CARD11 and CARD14 Are Novel Caspase Recruitment Domain (CARD)/Membrane-associated Guanylate Kinase (MAGUK) Family Members that Interact with BCL10 and Activate NF-κB*

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The caspase recruitment domain (CARD) is a protein-binding module that mediates the assembly of CARD-containing proteins into apoptosis and NF-κB signaling complexes. We report here that CARD protein 11 (CARD11) and CARD protein 14 (CARD14) are novel CARD-containing proteins that belong to the membrane-associated guanylate kinase (MAGUK) family, a class of proteins that functions as molecular scaffolds for the assembly of multiprotein complexes at specialized regions of the plasma membrane. CARD11 and CARD14 have homologous structures consisting of an N-terminal CARD domain, a central coiled-coil domain, and a C-terminal tripartite domain comprised of a PDZ domain, an Src homology 3 domain, and a GUK domain with homology to guanylate kinase. The CARD domains of both CARD11 and CARD14 associate specifically with the CARD domain of BCL10, a signaling protein that activates NF-κB through the IkB kinase complex in response to upstream stimuli. When expressed in cells, CARD11 and CARD14 activate NF-κB and induce the phosphorylation of BCL10. These findings suggest that CARD11 and CARD14 are novel MAGUK family members that function as upstream activators of BCL10 and NF-κB signaling.

Modular protein interaction domains play an important role in signal transduction by mediating the assembly of components into specific signaling complexes (1). The interchange of protein modules between signaling molecules has allowed nature to rapidly evolve new signal transduction pathways that respond to specific stress and developmental stimuli. The caspase recruitment domain (CARD)§ is a protein module that participates in apoptosis signaling through protein-protein interactions (2). CARD domains consist of six or seven antiparallel α-helices that form highly specific homophilic interactions between signaling partners. CARD family members include the majority of class I caspases, CED-4 family members Apaf-1 and CARD4 (Nod1), IAP family members cIAP-1 and cIAP-2, RICK kinase, ARC, BCL10, RAIDD, ASC, CARD9, and Iceberg (2–9). Confirming the selectivity of CARD-CARD interactions, several CARD protein family members have been found to assemble into discrete signaling complexes. For example, Apaf-1 and caspase-9 assemble together in the presence of cytochrome c and dATP resulting in caspase oligomerization and activation (10). Other CARD proteins that segregate with discrete binding partners include CARD4 with RICK, RAIDD with caspase-2, and CARD9 with BCL10 (3, 8, 11). The mechanisms by which upstream stimuli activate and/or assemble these CARD-CARD signaling complexes are not presently understood.

Recent studies have found that CARD proteins can also function as components of signaling pathways that lead to activation of the transcription factor NF-κB. CARD4, RICK, BCL10, and CARD9 induce NF-κB activity through the IKK complex when overexpressed in cells (3, 4, 6, 8, 12). NF-κB plays a central role in the activation of genes involved in immunity, inflammation, and apoptosis (13, 14). In unstimulated cells, NF-κB is sequestered in the cytoplasm through interactions with inhibitory IkB proteins. In response to a variety of signals including the cytokines interleukin-1 and tumor necrosis factor α, bacterial lipopolysaccharide, and virus infection, IkBα is phosphorylated and targeted to degradation by the proteosome through covalent modification by ubiquitin. The degradation of IkBα results in the translocation of NF-κB to the nucleus where it binds to specific promoters and activates transcription. Phosphorylation of IkBα is mediated by the IKK complex, which consists of two catalytic subunits called IKKa and IKKβ and one regulatory subunit called IKKγ. Although the mechanism by which IKKγ regulates IKK activity is presently unknown, it has been proposed to link the IKKs to upstream regulatory molecules (15–17). The CARD protein RICK binds directly to IKKγ suggesting that it functions as an adaptor molecule between the IKK complex and its upstream binding partner CARD4 (17). Activation of the IKK complex may occur through an oligomerization signal initiated by the self-association of CARD4. Thus, CARD-CARD signaling complexes such as CARD4/RICK can function as important mediators of NF-κB signaling. BCL10 (also known as CLAP/CIPER/eE10/CARMEN) is an activator of apoptosis and NF-κB signaling pathways that has been implicated in B cell lymphomas of mucosa-associated...
lymphoid tissue (6, 12, 18–21). BCL10 has a bipartite structure consisting of an N-terminal CARD and a C-terminal domain that is rich in serine-threonine residues. Because enforced oligomerization of the C terminus of BCL10 induces NF-κB activation, the CARD domain has been proposed to function as an oligomerization domain that transduces the activation signal to the IKK complex through the C-terminal domain of BCL10 (12). The C terminus of BCL10 may function in a manner analogous to the NF-κB activators RIP and RICK and activate the IKK complex through binding and oligomerization of IKKγ (16, 17). We recently identified a novel CARD NF-κB activator called CARD9 that assembles into a CARD-CARD signaling complex with BCL10 (8). We report here the identity and characterization of two additional CARD proteins, CARD11 and CARD14, that assemble BCL10 into NF-κB signaling complexes. Unlike CARD9, both CARD11 and CARD14 are members of the membrane-associated guanylate kinase (MAGUK) family, a class of proteins that functions as molecular scaffolds for the assembly of multiprotein complexes at the plasma membrane. We propose that CARD11 and CARD14 form discrete CARD-CARD signaling complexes with BCL10 and signal the activation of NF-κB.

