Cellular Immunology 340 (2019) 103922

Contents lists available at ScienceDirect

Cellular Immunology

journal homepage: www.elsevier.com/locate/ycimm

Regulation of T cell differentiation and function by ubiquitin-specific proteases

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ABSTRACT

T cells play critical roles in immune responses to pathogens, autoimmunity, and antitumor immunity. During the past few decades, increasing numbers of studies have demonstrated the significance of protein ubiquitination in T cell-mediated immunity. Several E3 ubiquitin ligases and deubiquitinases (DUBs) have been identified as either positive or negative regulators of T cell development and function. In this review, we mainly focus on the roles of DUBs (especially ubiquitin-specific proteases (USPs)) in modulating T cell differentiation and function, as well as the molecular mechanisms. Understanding how T cell development and function is regulated by ubiquitination and deubiquitination will provide novel strategies for treating infection, autoimmune diseases, and cancer.

1. Introduction

1.1. The ubiquitin pathway

Ubiquitin (Ub) is a 76-amino-acid protein highly conserved in all eukaryotic cells and regulates a myriad of important cellular functions by conjugating to the lysine residues of diverse proteins [1,2]. Protein modification by Ub, referred to as protein ubiquitination, is catalyzed by an enzymatic cascade comprising the E1 ubiquitin activating enzyme, the E2 ubiquitin conjugating enzyme, and the E3 ubiquitin ligase [2–4]. At the beginning, the ubiquitin activating enzyme E1 activates the ubiquitin in an adenosine triphosphate-dependent manner by forming the high-energy isopeptide bond between the C-terminal glycine residue of ubiquitin and E1 active cysteine group. Subsequently, the activated ubiquitin is transferred to E2 ubiquitin conjugating enzyme through similar isopeptide bond. Eventually, E3 ligases catalyze the isopeptide bond formation between the lysine residue on a substrate and the C-terminal glycine group of the ubiquitin (Fig. 1). In this process, E3 ligases strictly control both the efficiency and substrate specificity of the ubiquitination reaction [2].

According to the ubiquitin linkage types on the substrates, various forms of ubiquitination have been identified (Fig. 2): monoubiquitination, multi-monoubiquitination, Lys6-, Lys11-, Lys27-, Lys29-, Lys33-, Lys48-, and Lys63-linked polyubiquitination, Met1-linked linear polyubiquitination, and mixed-linkage polyubiquitination [5,6]. Diverse types of ubiquitin linkage endow ubiquitination with distinct functions in diverse cellular processes. Extensive studies have established that Lys48-linked polyubiquitination targets proteins to undergo proteasome-dependent degradation, whereas modification of target proteins by K63-linked polyubiquitination results in the regulation of cellular signal transduction via proteasome-independent mechanism.

1.2. Ubiquitin-specific proteases

Ubiquitination is a reversible process, in which the ubiquitin chains on the substrates can be removed and hydrolyzed into single ubiquitin molecules by deubiquitinating enzymes or deubiquitinases (DUBs) (Fig. 1), and this process is called deubiquitination [7,8]. According to their sequence and structural similarity, approximately 100 DUBs were found in the human genome and subdivided into six families: ubiquitin-specific proteases (USPs), ubiquitin carboxy-terminal hydrolases (UCHs), ovarian-tumor proteases (OTUs), Machado-Joseph disease protein domain proteases (MJDs), JAMM/MPN domain-associated metallopeptidases (JAMMs) and monocyte chemotactic protein-induced proteins (MCPIPs) [9–11]. DUBs play critical roles in both ubiquitin homeostasis and control of protein stability via enzymatic activities, thus, they can be divided into three categories: ubiquitin precursor processing, ubiquitin deconjugation and editing of ubiquitin conjugates [10,12].

The USP family represents the majority of DUBs, with at least 50 members [13]. The catalytic domain of USPs contains two conserved motifs, called Cys and His boxes, including the residues crucial for

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https://doi.org/10.1016/j.cellimm.2019.103922
Received 23 April 2019; Accepted 2 May 2019
Available online 03 May 2019

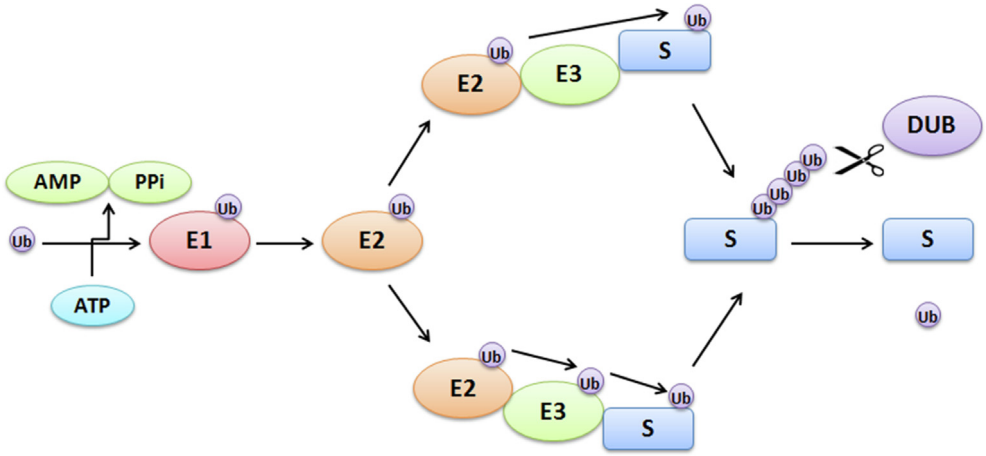

Fig. 1. The cascade of ubiquitination. Ubiquitination is catalyzed by three enzymes: ubiquitin- activating enzyme E1, ubiquitin-conjugating enzyme E2 and ubiquitin ligase E3, which is reversed by deubiquitinating enzymes or deubiquitinases (DUBs). Ub, ubiquitin; S, substrate.

