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MALT1 protease: a new therapeutic target in B-lymphoma and beyond?

Linda M. McAllister-Lucas[1], **Mathijs Baens**[2,3], and **Peter C. Lucas**[4]

[1]Department of Pediatrics and Communicable Diseases, University of Michigan, 1150 W. Medical Center Dr., Ann Arbor, MI, 48109, USA

[2]Human Genome Laboratory, Molecular Genetics, Center for Human Genetics, Catholic University Leuven, B-3000 Leuven, Belgium

[3]Human Genome Laboratory, Department of Molecular and Developmental Genetics, Flanders Institute for Biotechnology (VIB), B-3000 Leuven, Belgium

[4]Department of Pathology, University of Michigan, 1150 W. Medical Center Dr., Ann Arbor, MI, 48109, USA

Abstract

The identification of *MALT1* as a gene that is perturbed in the B cell neoplasm MALT lymphoma, already more than a decade ago, was the starting point for an intense area of research. The fascination with MALT1 was fueled further by the observation that it contains a domain homologous to the catalytic domain of caspases and thus potentially could function as a protease. Discoveries since then initially revealed that MALT1 is a key adaptor molecule in antigen receptor signaling to the transcription factor NF-κB, which is crucial for lymphocyte function. However, recent discoveries show that this function of MALT1 is not restricted to lymphocytes, witnessed by the ever increasing list of receptors from cells within and outside of the immune system that require MALT1 for NF-κB activation. Yet, a role for MALT1 protease activity was demonstrated only recently in immune signaling and its importance was then further strengthened by the dependency of NF-κB-addicted B cell lymphomas on this proteolytic activity. Therapeutic targeting of MALT1 protease activity might therefore become a useful approach for the treatment of these lymphomas, and additionally, an effective strategy for treating other neoplastic and inflammatory disorders associated with deregulated NF-κB signaling.

Background

MALT1, a regulator of NF-κB signaling

The *Mucosa Associated Lymphoid Tissue lymphoma translocation 1 (MALT1)* gene was first identified by virtue of its involvement in the recurrent t(11;18)(q21;q21) chromosomal translocation in the B-cell neoplasm, MALT lymphoma (1-3). This translocation creates a fusion oncoprotein consisting of the carboxy terminus of MALT1 linked to the amino terminus of cellular inhibitor of apoptosis 2 (abbreviated as cIAP2 or API2) (Fig. 1A). MALT1 was noted to contain a putative proteolytic domain that bears similarity to the active site of the caspase family of cysteine proteases (3-5). However, structural analyses suggested that, in contrast to caspases, MALT1 would show specificity for substrates with a

Corresponding Author: Linda M. McAllister-Lucas, 3520 MSRB1, 1150 Medical Center Dr. University of Michigan Medical Center, Ann Arbor, MI 48109. Phone: 734-232-2788, Fax: 734-763-9512, lindaluc@umich.edu.

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basic or uncharged amino acid in the P1 position (amino-terminal to the cleavage site). Hence, MALT1 has been classified as a 'paracaspase' to distinguish it from caspases and to recognize its similarity to other 'paracaspase' family members found in zebrafish and *Dictyostelium* (5).

The discovery that expression of API2-MALT1 results in constitutive activation of the canonical NF-κB pathway (4,5) led to numerous investigations of the role of MALT1 as a regulator of the NF-κB family of transcription factors. MALT1 binds to the adaptor protein, BCL10, and synergizes with BCL10 in promoting canonical NF-κB activation (4,5). Notably, *MALT1* and *BCL10* can each be deregulated via the recurrent t(14;18)(q32;q21) and t(1;14)(p22;q32) translocations in MALT lymphoma, respectively, because these translocations bring the *MALT1* or *BCL10* gene under the control of the Ig-heavy-chain gene enhancer, thus leading to inappropriately enhanced expression (6). In addition to its "caspase-like" proteolytic domain, MALT1 contains an amino-terminal death domain (DD) and three Ig-like protein-protein interaction domains (Fig. 1A). BCL10 binds to a region of MALT1 that comprises the DD and first Ig domain, and this interaction induces the oligomerization of MALT1 (4,7). MALT1 oligomerization triggers activation of the Inhibitor of kappa B kinase (IKK) complex, leading to phosphorylation dependent-degradation of inhibitor of kappa-Bα (IκBα) and release of transcriptionally active NF-κB dimers, composed primarily of p65(relA) and p50, into the nucleus (Fig. 1B) (4,8). In the case of API2-MALT1, API2 moiety-mediated auto-oligomerization allows for constitutive NF-κB activation in the absence of BCL10 (9,10), and API2 moiety-mediated recruitment of other NF-κB signaling proteins, such as TRAF2, also contributes to API2-MALT1-dependent NF-κB activation (7,9,11). The precise mechanism by which MALT1 or API2-MALT1 stimulates IKK activation is not completely understood, but involves recruitment of the ubiquitin ligase, TRAF6, (7,8) and the TRAF6-directed, K63-linked ubiquitination of several proteins, including IKKγ, BCL10 and MALT1 itself (12-14). Early studies suggested that the MALT1 "caspase-like" domain plays a role in NF-κB signaling, as substitution of the predicted active-site cysteine caused a reduction in NF-κB activation by BCL10 / MALT1 or API2-MALT1 (4,5).

