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Review article

Ubiquitination and phosphorylation of the CARD11-BCL10-MALT1 signalosome in T cells

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ABSTRACT

Antigen receptor-induced signaling plays an important role in inflammation and immunity. Formation of a CARD11-BCL10-MALT1 (CBM) signaling complex is a key event in T- and B cell receptor-induced gene expression by regulating NF-κB activation and mRNA stability. Deregulated CARD11, BCL10 or MALT1 expression or CBM signaling have been associated with immunodeficiency, autoimmunity and cancer, indicating that CBM formation and function have to be tightly regulated. Over the past years great progress has been made in deciphering the molecular mechanisms of assembly and disassembly of the CBM complex. In this context, several posttranslational modifications play an indispensable role in regulating CBM function and downstream signal transduction. In this review we summarize how the different CBM components as well as their interplay are regulated by protein ubiquitination and phosphorylation in the context of T cell receptor signaling.

Abbreviations: ABC-DLBCL, activated-B-Cell-like diffuse large B cell lymphoma; ADAP, adhesion and degranulation-promoting adapter protein; AIP, AH receptor-interacting protein; Akt, protein kinase B; AP-1, activator protein 1; API2, apoptosis Inhibitor 2; ATG12, autophagy related 12; BCL10, B-cell lymphoma/leukemia 10; BCR, B cell receptor; BENTA, B cell expansion with NF-κB and T cell anergy; βTRCP, β-transducing repeat-containing protein; BIR, baculoviral inhibitor of apoptosis (IAP)-repeats; BIRC3, baculoviral inhibitor of apoptosis (IAP) repeat-containing 3; CaMK, Ca^{2+}/calmodulin-dependent kinase; CARD, caspase recruitment domain; CARD11, caspase recruitment domain family member 11; Carma, caspase recruitment domain (CARD)-containing MAGUK proteins; Cbl-b, casitas B-lineage lymphoma proto-oncogene-b; CBM, CARD11-BCL10-MALT1 complex; cIAP, cellular inhibitor of apoptosis; CID, combined immunodeficiency; CK1α, casein kinase 1α; CYLD, cylindromatosis; DAG, diacylglycerol; DUB, deubiquitinase; Erk1, extracellular signal-regulated kinase 1; FOXP3, forkhead box P3; GSK3β, glycogen synthase kinase 3 beta; GST, glutathione S-transferase; GUK, guanylate kinase-like; HECT, homologous to the E6AP carboxyl terminus; HOIL-1, heme-oxidized IRP2 ligase-1; HOIP, heme-oxidized IRP2 ligase-1 (HOIL-1)-Interacting Protein; HPK1, hematopoietic progenitor kinase 1; Ig, immunoglobulin; IKK, IκB kinase; IP3, inositol trisphosphate; ITAM, immunoreceptor tyrosine-based activation motif; ITCH, itchy E3 ubiquitin protein ligase; IκBα, inhibitor of NF-κB α; JNK, c-jun *N*-terminal kinase; LAMP1, lysosomal-associated membrane protein 1; LAT, linker for the activation of T cells; LC3, microtubule-associated protein 1A/1B-light chain 3; Lck, lymphocyte cell-specific protein-tyrosine kinase; LUBAC, linear ubiquitin chain assembly complex; MAGUK, membrane-associated guanylate kinase; MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein 1; MAPK, mitogen-associated protein kinase; MHC, major histocompatibility complex; MIB2, mindbomb E3 ubiquitin protein ligase 2; NEDD, neuronal precursor cell-expressed developmentally downregulated; NEMO, NF-κB essential modulator; NF-AT, nuclear factor of activated T cells; NF-κB, nuclear factor-κB; NKT, natural killer T cell; NZF, Npl4 zinc finger domain; p62, sequestosome 1; PDZ, postsynaptic density 95/disc large/zona occludens 1 domain; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol 4,5 bisphosphate; PKC, protein kinase C; PLCγ, phospholipase C; PMA, phorbol 12-myristate 13-acetate; POLKADOTS, punctate and oligomeric killing or activating domains transducing signals; PP2A, protein phosphatase 2; PRD, PKC regulated domain; PTM, posttranslational modification; RIPK2, receptor interacting serine/threonine kinase 2; RNF, ring finger protein; SH3, Src homology 3; SHARPIN, SHANK associated RH domain interactor; SLP-76, Src homology 2 domain-containing leukocyte phosphoprotein of 76 kDa; STUB1, Stress Induced Phosphoprotein 1 (STIP1) homology and U-box containing protein 1; SUMO, Small ubiquitin-like modifier; TAB2/3, TAK1-binding proteins 2 and 3; TAK1, Transforming growth factor beta (TGFβ)-activated kinase 1; TBK1, TRAF Family Member Associated NF-κB Activator (TANK) binding kinase 1; TCR, T cell receptor; TRAF6, tumor necrosis factor (TNF) receptor-associated factor 6; T6BM, TRAF6-binding motif; UBAN, ubiquitin binding in A20 binding inhibitor of NF-κB (ABIN) and NEMO; Ubc13, ubiquitin conjugating enzyme E2N; UBD, ubiquitin binding domain; Uev1A, ubiquitin-conjugating enzyme E2 variant 1; USP, ubiquitin-specific protease; ZAP-70, ζ-associated protein of 70 kDa

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1. Introduction

The immune system is a complex interplay between different cells, tissues and organs, developed to protect the organism from invading threats. As a signaling system, the immune system is facing a unique and interesting challenge in that pathogens typically have much shorter generation times and consequently evolve much faster than their hosts, which means that the immune system needs to be vigilant and responsive to novel threats. At the same time is a poorly regulated immune response detrimental to the organism, which means that an effective negative regulation of immune responses is also important. Physical barriers and the innate immune system serve as the first lines of defense. Conserved components of pathogens are sensed by pattern recognition receptors on cells, which elicit an innate immune response by production of antimicrobial factors and inflammatory mediators. Innate immunity also regulates the recruitment and activation of adaptive immune cells [1]. Adaptive immunity depends on T and B lymphocytes carrying highly specific antigen-recognition receptors, the B cell receptor (BCR) and T cell receptor (TCR). Once activated, B cells produce antibodies against pathogens mediating the humoral immune response. CD4 T cells help B cells in the humoral response, while CD8 T cells and natural killer cells play a role in the cell-mediated immune response to e.g. kill virus infected cells or cancer cells [2].

Immune cell signal transduction needs to be tightly regulated, which highly depends on posttranslational modifications (PTMs). There is a wide range of PTMs like acetylation, lipid conjugations, oxidation, phosphorylation, proteolytic processing, ubiquitination and ubiquitin-like modification, which all can play a direct role in signal transduction, but possibly also serve as "memory" to influence or cross-talk with other signaling events. This complex change in the "epitransduction code" by inducible PTMs is highly interesting, yet very complex to study [3]. Two of the most prominent PTMs that have been studied in signal transduction research are phosphorylation and ubiquitination (Fig. 1). While phosphorylation and de-phosphorylation was long thought to be the predominant on and off switch of protein activity and fate, ubiquitination has emerged over the past decades to be involved in virtually all cellular processes. While the addition of a phosphate group to a substrate protein is a rather straightforward single step mechanism, the covalent attachment of ubiquitin to the side chain of a lysine (K) residue in a target protein requires the concerted action of three different enzymes: an ubiquitin-activating enzyme (E1), an ubiquitin conjugating enzyme (E2), and an ubiquitin ligase enzyme (E3) (Fig. 1). Ubiquitin itself contains seven lysine residues that can also serve as ubiquitin acceptor sites, allowing the formation of structurally different types of polyubiquitin chains (K6, K11, K27, K29, K33, K48 and K63). In addition, a ubiquitin molecule can be attached to the *N*-terminal methionine (M1) of the proximal ubiquitin residue, leading to the formation of linear ubiquitin or M1 chains [4]. Different types of polyubiquitination form a kind of ubiquitin code that is recognized by specific ubiquitin-binding domain (UBD)-containing proteins that mediate downstream signaling. Ubiquitin can also be attached to serine, threonine or cysteine residues, but they are less stable and to date very little is known about these modifications [5]. The ubiquitin code proved to be even more complex when mixed chain types such as M1/K63 and K48/K63 hybrid chains were identified [6,7]. There are also hybrid chains of ubiquitin-like modifications and ubiquitin such as ubiquitin-SUMO or ubiquitin-NEDD8 hybrid conjugates. Furthermore, ubiquitin itself can be subject to PTMs, for example acetylation of its lysine residues or phosphorylation on serine (S), threonine (T) or tyrosine (Y) residues. In particular S65 phosphorylation has been studied extensively in the context of mitophagy [8]. Each of these ubiquitin modifications can alter the charge and surface properties of ubiquitin and can hence dramatically affect signaling outcome. While K48-linked polyubiquitination mainly targets proteins for proteasomal degradation, K63- and M1-linked polyubiquitin chains can regulate protein activity, protein subcellular localization or protein-protein interaction in various signaling pathways [9]. Like phosphorylation, ubiquitination is a rapid and reversible process and can be counteracted by specific deubiquitinating enzymes (DUBs) (Fig. 1).

