Review

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Lymphocyte signaling and activation by the CARMA1-BCL10-MALT1 signalosome

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Abstract: The CARMA1-BCL10-MALT1 (CBM) signalosome triggers canonical NF-κB signaling and lymphocyte activation upon antigen-receptor stimulation. Genetic studies in mice and the analysis of human immune pathologies unveiled a critical role of the CBM complex in adaptive immune responses. Great progress has been made in elucidating the fundamental mechanisms that dictate CBM assembly and disassembly. By bridging proximal antigen-receptor signaling to downstream signaling pathways, the CBM complex exerts a crucial scaffolding function. Moreover, the MALT1 subunit confers a unique proteolytic activity that is key for lymphocyte activation. Deregulated 'chronic' CBM signaling drives constitutive NF-κB signaling and MALT1 activation, which contribute to the development of autoimmune and inflammatory diseases as well as lymphomagenesis. Thus, the processes that govern CBM activation and function are promising targets for the treatment of immune disorders. Here, we summarize the current knowledge on the functions and mechanisms of CBM signaling in lymphocytes and how CBM deregulations contribute to aberrant signaling in malignant lymphomas.

Keywords: adaptive immunity; CBM complex; diffuse large B cell lymphomas; lymphocyte signaling.

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Introduction

The adaptive immune system protects mammalian organisms from pathogenic infection by bacteria, viruses, fungi and parasites and recognizes and destroys malignant cancer cells. Recognition of foreign antigens by T- and B-cell antigen receptors (TCR and BCR) expressed on lymphocytes is critical for conveying immunity to specific pathogens and it is also required to build up immune memory and protection from reinfection. Antigenic stimulation through the TCR or BCR induces activation of signaling pathways that ultimately trigger cytokine production, survival, proliferation and differentiation of T and B lymphocytes. Thus, the cellular pathways that trigger lymphocyte activation upon antigen binding are key to mount a productive adaptive immune response.

Activation of transcription factor NF-κB is involved in many processes of lymphocyte activation and differentiation. NF-κB comprises a family of five proteins that are ubiquitously expressed, but whose activity is tightly controlled by inhibitory IκB proteins that sequester dimeric NF-κB proteins in the cytosol. Many stimuli – including inflammatory cytokines, pathogenic agents or antigenic peptides – induce activation of NF-κB by either the canonical or non-canonical pathway (Hayden and Ghosh, 2012). Antigenic ligands that bind to the TCR or BCR induce primarily canonical NF-κB signaling, which relies on activation of the IκB kinase (IKK) complex consisting of the catalytic subunits IKKα (IKK1) and IKKβ (IKK2) and the regulatory component NEMO/IKKγ (Hinz and Scheidereit, 2014). The IKK complex phosphorylates cytosolic IκB proteins (e.g. IκBα), which are degraded by the proteasome to release NF-κB for nuclear translocation, DNA binding and induction of target genes (Hayden and Ghosh, 2012). All NF-κB activating signals converge at the IKK complex, but different upstream processes induce IKK activation in response to specific stimuli.

In lymphocytes, a high molecular weight complex consisting of CARMA1 (CARD11), BCL10 and MALT1 (CBM) is essential to bridge TCR or BCR upstream signaling to the canonical IKK/NF-κB pathway. Whereas CARMA1 (caspase

recruitment domain (CARD)-containing MAGUK 1) is expressed in lymphoid and myeloid cells, BCL10 (B Cell CLL/Lymphoma 10) and MALT1 (Mucosa-Associated Lymphoid Tissue protein 1) are expressed ubiquitously and can assemble with CARMA1 or its homologs, e.g. CARMA2/CARD14, CARMA3/CARD10 or CARD9, to form distinct CBM complexes for activation in various signaling pathways (Wegener and Krappmann, 2007; Hara and Saito, 2009; Afonina et al., 2016; Howes et al., 2016). For historical reasons, the prototype CARMA1-BCL10-MALT1 complex is referred to as CBM signalosome, which selectively induces an adaptive immune response upon antigen-dependent stimulation of T and B lymphocytes (Hara et al., 2008).

Physiological role of the CBM complex in lymphocytes

The analysis of mice with specific ablations in CARMA1, BCL10 and MALT1 disclosed the critical requirement of the CBM complex for T and B lymphocyte activation. Deficiencies of CBM proteins abrogate antigen-receptor signaling to NF-κB and a productive immune response. The scaffold protein CARMA1 is critical for activation of NF-κB and JNK (c-Jun N-terminal kinase) signaling in both T and B cells, which is essential for lymphocyte proliferation and cytokine production (Egawa et al., 2003; Hara et al., 2003). This is in line with data from T and B cells taken from BCL10 knockout mice, which failed to activate NF-κB and JNK and do not proliferate in response to antigen stimulation (Ruland et al., 2001). NF-κB signaling and concomitant activation, proliferation and cytokine response in T and B cells also relies on MALT1 (Ruefli-Brasse et al., 2003; Ruland et al., 2003), but the effects of MALT1 deficiency on signaling, activation and proliferation in T cells are less severe compared to loss of BCL10 (Kingeter and Schaefer, 2008). Moreover, in B cells, MALT1 selectively activates the NF-κB subunit c-Rel upon BCR stimulation, indicating that MALT1 ablation may only cause a partial defect in immune activation (Ferch et al., 2007). The phenotype of MALT1 deficient mice is also caused by the loss of protease activity and substrate cleavage that exerts effects beyond NF-κB signaling and serves an immune balancing role (see section 'Function of MALT1 protease activity for T cell activation').

Whereas CARMA1, BCL10 and MALT1 are dispensable for the development of immature B cells, they are required for the formation of marginal zone and B1 B cells and to a lesser extent for follicular B cells, implying a role of CBM signaling in the generation of mature B cells (Ruefli-Brasse et al., 2003; Ruland et al., 2003; Xue et al., 2003; Pappu and Lin, 2006). Regarding T cell development, ablation of CARMA1, BCL10 or MALT1 did not affect the maturation of CD4/CD8 double-positive thymocytes into CD4 and CD8 single-positive T cells. However, commitment to the regulatory T cell (T_{reg}) lineage in the thymus depends on CBM proteins (Schmidt-Supprian et al., 2004; Barnes et al., 2009; Molinero et al., 2009; Brustle et al., 2015) and the development of thymic T_{reg} cells requires MALT1 proteolytic activity (Gewies et al., 2014; Jaworski et al., 2014; Bornancin et al., 2015). Further, peripheral differentiation of effector cells from naive CD4 T cell is controlled by the CBM complex. CARMA1 is supporting T_H2 cell differentiation and cytokine responses in a murine model of allergic airway inflammation (Ramadas et al., 2011). Moreover, T_H17 cell differentiation is impaired in CARMA1 and MALT1 KO mice and again MALT1 protease activity is necessary to trigger generation of T_H17 cells (Brustle et al., 2012; Molinero et al., 2012; Bornancin et al., 2015). Consequently, both MALT1 KO and MALT1 protease deficient mice were protected from T_H17-driven experimental autoimmune encephalomyelitis (EAE) in a murine multiple sclerosis model (Brustle et al., 2012; Mc Guire et al., 2013; Gewies et al., 2014; Jaworski et al., 2014; Bornancin et al., 2015). Overall, the requirement for the development of immune suppressive T_{reg} cells in the thymus and immune activating effector T cells in the periphery reveals a critical immune balancing function of the CBM complex, which is important for maintaining immune homeostasis and peripheral tolerance.

