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Dysregulation of the antigen-induced NF-κB signaling pathway in the development of human B-cells lymphomas

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Key words: NF-κB, CARMA1, BCL10, MALT1, DLBCL, MALT lymphoma

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ABSTRACT
The adaptive immune response is initiated when microbial or tumor-specific molecules are recognized by antigen receptors present at lymphocyte cell surface. Engagement of these immunoreceptors induces signaling cascades that ultimately activate the transcription factors NF-κB (Nuclear Factor-κB) and NFAT (nuclear factor of activated T-cells) responsible for the establishment of gene expression programs controlling the stimulation, proliferation and survival of activated lymphocytes. Cloning the products of three distinct translocation events found in lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) led to the identification and characterization of a novel NF-κB-activating complex following antigenic stimulation composed by the CARMA1, BCL10, and MALT1 proteins and called the CBM complex. Since the identification of this complex, other regulatory components were discovered which greatly improve our understanding of this signaling pathways.
Interestingly, CBM complex activity is not only altered in MALT lymphomas but also in a subtype activated B cell-like (ABC) of diffuse large B-cell (DLBCL) lymphoma. In this review, we described the key players involved in antigen-induced NF-κB activation and cover the recent advances in the molecular mechanisms that are responsible for the regulation of the components of the CBM complex. Understanding these mechanisms is critical for the elucidation of the role of this NF-κB signaling network in both normal and pathologic conditions and we described how deregulation of this network leads to the uncontrolled activation of NF-κB and development of two particular subtypes of human B cell lymphomas: the MALT and the DLBCL lymphomas.

I- Introduction

The immune system can be roughly divided in two groups, the innate and the adaptive immunity. Innate immunity constitutes the first line of defense against invading organisms and refers to nonspecific defense mechanisms that are rapidly triggered upon infection. The adaptive immune response is initiated upon recognition of microbial or tumor-specific molecules by antigen receptors present at the lymphocyte cell surface. Antigen-receptor engagement leads to signaling events that trigger gene expression programs controlling activation of the stimulated lymphocytes and their clonal proliferation and survival. The nuclear factor (NF)-κB transcription factor participates in both innate and adaptive immunity as a critical regulator of the expression of target genes including those encoding anti-apoptotic molecules, cell cycle regulators, cytokines and surface receptors. In resting cells, NF-κB proteins are sequestered in the cytoplasm due to their interaction with the IκB inhibitors. Antigenic stimulation of B- or T-lymphocytes or recognition of bacterial and viral products by Toll-like receptors present on the surface or in the endosomes of immune cells leads to the activation of a cytoplasmic kinase complex composed of two catalytic subunits, the kinases IKKα and IKKβ and a regulatory subunit called NEMO, that induces phosphorylation, followed by ubiquitination and, consequently, proteasome-mediated degradation of IκB proteins. Free NF-κB dimers subsequently translocate to the nucleus and activate their target genes.

Nuclear factor-κB (NF-κB) is activated upon triggering of a wide variety of antigen-dependent receptors, including T-cell receptor (TCR), B-cell receptor (BCR), Fc receptors (FcRs), NK cell receptors, and various immunoglobulin (Ig)- or C-type lectin- family receptors specifically expressed on myeloid cells that associate with cytoplamic ITAMs (Immunoreceptor Tyrosine-based activation motifs)-containing signaling chains (such as: CD3s, Igα and Igβ, FcRγ and DAP12) [1]. Engagement of these receptors initiate a signal-activation cascade that includes phosphorylation of two specific tyrosine residues located in the ITAM by the Src family kinases [1]. Tyrosine kinase Syk or ZAP-70 (zeta-chain-associated protein 70 kD) are then recruited to the phosphorylated ITAM through their tandem Src homology 2 (SH2) regions, initiating downstream signaling cascades that lead to the stimulation of mitogen-activated protein kinase (MAPK) activities and ultimately to the activation of the transcription factors NF-κB and NF-AT (nuclear factor of activated T-cells).

An outstanding issue of lymphocyte activation was the identification of a complex of proteins comprising CARMA1, BCL10 and MALT1 (also called the CBM complex) as critical regulators of the immunoreceptor signaling pathways. In this review, we will focus on the recent advances concerning the role of the CBM function in antigen-induced NF-κB signaling and detail how this pathway may selectively become deregulated in lymphoma.

II- The key players of antigen-mediated NF-κB activation

Antigen receptor activation initiates a phosphorylation cascade that promotes assembly of the CBM signalosome complex composed of CARMA1, BCL10, and MALT1 that ultimately activates the NEMO/IKK complex to promote NF-κB transcription (**Figure 1**). In this paragraph, we provide a description of the CBM components and detail the molecular mechanisms of their regulation.

CARMA1:

CARMA1 (CARD 11/Bimp3) belongs to a family of proteins including CARMA2 (also called CARD14 or Bimp2) and CARMA3/CARD10/Bimp1 that were initially identified based on bioinformatics analyzes of their CARD domain homology [2,3]. Among this family, only CARMA1 is specifically expressed in hematopoietic cells. CARMA1 contains multiple protein-protein association domains that individually contribute to the formation of protein complexes required for transduction of these signaling pathways. Indeed, CARMA1 contains N-terminal caspase-recruitment (CARD) and coiled-coil (CC) domains and a C-terminal membrane-associated kinase (MAGUK) domain [2,3]. Because of this last domain, CARMA1 belongs to the MAGUK family, characterized by their C-terminal PDZ-SH3-GUK tripartite modular domains. CARMA1 resides in lymphocytes in a closed, latent state by an auto-inhibitory mechanism involving an inhibitory domain (ID), positioned between the coiled-coil and PDZ domains and requiring intra-molecular interactions with the CARD and coiled-coil domains. Using mice deficient for CARMA1 or expressing mutated forms of this protein, studies demonstrated an important role of this protein *in vivo* after TCR/BCR signaling (**Table 1**). These mice exhibit immunodeficiency, defective B lymphocyte development and lymphocyte proliferation probably as a consequence of the impairment of NF-κB and JNK activation [4-7]. Other studies have shown that phosphorylation of CARMA1 (mediated by PKCβ or PKCθ and CaMKII) activates the NF-κB pathway by promoting the formation and stabilization of the CBM complex [8-10]. As a consequence of BCR or TCR engagement, PKC-mediated phosphorylation of the ID allows a conformational change leading to binding of the CARD motif of CARMA1 to BCL10 and

