Role of the CARMA1/BCL10/MALT1 complex in lymphoid malignancies

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Purpose of review
The CARMA1/BCL10/MALT1 (CBM) complex is a multimeric signaling complex controlling several important aspects of lymphocyte activation. Gain-of-function mutations in the genes encoding CBM proteins or their upstream regulators are associated with lymphoid malignancies, whereas loss-of-function mutations lead to immunodeficiency. This review reports on recent findings advancing our understanding of how CBM proteins contribute to malignant and nonmalignant hematological diseases in humans.

Recent findings
Somatic gain-of-function mutations of CARMA1 (also known as CARD11), originally described for patients with diffuse large B-cell lymphoma, have recently been identified in patients with acute T-cell leukemia/lymphoma or Sézary syndrome, and in patients with a B-cell lymphoproliferative disorder known as BENTA. Loss-of-function mutations of *CARMA1* and *MALT1*, on the other hand, have been reported to underlie human immunodeficiency. Lately, it has become clear that CBM-dependent signaling promotes lymphomagenesis not only via NF-κB activation, but also via the AP-1 family of transcription factors. The identification of new substrates of the protease MALT1 and the characterization of mice expressing catalytically inactive MALT1 have deepened our understanding of how the CBM complex controls lymphocyte proliferation through promoting MALT1's protease activity.

Summary
The discovery of *CARMA1* gain-of-function mutations in T-cell malignancies and BENTA patients, as well as the association of *CARMA1* and *MALT1* mutations with human immunodeficiency highlight the importance of CBM proteins in the regulation of lymphocyte functions, and suggest that the protease activity of MALT1 might be targeted to treat specific lymphoid malignancies.

Keywords
AP-1, CARD11, immunodeficiency, lymphoma, NF-κB

INTRODUCTION

The multimeric CARMA1/BCL10/MALT1 (CBM) complex, composed of the scaffold protein CARMA1 (also known as CARD11), the adaptor protein BCL10, and the protease MALT1, plays an important role in signal transmission after antigen receptor stimulation [1]. Triggering of the antigen receptor induces a protein kinase C (PKC)-dependent phosphorylation of CARMA1, which leads to a conformational change in CARMA1. This nucleates the formation of a fibrillar, high molecular weight complex containing CARMA1 together with oligomerized BCL10 and MALT1 [2,3]. CBM complex formation is required for the activation of the transcription factors NF-κB and AP-1, which regulate various aspects of lymphocyte proliferation, differentiation, and survival [4]. The CBM complex also controls transcription-independent aspects of lymphocyte activation, such as regulation of transcript stability, cellular adhesion, and metabolic changes [4]. Genetic studies using mice deficient in CARMA1, BCL10, or MALT1 have revealed an essential role for these CBM proteins in immunoreceptor-induced cellular activation, as mice lacking these proteins are immunodeficient [4]. Moreover, inactivating germline mutations of

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KEY POINTS

- Constitutive CBM signaling is present in various B- and T-cell lymphomas, including DLBCL, MCL, ATLL, and Sézary syndrome.
- CBM signaling promotes lymphomagenesis via activation of the NF-kB and AP-1 transcriptional pathways.
- Targeting the protease activity of MALT1 may be a promising option in the treatment of CBM-driven lymphomas.

CARMA1 and *MALT1* have recently been identified in a small number of common immunodeficiency patients [5]. CBM hyperactivity, on the other hand, has emerged as a hallmark of lymphomagenesis. Originally, chromosomal translocations of *BCL10* or *MALT1* had been identified in lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma) [1]. Subsequently, gain-of-function mutations in CARMA1 or its upstream regulator, the B-cell receptor (BCR)-associated CD79 chains, have been described in diffuse large B-cell lymphoma (DLBCL) of the activated B-cell (ABC) subtype [6]. The purpose of this review is to update on recent findings describing novel gain-of-function mutations in CARMA1 and other CBM signaling components in an increasing number of B- and T-cell malignancies [7,8,9▪▪–11▪▪] and in patients with a lymphoproliferation disorder known as BENTA disease [12,13▪,14▪]. We also highlight novel molecular insights into aspects of lymphocyte activation that are controlled by CBM-dependent AP-1 activation [15▪▪–17▪▪] and by the MALT1-dependent cleavage of specific cellular substrates [18–20,21▪, 22▪,23–26].