Analysis of MALT1 knock-out mice revealed that MALT1 plays a critical role in the adaptive immune response by mediating antigen-dependent NF-κB activation in lymphocytes (15,16). Biochemical studies then elucidated the specific molecular mechanisms by which MALT1 can be activated in response to antigen receptor engagement. T-cell receptor (TCR) or B-cell receptor (BCR) stimulation induces PKC-dependent phosphorylation of CARMA1, a member of the MAGUK family of scaffolding proteins. This phosphorylation induces a conformational change that allows CARMA1 to recruit BCL10/MALT1 to the receptor and form the CARMA1-BCL10-MALT1 (CBM) complex (17,18) (Fig. 1B). In the T-cell, formation of the CBM complex is assisted by the coordinated engagement of the CD28 co-receptor which stimulates PI3-kinase dependent phosphorylation of PDK1. Activated PDK1 then stimulates PKCθ and serves to scaffold the TCR with the CBM complex (19,20). CBM-mediated recruitment of multiple signaling proteins, such as TRAF6 and the IKK complex, then sets in motion canonical NF-κB activation, leading to cytokine production and cellular proliferation in response to antigen. This precise role for MALT1 is less firmly established in B-cells, as compared to T-cells. While MALT1-deficient T-cells fail to induce IKK-dependent stimulation of NF-κB, proliferate and secrete IL-2 in response to TCR stimulation (15,16), the nature of the relationship between BCR stimulation, MALT1-dependent NF-κB signaling, and B-cell activation remains less well understood. Recent studies suggest that MALT1 may be specifically required only for activation of the c-Rel NF-κB subunit, but not essential for IKK recruitment or activation after BCR engagement (21).

In addition to its role in lymphocyte antigen receptor signaling, MALT1 has now been shown to have a critical function downstream of a variety of other cell surface receptors, both within and outside of the immune system (Table 1). For example, MALT1 mediates BAFF-dependent antiapoptotic gene induction in marginal zone B-cells (22) and IgE FcεRI receptor-mediated secretion of TNFα and IL-6 in mast cells (23). In macrophages, MALT1 has been implicated in mediating NF-κB activation downstream of the innate immune / pattern recognition receptors TLR4 and Dectins-1 and -2 (24-26), and in natural killer cells, MALT1 operates downstream of multiple ITAM-coupled receptors (27). Together, these studies demonstrate that MALT1 plays a significant and complex role in multiple aspects of immunity.

Moreover, recent studies reveal that the MALT1-containing CBM complex also plays a role downstream of G protein-coupled receptors (GPCRs) in a variety of non-immune cell types. In these cases, GPCR-dependent PKC activation triggers the assembly of a CBM complex containing CARMA3, a homolog of CARMA1 that is expressed in cells outside of the hematopoietic system (Fig. 1B). Thus far, evidence suggests that MALT1 plays a critical role in mediating NF-κB activation downstream of the GPCRs for lysophosphatidic acid (LPA), angiotensin II (Ang II), CXCL8/IL-8, CXCL12/SDF-1α and thrombin (28-32). As a mediator of GPCR-dependent signaling, MALT1 may play a critical role in the pathophysiology of NF-κB-driven carcinomas and inflammatory diseases. For example, LPA stimulates the proliferation, migration and survival of ovarian cancer cells, and this effect is due, in part, to upregulation of urokinase plasminogen activator (uPA). MALT1 silencing inhibits LPA-mediated uPA upregulation, suggesting that MALT1 may play a role in ovarian cancer pathogenesis (33). Similarly, MALT1 silencing in oral squamous cell carcinoma inhibits cellular invasion in response to CXCL12/SDF-1α (31). MALT1 is also expressed in vascular smooth muscle cells and endothelial cells, where it is required for CXCL8-dependent up-regulation of the proangiogenic growth factor, VEGF, and for thrombin-dependent adhesion of monocytes, suggesting that MALT1 has a role in neovascularization, endothelial dysfunction, and atherosclerosis (30,32,34) These ongoing investigations into GPCR-dependent MALT1-mediated signaling indicate that, in addition to its classical role in lymphocyte function and lymphomagenesis, MALT1 may also play a significant role in solid tumor biology and vascular pathophysiology.