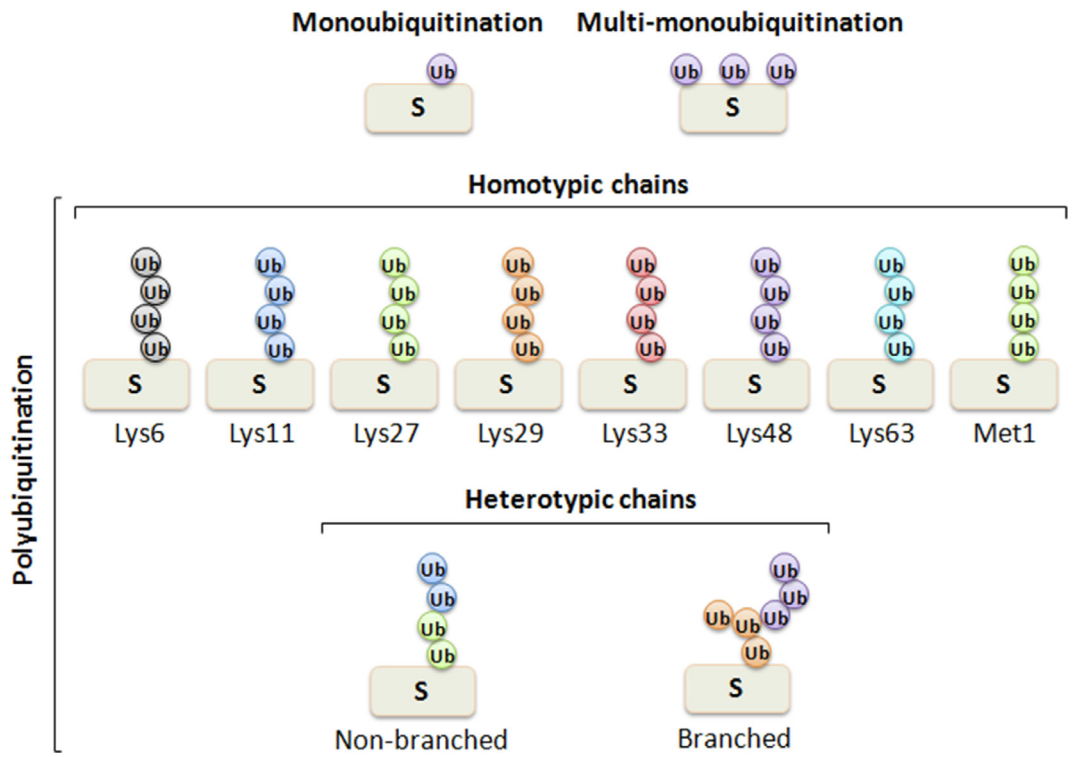

Fig. 2. Overview of the various forms of ubiquitination. A substrate can be modified by mono, multi-mono or polyubiquitin chains. Polyubiquitination can contain a single type of linkage (termed homotypic chains) or more than one linkage type (called heterotypic chains). Heterotypic chains contain more than one linkage type in non-branched or branched polymers. Ub, ubiquitin; S, substrate.

catalysis. Whereas many USPs lack catalytic residues, such as USP16, USP30, USP39, USP45 and USP52 [11]. Moreover, several USPs have additional domains that play important roles in their activity and specificity. For instance, CYLD exhibits the B-box domain; USP3, USP5, USP39, USP44, USP45, USP49 and USP51 have the zinc-finger USP domain; USP25 and USP37 show the ubiquitin-interacting motif; USP4, USP11, USP15, USP20, USP33 and USP48 exhibit the domain in USPs (DUSP); USP4, USP7, USP14, USP32, USP47 and USP48 display the ubiquitin-like domain that can be located both within and outside the catalytic domains [9,10,13,14].

1.3. USPs in the immune response

CD4 T cells play central roles in mediating adaptive immunity to pathogens, and are also involved in autoimmunity, asthma, and allergy as well as in antitumor immunity [15]. After antigen stimulation, naive CD4 T cells are activated by the engagement of T cell receptors (TCRs) and co-stimulatory receptors [16,17]. In a particular cytokine milieu, CD4 T cells differentiate into one of five subtypes of CD4 T helper (Th) cells, including Th1, Th2, Th17, T follicular helper (Tfh) and regulatory T cell (Treg) [15,18]. These subsets of CD4 T cells secrete different kinds of cytokines and exert distinct functions. Th1 cells mainly secrete IFN-γ to activate macrophages and natural killer cells and induce cellular immunity against intracellular pathogens such as viruses. Th2 cells produce interleukin (IL)-4, IL-5 and IL-13 and induce humoral immunity. Th17 cells mainly secrete IL-17A, IL-17F, IL-22 and induce immune response to extracellular pathogens such as fungi [19–22]. Tfh cells function within germinal centers and help B cells produce

Table 1
DUBs modulate T cell differentiation and function.

DUBs	Targets	Functions
CYLD	Lck	Regulates T cell development
	TAK1	Inhibits T cell activation
	Smad7, Akt	Negatively modulates TGF-β signaling and Treg cell function
USP4	RORγt	Promotes Th17 cell differentiation and function
	IRF8	Positively regulates Treg cell function
	IRF4	Facilitates Th2 cell function
USP7	FOXP3, Tip60	Promotes Treg cell suppressive capacity and antitumor immunity
USP8	Gads, CHMP5	Regulates T cell development and homeostasis
USP9X	Bcl10, ZAP70, Themis	Positively modulates TCR signaling and T cell tolerance
USP10	T-bet	Controls Th1 cell differentiation and function
USP12	LAT, Trat1	Stabilizes the TCR complex at the cell surface
USP15	RORγt	Stimulates Th17 cell differentiation
	MDM2	Negatively regulates CD4 T cell activation and differentiation into Th1 cells as well as antitumor T cell response
USP17	RORγt	Positively modulates Th17 cell function
USP18	TAK1	Negatively regulates T cell activation and Th17 cell differentiation Enhances antitumor immunity
USP21	GATA3, FOXP3	Facilitates Treg cell function and immune tolerance
USP22	NFATc2	Promotes IL-2 expression and T cell activation
USP2a	TRAF6	Positively regulates TCR-induced NF-κB activation and IL-2 production
USP20	TRAF6, Tax	Suppresses IL-1β- and Tax-induced NF-κB activation
USP25	TRAF5, TRAF6	Negatively modulates IL-17-mediated signaling and inflammation
USP34	NF-κB pathway	Negatively regulates NF-κB signaling upon TCR engagement
Otud7b	ZAP70	Promotes T cell activation and Th1 cell differentiation
DUBA	UBR5	Inhibits Th17 cell differentiation
A20	RIPK3	Positively regulates CD4 T cell survival
	mTORC1	Negatively regulates Treg cell development
	RelA	Maintains the tolerance of self-reactive T cells
	NF-κB pathway	Modulates CD8 T cell response
Trabid	Jmjd2b	Promotes Th1 and Th17 cell differentiation

antibody in response to T cell-dependent antigens. They produce large amounts of IL-21 and small amounts of IL-4, IFN-γ or IL-17 [23]. $CD4^+CD25^+FOXP3^+$Treg cells produce TGF-β and IL-10 and are responsible for immune suppression; therefore, they play indispensable roles in immune tolerance and homeostasis [24,25].

A large number of studies have demonstrated that protein ubiquitination plays critical roles in adaptive immunity, especially in T cell differentiation and function. Numerous studies have identified some E3 ligases are indispensable for T cell differentiation and function, such as Itch, Cbl-b and GRAIL, whereas the roles of DUBs in this issue are poorly defined. In this review, we briefly introduce how several key DUBs (especially USPs) modulate T cell differentiation and function and the underlying mechanisms (Table 1).