CONSTITUTIVE CARMA1/BCL10/MALT1 SIGNALING CHARACTERIZES DIFFUSE LARGE B-CELL LYMPHOMA AND MANTLE CELL LYMPHOMA SUBSETS

Over the last few years, constitutive activation of CBM signaling has been recognized as a common feature of an increasing number of B- and T-cell malignancies and B-cell proliferative diseases (Fig. 1). Generally, this has been linked to gain-of-function mutations of CARMA1 or its upstream regulators, and/or to self-antigen-driven, constitutive BCR signaling [1,6].

A pathogenic role for CBM signaling was originally discovered in ABC DLBCL, in which this pathway can be activated or sustained by gain-of-function mutations in *CARMA1* [27], or its upstream regulator, the BCR-associated CD79A/B complex [28], and by self-antigen driven BCR stimulation [29] (Fig. 1a). Mutations in CARMA1, which were present in 9.6% of the cases, were exclusively located in proximity of or within the coiled-coil region of CARMA1, which is required for the induction of an active conformation and oligomerization of this protein [27] (Fig. 2a). Functional

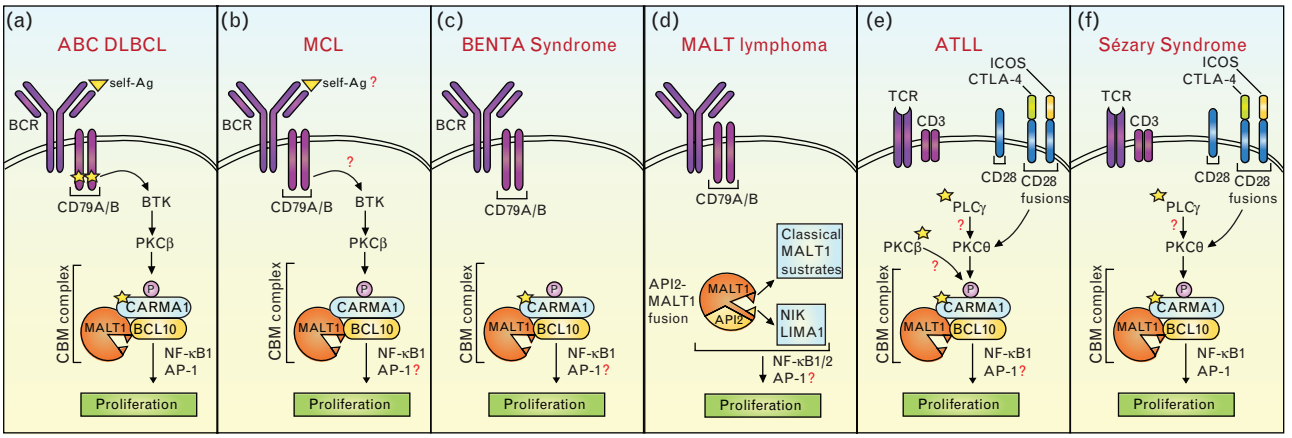

FIGURE 1. Constitutive CBM signaling in B- and T-cell malignancies. Underlying mechanisms include (a) mutations in CD79A or CD79B and CARMA1/CARD11, and self-antigen recognition, (b) self-antigen recognition or mutations upstream of BTK, (c) germline mutations in CARMA1, (d) generation of a MALT1-API2 fusion protein that activates the classical (NF-κB1) and nonclassical (NF-κB2) pathway, (e, f) gain-of function mutations in PLCγ1, PKCβ, or CARMA1, and in frame mutations of the T-cell co-receptor CD28 with ICOS or CTLA-4. In all figure panels, recurrent mutations are indicated with a yellow star. ABC, activated B-cell; ATLL, acute T-cell leukemia/lymphoma; BENTA, B-cell expansion with NF-κB and T-cell anergy; BCR, B-cell receptor; CBM, CARMA1/BCL10/MALT1; CTLA-4, cytotoxic T lymphocyte-associated protein 4; DLBCL, diffuse large B-cell lymphoma; ICOS, inducible costimulator; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphomas; PKC, protein kinase C; TCR, T-cell receptor.

