD3 promoted Th17 cells via non degradative K27-linked and K29-linked polyubiquitin chains on STAT3 and Malt1 (33). *Hectd3*-deficient

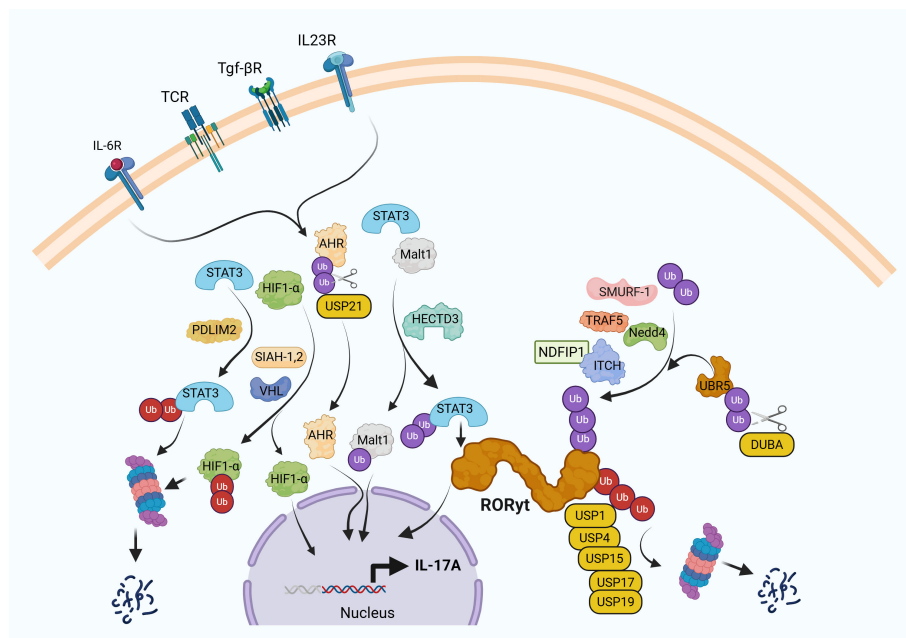


FIGURE 1

Ubiquitin pathway regulates IL-17A expression in Th17 cells. T cell receptor (TCR) ligation in the presence of IL-6, TGF- $\beta$ , and IL-23 induces differentiation of naïve CD4<sup>+</sup> T cells into Th17 cells through activation of key transcription factors, including ROR $\gamma$ t, aryl hydrocarbon receptor (AHR), MALT1, and HIF-1 $\alpha$ , which collectively drive IL-17A expression. Ubiquitin-mediated post-translational modifications tightly control this process. E3 ubiquitin ligases such as Itch and SMURF1 target ROR $\gamma$ t for ubiquitination, thereby limiting chronic IL-17A production. In contrast, TRAF5 and NEDD4 promote IL-17A expression, supporting Th17 polarization. HECTD3 enhances Th17 pathogenicity by ubiquitinating STAT3 and MALT1, while SLIM/PDLIM2 facilitates proteasomal degradation of STAT3. SIAH1/2 stabilizes HIF-1 $\alpha$  to promote Th17 differentiation, whereas the E3 ligase VHL paradoxically also contributes to Th17 development by ubiquitinating HIF-1 $\alpha$  for degradation, reflecting the context-dependent roles of these factors. Deubiquitinases (DUBs) further fine-tune this regulatory network. DUBA interacts with UBR5 to modulate ROR $\gamma$ t ubiquitination, acting as a negative regulator of IL-17A expression. Additional DUBs, including USP1, USP4, USP15, and USP17, contribute to the precise control of ROR $\gamma$ t activity. USP21 stabilizes AHR, thereby indirectly enhancing Th17 differentiation. These findings underscore the complexity and specificity of ubiquitin-mediated regulation in IL-17A-driven immune responses, highlighting potential targets for therapeutic intervention in autoimmune diseases.

mice exhibited reduced EAE severity and defective Th17 cell differentiation (33).