2. CYLD

Cylindromatosis (CYLD) was previously identified as a tumor suppressor that was broadly mutated in patients with familial cylindromatosis. CYLD consists of three cytoskeletal-associated protein-glycine-conserved (CAP-GLY) domains and one deubiquitinase catalytic domain [26]. Previous studies have revealed that CYLD is a member of deubiquitinating enzymes and removes K63-linked polyubiquitin chains from TNF receptor-associated factor (TRAF)2, TRAF6 and NEMO to negatively regulate the activation of NF-κB signaling pathway [27–30].

2.1. CYLD regulates T cell development

A number of studies have demonstrated that CYLD has fundamental roles in T cell development. The first paper related to the role of CYLD in T cells was published in 2006. CYLD in mice was eliminated through the germ-line removal of the exon 2 from the *Cyld* locus. CYLD-deficient mice show defective thymocyte development: the proportion of double-positive (DP) thymocytes is augmented while the proportion of CD4 and CD8 single-positive (SP) thymocytes is reduced, which indicates that CYLD regulates the DP-to-SP transition. Consistent with its thymocyte-intrinsic function, CYLD positively regulates proximal TCR signaling in DP thymocytes. For one thing, CYLD interacts with active Lck and promotes the recruitment of active Lck to its substrate Zap70. For another, CYLD removes both K63- and K48-linked polyubiquitin chains from active Lck. This study reveals a critical role of CYLD in regulating DP-to-SP transition of thymocytes via proximal TCR signaling [31].

The function of CYLD in T cell development was questioned by another line of mice in which CYLD was disrupted by the germ-line removal of exons 2 and 3 from the *Cyld* gene. These mice have no defects in thymocyte development, although lymphocytes exhibit enhanced activation of NF-κB and JNK in response to stimulation [32]. To investigate the specific role of CYLD in T cell ontogeny, conditionally targeted mice were generated by crossing $Cyld^{flx9/flx9}$ mice with *Lck-Cre* mice. These *LckCre-*$Cyld^{flx9/flx9}$ mice possess a T cell-specific defect in the deubiquitinating catalytic activity of CYLD, because exon 9 of the *Cyld* gene encodes an essential part of the deubiquitinating domain of CYLD. *LckCre-*$Cyld^{flx9/flx9}$ mice show dramatically reduced SP thymocytes and a substantial loss of peripheral T cells. SP thymocytes of these mice divert from a destiny of positive selection to enhanced deletion, which suggests CYLD has an essential role in the positive selection of thymocytes, by maintaining a proper threshold of activation. Thymocytes of *LckCre-*$Cyld^{flx9/flx9}$ mice exhibit aberrant activation of NF-κB and JNK. Importantly, inactivation of NEMO, which plays an essential role in NF-κB activation, restores the NF-κB activity and developmental defects of thymocytes, whereas TCR signaling fails to rescue. This study demonstrates an essential role for CYLD with catalytic activity in establishing the proper threshold of activation for thymocyte positive selection via NEMO-dependent NF-κB signaling [33].

CYLD also regulates the differentiation and maturation of medullary thymic epithelial cells (mTECs), which mediate the elimination of self-reactive thymocytes, thus indirectly affecting T cell development. $CYLD^{ex7/8}$ mice lack the full-length CYLD but overexpress a short splice variant CYLD (sCYLD), which lacks exon 7 and 8 of the *Cyld* gene and is devoid of TRAF2 and NEMO binding sites. These mice exhibit a defect in mTEC maturation and an impaired negative selection of thymocytes [34].

2.2. CYLD regulates T cell function

CYLD also has been reported to play pivotal roles in controlling T cell activation, function and homeostasis. T cells derived from *Cyld*-deficient mice are hyperresponsive to TCR stimulation and these mice develop spontaneous autoimmune symptoms and colonic inflammation that resemble inflammatory bowel disease (IBD). Adoptive transfer of *Cyld*-deficient T cells into $RAG1^{-/-}$ recipient mice spontaneously developed colitis, revealing that *Cyld*-deficient T cells are sufficient to induce IBD-like symptoms. CYLD interacts with TGF-β-activated kinase 1 (TAK1) and inhibits its ubiquitination and autoactivation. Loss of CYLD in T cells leads to constitutive activation of TAK1 and its downstream kinases c-Jun *N*-terminal kinase (JNK) and IκB kinase β (IKKβ). These findings identify CYLD as a negative regulator in T cell activation and homeostasis by preventing spontaneous activation of the TAK1 axis of TCR signaling [35].

Indirect evidences also indicate the role of CYLD in regulating T cell activation. CYLD is cleaved by MALT1 after TCR stimulation [36]. During experimental autoimmune encephalomyelitis (EAE), CYLD

processing also depends on MALT1 in T cells [37]. Therefore, CYLD could inhibit T cell activation in the absence of MALT1 proteolytic activity.

The regulatory function of CYLD in T cell activation is also relevant to some immune diseases. After induction of experimental asthma, $CD4^+CYLD^{ex7/8}$ mice (overexpressing sCYLD) exhibit higher serum IgE level and stronger eosinophilia and mucus production in the lungs, as well as elevated IL-9 production in T cells. IL-9 blockade in these mice alleviates the disease development. Thus, sCYLD could favor the development of asthma by promoting cytokine production from T cells [38].

2.3. CYLD modulates TGF-β signaling and Treg cell function

Recently, it has been reported that CYLD regulates TGF-β signaling and the development and function of Treg cells. The first study revealed that CYLD deficiency resulted in constitutive activation of NF-κB signaling in thymocytes, which was relevant to enhanced proportion of Treg cells [39]. CYLD knockout mice have dramatically increased proportion of Treg cells in periphery but not in the thymus, whereas Treg cells of these mice show unaffected suppressive capacity of responder T cells. CYLD-deficient naive T cells have an enhanced capacity to differentiate into Treg cells following anti-CD3/28 and TGF-β stimulation. Importantly, CYLD hydrolyzes Lys-63-linked polyubiquitin chains of Smad7 at lysine 360 and 374 residues, which regulates TAK1 and p38 MAPK activities in response to TGF-β. These findings demonstrate that CYLD functions as a negative regulator of TGF-β signaling and Treg cell development through deubiquitination of Smad7 [40].

The negative regulation function of CYLD in TGF-β signaling was also studied in a lung fibrosis model. After Streptococcus pneumoniae infection, CYLD deficiency results in the development of lung fibrosis in mice, with enhanced TGF-β signaling. CYLD inhibits TGF-β signaling and prevents mice from lung fibrosis by deubiquitinating K63-linked polyubiquitinated Akt, leading to impairment of Smad3 stability. Smad3 plays essential roles in activating the TGF-β signaling pathway and enhancing Foxp3 expression [41,42].