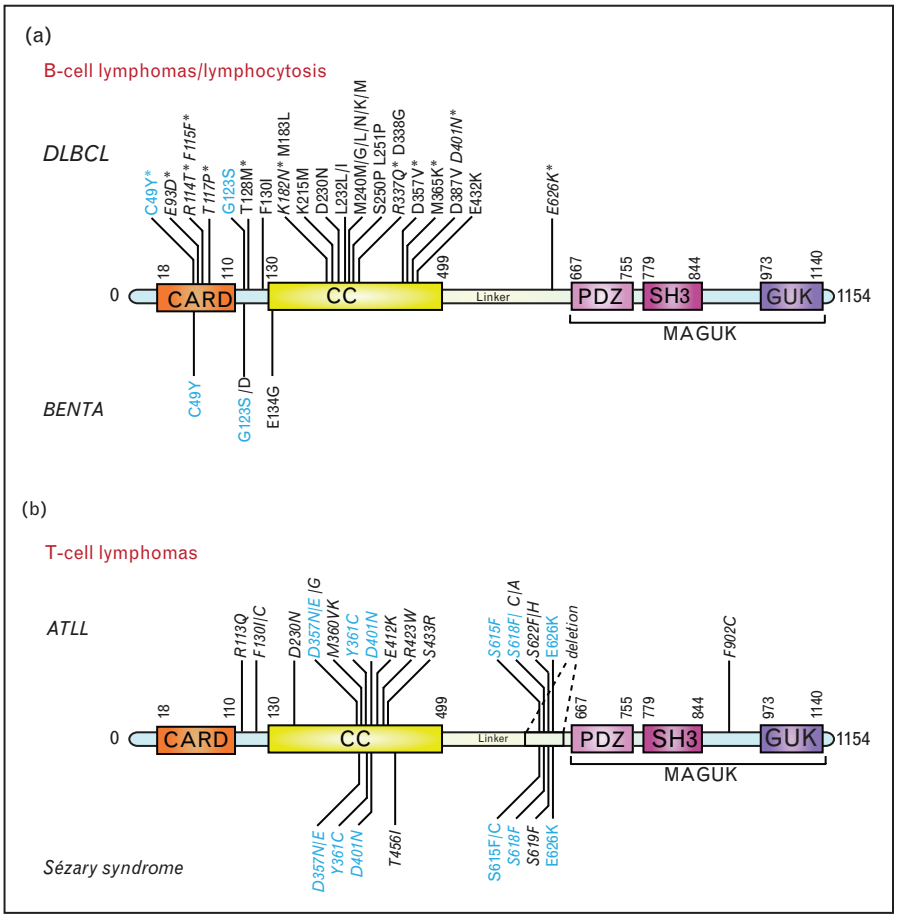

FIGURE 2. Described CARMA1/CARD11 mutations (a) Mutations found in ABC DLBCL and BENTA. An asterisk indicates mutations in DLBCL that were not clearly identified as ABC DLBCL. Amino acid numbers of some CARMA1 mutations [7] have been adjusted to the UniProt sequence. (b) Mutations identified in ATLL and Sézary syndrome; 8% of ATLL cases have a CARMA1 deletion within the linker domain. Mutations that were not functionally tested are indicated in italics. Mutations common to DLBCL and BENTA (a) or common to Sézary syndrome and ATLL (b) are highlighted in blue. ABC, activated B-cell; ATLL, acute T-cell leukemia/lymphoma; BENTA, B-cell expansion with NF-κB and T-cell anergy; CARD, caspase recruitment domain; CC, coiled coil; DLBCL, diffuse large B-cell lymphoma; GUK, guanylate kinase domain; MAGUK, membrane-associated guanylate kinase; PDZ, domain found in the proteins PSD95, Dlg1 and ZO-1; SH3, Src homology-3 domain.

characterization of these point mutants identified for the first time CARMA1 as a 'bona fide' oncogene [27]. CARMA1 mutations were independently identified in DLBCLs in several other studies [8,30–33]. Most of these mutations resided in the CARD-CC hot spot region, and are thus likely gain-of-function mutations.

Other recurrent alterations found in ABC DLBCL are mutations in the BCR-associated CD79A/B chains [28]. In contrast to the CARMA1 mutations, CD79 mutations are not sufficient to activate NF-κB signaling, but increase the surface expression of the BCR [28]. A recent study proposes that self-antigen stimulation is required in addition to CD79 mutations to sustain CBM signaling in ABC DLBCL [29]. Self-antigens may also drive the growth of other ABC DLBCL patients without detectable CD79 mutations [34] (Fig. 1a).

In addition to ABC DLBCL lymphomas, a subset of mantle cell lymphomas (MCL) has recently been shown to depend on chronic BCR-dependent signaling, and to present constitutive MALT1 and NF-κB activation [35]. Genome sequencing revealed no mutations in the BCR pathway that could explain why this subset is BCR addicted [35]. It is possible that these MCL cases are driven by yet unknown gene mutations and/or by nongenetic mechanisms such as self-antigen recognition, since the repertoire of the immunoglobulin heavy variable genes of MCL is biased [36] (Fig. 1b).

CONSTITUTIVE CARMA1 ACTIVATION CAN CAUSE BENTA SYNDROME

Recently, germline gain-of-function mutations in *CARMA1* were identified in patients with a B-cell