The relevance of the CBM complex for cellular and humoral immune responses is further underscored by the fact that germline-encoded CBM complex mutations are associated with human combined immunodeficiency (CID). Genetic evaluation of CARMA1-deficient patients revealed that homozygous mutations cause either a complete loss of CARMA1 protein or expression of a C-terminally truncated CARMA1 (Greil et al., 2013; Stepensky et al., 2013). Patients suffered from infections such as *Pneumocystis jirovecii* pneumonia and sinopulmonary bacterial infections. The lack of functional CARMA1 also promotes progressive hypogammaglobulinemia accompanied by the inability to produce specific antibodies. As observed in CARMA1 deficient mice, total T cell and B cell numbers were not affected, but NF-κB activation and T cell proliferation were abrogated in patients with loss of function mutations in *CARMA1*. In addition, mature B cells as well as T_{reg} cells are not detectable. Also, a homozygous splice site mutation in *BCL10* has been described, which causes a complete loss of BCL10 expression and

severe immunodeficiency (Torres et al., 2014). Homozygous missense mutations in *MALT1* either result in loss or decreased expression of MALT1 or a reduction of MALT1 protease activity (Jabara et al., 2013; McKinnon et al., 2014; Punwani et al., 2015; Charbit-Henrion et al., 2016). As expected, MALT1 loss-of-function mutations impaired NF-κB activation and T cell proliferation. Surprisingly, MALT1 defects provoked auto-inflammatory responses, especially affecting the gastrointestinal tract and the skin, which is reminiscent of MALT1 paracaspase mutant mice (Gewies et al., 2014; Jaworski et al., 2014) (see section 'Function of MALT1 protease activity for T cell activation'). Indeed, human MALT1 deficiency can lead to immunodeficiency in combination with an IPEX-like syndrome (Immunodeficiency-Polyendocrinopathy and Enteropathy-X-linked), which is characterized by severe autoimmunity (Charbit-Henrion et al., 2016). However, in contrast to the murine situation, no homogenous picture regarding T and B cell numbers have been observed in the *MALT1* mutant patients, which is most likely due to the different degree of MALT1 inactivation and the varying genetic background. Nevertheless, the data indicate that human MALT1 is involved in activating immune responses as well as controlling immune homeostasis.

Besides immunodeficiency caused by loss-of-function mutations in CARMA1, germline CARMA1 gain-of-function mutations have been identified that trigger an immune disorder called BENTA (B cell expansion with NF-κB and T cell anergy) (Snow et al., 2012; Brohl et al., 2014; Buchbinder et al., 2015). BENTA patients are characterized by a B cell lymphoproliferative disorder while the T cells become unresponsive. Similar to the somatic oncogenic CARMA1 mutations that drive B cell malignancies, activating point mutations in BENTA patients are positioned within the CARD and coiled-coil (CC) domains of CARMA1 (see section 'Chronic BCR signaling promotes aberrant CBM formation in lymphoma'). Currently, it is unclear why germline expression of hyperactive CARMA1 drives constitutive activation of NF-κB and proliferation in B cells, but causes hypo-responsiveness of T cells (Snow et al., 2012). Clearly, distinct mechanisms must exist to counteract CBM activity in the different lymphocyte populations. Importantly, the effects of CARMA1 mutations in B cells provide a rational explanation why CBM alterations are predominately found in B cell lymphoid malignancies. BENTA patients may be predisposed to lymphomagenesis, but additional genomic alterations are required to develop B cell lymphomas (Brohl et al., 2014). Collectively, these data prove that CBM mutations alter lymphocyte activation, reflecting that CARMA1, BCL10 and MALT1 are essential for adaptive immune responses.

Structural features of CBM complex components

CARMA1 – a multi-domain scaffold protein

CARMA1 (CARD11), CARMA2 (CARD14) and CARMA3 (CARD10) belong to the family of MAGUK (membrane associated guanylate kinase) containing CARD proteins (CARMA family) that share high degrees of sequence and structural homology, but differ in their expression pattern (Blonska and Lin, 2011). The CARMA proteins are large molecular scaffolds and CARMA1 is the founding member and the only CARMA protein expressed in the hematopoietic tissues such as spleen, thymus and peripheral lymphocytes.

CARMA1 is a protein of ~130 kDa that encodes an N-terminal CARD (Figure 1A). CARDs represent protein-protein interaction platforms that are involved in the assembly of signaling clusters in cell death, antigen signaling, inflammosome activation and many other processes (Kao et al., 2015). Within the CBM complex, CARMA1 is recruiting the adapter protein BCL10 via heterotypic CARD-CARD interaction upon TCR stimulation (Gaide et al., 2002). Structural and mutational analyses revealed that coupling of basic patches on CARMA1 to acidic residues on BCL10 is critical for CBM formation (Li et al., 2012). No structural information is available for the CC and linker regions C-terminal to the CARD of CARMA1. However, the oligomerization of the CC and the existence of various mutations in the CC region promoting chronic CBM assembly underscores that the domain is critical for signal activation as well as auto-inhibition of CARMA1 (Tanner et al., 2007; Lenz et al., 2008; Lamason et al., 2010). The linker region contains multiple phosphorylation sites that are critical for CBM assembly upon antigenic stimulation (see section 'Regulation of CBM complex assembly and disassembly') (Matsumoto et al., 2005; Sommer et al., 2005). Mechanistically, in resting cells the linker acts as a repressor that interacts with the CARD-CC to keep CARMA1 in a closed, inactive confirmation that is released by phosphorylation upon antigenic stimulation (Figure 2) (McCully and Pomerantz, 2008; Jattani et al., 2016). In its open conformation, CARMA1 recruits BCL10-MALT1, which induces the formation of BCL10 filaments and activation of the MALT1 protease (Figure 1B) (Qiao et al., 2013).

In addition, the C-terminal MAGUK domain of CARMA1 is critical for T cell activation. It mediates membrane association, which is required for recruitment of CARMA1 to PKCθ at the immunological synapse (Hara et al., 2004;

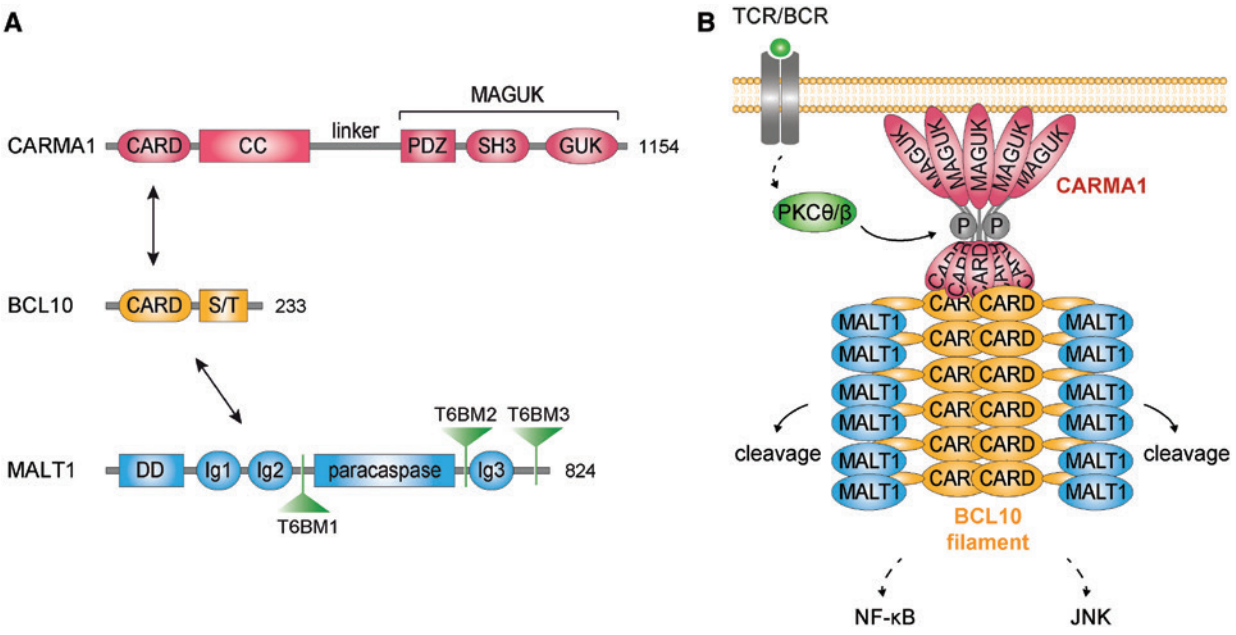

Figure 1: Molecular structure and high-order assembly of CARMA1, BCL10 and MALT1.
(A) The scaffold protein CARMA1 consists of an N-terminal CARD domain followed by a coiled-coil domain (CC), a linker region and a C-terminal MAGUK domain. The latter comprises PDZ, SH3 and GUK domains being crucial for CARMA1 localization and cluster formation. Via CARD-CARD interaction, CARMA1 interacts with the adapter protein BCL10. The Ser/Thr (S/T)-rich C-terminus in BCL10 is targeted for post-translational modifications. BCL10 is constitutively associated with the paracaspase MALT1. MALT1 consists of a death domain (DD), three immunoglobulin-like (Ig) domains and the paracaspase domain in between Ig2 and Ig3. In addition, it harbors three binding motifs for the E3 ligase TRAF6 (T6BM1/2/3). (B) The CBM complex assembles into a high-order filamentous machinery. Upon lymphocyte stimulation, CARMA1 gets phosphorylated by PKCθ/β and oligomerizes via its CC domain. Oligomerized CARMA1 recruits BCL10/MALT1 via CARD-CARD interaction and thus acts as a nucleator for the formation of BCL10 filaments. The high molecular weight complex triggers NF-κB and JNK activation. In addition, recruited MALT1 paracaspase gets activated to catalyze substrate cleavage.

