

Genetic errors of the human caspase recruitment domain–B-cell lymphoma 10–mucosa-associated lymphoid tissue lymphoma-translocation gene 1 (CBM) complex: Molecular, immunologic, and clinical heterogeneity

Rebeca Pérez de Diego, PhD,^{a,b} Silvia Sánchez-Ramón, MD, PhD,^c Eduardo López-Collazo, PhD,^{b,d}
 Rubén Martínez-Barricarte, PhD,^e Carolina Cubillos-Zapata, PhD,^{b,d} Antonio Ferreira Cerdán, MD, PhD,^g
 Jean-Laurent Casanova, MD, PhD,^{e,f,h,i,j,*} and Anne Puel, PhD^{e,h,i,*} *Madrid, Spain, New York, NY, and Paris, France*

Three members of the caspase recruitment domain (CARD) family of adaptors (CARD9, CARD10, and CARD11) are known to form heterotrimers with B-cell lymphoma 10 (BCL10) and mucosa-associated lymphoid tissue lymphoma-translocation gene 1 (MALT1). These 3 CARD-BCL10-MALT1 (CBM) complexes activate nuclear factor κ B in both the innate and adaptive arms of immunity. Human inherited defects of the 3 components of the CBM complex, including the 2 adaptors CARD9 and CARD11 and the 2 core components BCL10 and MALT1, have recently been reported. Biallelic loss-of-function mutant alleles underlie several different immunologic and clinical phenotypes, which can be assigned to 2 distinct categories. Isolated invasive fungal infections of unclear cellular basis are associated with CARD9 deficiency, whereas a broad range of clinical manifestations, including those characteristic of T- and B-lymphocyte defects, are associated with CARD11, MALT1, and BCL10 deficiencies. Interestingly, human subjects with these mutations have some features in common with the corresponding knockout mice, but other features are different

between human subjects and mice. Moreover, germline and somatic gain-of-function mutations of *MALT1*, *BCL10*, and *CARD11* have also been found in patients with other lymphoproliferative disorders. This broad range of germline and somatic CBM lesions, including loss-of-function and gain-of-function mutations, highlights the contribution of each of the components of the CBM complex to human immunity. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: Primary immunodeficiency, combined immunodeficiency, B-cell lymphoma 10, mucosa-associated lymphoid tissue lymphoma-translocation gene 1, CARMA1, caspase recruitment domain 9

From ^athe Laboratory of Immunogenetics of Diseases, ^bthe Innate Immunity Group, ^cthe Laboratory of Tumor Immunology, IdiPAZ Institute for Health Research, La Paz University Hospital, Madrid; ^dthe Clinical Immunology Department, San Carlos Clinical Hospital, Madrid; ^eSt Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, Rockefeller University, New York; ^fthe Howard Hughes Medical Institute, New York; ^gthe Immunology Unit, La Paz University Hospital, Madrid; ^hthe Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, and ⁱthe Pediatric Hematology-Immunology Unit, AP-HP, Necker Hospital for Sick Children, Paris; and ^jUniversity Paris Descartes, Imagine Institute, Paris.

*These authors contributed equally to this work.

Supported by the Ramon Areces Foundation, grant XVII Concurso Nacional de Ayudas a la Investigación; FIS grant reference PI14/00616; the St. Giles Foundation, Rockefeller University; the Jeffrey Modell Foundation; Institut National de la Santé et de la Recherche Médicale, University Paris Descartes, the French National Research Agency (ANR) under the “Investments for the future” program (grant no. ANR-10-IAHU-01); and grant 8 UL1 TR000043 from the National Center for Research Resources and the National Center for Advancing Sciences (NCATS), National Institutes of Health. R.M.-B. is supported by an EMBO long-term fellowship. R.P.D. is supported by the “Ramon y Cajal” program (MINECO, Spain; no. RYC-2011-07597) and EMBO short-term fellowship ASTF no. 119-2013.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication April 15, 2015; revised June 2, 2015; accepted for publication June 12, 2015.

Corresponding author: Rebeca Pérez de Diego, PhD, Laboratory of Immunogenetics of Diseases, IdiPAZ Institute for Health Research, La Paz University Hospital, Paseo Castellana 261, Madrid 28046, Spain. E-mail: rebeca.perez@idipaz.es.

0091-6749/\$36.00

© 2015 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2015.06.031>

The CBM complex is a cytosolic heterotrimer formed by a caspase recruitment domain (CARD) protein, B-cell lymphoma 10 (BCL10), and mucosa-associated lymphoid tissue lymphoma-translocation gene 1 (MALT1). Three CARD family adaptor molecules have been shown to form CBM complexes: CARD9, CARD10 (also known as CARD-containing MAGUK protein 3 [CARMA3]), and CARD11 (also known as CARMA1). Human CARD9 is a 536-amino-acid adaptor protein. It possesses an N-terminal CARD domain (mediating homophilic interactions between CARD-containing molecules) and a C-terminal coiled-coil region that serves as an oligomerization domain. CARD10 is a 1032-amino-acid protein that binds to BCL10-MALT1.¹ CARD11 is 1154 amino acids long and belongs to both the membrane-associated guanylate kinase (MAGUK)² and CARD families. MALT1 is an 824-amino-acid caspase-like cysteine protease that contains a CARD domain, 2 immunoglobulin-like domains, and a C-terminal caspase-like domain. Finally, BCL10 is a 233-amino-acid intracellular signaling protein characterized by an amino-terminal CARD motif and a Ser/Thr-rich carboxyl terminus of unknown function.^{3,4} The 2 immunoglobulin-like domains of MALT1 bind to BCL10 through a motif composed of a short stretch of amino acids located just after the CARD of BCL10. CARD motifs of BCL10 and MALT1 allow binding to the 3 CARD proteins forming the heterotrimer.

In human subjects and mice the CBM complex mediates nuclear factor κ B (NF- κ B) and mitogen-activated protein kinase activation in a cell type-specific and nonredundant manner after stimulation of various immune receptors, as described below. The NF- κ B transcription factor plays a critical role in innate and adaptive immune regulation, cell memory, cell survival/

Abbreviations used

AR:	Autosomal recessive
BCL10:	B-cell lymphoma 10
BCR:	B-cell receptor
CARD:	Caspase recruitment domain
CARMA3:	CARD-containing MAGUK protein
CBM:	CARD-BCL10-MALT1
ConA:	<i>Concanavalin A</i>
DC:	Dendritic cell
GOF:	Gain of function
MAGUK:	Membrane-associated guanylate kinase
MALT1:	Mucosa-associated lymphoid tissue lymphoma-translocation gene 1
NF- κ B:	Nuclear factor κ B
NK:	Natural killer
PMA:	Phorbol 12-myristate 13-acetate
PWM:	Lectin from <i>Phytolacca americana</i> (pokeweed)
TCR:	T-cell receptor
TLR:	Toll-like receptor

apoptosis, and cell-cycle progression. Different cell types contain different members of the CARD family: CARD9 in myeloid cells,⁵ CARD10 in epithelial cells,⁶⁻⁸ and CARD11 in lymphocytes⁵ (Fig 1). In lymphocytes the CBM complex acts downstream of the T-cell receptor (TCR) or B-cell receptor (BCR), controlling lymphocyte activation and adaptive immunity.⁹⁻¹² It has also been implicated in B-cell activating factor receptor and Toll-like receptor (TLR) 4 signaling in B cells^{13,14} and in the signaling of several natural killer (NK) receptors, such as NK1.1, Ly49H, NKG2D, and Ly49D.^{15,16} In myeloid cells the CBM complex is involved in innate immune responses, in which it acts downstream from C-type lectin receptors, such as Dectin-1, Dectin-2, or Mincle,¹⁷⁻²⁴ or other receptors, such as Fc γ R and TLRs. Finally, the CBM complex is involved in signaling downstream of TLR4^{17,25,26} and G protein-coupled receptor signaling in epithelial cells (Fig 1).^{27,28} We describe here the broad spectrum of clinical and immunologic features of the primary immunodeficiencies caused by inborn errors of 4 of the 5 individual members of the human CBM complex. Studies of these primary immunodeficiencies should improve our understanding of the specific role of each of these components in immunity.