**EXPERIMENTAL PROCEDURES**

**Expression Plasmids**—Plasmids expressing either CARD11 or CARD14 with C-terminal Myc epitopes were constructed using pCMV-Tag 5A (Stratagene). Constructs encoding epitope-tagged BCL10 were described previously (12). For mammalian two-hybrid assays, pCMV-CARD11-CARD/AD and pCMV-CARD14-CARD/AD plasmids were constructed by inserting the CARD domain of CARD11 (residues 1–126) and CARD14 (residues 1–118) into pCMV-AD (Stratagene). The panel of CARD domains used for the mammalian two-hybrid screen was described previously (8).

**Reporter Gene Assays**—For mammalian two-hybrid assays, 293T cells in six-well plates (35-mm wells) were transfected with the following plasmids: 750 ng of pCMV-CARD11/AD or pCMV-CARD14/AD, 750 ng of pCMV-BD fused to individual CARD domains, 250 ng of pFR-Luc firefly reporter (Stratagene), and 250 ng of pRL-TK renilla reporter (Promega). For NF-κB

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**Fig. 1.** Sequence and domain structure of human CARD11 and CARD14. A, amino acid alignment of CARD11 and CARD14. Black shading indicates identical residues. B, domain structure of CARD11 and CARD14 showing CARD, coiled-coil, PDZ, SH3, and GUK domains. C, alignment of the CARD of CARD11 (residues 19–105) and CARD14 (residues 23–109) with CARDs found in CARD9 (residues 14–100), BCL10 (residues 21–105), RAIDD (residues 9–95), and caspase-9 (residues 9–93). D, alignment of the PDZ domain of CARD11 (residues 660–742) and CARD14 (residues 570–653) with PDZ domains found in PSD-95 (repeat 3, residues 355–430), ZO-1 (repeat 3, residues 411–485) and ZO-2 (repeat 3, residues 511–587). E, alignment of the SH3 domain of CARD11 (residues 766–840) and CARD14 (residues 676–750) with SH3 domains found in PSD-95 (repeat 3, residues 471–540), ZO-1 (repeat 3, residues 504–571) and ZO-2 (repeat 3, residues 604–668). F, alignment of the GUK domain of CARD11 (residues 954–1142) and CARD14 (residues 814–999) with GUK domains found in P55 (repeat 3, residues 269–460) and PSD-95 (repeat 3, residues 564–761).
assays, 293T cells were transfected with the following plasmids: 900 ng of pNF-κB luciferase reporter (Stratagene), 100 ng of pRL-TK renilla reporter (Promega), and 1000 ng of indicated expression plasmids. Cells were harvested 24 h after transfection, and firefly luciferase activity was determined using the Dual-Luciferase Reporter Assay System (Promega). In addition, renilla luciferase activity was determined and used to normalize transfection efficiencies.