MALT1 is a protease

Despite early recognition of the structural similarity between the MALT1 ‘paracaspase’ and the caspase family of cysteine proteases, attempts to demonstrate MALT1 protease activity were initially unsuccessful (5,35). Several years later, the MALT1-binding partner, BCL10, and the ubiquitin editing protein, A20, were identified as MALT1 proteolytic substrates. In both cases, mapping of the specific site of cleavage demonstrated that, in contrast to caspases which cleave their substrates after a negatively charged Asp residue, MALT1 cleaves protein substrates after a positively-charged Arg residue (36,37). This finding was consistent with predictions that had been made years earlier, based on the amino acid composition of the presumed substrate recognition pocket (5). MALT1-mediated BCL10 cleavage is induced following stimulation of the TCR or BCR, and cleavage occurs at a single site five amino acids from the carboxy-terminal end of the protein, between Arg228 and Thr229. Interestingly, BCL10 cleavage is not required for antigen-dependent NF-κB activation, but may play a role in integrin-mediated T-cell adhesion (Fig. 1B) (36).

A20, a ubiquitin editing enzyme that negatively regulates NF-κB, possesses dual functions: the enzyme removes K63-linked polyubiquitin from its substrates, and can then catalyze K48-linked polyubiquitination, thus targeting its substrates for proteasome-mediated degradation (38). In T-cells, A20 inhibits antigen receptor-mediated NF-κB activation, likely via its ability to remove K63-linked polyubiquitin chains from multiple substrates, including

TRAF2, TRAF6, receptor interacting protein 1 (RIP1), BCL10, the IKK-γ subunit and even MALT1 itself (37,39,40). A20 deficiency protects B-cells from cell death, and *A20* is frequently inactivated in B-lineage lymphomas, indicating its role as a critical tumor suppressor (41-43). In response to TCR or BCR stimulation, MALT1 proteolytically cleaves human A20 after Arg439, thereby separating the deubiquitinase (DUB) domain from the C-terminal zinc finger substrate-interaction / ubiquitin ligase domain, and this cleavage results in loss of A20's NF-κB inhibitory function (37) (Fig. 1A). It is speculated that separation of the N-terminal DUB domain from the C-terminal substrate interaction domain prevents the removal of K63-linked polyubiquitin from A20 substrates, thereby preserving activating ubiquitination events and promoting NF-κB activity (Fig. 1B) (37). In this way, MALT1 protease activity amplifies the degree of NF-κB-dependent gene expression. A later report demonstrated that two other potential MALT1 cleavage sites are present within A20, and cleavage by MALT1 induces the cytosolic release of an N-terminal A20 fragment, suggesting that changes in cellular compartmentalization may also be a mechanism by which MALT1-mediated cleavage alters A20 activity (44).

A third MALT1 proteolytic substrate, CYLD, was recently identified (45). Like A20, CYLD is a tumor suppressor deubiquitinating enzyme that negatively regulates NF-κB (40). *CYLD* was originally identified as a gene that is mutated in familial cylindromatosis, a disorder in which mutations resulting in truncated CYLD proteins lacking DUB activity are associated with benign tumors of the skin adnexa (46). Subsequently, CYLD has been more broadly implicated as a tumor suppressor for multiple types of cancer including the B-cell neoplasm, multiple myeloma (40). Interestingly, CYLD de-ubiquitinates many of the same substrates as A20, including TRAF2, TRAF6, RIP1 and IKKγ (40). In response to TCR stimulation, MALT1 cleaves CYLD after Arg324 (Fig. 1B and Table 1). Surprisingly, a non-cleavable CYLD mutant does not impair TCR-dependent canonical NF-κB activation, but does block activation of JNK, a critical step in TCR-induced stimulation of multiple transcription factors and production of IL-2 (45).

A new study now suggests that in addition to its role in adaptive immunity, MALT1 protease activity also contributes to the innate immune response by mediating Dectin-dependent signaling in human primary dendritic cells (DCs) (26). Dectin -1 and -2 are C-type lectins that interact with the carbohydrate structures present in the cell wall of fungi and thereby play an important role in anti-fungal immune responses. Blockade of MALT1 proteolytic activity with the cell-permeable peptide inhibitor, z-VRPR-FMK (36), specifically prevents nuclear translocation and DNA binding of c-Rel in response to dectin-1 or 2 stimulation, without affecting other NF-κB subunits. Interestingly, a related observation has been made in B-cells in which MALT1-deficiency selectively impairs c-Rel nuclear translocation following BCR stimulation, without affecting RelA / p65 (21). Together, these results imply that the MALT1 protease may cleave a substrate, both in dendritic cells and in B-cells, that is somehow involved in c-Rel, but not RelA activation. The identity of this substrate and the specific mechanism whereby MALT1 protease activity selectively influences c-Rel are not yet known.