A large body of evidence demonstrates that TCR signaling is regulated by ubiquitination of various effector molecules. The E2 ubiquitin activating enzyme Ubc13, the only E2 described to regulate K63-linked ubiquitination, has been shown to play a fundamental role in TCR signaling as mice lacking Ubc13 specifically in T cells display severely reduced T cell numbers and defective T cell proliferation [10]. Multiple E3 ubiquitin ligases including Cbl-b, RNF128 and Itch have been

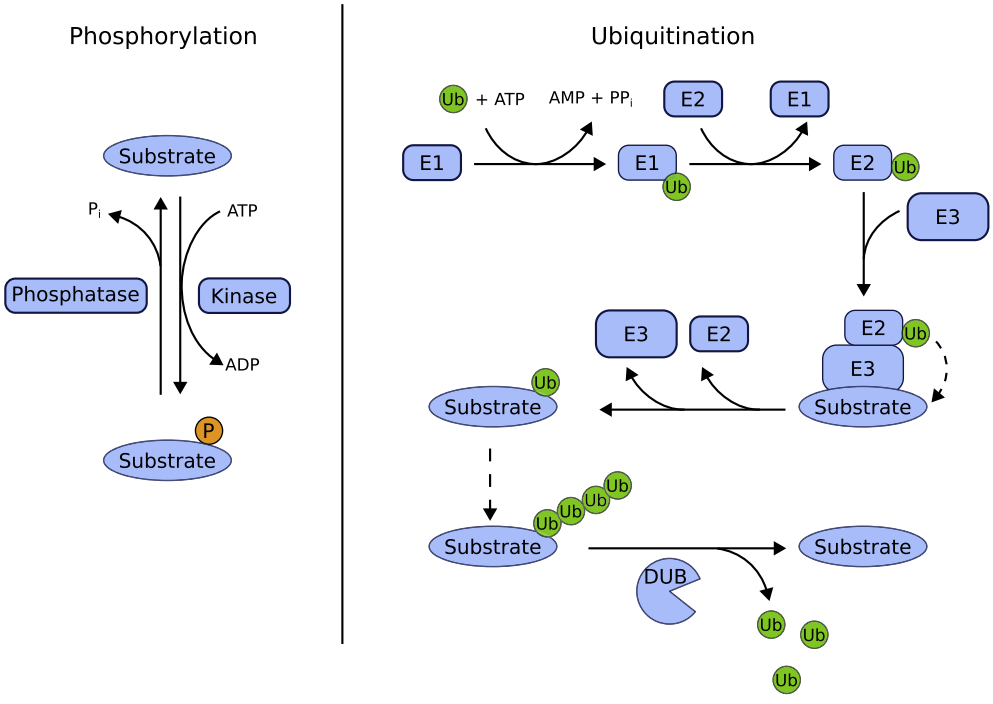

Fig. 1. Comparison of the phosphorylation and ubiquitination machinery. Phosphorylation and ubiquitination are rapid and reversible posttranslational modifications. The attachment of a phosphate group to a substrate occurs in a simple one step reaction facilitated by a kinase and can be counteracted by phosphatases (left). Ubiquitin attachment to a substrate (or to an already attached ubiquitin) depends on the concerted action of ubiquitin activating enzymes (E1), ubiquitin conjugating enzymes E2) and ubiquitin ligases (E3) and can be reversed by deubiquitinases (DUBs) (right).

described to regulate proximal TCR effectors thereby regulating T cell function and preventing autoimmunity [11–14]. Similarly, the DUBs CYLD and A20 were shown to regulate the ubiquitination state of several TCR signaling intermediates and mice deficient in either one show increased T cell proliferation and inflammatory phenotypes [15]. Recently, M1 ubiquitination has emerged as an important regulator of immune and inflammatory signaling. M1 chains are assembled by the linear ubiquitin chain assembly complex (LUBAC), which consists of HOIL-1, HOIP and SHARPIN, with HOIP harboring the E3 ligase activity [16]. Specific deletion of HOIP and HOIL-1 in T cells demonstrates an important role for LUBAC in regulatory T cell development and homeostasis [17] and also patients with HOIP or HOIL-1 loss of function mutations show evidence of T cell defects [18,19]. In this review we will discuss the importance of posttranslational modifications in signal transduction downstream of the TCR, specifically focusing on ubiquitination and phosphorylation of components of the CARD11-BCL10-MALT1 (hereafter referred to as CBM) signaling complex, which plays a central role in a multitude of T lymphocyte functions by regulating TCR-induced signal transduction.

2. T cell receptor signal transduction

TCRs consist of two different subunits, and the combination of subunits is determined early during thymocyte development. Most T cells consist of the highly variable alpha (α) and beta (β) chains, referred to as αβ T cells, and are expressed as part of a complex with the invariant CD3 chain molecules. A minority of T cells express an alternate receptor, formed by variable γ and δ chains, referred to as γδ T cells. Activation of T cells requires both ligation of the TCR by antigen bound to MHC molecules on antigen presenting cells, as well as co-stimulatory molecules, mainly CD28. TCR simulation leads to a conformational change of the receptor chains, rendering the immunoreceptor tyrosine-based activation motifs (ITAMs) in the CD3ζ chain accessible for phosphorylation by tyrosine kinase Lck (Fig. 2). Upon phosphorylation, the ITAMs serve as recruitment platform for tyrosine kinase ZAP-70, which in turn induces a cascade of phosphorylation events, including the phosphorylation of the transmembrane adapter protein LAT and the cytosolic adapter protein SLP-76. This proximal signaling complex results in the activation of PLCγ, which hydrolyzes the membrane lipid PIP2 to form the second messenger molecules IP3 and DAG. IP3 induces the release of calcium from the endoplasmatic reticulum, increasing the intracellular calcium levels, which leads among others to the activation of CaMK as well as the phosphatase Calcineurin. Calcineurin dephosphorylates NF-AT family members rendering them capable of translocating to the nucleus, where they cooperate with other transcription factors e.g. AP-1 or FOXP3 to induce specific transcriptional programs. DAG activates mainly two signaling axes involving Ras and PKC. Ras is important for the activation of serine-threonine kinase Raf-1 resulting in the activation of the MAPKs Erk1 and Erk2. On the other hand DAG binds to PKCθ in T cells, which is required for PKC recruitment to the plasma membrane [20]. PKCθ phosphorylates CARD11, inducing a conformational change to activate CARD11 (see below) [21,22]. Activated CARD11 forms a complex with BCL10 and MALT1 [23]. Next, the E3 ligase TRAF6 is recruited to the CBM complex binding directly to MALT1 via multiple TRAF6-binding motifs (T6BM, see Fig. 3A) [24]. Oligomerization of MALT1/BCL10 activates the E3 ligase activity of associated TRAF6 resulting in auto-ubiquitination, ubiquitination of CBM components as

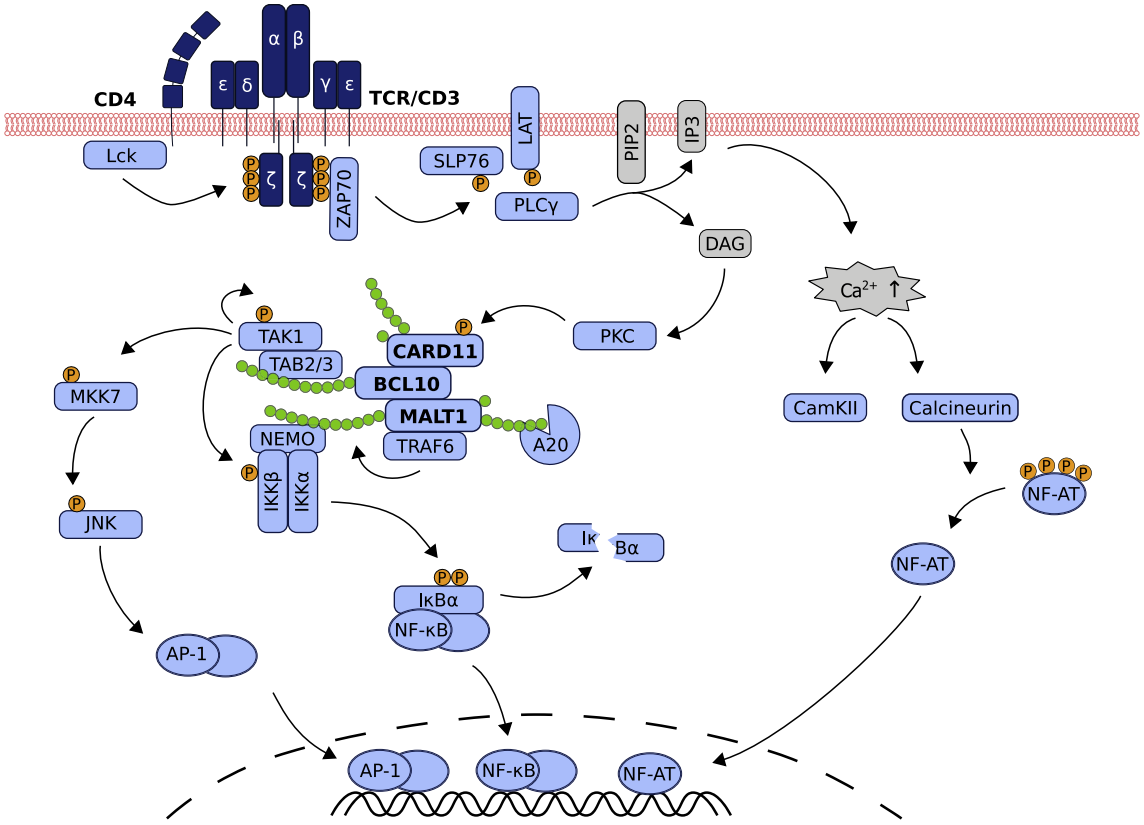

Fig. 2. Schematic representation of the TCR signaling pathway to NF-κB, AP-1 and NF-AT. TCR signaling towards the activation of major transcription factors involves the activation of multiple signaling molecules, including distinct kinases and E3 ubiquitin ligases that regulate specific protein-protein interactions and enzymatic activities. The formation of a CARD11-BCL10-MALT1 (CBM) signaling complex plays a central role in TCR signaling. Green circles depict ubiquitin; only shown for the CBM complex. For more details, see main text.

