CARD14-Mediated Activation of Paracaspase MALT1 in Keratinocytes: Implications for Psoriasis

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Mutations in *caspase recruitment domain-containing protein 14 (CARD14)* have been linked to susceptibility to psoriasis. CARD14 is an intracellular scaffold protein that regulates proinflammatory gene expression. Recent studies have offered novel insights into the mechanisms of CARD14-mediated signaling in keratinocytes and the molecular impact of psoriasis-associated CARD14 mutations. CARD14 forms a signaling complex with BCL10 and the paracaspase MALT1, and this process is enhanced upon pathogenic CARD14 mutation, culminating in the activation of MALT1 protease activity and psoriasis-associated gene expression. This review summarizes the current knowledge of CARD14/MALT1-mediated signaling in keratinocytes and its therapeutic implications in psoriasis.

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PSORIASIS, A SKIN DISEASE WITH A STRONG GENETIC COMPONENT

Psoriasis is a common chronic autoinflammatory skin disease that affects 2–3% of the world's population and greatly impairs the quality of life of affected individuals. Psoriasis vulgaris, the most prevalent disease type, is characterized by well-demarcated red, scaly plaques. More rare types of psoriasis also exist, such as pustular, palmoplantar, inverse, erythrodermic, and guttate psoriasis (Deng et al., 2016; Lowes et al., 2014; Nestle et al., 2009). Furthermore, psoriasis is associated with several comorbidities, and almost 30% of patients suffer from psoriatic arthritis, indicating that this disease is not only restricted to the skin (Mease et al., 2013).

Psoriasis-affected skin is characterized by a thickened epidermis with scaly patches, due to excessive proliferation and aberrant differentiation of keratinocytes, as well as redness caused by increased dilatation of the dermal blood vessels and infiltration of immune cells (Lowes et al., 2014). Although the pathogenesis of psoriasis has not yet been completely elucidated, it is generally believed to arise from a complex interplay between hyperproliferating keratinocytes and infiltrating, activated immune cells, mainly dendritic cells and T cells. Skin injury or associated infections trigger keratinocytes to elicit IL-23 and IL-12 production in dendritic cells. These cytokines in turn activate T cells and induce the production of several psoriatic cytokines, such as IL-17, IFN-γ, tumor necrosis factor (TNF), and IL-22, which further induce keratinocyte hyperproliferation as well as the production of chemokines to sustain the recruitment and activation of immune cells (Lowes et al., 2014).

Even though the etiology of psoriasis is still largely unknown, the concordance rate of psoriasis in monozygotic twins of approximately 70% illustrates that there is a strong genetic component. Through linkage disequilibrium studies in psoriasis-affected families, multiple psoriasis susceptibility (*PSORS*) loci have been identified (Lowes et al., 2014). However, most of the genes responsible for the observed susceptibility are not known (Harden et al., 2015; Lowes et al., 2014). Recently, mutations in *caspase recruitment domain-containing protein 14* (*CARD14*), a gene located in the *PSORS2* locus, have been linked to psoriasis susceptibility (Jordan et al., 2012a, 2012b). Here, we review the role of CARD14-mediated signaling in keratinocytes and its potential implications for psoriasis therapy.

CARD14 structure and function

CARD14, also known as CARD-containing MAGUK protein 2 (CARMA2) and Bimp2, is a member of the CARMA family of proteins, which also includes CARD11/CARMA1 and CARD10/CARMA3 (Bertin et al., 2001; Gaide et al., 2001; McAllister-Lucas et al., 2001; Scudiero et al., 2014). Similar to CARD10 and CARD11, CARD14 acts as a scaffolding protein that can activate the inflammatory transcription factor NF-κB (Bertin et al., 2001). The CARMA proteins have a uniform domain structure consisting of an N-terminal CARD domain followed by a coiled-coil (CC) domain, a linker region, and a C-terminal membrane-associated guanylate

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Abbreviations: BCL10, B-cell lymphoma/leukemia 10; CARD14, caspase recruitment domain-containing protein 14; CARMA, CARD-containing MAGUK protein; CC, coiled coil; MAGUK, membrane-associated guanylate kinase; MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein 1; PKC, protein kinase C; TNF, tumor necrosis factor