Another study used $CYLD^{ex7/8}$ mice to explain the role of CYLD in Treg cell development and function. T cells of $CYLD^{ex7/8}$ mice display a hyperactive phenotype with increased inflammatory cytokine production and constitutive activation of the NF-κB signaling. Furthermore, Treg cells in $CYLD^{ex7/8}$ mice have increased numbers in thymus, spleen, and lymph nodes, exhibiting reduced expression levels of CD25 and CTLA-4, as well as impaired suppressive function in vivo. These findings emphasize a pivotal role of CYLD in maintaining T cell homeostasis and Treg cell function [43]. Whereas several studies have identified CYLD as a regulator in Treg cell function, the exact role and its underlying mechanism needs to be further explored.

3 USP4

Ubiquitin-specific protease 4 (USP4) was identified as a proto-oncogene and a member of the USP family. It has been shown that USP4 deubiquitinates K63-linked polyubiquitin chains from TAK1, TRAF2 and TRAF6, and stabilizes some proteins by deubiquitinating K48-linked polyubiquitination [44–47]. A recent study has demonstrated that AKT mediates the nuclear-to-cytoplasmic transport of USP4, leading USP4 to interact with and deubiquitinate TGF-β type I receptor (TβRI), which indicates USP4 as a critical determinant for the crosstalk between AKT and TGF-β signaling pathways [48].

3.1. USP4 promotes Th17 cell differentiation and function

Our laboratory was the first one to investigate the role of USP4 in T cell function. We identified that USP4 was pivotal for stabilizing RORγt and maintaining Th17 cell function. Th17 cells express a high level of USP4. Inhibition of the catalytic activity of USP4 with vialinin A, an inhibitor of USP4 isolated from the Chinese mushroom, impairs Th17 differentiation, suggesting that USP4 promotes Th17 differentiation. Importantly, USP4 interacts with RORγt and deubiquitinates its K48-linked polyubiquitination, thereby stabilizing RORγt and facilitating its function. Furthermore, TGF-β and IL-6 enhances USP4-mediated deubiquitination of RORγt. $CD4^+$ T cells from patients with rheumatic heart disease, a kind of autoimmune diseases, display elevated mRNA level of USP4 and IL-17 [49].

3.2. USP4 positively regulates Treg cell function

We found that USP4 promoted the suppressive function of Treg cells by stabilizing interferon regulatory factor (IRF)8. USP4 interacts with and stabilizes IRF8 by deubiquitination of K48-linked polyubiquitination. USP4 deficiency promotes K48-linked polyubiquitination of IRF8 and upregulates the gene expression levels of type 2 inflammatory cytokines in Treg cells, such as IL-4, IL-5 and IL-13. Furthermore, USP4 depletion also impairs the suppressive function of Treg cells. Therefore, this work identifies USP4 as a critical positive regulator of Treg cell function [50].

3.3. USP4 facilitates Th2 cell function

It has been reported that USP4 regulates Th2 cell function by stabilizing IRF4. USP4 interacts with IRF4 and deubiquitinates K48- and K63-linked polyubiquitination, thereby stabilizing IRF4. Importantly, USP4 and IRF4 synergize with nuclear factor of activated T cell-2 (NFATc2) to specifically enhance NFAT-mediated activation of the IL-4 promoter. USP4 knockdown reduces IRF4 expression level and mRNA level of Th2-related cytokines, such as IL-4, IL-10 and IL-13. In peripheral blood mononuclear cells (PBMCs) from RHD patients, the expression levels of IL-4 and IRF4 are increased. Therefore, USP4 deubiquitinates and stabilizes IRF4 protein and facilitates Th2-related cytokine expression [51].

4. USP7 promotes Treg cell suppressive capacity and antitumor immunity

Ubiquitin-specific protease 7 (USP7) is also known as herpes associated ubiquitin-specific protease (HAUSP), so called because it was first identified by its ability to stabilize infected cell polypeptide 0 (ICP0) and enhance herpesvirus replication [52]. USP7 has been shown to regulate the tumor suppressor p53 and its ubiquitin ligase, murine double minute 2 protein (MDM2) by deubiquitination, thereby being extensively studied in tumor biology [53–56]. Recent studies have reported that USP7 is also involved in Treg cell function.

Polyubiquitination of Foxp3 protein at multiple lysine residues leads to rapid proteasome-mediated degradation of Foxp3, thus, regulating Treg cell function. USP7 is upregulated and active in primary Treg cells, and interacts with Foxp3 in the nucleus. Ectopic expression of USP7 decreases the polyubiquitination of Foxp3 and increases the expression level of Foxp3 protein. On the contrary, USP7 knockdown in Treg cells promotes Foxp3 polyubiquitination, decreases Foxp3 protein expression, and abrogates Treg-cell-mediated suppressive function in vitro. Adoptive-transfer induced colitis model also reveals that USP7 knockdown in Treg cells impairs their capacity to suppress inflammation in vivo. Taken together, these findings demonstrate that USP7-mediated Foxp3 deubiquitination enhances Treg cell suppressive capacity [57].

Another study emphasized the importance of USP7 in Treg cell function and antitumor immunity by using conditional knockout mice and USP7-specific inhibitors. The authors conditionally deleted USP7 in murine Treg cells by crossing $Usp7^{fl/fl}$ and $Foxp3^{YFP/Cre}$ mice to generate $Usp7^{fl/fl}$ $Foxp3^{YFP/Cre}$ mice. Conditional deletion of USP7 in Treg cells leads to lethal systemic autoimmunity, associated with increased T cell numbers and activation, but decreased Treg cell numbers in peripheral lymphoid tissues. USP7 deletion in Treg cells or treatment with USP7-

specific inhibitors also inhibits the in vitro development of inducible Treg (iTreg) cells and disrupts Treg cell suppressive function in vitro and in vivo [58]. Importantly, they found that USP7 was important for the regulation of Tip60 expression in Treg cells, a key histone/protein acetyltransferase (HAT) in Treg cells regulating Foxp3 dimerization and Treg cell function [59,60]. Since Treg cells isolated from WT or *Usp7*$^{fl/fl}$ *Foxp3*$^{YFP/Cre}$ mice show comparable expression level of Foxp3 but markedly decreased Tip60 expression, and treatment with USP7-specific inhibitor negligibly decreases Foxp3 but markedly reduces Tip60 expression. This study also points to the importance of Tip60 to maintaining Foxp3 expression in Treg cells. Furthermore, USP7 facilitates Treg cell function mainly by stabilizing Tip60 expression and promoting the multimerization of Tip60 and Foxp3 rather than via direct effect on Foxp3 alone. Moreover, specific USP7 inhibitors can promote antitumor immunity by impairing Treg cell function while preserving T effector cell activity, and enhance the efficacy of antitumor vaccines and immune checkpoint therapy with anti-PD1 antibody [58].

Promoting USP7-mediated Foxp3 deubiquitination could be a novel therapeutic strategy for autoimmune diseases. The novel compound cambogin, ameliorates Dextran sulphate sodium (DSS)-induced colitis in mice and prevents Foxp3 loss in human primary Treg cells by promoting USP7-mediated Foxp3 deubiquitination. Therefore, cambogin could be a novel drug for treating colitis and other Treg cell-related autoimmune diseases [61].