Clinical-translational advances

MALT1 protease activity promotes B-lymphomagenesis

In addition to its well-established role in MALT lymphomagenesis, a central role for MALT1 in the pathogenesis of another B-cell malignancy, diffuse large B-cell lymphoma (DLBCL), has more recently emerged. Constitutive NF-κB activity is characteristic of activated B-cell like (ABC) DLBCL, a subtype of DLBCL that is associated with a particularly poor prognosis (47). An shRNA-based ‘Achilles heel’ screen recently identified CARMA1, BCL10 and MALT1 as essential to the survival of ABC-DLBCL cells (48).

Subsequent studies identified activating oncogenic mutations in CARMA1 in about 10% of ABC-DLBCLs, further confirming the critical role of the CBM complex in this malignancy (41,43,49). Moreover, approximately 20% of ABC-DLBCLs harbor mutations in the BCR subunits, CD79A or CD79B, and these mutations are associated with increased BCR expression and enhanced BCR-CBM-dependent NF-κB signaling (50). These findings prompted investigation into the role of MALT1 protease activity in ABC-DLBCL. Two studies demonstrated that in contrast to germinal center B-cell like (GCB)-DLBCL cells, ABC-DLBCL cells contain preassembled CBM complexes which constitutively process the MALT1 substrates, BCL10 and A20 (Fig. 1B) (51,52). Furthermore, treatment of ABC-DLBCL cells with the MALT1 protease inhibitor, z-VRPR-FMK, blocks A20 and BCL10 cleavage, reduces NF-κB dependent gene transcription, and impairs cell proliferation and survival. These pivotal findings thus provided the first indication that pharmacological inhibition of MALT1 protease activity could potentially represent a promising new approach for the treatment of specific subtypes of lymphoma.

Importantly, *A20* deletion or inactivation occurs in 10-30% of DLBCLs (41-43). Thus far, the ability of MALT1 protease inhibitor to impair cell growth and survival has been demonstrated in four distinct ABC-DLBCL cell lines, and each of these lines contains at least one wild-type A20 allele (51,52). If blockade of MALT1-dependent A20 cleavage is essential for MALT1 protease inhibitor to impair cell survival and proliferation, then inhibiting MALT1 protease activity may not represent an effective treatment approach for DLBCLs lacking A20. Also, activating mutations in *MYD88*, an adaptor protein that mediates toll-like and IL-1 receptor signaling, have been identified in 37% of ABC-DLBCL tumors, and in some of these cases, abnormalities in A20, CD79B/A and CARMA1 are also present (53). Whether MALT1 protease inhibition impairs cell growth and survival in cells harboring *MYD88* mutation has not yet been investigated.

Our group recently demonstrated that the MALT1 protease domain within the API2-MALT1 fusion oncoprotein cleaves NF-κB inducing kinase (NIK) after Arg 325 (Table 1) (54). Importantly, API2-MALT1-dependent cleavage of NIK requires the concerted actions of the API2 moiety, which recruits NIK, and the MALT1 protease domain, which cleaves NIK. NIK is an essential mediator of “noncanonical” NF-κB signaling, a pathway critical to the development of secondary lymphoid organs and lymphocyte survival that is stimulated downstream of a subset of TNF receptor family members (55). In this pathway, receptor stimulation leads to NIK-dependent phosphorylation and activation of IKKα, which then triggers the phosphorylation of NFκB2/p100, leading to proteasome-mediated partial degradation of p100 to p52 and generation of transcriptionally active p52/RelB NF-κB dimers. Under resting conditions, NIK associates with the adaptor protein, TRAF3, via an N-terminal NIK domain, and this interaction targets NIK for proteasomal degradation. Basal NIK levels are thus very low in B-cells, and receptor stimulation leads to enhanced NIK stabilization and noncanonical NF-κB activation by triggering dissociation of NIK from TRAF3 (56,57). API2-MALT1-dependent NIK cleavage separates the C-terminal NIK kinase domain from the N-terminal TRAF3-binding domain of NIK, thereby generating a C-terminal NIK fragment that retains kinase activity and is resistant to proteasomal degradation, and this leads to deregulated noncanonical NF-κB activity (Fig. 1). This active C-terminal NIK fragment is required for API2-MALT1-dependent protection of B-cells from dexamethasone-induced cell death and API2-MALT1-induced adhesion of B-cells to endothelium. We speculate that these consequences of API2-MALT1-dependent NIK cleavage contribute to the treatment resistance and higher rate of tumor spread that is associated with API2-MALT1-expressing t(11;18)-positive MALT lymphomas. Our findings suggest that, as in ABC-DLBCL, MALT1 protease inhibition may also represent a novel pharmaceutical approach for the treatment of refractory t(11;18)-positive MALT lymphomas.