E3 ubiquitin protein ligase Itch regulates IL-17A production by ubiquitination of ROR $\gamma$ t in Th17 cells (34). Itch recognizes the PPLY region on ROR $\gamma$ t through its WW domain resulting in proteasomal degradation leading to inhibition of IL-17A expression. Itch deficiency resulted in spontaneous dermatitis and colitis, which was associated with elevated IL-17A expression (34). A defect in ITCH-mediated ROR $\gamma$ t degradation was demonstrated in colorectal cancer (CRC) patients, where Colon rectal neoplasia differentially expressed (CRNDE-h) protein was shown to associate with the conserved PPLY region within ROR $\gamma$ t in Th17 cells infiltrated to tumors (35). CRNDE-h binding of to ROR $\gamma$ t prevented ubiquitination of ROR $\gamma$ t by blocking its binding to ITCH (35). Not surprisingly, the percentage of Th17 cells among tumor-infiltrating lymphocytes (TILs) from CRC patients was positive correlated with CRNDE-h expression (35). This further supported the observed aggressive colon cancer growth in Itch $^{-/-}$  mice. This data further highlighted the involvement of ITCH in Th17-mediated tumor-promoting inflammation. Another report showed that Nedd4 targets ROR $\gamma$ t for K27-linked ubiquitination, which promotes IL-17A, and Nedd4 deficiency resulted in attenuated IL-17A production and EAE (36). Further, HECTD3 family interacting protein 1 (Ndfip1), a co-activator of the E3 ubiquitin ligase Itch, attenuates the frequency and Th17 cells pathogenicity (37, 38). NDFIP1 binds to Itch and promotes its ligase activity in murine CD4 $^{+}$  T cells following TCR ligation via recruitment of ubiquitin-conjugating enzyme E2 (UBCH7) to Itch (39). Similar to Itch $^{-/-}$  Th17 cells, when adoptively transferred, Ndfip1 deficient Th17 cells produced more IL-17A and induced severe colitis, indicating a pivotal role for the NDFIP1-ITCH pathway in the regulation of IL-17A-mediated inflammation (37, 38).

What triggers the Itch-mediated ubiquitination of ROR $\gamma$ t? It was shown that p21-activated kinase 2 (Pak2), a serine (S)/threonine (T) kinase, was shown to recognize a conserved KRLS motif within ROR $\gamma$ t and phosphorylates the S-316 within this motif (40). Pak2-mediated phosphorylation enhanced ROR $\gamma$ t ubiquitination. The genetic deletion of Pak2 in Th17 cells reduces ROR $\gamma$ t phosphorylation and increases IL-17A expression. Similarly, the reconstitution of ROR $\gamma$ t-S316A mutant in Rorc $^{-/-}$  Th17 cells enhanced IL-17A expression due to reduced ubiquitination (40). In silico analysis of the modeled structure of ROR $\gamma$ t showed that S316 makes an H-bond (3.6 Å) with a side-chain amino group of asparagine (N) 253 of the neighboring  $\alpha$ -helix and stabilizes the ligand-binding domain (LBD) of ROR $\gamma$ t, which reduces the accessibility of the PPLY motif. When S316 was substituted with phospho-mimetic aspartic acid residues (D) 316, the H-bond interaction between S316 and N253 was abolished, suggesting that phosphorylation provides increased accessibility of the PPLY motif of ROR $\gamma$ t to ITCH (40). This suggested that a crosstalk between phosphorylation and ubiquitination plays a critical role in regulating the stability of ROR $\gamma$ t and IL-17A expression. While Itch promoted degradation of ROR $\gamma$ t, tumor necrosis factor receptor-associated factor 5 (TRAF5) interacts with and ubiquitinates ROR $\gamma$ t

via Lys-63-linked polyubiquitination (41). TRAF5 stabilizes the ROR $\gamma$ t protein level depending on its RING finger domain. Depletion of TRAF5 in Th17 cells destabilizes ROR $\gamma$ t protein and downregulates Th17-related genes, including *Il17a* (41).

Screening of a cDNA library to identify specific modulators for *Il17a* promoter activity led to the identification of the E3 ubiquitin ligases SIAH1 and SIAH2, as positive regulators of *Il17a* promoter activity in a T-cell line and promoted Th17 development *ex vivo* (42). This enhancement was a consequence of increased HIF-1 $\alpha$  protein. Without HIF-1 $\alpha$ , both ubiquitin ligases had little effect on Th17 cell differentiation (42). These results suggest that SIAH1 and SIAH2 play a pivotal role in promoting Th17 cell differentiation via the modulation of the stability of HIF-1 $\alpha$  protein. Also, deletion of von Hippel-Lindau (VHL), an E3 ubiquitin ligase that targets HIF-1 $\alpha$ , promoted Th17 differentiation (43). Mice deficient in VHL in their T cells were resistant to EAE. In the absence of VHL, Th17 cells had decreased activation of STAT3 and SMAD2 (43) (Table 1).