MALT1 DEFICIENCY**Clinical findings**

The first patients with autosomal recessive (AR) MALT1 deficiency to be reported were 2 siblings from a consanguineous Lebanese family (P1 and P2).²⁹ Both had experienced recurrent pulmonary infections since the age of 4 months, resulting in bronchiectasis. Both also had mastoiditis, chronic aphthous ulcers, cheilitis, gingivitis, esophagitis, gastritis, and duodenitis. Despite a history of vaccination with tetanus and unconjugated pneumococcal polysaccharide vaccines, anti-tetanus antibody and antibodies to all pneumococcal serotypes titers were nonprotective in both patients. P1 also had meningitis (caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*). Biopsy of the small intestine showed villous atrophy in P1 and abnormally large numbers of intraepithelial lymphocytes in P2. *Candida albicans* was cultured from the duodenal biopsy sample and stools of P2. Cytomegalovirus was repeatedly recovered in the urine of both

patients. Both patients had growth retardation but normal neurologic development. Despite intravenous immunoglobulin replacement therapy, both died from respiratory failure, P1 at 13.5 years of age and P2 at 7 years of age.

A third patient (P3) was subsequently described by McKinnon et al.³⁰ This patient, a 15-year-old girl with consanguineous parents of Kurdish descent, presented with growth retardation, an eczema-like rash since age 2 weeks, and persistent severe dermatitis, skin infections with *Staphylococcus aureus*, varicella-zoster virus, and herpes simplex virus 1. P3 also had severe inflammatory gastrointestinal disease and multiple episodes of pneumonia, chronic inflammatory lung disease, bronchiectasis, clubbing, and chronic granulation tissue.

Very recently, a fourth patient (P4) has been reported. This patient, a male infant with nonconsanguineous parents, had generalized rash, intestinal inflammation, and severe infections, including cytomegalovirus pneumonitis.³¹

Genetic and immunologic findings

P1 and P2 were homozygous for a missense mutation (S89I) located in the CARD domain of MALT1. The mutation had no effect on *MALT1* mRNA levels, but no protein was detectable in the lysates of PHA T-cell blasts. P1 and P2 had normal numbers of CD3⁺CD4⁺, CD3⁺CD8⁺, and CD19⁺ cells and normal serum immunoglobulin levels. An analysis of naive and memory T cells was performed once on CD4⁺ cells from P1, and the percentages were within normal ranges (68% CD4⁺CD45RA⁺ cells and 38% CD4⁺CD45RO⁺ cells). B-cell subsets were not examined.²⁹ P3 was homozygous for a missense mutation (W580S). This residue is part of an α -helical linker region, and the aromatic group of W580 interacts with hydrophobic residues of the caspase-like domain. The mutation resulted in normal *MALT1* mRNA levels but very low protein levels. Lymphocyte numbers were within the normal range. The proportion of CD31⁺ T cells was high, with skewing toward the CD4⁺ T helper subset. CD4⁺CD25⁺CD127⁺¹⁰ forkhead box protein 3–positive regulatory T-cell numbers were normal. However, P3 had very low B-cell counts, with developmental arrest characterized by high percentages of naive B cells and an almost complete absence of marginal zone B cells and low levels of switched memory B cells. Serum immunoglobulin levels were normal.³⁰ P4 was a compound heterozygote with 2 nonsynonymous variants affecting MALT1 exon 10, a splice acceptor defect (cDNA c.1019-2A>G), and a single nucleotide deletion, leading to a frameshift within the paracaspase domain and truncation after 18 missense codons (Y353fs*18). No protein was detectable in the lysates of PBMCs. P4 showed expansion of CD4⁺ and CD8⁺ T-cell populations, with high proportions of naive CD45RA⁺ T cells. B and NK cells were present, but immunoglobulin levels were low (Fig 1 and Table I).²⁹⁻³⁴

Cellular function and comparison with mice

PBMCs from P1 and P2 displayed impaired proliferative responses to mitogens (PHA, *concanavalin A* [ConA], and lectin from *Phytolacca americana* [pokeweed {PWM}]), and anti-CD3), or antigens (tetanus toxoid, diphtheria toxin, and *Candida* species). Their T cells (PHA T-cell blasts) did not degrade I κ B- α or produce IL-2 after stimulation with phorbol 12-myristate 13-acetate (PMA) plus ionomycin (PMA/ionomycin).²⁹ Similarly, no I κ B- α degradation or p65 phosphorylation was observed in primary T cells from P3 after PMA/ionomycin stimulation. The roles

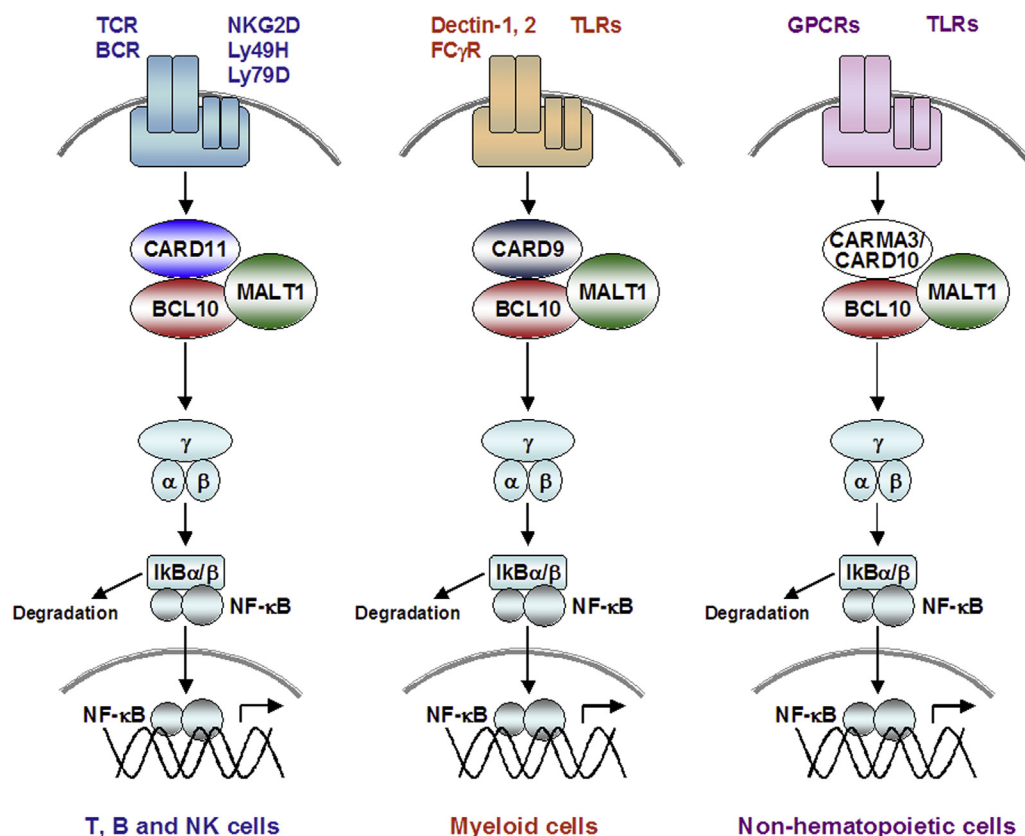


FIG 1. Summary of the human CBM complex mutations (*MALT1*, *BCL10*, *CARD11*, and *CARD9*) and their effects on different receptors. *GPCRs*, G protein-coupled receptors.

of MALT1 in PBMCs from P3 were investigated by testing the effect of the mutation on paracaspase activity and the scaffold function central to CBM complex formation. MALT1 paracaspase activity was studied by assessing the cleavage of its substrate, BCL10, and was found to be absent in P3.^{30,35} PBMCs from P4 displayed impaired proliferative responses to PHA and ConA. Moreover, these cells were unable to phosphorylate NF- κ B or degrade I κ B. After activation with PMA/ionomycin or anti-CD3/CD28, P4's T cells had reduced levels of IL-2 and IFN- γ .³¹

Like the patients, *Malt1*-deficient mice had normal numbers of peripheral T cells with a normal subset distribution but a defective proliferative response to mitogens or anti-CD3 antibody. The number of follicular B cells in the spleens of *Malt1*^{-/-} mice was normal, but there were very few marginal zone B cells and peritoneal B1 cells, the cells responsible for producing antibodies against type II T-independent antigens. B-cell activating factor receptor signaling was impaired in the mutant mice, and immunoglobulin levels were low, which was at odds with the findings for the human deficiency. As in humans, Malt1 was found essential for T-cell activation, proliferation, and IL-2 production in response to TCR ligation. It was also found required for the NF- κ B activation induced by the TCR, but not for TNF- α or IL-1 signaling (Table II).^{9-11,13,15,21,23,27,37-42}

BCL10 DEFICIENCY

Clinical findings

In 2014, an Amerindian boy (P5) from Ecuador, who was born to consanguineous parents, was reported to have AR complete

BCL10 deficiency. P5 presented with gastroenteritis, otitis, and respiratory tract infections from the age of 6 months. He was subsequently hospitalized for severe viral infections: influenza A and B with pulmonary infiltrate, adenovirus, and respiratory syncytial virus. He had acute respiratory failure secondary to infection, oral candidiasis, and diaper dermatitis.