5. USP8 is critical for T cell development and homeostasis

Ubiquitin-specific protease USP8 (UBPY) participates in the endosomal sorting of transmembrane proteins and interacts with the proline-rich SH3 domain of the signal-transducing adaptor STAM2, a component of the endosomal sorting complex ESCRT-0 [62–64]. It has been shown that USP8 deubiquitinates both cargo proteins and ESCRT-0 proteins, thus, modulating their stability and function [62,63]. Proteolytic cleavage of USP8 increases its enzymatic activity, and somatic mutations that promote USP8 cleavage can cause Cushing's disease [65]. USP8 contains two atypical SH3-binding motifs (SH3BMs) that can bind to the 14-3-3 family of regulatory proteins, which inhibit USP8 activity [64–67]. Previous peptide-binding studies showed that the amino-terminal SH3BM of USP8 displayed a higher binding affinity for an SH3 domain of Gads, a signaling adaptor downstream of TCR [68,69].

A recent study established the roles of USP8 in the development and homeostasis of T cells. First, the authors found that USP8 could bind to the TCR adaptor Gads and the regulatory molecule 14-3-3, whereas USP8 was regulated in a caspase-dependent manner. T cell-specific deletion of USP8 in mice reveals that USP8 is critical for thymocyte maturation and thymocyte proliferation. They also revealed USP8 could affect thymocyte development via the Foxo1-IL-7Rα axis. *Usp8*$^{f/f}$*Cd4*-Cre mice spontaneously develop colitis and USP8 is an intrinsic regulator of thymocyte development and peripheral T cell homeostasis. Furthermore, USP8 is dispensable for canonical TCR signaling induced by CD3-CD28. Both the catalytic activity and the SH3BMs of USP8 are crucial for its function in T cells, but binding of 14-3-3 is not. Finally, USP8 is essential for the maintenance of immune tolerance by Treg cells via suppression of an inflammatory response mediated by intestinal γδ T cells [70]. Another study identified USP8 as a specific deubiquitinase for CHMP5 (a component of ESCRT complex) and revealed the involvement of CHMP5-USP8 complex in modulating the positive selection of thymocytes [71].

6. USP9X is a crucial positive regulator of TCR signaling and T cell tolerance

Ubiquitin-specific protease 9X (Usp9X) is a USP domain-containing DUB that was originally identified as a mammalian homolog of *Drosophila* developmental gene *fat facets (faf)* [72]. It has been reported that USP9X plays critical roles in regulating cell survival and TGF-β signaling by deubiquitination of myeloid leukemia cell differentiation protein 1 (Mcl1), Itch and Smad4 [73–75]. Importantly, an increasing number of studies have revealed the involvement of USP9X in TCR signaling and T cell function.

Both in vitro and in vivo knockdown of USP9X attenuates T cell proliferation, cytokine production, and the differentiation of Th1, Th2, and Th17 cells, indicating that USP9X is essential for the above processes. USP9X knockdown in both human T cells and mouse primary T cells decreases TCR signaling-induced NF-κB activation. USP9X modulates upstream signaling molecules of the NF-κB pathway, but not TCR proximal or other downstream signaling events, thereby regulating NF-κB activation. Mechanistically, USP9X interacts with Bcl10, a component of the Carma1-Bcl10-Malt1 (CBM) complex, and regulates CBM complex formation by modulating Bcl10 ubiquitination, which facilitates the association of Carma1 with Bcl0-Malt1. These findings indicate that USP9X positively modulates the TCR signaling pathway by facilitating CBM complex assembly and subsequent TCR-induced NF-κB activation [76].

The study of another group did not support that USP9X modulated the CBM complex, rather, it was found that it directly regulated proximal TCR signaling events during T cell activation. Specifically, USP9X was required for transduction of the activation signal from ZAP70 to its substrates. USP9X-deficient T cells are hypoproliferative. Elevated numbers of antigen-experienced (effector-memory), PD-1 and OX40-expressing T cells, consistent with immune hyperactivity are observed in mice with T cell-specific deletion of USP9X. USP9X deficiency in T cells leads to spontaneous lupus-like autoimmunity and lymphoproliferative disease. The reason for which is that USP9X deficiency in T cells causes defective development of intrathymic T cells. To be exact, fewer thymocytes reach the threshold for negative selection and, as a consequence, fewer T cells with autoreactive TCRs are eliminated. Thus, USP9X is a T cell-intrinsic regulator for proximal TCR signaling and immune tolerance [77].

The remaining question to be determined was whether USP9X targeted ZAP70 directly or indirectly. The above mentioned group expanded their work by defining the role of USP9X in regulation at the level of ZAP70. USP9X functions as a positive regulatory switch during T cell activation via removal of the inhibitory monoubiquitination from ZAP70. USP9X deficiency leads to an increased amount of ZAP70 localized to early endosomes consistent with the role of monoubiquitin in endocytic sorting. USP9X becomes competent to deubiquitinate the monoubiquitination of ZAP70 by TCR-dependent phosphorylation and enhancement of its catalytic activity and interaction with the LAT signalosome. The authors also demonstrated that USP9X was a positive regulator of B cell receptor (BCR)- and NF-κB-dependent B cell survival by modulating PKCβ kinase activity [78].

Themis, a new component of TCR signaling machinery that has an important role during T cell development [79–81], has been reported to be regulated by USP9X. The protein level of Themis is augmented in double-positive thymocytes undergoing positive selection and is sustained in immature single-positive thymocytes. USP9X regulates Themis stability by removing K48-linked polyubiquitin chains from Themis following TCR engagement. USP9X binds directly to the *N*-terminal cysteine-containing, all-β in Themis (CABIT) domain of Themis and indirectly to the adaptor protein Grb2, which promotes the recruitment of Themis/USP9X complexes to LAT, thereby maintaining Themis expression following positive selection. Together, these findings indicate that TCR signaling enhances Themis stability upon T cell development and USP9X is critical for Themis protein turnover [82].

7 USP10

Ubiquitin-specific protease 10 (USP10) is an anti-stress factor against various environmental stresses, including virus infection and

oxidative stress. USP10 is a component of stress granules (SGs) and has important roles in several SG-mediated activities. On exposure to arsenic, an oxidative stress inducer, USP10 is recruited into SGs, and USP10-containing SGs reduce the production of reactive oxygen species (ROS) and inhibit ROS-dependent apoptosis [83,84].

Human *T*-cell leukemia virus type 1 (HTLV-1) is an agent of adult *T*-cell leukemia (ATL). HTLV-1 encodes the oncoprotein Tax, which plays critical roles in the immortalization of virus-infected T cells, accumulation of gene mutations in infected cells, and leukemogenesis [85,86]. A recent study identified USP10 as an interacting DUB of Tax in HTLV-1-infected T cells. Binding of Tax with USP10 reduces arsenic-induced SG formation, stimulates ROS production, and enhances ROS-dependent apoptosis in HTLV-1-infected T cells. Knockdown assay of USP10 in T cells indicates that USP10 in T cells promotes SG formation and impairs arsenite-induced apoptosis. These findings reveal that USP10 is a host factor that inhibits stress-induced ROS production and ROS-dependent apoptosis in HTLV-1-infected T cells, whereas its activities are inhibited by Tax [84].