Beyond B-cell lymphoma: MALT1 protease inhibition as treatment for other diseases?

Inhibition of MALT1 protease activity may also represent a novel treatment approach for other neoplastic disorders, in addition to ABC-DLBCL and MALT lymphoma, or for inflammatory/autoimmune diseases. Significantly, impairing MALT1 protease activity in T-cells *in vitro*, either via mutation of the catalytic cysteine within the proteolytic site or treatment with the z-VRPR-FMK inhibitor, results in loss of TCR-induced secretion of IL-2 (36,37), a cytokine that plays a central role in immunity and inflammation. Circulating IL-2 and T-cell IL-2 receptor α (IL-2Rα) are present only at low concentrations under basal conditions, but following TCR activation, expression of IL-2Rα is induced along with IL-2, forming an autocrine/paracrine signaling loop that promotes T-cell proliferation (58). Thus, blocking IL-2 signaling is potentially a powerful approach for immunosuppressive therapy. Indeed, IL-2Rα blockers have been used with some success in preventing organ transplant rejection, managing specific autoimmune conditions and treating adult T-cell leukemia (59). It will be of great interest to determine whether blockade of MALT1 protease-dependent IL-2 production can be achieved *in vivo* and if such an approach is effective in treating these disorders.

One important caveat, however, is that IL-2 also plays a critical role in the thymic development of regulatory T (Treg) cells and self-tolerance. Somewhat paradoxically, failure to produce normal IL-2 upon TCR activation is associated with severe autoimmune disease in mice and systemic lupus erythematosus in humans (60). It is thought that precise control of both systemic and local amounts of IL-2 is required to achieve the necessary balance between T effector activity and Treg function. Genetic ablation of BCL10 or CARMA1 in mice is associated with impaired Treg differentiation, suggesting that MALT1 likely plays a role in this process as well (61). It will be important to investigate how inhibition of MALT1 protease-dependent IL-2 production might affect this critical balance.

Blockade of MALT1 protease activity has recently been found to also inhibit the production of IL-1β and IL-23 by human DCs and thereby block the ability of DCs to induce a “Th17” cellular response to fungi (26). Th17 cells are a newly recognized subset of T helper cells that secrete IL-17, a cytokine that stimulates the mobilization of neutrophils. Although Th17 cells perform a beneficial role in host defense against extracellular bacteria and fungi, Th17 cells are thought to play a detrimental role in the development of a variety of inflammatory disorders, including atopic dermatitis, psoriasis, multiple sclerosis, rheumatoid arthritis and others, and blockade of Th17 signaling has shown promise as an effective treatment approach in mice and humans with these conditions (62). There may be a future role for therapeutic inhibition of MALT1 protease in the treatment of these disorders, but how blocking MALT1 protease activity would disrupt the delicate balance between Th17-mediated host defense and Th17-mediated autoimmunity remains to be investigated.

Finally, in addition to its potential role in B-cell lymphoma and inflammatory disorders, deregulated MALT1 is also implicated as contributing to varied disease processes linked to inappropriate GPCR stimulation. For example, recent studies suggested that MALT1 is required for ovarian and oral squamous cancer cell invasion in response to GPCR stimulation by LPA and CXCL12, respectively (31,33). However, whether MALT1 proteolytic activity is stimulated following ligation of the LPA receptor or CXCR4, or whether cleavage of specific MALT1 proteolytic substrates contributes to GPCR-induced malignant phenotypes has not yet been addressed. Similarly, several reports implicate MALT1 in mediating GPCR-induced endothelial dysfunction and atherosclerosis (30,32,34), but the role of MALT1 protease activity in these processes has not been investigated. The contribution of MALT1 protease activity to GPCR-dependent signaling, both in normal physiology and in disease, is certain to become a topic of intense investigation.

Concluding Comments

Thus far, only peptide inhibitors of the MALT1 protease, z-VRPR-fmk and Ac-LSSR-CHO, have been reported (36,54), and it is not yet known if pharmaceutically suitable compounds that can inhibit MALT1 protease activity *in vivo* and can be safely administered to patients will be identified. Only three proteolytic substrates for wild-type MALT1 (BCL10, A20 and CYLD) and one unique substrate for API2-MALT1 (NIK) have been identified so far, and little information is available regarding the structural requirements for MALT1 protease interaction with its substrates. To date, MALT1 protease activity has been implicated in three distinct aspects of NF-κB signaling: canonical NF-κB signaling in T-cells, c-Rel activation in B-cells and dendritic cells, and noncanonical NF-κB activation in B-cells expressing the API2-MALT1 fusion oncoprotein (26,37,51,54). In addition, MALT1-mediated cleavage of BCL10 and CYLD in T-cells have been implicated in contributing to integrin-mediated adhesion and JNK signaling, respectively (36,45). Clearly, much remains to be learned in order to determine if targeting MALT1 protease activity will represent a viable therapeutic approach for specific B-cell lymphomas or other diseases.