Prolonged diarrhea and chronic nonspecific colitis with moderate lymphocytic infiltration in the lamina propria were observed. At the age of 2 years and 10 months, P5 had seizures and *status epilepticus*. Secondary diffuse leukoencephalopathy was diagnosed. At the age of 3 years and 4 months, P5 had from diarrhea caused by *Clostridium difficile*, and after 24 hours, he experienced dizziness, disorientation, and generalized weakness, with focal abnormal movements. Encephalitis of unknown cause was suspected, and P5 eventually died of respiratory failure.³²

Genetic and immunologic findings

P5 had a homozygous splice-site mutation (G/A) affecting the first G residue of intron 1 of the gene encoding BCL10 (g.85741978C>T; IVS1+1G>A). This nucleotide is the first nucleotide of intron 1 and is invariant because it is part of the donor site for splicing. The *BCL10* mutation resulted in an absence of wild-type mRNA and protein. This patient was found to have a profound deficit of memory T and B cells and abnormally small numbers of CD4⁺ central memory T cells and CD4⁺ regulatory T cells. Most B cells (97.1%) were naive, which is consistent with the profound hypogammaglobulinemia observed in this patient treated with intravenous immunoglobulin (Fig 1 and Table I).³²

TABLE I. Summary of the 3 human CMB complex deficiencies associated with CIDs

	Clinical diagnosis	Lymphocyte phenotype	Patients	Mutation	Consanguinity	Cellular response
MALT1	CID ²⁹	Normal total numbers of T and B cells	Siblings P1 and P2 (both deceased)	- Homozygous - Loss of protein expression; c.266G>T S89I	Parents were first cousins	- Impaired proliferative response of PBMCs to mitogens PHA, ConA, PWM, and anti-CD3 and antigens (tetanus toxoid, diphtheria toxin, and <i>Candida</i> species) - Impaired IκB-α degradation and IL-2 production on TCR stimulation
	CID ³⁰	Severe B-cell lymphopenia; developmental arrest: small numbers of transitional B cells, increased percentages of naive B cells, almost no marginal zone and low levels of switched memory B cells	P3	- Homozygous - Very low levels of protein expression; W580S	Parents were first cousins	- Absence of IκB-α degradation and p65 phosphorylation in primary T cells after PMA/ionomycin stimulation - Paracaspase activity affected - Absence of T-cell proliferation and blast formation after PHA stimulation and abolition of IL-2 secretion
	CID ³¹	- Expansion of CD4⁺ and P4 CD8⁺ T-cell populations with high proportions of naive CD45RA⁺ T cells - B and NK cells were present, but immunoglobulin levels were low.		- Compound heterozygote mutations - Loss of protein expression - Splice acceptor defect, cDNA c.1019-2A>G, and a single nucleotide deletion (Y353fs*18)	Nonconsanguineous parents	- PBMCs: Impaired proliferative responses to PHA and ConA and inability to phosphorylate NF-κB or degrade IκB - Reduced levels of IL-2 and IFN-γ after activation with PMA/ionomycin or anti-CD3/CD28 in T cells
BCL10	CID ³²	Normal total numbers of T and B cells but mostly with a naive phenotype	P5 (deceased)	- Homozygous - Loss of protein expression, g.85741978C>T; IVS1+1G>A	Parents were first cousins	- Normal responses to TLR1/2, TLR4, TLR2/6, and Dectin-1 signaling by MDMs and MDDCs - Impaired TLR4, TLR2/6, and Dectin-1 signaling in fibroblasts - Blocked T-cell proliferation in response to TCR stimulation
CARD11	CID ³³	- Normal T- and B-cell numbers - Predominantly naive phenotype of CD4⁺ and CD8⁺ T cells - Peripheral blood B cells, mostly naive, with a transitional B-cell phenotype - Absence of regulatory T cells	P6	- Homozygous - Protein detected, Q945X	Parents were first cousins	- Impaired T-cell proliferation after PBMC stimulation with T-cell mitogens (PHA, ConA, or anti-CD3 mAb) - Strongly impaired proinflammatory cytokine production after LPS stimulation and weak production after PMA/ionomycin stimulation - Disturbed TCR-mediated T-cell function

(Continued)

TABLE I. (Continued)

Clinical diagnosis	Lymphocyte phenotype	Patients	Mutation	Consanguinity	Cellular response
CID ³⁴	- Normal CD4 and CD8 T-cell counts but with a predominantly naive phenotype, very low levels of regulatory T cells, effector memory cells, and terminally differentiated effector cells - B cells are mostly naive and transitional	P7	- Homozygous 1377-bp genomic deletion encompassing the entire sequence of exon 21 - No protein expression	Parents were first cousins	- No IkB-α degradation or p65 phosphorylation after anti-IgM and PMA stimulation - No induction of intracellular adhesion molecule 1 and CD25 in B cells after BCR stimulation - Low percentages of IL-2, IL-17, and IFN-γ in CD4 T cells after PMA/ionomycin stimulation - Impaired upregulation of OX40, CD25, and ICOS expression in response to TCR/CD28 stimulation - Abolished proliferation of T cells in response to CD3/CD28 stimulation

CID, Combined immunodeficiency; ICOS, inducible costimulator; MDDC, monocyte-derived dendritic cell; MDM, monocyte-derived macrophage.

Cellular function and comparison with mice

Myeloid cells form CARD9-BCL10-MALT1 heterotrimer. BCL10-deficient myeloid cells displayed a normal pattern of cytokine production in response to stimulation with TLR1/2, TLR4, TLR2/6, and Dectin-1. By contrast, BCL10-deficient fibroblasts (CARD10-BCL10-MALT1 is the heterotrimer formed in fibroblasts) were unable to translocate the NF- κ B p65 subunit to the nucleus, and cytokine production in response to stimulation with TLR4, TLR2/6, and Dectin-1 was abolished. Mouse studies performed on epithelial cells, such as intestinal cells, showed that IL-8 production on TLR4 stimulation was BCL10 dependent. However, other studies suggested that TLR4 signaling could occur through both BCL10-dependent and BCL10-independent pathways.^{17,25,43-45} BCL10 silencing in mouse macrophages resulted in impaired TLR4 responses.^{20,37} Furthermore, mouse *Bcl10*^{-/-} dendritic cells (DCs) responded poorly to zymosan in terms of TNF- α and IL-10 production.³⁸ Finally, by contrast to the findings for human subjects, some studies on mouse macrophages have shown that the Dectin-1 signaling pathway activates NF- κ B through the Syk-CARD9-BCL10 complex.^{23,32} Human BCL10 deficiency affected the final maturation of T and B cells into memory cells but not the development of naive T and B cells. Human T-cell proliferation was blocked after TCR stimulation *in vitro*. As in human subjects, mouse *Bcl10* has been implicated in NF- κ B activation in response to stimulation of the BCR and TCR.^{3,4,39,45} Despite normal early development in the bone marrow, mouse mature B-cell levels were low in peripheral blood.⁴⁰ It has been shown that double-positive thymocytes differentiate to generate normal numbers of total CD4⁺ and CD8⁺ cells, producing normal amounts of TCR- α /TCR- β /CD3 complexes (Table II).⁶

CARD11 DEFICIENCY

Clinical findings

In 2 different studies 2 patients (P6 and P7) were found to have AR CARD11 deficiency.^{33,34} P6 was a girl born to

consanguineous parents of Central European ancestry. At 6 months of age, she presented with severe tachypnea and required oxygen supplementation and mechanical ventilation. She had severe interstitial pneumonia caused by *Pneumocystis jirovecii*. P7, a girl born to consanguineous parents of Palestinian descent, presented with an upper respiratory tract infection at 9 months of age. At the age of 13 months, she presented with fever and severe dyspnea caused by *P jirovecii* pneumonia. P7 was treated with intravenous immunoglobulin.