## DUBs and IL-17A

Ubiquitination is a highly dynamic and reversible process, and the removal of Ub chains bound to protein substrates is mediated by deubiquitinating enzymes (DUBs). DUBA is a deubiquitylating enzyme that negatively regulates IL-17A production in T cells (44). DUBA is associated with the UBR5 (a ubiquitin ligase), suppressing abundance of DUBA in naive T cells. Accumulated DUBA stabilized UBR5, which then ubiquitylated ROR $\gamma$ t in response to TGF- $\beta$  signaling in activated T cells (44). Th17 cells highly express the deubiquitinase ubiquitin-specific protease (USP)4, which is essential for maintaining ROR $\gamma$ t and Th17 cell function. USP4 interacted and deubiquitinated K48-linked polyubiquitination of ROR $\gamma$ t, thereby promoting ROR $\gamma$ t function and *Il17a* transcription (47). Further, it was shown that USP17 stabilizes ROR $\gamma$ t protein expression by reducing ROR $\gamma$ t polyubiquitination at its Lys-360 residue (49). In contrast, knockdown of endogenous USP17 in Th17 cells resulted in decreased ROR $\gamma$ t protein levels and downregulation of Th17-related genes. Furthermore, USP17 expression was upregulated in CD4 $^{+}$  T cells from systemic lupus erythematosus patients (49). USP19 was shown to suppress Th17 cells *in vitro* and Th17-mediated pathogenesis *in vivo*. Mechanistically, USP19 removed the K63-linked ubiquitin chain from ROR $\gamma$ t lysine 313, which is essential for recruiting the coactivator SRC3 (50). In contrast, USP1 promoted Th17-cell differentiation by attenuating Treg-cell differentiation. USP1 in CD4 $^{+}$  T cells enhanced the activity of ROR $\gamma$ t but promoted the proteasomal degradation of Foxp3 (46). USP15 interacts with ROR $\gamma$ t and removes ubiquitin from K446, and stimulates ROR $\gamma$ t activity by enhancing coactivator SRC1 recruitment. Knockdown of USP15 or expression of inactive USP15 impaired Th17 differentiation, suggesting a positive role for USP15-mediated deubiquitination of ROR $\gamma$ t in Th17 differentiation (48). USP21 was shown to interact with and stabilize AhR by removing the K48-linked polyubiquitin chains from AhR (51). USP21 inhibits the transcriptional activity of AhR in a deubiquitinating-dependent manner. USP21 deubiquitinates at the K432 residue, and ubiquitination on this site is required for the transcriptional activity

TABLE 1 List of E3 ligases and DUBs and their function in IL-17A expression.

E3 ligase	Function	Disease model	Ref.
ITCH, NDFIP1, and UBR5.	Promotes degradation of ROR $\gamma$ t	IBD, EAE, RA.	(34, 36–38, 40, 44)
TRAF5 and SMURF1.	Stabilizes ROR $\gamma$ t, leading to enhanced IL-17A expression	EAE	(41, 45)
PDLIM2	Attenuates Th17 cell differentiation by targeting STAT3 for degradation.	EAE	(31, 32)
HECTD3	Necessary for pathogenic Th17 cell generation by promoting polyubiquitination of STAT3 and Malt1.	EAE	(33)
NEDD4	This E3 ligase enhances ROR $\gamma$ t activity during Th17 cell development by catalyzing K27-linked polyubiquitination.	EAE	(36)
Von Hippel-Lindau (VHL)	Promotes Th17 differentiation and regulates cellular metabolism in Th17 cells.	EAE	(43)
Deubiquitinating enzymes (DUBs)	Function	Disease model	Ref.
DUBA (Deubiquitinase A)	Stabilizes UBR5	Autoimmune diseases	(44)
USP-1	Enhances ROR $\gamma$ t activity while promoting Foxp3 degradation.	Inflammatory diseases	(46)
USP-4	Maintains ROR $\gamma$ t function in Th17 cells.	Inflammatory disease	(47)
USP-15	Interacts with ROR $\gamma$ t removing ubiquitin from K446 and stimulates ROR $\gamma$ t activity by enhancing SRC1.	Autoimmune diseases.	(48)
USP-17	Stabilizes ROR $\gamma$ t protein expression by reducing polyubiquitination at Lys-360.	Systemic lupus erythematosus.	(49)
USP-19	Removes K63-linked ubiquitin from ROR $\gamma$ t lysine 313, crucial for SRC3 coactivator recruitment.	EAE	(50)
USP-21	Deubiquitinates AhR at K432. Its deficiency enhances Th17 cell differentiation.	–	(51)

of AhR. Deficiency of USP21 enhanced the differentiation of Th17 cells *in vitro* and *in vivo* (51). The USP21-deficient T cells were more colitogenic upon adoptive transfer to *Rag1*<sup>−/−</sup> mice (51). Thus, IL-17A expression is tightly regulated by the ubiquitin pathway by targeting key signaling intermediates and transcription factors (Table 1).