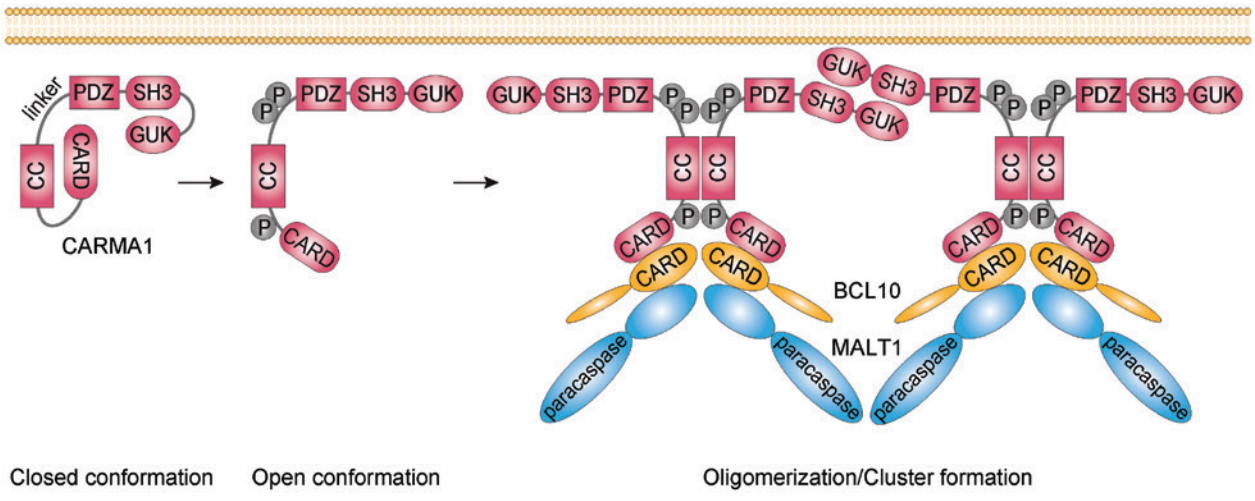

Figure 2: Model for CARMA1 activation.
In resting cells, CARMA1 is maintained in an inactive, double closed conformation, which is stabilized by intra-molecular interactions between the linker and CARD-CC regions as well as the GUK-SH3 domains. Furthermore, CARMA1 associates with the plasma membrane via the SH3 domain. Antigen-receptor stimulation initiates CARMA1 phosphorylation, releasing its inactive status. In the open conformation, CARMA1 oligomerizes via its CC domain. The signal is amplified by the formation of CARMA1 clusters mediated by intra- or inter-molecular SH3-GUK interactions. Multimerized CARMA1 clusters recruit BCL10/MALT1 to trigger activation of downstream signaling.

Wang et al., 2004). Like other MAGUK proteins, CARMA1 contains a PDZ (PSD-95, Dlg and ZO-1), an SH3 (Src homology 3) and a catalytically inactive GUK (guanylate kinase) domain (Funke et al., 2005). Intra- or intermolecular interactions of the SH3 and GUK domains are crucial for CBM complex assembly and CARMA1 localization to the immunological synapse (Figure 2) (Hara et al., 2015). Thus, the domain structure indicates that CARMA1 is a multimodular scaffold protein and only coordinated conformational changes of the N-terminal and C-terminal domains are likely to drive activation and promote CBM assembly and signal propagation. These structural rearrangements are controlled by post-translational modifications (see section 'Regulation of CBM complex assembly and disassembly'), but accessory factors may also play a role. ADAP (adhesion and degranulation-promoting adapter protein) binds to CARMA1 MAGUK to enhance CBM complex formation and NF-κB signaling in T cells (Medeiros et al., 2007). Similarly, AIP (AhR interacting protein) associates with the CBM by binding to the CARMA1 PDZ-SH3 and counteracting GUK association to facilitate the open conformation of CARMA1 (Schimmack et al., 2014). In addition, PKCδ binds to the MAGUK and inhibits CARMA1-driven NF-κB activation independent of its catalytic activity (Liu et al., 2012). Given the complex conformational changes, structural insights are urgently needed to elucidate the multifaceted regulation of CARMA1.

BCL10 – the CBM bridging factor

The ~27 kDa BCL10 adapter protein was originally identified from the recurrent translocation breakpoint t(1;14)(p22;q32) that leads to its overexpression in MALT lymphoma (Willis et al., 1999). The N-terminal CARD of BCL10 interacts with the CARD of CARMA1 (Figure 1A). In its monomeric form, the BCL10 CARD is largely unstructured and highly dynamic, but it tends to aggregate and form stable filaments especially in the presence of CARMA1 (Guiet and Vito, 2000; Bertin et al., 2001). Accordingly, CARMA1 was suggested to function as a molecular seed or nucleator that induces the formation of BCL10 filaments to build up the higher order CBM complex with a molecular mass of more than 1.5 MDa (Figure 1B) (Oeckinghaus et al., 2007; Qiao et al., 2013). BCL10 is constitutively bound to MALT1, but it associates with CARMA1 in lymphocytes only upon antigen stimulation (Matsumoto et al., 2005; Sommer et al., 2005). Upon stimulation, the pre-assembled BCL10-MALT1 complex is recruited to active CARMA1 in its open conformation via heterotypic CARD-CARD interaction (Li et al., 2012). Even though CARD mutations that abrogate CARMA1 association do not interfere with BCL10-MALT1 binding, an extended surface comprising the BCL10 CARD and adjacent residues is required for MALT1 association (Langel et al., 2008). The C-terminal Ser/Thr-rich region of BCL10 is not essential for MALT1 binding, but it stabilizes the BCL10-MALT1 association, which can be modulated by phosphorylation (see section 'Regulation of CBM complex assembly and disassembly') (Wegener et al., 2006). Thus, BCL10 functions as the critical bridging factor in the CBM complex.

MALT1 – a scaffold and a protease

MALT1 was first identified from the recurrent translocation t(11;18)(q21;q21) in MALT lymphoma that creates the oncogenic fusion protein API2-MALT1 consisting of the N-terminal BIR domains of cIAP2 (inhibitor of apoptosis 2) and the C-terminal paracaspase-Ig3 domain of MALT1 (Rosebeck et al., 2016). Mammalian MALT1, also referred to as paracaspase1 (PCASP1), encodes a ~92 kDa protein comprising an N-terminal death domain (DD), three immunoglobulin-like (Ig) domains and the paracaspase (caspase-like) domain in between Ig2 and Ig3 (Figure 1A). MALT1 contains three potential binding motifs for the E3 ligase TRAF6 (tumor-necrosis factor associated receptor-associated factor 6) (Sun et al., 2004; Noels et al., 2007) of which T6BM1 adjacent to Ig2 and T6BM3 in the very C-terminus contribute to TCR-triggered TRAF6 recruitment and NF-κB signaling (Meininger et al., 2016).

The N-terminus of MALT1 is responsible for BCL10 interaction, which is mediated by the Ig1 and Ig2 domains and stabilized by the DD (Lucas et al., 2001; Langel et al., 2008). In contrast to CARMA1 and BCL10, MALT1 does not only exert scaffolding functions, but it also encodes a protease that is activated upon antigen stimulation in lymphocytes (Coornaert et al., 2008; Rebeaud et al., 2008). The MALT1 protease belongs to the family of vertebrate paracaspases (PCASP) that display highest sequence homology to metacaspase found in plants, fungi and protozoa (Uren et al., 2000; Hulpiau et al., 2015). Despite lower sequence homology, caspases are the closest homologs in mammals and the crystal structure of the MALT1 paracaspase-Ig3 domain underscores the conservation. As for classical caspases, the paracaspase domain dimerizes and Cys464 and His415 form a catalytic dyad in the active substrate bound conformation (Yu et al., 2011; Wiesmann et al., 2012). However, whereas caspases cleave substrates after Asp, MALT1 stringently requires Arg in the P1 site, which resembles the Arg/Lys specificity of metacaspases (Hachmann et al., 2012).