A third patient with a compound heterozygous mutation has also been described, but the data for this patient have yet to be published.

Genetic and immunologic findings

P6 had a homozygous premature stop codon mutation, Q945X, resulting in truncation of the essential guanylate kinase-like domain of CARD11.³³ This mutation led to production of a truncated protein in transfected CARD11-deficient JPM50.6 cells. P6 had agammaglobulinemia, but her T- and B-cell counts were unexpectedly normal. Immunophenotyping revealed a predominantly naive phenotype in CD4⁺ and CD8⁺ T cells. B cells from peripheral blood were mostly naive and had a transitional B-cell phenotype. Regulatory T cells were absent. P7 had a homozygous 1377-bp genomic deletion encompassing the entire sequence of exon 21, encoding amino acids 902 to 946. The corresponding protein was not detected in EBV-transformed B cells.³⁴ Like P6, P7 had hypogammaglobulinemia. She had normal CD4 and CD8 T-cell counts, with a predominantly naive phenotype and very low levels of regulatory T cells, effector memory cells, and terminally differentiated effector cells. Most of her B cells were naive transitional B cells (Fig 1 and Table I).³⁵

Cellular function and comparison with mice

Lymphocyte proliferation was strongly impaired after stimulation of PBMCs from P6 with T-cell mitogens, such as PHA, ConA, or anti-CD3. By contrast, the proliferation induced by the

TABLE II. Summary of the main cellular studies of mouse CBM complex deficiencies

<i>Malt1</i> ^{-/-} mice	<i>Bcl10</i> ^{-/-} mouse	<i>Card11</i> ^{-/-} mouse	<i>Card9</i> ^{-/-} mouse
• Normal numbers and subset distribution of peripheral T cells. • Defective proliferation in response to mitogens and anti-CD3 antibody. • Normal number of follicular B cells in the spleen but severe reduction of marginal zone B cells and peritoneal B1 cells, which produce antibodies against type II T-independent antigens. • BAFF receptor signaling impaired. • Low immunoglobulin levels. • Affected T-cell activation, proliferation, and IL-2 production in response to TCR signaling. • Required for signal-specific NF-κB activation induced by the TCR but not TNF-α or IL-1 signaling.^{11,36}	• <i>Bcl10</i>^{-/-}/<i>Bcl10</i> silenced in macrophages and DCs: TLR4 signaling is Bcl10 dependent³⁷; in DCs impaired zymosan signaling³⁸; in macrophages Dectin-1/NF-κB signaling is Bcl10 dependent.²³ • <i>Bcl10</i>^{-/-} mice in intestinal cells: TLR4 signaling is Bcl10 dependent.^{13,21,38,39} • Normal early development in the bone marrow and small numbers of mature B cells in the peripheral blood.⁴⁰ • Double-positive thymocytes differentiate to generate normal total numbers of total CD4⁺ and CD8⁺ cells, expressing TCR-α/TCR-β/CD3 complexes in normal amounts; normal total T-cell numbers. • Blocked T-cell proliferation in response to TCR signaling.¹⁰	• Selective defect in NF-κB activation, affecting antigen receptor- or PKC-mediated proliferation and defective cytokine production in T and B cells. • Normal antigen-independent development of T and B cells in thymus and bone marrow. • Altered peripheral activation-dependent proliferation and differentiation of lymphocytes. • Disrupted development of CD5⁺ peritoneal B cells and B-cell proliferation in response to BCR and CD40 signaling. • Low serum immunoglobulin levels; after vaccination, poor responses to T-dependent and T-independent antigens. • Reduced mature B cells. • Defective BCL10 recruitment to clustered TCR complexes and lipid rafts, impaired NF-κB activation, and IL-2 production on TCR stimulation.^{9,15,41}	• Normal development of T- and B-cell subsets, including regulatory T cells, recirculating B cells, mature follicular and marginal zone B cells, and B1 B cells. • Small numbers of T_H17 cells, which are involved in adaptive antifungal immunity. • No significant differences in basal immunoglobulin levels. • CARD9 is specifically required to transduce zymosan-activated Dectin-1 signals to NF-κB. • Impaired cytokine production after stimulation with zymosan or whole <i>C albicans</i> in DCs.^{27,38,42}

BAFF, B-cell activating factor; PKC, protein kinase C.

classical B-cell mitogen PWM was similar to that for healthy control subjects. In P6 the mutation was loss of function and disturbed TCR-mediated T-cell function. Studies in PBMCs showed that mRNA levels after stimulation with LPS (*IL1β*, *IL6*, and *CXCL8*) or PMA/ionomycin (*IL2*, *IFNγ*, *IL4*, *IL5*, *IL10*, *IL17*, and *IL22*) were very low. Studies on PBMCs from P7 showed that degradation of IκB-α and phosphorylation of p65 after stimulation with anti-IgM antibody or PMA were abolished, whereas the response to stimulation with CD40 ligand was normal. Furthermore, on BCR stimulation, no induction of intracellular adhesion molecule 1 and CD25 was observed in B cells. After PMA/ionomycin stimulation, the percentages of IL-2-, IL-17-, and IFN-γ-producing CD4⁺ T cells were low. The upregulation of OX40, CD25, and inducible costimulator expression after TCR/CD28 stimulation was also strongly impaired. Finally, T-cell proliferation in response to CD3/CD28 stimulation was completely abolished *in vitro*.^{33,34} These immunologic findings for human patients with CARD11 deficiency are consistent with the phenotype of *Card11*^{-/-} mice, which display a selective defect of NF-κB activation, impairing antigen receptor- or protein kinase C-induced proliferation and cytokine production in T and B cells.⁵ In *Card11*^{-/-} mice or mice homozygous for a hypomorphic allele, the antigen-independent development of T and B cells in the thymus and bone marrow, respectively, was normal, but peripheral activation, antigen-dependent proliferation, and lymphocyte differentiation were impaired.^{15,41} The development of CD5⁺ peritoneal B cells was disrupted in these mice, as was B-cell proliferation in response to the ligation of both BCR and CD40. Serum immunoglobulin levels were low, and after vaccination, *Card11* mutant mice responded poorly to T-dependent and T-independent antigens.⁴¹ Mature B-cell

numbers were found to be very low in mouse models.^{9,41} The crucial defect in late B-cell differentiation leading to low serum immunoglobulin levels and defective T-dependent and T-independent immune responses was common to all mouse models.^{9,15,41} *Card11*^{-/-} T cells were defective for the recruitment of BCL10 to clustered TCR complexes and lipid rafts, NF-κB activation, and induction of IL-2 production (Table II). Thus in both human subjects and mice, CARD11 plays a key role in antigen receptor signaling, leading to the activation and proliferation of B and T cells.⁴⁶

CARD9 DEFICIENCY

Clinical findings

Since with the first description of AR CARD9 deficiency in 2009, 38 patients with this condition have been reported, making it by far the most common genetic disorder of the CBM complex (Table III).⁴⁷⁻⁵⁵ All these patients displayed selective susceptibility to various fungal diseases, including mucocutaneous candidiasis, superficial, extensive or deep dermatophytosis, subcutaneous phaeohyphomycosis, *Candida* species central nervous system or digestive tract infections, or invasive *Exophiala* species infection (Table III).⁴⁷⁻⁵⁵

Genetic and immunologic findings

Thirteen different mutations have been identified and have been found in the homozygous (R18W,⁵² R35Q,⁵⁵ R70W,⁵⁵ Y91H,⁵¹ R101C,⁵⁰ D274fsX60,⁵⁴ Q289X,^{50,53,55} Q295X,^{47,55} and E323del⁵²) or compound heterozygous (L64fsX59/Q158X⁵⁴ and G72S/R373P⁴⁸) state. The patients analyzed had