to recruitment of several signaling molecules including the paracaspase MALT1, the E3 ligase TRAF6, the kinases TAK1 and IKKα/β and the protease caspase-8 [11]. Accordingly, mutations of the coiled-coil, CARD, or LATCH (a short 19 amino acids region between the CARD and the coiled-coil) domain disrupt the ID binding and constitute dominant-active forms of CARMA1 that result (when overexpressed) in increased association and co-localization with BCL10 and IKK and constitutive NF-κB activation [12]. As a post-inductional repression mechanism, the CBM/IKK/NF-κB signal pathway can be negatively regulated by the phosphatase PP2A regulatory subunit PPP2R1A by binding to CARMA1 and removing PKCθ-dependent phosphorylation of CARMA1 [13].

CARD9, another CARD protein, is structurally similar to the CARMA family members [14]. As for the CARMA family of proteins, CARD9 contains N-terminal CARD and coiled-coil domains, but lacks the C-terminal MAGUK domain. In contrast, CARD9 is mostly expressed in myeloid cells including dendritic cells and macrophages. CARD9 is a critical mediator of the innate immune response to fungal infections, but is dispensable for antigen receptor-induced signaling pathway that involve BCL10 and MALT1. In contrast, recent studies suggest that CARD9 forms a complex with MALT1 and BCL10 that was found to be involved in the C-type lectin receptor (CLR)-induced signaling pathways after fungal stimulation and to activate the IKK complex, leading to activation of NF-κB [15,16].

BCL10 :

B cell lymphoma 10 (BCL10) is an adaptor protein containing a N-terminal caspase recruitment domain and a C-terminal Ser/Thr-rich region. BCL10, identified as a novel member of a family of proteins containing a CARD domain, was initially suggested to act as a regulator of the proapoptotic signaling pathways, as many proteins containing a CARD motif were originally involved in the control of apoptosis. Analyzes of the BCL10 deficient mice did not substantiate these hypothesis, but rather revealed unexpected roles of this protein in innate and adaptive immune responses, in antigen-induced proliferation of T and B cells and in NF-κB activation. In addition, BCL10 is critical not only for the function, but also for the maturation of B cells, since knocked-down of its expression leads to reduced number of follicular and marginal cells of the B cell zone (**Table 1**) [17]. Furthermore, BCL10-deficient mice show defects in neural tube closure [18]. In concert with activation of NF-κB by TCR, proteolysis of BCL10 occurs and this degradation is a specialized function of differentiated T cells, since it was not observed in naïve T cells. Although these studies suggested that BCL10 degradation might constitute a regulatory mechanism to reduce NF-κB activation by TCR, the molecular mechanism responsible for BCL10 degradation remains highly controversial since several groups published data supporting different BCL10 proteolysis mechanisms [19-23]. Thus, BCL10 was shown to be phosphorylated at several Ser and Thr residues of its C-terminal domain and then degraded through the ubiquitin-dependent proteasome machinery [20]. However, BCL10 degradation is only partially altered by proteasome inhibitors and may involved ubiquitin conjugation and subsequent lysosomes trafficking, since BCL10 degradation is preceded by its localization in vesicular compartments identified as late endosomes or lysosomes [21]. A recent study indicated that TCR stimulation induces autophagy and that inhibition of autophagy enhances TCR-mediated NF-κB activation [24]. Interestingly, BCL10 can be degraded via selective autophagy, thus limiting the NF-κB-dependent responses through reduction of TCR-mediated activation of NF-κB. Actually, upon TCR stimulation, BCL10 undergoes K63-linked polyubiquitination of its CARD domain, an event required for NF-κB activation. Selective autophagy of K63-modified BCL10 requires the autophagy adaptor protein p62 and inhibition of p62 expression not only altered BCL10 degradation, but also impaired NF-κB activation [24]. The attachment of K63-linked ubiquitin chains on BCL10 can also be recognized by NEMO (a subunit in the IKK complex) leading to the increased interaction efficiency between components of the IKK complex and the CBM complex [22]. Using genetically deficient B cell lines, it has been recently shown that CARMA1 and TAK1, but not IKKβ are necessary for antigen receptor- (or phorbol esters)- mediated BCL10 degradation, further suggesting that TAK1 functions as an adaptor for the E3 ligases ITCH and NEDD4 (involved in K63-ubiquitination of BCL10) and plays a feedback role for BCR-mediated NF-κB activation [25].

MALT1 :

The human paracaspase MALT1 has also been recently identified as a caspase-like protein involved in NF-κB activation [26-29]. Like BCL10, MALT1 was originally found as interactant of CARMA1 and inducer of the NF-κB signaling pathway following the characterization of the *IGH-BCL10, IGH-MALT1* and *API2-MALT1* translocations [30,31] (see below). MALT1 contains a N-terminal death domain (DD), two immunoglobulin (Ig)-like domains and a C-terminal caspase-like domain. The interaction between BCL10 and MALT1 that requires the central Ig-like domains of MALT1 and a region C-terminal to the CARD domain of BCL10, induces the oligomerization of MALT1. Because of its caspase-like domain,

MALT1 was further identified as a member of the paracaspase family. For long times, MALT1 was thought to act solely as a scaffolding protein, but many groups have recently shown that the caspase-like domain of MALT1 exhibits important proteolytic activities. This protease cleaves specific substrates following arginine residues unlike conventional caspases that cleave after aspartate residues, and promotes T cell activation [32]. Thus, MALT1 cleaves and inactivates negative regulators of the canonical NF-κB pathway, such as RelB, A20 (TNFAIP3) and CYLD [33]. MALT1 also targets BCL10 for proteolysis, potentiating the NF-κB signaling pathway [34]. In addition, this specific cleavage was shown to play an important role in T-cell antigen receptor-induced integrin adhesion.