Structural analyses unraveled a unique mechanism of MALT1 protease activation. MALT1 can be auto-cleaved (Baens et al., 2014), but labeling with activity-based probes shows that MALT1 is active in its full length form (Eitelhuber et al., 2011; Hachmann et al., 2015). Induction of catalytic activity involves conformational changes in the C-terminal Ig3 domain, which exerts an auto-inhibitory function but it is also essential for paracaspase activity (Wiesmann et al., 2012). A two-step activation model for MALT1 has been suggested. First, the MALT1 paracaspase dimerizes, but is retained in an inactive state by Ig3-mediated auto-inhibition. Second, substrate binding induces structural rearrangements that release the paracaspase from auto-inhibition (Wiesmann et al., 2012). The two-step activation model was confirmed by the identification of allosteric small molecule MALT1 inhibitors, which prevent the conformational rearrangement required for activation by binding to a hydrophobic pocket formed at the interface of the paracaspase and Ig3 domains (Schlauderer et al., 2013). The critical role of the Ig3 domain for cellular MALT1 activation is also supported by the finding that mono-ubiquitination at Lys644 is inducing MALT1 proteolytic activity upon T cell stimulation (Pelzer et al., 2013). MALT1 activation relies on CBM assembly, but the exact pathways and mediators regulating Ig3 rearrangements and modification to obtain active MALT1 need to be elucidated. Further, how MALT1 scaffolding function and proteolytic activity is coordinated within the CBM complex is still elusive.

Regulation of CBM complex assembly and disassembly

CARMA1 undergoes complex structural rearrangements for the transition from inactive closed to an active open conformation that facilitates recruitment of BCL10-MALT1 (Figure 2). BCR and TCR signaling leads to full NF-κB activation within 5–10 min after antigen ligation, indicating that signaling processes must by tightly coordinated (Oeckinghaus et al., 2007; Shinohara et al., 2014). In line, assembly, activity and disassembly of the CBM signalosome are controlled by multiple post-translational modifications that exert positive or negative regulatory effects.

Initial CBM assembly is governed by CARMA1 phosphorylation. Upon lymphocyte activation, phosphorylation of human CARMA1 by PKCθ in T cells and PKCβ in B cells impairs intra-molecular association of the linker region to the CARD-CC region, rendering the CARD accessible for BCL10 binding (Figure 2) (Matsumoto et al., 2005; Sommer et al., 2005). Ser552, Ser637 and Ser645 in the CARMA1 linker have been identified as major PKC phosphorylation sites (Sommer et al., 2005). Indeed PKCβ phosphorylation of CARMA1 at Ser645 takes place within 1–2 min of BCR stimulation (Shinohara et al., 2007; Moreno-Garcia et al., 2009). Also upon TCR engagement, Ser645 phosphorylation by PKCθ is maximal after 5 min and the critical role of this modification has been proven by the identification of phosphatase PP2A that antagonizes phosphorylation, CBM assembly and IKK/NF-κB activation (Eitelhuber et al., 2011). Activation of PDK1 (phosphoinositide-dependent kinase 1) by the CD28 co-receptor supports PKCθ catalyzed CARMA1 phosphorylation, providing a co-stimulatory signal for optimal T cell activation (Lee et al., 2005; Park et al., 2009). Loosening of the intra-molecular linker-CARD interaction is thought to facilitate BCL10-MALT1 dependent recruitment of TAK1 (transforming growth factor β activated kinase-1) and IKKs to the immunological synapse to induce downstream signaling (Matsumoto et al., 2005; Sommer et al., 2005; Shinohara et al., 2007). As mentioned earlier, PKCθ or PKCβ also phosphorylate Ser637 of human CARMA1 (Sommer et al., 2005). However, Ser637 phosphorylation is considerably delayed compared to Ser645 phosphorylation, and accordingly it contributes a negative feedback mechanism that impairs downstream signaling (Moreno-Garcia et al., 2009). Thus, PKC phosphorylation can exert positive and negative effects on CARMA1 and the phosphorylation status at distinct sites is critical for controlling the activation threshold.

PKCθ/β phosphorylation of CARMA1 is essential but not sufficient to trigger robust downstream signaling. Interestingly, activity of the putative downstream kinase IKKβ is also required for TCR- and BCR-induced CBM assembly (Wegener et al., 2006; Shinohara et al., 2007). IKKβ phosphorylates the linker of CARMA1 at Ser555, which constitutes a positive feed-forward mechanism that facilitates activation (Shinohara et al., 2007). In fact, PKCβ dependent recruitment of TAK1/IKKβ to CARMA1 and IKKβ phosphorylation at Ser555 provokes a switch-like mechanism for activation of NF-κB signaling upon BCR stimulation (Shinohara et al., 2014). Thus, multiple phosphorylations set the threshold to turn on the switch and this explains why single mutations of individual phosphorylation sites are sufficient to abolish downstream signaling (Matsumoto et al., 2005; Shinohara et al., 2007).

A number of other protein kinases and phosphorylation sites have been reported to regulate CARMA1 functions. CARMA1 can also be phosphorylated by HPK1 (hematopoietic progenitor kinase1) on Ser549/551/552 and

by AKT on Ser551/637/645 and these residues partially overlap with the previously described PKC sites, revealing that different protein kinases may provide alternative mechanisms for controlling CARMA1 (Brenner et al., 2009; Cheng et al., 2014). However, HPK1 deficiency does not impair TCR-induced JNK signaling downstream of CARMA1 and the physiological role of HPK1 for controlling the CBM complex needs to be clarified (Shui et al., 2007). A key role for CBM regulation has been attributed to the protein kinase CK1α (casein kinase 1α) that associates and phosphorylates the CARMA1 linker region upon TCR/CD28 co-stimulation (Bidere et al., 2009). CK1α binds to CARMA1 and enhances NF-κB activation independent of its kinase activity, but it also dampens downstream signaling by phosphorylating Ser608, which putatively induces CARMA1 degradation (Bidere et al., 2009). Thus, reminiscent to PKCθ (see above), CK1α acts as a bifunctional modulator of the CBM complex and adaptive immune signaling. CARMA1 is also phosphorylated outside the linker in activated T and B cells at Ser109 and Thr110 and CamKII can phosphorylate Ser109 (Ishiguro et al., 2006; Shinohara et al., 2007). Phosphorylation at these residues adjacent to the CARD is also critical for CARMA1 activation, suggesting that modifications within the linker as well as the CARD-CC interfaces are needed to induce an open, active CARMA1 conformation (Figure 2) (Ishiguro et al., 2006; Shinohara et al., 2007). So far, no functional MAGUK phosphorylations have been identified, even though it is very likely that modifications facilitate the structural alterations in the CARMA1 C-terminus (Hara et al., 2015).

Besides CARMA1, the adaptor protein BCL10 is highly phosphorylated upon T cell stimulation (Cannons et al., 2004). In contrast to CARMA1, phosphorylation of BCL10 seems to primarily function as a negative feedback mechanism to terminate T cell activation. Upon recruitment to the CBM complex, IKKβ phosphorylates a stretch of Ser residues (134/136/138/141/145) in the C-terminus of BCL10 and thereby disturbs the interaction to MALT1 and impairs NF-κB signaling and T cell activation (Wegener et al., 2006). Thus, besides its classical role in mediating IκB degradation, IKKβ facilitates CBM complex assembly by CARMA1 phosphorylation and it terminates downstream signaling by catalyzing BCL10 phosphorylation. CamKII can also catalyze phosphorylation of Ser138, which counteracts T cell signaling by inducing BCL10 degradation (Ishiguro et al., 2007; Zeng et al., 2007). C-terminal BCL10 phosphorylation is removed by the phosphatase Calcineurin, which thereby augments CBM complex formation and NF-κB signaling (Frischbutter et al., 2011; Palkowitsch et al., 2011).