Several features of the MALT1 protease suggest that it could potentially represent a promising new drug target. First, unlike most proteins, which belong to a family of structurally and functionally related proteins, MALT1 is the only human paracaspase (5). This suggests that designing pharmaceuticals that specifically target MALT1 and do not cause unwanted off-target effects by interacting with other related proteins, may be possible. Second, MALT1 deficient animals are fertile and fairly healthy (15,16), suggesting that inhibition of MALT1 activity may be tolerable in human patients. Third, although MALT1-deficient T-cells are defective in antigen-receptor-induced cytokine production and proliferation, blockade of MALT1 proteolytic activity only partially inhibits TCR-induced cytokine production by 40-60% (36). It has been suggested that this partial effect on cytokine production may indicate that the scaffolding function of MALT1 is still preserved when MALT1 enzymatic activity is inhibited. Therefore, the effect of MALT1 protease inhibition on lymphocyte function may be less severe than the effect of MALT1 deficiency and the degree of immune suppression may be acceptable (52). Fourth, the many investigations described in this review indicate that MALT1 protease activity plays a prominent role in both MALT lymphoma and ABC-DLBCL, and also likely contributes to other neoplastic and inflammatory disorders.

There is some track record of success in pharmacological inhibition of protease activity as a strategy for drug development. Of the approximately 400 known human proteases, about 15% are under investigation as drug targets (63). Two prominent examples include HIV protease inhibition in the prevention and treatment of AIDS and proteosome inhibition in the treatment of multiple myeloma and other B-lymphoproliferations. Many other diseases, including coagulopathy, hypertension, osteoporosis, neurodegeneration, metastatic carcinoma, and bacterial and parasitic infection, are also being treated successfully with protease inhibitors (64). Perhaps the MALT1 protease, a protein that was discovered as a target of recurrent chromosomal translocation in MALT lymphoma, will join the ranks of the many proteases that can be successfully targeted for the treatment of human disease. Future studies of MALT1 will hopefully lead to identification of new proteolytic substrates, elucidation of the structural requirements for MALT1 catalytic activity, further characterization of the biologic role of MALT1, and improved treatment strategies for B-cell lymphoma and beyond.

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List of Abbreviations

ABC/GCB-DLBCL	activated B-cell / Germinal center B-cell like - diffuse large B-cell lymphoma
AIDS	Acquired Immunodeficiency Syndrome
Ang II	angiotensin II
API2 or cIAP2	Cellular inhibitor of apoptosis 2
BAFF	B cell activation factor of the TNF family
CARMA	CARD domain containing MAGUK protein
CBM	CARMA / BCL10 / MALT1
CXCL/R	cysteine X cysteine chemokine ligand / receptor
CYLD	cylindromatosis
DC	dentritic cell
DD	Death domain
DUB	deubiquitinase
GPCR	G protein-coupled receptor
IκB	Inhibitor of kappa B
IKK	Inhibitor of kappa B kinase

ITAM	immunoreceptor tyrosine based activation motif
IL	interleukin
JNK	c-jun N-terminal kinase
LPA	lysophosphatidic acid
MAGUK	Membrane associate guanylate kinase
MALT1	Mucosa Associated Lymphoid Tissue Lymphoma Translocation 1
NIK	NF-kappa B inducing kinase
PDK1	3-phosphoinositide-dependent protein kinase 1
PI3K	phosphoinositide 3 kinase
PKC	protein kinase C
SDF-1	stromal cell derived factor-1
TAK1	transforming growth factor β-activated kinase 1
TCR / BCR	T-cell receptor / B-cell receptor
Th17	T helper 17
TLR4	toll-like receptor 4
TRAF	tumor necrosis factor receptor associated factor
Treg	regulatory T cell
uPA	urokinase plasminogen
VEGF	vascular endothelial growth factor