Structure of the human MALT1 caspase-like domain in complex with a peptide inhibitor showed that the paracaspase domain adopts a fold similar to that of classical caspases. The crystal structure of the MALT1 caspase-like domain further provided clues about the mechanism of MALT1 activation: in the absence of stimulation, MALT1 is not active by itself, since the caspase-like domain is autoinhibited by its interaction with the Ig3 domain. Its activation requires a first dimerization step and a second step in which caspase substrate binding causes substantial structural reorganization, allowing the release of the caspase-like domain of MALT1 from the Ig3 inhibitory domain [35]. Using mice lacking MALT1, two different studies reported impaired TCR-mediated NF-κB activation, defective lymphocyte proliferation and decreased IL-2 production (**Table 1**). However, they present conflicting results regarding the role of MALT1 in BCR-mediated NF-κB and JNK activation [18,27].

III- Regulation of the CBM complex

III. 1. Role of ubiquitination in the CBM function

Ubiquitination plays a crucial role in the NF-κB activation pathway. The presence of isopeptide linkages at each of the seven lysine residues of ubiquitin has been reported and the type of conjugated polyubiquitin seems to determine the mode of regulation of conjugated proteins. In particular, the role of lysine 63-linked chains in NF-κB activation has been extensively studied. CBM assembly promotes polymerization of lysine 63-linked ubiquitin chains and subsequent activation of TAK1 to stimulate NF-κB-mediated transcription [36]. It is also clear that formation of the CBM complex is required for the inducible lysine 63 ubiquitination of NEMO. Like NEMO, TRAF6, MALT1, and BCL10 constitute targets for Lys-63 polyubiquitination. Their primary ubiquitination sites have been mapped and were shown to be critical for NF-κB activation [37]. Ubiquitination of BCL10 has also been first suggested to facilitate TCR activation, and thereafter to limit NF-κB activation, this discrepancy remaining to be clarified (see above). The lysine 63 polyubiquitination of BCL10 is required for NEMO recruitment via its ubiquitin-binding domain (UBD) and for the subsequent activation of the IKK kinase complex. In response to T cell activation, TRAF6 associates with MALT1 and therefore co-purified with the CBM complex in TCR-activated cells. In addition, TRAF6 can function *in vitro* and *in vivo* as an E3 ligase for MALT1, catalyzing its lysine 63-linked ubiquitination [38]. Recently, linear polyubiquitin chains, in which the C-terminal glycine of one ubiquitin is conjugated to the amino group of the N-terminal methionine of another ubiquitin, were reported to be involved in NF-κB activation. A unique ligase complex named LUBAC generates linear polyubiquitin chains. It is composed of three subunits: HOIL-1, HOIP and Sharpin. LUBAC has been shown to bind to NEMO in the IKK complex and to conjugate linear chains to NEMO, this process being critical for TNF-α-mediated NF-κB activation. Interestingly, a recent study indicates that HOIL-1-deficient patients present clinical features of autoinflammation and immunodeficiency, which correlates with a defect in the activation of NF-κB in fibroblasts, whereas monocytes from these patients present an abnormal sensitivity to stimulation by IL1-β [39]. An interesting future issue will be therefore to determine the role played by linear polyubiquitin chains in antigen-mediated NF-κB signaling.

Ubiquitination is a covalent modification that can be reversed by deubiquitinating enzymes (DUBs). Not surprisingly, DUBs were shown to be critical for repressing NF-κB activation. Among those, the cylindromatosis tumour suppressor protein CYLD was found to interfere with IKK activation by cleaving K63-linked polyubiquitin chains on several proteins, including TRAF2, TRAF6 and NEMO [40]. Several other reports have established that another DUB called A20 acts as an inhibitor of NF-κB activity by forming a complex with three partners, TAX1BP1 and the E3 ligases Itch and RNF11 [41]. Interestingly, A20 is constitutively expressed in lymphoid cells, in contrast to other cell types in which A20 is induced by NF-κB providing a negative-feedback mechanism to prevent sustained NF-κB signaling. MALT1-induced A20 cleavage was thereafter proposed as a mechanism responsible for A20 inactivation and thereby upregulation of antigen-mediated NF-κB activation (see above).

III. 2. Role of other regulatory components

Besides post-translational modifications that could affect components of the CBM complex, other

proteins were shown to play a regulatory role.

PKCθ and PKCβ

PKCθ and PKCβ are members of two different subfamilies of protein kinase C family [42]. The role of PKCθ has been well established by studies on knock-out mice showing its major role in the development and function of both effector and regulatory T cells (**Table 1**) via regulation of NF-κB, AP-1 and NF-AT activation [43-46]. In order to be fully activated, PKCθ requires the engagement of both TCR and CD28 receptors. Thus, binding of PKCθ to the DAG that is released upon TCR simulation is sufficient to promote its localization to the plasma membrane and CD28 engagement leads to recruitment of PKCθ to the immune synapse via formation of a tripartite CD28-LCK-PKCθ complex [47-49]. Role of PKCθ and PKCβ in NF-κB activation have been reported in different studies. For example, it has been shown that PKCθ and PKCβ phosphorylate the serine 645 and 552 of the linker domain of human CARMA1, triggering its activation and subsequently its interaction with BCL10-MALT1 [8,9].