Besides phosphorylation, CBM components are decorated by multiple ubiquitin chains as evident from a global mass spectrometry approach following BCR stimulation (Satpathy et al., 2015). Whereas ubiquitin chains on BCL10 or MALT1 are involved in connecting downstream pathways (see section 'Mechanisms of CBM-triggered NF-κB and JNK activation'), ubiquitination of CARMA1 and BCL10 is also essential for CBM disassembly and termination of signaling. Given the stimulation-induced assembly of large BCL10 filaments (Schaefer et al., 2004; Qiao et al., 2013), disassembly of these clusters is critical to prevent chronic antigenic signaling. IKKβ can phosphorylate Thr81 and Ser85 in the CARD of BCL10, which promotes its ubiquitination and proteasomal degradation (Lobry et al., 2007). However, autophagy and lysosomal degradation represents the major pathway responsible for post-inductive BCL10 degradation (Scharschmidt et al., 2004; Zeng et al., 2007; Paul et al., 2012) and it seems reasonable that the higher order BCL10 clusters cannot be efficiently removed by the proteasome. Even though several E3 ubiquitin ligases have been shown to conjugate Lys63 (K63) or Lys48 (K48) ubiquitin chains to BCL10 and to promote degradation (Hu et al., 2006; Lobry et al., 2007), the exact processes involved in BCL10 elimination and thus CBM disassembly have not been resolved. Of note, several adaptor complexes have been shown to positively (p62 sequestosome and TAK1/TAB1 complex) or negatively (COP9 signalosome) influence BCL10 degradation (Welteke et al., 2009; Paul et al., 2012; Moreno-Garcia et al., 2013). Also, CARMA1 ubiquitination was suggested to trigger CBM complex disruption either by K48 ubiquitin chains and CARMA1 proteasomal degradation or by mono-ubiquitination and CARMA1-BCL10 dissociation (Kojo et al., 2009; Moreno-Garcia et al., 2010). Overall, the results indicate that termination of CBM signaling is critical to prevent chronic antigen signaling that causes NF-κB-mediated survival and lymphomagenesis (see section 'Function of MALT1 protease activity for T cell activation').

Mechanisms of CBM-triggered NF-κB and JNK activation

The assembly of the CBM complex into a high-order filamentous signaling machinery serves as an essential step in the transmission of antigen-receptor signaling to downstream IKK/NF-κB signaling (Thome et al., 2010; Qiao et al., 2013). The molecular scaffold protein CARMA1 adopts a key role in IKK activation as it recruits preassembled BCL10-MALT1 molecules and the IKK complex

into lipid rafts at the immunological synapse, initiating IKK/NF-κB activation (Figure 3) (Hara et al., 2004; Wang et al., 2004).

The recruitment of the IKK complex to the CBM signalosome is facilitated by the attachment of K63-linked polyubiquitin chains to BCL10 and MALT1, which are specifically recognized by the IKK regulatory subunit NEMO and the TAB/TAK1 complex (Figure 3) (Oeckinghaus et al., 2007; Wu and Ashwell, 2008). In line with this, the recruitment of the deubiquitinase A20 counteracts T cell activation by promoting the removal of MALT1 ubiquitin chains (Duwel et al., 2009). In this respect, the scaffolding function of MALT1 exerts an important function in the initiation of K63-linked ubiquitination events

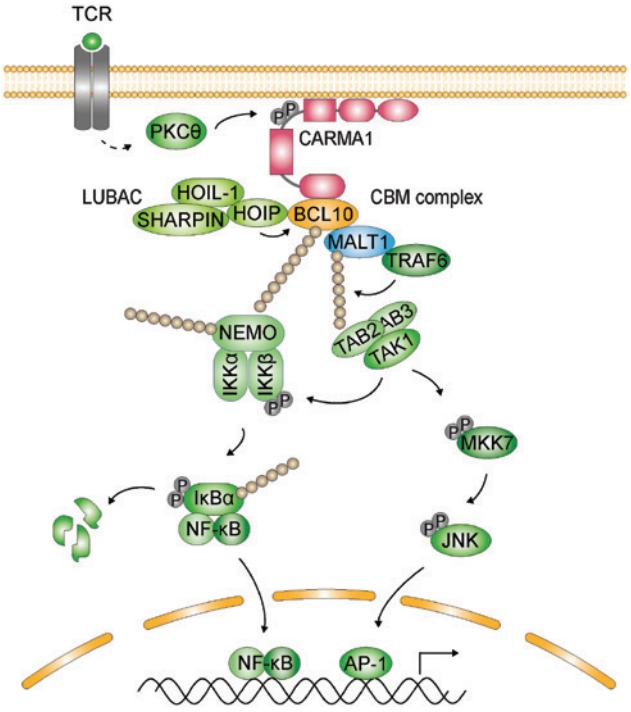

Figure 3: NF-κB and JNK activation by the CBM complex. TCR activation leads to the activation of PKCθ, which in turn phosphorylates CARMA1 triggering CBM complex assembly. MALT1 recruits the E3 ligase TRAF6, inducing its oligomerization and activation, which results in ubiquitination of MALT1 and NEMO. BCL10 is ubiquitinated potentially by the linear ubiquitin chain assembly complex (LUBAC) that associates with the CBM complex to support NF-κB signaling. Overall, polyubiquitination induces the proximity of the TAB2/3-TAK1 and the IKK complexes that contain distinct ubiquitin-binding motifs. TAK1 mediates phosphorylation of IKKβ to activate IKKβ, which phosphorylates IκBα, triggering its ubiquitin-dependent proteasomal degradation. IκBα degradation enables the release of canonical NF-κB members and their concomitant translocation into the nucleus, where they promote target gene expression. In addition, TAK1 activates MKK7 to phosphorylate JNK, which contributes to c-Jun accumulation and phosphorylation and thus AP-1 activation.

upon antigen-receptor signaling. It has been shown, that MALT1 recruits the E3 ligase TRAF6 through its TRAF6 binding motifs inducing TRAF6 oligomerization and activation, which results in the conjugation of polyubiquitin chains to MALT1 and NEMO (Oeckinghaus et al., 2007; Shambharkar et al., 2007). TRAF6 further interacts with the ubiquitin adapter protein p62, which recognizes polyubiquitinated BCL10-MALT1 molecules forcing the formation of large cytosolic p62-BCL10-MALT1 signaling clusters, which also recruit the IKK complex and thus provide a compartment to enhance downstream signaling (Paul et al., 2014). Of note, IKK activation was suggested to be driven by a dual process involving CBM and TRAF6 dependent NEMO ubiquitination and PKCθ-TAK1 catalyzed IKKβ phosphorylation, the latter independent of CBM assembly (Shambharkar et al., 2007).

The relevance of K63-linked ubiquitination for IKK activation is underscored by the fact that T cell specific deletion of the ubiquitin conjugating E2 enzyme Ubc13 inhibits TCR-induced NF-κB signaling (Yamamoto et al., 2006). However, the role of TRAF6 in antigen-receptor induced NF-κB signaling remains questionable, as TRAF6 deletion in T cells did not impair TCR-induced NF-κB activation (King et al., 2006). Whereas TRAF6 itself seems to be dispensable, mutation of TRAF6 binding motifs within MALT1 completely abrogated antigen-receptor mediated NF-κB signaling (Meininger et al., 2016). Interestingly, MALT1 scaffolding function is modulated by alternative splicing leading to the expression of two distinct isoforms, MALT1A and MALT1B, which differ in inclusion or exclusion of exon7 encoding an additional TRAF6 binding site between the Ig2 domains and the paracaspase domain of MALT1 (T6BM1) (Figure 1) (Meininger et al., 2016). TCR-induced inclusion of exon7 and the additional TRAF6 binding motif within MALT1A enhances TRAF6 recruitment, more potent NF-κB signaling and concomitant T cell activation, revealing the importance of TRAF6 binding motifs in MALT1 for lymphocyte activation. One can assume that other TRAF proteins or E3 ligases can compensate for the loss of TRAF6 (King et al., 2006). Interestingly, TRAF6 and TRAF2 have redundant functions in TCR mediated NF-κB signaling as knockdown of both proteins impaired IKK activation upon TCR stimulation (Sun et al., 2004). A more recent study reports that the E3 ligases cIAP1 and cIAP2 are critical for K63 ubiquitination of BCL10 in an oncologic scenario of BCR driven lymphoma, but their role under physiological conditions of TCR/BCR stimulation remains unknown (Yang et al., 2016).