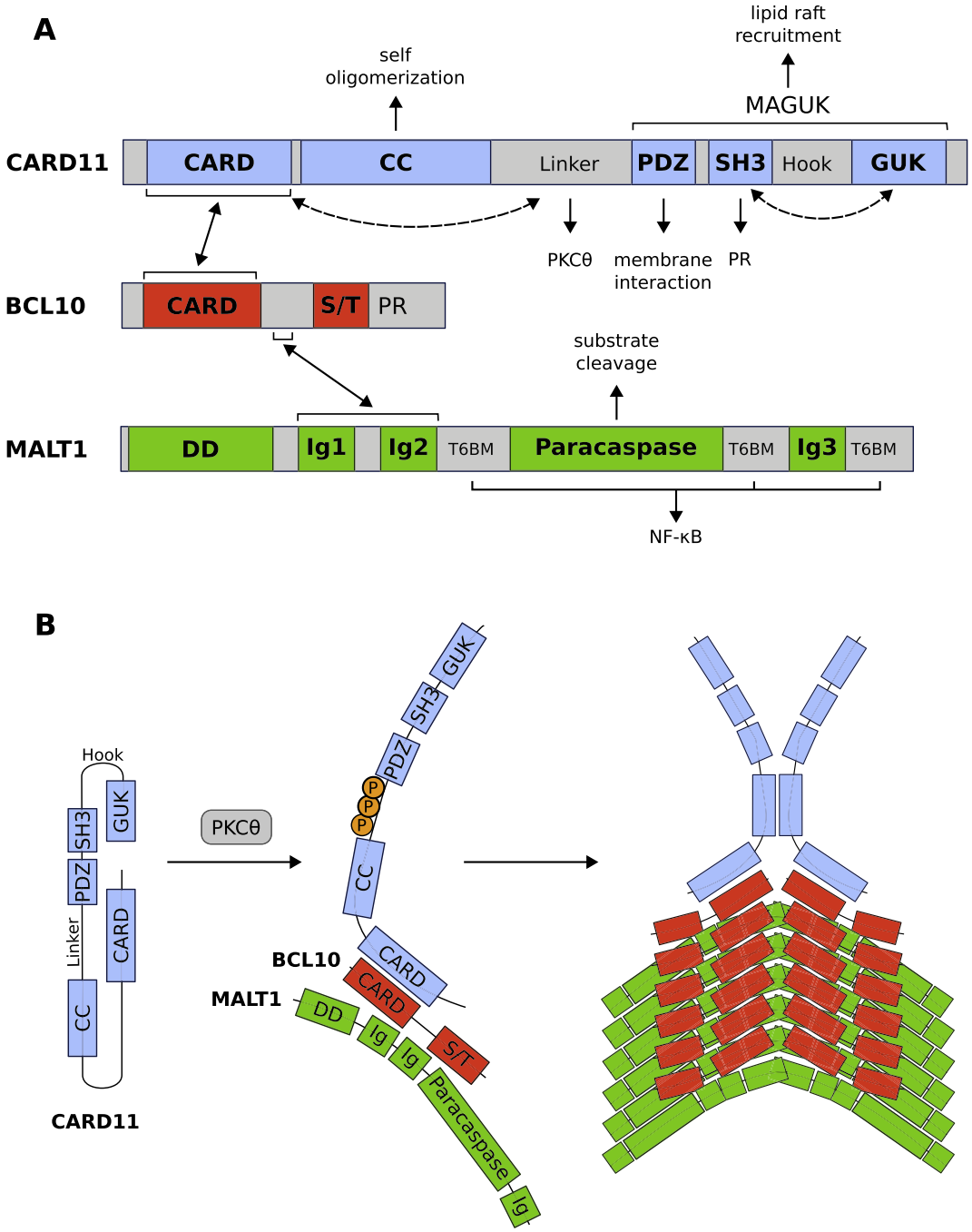

Fig. 3. (A) Schematic representation of domain organization and function in CARD11, BCL10 and MALT1. Arrows indicate inter- and intramolecular interactions and domain functions. CARD, Caspase Recruitment Domain; MAGUK, membrane-associated guanylate kinase; PDZ, postsynaptic density 95/disc large/zona occludens 1 domain; SH3, Src homology 3; GUK, guanylate kinase domain; PR, proline rich; S/T, serine/threonine rich; DD, dead domain; Ig, immunoglobulin-like; T6BM, TRAF6-binding motif. (B) Model of CBM complex formation. In unstimulated cells, CARD11 is auto-inhibited by intramolecular interactions between the CARD domain and the linker region as well as between the GUK and SH3 domains. Upon TCR stimulation, CARD11 gets phosphorylated by PKCθ in the linker region, resulting in an open conformation and CARD11 oligomerization. BCL10, is then recruited to CARD11 via CARD-CARD interactions, and CARD11 nucleates BCL10 filament formation. Because MALT1 is constitutively bound to BCL10, the filament formation brings MALT1 monomers into proximity to promote their dimerization and proteolytic activation.

well as the downstream signaling adapter NEMO [24,25]. The E2 enzyme complex Ubc13–Uev1A is essential for TCR-induced ubiquitination and signal transduction [24]. Interestingly, TRAF6 has been shown to be dispensable for TCR-induced signal transduction, indicating that there might be redundancy with other E3 ligases like TRAF2, Pellino-1 or MIB2 [24,26–28]. On the other hand, the T6BM in MALT1 was proven to be crucial for the MALT1 scaffolding function and TCR-induced signal transduction [29]. The ubiquitin chains serve as docking platforms for downstream signaling complexes that get recruited via UBD-containing proteins. The TAK1-binding proteins TAB2 and TAB3 bind to ubiquitin chains via their NZF domain leading to the recruitment and activation of TAK1, while the IKK complex gets recruited to ubiquitin chains via NEMO's UBAN motif [24,30,31]. TAK1 then phosphorylates IKKβ in its activation loop at S177 and S181, rendering the kinase active [32]. The combined IKKβ phosphorylation and NEMO ubiquitination activate the IKK complex, leading to the phosphorylation

of inhibitor of NF-κB (IκB) α. IκBα phosphorylation renders it prone to K48-linked ubiquitination followed by its proteasomal degradation, which allows NF-κB to translocate to the nucleus [33]. Intriguingly, while CARD11 is essential to regulate NEMO ubiquitination upon TCR stimulation, it was shown that IKKβ can be phosphorylated by TAK1 in a CARD11-independent manner [34]. Next to the activation of the NF-κB pathway, TAK1 also mediates activation of a MAPK cascade resulting in the activation of JNK and translocation of transcription factor AP-1 into the nucleus [32]. In the nucleus, NF-κB and AP-1 regulate the expression of specific genes that mediate e.g. T cell proliferation and survival.

3. The CARD11-BCL10-MALT1 complex

The CARD11-containing CBM complex that is formed in T cells is also formed upon B cell receptor (BCR) stimulation. In fact, there are four related CARD-coiled coil (CC) proteins (CARD9, -10, -11 and 14) in mammals that can form specific CBM complexes in different cell types in response to specific stimuli, and which share a single common ancestor in the first vertebrates [35]. CARD11 (Carma1), CARD14 (Carma2) and CARD10 (Carma3) also contain a MAGUK domain in their C-terminus, and are therefore also termed CARD-containing MAGUK proteins (Carma) [36,37] (Fig. 3A). MAGUK family members are scaffolding proteins that recruit multi-molecular complexes for signaling pathways to the membrane of mammalian cells [38]. They are characterized by a distinct domain structure consisting of one to three PDZ domains, an SH3 domain and a GUK domain in their C-terminus, which are all involved in protein-protein interactions [38] (Fig. 3A). SH3 domains are well characterized for binding to proline-rich motifs, while PDZ domains recognize short motifs in C-termini of proteins [39,40]. CARD11 is constitutively localized to lipid rafts, micro domains in the plasma membrane that are rich in specific lipids and cholesterol, which have been shown to be important for TCR signaling [41,42]. CARD11 likely associates with integral lipid raft components rather than carrying a lipid modification e.g. myristoylation or palmitoylation itself [41]. The PDZ domain of CARD11 might be responsible for the membrane targeting of CARD11, as PDZ domains of other MAGUK proteins have been shown to primarily bind to the cytoplasmatic tails of membrane proteins [38]. Upon TCR stimulation, CARD11 co-localizes with aggregated CD3 [41]. The SH3 and GUK domain have been shown to be particularly important for the formation of CARD11 microclusters at the immunological synapse [43]. In analogy to other MAGUK proteins, it has been proposed that intramolecular interactions between the SH3 and the GUK domain keep CARD11 in a closed conformation. Deletion of the region connecting the SH3 and GUK domain, termed the Hook region, was hypothesized to result in an open conformation, exposing residues for regulatory modifications [44]. CARD11 has a serine/threonine rich linker region connecting the CC and the MAGUK domain (Fig. 3A). As phosphorylation in this region by PKC is crucial for CARD11 activation, it is also referred to as the PKC-regulated domain (PRD) [45]. Deletion of the PRD domain results in a constitutively active CARD11 protein capable of assembling the CBM complex in the absence of stimulation [22]. The CC domain of CARD11 is essential for self-oligomerization and subcellular localization in lipid rafts [46,47]. In resting state, CARD11 is thought to remain in an auto-inhibited conformation that is mediated through multiple intramolecular interactions involving the CARD and CC regions [22] (Fig. 3). Upon TCR-activation, PKCθ phosphorylates CARD11 in the linker region, overcoming the auto-inhibition and making the CARD domain accessible to specifically interact with the CARD domains in BCL10, which is then co-recruited into lipid rafts [21,22,36,37,41]. Binding of several proteins, including ADAP, PKC and AIP, facilitates the open conformation [48–50]. A CARD11 mutant (CARD11 L39R) that does no longer bind BCL10 acts as a dominant negative inhibitor of TCR-induced NF-κB activation [41]. All four CARD-CC proteins seem to be regulated in the same way, since deletion of the sequence downstream of the CC domain results in spontaneous activation for all of them [35].