Coimmunoprecipitation Assays—293T cells transfected with plasmids were lysed in 50 mM Tris, pH 8.0, 120 mM NaCl, 1 mM EDTA, and 0.5% Nonidet P-40 buffer and incubated with a BCL10 monoclonal antibody (22). The immune complexes were precipitated with protein G-Sepharose (Amersham Pharmacia Biotech), washed extensively, and then subjected to SDS-polyacrylamide gel electrophoresis and immunoblotted with polyclonal anti-Myc antibodies (Santa Cruz Biotechnology, Inc.).

In Vitro Binding Assays—In vitro binding assays between BCL10 and either CARD11 or CARD14 proteins were performed as described previously (23). In brief, BCL10 wild type and L41R mutant were expressed in DH5 Alpha bacteria as GST fusion proteins, and equal amounts of protein were immobilized on glutathione-Sepharose (Amersham Pharmacia Biotech). An equal amount of CARD11 or CARD14 protein labeled with [35S]methionine was incubated with the protein-bound Sepharose beads in 100 μl of binding buffer (50 mM Tris-HCl, pH 7.6, 120 mM NaCl, 0.5% Brij, and protease inhibitors) for 3 h. The beads were washed four times with the same buffer and boiled in SDS sample buffer. The proteins were then resolved on a 10% SDS gel and visualized by autoradiography.

Immunostaining and Image Analysis—Rat-1 cells were transfected in poly-d-lysine-coated glass chamber slides (BioCoat, Becton-Dickinson Labware) with plasmids expressing HA-tagged BCL10 and either Myc-tagged CARD11 or CARD14 using FuGENE-6 (Roche Molecular Biochemicals) for 20 h. Cells were fixed in 4% paraformaldehyde, permeabilized and blocked in a buffer containing 0.4% Triton X-100, and sequentially incubated with the following primary and secondary antibodies: rabbit anti-HA polyclonal Y-11 (Santa Cruz Biotechnology), mouse anti-Myc monoclonal 9E10 (Oncogene Research Products), Alexa-488 goat anti-mouse IgG (Molecular Probes), and Alexa-594 goat anti-rabbit IgG (Molecular Probes). No cross-reactivity was observed between any of the antibodies (data not shown). Images were acquired using a Nikon TE200 microscope with a 60× oil objective and an Orca-I digital CCD camera (Hamamatsu, Inc.) driven by MetaMorph software (Universal Imaging Corp.). Final images were prepared using Adobe Photoshop.

RESULTS AND DISCUSSION

We searched public and proprietary data bases for novel members of the CARD family of apoptosis and NF-κB signaling proteins. Human CARD11 is a novel CARD family member of 1147 amino acids with a predicted molecular mass of 132.6 kDa (Fig. 1A). A second protein (1004 amino acids, 113.5 kDa) displaying significant similarity to CARD11 was also identified and designated CARD14 (Fig. 1A). Analysis of their amino acid sequences revealed that CARD11 and CARD14 were homologous in structure and were comprised of at least five putative functional domains (Fig. 1B). Both proteins contain an N-terminal CARD domain and a central coiled-coil domain and possess a C-terminal tripartite structure comprised of a PDZ domain, an SH3 domain, and a GUK domain with homology to guanylate kinase. Although their CARD domains (residues 1–87) show significant similarity to those found in other CARD family members, they are most similar to each other (52% identity) and to the CARD of CARD9 (CARD11, 56% identity; CARD14, 47% identity) (Fig. 1C). Adjacent to the N-terminal CARD domains are extensive regions of heptad repeats found in coiled-coil structures that function in protein oligomerization and activation (24). The COILS2 program (25) predicts with a probability of >80% at least two coiled-coil structures, an CARD11 (residues 130–158 and 165–433) and five coiled-coil structures in CARD14 (residues 128–198, 205–238, 245–272, 281–330, and 356–409) that are interrupted by regions with a lower coiled-coil potential. The PDZ/SH3/GUK tripartite structure located at the C terminus of CARD11 and CARD14 are domains that have not been previously found in CARD proteins (Fig. 1, D–F). These domains function as sites for specific protein-protein interactions and classify CARD11 and CARD14 as novel members of the MAGUK family of proteins that function to organize signaling complexes at plasma membranes (26).