Besides K63-linked ubiquitin chains, linear Met1-linked ubiquitin chains play a major role in canonical NF-κB signaling. Linear polyubiquitin chains are formed

by the linear ubiquitin chain assembly complex (LUBAC) consisting of HOIL1 (heme-oxidized IRP2 ubiquitin ligase 1), HOIP (HOIL1-interacting protein; also known as RNF31) and SHARPIN (SHANK-associated RH domain interacting protein). The subunit HOIP confers E3 ligase activity to the LUBAC complex (Tokunaga and Iwai, 2012). CBM complex association with the LUBAC complex upon T cell stimulation was shown to contribute to optimal NF-κB activation independent of HOIP ligase activity (Figure 3) (Dubois et al., 2014). Similarly, deletion of the catalytic domain of HOIP in B cells did not affect BCR driven NF-κB activation (Sasaki et al., 2013). However, a more recent study revealed that LUBAC-mediated linear ubiquitination of BCL10 supports NF-κB activation in a mouse B cell line upon BCR stimulation (Satpathy et al., 2015). Of note, BCL10 is also modified by linear ubiquitin chains during chronic BCR signaling in lymphomas (see section 'Chronic BCR signaling promotes aberrant CBM formation in lymphoma') (Yang et al., 2016), but whether Met1-linked ubiquitin chains are essential for antigen-receptor induced NF-κB activation under physiological conditions requires further investigations. Given the association of LUBAC and TRAF6, it is tempting to speculate that the combined recruitment of NEMO/IKKβ to LUBAC-catalyzed linear chains on BCL10 and TAB2/TAK1 to TRAF6-dependent K63-chains on MALT1 is necessary for productive activation of CBM downstream pathways. Certainly, more genetic and structural models are needed to clarify how LUBAC and TRAF6 cooperate in lymphocyte signaling.

Ubiquitination of BCL10, MALT1 and NEMO allows the recruitment of kinases, which mediate IKKα and IKKβ phosphorylation and thus IKK activation (Figure 3). TAK1, which is associated with the adaptors TAB2 and TAB3, acts as an upstream kinase of IKK upon TCR stimulation (Sun et al., 2004). K63-linked ubiquitin chains trigger the recruitment and activation of TAK1 to MALT1 via the ubiquitin-binding domain of TAB2 and TAB3 leading to phosphorylation of IKKα and IKKβ (Sun et al., 2004; Oeckinghaus et al., 2007). However, different groups observed contradictory results concerning the necessity of TAK1 in T cell and B cell receptor dependent NF-κB activation (Sato et al., 2005; Sato et al., 2006; Schuman et al., 2009). Since also MEKK3 positively regulates IKK kinase activity upon TCR stimulation, TAK1 and MEKK3 may synergize or compensate to activate the IKK complex (Shinohara et al., 2009). However, further data are needed to dissect the individual contribution of TAK1, MEKK3 and other putative kinases towards their IKK activating potential in T and B cells.

Upon TCR and BCR stimulation, CBM complex formation also triggers the activation of JNK signaling. Activation of JNK requires sequential phosphorylation of a MAP (mitogen-activated-protein) kinase module including MAPK, a MAPK kinase (MAP2K) and a MAP2K kinase (MAP3K) (Blonska and Lin, 2009). CARMA1-deficient T cells exhibit defects in JNK signaling and the CBM complex facilitates the recruitment of kinases mediating JNK phosphorylation and activation (Hara et al., 2003; Jun et al., 2003). Indeed, the IKK activating kinase TAK1 also serves as an upstream kinase of JNK. TCR stimulation triggers the recruitment of TAK1 to CARMA1-activated BCL10 oligomers, which are also associated with MKK7 leading to JNK2 activation and concomitant c-Jun accumulation and phosphorylation (Figure 3) (Blonska et al., 2007; Blonska and Lin, 2009). In line, MALT1 is indispensable for JNK signaling in T cells (Gewies et al., 2014; Jaworski et al., 2014; Meininger et al., 2016). Thus, CARMA1, BCL10 and MALT1 do not only activate IKK/NF-κB signaling, but also mediate a crosstalk to the JNK pathway. Besides TAK1, the MAP3K MEKK1 was shown to regulate TCR and CARMA1-dependent JNK activations indicating that association of the CBM complex with several MAP3K kinases is linking the CBM signalosome to the JNK pathway (Suddason et al., 2016).

Function of MALT1 protease activity for T cell activation

MALT1 harbors a paracaspase domain that shares high structural homology with metacaspases and mammalian caspases (Uren et al., 2000). However, initial studies failed to demonstrate proteolytic MALT1 activity and suggested that MALT1 is solely functioning as a signaling adaptor (Uren et al., 2000; Snipas et al., 2004), until evidence was provided that MALT1 indeed acts as a protease and cleaves distinct substrates upon TCR stimulation (Coornaert et al., 2008; Rebeaud et al., 2008).

Studies in mice expressing paracaspase mutant MALT1 revealed that the proteolytic activity of MALT1 plays a crucial role in adaptive immune responses (Gewies et al., 2014; Jaworski et al., 2014; Yu et al., 2015; Bornancin et al., 2015). Protease inactivation led to severe defects in T cell proliferation, IL-2 secretion as well as T_H17 cell differentiation, revealing the importance of MALT1 protease for T cell activation and differentiation. In line with observations from MALT1 deficient mice, also the development of B1 and marginal zone B cells is compromised in MALT1 protease dead mice. Further, inactivation of MALT1 protease protects mice from autoimmunity in a murine EAE model and in a T cell induced colitis model, suggesting

that MALT1 paracaspase might serve as a promising therapeutic target for the treatment of autoimmune diseases (Gewies et al., 2014; Jaworski et al., 2014; Bornancin et al., 2015). However, genetic inactivation of MALT1 activity also resulted in the development of spontaneous autoimmunity in multiple organs, which is caused by defects in T_{reg} cell differentiation and a failure to counterbalance immune activation by MALT1 scaffolding function (Gewies et al., 2014; Jaworski et al., 2014; Bornancin et al., 2015; Yu et al., 2015). Consequently, permanent MALT1 protease inactivation shifts the balance from tolerance to autoimmune activation. Thus, MALT1 protease promotes differentiation of T effector and T regulatory cells and thereby is of high importance for immune homeostasis.

Several MALT1 substrates have been identified (Figure 4). Interestingly, MALT1 itself and the constitutive binding partner BCL10 are cleaved upon TCR stimulation (Rebeaud et al., 2008; Baens et al., 2014). The function

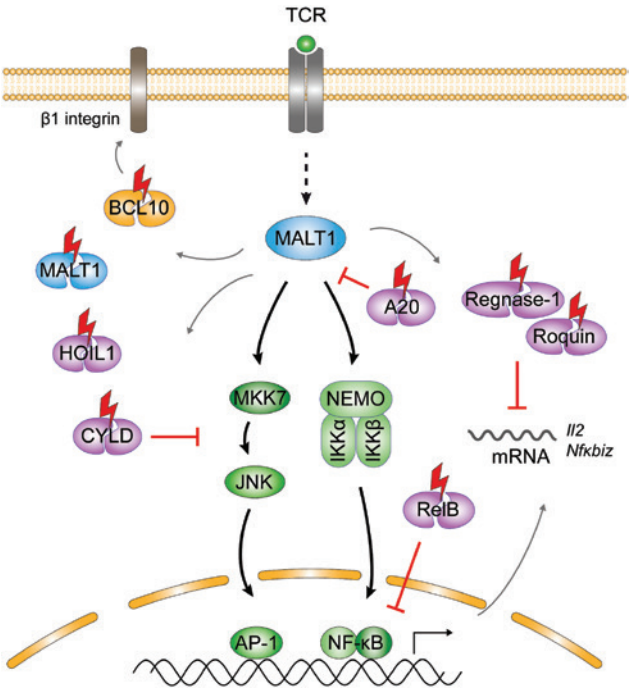

Figure 4: MALT1 protease supports optimal T cell activation. TCR stimulation triggers MALT1 paracaspase activation, which cleaves various regulators of NF-κB and JNK signaling, cell adhesion and mRNA stability. Whereas the relevance of MALT1 auto-cleavage is not understood, BCL10 cleavage can support T cell adhesion to fibronectin. MALT1 inactivates CYLD, A20 and RelB, which act as potential negative regulators of JNK or canonical NF-κB signaling. In contrast, cleavage of HOIL1 might serve as a negative feedback mechanism to dampen NF-κB activation. By cleaving RNA regulators Regnase-1 and Roquins, MALT1 protease stabilizes pro-inflammatory transcripts such as *IL2* and *NFKBIZ*, implicating a role of MALT1 in post-transcriptional gene regulation.