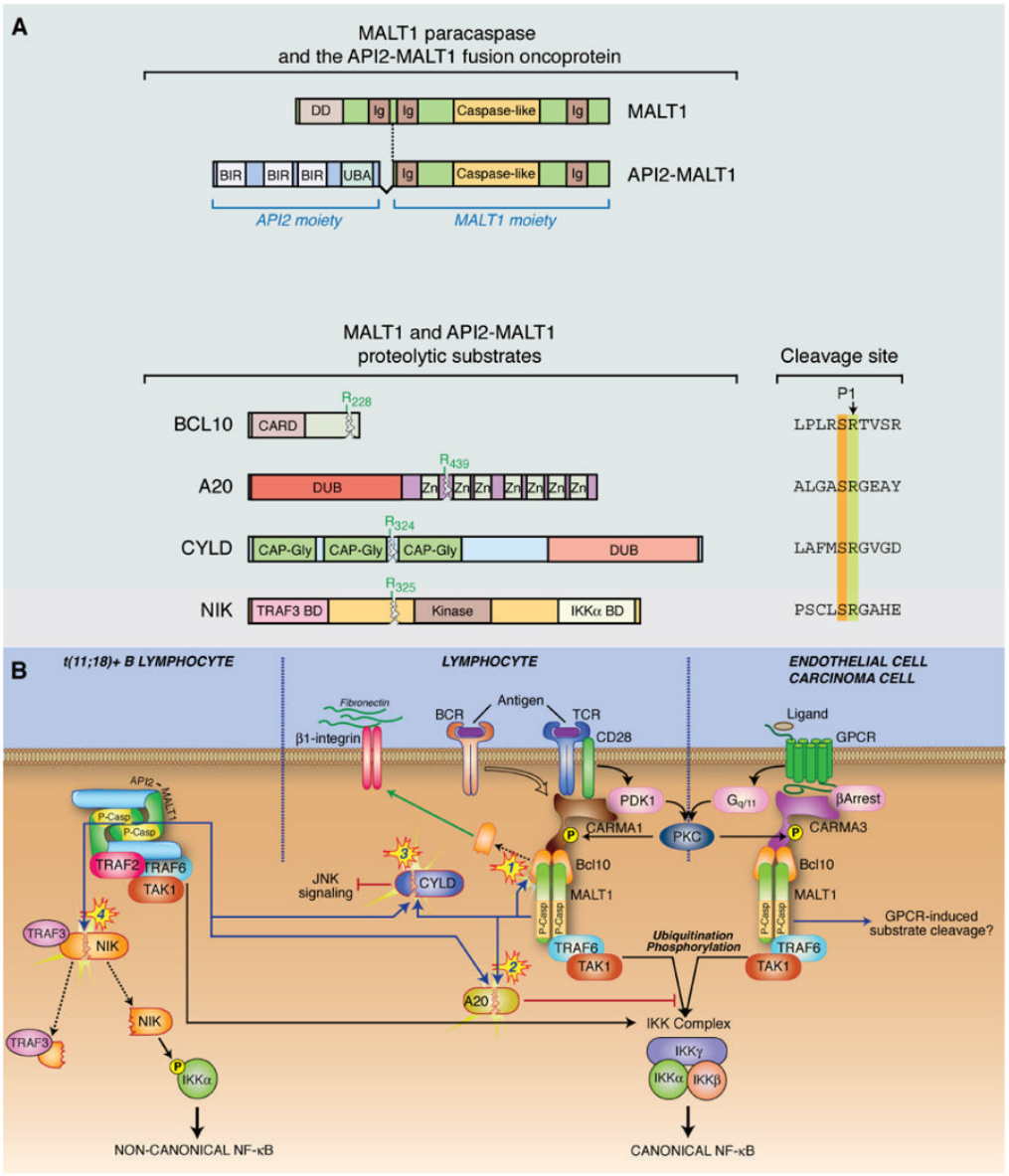

Figure 1.

MALT1 protease and its known proteolytic substrates. A, Domain structure of MALT1, API2-MALT1, and MALT1 proteolytic domain substrates. Several API2-MALT1 fusion variants, resulting from varied breakpoints within the *API2* and *MALT1* genes, have been identified, and the most commonly occurring variant is shown. All reported API2-MALT1 fusions retain the three API2 BIR domains and the MALT1 caspase-like proteolytic domain. Studies thus far indicate that NIK cleavage within the cell can be carried out by API2-MALT1 but not by wild-type MALT1. DD, death domain; Ig, immunoglobulin-like domain; 'caspase-like', proteolytic domain which bears resemblance to the proteolytic domain of caspases; BIR, baculovirus Inhibitor of apoptosis repeat; UBA, ubiquitin-associated domain; CARD, caspase recruitment domain; DUB, deubiquitinase domain; Zn, Zinc finger; CAP-Gly, cytoskeletal-associated protein-glycine conserved domain; BD, binding domain. B, Summary of MALT1-mediated signaling. The four known substrates of the MALT1 proteolytic domain, (Bcl10, A20, CYLD and NIK), are indicated by yellow stars numbered