The structure of CARD11 and CARD14 is most similar to CARD9 which contains an N-terminal CARD domain followed by multiple coiled-coil domains (8). CARD11 and CARD14 may therefore function in a manner similar to CARD9 and activate downstream CARD proteins through their N-terminal CARD domains. Although CARD11 and CARD14 have homologous structures, Northern blot analysis revealed differences in expression profiles (Fig. 2). CARD11 is expressed as a 4.4-kilobase transcript in a variety of adult tissues including thymus, spleen, liver, and peripheral blood leukocytes (Fig. 2A). CARD11 also showed abundant expression in specific cancer cell lines, including promyelocytic leukemia HL-60 cells, chronic myelogenous leukemia K562 cells, Burkitt’s lymphoma Raji cells, and colorectal adenocarcinoma SW480 cells (Fig. 2B). In contrast, the 4.4-kilobase CARD14 transcript showed expression only in placenta (Fig. 2C) and HeLa S3 cancer cells (Fig. 2D).

Because CARD proteins have been implicated in NF-κB signaling pathways, we determined whether CARD11 and CARD14 can induce NF-κB activity using a luciferase reporter gene. When either CARD11 or CARD14 were expressed in 293T cells, NF-κB activity was induced 20–40-fold compared...
with empty vector (Fig. 3, A and B). NF-κB signaling occurred through the IKK complex because dominant-negative versions of IKK-γ and IKK-β blocked the abilities of CARD11 and CARD14 to induce NF-κB activity (data not shown). To determine the role of individual domains in NF-κB signaling, we constructed a series of N- and C-terminal truncation mutants of CARD11 and CARD14 (Fig. 3C). The N-terminal CARD of both CARD11 and CARD14 was essential for NF-κB signaling because deletion of this domain eliminated the induction of NF-κB activity (Fig. 3, D and E). Immunoblot analysis revealed that the mutant proteins were expressed at levels similar to wild type protein indicating that loss of function was not due to reduced levels of expression. In contrast, the C-terminal PDZ, SH3, and GUK domains were not required for NF-κB signaling because deletion of these domains did not reduce the ability of CARD11 and CARD14 to induce NF-κB activity. However, a CARD11 mutant lacking its C-terminal PDZ, SH3, and GUK domains induced NF-κB activity to levels 4–5-fold greater than that obtained with wild type protein (Fig. 3D). Thus, the C-terminal domains may function to negatively regulate induction of NF-κB signaling by CARD11.

The N-terminal CARDs of CARD11 and CARD14 likely interact with other CARD-containing proteins to signal activation of NF-κB. To identify the binding partners of CARD11 and CARD14, we performed a mammalian two-hybrid analysis and screened their N-terminal CARDs for binding to the CARD domains of 15 known proteins. The CARD of CARD11 interacted with the CARD of BCL10 resulting in a 17-fold increase in relative luciferase activity (Fig. 4A). Co-expression of CARD11-CARD with other CARD domains failed to activate luciferase expression indicating that the CARD of CARD11 interacts selectively with the CARD of BCL10. Likewise, the CARD of CARD14 interacted selectively with the CARD of BCL10 resulting in a 999-fold increase in relative luciferase activity. These data suggest that both CARD11 and CARD14 are signaling partners of the NF-κB activator BCL10. We next tested whether CARD11 and CARD14 interact with endogenous BCL10 when overexpressed in cells. Expression of either Myc-tagged CARD11 or Myc-tagged CARD14 co-precipitated endogenous BCL10, confirming that both CARD proteins interact with BCL10 (Fig. 5A, lanes 1 and 3). We also examined the interaction of radiolabeled CARD11 and CARD14 with GST-BCL10 in vitro and found that both proteins associate directly with BCL10 through their N-terminal CARD domains (Fig. 5B, lane 3). Confirming the importance of the BCL10 CARD domain, radiolabeled CARD11 and CARD14 did not associate with a variant of BCL10 (L41R) that is unable to homodimerize (Fig. 5B, lane 4; Ref. 12).