### Ubiquitination in IL-17A receptor signaling

Upon binding to the IL-17RA-IL-17RC receptor complex, IL-17A activates NF- $\kappa$ B to induce the expression of *Il17a* target genes (5). While IL-17RA is expressed ubiquitously, IL-17RC expression is restricted, which limits IL-17A signaling to epithelial and mesenchymal cells (5). The cytoplasmic tail of the IL-17R contains a conserved SEFIR domain (52). A SEFIR domain was also found in the adaptor protein Act1, which is implicated in the activation of NF- $\kappa$ B (52). Subsequent work showed that Act1 was recruited to IL-17RA in an IL-17-dependent manner. Act1 contains a tumor-necrosis factor receptor-associated factor (TRAF)-binding motif that recruits TRAF6 (53, 54). This results in K63-linked ubiquitination of TRAF6, activating the kinase TAK1 and NF- $\kappa$ B (53, 54). Unrestrained IL-17A signaling is prevented by K48-linked ubiquitination of Act1 by F-box E3 ubiquitin ligase  $\beta$ -TrCP (55). A20, a deubiquitinase, also fine-tunes IL-17A signaling (56). A20 is recruited via the CBAD to IL-17RA and removes the K63-linked ubiquitin chains on TRAF6, which tempers IL-17A signaling as a negative feedback mechanism (56). Similarly, the ubiquitin-specific protease USP25 was shown to deubiquitinate TRAF6

and prevent excessive IL-17A-induced signaling and IL-17A-dependent experimental autoimmune encephalomyelitis (EAE) (57). Thus, IL-17A-mediated inflammation is prevented by the ubiquitin pathway at multiple levels.

### Conclusion

In conclusion, the regulation of IL-17-mediated inflammation by ubiquitination represents a critical layer of control in immune signaling, balancing host defense and the prevention of excessive inflammation. Ubiquitination modulates key components of IL-17A expression and signaling by targeting key signaling intermediates and transcription factors, such as ROR $\gamma$ t and STAT3. This post-translational modification fine-tunes the intensity and duration of IL-17-driven responses, thereby shaping the overall immune milieu. Disruptions in this regulatory network are increasingly linked to the pathogenesis of autoimmune diseases, where unchecked IL-17 signaling contributes to chronic inflammation and tissue damage.

Targeting IL-17A and IL-17 receptors using antibodies (e.g., the IL-17 inhibitor secukinumab and the IL-17R inhibitor brodalumab) has achieved remarkable success in treating psoriasis (58). However, these agents have unexpectedly low efficacy in IL-17-related diseases such as rheumatoid arthritis (RA) and multiple sclerosis (MS). This was suggested to be due to autonomous activation of IL-17R signaling and resistance to IL-17-directed therapy (59). Moreover, there is a potential risk of systemic inactivation of IL-17A activity, which



provides host defense and barrier function at mucosal surfaces (60–63). As a result, treatment with IL-17A inhibitors is linked to new-onset and exacerbations of inflammatory bowel disease and colitis (8).

The advancements in the understanding of ubiquitin-mediated regulation could aid in developing strategies to inhibit selective aspects of IL-17A-mediated inflammation in a site-specific manner. Targeted modulation of ubiquitin-related enzymes within the IL-17A pathway holds tremendous promise for the treatment of autoimmune disorders. Small molecules that block or promote interactions between E3 ligases and their substrates could be developed to dampen pathological IL-17 activity without broadly compromising host defense. Moreover, the development of proteolysis-targeting chimeras (PROTACs) presents an exciting avenue for increasing the specificity of substrate degradation, thereby enabling the selective removal of pro-inflammatory signaling proteins. These strategies reflect a shift toward precision immunomodulation, where leveraging the specificity of the ubiquitin system may yield next-generation therapeutics capable of restoring immune balance in autoimmune conditions. Overall, targeting the ubiquitin machinery within the IL-17 axis holds promise for precision immunomodulation, offering opportunities to mitigate chronic inflammation while preserving protective immunity.

## Author contributions

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## Conflict of interest

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