1-4. Left: The API2-MALT1 fusion oncoprotein stimulates activation of both the canonical and noncanonical NF-κB signaling pathways. Like wild-type MALT1, API2-MALT1 proteolytically cleaves A20 and CYLD. In addition, the API2 moiety of API2-MALT1 recruits NIK, thereby making NIK available as a proteolytic substrate for the MALT1 protease domain within API2-MALT1. API2-MALT1-dependent NIK cleavage separates the TRAF3 binding site from the active NIK kinase domain, and the stabilized NIK fragment containing the kinase domain promotes deregulated noncanonical NF-κB signaling. The fact that NIK cleavage is required for API2-MALT1-induced protection of B-cells from apoptosis and B-cell adhesion to the endothelium suggests that NIK cleavage is likely critical to API2-MALT1-dependent B-lymphomagenesis. Center: MALT1 mediates antigen-dependent NF-κB signaling in lymphocytes. TCR or BCR stimulation leads to PKC-dependent phosphorylation of CARMA1, which allows for the formation of a CARMA1-BCL10-MALT1 (CBM) signaling complex. TCR-dependent activation of the canonical NF-κB pathway requires CD28 coreceptor stimulation and recruitment and activation of PDK1. TCR stimulation leads to MALT1-dependent cleavage of BCL10, A20 and CYLD. Bcl10 cleavage may be required for T-cell adhesion to fibronectin. Cleavage of A20 prevents A20-mediated inhibition of TCR-dependent NF-κB activation. CYLD cleavage may be required for TCR-induced JNK activation. The hollow line indicates that the mechanisms by which stimulation of the BCR leads to activation of a CBM complex are less well understood. An important role for MALT1-dependent signaling in B-lymphomagenesis is suggested by the findings that ABC-DLBCL cells contain preassembled CBM complexes and constitutive MALT1-dependent cleavage of A20 and BCL10. Furthermore, activating somatic mutations of the BCR subunits, CD79A and CD79B, and CARMA1 are commonly present in ABC-DLBCL cells, and inhibition of MALT1 proteolytic activity in these cells impairs cell proliferation and survival. Right: A CARMA3-BCL10-MALT1 complex mediates canonical NF-κB activation downstream of several GPCRs in a variety of cell types (see text). The specific G-protein subunits involved in coupling GPCRs to CBM-dependent signaling have not yet been determined, but $G\alpha_{q/11}$ can mediate GPCR-dependent PKC activation. In contract to TCR signaling, PDK1 is not necessary for CBM activation, but instead, β arrestins can serve as a scaffold linking GPCRs to the CBM complex. The role of MALT1 proteolytic activity in GPCR-dependent signaling is not yet known.

Table 1

Summary of cell surface receptors known to induce MALT1-dependent signaling. ND, not determined.

	Receptor	Ligand	Cell Type	Upstream MALT1 Adaptor	MALT1 Proteolytic Substrate	Effect of MALT1-dependent Proteolytic Cleavage	Reference
Lymphoid cells	TCR/BCR	Antigen	T/B cell	CARMA1-BCL10	A20	Canonical NF-κB activation	37
					BCL10	Integrin-dependent T cell adhesion	36
					CYLD	JNK activation	45
	None	None	API2-MALT1 + B lymphoma	None	NIK	Non-canonical NF-κB activation	54
	ITAM-coupled NK receptors NK1.1. Ly49D, Ly49H, and NKG2D	Varied	NK cell	CARMA1-BCL10	*ND*	*ND*	27
	BAFF-R	BAFF	B cell	TRAF3	*ND*	*ND*	22
Myeloid cells	FCεRI	IgE	Mast cell	*ND*	*ND*	*ND*	23
	TLR4	LPS	Macrophage	IRAKI-BCL10	*ND*	*ND*	24
	Dectin-1	Zymosan/β-glucan	BM-derived dendritic cell	CARD9-BCL10	*ND*	*ND*	25
	Dectins-1 and -2	Curdlan/Ab cross-linking	Human primary dendritic cell	CARD9-BCL10	*ND*	Selective c-rel activation	26
Non-Immune cells	Edg subfamily of GPCRs	LPA	MEF	CARMA3-BCL10	*ND*	*ND*	28
			Ovarian Ca cell				33
	AT_1R	Ang II	Hepatocyte	CARMA3-BCL10	*ND*	*ND*	29
			Vascular smooth muscle cell				34
	CXCR2	CXCL8/IL-8	Endothelial cell	CARMA3-BCL10	*ND*	*ND*	30
	CXCR4	CXCL12/SDF-1	Oral squamous Ca cell	CARMA3-BCL10	*ND*	*ND*	31
	PAR-1	Thrombin	Endothelial cell	CARMA3-BCL10	*ND*	*ND*	32