Human BCL10 is a 233 amino acid protein containing an *N*-terminal CARD domain as well as a C-terminal serine/threonine (S/T) rich region [51] (Fig. 3A). TCR stimulation induces CARD-mediated binding of BCL10 to CARD11 and redistribution of BCL10 to clustered TCR complexes at the immunological synapse [41,52]. More specifically, BCL10 has been shown to form punctate cytoplasmatic structures upon antigen stimulation, which were termed punctate and oligomeric killing or activating domains transducing signals (POLKADOTS) [53]. Interestingly, sequence alignment of BCL10 from species ranging from human to corals reveals a highly conserved but not yet annotated proline rich (PR) region between residues 193 and 205 [35] (Fig. 3A). PR regions, especially when adopting a left-handed polyproline 2 conformation, serve as binding platforms for SH3 domain containing proteins [54]. As CARD11 carries an SH3 domain in its C-terminus, there might be a role for PR-SH3 interaction in supporting or stabilizing the BCL10-CARD11 interaction. BCL10 is constitutively associated with MALT1, which is dependent on a region spanning amino acids 107–119 in BCL10, and mediates the recruitment of MALT1 to CARD11, thus forming the CBM complex [55–58].

MALT1 (PCASP1) is a type 1 paracaspase, which is characterized by a predicted death domain (DD) with unknown function followed by two Ig-like domains, a paracaspase domain that shares homology with caspases and metacaspases [58], and a third Ig-like domain at its C-terminus followed by an unstructured sequence [59] (Fig. 3A). The first two Ig-like domains in MALT1 are responsible for its interaction with BCL10 [56]. It was further shown that BCL10 and MALT1 oligomerize to higher order molecular weight complexes, which is crucial to transmit downstream signaling [24] (Fig. 3B). Recent structural data show that the CBM complex is a supermolecular filamentous complex, in which CARD11 nucleates BCL10 polymerization and filament formation [60], the assembly of which is unidirectional [61]. This nucleation process is a mechanism in which the initial signal is amplified, so that only minimal amounts of activated CARD11 are needed to activate a large number of BCL10 molecules. MALT1 has been shown to recruit the E3 ligase TRAF6 to the CBM complex via TRAF6-binding motifs, and the oligomerization of TRAF6 is thought to activate its E3 ligase activity [24,62]. Next to this role of MALT1 as a scaffold integrating signal transduction from the TCR to downstream activation of NF-κB and MAPKs, MALT1 also has proteolytic activity via its paracaspase domain. Dimerization of the MALT1 paracaspase domain has been shown to be necessary for its proteolytic activity [63,64]. This is believed to be enabled by the formation of the above mentioned BCL10 filaments, which brings MALT1 monomers in proximity (Fig. 3B). Since the discovery of MALT1 catalytic activity, a limited number of substrates have been discovered [65]. These include, among others, negative regulators of NF-κB and AP-1 activation (A20 and CYLD) and mRNA destabilizing proteins (Roquin-1, -2, Regnase 1), whose cleavage results in the fine-tuning of gene expression [66–69].

4. Physiological roles of the CBM complex

Depletion of CARD11, BCL10 or MALT1 in cells or mice has demonstrated that all three CBM components are indispensable for TCR-induced signaling, T cell activation and survival.

CARD11 was first shown to be crucial for TCR signal transduction to NF-κB in the Jurkat T cell line [41,70,71]. More specifically, the CARD11 deficient Jurkat T cell clone JPM50.6 showed defective TCR-induced NF-κB activation and consequent IL-2 production, which could be fully rescued by reconstitution with CARD11 [71]. Mice lacking CARD11 show mild defects in T cell development (increased CD4/CD8 double negative (DN) T cells in DN3-DN4 stage, increased DN cell apoptosis), reduced numbers of peritoneal $CD5^{+}B220^{+}$ B1 cells and reduced basal serum immunoglobulin [52]. CARD11 knockout mice generated independently by another group show a complete absence of

peritoneal B1 cells, as well as defective natural killer cell differentiation [43]. Though, no or only mild defects in T cell development were observed in both CARD11 deficient mouse strains, both show severely reduced activation and proliferation of mature T cells induced by anti-CD3/CD28 *ex vivo* [43,52]. This is mainly due to reduced IL-2 production, as proliferation can be restored by adding exogenous IL-2. Furthermore, NF-κB and JNK activation following antigen receptor stimulation is drastically reduced in CARD11-deficient cells and BCL10 is not able to translocate to the immunological synapse. CARD11 knockout mice are no longer able to elicit an immune response when challenged with ovalbumin [43].

Similar to CARD11 knockout mice, BCL10 knockout mice are markedly immune-deficient with reduced basal levels of serum IgGs and increased susceptibility to viral infection [72]. BCL10-deficient lymphocytes show decreased antigen receptor-induced activation and proliferation and fail to activate NF-κB. One third of BCL10 knockout embryos die prematurely due to a neural tube closure defect, demonstrating an additional role for BCL10 in central nervous system development.

Mice lacking MALT1 are viable and fertile with normal B and T cell development, but premature maturation of DN thymocytes similar to BCL10 knockout mice [73,74]. Remarkably, marginal zone B cells are severely reduced and germinal center B cells are completely absent in MALT1 knockout mice. While T cell numbers in spleen and lymph nodes are comparable to wild type mice, MALT1 knockout mice have fewer activated T cells in the periphery and mature T cells show defective proliferation and reduced IL-2 production in response to anti-CD3/CD28 or PMA/ionomycin treatment *ex vivo*. This is reflected in decreased TCR-induced NF-κB and JNK activation, but intact ERK activation in response to TCR stimulation [73–76]. The importance of MALT1 to mount a productive immune response is shown by a reduced IgM and IgG1 antibody response after immunization with ovalbumin or keyhole limpet haemocyanin in the absence of MALT1. Furthermore, MALT1 was shown to be important for regulatory T cell development and Th17 differentiation [77]. Importantly, a T cell intrinsic role for MALT1 in eliciting an adaptive immune response was recently demonstrated by the generation of T cell specific MALT1 knockout mice, which become susceptible to an otherwise avirulent live attenuated rabies virus vaccine strain [78]. To specifically study the role of MALT1 catalytic activity, leaving its scaffold function intact, several groups have generated knock-in mice expressing a catalytically inactive MALT1 (C472A) protein (referred to as MALT1-PD (protease dead)) [75,76,79,80]. Although less pronounced, MALT1-PD mice mimic the phenotype of MALT1 knockout mice. However, in contrast to MALT1 knockout mice, MALT1-PD mice spontaneously develop autoimmunity in multiple organs accompanied by increased numbers of infiltrating lymphocytes. This inflammatory phenotype is caused by the absence of regulatory T cells, resulting in increased numbers of effector T cells. Of note, pharmacological inhibition of MALT1 does not lead to a reduction in regulatory T cells and autoimmunity, which might reflect temporal or quantitative differences between genetic and pharmacological MALT1 inhibition [81].

In humans several chromosomal translocations of CBM components have been identified in MALT lymphoma [82]. The *MALT1* gene was originally identified as break point resulting in the constitutively active API2-MALT1 chimeric protein, which is composed of the BIR domains of cIAP2 (also known as BIRC3 or API2) fused to the C-terminus of MALT1 upstream of the caspase-like domain. Another translocation brings the *BCL10* and *MALT1* genes under control of the Ig heavy chain enhancer, resulting in deregulated expression and NF-κB activation. Constitutive CBM signaling caused by gain-of-function mutations in CARD11 or upstream regulators is characteristic for activated-B-cell-like diffuse large B cell lymphoma (ABC DLBCL) [83]. Loss-of-function mutations in CARD11 or MALT1 have been associated with combined immunodeficiency (CID) in patients [84]. Gain-of-function CARD11 mutations are linked to B cell expansion with NF-κB and T cell Anergy (BENTA) disease, which is characterized by polyclonal B cell lymphocytosis and mild immunodeficiency [84].