PDK1

PDK1 possesses a pleckstrin homology (PH) domain that binds to the second messenger PtdIns(3,4,5)P_3. Recent studies have established that PDK1 is critical for efficient activation of PKCθ in T cells and PKCβ in B cells by the PI3K pathway. PDK1 is also required for the subsequent assembly of the CBM complex to activate NF-κB during coordinated stimulation of the TCR and co-stimulatory receptor CD28 or during activation of the BCR [50,51]. PDK1 phosphorylates PKCθ and has a dual role in TCR-mediating NF-κB activation by recruiting PKCθ and CARMA1 into lipid rafts [52]. Using B-cell specific conditional PDK1 knock-out mice and chemical inhibitor approaches, it was demonstrated that PDK1 plays a critical role in B-cells by promoting transduction of the BCR signalings that are essential for the activation of both NF-κB and Foxo transcription factors. PDK1 is required for the survival of resting and activated B cells through the activation of Foxo and NF-κB respectively [50].

ADAP

ADAP (adhesion- and degranulation-promoting adaptor protein) was identified as an adapter protein that becomes tyrosine phosphorylated upon association with the TCR complex, creating docking sites for the SH2 domains of the Fyn kinase and SLP-76 protein [53,54]. ADAP contains two regions exhibiting similarities with the SH3 domains and mediating interaction with a proline-independent motif of SKAP55 [55]. Through this interaction, ADAP has been shown to play an important role in T-cell receptor-mediated integrin activation. As PDK1, ADAP plays a role in TCR-induced NF-κB activation, although ADAP is not involved in the activation of PKCθ [56]. ADAP participates in the assembly of the CARMA1–BCL10–MALT1 complex by interacting with the C-terminal region of CARMA1 through its N-terminal helical SH3 domain and E/K-rich region. Interestingly, a site in the C-terminal end of ADAP is critical for recruitment of TAK1 [57]. This TAK1 binding site is required for IKKα/β phosphorylation, whereas ADAP-binding site of CBM components regulates NEMO ubiquitination. Finally, using resting naive T cells from $ADAP^{-/-}$ mice reconstituted with ADAP mutant constructs, it was demonstrated that formation of the ADAP/SKAP55 complex required for integrin activation is dispensable for CBM complex assembly, suggesting differential control of integrin and NF-κB-dependent pathways by ADAP [58].

Caspase-8

Caspase-8 was first characterized by its critical role in death receptor-mediated apoptosis. Activation of caspase-8 leads to stimulation of effector caspase activities and ultimately to cell death. Besides its apoptotic function, caspase-8 is also involved in antigen receptor-induced NF-κB activation, as caspase-8 is essential for lymphocyte proliferation in response to antigen stimulation [59,60]. TCR-mediated activation of NF-κB is impaired in T cells from caspase-8 deficient patients or mice as well as in caspase-8 deficient Jurkat cells [60]. Caspase-8 deficient patients show clear defects in T and B lymphocytes and NK cells activations that were accompanied by recurrent sinopulmonary herpes simplex virus infections and poor responses to immunization [61]. Not only NF-κB signaling is impaired in caspase-8 deficient T cells, but also in their human B and NK cells, as shown by the inability of B and NK cells from these patients to translocate p65 to the nucleus upon BCR engagement [60]. These effects appeared to be selective for the TCR signaling pathway, since caspase-8 inhibitor or knockdown caspase-8 expression did not affect TNF-α-induced NF-κB activation. The same study identified active caspase-8 as a critical link between the CBM and IKK complexes leading to NF-κB activation in both lymphoid cell lines and isolated human lymphocytes. Actually, TCR stimulation induces caspase-8 interaction with the BCL10-MALT1 complex followed by recruitment of IKK. Subsequently, the E3 ubiquitin ligase TRAF6 was

shown to interact and activate caspase-8, unraveling a novel role of TRAF6 in induction of apoptosis [62], but also to interact with CARMA1 in association with caspase-8 following TCR stimulation, an event that facilitates the movement of caspase-8 into lipid rafts [63]. Interactions of caspase-8 and TRAF6 with CARMA1 were enhanced when the inhibitory domain (ID) of CARMA1 was deleted. Strikingly, TRAF6, caspase-8, NEMO and TAK1 may associate with CARMA1 in a BCL10-independent manner, as suggested by the mapping of the domains required for the association of these proteins with the activated form of CARMA1 (DID). The caspase-8 function in TCR-induced NF-κB signaling seems to involved the caspase-8 dependent cleavage of $cFLIP_L$ into a $p43^{FLIP}$ isoform that exhibits a greater capacity to recruit RIP1 and TRAF2 compared to its uncleaved counterpart, resulting in enhanced NF-κB activation and IL-2 production [64,65]. Altogether, these studies demonstrate that caspase-8 and TRAF6 are both required for programmed cell death and antigen-mediated NF-κB activation.

CaMKII

CaMKII could also be involved in TCR-mediated NF-κB activation since treatment with CaM or CaMKII inhibitors blocks this signaling pathway. Upon cross-linking of the TCR, CaMKII is recruited to the immunological synapse where it interacts with and phosphorylates both BCL10 and the CARD domain of CARMA1. These phosphorylations facilitate the interaction between CARMA1 and BCL10 and enhance NF-κB activation [10,66]. Interestingly, CARMA1 interacted constitutively with BCL10 when CaMKII was over-expressed.

Casein kinase 1α (CK1α)

CK1α was identified using a mass spectrometry screen of CARMA1 protein interactants [67]. Silencing CK1α reduces TCR-induced IL-2 production while it had no effect on TNF-α signaling, underscoring the selective involvement of this kinase in the TCR-NF-κB pathway. Moreover, CK1α associates with CARMA1 independently of PKCθ and BCL10 and has also a negative regulatory role on TCR-mediated NF-κB activation, since it promotes the phosphorylation and inactivation of CARMA1.