TABLE III. Summary of human CARD9 deficiency underlying invasive fungal infections

Clinical diagnosis	Lymphocyte phenotype	No. of patients	Mutation	Consanguinity	Cellular response	Reference
- Family with a history of <i>Candida</i> species infections, CMC and superficial dermatophytosis - Some family members had <i>Candida</i> species infection of the brain.	- Complete blood counts in normal range and normal T-cell counts - Significantly lower than normal mean proportion of T_H17 cells - Normal basal immunoglobulin levels	Large consanguineous multiplex kindred of Iranian origin	- Homozygous Q295X mutation affecting the family - Family members display no CARD9 expression	Yes	- TNF-α production in response to Dectin-1 stimulation affected in innate immune cells - Monocytes display no <i>Candida</i> species-induced IL-6 and IL-1β release (studies performed in mouse Card9^{-/-} cells)	Glocker et al, 2009 ⁴⁷
Patient with <i>Candida dubliniensis</i> meningoencephalitis	Low levels of T_H17 cell-derived IL-17	One patient	- Compound heterozygous mutations, G72S and R373P; both of these residues of the CARD9 protein are highly conserved among vertebrates - No protein expression	No	Impaired unopsonized <i>C. albicans</i> neutrophil killing	Drewniak et al, 2013 ⁴⁸
Families with histories of deep dermatophytosis	- No detectable T- or B-cell phenotype - Reduced proportion of IL-17A-producing T cells	Eight unrelated Tunisian, Algerian, and Moroccan families	- Eight Algerian and 4 Tunisian patients: homozygous mutation Q289X - Two Moroccan siblings: homozygous missense mutation, R101C - Amino acid substitution located only a few amino acids after the end of the CARD domain - The R101C mutation allows protein expression, whereas the Q289X mutation does not.	Yes	Low levels of IL-6 production after stimulation with heat-killed <i>C. albicans</i> and heat-killed <i>S. cerevisiae</i>⁴⁹	Lanternier et al, 2013 ⁵⁰
Patient with relapsing <i>C. albicans</i> meningoencephalitis	- Normal numbers of neutrophils, monocytes, and lymphocytes - Normal T_H17 levels	French Canadian patient	- Homozygous Y91H mutation affecting the CARD domain - Normal mRNA and protein levels	No	- Normal IL-17 but reduced GM-CSF levels after PBMC stimulation with zymosan - Normal <i>IL1</i> and <i>IL6</i> mRNA induction by zymosan-stimulated PBMCs	Gavino et al, 2014 ⁵¹
Patients with invasive <i>Exophiala</i> disease: <i>E. dermatitidis</i> liver and brain infection (R18W/R18W patient) or <i>E. spinifera</i> subcutaneous, bone, and lung infection (E323del/E323del patient)	Normal T_H17 levels	Two unrelated patients	- One patient homozygous for the R18W allele (affecting the N-terminal CARD domain) and 1 patient homozygous for the E323del allele (affecting the coiled-coil domain) - Normal expression of the R18W mutant protein	R18W: no E323del: yes	- Impaired R18W/R18W whole blood cell IL-6 production in response to <i>S. cerevisiae</i>, <i>E. dermatitidis</i>, and <i>C. albicans</i> but normal to zymosan, LPS, <i>S. aureus</i>, VSV, and PMA/ionomycin - Impaired TNF-α production by R18W/R18W MDDC in response to fungal ligands (curdlan, zymosan, <i>S. cerevisiae</i>, <i>C. albicans</i>, and <i>E. dermatitidis</i>) but normal to <i>S. aureus</i> or LPS - Normal IL-17 T-cell production	Lanternier et al, 2014 ⁵²

(Continued)

TABLE III. (Continued)

Clinical diagnosis	Lymphocyte phenotype	No. of patients	Mutation	Consanguinity	Cellular response	Reference
• Patient with extensive superficial <i>Trichophyton rubrum</i> infection of the skin and nails	• Normal levels of T, B, and NK cells	• Egyptian patient	• Homozygous Q289X mutation (affecting the coiled-coil domain)	No		Jachiet et al, 2015 ⁵³
• Patients with subcutaneous phaeohyphomycosis caused by <i>P verrucosa</i>	• T_H17 cell deficiency	• Four Chinese unrelated patients (PA, PB, PC, and PD)	• Two compound heterozygous mutations in PA (c.191-192insTGCT and c.472C>T, p.L64fsX59 and p.Q158X) and a homozygous frameshift mutation (c.819-820insG, p.D274fsX60) in PB, PC, and PD • mRNA was produced but not protein.	No	• Reduced IL-6, IL-1β, TNF-α and IL-23p19 macrophage and DC production on <i>P verrucosa</i> activation	Wang et al, 2014 ⁵⁴
• Invasive disease of the central nervous system, digestive tract, or both caused by <i>Candida</i> species • <i>Candida</i> species meningoencephalitis in 3 patients associated with <i>Candida</i> species colitis in a fourth patient and <i>Candida</i> species colitis in the fifth • Patients E, F, G, H, and I	• Patient E: normal counts of T and NK cells; B-cell lymphopenia • Patients F and G: normal counts of T, B, and NK cells and normal immunoglobulin levels • Patient H: normal lymphocyte subsets	• Five patients (children and adults) of Turkish (2 patients), Iranian, Moroccan, or Pakistani origin	• Two patients with a homozygous R70W mutation (CARD domain) and lower protein levels • One patient with a homozygous R35Q mutation (CARD domain) and normal protein production • One patient with a homozygous Q289X mutation and another with a homozygous Q295X mutation (both coiled-coil domain)	Yes	• Poor TNF-α and IL-6 production by MDDCs in response to fungal agonists (curdlan, heat-killed <i>C albicans</i>, <i>S cerevisiae</i>, and <i>E dermatitidis</i>) and impaired TNF-α and IL-6 production by whole blood cells after stimulation with <i>S cerevisiae</i>, <i>C albicans</i>, and <i>E dermatitidis</i> • Normal IL-17 production by whole blood cells after PMA/ionomycin stimulation	Lanternier et al, 2015 ⁵⁵

CMC, Chronic mucocutaneous candidiasis; MDDC, monocyte-derived dendritic cell; VSV, vesicular stomatitis virus.

complete blood counts within the normal ranges, with normal counts of CD3⁺, CD4⁺, and CD8⁺ T cells; memory T cells; follicular helper T cells; effector memory T cells; regulatory T cells; B cells; and NK cells and normal basal levels of serum immunoglobulins. Most but not all patients had significantly lower proportions of IL-17-producing T cells than healthy donors (Fig 1 and Table III).^{47,48,50,54}

Cellular function and comparison with mice

Glocker et al⁴⁷ showed that the mutation identified (Q295X) impaired the production of TNF- α in response to curdlan (Dectin-1 agonist) stimulation in transfected bone marrow-derived macrophages from *Card9*^{-/-} mice, whereas the wild-type *CARD9* allele corrected the Dectin-1 signaling defect, and studies in monocytes showed that *Candida* species-induced IL-6 and IL-1 β release was abolished. Drewniak et al⁴⁸ showed that the release of IL-6 and IL-1 β by *CARD9*^{-/-} leukocytes after stimulation with *C albicans* was impaired, whereas that after stimulation with *Staphylococcus aureus* was not. They also reported a significant impairment of *C albicans* killing by *CARD9*-deficient neutrophils (mostly for unopsonized *C albicans*). In 2013, Lanternier et al⁵⁰ showed that IL-6 production by whole blood stimulated with heat-killed *C albicans* or *Saccharomyces cerevisiae* was impaired. Gavino et al⁵¹

reported an impairment of GM-CSF production by zymosan-stimulated PBMCs. In 2014 and 2015, Lanternier et al^{52,55} showed that TNF- α production by monocyte-derived dendritic cells in response to fungal agonists (curdlan, zymosan, heat-killed *S cerevisiae*, *C albicans*, and *Exophiala dermatitidis* stimulation) was impaired. Similarly, Wang et al⁵⁴ studied macrophages and DCs stimulated with *Phialophora verrucosa* and found that levels of IL-1 β , IL-23p19, IL-6, and TNF- α were lower in the patient's cells than control cells. Table III summarizes the cellular phenotypes observed in the various *CARD9*-deficient patients studied. *Card9*^{-/-} mice display normal development of T- and B-cell subsets, including regulatory T cells, recirculating B cells, mature follicular and marginal zone B cells, and B1 B cells. Like some *CARD9*-deficient patients, they have small numbers of T_H17 cells, which have been implicated in mucocutaneous antifungal immunity.^{47,48,50,54} No significant differences in basal immunoglobulin levels were detected. TCR- and BCR-induced NF- κ B activation was normal; *CARD9* is specifically required to transduce zymosan-activated Dectin-1 signals to NF- κ B.^{38,42} *Card9*^{-/-} mice display impaired cytokine production by DCs after stimulation with zymosan or whole *C albicans*,^{27,38} demonstrating the importance of *CARD9* for innate antifungal immunity (Table II).¹⁹