Given the important role of CARD11, BCL10 and MALT1 in T cell mediated immune responses, their activity needs to be strictly controlled. Specific phosphorylation and ubiquitination events are positively or negatively regulating CBM complex formation and recruitment of downstream signaling effectors, or target CBM components for degradation. Below, we give a detailed overview of the occurrence and functional role of ubiquitination and phosphorylation of the different CBM components.

5. CARD11

5.1. CARD11 ubiquitination

CARD11 protein turnover upon TCR or BCR stimulation was shown to be regulated by K48-linked ubiquitination, which could be facilitated by co-expression with cIAP2 and to a lesser extent NEDD4 [44] (Fig. 4/Table 1). However, in this study depletion of cIAPs using a cIAP antagonist did not abolish CARD11 degradation *in vivo*, suggesting redundancy with other E3 ligases. CARD11 ubiquitination is abolished when all 29 lysines in the MAGUK domain are mutated to arginine and is accompanied by reduced CARD11 turnover. In agreement, expression of such a ubiquitination defective CARD11 mutant led to increased basal and PMA/ionomycin induced NF-κB and JNK activation. Interestingly, CARD11 lacking the PKC-regulated domain (CARD11 deltaPRD), which is constitutively active, was found to be constitutively K48-ubiquitinated and degraded [44]. The authors proposed a model in which inactive CARD11 remains in a closed conformation, while stimulation leads to the phosphorylation of CARD11 (see below) resulting in an open conformation – mimicked by deletion of the PRD – rendering the lysines in the MAGUK domain accessible for ubiquitination.

CARD11 has been reported to be monoubiquitinated by the E3 ligase Cbl-b in natural killer T (NKT) cells, which was shown to inhibit its interaction with BCL10 [85]. In this context, Cbl-b ligase activity was found to be important for NKT cell anergy induction. Cbl-b has also been shown to regulate T cell activation and tolerance by targeting multiple proximal TCR effector signaling proteins, adding another level of fine-tuning to the Cbl-b mediated regulation of TCR signaling [86].

In addition to the above mentioned negative regulatory role of CARD11 ubiquitination, CARD11 ubiquitination can also have a positive effect. The E3 ligase STUB1 directly interacts with and modifies CARD11 with K27-linked ubiquitin [87]. This interaction and ubiquitination is dependent on CARD11 PDZ and SH3 domains and mutation of specific lysines in this region, in particular K689 and K696, leads to a mild decrease of CARD11 ubiquitination and NF-κB activation upon CARD11 overexpression. On the other hand, knockdown of STUB1 leads to a pronounced decrease in PMA/Ionomycin-induced CARD11 ubiquitination as well as NF-κB activation and IL-2 production in Jurkat T cells [87]. Therefore, it is likely that multiple sites serve as ubiquitin acceptor sites and that combined mutation of all sites would be needed to fully recapitulate the effect of STUB1 depletion. Alternatively, it cannot be excluded that STUB1 has additional substrates that play an essential role in TCR mediated signaling. K27-linked ubiquitin is one of the least characterized ubiquitin modifications and to date only few specific K27 binding proteins have been described. Therefore it will be of particular interest to identify how and by which proteins K27-linked ubiquitination is recognized, and what its importance for immune signaling is. Interestingly, also the IKK adaptor protein NEMO has been shown to be K27-ubiquitinated in the context of innate immune signaling resulting in context-dependent NF-κB activation or inhibition [88,89].

In a proteomic approach to identify M1-ubiquitinated proteins in response to BCR signaling, CARD11 has been shown to co-purify with the GST-tagged UBAN domain of NEMO, which was used to specifically pull down M1-ubiquitinated proteins [90]. However, when repeated

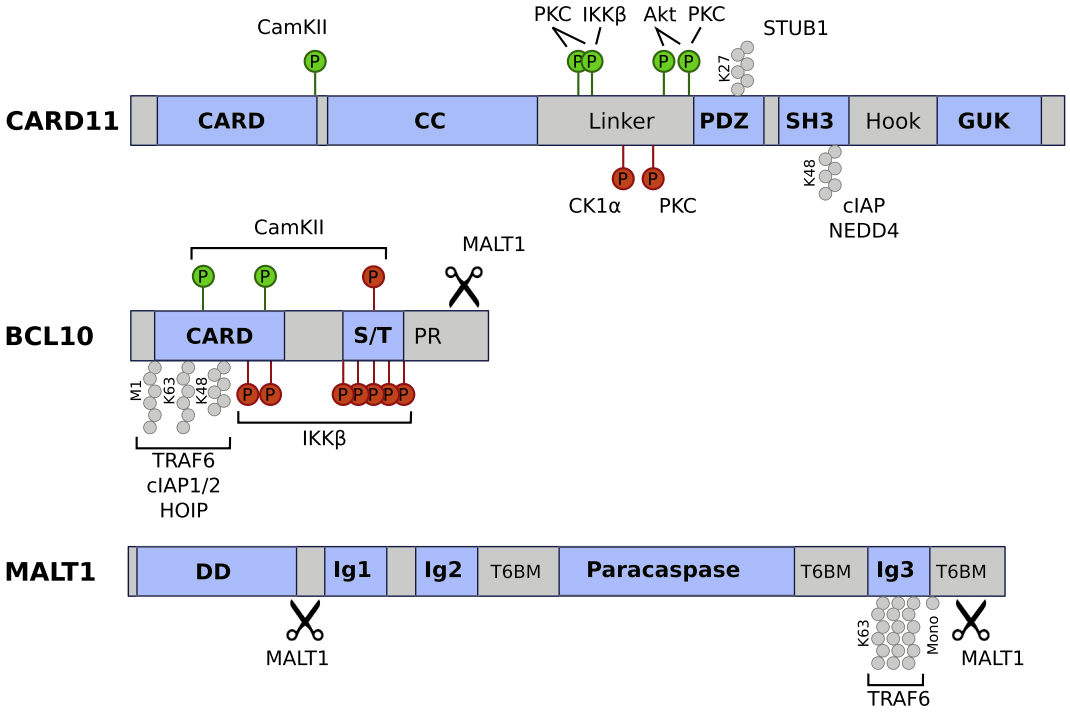

Fig. 4. Overview of known ubiquitination and phosphorylation events of CARD11, BCL10 and MALT1. Activating phosphorylation is indicated with green circles and inhibitory phosphorylation with red circles. Different types of polyubiquitin chains are indicated as strings of grey circles. Kinases and E3 ubiquitin ligases that have been shown to be responsible for the indicated phosphorylation and ubiquitination, respectively, are also depicted. Cleavage sites for MALT1 are indicated by scissors. The exact phosphorylation and ubiquitination sites and the corresponding functional effects can be found in Tables 1–5.

Table 1
CARD11 ubiquitination sites, E3 ligases involved, context and function. nd: not determined.

Chain type	Position	Context	E3 ligase	Functional effect	Ref
Mono	nd	Ionomycin + TCR-crosslinking (NKT cells), co-expression with Cbl-B (HEK293)	Cbl-B	Inhibition of CARD11-BCL10 interaction	[85]
K48	29 Ks in MAGUK domain	TCR/BCR-crosslinking or PMA/ionomycin (cell lines and primary B and T cells), co-expression of CARD11 ΔPRD (HEK293)	cIAP2, NEDD4	Proteasomal degradation of CARD11	[44]
K27	K689, K696	PMA/ionomycin (Jurkat)	STUB1	NF-κB activation and IL-2 production	[87]

under more stringent washing conditions, CARD11 could not be detected, indicating that not CARD11 itself but interacting proteins (e.g. BCL10, see below) are M1-ubiquitinated.

5.2. CARD11 phosphorylation

A number of CARD11 phosphorylation events by several kinases have been proven essential for TCR-mediated signal transduction. Most identified phosphorylation sites are located in the linker region, also termed PKC-regulated-domain (PRD) (Fig. 4/Table 2), and phosphorylation at these residues was shown to result in a conformational change of CARD11. In resting cells, CARD11 intramolecular interactions between the linker and CARD-CC domain keep CARD11 in an auto-inhibited conformation preventing the CARD11 CARD domain to interact with BCL10 CARD domains. Phosphorylation of S552 and S645 in the linker region reduces its affinity for binding to CARD-CC *in vitro*, releasing auto-inhibition [22]. Mutation of one of the critical phospho acceptor sites of CARD11 in chicken DT40 cells (S668, corresponding to S645 in humans) abolishes CBM complex formation [91], indicating that this critical phosphorylation site has been conserved at least as far back as the last common ancestor of mammals and dinosaurs. CARD11 in its open confirmation facilitates assembly of the IKK signalosome and its recruitment to lipid rafts, resulting in NF-κB activation [22]. In agreement, cells expressing a CARD11 mutant lacking the linker region show constitutive CARD11 membrane localization and NF-κB activation [22]. PKCs were proposed as the predominant kinases mediating CARD11 phosphorylation and activation [21,22,91–93], but other kinases are involved as well (Fig. 4/Table 2). Akt, a kinase activated downstream of PI3K, was shown to phosphorylate CARD11 at S637 and S645, which positively regulates TCR-induced NF-κB activation and IL-2 production [94]. HPK1 can phosphorylate CARD11 S549 and S551, with S551 emerging as the critical residue for HPK1-mediated T cell activation [92]. However, HPK1 is likely a modulator rather than an indispensable trigger for TCR-mediated signal transduction, as HPK1 phosphorylation sites are not conserved as far back as chicken. It was further shown that IKKβ, a kinase downstream of the CBM complex, phosphorylates CARD11 at S555, thereby enhancing CBM assembly and thus resulting in a positive feed-forward mechanism [91]. Mathematical modeling revealed a switch-like mechanism for NF-κB activation, in which IKK activity is regulated by the positive feedback from IKKβ [95]. While most phosphorylation sites in CARD11 are restricted to the linker region, CamKII phosphorylates CARD11 at S109 between the CARD and CC domains, contributing to BCL10 interaction and NF-κB activation [96]. Interestingly, CARD11 phosphorylation is counteracted

Table 2
CARD11 phosphorylation sites, kinases involved, context and function. Phosphorylation sites in human CARD11 are based on the short splice variant. Experimentally determined sites are indicated in bold; sites indicated in italics refer to the corresponding sites in mouse and chicken found by sequence alignment. nd: not determined, nc: residue not conserved. A questionmark indicates that controversial results have been reported.