IV- Three-dimensional requirement for TCR-mediated NF-κB activation

The CBM complex appears essential for the organization of an immunological synapse and subsequent NF-κB activation. The molecular mechanisms responsible for the recruitment and activation of the CBM complex to the immunological synapse are not fully understood. Over the last several years, new approaches using various cell imaging techniques have been used to address the spatial and dynamic characteristics of these events [68]. They clearly demonstrated that intracellular signaling molecules, adaptors and cytoskeletal proteins associated with highly spatially and temporally organized structures called supra-molecular activation clusters (SMACs). The area formed at the contact site between T cells and antigen-presenting cells (APC) has been termed the 'immunological synapse' (IS), formation of this synapse being correlated with a dramatic induction of cell polarity. Over the past few years, several groups have shown that the signaling components of TCR-mediated NF-κB activation are localized in the IS.

Importance of IS for the positive regulation of antigen-mediated NF-κB activation

CARMA1 is a member of the membrane-associated guanylate kinase (MAGUK) family of proteins, characterized by their association with membrane proteins. CARMA1 is localized in specialized parts of the membrane called lipid rafts, where NF-κB signaling pathways are initiated. Following TCR stimulation, CARMA1 is recruited to the IS (and therefore enriched in the lipid rafts), where it colocalizes with BCL10 [69,70]. Analyzes of mutants of the transmembrane and cytoplasmic domains of the TCR-β chain reveal that the integrity of the TCR-β chain is critical for recruitment of CARMA1 and BCL10, and consequently NF-κB activation [71]. Besides its involvement in BCL10 recruitment to the IS, CARMA1 may also be important for the IS localization of PKCθ following TCR stimulation [72,73]. However, this conclusion is in contradiction with data showing that PKCθ recruitment to central and peripheral IS normally occurs in CARMA1 deficient T cells [74]. Two other components of the IS, SAP and the receptor SLAM, would also be involved in PKCθ recruitment to the IS [75].

Finally, the NEMO/IKK complex is also recruited to the IS and associates with the TCR following stimulation [76]. Accordingly, artificial targeting of NEMO to the IS is sufficient to activate NF-κB activation following TCR stimulation. Recruitment of NEMO/IKK complex to the IS is also supported by the finding that CARMA1 is important for recruitment of IKK into cSMAC and for its activation [70,74].

Importance of IS for the negative regulation of antigen-mediated NF-κB activation

It is now generally admitted that the IS constitutes a specialized domain of the membrane where sustained

engagement and signaling of TCR occur. Increasing evidences indicate that the IS is not only the area where TCR signaling pathways are initiated, but also the place where TCR-induced protein ubiquitination and degradation of key activation molecules occur [77,78]. Whether components of the TCR-activated NF-κB signaling pathway are also degraded in the IS remains to be investigated.

Although, it remains unclear how CARMA1 is recruited to the IS, an expression-cloning screen for regulators of CARMA1 identified GAKIN as a protein that can remove CARMA1 from the central IS. Interestingly, GAKIN interacts with CARMA1 in an inducible manner following TCR activation, competes with BCL10 for the association with CARMA1 and ultimately downregulates NF-κB activation [79]. Altogether these data indicate that GAKIN dynamically localizes to the IS and regulates the duration of CARMA1 occupancy to the IS at the benefit of the peripheral IS.

Localization and function of PKCθ in the IS

Although the relationship between the IS and lipid rafts remains to be determined, several studies have pointed that PKCθ colocalizes with rafts at the central region of the IS [80,81]. In naive $CD4^+$ T cells, TCR-mediated signals are sufficient to induce the capping of PKCθ to the area of the TCR, although CD28-mediated signals seem also to be required for the localization of PKCθ to the SMAC of the synapse [81].

Studies of PKCθ-deficient T cells on lipid bilayers containing pMHC and ICAM1 demonstrated that there is a clear relationship between TCR signaling, IS assembly and motility [82]. Those studies were the first to document T cells migrating, while engaging agonist pMHC complexes on bilayers, and to show that cells lacking PKCθ were less mobile. This observation suggests that autonomous signals within the T cell enhanced motility and that a stable synapse can be observed upon inhibition of PKCθ. More recently, it was demonstrated that motility arrest is not required for TCR signaling to take place [83,84].

Microclusters in the IS

The structure of the IS is highly ordered and dynamic. Imaging microscopy techniques have shown that TCR and its signaling molecules aggregate onto dynamic microclusters, formed at the periphery of the IS (at the peripheral SMAC or pSMAC) and migrating toward its center (at the centralized SMAC or cSMAC) [85-87]. Although the TCR microclusters can also include molecules like CD2, CD4, CD8, and CD28, they exclude the tyrosine phosphatase CD45 [48,88]. The dynamics of cluster coalescence may involve multiple mechanisms. Although a centralized cluster (cSMAC) is typically always formed, different events may coordinately act to give the final aggregated structure. While membrane movement may constrain aggregation cluster within a given domain, the contact between individual membrane-membrane may also be required to reorganize contacts in the IS [89]. The activity of microclusters progressively decreases as they are centralized toward the cSMAC, where they are ultimately internalized [88].

Formation of the IS also requires stabilization of the interaction between the T cell and the APC [90]. Such stabilization can be achieved by the binding of the adhesion molecule LFA-1 (lymphocyte function-associated antigen 1) located on T cells with its ligand ICAM-1 (intercellular adhesion molecule 1) present on the APC, the binding affinity between these molecules being greatly enhanced by the structural change induced following antigen recognition and signaling by the TCR.