SOMATIC *MALT1*, *BCL10*, AND *CARD11* AND GERMLINE *CARD11* GAIN-OF-FUNCTION MUTATIONS

MALT1 was first implicated in MALT lymphoma, a B-cell lymphoma frequently involving the gastrointestinal tract, in 1983. This type of tumor constitutes the most common subset of extranodal non-Hodgkin lymphomas.⁵⁶ In 1999, chromosomal translocations of *BCL10* (t[1;14][p22;q32] and t[11;18][q21;q21]) were also shown to be associated with MALT lymphomas.⁵⁷⁻⁵⁹ These translocations generate *MALT1* and *BCL10* somatic gain-of-function (GOF) mutations, leading to the constitutive activation of NF- κ B signaling. *BCL10* is also a molecular determinant of other types of lymphoma.⁶⁰⁻⁶² Somatic GOF mutations affecting the coiled-coil domain of *CARD11* have also been observed in several forms of diffuse large B-cell lymphoma, and as in *MALT1* lymphomas, these mutations cause the constitutive activation of NF- κ B signaling.⁶²⁻⁶⁸ Germline GOF *CARD11* mutations have also been described in other patients.⁶⁹ These mutations cause a congenital B-cell lymphoproliferative disease. Six affected patients have been identified, and the data for 2 of these patients remain unpublished. In the 4 patients described to date, there is a family history of polyclonal expansion of naive B cells, splenomegaly, and a potential predisposition to B-cell malignancy.⁶⁹ All carry a novel heterozygous germline mutation, E127G, affecting the coiled-coil domain of *CARD11*. Another heterozygous mutation, G116S, was also identified in a different patient with very similar signs of disease. All these mutations promote constitutive NF- κ B activation, but they render the patients' T cells less responsive to antigen receptor-induced activation. Finally, a third GOF missense mutation, G123D, has been described in another patient with persistent polyclonal B-cell lymphocytosis.⁷⁰ The oncogenic potential of constitutive NF- κ B activation caused by germline *CARD11* GOF mutations might promote B-cell malignancy because of the larger number of naive B cells.⁶⁹

CONCLUSION

In this review we have summarized and compared the recently described human CBM complex deficiencies. Some of these deficiencies were first reported in studies of single patients.⁷¹ In-depth mechanistic studies can now establish the causal role of single-gene inborn errors in immunodeficient patients.⁷¹⁻⁷³ Such studies are essential to determine the role of these genes in human immunity.⁷¹ They reveal both similarities to and differences from the situation in mice, such as the differences in innate response found for *BCL10* deficiency and differences in immunoglobulin production for *MALT1* deficiency. No germline or somatic mutations of human *CARD10* have yet been identified; studies in *Card10*^{-/-} mice have shown these mice to have impaired NF- κ B activation after stimulation with epidermal growth factor and to display several characteristics of epidermal growth factor receptor-associated malignancy, including cell proliferation, survival, migration, and invasion.⁶ The overexpression of *CARD10* has been shown to be associated with cancer.⁷⁴ Given the specificity of *CARD10* expression in the CBM complex of epithelial cells, human *CARD10* deficiency would be unlikely to result in a combined immunodeficiency. Because TLR4 signaling occurs upstream of the *CARD10*-*BCL10*-*MALT1* complex in epithelial cells and some studies have shown TLR4-*BCL10*^{-/-} status to be

associated with inflammation and colitis,^{6,17,25,43,44,75} it could also be hypothesized that *CARD10* defects would be associated with inflammatory colitis.

Overall, defects of *CARD11*, *BCL10*, and *MALT1* generate severe forms of combined immunodeficiency. The *BCL10*-deficient patient and 2 of the 4 *MALT1*-deficient patients died, whereas 1 *MALT1*-deficient patient and 1 of the 2 *CARD11*-deficient patients had undergone bone marrow transplantation and the other patient is awaiting transplantation. Bone marrow transplantation appears to be the best treatment for these 3 related disorders, given the tragic outcomes of patients not treated in this way. By contrast, in patients with *CARD9* deficiency innate immunity is affected in a very specific way, as shown by the patterns of susceptibility to invasive disease, which is generally caused by a single fungal pathogen in each patient (and thus by diverse fungi at the population level). None of the *CARD9*-deficient patients described to date had pulmonary fungal infection. In one *CARD9*-deficient patient with *C. albicans* meningoencephalitis,⁵¹ adjuvant GM-CSF treatment appears to have been beneficial. In addition, for *CARD9*-deficient patients with extensive dermatophytosis, terbinafine has been shown to be successful as a first-line treatment and posaconazole as a second-line treatment.⁵³

Finally, the overproduction of *MALT1* and *BCL10* has been implicated in MALT lymphoma,⁵⁷⁻⁵⁹ and several therapeutic studies have thus focused on inhibiting expression of the CBM complex.⁷⁶ *BCL10* deficiency appears to have an effect on lymphocytes and fibroblasts but not on myeloid cells. This finding is highly pertinent and should be taken into account when considering treatment options for MALT lymphoma because *BCL10* inhibition can have consequences for lymphocytes and nonhematopoietic cells.

We thank the members of the Laboratory of Human Genetics of Infectious Diseases and Dr Susana Alemany for helpful advice.

REFERENCES

1. Thome M. Multifunctional roles for *MALT1* in T-cell activation. *Nat Rev Immunol* 2008;8:495-500.
2. Caruana G. Genetic studies define MAGUK proteins as regulators of epithelial cell polarity. *Int J Dev Biol* 2002;46:511-8.
3. Thome M. *CARMA1*, *BCL10* and *MALT1* in lymphocyte development and activation. *Nat Rev Immunol* 2004;4:348-59.
4. Thome M, Charton JE, Pelzer C, Hailfinger S. Antigen receptor signaling to NF- κ B via *CARMA1*, *BCL10*, and *MALT1*. *Cold Spring Harb Perspect Biol* 2010;2:a003004.
5. Hara H, Saito T. *CARD9* versus *CARMA1* in innate and adaptive immunity. *Trends Immunol* 2009;30:234-42.
6. Jiang T, Grabiner B, Zhu Y, Jiang C, Li H, You Y, et al. *CARMA3* is crucial for EGFR-Induced activation of NF- κ B and tumor progression. *Cancer Res* 2011;71:2183-92.
7. McAllister-Lucas LM, Jin X, Gu S, Siu K, McDonnell S, Ruland J, et al. The *CARMA3*-*Bcl10*-*MALT1* signalosome promotes angiotensin II-dependent vascular inflammation and atherogenesis. *J Biol Chem* 2010;285:25880-4.
8. McAllister-Lucas LM, Ruland J, Siu K, Jin X, Gu S, Kim DS, et al. *CARMA3*/*Bcl10*/*MALT1*-dependent NF- κ B activation mediates angiotensin II-responsive inflammatory signaling in nonimmune cells. *Proc Natl Acad Sci U S A* 2007;104:139-44.
9. Hara H, Wada T, Bakal C, Kozieradzki I, Suzuki S, Suzuki N, et al. The MAGUK family protein *CARD11* is essential for lymphocyte activation. *Immunity* 2003;18:763-75.
10. Ruland J, Duncan GS, Elia A, del Barco Barrantes I, Nguyen L, Plyte S, et al. *Bcl10* is a positive regulator of antigen receptor-induced activation of NF- κ B and neural tube closure. *Cell* 2001;104:33-42.
11. Ruland J, Duncan GS, Wakeham A, Mak TW. Differential requirement for *Malt1* in T and B cell antigen receptor signaling. *Immunity* 2003;19:749-58.