Phosphorylation site			Kinase	Context	Functional effect	Ref
Human	Mouse	Chicken				
S109	*S116*	*S118*	CamKIIγ	TCR-crosslinking (Jurkat), *in vitro* kinase assay	Interaction of CARD11 with BCL10; NF-κB activation	[96]
S110	*S117*	**T119**	nd	BCR-crosslinking (DT40)	NF-κB and JNK activation	[91]
S549	*S561*	nc	HPK1	TCR-crosslinking (Jurkat)	nd	[92]
S551	*S563*	nc	HPK1, Akt	TCR-crosslinking (Jurkat), *in vitro* kinase assay with Akt	NF-κB activation and IL-2 production?	[92,94]
S552	**S564**	*S575*	PKCβ/θ	BCR-crosslinking (B cell lines), PMA/anti-CD28 (Jurkat) or PMA/Ionomycin (DT40), co-expression with active PKCθ, *in vitro* kinase assay with PKCθ	Conformational change releasing CARD11 auto-inhibition; recruitment of BCL10 and NEMO into lipid rafts, assembly and activation if the IKK complex, NF-κB/JNK activation	[21,22,92,93]
S555	*S567*	**S578**	PKCθ, IKKβ	PMA/anti-CD28 (Jurkat), BCR-crosslinking (DT40), active PKCθ co-expression (HEK293), *in vitro* kinase assay	MALT and BCL10 recruitment and NF-κB/JNK activation	[21,91,92,95]
S565	*S577*	*S588*	nd	PMA/anti-CD28 (Jurkat), active PKCθ co-expression (HEK293), *in vitro* kinase assay	NF-κB activation	[21]
S637	*S649*	*S660*	Akt	TCR-crosslinking (Jurkat), *in vitro* kinase assay	NF-κB activation and IL-2 production	[94]
S645	**S657**	**S668**	PKCβ/θ, Akt	PMA/anti-CD28 (Jurkat), BCR/TCR crosslinking (B and T cell lines, primary T cells), active PKCθ co-expression (HEK293), *in vitro* kinase assay	Conformational change releasing CARD11 auto-inhibition; NF-κB/JNK activation and IL-2 production; counteracted by PP2A	[21,22,91,93,94,97]
S608	*S620*	*S631*	CK1α	co-expression with CK1α (HEK293)	Negative regulation of CARD11-mediated NF-κB activation	[98]
S637	**S649**	*S660*	PKCβ/θ, novel PKCs	PMA/ionomycin or BCR/TCR-crosslinking (B and T cell lines), *in vitro* kinase assay	Negative regulation of CARD11-mediated NF-κB/JNK activation?	[22,93]

by the phosphatase PP2A [97]. By dephosphorylating CARD11 at S645, PP2A negatively regulates TCR-induced CBM complex formation and NF-κB activation. PP2A is constitutively associated with CARD11, indicating that it also prevents CARD11 phosphorylation in the absence of stimuli to prevent chronic T cell activation.

Distinct phosphorylation events have also been shown to negatively regulate CARD11-mediated signal transduction. Interestingly, this occurs with different kinetics than the activating phosphorylation [93]. While initial phosphorylation at S552 and S645 by PKCs and other kinases occurs rapidly and transitory, peaking within 5 min after antigen receptor stimulation, there is a second wave of PKC-dependent phosphorylation targeting S649 in mouse CARD11 (S637 in humans) between 15 and 60 min post stimulation [93]. Mutation of this serine residue to alanine leads to increased antigen receptor-induced NF-κB and JNK activation, demonstrating that phosphorylation at S649 negatively regulates CARD11 activation. Using PKC inhibitors and knockout cells it was shown that this phosphorylation was partially dependent on PKCβ, but also novel PKCs were shown to contribute to the phosphorylation. CK1α was proposed as a bifunctional modulator of CBM-induced NF-κB activation [98]. On the one hand, CK1α associates with the CBM complex where it exerts a kind of scaffold function, augmenting TCR-induced NF-κB activation and cytokine production. On the other hand, CK1α kinase activity results in CARD11 phosphorylation at S608, which impairs its NF-κB activating capacity.

6. BCL10

6.1. BCL10 ubiquitination

BCL10 was shown to be heavily decorated with different kinds of ubiquitin chains upon antigen receptor stimulation, resulting either in downstream signal transduction or degradation of BCL10 to terminate signaling (Fig. 4/Table 3).

Attachment of K63-linked ubiquitin to BCL10 in response to TCR stimulation facilitates recruitment of NEMO to the CBM complex [99], which is dependent on the NEMO ubiquitin binding domain since the ubiquitin binding deficient NEMO (L329P) mutant no longer binds BCL10. Residues K31 and K63 in BCL10 serve as ubiquitin acceptor sites and their mutation to arginine abolishes PMA/ionomycin-induced BCL10 ubiquitination and NEMO interaction. Finally, BCL10 ubiquitination at these residues was found to be crucial for TCR-induced NF-κB activation. Interestingly, BCL10 ubiquitination is dependent on MALT1 and CARD11, indicating that a fully assembled CBM complex is necessary for BCL10 ubiquitination. Although not yet shown, recruitment of the E3 ligase TRAF6 via MALT1's T6BM might contribute to BCL10 ubiquitination.

Next to K63-linked ubiquitination, BCL10 has also been shown to be M1-ubiquitinated upon TCR and BCR stimulation as well as in ABC-DLBCL cell lines, which are characterized by constitutive BCR signaling [90,100,101]. M1-ubiquitination is dependent on HOIP, the catalytic subunit of LUBAC. BCR-induced M1-ubiquitination of BCL10 was shown to also depend on the K63-specific E3 ligase TRAF6 [90]. K63-linked ubiquitin chains likely serve as a docking platform for LUBAC recruitment, which then in turn attaches M1-linked ubiquitin to BCL10 and NEMO. In line, M1 ubiquitination in ABC-DLBCL cell lines was shown to be preceded by cIAP1/2-dependent K63-linked ubiquitination of BCL10 and cIAP1/2 auto-ubiquitination [100]. *In vitro* deubiquitination using chain-specific deubiquitinases further demonstrated that BCL10 is modified with both, K63- and M1-linked ubiquitin chains [90]. Next to the above described K63-ubiquitinated lysine residues, K31 and K63, K17 was shown to be an important ubiquitin acceptor site, whose ubiquitination was again dependent on both CARD11 and MALT1 [101]. Similar to K63-linked ubiquitination, M1-ubiquitination of BCL10 is important for NEMO recruitment and downstream NF-κB activation. Mutation of any of the three critical lysine residues diminished TCR-induced NF-κB activation [101], while expression of a M1-

Table 3
BC10 ubiquitination sites, E3 ligases involved, context and function. nd: not determined.

Chain type	Position	Context	E3 ligase	Functional effect	Ref
nd	nd	TCR-crosslinking or PMA/ionomycin (Jurkat, primary human T cells), co-expression with cIAP2, API2-MALT1, NEDD4, ITCH, β-TrCP (HEK293), *in vitro* ubiquitination by cIAP2	cIAP2, NEDD4, ITCH, β-TrCP, others?	BCL10 degradation (proteasomal/lysosomal); negative regulation of NF-κB activation and IL-2 production; preceded by BCL10 phosphorylation (S138; T81/S85)	[102–106,109,110,126]
K48	nd	TCR-crosslinking (Jurkat, primary T cells), *in vitro* ubiquitination by RNF181	RNF181, others?	BCL10 degradation (proteasomal/lysosomal); counteracted by deubiquitinase USP9X	[99,107,111]
K63	K31, K63	TCR-crosslinking or PMA/ionomycin (T cell lines), co-expression with oncogenic CARD11 mutants	nd	NEMO recruitment and NF-κB activation; p62-dependent recruitment to autophagosomes	[99,108,131]
K63, M1	K31, K63	ABC DLBCL cell lines (constitutively active)	dependent on cIAP1/2	Constitutive NEMO association; NF-κB activation and ABC DLBCL survival	[100]
M1	K17, K31, K63	TCR and BCR-crosslinking (Jurkat, A20 B cells), co-expression with oncogenic CARD11 mutants	HOIP (dependent on TRAF6)	NEMO recruitment and NF-κB activation	[90,101]

Ub/BCL10 fusion protein led to higher NF-κB activation compared to expression of wild type BCL10 [90]. Interestingly, neither mutation of each of the ubiquitin acceptor sites separately, nor HOIP depletion completely abolished NF-κB activation, indicating that there might be redundancy between multiple ubiquitination sites, different types of ubiquitin chains and different E3 ligases [101].