Molecular requirements for the polarization of the IS

A hallmark of T-cell activation is the reorientation of the microtubule organizing center (MTOC) to a position beneath the IS [91] and therefore the MTOC constitutes a marker of changes in T-cell polarization in response to antigen stimulation. In fact, TCR stimulation induces actin polymerization at the immune synapse and MTOC reorientation [92]. In addition, direct contact of the MTOC with the IS plays a critical role by allowing directed secretion of cytotoxic granules by killer lymphocytes [93]. The formation of microclusters and SMACs depends on the actin cytoskeleton [88,94]. Recently, it was shown that clathrin, a protein involved in endocytic processes, in intracellular compartments and vesicle formation, as well as in the formation of late endosomes termed multivesicular bodies (MVBs), is recruited to and regulates actin accumulation at the IS suggesting that some interactions might occur between MVBs and the IS [95]. Actin polymerization occurs and is enhanced at the edge of the synapse, as the cell spreads to achieve synapse formation [83]. Actin polymerization then appeared to be a key factor in the migration of microclusters. Interestingly, the adaptor ADAP is linked to the actin cytoskeleton and, upon antigenic stimulation, is recruited to the actin-rich periphery of the immune synapse, where it associates with the microtubule motor Dynein [96]. Furthermore, ADAP was shown to play a role in the relocation of the MTOC to the IS through its interaction with dynein.

Molecular requirements for the spatio-temporal organization of the IS

The time-dependent molecular composition and the functional role of the SMAC and the IS are under intense investigation. For example, following complete or partial activation, the kinetics of intracellular protein recruitment to the T-cell-APC contact site may be correlated with specific functions of a signaling molecule. In addition, the spatial segregation of intracellular proteins in distinct areas of the cSMAC and pSMAC correlates with their importance in the activation pathway. Thus, TCR-mediated tyrosine kinase activities primarily occurs at the periphery of the synapse and is terminated before mature IS is formed.

V- NF-κB and lymphoma

NF-κB transcription factors can be uncoupled from their normal regulation and promote tumorigenesis in different ways. For example, mutations of the key components of the antigen-mediated signaling pathways are associated with constitutive CBM-mediated signaling, and with the development of particular subtypes of human B-cell lymphomas, including MALT and DLBCL lymphomas [97].

V-1 MALT lymphoma

B-cell lymphomas of mucosa-associated lymphoid tissue, which represent the most common extranodal lymphomas (8% of all non-Hodgkin's lymphomas), occur in different anatomic sites including stomach, ocular adnexa (conjunctiva and orbit), lung and thyroid [97]. Several molecular events involved in the lymphomagenesis of MALT lymphomas, where chronic antigenic stimulation plays a pivotal role, have been described. This chronic inflammation is induced by microbial infection, i.e. *Helicobacter pylori* (*Hp*) for gastric lymphomas and *Chlamydia psittaci* (*Cp*) for ocular adnexa lymphoma, or autoimmune disorders. Because the majority of cases arise in the stomach, most of our understanding comes from studies on gastric MALT lymphoma. In chronic inflammation and early stages of lymphoma development, an antigen-driven expansion of polyclonal B-cell expansion and specific T cells is induced, promoting an interaction between normal BCL10 and MALT1 proteins that leads to NF-κB activation [98]. A subclone with molecular genetic abnormalities may eventually emerge, eliminating the need for persistent infection and/or chronic inflammation. Moreover, at early stage, eradicating the source of infection can successfully treat gastric lymphomas. However, recurrent cytogenetic alterations can promote disease progression. The most common alteration in gastric lymphoma and first-described chromosomal abnormality found in MALT lymphoma is t(11;18)(q21;q21), which fused the gene encoding the *inhibitor of apoptosis 2* (API2; also known as *cIAP2)* with *MALT1.12-14*. Another translocation t(1;14)(p22;q32) places the *BCL10* gene under the control of the immunoglobulin (Ig) heavy-chain enhancer promoter element (*IGH-BCL10*) leading to its overexpression [99,100]. The most common in ocular adnexa lymphoma is t(14;18)(q32;q21) which was originally found in MALT lymphoma of the liver and skin and involves the placement of the *MALT1* gene under the control of the Ig heavy chain enhancer (*IGH-MALT1*) [101]. Others have been reported including trisomy 3 or 18 occurring most frequently in intestinal and salivary gland MALT lymphoma [102] and, more recently, t(3;14)(p14.1;q32), involving the *IGH* and *forkhead box protein P1* (*FOXP1*), that was also reported in DLBCL [103].

Forkhead box P1 (FoxP1) contains a N-terminal glutamine-rich region, a zinc finger, a leucine zipper, a forkhead and an acid-rich domain. By its involvement in the regulation of Rag1 and Rag2 expression, FoxP1 is essential for B cell development [104]. Given that MALT lymphoma and some types of DLBCL are characterized by constitutive NF-κB activation, it has been speculated that Foxp1 may be a regulator of NF-κB activation. Accordingly, various Foxp1 isoforms are capable of activating the NF-κB reporter in both B and T cell lines [98]. Recently, the deubiquitinase A20 was also implicated in the arising of MALT lymphomas. Importantly, A20 was found inactivated by somatic deletion, mutation or promoter methylation in around 30% of translocation-negative ocular adnexal MALT lymphoma [98,105]. These A20 alterations were also significantly associated with increased expression of NF-κB target genes CCR2, TLR6 and BCL2 [105]. Interestingly, it has been shown that ocula MALT lymphoma have preferential loss of the *TNFAIP3/A20* region.