12. Wang D, You Y, Case SM, McAllister-Lucas LM, Wang L, DiStefano PS, et al. A requirement for CARMA1 in TCR-induced NF-kappa B activation. *Nat Immunol* 2002;3:830-5.
13. Fischer KD, Tedford K, Wirth T. New roles for Bcl10 in B-cell development and LPS response. *Trends Immunol* 2004;25:113-6.
14. Yu M, Chen Y, He Y, Podd A, Fu G, Wright JA, et al. Critical role of B cell lymphoma 10 in BAFF-regulated NF-kappaB activation and survival of anergic B cells. *J Immunol* 2012;189:5185-93.
15. Gross O, Grupp C, Steinberg C, Zimmermann S, Strasser D, Hanneschlagel N, et al. Multiple ITAM-coupled NK-cell receptors engage the Bcl10/Malt1 complex via Carma1 for NF-kappaB and MAPK activation to selectively control cytokine production. *Blood* 2008;112:2421-8.
16. Malarkannan S, Regunathan J, Chu H, Kutlesa S, Chen Y, Zeng H, et al. Bcl10 plays a divergent role in NK cell-mediated cytotoxicity and cytokine generation. *J Immunol* 2007;179:3752-62.
17. Bhattacharyya S, Xue L, Devkota S, Chang E, Morris S, Tobacman JK. Carrageenan-induced colonic inflammation is reduced in Bcl10 null mice and increased in IL-10-deficient mice. *Mediators Inflamm* 2013;2013:397642.
18. Dong W, Liu Y, Peng J, Chen L, Zou T, Xiao H, et al. The IRAK-1-BCL10-MALT1-TRAF6-TAK1 cascade mediates signaling to NF-kappaB from Toll-like receptor 4. *J Biol Chem* 2006;281:26029-40.
19. Goodridge HS, Shimada T, Wolf AJ, Hsu YM, Becker CA, Lin X, et al. Differential use of CARD9 by dectin-1 in macrophages and dendritic cells. *J Immunol* 2009;182:1146-54.
20. Gringhuis SI, Wevers BA, Kaptein TM, van Capel TM, Theelen B, Boekhout T, et al. Selective C-Rel activation via Malt1 controls anti-fungal T(H)-17 immunity by dectin-1 and dectin-2. *PLoS Pathog* 2011;7:e1001259.
21. Marion S, Mazzolini J, Herit F, Bourdoncle P, Kambou-Pene N, Hailfinger S, et al. The NF-kappaB signaling protein Bcl10 regulates actin dynamics by controlling API and OCRL-bearing vesicles. *Dev Cell* 2012;23:954-67.
22. Strasser D, Neumann K, Bergmann H, Marakalala MJ, Guler R, Rojowska A, et al. Syk kinase-coupled C-type lectin receptors engage protein kinase C-sigma to elicit CARD9 adaptor-mediated innate immunity. *Immunity* 2012;36:32-42.
23. Tada R, Ikeda F, Aoki K, Yoshikawa M, Kato Y, Adachi Y, et al. Barley-derived beta-D-glucan induces immunostimulation via a dectin-1-mediated pathway. *Immunol Lett* 2009;123:144-8.
24. Xu S, Huo J, Lee KG, Kurosaki T, Lam KP. Phospholipase Cgamma2 is critical for Dectin-1-mediated Ca2+ flux and cytokine production in dendritic cells. *J Biol Chem* 2009;284:7038-46.
25. Bhattacharyya S, Dudeja PK, Tobacman JK. Lipopolysaccharide activates NF-kappaB by TLR4-Bcl10-dependent and independent pathways in colonic epithelial cells. *Am J Physiol Gastrointest Liver Physiol* 2008;295:G784-90.
26. Bhattacharyya S, Dudeja PK, Tobacman JK. Tumor necrosis factor alpha-induced inflammation is increased but apoptosis is inhibited by common food additive carrageenan. *J Biol Chem* 2010;285:39511-22.
27. LeibundGut-Landmann S, Gross O, Robinson MJ, Osorio F, Slack EC, Tsoni SV, et al. Syk- and CARD9-dependent coupling of innate immunity to the induction of T helper cells that produce interleukin 17. *Nat Immunol* 2007;8:630-8.
28. Wegener E, Krappmann D. CARD-Bcl10-Malt1 signalosomes: missing link to NF-kappaB. *Sci STKE* 2007;2007:pe21.
29. Jabara HH, Ohsumi T, Chou J, Massaad MJ, Benson H, Megarbane A, et al. A homozygous mucosa-associated lymphoid tissue 1 (MALT1) mutation in a family with combined immunodeficiency. *J Allergy Clin Immunol* 2013;132:151-8.
30. McKinnon ML, Rozmus J, Fung SY, Hirschfeld AF, Del Bel KL, Thomas L, et al. Combined immunodeficiency associated with homozygous MALT1 mutations. *J Allergy Clin Immunol* 2014;133:1458-62, e1-7.
31. Punwani D, Wang H, Chan AY, Cowan MJ, Mallott J, Sunderam U, et al. Combined immunodeficiency due to MALT1 mutations, treated by hematopoietic cell transplantation. *J Clin Immunol* 2015;35:135-46.
32. Torres JM, Martinez-Barricarte R, García-Gómez S, Mazariegos MS, Itan Y, Boisson B, et al. Inherited BCL10 deficiency impairs hematopoietic and nonhematopoietic immunity. *J Clin Invest* 2014;124:5239-48.
33. Greil J, Rausch T, Giese T, Bandapalli OR, Daniel V, Bekeredjian-Ding I, et al. Whole-exome sequencing links caspase recruitment domain 11 (CARD11) inactivation to severe combined immunodeficiency. *J Allergy Clin Immunol* 2013;131:1376-83.e3.
34. Stepsky P, Keller B, Buchta M, Kienzler AK, Elpeleg O, Somech R, et al. Deficiency of caspase recruitment domain family, member 11 (CARD11), causes profound combined immunodeficiency in human subjects. *J Allergy Clin Immunol* 2013;131:477-85.e1.
35. Turvey SE, Durandy A, Fischer A, Fung SY, Geha RS, Gewies A, et al. The CARD11-BCL10-MALT1 (CBM) signalosome complex: stepping into the lime-light of human primary immunodeficiency. *J Allergy Clin Immunol* 2014;134:276-84.
36. Tusche MW, Ward LA, Vu F, McCarthy D, Quintela-Fandino M, Ruland J, et al. Differential requirement of MALT1 for BAFF-induced outcomes in B cell subsets. *J Exp Med* 2009;206:2671-83.
37. Liu Y, Dong W, Chen L, Xiang R, Xiao H, De G, et al. BCL10 mediates lipopolysaccharide/toll-like receptor-4 signaling through interaction with Pellico2. *J Biol Chem* 2004;279:37436-44.
38. Gross O, Gewies A, Finger K, Schafer M, Sparwasser T, Peschel C, et al. CARD9 controls a non-TLR signalling pathway for innate anti-fungal immunity. *Nature* 2006;442:651-6.
39. Blonska M, Lin X. NF-kappaB signaling pathways regulated by CARMA family of scaffold proteins. *Cell Res* 2011;21:55-70.
40. Xue L, Morris SW, Orihuela C, Tuomanen E, Cui X, Wen R, et al. Defective development and function of Bcl10-deficient follicular, marginal zone and B1 B cells. *Nat Immunol* 2003;4:857-65.
41. Jun JE, Wilson LE, Vinuesa CG, Lesage S, Blery M, Miosge LA, et al. Identifying the MAGUK protein Carma-1 as a central regulator of humoral immune responses and atopy by genome-wide mouse mutagenesis. *Immunity* 2003;18:751-62.
42. Hsu YM, Zhang Y, You Y, Wang D, Li H, Duramad O, et al. The adaptor protein CARD9 is required for innate immune responses to intracellular pathogens. *Nat Immunol* 2007;8:198-205.
43. Bhattacharyya S, Gill R, Chen ML, Zhang F, Linhardt RJ, Dudeja PK, et al. Toll-like receptor 4 mediates induction of the Bcl10-NF-kappaB-interleukin-8 inflammatory pathway by carrageenan in human intestinal epithelial cells. *J Biol Chem* 2008;283:10550-8.
44. Borthakur A, Bhattacharyya S, Dudeja PK, Tobacman JK. Carrageenan induces interleukin-8 production through distinct Bcl10 pathway in normal human colonic epithelial cells. *Am J Physiol Gastrointest Liver Physiol* 2007;292:G829-38.
45. Schulze-Luehrmann J, Ghosh S. Antigen-receptor signaling to nuclear factor kappa B. *Immunity* 2006;25:701-15.
46. Egawa T, Albrecht B, Favier B, Sunshine MJ, Mirchandani K, O'Brien W, et al. Requirement for CARMA1 in antigen receptor-induced NF-kappa B activation and lymphocyte proliferation. *Curr Biol* 2003;13:1252-8.
47. Glocker EO, Hennigs A, Nabavi M, Schaffer AA, Woellner C, Salzer U, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. *N Engl J Med* 2009;361:1727-35.
48. Drewniak A, Gazendam RP, Tool AT, van Houdt M, Jansen MH, van Hamme JL, et al. Invasive fungal infection and impaired neutrophil killing in human CARD9 deficiency. *Blood* 2013;121:2385-92.
49. Ye H, Gesk S, Martin-Subero JJ, Nader A, Du MQ, Siebert R. BCL10 gene amplification associated with strong nuclear BCL10 expression in a diffuse large B cell lymphoma with IGH-BCL2 fusion. *Haematologica* 2006;91:ECR28.
50. Lantermier F, Pathan S, Vincent QB, Liu L, Cypowyj S, Prando C, et al. Deep dermatophytosis and inherited CARD9 deficiency. *N Engl J Med* 2013;369:1704-14.
51. Gavino C, Cotter A, Lichtenstein D, Lejtenyi D, Fortin C, Legault C, et al. CARD9 deficiency and spontaneous central nervous system candidiasis: complete clinical remission with GM-CSF therapy. *Clin Infect Dis* 2014;59:81-4.
52. Lantermier F, Barbati E, Meinzer U, Liu L, Pedergrana V, Migaud M, et al. Inherited CARD9 deficiency in 2 unrelated patients with invasive *Exophiala* infection. *J Infect Dis* 2015;211:1241-50.
53. Jachiet M, Lantermier F, Rybojad M, Bagot M, Ibrahim L, Casanova JL, et al. Posaconazole treatment of extensive skin and nail dermatophytosis due to autosomal recessive deficiency of CARD9. *JAMA Dermatol* 2015;151:192-4.
54. Wang X, Wang W, Lin Z, Li T, Yu J, Liu W, et al. CARD9 mutations linked to subcutaneous phaeoerythromycosis and TH17 cell deficiencies. *J Allergy Clin Immunol* 2014;133:905-8.e3.
55. Lantermier F, Mahdavi SA, Barbati E, Chaussade H, Koumar Y, Levy R, et al. Inherited CARD9 deficiency in otherwise healthy children and adults with *Candida* species-induced meningoencephalitis, colitis, or both. *J Allergy Clin Immunol* 2015;135:1558-68.e2.
56. Isaacson P, Wright DH. Malignant lymphoma of mucosa-associated lymphoid tissue. A distinctive type of B-cell lymphoma. *Cancer* 1983;52:1410-6.
57. Spencer J. Aggressive mucosa associated lymphoid tissue lymphomas are associated with mutations in Bcl10. *Gut* 1999;44:778-9.
58. Willis TG, Jadavay DM, Du MQ, Peng H, Perry AR, Abdul-Rauf M, et al. Bcl10 is involved in t(1;14)(p22;q32) of MALT B cell lymphoma and mutated in multiple tumor types. *Cell* 1999;96:35-45.
59. Zhang Q, Siebert R, Yan M, Hinzmann B, Cui X, Xue L, et al. Inactivating mutations and overexpression of BCL10, a caspase recruitment domain-containing gene, in MALT lymphoma with t(1;14)(p22;q32). *Nat Genet* 1999;22:63-8.
60. Nakagawa M, Seto M, Hosokawa Y. Molecular pathogenesis of MALT lymphoma: two signaling pathways underlying the antiapoptotic effect of API2-MALT1 fusion protein. *Leukemia* 2006;20:929-36.