Removal of BCL10 by degradation is important to terminate sustained CBM signaling in activated T cells [102,103]. Both, proteasomal and lysosomal pathways have been proposed to be responsible for BCL10 degradation. Lobry et al showed that BCL10 degradation in response to TCR stimulation is prevented by the proteasome inhibitor ALLN [104], while other groups found no or only a partial effect on BCL10 degradation when using proteasome inhibitors ALLN or MG-132 [105,106]. K48-linked ubiquitination of BCL10, which is indicative for proteasomal degradation, has been shown by several groups [99,107]. K48-linked ubiquitination of K31 and K63 occurs at later time points compared to K63-linked ubiquitination (K63 ubiquitination after 5 min, K48 ubiquitination after 20 min) [99]. On the other hand, TCR stimulation leads to co-localization of BCL10 with lysosomal vesicles, as shown by co-staining with cathepsin B and LAMP1, markers for late endosomal and lysosomal vesicles, indicating a role for lysosomal degradation [105]. Another report shows colocalization of BCL10 with LAMP1 as well as the autophagosomal markers LC3 and ATG12 on the above described POLKADOTS [108]. Furthermore, inhibition of lysosomal peptidases stabilizes BCL10 [109]. The autophagy receptor p62 acts as an adapter to bridge K63-ubiquitinated BCL10 to LC3 and autophagosomes. p62 was also shown to be necessary for TCR-induced NF-κB activation, giving it a dual role in the propagation and termination of signal transduction, respectively. Interestingly, MALT1 was neither associated with autophagosomes nor degraded, though to be constitutively associated with BCL10, indicating a highly selective mechanism targeting BCL10 for degradation [108]. Since proteasome as well as autophagy inhibitors only partially inhibit BCL10 degradation, it is likely that both processes contribute to BCL10 removal [108]. Interestingly, similar to IκBα degradation, BCL10 degradation is preceded by phosphorylation [104,106]. Zeng et al. showed that phosphorylation of BCL10 at S138 is important for its ubiquitination, while Lobry at al. demonstrated that IKK-dependent phosphorylation at T81 and S85 is important for recruitment of the E3 ligase βTRCP. Several other E3 ligases have been implicated in the degradative ubiquitination of BCL10. The HECT type E3 ligases NEDD4 and ITCH were able to ubiquitinate BCL10 upon co-expression in HEK293 cells [105], and PMA/ionomycin-induced BCL10 degradation is delayed in ITCH-deficient primary T cells [110]. Of interest, the kinase TAK1, independently of its kinase activity, was proposed to serve as an adapter that recruits NEDD4 and ITCH to BCL10 [110]. The E3 ligase cIAP2 was also shown to ubiquitinate BCL10 upon co-expression in HEK293 cells as well as *in vitro*, and ectopic expression of cIAP2, but not its E3 ligase-deficient counterpart, led to augmented TCR-induced BCL10 degradation in primary human T cells [102,103]. However, another report shows that depletion of cIAPs using the SMAC-mimetic BV6 does not affect BCL10 degradation in B cells [110]. While the aforementioned E3 ligases seem to regulate BCL10 stability upon stimulation as a kind of negative feedback loop, RNF181 K48-ubiquitinates BCL10 under basal conditions, limiting the amount of available BCL10 to form CBM complexes upon antigen receptor stimulation [111]. Taken together, it is evident that multiple E3 ligases and protein destructing mechanisms (lysosomal/proteasomal degradation) are employed by cells to ensure efficient control and termination of aberrant signaling.

For completeness, it should be mentioned that the E3 ligase MIB2 was shown to directly interact with BCL10 in PMA/ionomycin-stimulated primary thymocytes and to contribute to BCL10-mediated NF-κB activation, adding MIB2 to the list of potential E3 ligases responsible for BCL10 ubiquitination [28].

BCL10 ubiquitination was found to be counteracted by the deubiquitinase USP9X, adding another level of fine-tuning to CBM-dependent

signal transduction [107]. Knockdown of USP9X led to CBM complex destabilization and increased BCL10 degradation, and knockout mouse models showed the importance of this deubiquitinase for T cell proliferation.

Remarkably, partially overlapping ubiquitin acceptor sites (K31 and K63) have been identified for K63- and K48-linked ubiquitination of BCL10. It would be of great interest to determine how this is practically regulated, e.g. if distinct BCL10 molecules are either K63- or K48-ubiquitinated. It could also be, in analogy to RIPK1 in TNF-mediated signaling, that BCL10 is first K48-ubiquitinated, then deubiquitinated followed by attachment of K63-linked ubiquitin chains [112]. This is supported by the identification of USP9X as a deubiquitinating enzyme for BCL10, but there might be additional DUBs involved. Furthermore, it would be interesting to determine how the recruitment and interplay of different E3 ligases and DUBs is regulated.

6.2. BCL10 phosphorylation

Numerous reports show the importance of BCL10 phosphorylation for TCR-induced signaling to NF-κB (Fig. 4/Table 4). First indications for BCL10 phosphorylation came from the observation that co-expression of BCL10 with CARD11, CARD14 or PKCθ in HEK293 cells results in a mobility shift of BCL10 in SDS polyacrylamide gel electrophoresis, which could be reversed by phosphatase treatment [36,37,53,71]. The slower migrating bands ranged from 34 to 38 kDa for the hyper-phosphorylated forms, while 30 kDa corresponds to the non-phosphorylated form of BCL10. The first kinase proposed to be responsible for BCL10 phosphorylation was RIPK2, which was found to directly associate with BCL10 [73]. RIPK2 induces BCL10 phosphorylation upon co-expression, while RIPK2 depletion abolished BCL10 phosphorylation. In addition, T cells from RIPK2-deficient mice showed impaired TCR-induced NF-κB activation, IL-2 production and proliferation *ex vivo*, indicating a positive regulatory effect of RIPK2-dependent phosphorylation. In contrast, phosphorylation of BCL10 by the downstream kinase IKKβ in a serine cluster comprising S134, S136, S138, S141, S144, was shown to disrupt BCL10/MALT1 association and NEMO ubiquitination, and hence to negatively regulate NF-κB activation and cytokine production [113]. As discussed above, phosphorylation of T81 and T85 by IKKβ, as well as phosphorylation at S138 by a non-determined kinase, were shown to precede ubiquitination and degradation of BCL10, thus terminating signal transduction [104,106]. This gives IKKβ a dual role in TCR signaling, initially promoting CBM complex formation (maybe by CARD11 phosphorylation) as well as downstream signal transduction by phosphorylation of IκBα, and subsequently terminating signaling by phosphorylating BCL10 [113]. One of these critical serine residues, S138, was additionally found to be phosphorylated by CamKII, resulting in reduced NF-κB activation, likely due to dissociation of MALT1 and BCL10 [114]. CamKII was previously shown to redistribute to the immune synapse upon stimulation, where it is activated by PKCθ and Ca^{2+}/Calmodulin and then phosphorylates CARD11 to enhance its interaction with BCL10 (see above, [96]). CamKII was further shown to phosphorylate residues S48 and T91 of BCL10, which is required for BCL10 and NEMO ubiquitination and downstream NF-κB and JNK2 activation [115]. CamKII thus seems to regulate CBM mediated signaling on multiple levels by (1) promoting CBM complex formation through CARD11 phosphorylation at S109, (2) promoting BCL10 and NEMO ubiquitination by BCL10 phosphorylation at S48 and T91, and finally (3) inducing destabilization of the complex by BCL10 S138 phosphorylation. How these events are temporally or spatially regulated is not yet entirely clear. Another report claims that BCL10 phosphorylation at S138 is dispensable for TCR-induced NF-κB activation, but rather regulates actin polymerization [116]. Cytoskeletal rearrangements are crucial for the formation of the immunological synapse and occur rapidly upon TCR stimulation. BCL10, but not CARD11 or MALT1, was shown to be required for TCR-induced actin polymerization, and BCL10 phosphorylation at S138 was crucial for its

Table 4
BCL10 phosphorylation sites, kinases involved, context and function. Sites were experimentally determined in humans and corresponding sites in mouse and chicken are also indicated. nd: not determined, nc: residue not conserved.

Phosphorylation site			Kinase	Context	Functional effect	Ref
Human	Mouse	Chicken				
nd	nd	nd	RIPK2, GSK3β, IKKβ, others	Co-expression with CARD11, CARD14, PKCθ, RIPK2, IKKβ, GSKβ (HEK293), PMA/ionomycin or TCR-crosslinking (T cell lines, primary T cells)	NF-κB activation	[36,37,53,71,73,117,119]
T81, S85	T81, S85	nc, S92	IKKβ	Co-expression with IKKβ (HEK293), PMA/Ionomycin (Jurkat)	Proteasomal degradation of BCL10; negative regulation of IL-2	[104]
T91, S48	T91, S48	T98, T55	CamKII	PMA/ionomycin or TCR-crosslinking (Jurkat), *in vitro* kinase assay with CamKII	BCL10 and NEMO ubiquitination, NF-κB/JNK2 activation	[115]
S134, S136, S138, S141, S144	S134, nc, S138, S141, S144	S141, S143, S145, S148, nc	IKKβ	PMA/ionomycin or TCR-crosslinking (Jurkat, primary human and murine T cells), co-expression with IKKβ (HEK293), *in vitro* kinase reaction with immunoprecipitated IKKβ	Inhibition of BCL10-MALT1 interaction, NEMO ubiquitination, NF-κB activation and cytokine production	[113]
S138	S138	S143	CamKII, others	TCR-crosslinking or PMA/ionomycin (Jurkat, primary T cells), co-expression with active CAMKII (HEK293)	Ubiquitination and non-proteasomal degradation, negative regulation of NF-κB and IL-2; TCR-induced F-actin formation; counteracted by Calcineurin	[106,114,116,118]

Table 5
MALT1 ubiquitination sites, E3 ligases involved, context and function. nd: not determined.