BCL10 relocalisation from the cytosol to the nucleus is strongly observed in the nuclei from lymphomas carrying t(1;14)(p22;q32*)/BCL10-IGH* and moderately in gastric and pulmonary MALT lymphomas with t(11;18)(q21;q21)/*AP12-MALT1* fusion and is highly predictive of *Helicobacter pylori*-independent status in high-grade gastric MALT lymphoma [106-109]. BCL10 does not contain any identified nuclear localization signal and the mechanisms responsible for BCL10 nuclear localization are not fully understood, although several factors regulating BCL10 stability or nucleus-to-cytoplasm shuttling have been identified. For example, MALT1 contains nuclear export signals and can export BCL10 from the nucleus to the cytoplasm, and the subcellular localization of BCL10 depends upon the relative ratio of BCL10 and MALT1 expression [110]. API2 is an E3 ubiquitin ligase of BCL10 that targets it for degradation. In the t(11;18)(q21;q21)/*AP12-MALT1* translocation, the API2-mediated BCL10 degradation

is likely compromised resulting in its nuclear localization. Interestingly, BCL10 degradation can be also affected by mutation of IKK-dependent phosphorylation sites leading to BCL10 nuclear accumulation and to increased IL-2 production after T cell antigen-receptor activation [20]. Although nuclear function of BCL10 remains to be determined, BCL10 could be involved in the regulation of NF-κB transcriptional activities through its association with BCL3, a coactivator of NF-κB.
There is growing evidence indicating that chromosome translocations alone, including those identified in MALT lymphoma, do not account for full malignant transformation. Indeed, lymphoma was not observed in mice in which API2-MALT1 or BCL10 were expressed in B lymphocytes, suggesting that NF-κB activation may not be sufficient to promote malignant transformation [111,112]. Additional factors, such as surface receptor activation, should act in cooperation with these chromosome translocations to induce MALT lymphoma development. Lack of cellular models of human-like MALT lymphoma has hindered a better understanding of the disease pathogenesis and the development of MALT-specific therapies. However, a recent study has shown that mice in which MALT1 is specifically expressed in the hematopoietic stem/progenitor cells can constitute models of human lymphoma pathogenesis and tools for developing and testing MALT1 inhibitors [113]. This work also indicates that MALT1 signaling is required for the survival of murine lymphoma cells.

V-2 DLBCL

Gene expression profiling revealed three main molecular subtypes of DLBCL reflecting the signature of this lymphoma from B-cells at different stages of differentiation [114]: the ABC-DLBCL and the germinal-center B-cell-like (GCB) subtypes, as well as primary mediastinal B-cell lymphoma (PMBL) [115-118]. These subtypes are characterized by their gene expression, response to chemotherapy and clinical progression and are associated with distinct genetic lesions, indicating the involvement of different oncogenic pathways [114]. The ABC subtype of DLBCL is characterized by chronic active B-cell receptor signaling and constitutive activation of the NF-κB pathway and, for this reason, we therefore focus only on this subtype of lymphoma. ABC-DLBLCL is associated with poor overall survival, since patients have a five years survival rate of only 30% [119]. While MALT1 and BCL10 have been described as key factors in the pathogenesis of MALT lymphoma subtypes with *MALT1* or *BCL10* chromosomal translocations (see above), role of the CBM/NF-κB signaling pathway in other B-cell lymphoma development was largely unknown until recently. Indeed, it was recently shown that a hallmark of ABC-DLBCL is the constitutive signaling of the NF-κB pathway, linked to mutations in various genes regulating NF-κB, such as activating mutations of CARMA1, CD79A, CD79B, MyD88, and inactivating mutations of TNFAIP3/A20 [120]. Additional translocation/inactivation, including BCL6 translocations and inactivation of the acetyltransferase genes CREBBP and EP300, are shared by ABC-DLBCL and GCB-DLBCL [121]. Remarkably, most of the genes affecting by these mutations are critical for the survival of ABC-DLBCL through their involvement in NF-κB signaling. The B-cell receptor is composed of the antigen-binding IgH and IgL chains and the two signaling subunits, CD79A and CD79B. Over 20% of ABC lymphomas have mutations in *CD79A* or *CD79B* leading to chronic active B-cell-receptor signaling. Interestingly, the PKCβ activator PDK1 was shown to be essential for NF-κB activation and survival of a DLBCL cell line carrying a mutation in the BCR signaling subunit CD79B [122]. Downstream of CD9A/B, PKCβ propagates BCR signaling to the CBM complex. Using a loss-of-function screen to identify genes that are required for proliferation and survival of DLBCL cells, Ngo and coworkers elegantly demonstrated that shRNAs targeting the NF-κB pathway were critical for the survival of ABC-DLBCL, but not for that of GCB-DLBCL [123]. This screen uncovered a previously unsuspected role for CARMA1 in the pathogenesis of ABC-DLBCL and identified also BCL10 and CARMA1 as critical components for ABC-DLBCL survival. Indeed, approximately 10% of ABC-DLBCLs harbors activating missense mutations within the coiled-coil domain of CARMA1 and expression of these mutants leads to constitutive and enhanced antigen receptor-dependent activation of NF-κB [12,124,125]. It was further showed that these mutations alter the intra- and inter-molecular interactions that depend on the auto-inhibitory domain of CARMA1, thereby promoting constitutive NF-κB activity (see above). Furthermore, primary tumor biopsies of ABC-DLBCL lymphomas show consistently higher expression of CARMA1.
Whole-exome sequencing (WES) and genome-wide high-density single nucleotide polymorphism (SNP) array were also used to discover new non-silent mutations implicated in DLBCL pathogenesis [126]. The genes identified by these approaches include most of the known genes implicated in the pathogenesis of DLBCL, in addition to a few genes that have never been implicated in cancers. It was found that MALT1 is not mutated or translocated in ABC-DLBCL, while ABC-DLBCL cell lines are dependent on MALT1 catalytic activity [123,127,128]. Consequently, A20 and BCL10 are constitutively processed in these last lymphoma subtypes. Interestingly, MALT1 protease inhibitor, by preventing A20 and BCL10 cleavage, reduces NF-κB activity resulting in cell death and growth retardation. This study further suggests that