61. Shen L, Liang AC, Lu L, Au WY, Wong KY, Tin PC, et al. Aberrant BCL10 nuclear expression in nasal NK/T-cell lymphoma. *Blood* 2003;102:1553-4.
62. Boyle RJ, Le C, Balloch A, Tang ML. The clinical syndrome of specific antibody deficiency in children. *Clin Exp Immunol* 2006;146:486-92.
63. Chan W, Schaffer TB, Pomerantz JL. A quantitative signaling screen identifies CARD11 mutations in the CARD and LATCH domains that induce Bcl10 ubiquitination and human lymphoma cell survival. *Mol Cell Biol* 2013;33:429-43.
64. Dong G, Chanudet E, Zeng N, Appert A, Chen YW, Au WY, et al. A20, ABIN-1/2, and CARD11 mutations and their prognostic value in gastrointestinal diffuse large B-cell lymphoma. *Clin Cancer Res* 2011;17:1440-51.
65. Lamason RL, Kupfer A, Pomerantz JL. The dynamic distribution of CARD11 at the immunological synapse is regulated by the inhibitory kinesin GAKIN. *Mol Cell* 2010;40:798-809.
66. Lenz G, Davis RE, Ngo VN, Lam L, George TC, Wright GW, et al. Oncogenic CARD11 mutations in human diffuse large B cell lymphoma. *Science* 2008;319:1676-9.
67. Lohr JG, Stojanov P, Lawrence MS, Auclair D, Chapuy B, Sougnez C, et al. Discovery and prioritization of somatic mutations in diffuse large B-cell lymphoma (DLBCL) by whole-exome sequencing. *Proc Natl Acad Sci U S A* 2012;109:3879-84.
68. Montesinos-Rongen M, Schmitz R, Brunn A, Gesk S, Richter J, Hong K, et al. Mutations of CARD11 but not TNFAIP3 may activate the NF-kappaB pathway in primary CNS lymphoma. *Acta Neuropathol* 2010;120:529-35.
69. Snow AL, Xiao W, Stinson JR, Lu W, Chaigne-Delalande B, Zheng L, et al. Congenital B cell lymphocytosis explained by novel germline CARD11 mutations. *J Exp Med* 2012;209:2247-61.
70. Brohl AS, Stinson JR, Su HC, Badgett T, Jennings CD, Sukumar G, et al. Germline CARD11 mutation in a patient with severe congenital B cell lymphocytosis. *J Clin Immunol* 2015;35:32-46.
71. Casanova JL, Conley ME, Seligman SJ, Abel L, Notarangelo LD. Guidelines for genetic studies in single patients: lessons from primary immunodeficiencies. *J Exp Med* 2014;211:2137-49.
72. Casanova JL, Abel L. The genetic theory of infectious diseases: a brief history and selected illustrations. *Annu Rev Genomics Hum Genet* 2013;14:215-43.
73. Casanova JL, Abel L. Primary immunodeficiencies: a field in its infancy. *Science* 2007;317:617-9.
74. Xie C, Han Y, Fu L, Li Q, Qiu X, Wang E. Overexpression of CARMA3 is associated with advanced tumor stage, cell cycle progression, and cisplatin resistance in human epithelial ovarian cancer. *Tumour Biol* 2014;35:7957-64.
75. Bhattacharyya S, Borthakur A, Pant N, Dudeja PK, Tobacman JK. Bcl10 mediates LPS-induced activation of NF-kappaB and IL-8 in human intestinal epithelial cells. *Am J Physiol Gastrointest Liver Physiol* 2007;293:G429-37.
76. Ferch U, Kloos B, Gewies A, Pfander V, Duwel M, Peschel C, et al. Inhibition of MALT1 protease activity is selectively toxic for activated B cell-like diffuse large B cell lymphoma cells. *J Exp Med* 2009;206:2313-20.