The cellular localization of CARD14 was also examined. When epitope-tagged CARD14 and BCL10 were expressed alone, the two proteins displayed distinctly different patterns of cellular localization. As observed previously (8, 27), BCL10 exhibited either a discrete pattern of cytoplasmic filaments and aggregates or a diffuse whole-cell distribution (data not shown). In contrast, CARD14 exhibited a predominantly cytoplasmic, slightly punctate distribution but did not form...
large aggregates or filaments (Fig. 6, A–D). When these two proteins were co-expressed in the same cell, however, some of the CARD14 was found to co-localize with the BCL10 filaments or aggregates (Fig. 6, B–D). This finding is consistent with an intracellular interaction between CARD14 and BCL10 and suggests that CARD14 is recruited to a cytoplasmic signaling complex with BCL10. To test whether the CARD domain of CARD14 was required for this interaction, we examined the localization of a CARD14 truncation mutant lacking the N-terminal CARD domain (CARD14/D CARD). When expressed alone, CARD14/D CARD formed aggregates and showed a punctate distribution (Fig. 6, E). When co-expressed with BCL10, however, CARD14/D CARD did not co-localize with BCL10 (Fig. 6, F–H). Deletion of the C-terminal PDZ/SH3/GUK domain also resulted in co-localization with BCL10 (data not shown), indicating that the CARD and coiled-coil domains are sufficient for the interaction between CARD14 and BCL10 and that this interaction requires an intact CARD domain. A similar CARD-dependent co-localization was observed between CARD11 and BCL10 (data not shown).

BCL10 migrates in SDS gels as a triplet ranging in size from 29 to 32 kDa due to phosphorylation of its C-terminal domain (12, 18). Treatment of cell lysates with calf intestinal alkaline phosphatase eliminates the slower migrating forms demonstrating that the fastest migrating band represents unphosphorylated BCL10 (12). Because phosphorylation can play a critical role in signal transduction, we examined whether co-expression of either CARD11 or CARD14 induces the phosphorylation of BCL10 (Fig. 7, upper panel). When expressed alone, the majority of HA-tagged BCL10 exists in the unphosphorylated form (Fig. 7, lane 1, lower band). However, co-expression of either CARD11 or CARD14 markedly increased the amount of phosphorylated BCL10 represented by the slower migrating bands (Fig. 7, lanes 3 and middle and upper bands). The induction of BCL10 phosphorylation is dependent on the N-terminal CARD of CARD11 and CARD14 because co-expression of truncated mutants lacking these domains has no effect on BCL10 phosphorylation levels (Fig. 7, lanes 5 and 9). Immunoblot analysis revealed that the Myc-tagged truncation mutants were expressed at levels similar to wild type protein suggesting that loss of function is not due to reduced levels of expression (Fig. 7, lower panel). Taken together, these data suggest that CARD11 and CARD14 stimu-
late phosphorylation of BCL10 in a CARD-dependent manner.

We have identified CARD11 and CARD14 as specific regulators of BCL10 function. Our finding that CARD11 and CARD14 bind to BCL10 through a CARD-CARD interaction suggests that these molecules function as upstream activators of BCL10. CARD9 also binds to the CARD activation domain of BCL10 and signals NF-κB activation (8, 17). Thus, CARD11, CARD14, and CARD9 constitute a subclass of CARD proteins that likely functions to transduce distinct upstream stimuli to the activation of BCL10 and NF-κB. In response to upstream signals, the coiled-coil domains could mediate self-association of CARD11 and CARD14 resulting in the aggregation and activation of BCL10. BCL10 might then engage and oligomerize IKKx resulting in the activation of the IKK complex and NF-κB (16, 17). Thus, CARD11 and CARD14 could act in a manner analogous to Atpa-1 and CARD4 that functions to induce oligomerization and activation of the respective downstream CARD-binding partners. Our data also indicate that CARD11 and CARD14 induce the phosphorylation of BCL10 suggesting that signal transduction may involve the participation of a serine/threonine kinase. A unique feature of CARD11 and CARD14 is the presence of C-terminal PDZ/SH3/GUK domains. These domains may function in an analogous manner to the C-terminal leucine-rich repeat domain of CARD4 and the WD-40 domain of Apaf-1 to regulate protein activation by upstream signals (8, 10). PDZ/SH3/GUK domains identify MAGUK family members, a class of proteins that associate with the plasma membrane through interactions with transmembrane proteins (e.g. ion channels), cytoskeletal components, and signal transduction proteins (26). Interestingly, the PDZ domain found in many MAGUK proteins has been shown to interact with the intracellular domains of specific receptors. Thus, CARD11 and CARD14 may function as scaffolding proteins to assemble a multiprotein complex at the intracellular domains of receptors that signal the activation of NF-κB.

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