of auto-cleavage is unknown and BCL10 cleavage was suggested to control T cell adhesion, but the overall significance of BCL10 and MALT1 cleavage remains unclear. Initially, it was believed that MALT1 paracaspase mainly augments canonical NF-κB activation by cleaving mediators such as A20 and RelB (Coornaert et al., 2008; Hailfinger et al., 2011). Cleavage of the deubiquitinase A20, which acts as a negative regulator of NF-κB activation by removing K63-linked polyubiquitin chains from MALT1, decreases its ability to counteract NF-κB signaling (Coornaert et al., 2008; Duwel et al., 2009). However, upstream NF-κB signaling is largely unaffected by MALT1 protease activity, questioning the function of A20 cleavage at least for activation of naive CD4 T cells (Gewies et al., 2014; Jaworski et al., 2014). MALT1 cleaves the non-canonical NF-κB family member RelB, which was suggested to strengthen canonical NF-κB activation as inactivated RelB is no longer competing with canonical RelA or c-Rel for promoter occupancy (Hailfinger et al., 2011). The deubiquitinase CYLD is cleaved by MALT1 and it was shown that CYLD inactivation enhances JNK signaling in Jurkat T cells (Staal et al., 2011). However, MALT1 protease activity is not required for JNK signaling in CD4 T cells, revealing that the physiological role of CYLD cleavage is still elusive (Gewies et al., 2014; Jaworski et al., 2014). Recently, the LUBAC subunit HOIL1 was identified as a MALT1 substrate, which is in fact a positive regulator of NF-κB signaling (Klein et al., 2015; Douanne et al., 2016; Elton et al., 2016). Taken together, positive and negative regulators of lymphocyte signaling are substrates of MALT1 and we lack a complete picture how MALT1 cleavage affects signaling in the adaptive immune response.

The identification of the ribonuclease Regnase-1 (also known as Zcc3h12a and MCPIP1) and the RNA-binding proteins Roquin-1 and Roquin-2 as MALT1 substrates revealed a completely new biological function of MALT1 (Figure 4) (Uehata et al., 2013; Jeltsch et al., 2014). The RNAse Regnase-1 destabilizes a set of pro-inflammatory transcripts by cleaving their 3' UTRs and is thus essential for preventing aberrant T cell activation (Matsushita et al., 2009; Uehata et al., 2013). As deletion of Regnase-1 in mice causes systemic inflammation, Regnase-1 might be critical for preventing autoimmunity (Matsushita et al., 2009). RNA stability is further controlled by RNA-binding proteins, such as Roquin-1 and Roquin-2, which bind to decay elements in 3' UTRs and regulate mRNA half-life (Leppek et al., 2013). T cell specific loss of Roquins resulted in inflammation and lung pathology (Jeltsch et al., 2014). By cleaving Roquins and Regnase-1, MALT1 promotes stabilization of pro-inflammatory transcripts such as IL-6, c-Rel, IRF4, ICOS, IκBNS and IκBζ,

which are crucial factors for T_H17 cell differentiation (Jeltsch et al., 2014). In line with this, defective cleavage of Roquins as well as Regnase-1 was observed in T cells from MALT1 paracaspase dead mice (Gewies et al., 2014). The finding that MALT1 paracaspase regulates RNA stability reveals an unexpected role of MALT1 in the regulation of post-transcriptional gene expression. In addition, an involvement of MALT1 protease in metabolic signaling pathways has been described, as inhibition of the paracaspase prevents glutamine uptake and mTORC1 signaling (Hamilton et al., 2014; Nakaya et al., 2014). Collectively, it becomes clear that MALT1 paracaspase modulates mRNA stability and metabolic changes in T cells, which accounts for optimal T cell activation, differentiation and effector functions.

Despite the suggested consensus cleavage motif LXS/PR (Klein et al., 2015), it is still open how and where MALT1 recognizes its substrates. Antigen-triggered MALT1 activity relies on CARMA1 and is enhanced by association with BCL10 filaments, proposing that all substrates need to colocalize at the CBM complex (Qiao et al., 2013). However, CBM association is not required to maintain MALT1 in an active conformation (Eitelhuber et al., 2015), suggesting that, once activated, MALT1 may diffuse throughout the cell to reach and cleave diverse substrates. To evaluate the biological role, future studies will not only need to identify all MALT1 substrates, but they will also need to unravel how and where the substrates are cleaved.

As MALT1 activity is essential for adaptive immunity and lymphoma survival (see section 'Chronic BCR signaling promotes aberrant CBM formation in lymphoma'), many efforts have been pursued to develop specific MALT1 inhibitors. The peptide z-VRPR-fmk was the first identified MALT1 inhibitor, which blocks catalytic MALT1 activity in an irreversible manner (Rebeaud et al., 2008). However, as z-VRPR-fmk holds poor pharmacological properties, high throughput screening approaches have been undertaken to identify small molecule inhibitors. Two studies could identify either the phenothiazine-derivatives Mepazine and Thioridazine or the compound MI-2 as MALT1 inhibitors (Fontan et al., 2012; Nagel et al., 2012). MI-2 was suggested to irreversibly bind to the active site of MALT1, but recent data indicate that the compound is not specifically targeting the catalytic center of MALT1 (Xin et al., 2016). Mepazine and Thioridazine act as noncompetitive, reversible inhibitors by attaching to an allosteric binding site between the paracaspase and the Ig3 domain preventing the conformational changes needed for MALT1 activation (Schlauderer et al., 2013). Interestingly, treatment of mice with the phenothiazine mepazine attenuates induction and progression of EAE supporting the clinical use of MALT1 inhibitors for the treatment of autoimmune diseases (McGuire et al., 2014). The decreased number of T_{reg} cells in MALT1 paracaspase deficient mice raised concerns whether MALT1 inhibition might be a useful strategy to treat immunological diseases (Gewies et al., 2014; Jaworski et al., 2014; Bornancin et al., 2015). However, inactivation of MALT1 with Mepazine did not affect T_{reg} cell development in a murine multiple sclerosis model indicating a discrepancy between genetic and pharmacologic MALT1 inhibition (McGuire et al., 2014). Therefore, studies using long-term administration of MALT1 inhibitors are required to evaluate the effects of pharmacologic MALT1 inactivation on T_{reg} cell development and thus their therapeutic potential for the treatment of autoimmune inflammatory diseases.

Chronic BCR signaling promotes aberrant CBM formation in lymphoma

Recent clinical data have demonstrated that inhibition of BTK (Bruton's tyrosine kinase) that connects BCR upstream processes to CBM-triggered NF-κB signaling represents a promising approach to treat different B cell malignancies, such as chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL) and diffuse large B cell lymphoma (DLBCL) (Hendriks et al., 2014; Wilson et al., 2015). DLBCL comprise the largest group of non-Hodgkin lymphomas and classification-based gene expression profiling has defined the sub-entity of activated B cell type (ABC) DLBCL, which is the most aggressive lymphoma with a cure rate of ~40% (Staudt and Dave, 2005).

ABC DLBCLs originate from an activated B cell and are addicted to chronic BCR signaling. Accordingly, protein kinases such as SYK, BTK and PKCβ that connect the BCR to the IKK/NF-κB pathway are constitutively active and drive survival of the lymphoma cells (Lim et al., 2012) (Figure 5). Chronic BCR signaling can be caused by BCR ligation through self-antigens or oncogenic mutations in the BCR adaptor CD79A/B (~21% of cases) and these lymphomas are sensitive to BCR pathway inhibitors like Ibrutinib (BTK inhibitor) or Sotrastaurin (PKCβ inhibitor) (Davis et al., 2010; Naylor et al., 2011; Young et al., 2015). However, somatic gain-of-function mutations are also recurrently found in the downstream component CARMA1 (~10%), rendering lymphoma cells resistant to BCR pathway inhibitors (Lenz et al., 2008; Wilson et al., 2015). Importantly, the CBM complex is constitutively assembled in all ABC DLBCL cells that rely on chronic BCR