MALT1 protease activity is a potential target for pharmacological treatment of ABC-DLBCL. Using MALT1 activity assay, diverse MALT1 inhibitors were found and tested on ABC-DLBCL [129]. Notably, one of these inhibitors (MI-2) displayed a selective activity against ABC-DLBCL. As mentioned above, constitutive activity of PI3K and PDK1, its downstream kinase, is required for survival of a subset of ABC-DLBCL cell lines that carry mutations in the gene encoding the BCR signaling adaptor CD79B. By a pharmacological inhibitory approach, it was further demonstrated that PI3K/PDK1 activity was also required for constitutive MALT1 protease activity and subsequently for NF-κB activity in a subgroup of ABC-DLBCL [122]. Interestingly, additional screening uncovered that CK1α is selectively lethal for ABC-DLBCL cell lines [67], however, no mutations of its gene has been reported so far. Although, inactivation of the deubiquitinase A20 results in increased NF-κB activity in ABC-DLBL cells, expression of A20 alone is not sufficient for tumor development, suggesting that tumors bearing A20 inactivation rely on additional mechanisms to activate NF-κB signaling, such as chronic active B-cell-receptor signaling or a CARMA1 gene mutation.

Ngo and colleagues discovered that a leucine (CTG) to proline (CCG) exchange at position 265 (L265P) of the myeloid differentiation primary response gene 88 (MYD88) occurred in 29% of of ABC-DLBCL biopsies [123]. MYD88 has not been implicated in antigen-mediated NF-κB activation, but is an adaptor protein that transduces signals from most of the Toll-like receptors and receptors for interleukin (IL)-1 and IL-18 [130]. Recently, whole-exome sequencing studies have revealed that MYD88 is a recurrently mutated gene in DLBCL cases [131,132]. However, the incidence of MYD88 L265P mutation in Korean patients with DLBCL did not give the same incidence (6.5%) [133]. Finally, several FoxP1 isoforms and especially its smaller isoforms, are expressed at a much higher levels in the ABC-DLBCL compared to the GCB-DLBCL [134].

Concluding Remarks

For the last 10 years, our understanding of the signaling pathways that control normal physiologic processes and can lead to tumor and cancer development when perturbed, have considerably progressed, especially due to the characterization of well-established models of cancer such as MALT and DLBCL lymphomas. Indeed, identification of the alterations involved in development of these lymphoma subtypes led to the discovery of a novel complex of proteins, the CBM complex and highlighted the role of the CBM/NF-κB axis in both normal and pathological responses. Future works will certainly aim at designing therapeutic molecules or approaches that specifically target the CBM/NF-κB pathways to prevent the constitutive activation of NF-κB signaling as a treatment of lymphomas that are dependent on NF-κB hyperactivation. Therapies targeting the anti-apoptotic aspect of the NF-κB pathway would be particularly of great interest, given the growing number of studies involving this pathway in lymphoma development.

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Figure Legend

Figure 1. Immunoreceptor-mediated activation of the NF-κB pathway in T cells (A) and B cells (B). Activation of the CBM/NF-κB signaling pathway occurred following engagement of the TCR by the antigen-MHC complex and CD28-B7 interaction in T cells and after recognition of the antigen-MHC complex by the BCR in B cells. These early events lead to the formation of the CBM complex (CARMA1, BCL10 and MALT1) through the PKCθ- or PKCβ-mediated phosphorylation of CARMA1, in T and B cells, respectively. In T cells, assembly of this complex also involves the activation of PKCθ by the kinase PDK1 and the association of the adaptor ADAP with both CARMA1 and the NF-κB activating kinase TAK1. In B and T cells, CBM complex formation triggers the ubiquitination of NEMO through TRAF6/Caspase-8 complex and the phosphorylation of IKKβ by TAK1. Once activated, the NEMO/IKKs complex promotes the phosphorylation and degradation of the inhibitor proteins IκBs and the release and nuclear translocation of the transcription factor NF-κB that can activate expression of the target genes.

Table 1. Characteristics of CBM complex and PKCθ/PKCβ-deficient mice in T and B cells.

KO mice	Phenotype	Signaling pathways affected	References
CARMA1	- Defective TCR-mediated lymphocytes proliferation - Reduced number of mature B cells and complete absence B1 cells - Defective BCR-mediated proliferation	- Impaired TCR / BCR-mediated NF-κB and JNK activation - Deficient IL-2 production	[4-7]
BCL10	- Defective TCR-mediated lymphocytes proliferation - Reduced number of B1 cells. - Impaired B cell development and activation - Impaired neuronal-tube closure	- Impaired TCR/BCR-mediated NF-κB activation - Deficient IL-2 production	[17,18]
MALT1	- Defective TCR-mediated lymphocytes proliferation - Reduced number of B1 cells - Defective BCR-mediated proliferation	- Deficient IL-2 production - Impaired TCR/BCR-mediated NF-κB activation. - Effect in JNK activation remains controversial	[18,27]
PKCθ	- Normal development of naïve CD4 and CD8 in thymus - Normal $CD8^+$ proliferation and defective $CD4^+$ proliferation following TCR-mediated activation - Resistance to bacteria and virus pathogens	- Impaired NF-κB, NF-AT and AP1 activation - Deficient IL-2 production	[44,135-140]
PKCβ	- Reduced number of mature B cells and B1 cells	- Impaired NF-κB activation	[141]
Caspase8	- Defective hematopoietic development in bone marrow - T cell-specific age-dependant lethal lympho-proliferative and lympho-infiltrative immune disorder - Resting T cell proliferation - Defective antigen-induced T cell proliferation	- Impaired antigen-receptor-induced NF-κB activation - Reduced IL2 responses	[60,142-144]
PDK1	- Impaired T cell differentiation in thymus		[145]