Importantly, USP10 has been identified as a DUB for the *T*-box transcriptional factor *T*-bet, which controls the differentiation and function of Th1 cells [87]. USP10 interacts with *T*-bet in the nucleus, and stabilizes the expression level of *T*-bet protein via deubiquitination. Quercetin, an inhibitor of *T*-bet [88], could target USP10 for degradation, thus, promoting *T*-bet degradation in a proteasome dependent way. What is more, USP10 expression is upregulated in PBMCs of asthmatic patients, indicating that USP10 could be a target for diagnosis and therapy in inflammatory diseases [89].

8. USP12 stabilizes the TCR complex at the cell surface

Ubiquitin-specific protease 12 (USP12) is highly homologous to USP1 and USP46, and these three proteins are activated by complex formation with a WD40 repeat protein called USP1 associated factor (UAF1), also known as WDR48, which results in increased catalytic activity for these enzymes [90]. USP12 has been reported to stabilize the AKT phosphatases leading to decreased phosphorylation level of AKT. USP12 and USP46 can deubiquitinate histones H2A and H2B, thereby playing a critical role in Xenopus development [91].

Recently, USP12 was shown to stabilize the TCR complex at the cell surface by deubiquitinating TCR adaptor proteins LAT and Trat1. The researchers used a systematic and unbiased screening strategy to uncover DUBs that participate in TCR signaling in primary T cells under physiological settings, and captured USP12 and USP46 that are recruited to the cytosol on TCR stimulation, which had not been previously described. TCR stimulation leads to phosphorylation and translocation of USP12 from the nucleus to the cytosol. USP12-deficient Jurkat cells exhibit defective MAPK, NF-κB, and NFAT activities due to attenuated TCR expression at the cell surface, which are rescued by reconstitution of wild type USP12. LAT and Trat1 are ubiquitinated and degraded in the absence of USP12, thus downregulating TCR surface expression. Mechanistically, USP12 deubiquitinates LAT and Trat1, and inhibits lysosomal degradation of LAT and Trat1 to maintain the proximal TCR complex for the duration of signaling, which is the first time for USP12 to be identified as a positive regulator of TCR signaling pathway [92].

9. USP15

Ubiquitin-specific protease 15 (USP15) is an extensively studied USP that plays important roles in cancer cells. It has previously been implicated in the regulation of the NF-κB signaling pathway, caspase 3 and β-catenin stability, and TGF-β signaling pathway [93–98]. Recent studies have reported that USP15 regulates T cell function and differentiation, as well as antitumor T cell responses.

The first study identified USP15 as a critical negative regulator of T cell activation both in vitro and in vivo. USP15 deficiency promotes T cell responses to bacterial infection and tumor challenge. USP15 deficiency enhances NFATc2 activation in naive CD4 T cells, because USP15 deubiquitinates and stabilizes the E3 ubiquitin ligase MDM2, which negatively regulates NFATc2 activation and cytokine induction in T cells in a p53-independent manner. In cancer cells, USP15 stabilizes MDM2 and negatively regulates p53-mediated apoptosis. Thus, inhibiting USP15 may both induce cancer cell apoptosis and boost antitumor T cell response, which has important clinical applications for cancer therapy [99].

The role of IFN-γ in modulating antitumor immunity is paradoxical, showing both anti- and pro-tumorigenic functions. The above researchers previously found that USP15 could negatively regulate naive CD4 T cell activation and differentiation into the IFN-γ-producing Th1 cells. USP15-deficient mice mount stronger antitumor T cell responses in a transplantable melanoma model [99]. However, it remains unclear how the excessive production of IFN-γ by USP15-deficient T cells impacts the primary tumor development. To address this question, the authors employed the methylcholantrene (MCA)-induced fibrosarcomas model. USP15-deficient mice are more sensitive to MCA-induced fibrosarcomas. Excessive IFN-γ production in USP15-deficient mice promotes expression of PD-L1 and CXCL12, causing accumulation of *T*-bet$^+$ regulatory T cells and CD11b$^+$Gr-1$^+$ myeloid-derived suppressor cells, thereby contributing to immunosuppressive tumor microenvironment formation. Moreover, T cells serve as the main source of aberrant IFN-γ production in tumor-bearing USP15-deficient mice. Adoptive transfer experiments demonstrated a T cell-intrinsic role for USP15 in modulating IFN-γ production and tumor formation. Taken together, these findings indicate a T cell-intrinsic role for USP15 deficiency in promoting IFN-γ production and immunosuppressive tumor microenvironment formation [100].

However, another study identified USP15 as a positive regulator of Th17 differentiation. The authors identified K446 of RORγt as a functional ubiquitination site. Mutation of K446 to arginine augments the recruitment of steroid receptor coactivator 1 (SRC1), which is crucial for RORγt activity, thereby facilitating Th17 differentiation. Importantly, USP15 interacts with and deubiquitinates RORγt at K446, and stimulates RORγt activity and Th17 differentiation by enhancing the recruitment of coactivator SRC1. Knockdown of USP15 or expression of inactive USP15 attenuates Th17 differentiation, indicating a positive role for USP15-mediated deubiquitination of RORγt in Th17 differentiation. This study provides the therapeutic strategies that target the ubiquitination of RORγt to prevent Th17-mediated autoimmunity [101].

10 USP17

Ubiquitin-specific protease 17 (USP17), also known as DUB-3, belongs to a subfamily of cytokine-inducible DUBs. It is induced in response to IL-4 and IL-6, which regulate the growth and differentiation of leukocytes [102]. It has been reported that USP17 modulates GTPase Ras activation and cell proliferation by negatively regulating the activity of Ras-converting enzyme 1(RCE1) [103]. USP17 also regulates the cell cycle at G1/S phase, thereby regulating cell proliferation [104,105]. Furthermore, USP17 modulates virus-triggered type I IFN signaling by deubiquitinating Retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5) [106].

Our laboratory identified USP17 as a DUB for RORγt, thereby positively regulating Th17 cell function. USP17 operates directly on RORγt to enhance RORγt-mediated *Il17a* promoter transcriptional activation. USP17 interacts with and deubiquitinates the K48-linked polyubiquitination of RORγt at its K360 site, thus stabilizing RORγt protein. Knockdown of USP17 in Th17 cells decreases the expression levels of RORγt protein and Th17-related genes, such as IL-17A, IL-17F and IL-23R. What is more, the transcription level of USP17 is significantly augmented and positively correlated with IL-17A or IL-17F in CD4 T cells of systemic lupus erythematosus (SLE) patients. This study

indicates USP17 as a potential drug target for RORγt-mediated autoimmune diseases [107].