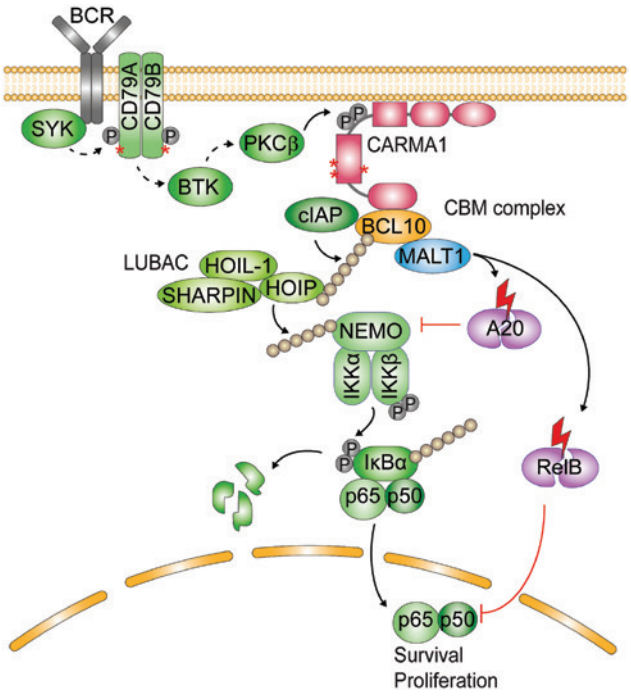

Figure 5: Chronic active BCR promotes canonical NF-κB signaling in ABC DLBCL.
ABC DLBCL cells are addicted to expression and activation of the BCR and downstream signaling mediators such as SYK, BTK and PKCβ. Chronic BCR signaling induces CARMA1 phosphorylation by PKCβ, which promotes constitutive CBM complex assembly, leading to canonical IKK/NF-κB signaling and activation of the MALT1 protease. In ABC DLBCL cells, NF-κB survival pathway is triggered by somatic gain-of-function mutations (red stars) in the BCR adaptor CD79A and CD79B or the CBM scaffold protein CARMA1. Whereas CD79 mutants still rely on a functional BCR, oncogenic CARMA1 mutations are disconnecting the CBM from upstream BCR signaling. Canonical IKK activation requires association of cIAPs and the linear ubiquitin chain assembly complex (LUBAC) to the CBM complex and the formation of linear and Lys63-linked ubiquitin chains on multiple signaling mediators. Constitutive MALT1 paracaspase catalyzes cleavage of substrates like the tumor suppressor A20 and RelB, which have been associated with inhibition of NF-κB dependent survival signaling in ABC DLBCL.

signaling or oncogenic CARMA1 mutations. Inactivation of CARMA1, BCL10 or MALT1 as well as the downstream effector IKKβ kills ABC DLBCL cells (Ngo et al., 2006; Ferch et al., 2009). Thus, the CBM signalosome does not only function as a critical signaling platform in lymphocytes upon antigen engagement, it also conveys chronic NF-κB activation and survival in lymphomas. Accordingly, the CBM and its control machinery are potential targets for anti-cancer therapy especially in patients that either fail to respond or develop resistance to BCR signaling drugs.

Oncogenic mutations in CARMA1 are largely confined to the CC domain (Lenz et al., 2008). *In vivo* studies underscore the potency of activating CARMA1 mutants, as their expression in activated B cells is preventing self-antigen induced cell death (Jeelall et al., 2012). Further, expression of oncogenic CARMA1 in murine B cells induces lymphocyte proliferation and post-natal lethality (Knies et al., 2015). As discussed earlier (see section 'Physiological role of the CBM complex in lymphocytes'), activating CARMA1 germline mutations induce the BENTA phenotype in humans that is characterized by B cell expansion, but at the same time T cell hyporesponsiveness and anergy (Snow et al., 2012). Even though CARMA1 mutation alone may not be sufficient to cause lymphomas, the B lymphocytes carrying CARMA1 germline or somatic mutation are likely more prone to lymphomagenesis (Brohl et al., 2014). Interestingly, T cell unresponsiveness in BENTA patients suggests the existence of specific negative regulatory mechanisms in T cells that may prevent formation of T cell lymphomas by oncogenic CARMA1.

Mechanistically, oncogenic CARMA1 is thought to induce the open conformation and oligomerization of CARMA1 that allows BCL10-MALT1 recruitment independent of upstream signaling (Figure 5). In line, activating CARMA1 mutations provoke the formation of large BCL10 filamentous aggregates in ABC DLBCL cells (Qiao et al., 2013). Despite the resistance of CARMA1 mutant DLBCL to BTK inhibitors, kinases like CK1α associate with oncogenic CARMA1 (Bidere et al., 2009; Bognar et al., 2016). Of note, even though deletion of the CARMA1 linker and CARMA1 CC mutations strongly induce NF-κB, only oncogenic mutants are leading to Ibrutinib resistance (Bognar et al., 2016).

Recent data unraveled a critical function of the LUBAC in connecting the pathologic CBM complex to IKK/NF-κB activation. The E3 ligases cIAP1/2 are associated with the constitutive CBM complex in ABC DLBCL cells and conjugate Lys63-linked ubiquitin chains to BCL10, which in turn recruits the LUBAC (Yang et al., 2016) (Figure 5). In line, SMAC mimetics that inhibit cIAP1/2 kill ABC DLBCL cells that rely on chronic BCR signaling. Again, ABC DLBCL cells carrying CARMA1 mutations are refractory to cIAP inhibitors, providing evidence that these mutations render CBM complex signaling independent of upstream events (Yang et al., 2016). Moreover, two human germline polymorphisms that induce hyper-activation of HOIP are significantly enriched in ABC DLBCL patients compared to healthy individuals (Yang et al., 2014). HOIP E3 ligase activity is required for canonical NF-κB activation and survival of CD79B mutant DLBCL (Yang et al., 2016). Altogether, these results reveal that LUBAC is a critical regulator of the CBM complex and thus a new putative drug

target for treatment of lymphomas that rely on chronic BCR signaling.

Congruent with antigen-driven activation in lymphocytes, the MALT1 protease is constitutively active in ABC DLBCL and required for growth and survival of the tumor cells (Ferch et al., 2009; Hailfinger et al., 2009). Similar substrate cleavage has been observed in ABC DLBCL and activated T cells and MALT1 cleaves A20, RelB and CYLD, which are thought to act as negative regulators of canonical NF-κB or JNK signaling (Ferch et al., 2009; Hailfinger et al., 2011; Fontan et al., 2012). However, the pathological consequences of the cleavage of these MALT1 substrates still await further analyses. Further, it will be interesting to see if the recently identified RNA-binding factors Regnase-1 and Roquins are also prone to MALT1 cleavage in ABC DLBCL and whether their inactivation contributes to lymphomagenesis. The impact of MALT1 has been proven by the identification of small molecule MALT1 inhibitors (see section 'Structural features of CBM complex components' and 'Function of MALT1 protease activity for T cell activation') that showed promising effects in preclinical ABC DLBCL tumor models (Fontan et al., 2012; Nagel et al., 2012). As targeting MALT1 is also effectively killing CARMA1 mutant DLBCL cells, MALT1 inhibition may be a strategy either to treat patients that do not respond to upstream BTK or cIAP inhibitors or for combinatorial treatment to reduce the chances of therapy induced resistances.

Conclusions

Significant progress has been made in our understanding of how antigen-receptor signaling triggers lymphocyte activation, which is key for mounting a specific adaptive immune response. Assembly of the higher order CARMA1-BCL10-MALT1 (CBM) signalosome is critical for NF-κB and JNK signaling in activated T and B cells. Chronic BCR signaling or oncogenic CARMA1 mutations promote lymphomagenesis, highlighting that CBM complex disassembly and termination of signaling are essential to avoid cancer. Studies addressing the kinetics of CARMA1 phosphorylations and a global mass spectrometry approach identifying CBM modifications gave first insights into the complexity of regulation upon BCR stimulation (Shinohara et al., 2014; Satpathy et al., 2015). More detailed quantitative proteomics are required to pin down which modifications over time are controlling the assembly, activity and disassembly of the CBM complex. In particular, it will be important to decipher how different ubiquitin ligases and ubiquitin chains orchestrate lymphocyte signaling. Despite striking similarities in the molecular CBM control machinery in B and T cells, there are also clear differences in the mechanisms counteracting deregulated signaling (Snow et al., 2012). It will also be important to unravel how the CBM complex is regulated in different immune cells with regard to pharmacological targeting. Recent data on MALT1 protease activation and inhibition reveal how a detailed understanding of the CBM complex can guide the way for new therapeutic strategies to treat malignant lymphomas or autoimmune diseases (Nagel et al., 2012; Mc Guire et al., 2014). However, future studies must address the intricate balance of how MALT1 controls immune activation versus homeostasis to be able to predict the clinical potential of MALT1 inhibitors.

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