Chain type	Position	Context	E3 ligase	Functional effect	Ref
Auto-Ub	nd	API2-MALT1 expression (MALT lymphoma)	API2 RING domain	Downregulation of API2-MALT1	[126]
K63	K633, K637, K650, K654, K666, K668, K691, K698, K703, K713, K813	TCR-crosslinking or PMA/ionomycin (Jurkat), co-expression with TRAF6 (HEK293)	TRAF6	NEMO recruitment, NF-κB activation and IL-2 production; counteracted by A20 and USP2a	[25,121]
K63 (partially)	nd	Co-expression of HECTD3	HECTD3 (indirect?)	increases MALT1 protein stability and cancer cell survival	[128]
Mono	K644	TCR-crosslinking or PMA/ionomycin (Jurkat), Co-expression with BCL10 and active CARD11 L244P (Jurkat)	–	activates MALT1 protease activity; releases autoinhibition by MALT1 C-terminal domain and favors MALT1 dimerization; NF-κB activation	[123–125]

regulation of F-actin formation. Furthermore, cells expressing the BCL10 S138A mutant also showed reduced TCR-induced IL-2 production [116].

Most recently GSK3β has been proposed as a kinase for BCL10, targeting phosphorylation sites overlapping with those of IKKβ [117]. Inhibition or silencing of GSK3β led to decreased TCR-induced CBM complex formation, NF-κB activation and remarkably MALT1 protease function.

BCL10 phosphorylation can be counteracted by the calcium-dependent protein phosphatase Calcineurin [118,119]. In this context, inhibition of Calcineurin with the pharmacological inhibitor cyclosporin A or Ca^{2+} depletion with EGTA-AM led to constitutive phosphorylation of BCL10 at S318, as shown upon immunoblotting and detection with a phospho-S318 specific antibody. Moreover, Calcineurin could directly dephosphorylate BCL10 *in vitro*. Inhibition or depletion of Calcineurin decreased PMA/ionomycin-induced CBM complex formation and NF-κB activation [118,119]. Noteworthy, the kinase phosphorylating BCL10 under basal conditions is yet to be identified.

In summary, different BCL10 phosphorylation events modulate CBM-induced signaling at several levels. Phosphorylation of multiple residues in BCL10 explains also the large mobility shift seen on SDS-PAGE. Early phosphorylation in the CARD domain (T91) facilitates BCL10 and NEMO ubiquitination, positively regulating NF-κB activation, while later phosphorylation events in the CARD (T81, S85) and S/T rich domains (S134, S136, S138, S141, S144) lead to BCL10/MALT1 dissociation and BCL10 degradation, respectively.

7. MALT1

7.1. MALT1 ubiquitination

It was initially proposed that MALT1 itself has E3 ligase activity, conferred by its paracaspase domain, and that MALT1 together with Ubc13 is able to ubiquitinate NEMO [120]. However, later it became clear that E3 ligases associated with MALT1 were responsible for the ubiquitination of NEMO as well as MALT1 itself [24,25]. The E3 ligase TRAF6 was shown to attach K63-linked ubiquitin chains to MALT1 [25]. This ubiquitination occurs relatively early after TCR stimulation and is important for its scaffold function by means of recruitment of the signaling adaptor NEMO. Several lysines in the C-terminus of MALT1 were identified as ubiquitin acceptor sites, and mutation of all 11 lysine residues in the C-terminus of MALT1 (K11R; see Fig. 4/Table 5) abrogates TCR-induced NF-κB activation and IL-2 production. MALT1 K63-linked ubiquitination can be counteracted by the deubiquitinase A20 [121], which causes dissociation of CBM and IKK complexes. Interestingly, MALT1 in turn cleaves and inactivates A20 to ensure optimal signal transduction [66]. Next to A20, the deubiquitinase USP2a has been shown to counteract K63-linked ubiquitination of MALT1 and TRAF6 [122]. It was also proposed that USP2a facilitates the interaction of MALT1 and TRAF6, and the resulting TRAF6 oligomerization and activation, by deSUMOylating TRAF6.

MALT1 is also modified by mono-ubiquitination at K644 in response to TCR stimulation or upon co-expression with BCL10 [123], activating its catalytic activity. It has been proposed that mono-ubiquitination releases auto-inhibition of the MALT1 protease domain by its C-terminal domain. It was later suggested that MALT1 dimerization precedes mono-ubiquitination, as mutation of residue E549 in the dimerization interface prevents mono-ubiquitination of MALT1 [124]. Subsequent mono-ubiquitination then stabilizes the proteolytically active MALT1 dimers. Interestingly, the MALT1 mono-ubiquitinated form accumulates in case a MALT1 proteolytic inactive mutant (C646A) is expressed or in the presence of MALT1 inhibitors [125,126]. However, this could be due to abolished MALT1 auto-cleavage at R149, masking the upshift of mono-ubiquitinated MALT1 upon SDS polyacrylamide gel electrophoresis. Next to enabling MALT1 proteolytic activity, mono-

ubiquitination was shown to be important for NF-κB activation and IL-2 production [123]. The responsible E3 ligase has not yet been described, but it is possible that MALT1 mono-ubiquitination results from trimming of previously added polyubiquitin chains. This hypothesis is supported by the observation that mono-ubiquitination peaks only after the initial K63-linked ubiquitination and that the mono-ubiquitinated lysine residue is among the lysines important for K63-linked ubiquitination of MALT1 [25,123].

While the MALT1 ubiquitination sites important for TCR-induced signal transduction are all located in its C-terminus, a proteomic approach revealed also a ubiquitination site in the paracaspase domain of MALT1 upon BCR stimulation [90]. However the functional relevance for this ubiquitination has not yet been determined.

MALT1 ubiquitination has also been shown in CBM complexes formed with CARD family members distinct from CARD11. More specifically, Telesio et al. found that MALT1 is ubiquitinated when co-expressed with the short isoform of CARD14, which is counteracted (likely indirectly) by the E3 ligase RNF7 [127].

MALT1 expression levels have been reported to be regulated by ubiquitination in the context of cancer. For example, in MALT lymphoma, auto-ubiquitination of the MALT1-API2 fusion protein occurs in a RING domain dependent manner, likely followed by proteasomal degradation to regulate its own abundance [126]. The E3 ligase HECTD3, on the other hand, was shown to stabilize MALT1 levels by non-degradative ubiquitination, resulting in survival of HeLa and MCF7 cancer cells [128].

7.2. MALT1 phosphorylation

To date, the presence of MALT1 phosphorylation is less well documented. Mass spectrometry-based proteomics to monitor the dynamics of BCR signaling complexes revealed the phosphorylation of mouse MALT1 at two sites (S125 and S279) [90]. In addition, numerous MALT1 phosphorylation sites, predominantly located in MALT1 *N*-terminus, have been documented in phosphorylation site databases (e.g. phosphosite.org). However, the functional role of these MALT1 phosphorylation events is still completely unknown and will be of high interest to study in the future.

8. Future perspectives and conclusions

Deciphering how signaling complexes are regulated is of fundamental importance to our understanding of biology. Several tremendous technological advances have been made, which allowed the identification of numerous types of PTMs, their functional role, and the enzymes involved. In this context, the regulation of TCR signaling, and in particular the CBM signalosome, by different PTMs is a very good example of how the field has been moving forward in recent years and how it is likely to proceed in the coming years. The interdependence between PTMs is getting increasingly complex and in many cases far exceeds our ability to understand their biological function. For example, the proteolytic cleavage of at least two DUBs (A20, CYLD) and one critical LUBAC complex component (HOIL-1) by MALT1 indicates that one important function of MALT1 catalytic activity is to influence the ubiquitination pattern of the cell, but with currently unknown signaling consequences. Moreover, other PTMs may also have an impact on the activity of these DUBs. For example, CYLD is phosphorylated by TBK1 and IKKε in response to TCR stimulation [15], and it will be interesting to study the interdependence between CYLD phosphorylation and its cleavage by MALT1, as well as the effect on signaling. Interestingly, a common theme for the MALT1 protease substrates A20, CYLD and HOIL-1 is that they all can regulate M1-ubiquitin dependent signaling: CYLD is known to remove M1-ubiquitin chains from substrates [129], A20 can bind M1-ubiquitinated proteins and prevent their recognition by other signaling proteins [130], and HOIL-1 is cooperating with the M1-ubiquitin forming E3 ligase HOIP. It will thus be highly interesting to crack the “ubiquitin code” downstream of normal TCR signaling in order to better understand the functional consequences of MALT1 protease inhibition or to design other therapeutic targeting strategies that aim to alter the ubiquitination pattern after TCR stimulation. Deciphering the interdependency and functional role of PTM networks in the context of human disease and therapy will likely benefit from data emerging from MS-based PTM studies and systems-level analyses. From a fundamental perspective, the role of other atypical ubiquitin linkages, such as K27-linked ubiquitin chains on CARD11, is quite intriguing and something that will keep us busy for some time.

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