11 USP18

USP18 was first identified in AML1-ETO leukemia [108]. It is expressed at low levels in multiple tissues and cell lines and its expression could be rapidly up-regulated by type I IFNs [109–111]. USP18 has been found to play important roles in innate immunity. USP18-deficient mice are protective from lethal LCMV and VSV infection [112]. It was shown that USP18 directly interacted with IFN-α/β receptor 2 (IFNAR2) in human KT-1 cells, and competed for the binding of JAK1 to suppress type I IFN signaling [113,114]. Recently, the attention was drawn to the function of USP18 in adaptive immune cells, especially T cells.

USP18-deficient T cells are defective in Th17 cell differentiation in vitro and USP18 knockout mice are defective in Th17 generation in vivo and resistant to the induction of experimental autoimmune encephalomyelitis (EAE). USP18 regulates Th17 differentiation and EAE development in a T cell-intrinsic manner. After TCR stimulation, USP18-deficient T cells display hyperactivation of NF-κB, JNK, and NFAT and produce increased level of IL-2. Mechanistically, USP18 interacts with the TAK1-TAB1 complex and deubiquitinates TAK1, thereby restricting TCR-mediated NF-κB and NFAT activation, and subsequent expression of IL-2. These findings demonstrate a previously uncharacterized role of USP18 in negatively regulating T cell activation and Th17 cell differentiation, indicating that USP18 may be targeted to treat Th17 cell-mediated autoimmune diseases [115].

It has been reported that USP18 is critical for IFN-γ-mediated inhibition of melanoma tumorigenesis and antitumor immunity. IFN-γ signaling induces USP18 expression in B16 melanoma tumor cells, thus suppressing tumor growth in vivo. USP18 expression in B16 melanoma tumor cells modulates immune cell phenotypes, including increasing MHC class-I expression, impairing tumor cell-mediated inhibition of T cell proliferation and activation, and restricting PD-1 expression in $CD4^+$ and $CD8^+$ T cells in tumor-bearing mice. USP18 expression in tumor cells also enhances the activity of cytotoxic T lymphocytes (CTLs) during adoptive immunotherapy. Mechanistically, USP18 inhibits tumor cell-mediated immune suppression by activating T cells, inhibiting T cell exhaustion, and reducing dendritic cell tolerance, thereby making tumor cells sensitive to immunotherapy. Therefore, stimulation of USP18 may be a feasible strategy to inhibit melanoma growth and enhance immunotherapy efficacy [116].

12 USP21

Ubiquitin-specific protease 21 (USP21) can catalyze the deubiquitination of a variety of ubiquitin chains, including K6-, *K*11-, K29-, K48-, K63-linked polyubiquitination and linear polyubiquitination [117]. It was demonstrated to deubiquitinate histone H2A and to promote transcriptional activation, especially in mouse hepatocytes during liver regeneration [118]. USP21 was also identified to remove ubiquitin chains from the deathdomain containing protein kinase RIPK1, transcription factor GATA3, the anti-viral pattern recognition receptor RIG-I, cytokine IL-33 [119–121]. Our recent studies have identified USP21 as a critical regulator in Treg cell function and immune tolerance.

GATA3 is critical for Treg cell function in suppressing inflammatory responses. USP21 augments GATA3-mediated *Il4* and *Il5* promoter activation. USP21 interacts with and deubiquitinates GATA3, thereby stabilizing the expression level of GATA3. In a Jurkat T cell line overexpressing FOXP3, TCR stimulation promotes USP21 expression and leads to the upregulation of GATA3 expression. Knockdown of USP21 results in the downregulation of GATA3 protein in both Treg and Th2 cells, indicating that USP21 can control GATA3 expression and function in both Treg and Th2 cells. Furthermore, FOXP3 could directly bind to the USP21 promoter and activate its transcription upon TCR stimulation; therefore, USP21, GATA3, and FOXP3 form a positive feedback loop to modulate Treg cell function [122].

USP21-deficient mice were generated to determine whether USP21 was a non-redundant regulator of GATA3 in vivo. USP21-deficient mice are viable and fertile, with no dysmorphology. These mice exhibit normal hematopoietic stem cell function, T cell development, and responses of antigen presenting cells to the stimulation of Toll like receptor (TLR) and TNFα-receptor (TNFR). However, GATA3 levels in hematopoietic stem cells or T cells remain unchanged [123], in contrast to the previous in vitro study [122]. Importantly, aged USP21-knockout mice display spontaneous T cell activation, which is not due to altered GATA3 levels in the affected cells, suggesting USP21 may regulate T cell function and homeostasis through other mechanisms. The observed phenotypes of USP21-knockout mice indicate that USP21 is redundant for the regulation of GATA3 expression and activity in hematopoietic stem cells and lymphocyte differentiation [123].

USP21-knockout mice display spontaneous T cell activation [123,124], indicating a potential role of USP21 in maintaining immune homeostasis in vivo. What is more, our previous study showed that USP21 is highly induced in Treg cells from asthma patients [122], suggesting a role of USP21 in Treg cells. Therefore, mice with conditional depletion of *Usp21* in Treg cells were generated to investigate the role of USP21 in Treg cells. $Usp21^{fl/fl}Foxp3^{Cre}$ mice develop spontaneous immune disorders, characterized by spontaneous T cell activation and excessive Th1 skewing of Treg cells into Th1-like Treg cells. USP21 deficiency in Treg cells perturbs the expression of Treg signature genes and impairs Treg cell suppressive activity. Mechanistically, USP21 stabilizes FOXP3 protein by mediating its deubiquitination, thus maintaining Treg signature gene expression and Treg cell function. Importantly, depletion of USP21 in murine Treg cells does not affect the expression level of GATA3 [125], which is consistent with a previous study showing USP21 is dispensable for the regulation of GATA3 during murine lymphocyte differentiation [123], whereas our previous study reported USP21 stabilizes GATA3 expression by deubiquitination in human Treg cells [122]. Perhaps this is because USP21 is non-redundant for stabilizing GATA3 expression in human Treg cells, but not in mice.

13 USP22

Ubiquitin-specific protease 22 (USP22) was originally identified as a subunit of the human SAGA complex (hSAGA), required for transcription activation. USP22 has been reported to regulate cell-cycle progression, apoptosis and tumorigenesis. For instance, USP22 can deubiquitinate histone H2B, thereby activating the transcription of Myc-target genes [126]. It can also modulate cell proliferation and tumorigenesis by deubiquitinating the far upstream element (FUSE)-binding protein 1 (FBP1) [127]. USP22 also regulates cell-cycle progression and apoptosis by deubiquitination of Sirt1, which antagonizes the transcriptional activity of p53 [128]. However, the role of USP22 in the immune system, especially in T cell immunity remains largely unknown.

We recently unveiled USP22 as a positive regulator of NFATc2, which promotes IL-2 expression and T cell activation. Knockdown of USP22 decreases IL2 expression in Jurkat cells upon activation. Depletion of USP22 in T cells inhibits IL2 transcription by regulating NFATc2 stability. Mechanistically, USP22 interacts with and deubiquitinases NFATc2, thereby stabilizing its protein level. Therefore, targeting USP22 could be a novel therapeutic strategy to modulate IL2 expression and T cell function [129].

14. Other USPs

Some other USPs which were not described above, were also identified as regulators of TCR, NF-κB and cytokine-induced signaling pathways, thereby regulating T cell activation, development and

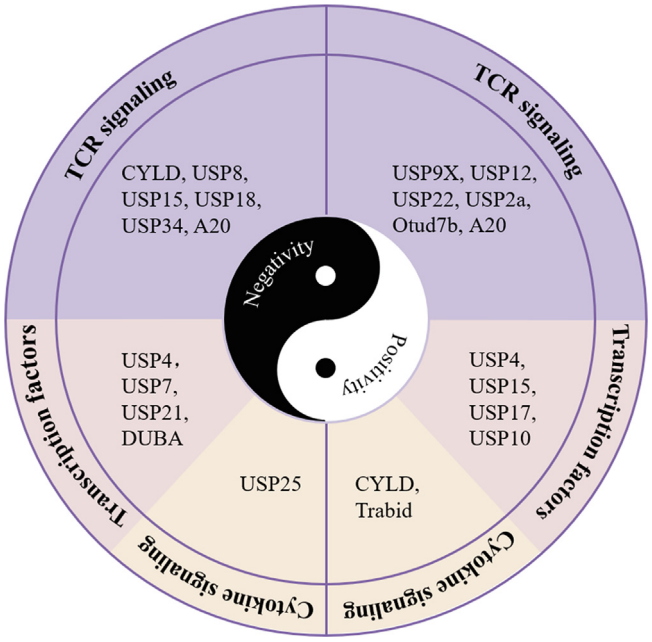

Fig. 3. DUBs function as positive or negative regulators of T cell-mediated immunity. DUBs modulate T cell differentiation and function by regulating TCR signaling pathways, key transcription factors or cytokine-induced signaling pathways. DUBs in the left or right semicircle are negative or positive regulators of T cell-mediated immunity respectively.

function. USP2a positively regulates TCR-induced NF-κB activation and IL-2 production through deSUMOylating TRAF6 and mediating TRAF6-MALT1 interaction [130]. However, USP34 functions as a negative regulator of NF-κB signaling upon TCR engagement, inhibiting the degradation of the NF-κB inhibitor IκBα and NF-κB binding activity to DNA [131]. USP20 suppresses IL-1β- and Tax-induced NF-κB activation, by deubiquitinating TRAF6 and Tax, thus, inhibiting HTLV-1-transformed cell growth [132]. Importantly, USP25 was identified as a negative regulator of IL-17-mediated signaling and inflammation. USP25 knockout mice display enhanced sensitivity to IL-17-mediated inflammation and autoimmunity in vivo. Mechanistically, after IL-17 stimulation, USP25 interacts with TRAF5 and TRAF6, and USP25 facilitates the removal of Act1-mediated K63-linked polyubiquitination of TRAF5 and TRAF6 [133].

15. Important OTUs

Several OTUs, another DUB family, have also been demonstrated to regulate T cell activation, differentiation and function [134]. For example, Otud7b-mediated ZAP70 deubiquitination inhibits the association of ZAP70 with a negative-regulatory phosphatase, Sts1 or Sts2, thereby promoting TCR/CD28-stimulated ZAP70 phosphorylation and activation. Otud7b positively regulates Th1 cell differentiation by facilitating TCR signaling and early induction of IFN-γ [135]. DUBA inhibits Th17 polarization by interacting with and stabilizing UBR5, which mediates ubiquitination and degradation of RORγt [136]. A20 positively regulates CD4 T cell survival through deubiquitination of RIPK3 and mTOR complex 1 (mTORC1) [137,138]. A20 has also been reported to negatively regulate thymic development of Treg cells, by inhibiting the canonical NF-κB member RelA [139]. Moreover, A20 inhibits the activation of dendritic cells (DCs) and maintains the tolerance of self-reactive T cells [140]. However, the roles of A20 in regulating CD8 T cell response are controversial [141,142]. Another OTU family member, Trabid, facilitates TLR-induced expression of IL-12 and IL-23 by deubiquitinating and stabilizing a histone demethylase, Jmjd2b, thereby promoting Th1 and Th17 cell differentiation [143].

16. Conclusion

T cells play critical roles in immune responses to pathogens, autoimmunity, and antitumor immunity. During the past few decades, increasing numbers of studies have demonstrated the significance of protein ubiquitination in T cell-mediated immunity. Several E3 ligases and DUBs have been identified as either positive or negative regulators of T cell development and function, although this review mainly focuses on the roles of DUBs (especially USPs) in this issue. A majority of DUBs modulate T cell development and function by regulating TCR signaling. For instance, CYLD, USP8, USP15, USP18, USP34 and A20 negatively regulate TCR signaling, whereas USP9X, USP12, USP22, USP2a and Otud7b positively modulate TCR signaling. Several DUBs deubiquitinate and stabilize the key transcription factors of T cell lineages, thus modulating T cell subset differentiation and function. To be exact, USP7 and USP21 could deubiquitinate and stabilize FOXP3, thereby positively regulating Treg cell function and immune tolerance. USP4, USP15 and USP17 stabilize RORγt, and promote Th17 cell differentiation and function. *T*-bet in Th1 cells could be stabilized by USP10, while IRF4 in Th2 cells could be stabilized by USP4. DUBA inhibits Th17 differentiation by stabilizing UBR5, which mediates ubiquitination and degradation of RORγt. Some DUBs regulate cytokine-induced signaling pathways, for example, CYLD functions as a negative regulator of TGF-β signaling and Treg cell development, whereas USP25 is a negative regulator of IL-17-mediated signaling and inflammation. Trabid facilitates IL-12 and IL-23 expression, thereby promoting Th1 and Th17 cell differentiation (Fig. 3). The research of the cooperation and antagonism of DUBs in T cells could unveil novel strategies for manipulating T cell function. Further understanding of the mechanisms behind ubiquitination and deubiquitination in T cells will not only expand the knowledge of T cell function regulation, but also provide novel therapeutic strategies for immune diseases such as infection, autoimmune diseases and cancer.

Acknowledgements

Our research is supported by National Science Fund for Distinguished Young Scholars 31525008; National Natural Science Foundation of China 81830051, 81330072, 31370863, NIH-NSFC collaborative grant 81161120417; Shanghai Rising Star program 10QA1407900, Shanghai Academic Research Leader 16XD1403800; SMCST 14JC1406100; the Science and Technology Commission of Shanghai (17DZ2260100).

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