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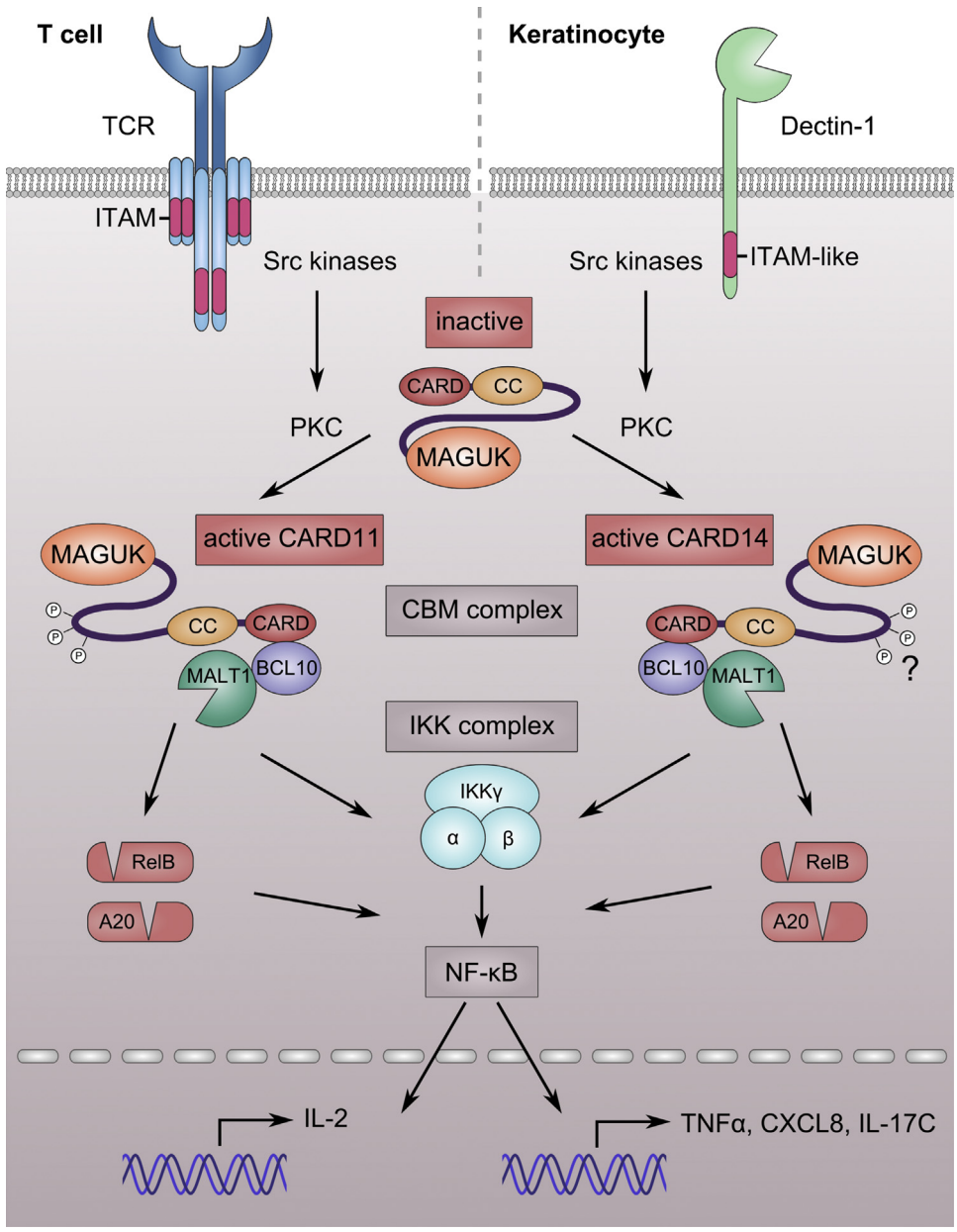

Figure 1. Comparison of CBM complex formation in T cells and keratinocytes. Triggering of the ITAM-containing receptors TCR and dectin-1 activates kinases from the Src and PKC families, which are believed to be required for the assembly of a CARD-BCL10-MALT1 (CBM) signaling complex. Whereas BCL10 and MALT1 are recruited to CARD11 in lymphocytes, a CARD14-containing complex is formed in keratinocytes. Both CARD11 and CARD14 interact with BCL10 via their CARD domains, which is only accessible in CARD11 after PKC-mediated phosphorylation of its linker region. The CBM complex subsequently activates the transcription factor NF-κB in two ways. First, it acts as a scaffold to recruit and activate the IKK complex, which phosphorylates and thus targets IκBα for proteasomal degradation, allowing the nuclear translocation of NF-κB. Secondly, it promotes optimal NF-κB activation by MALT1-mediated cleavage of RelB and A20. In both T cells and keratinocytes, NF-κB regulates the expression of proinflammatory cytokines. BCL10, B-cell lymphoma/leukemia 10; CARD14, caspase recruitment domain-containing protein 14; CBM, CARD-BCL10-MALT1; CC, coiled coil; ITAM, immunoreceptor tyrosine-based activation motif; IκB, inhibitor of κB; IKK, IκB kinase; MAGUK, membrane-associated guanylate kinase; MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein 1; PKC, protein kinase C; TCR, T cell receptor.

kinase domain (MAGUK) comprising PDZ, SH3, and GUK subdomains (Figure 1) (Bertin et al., 2001; Gaide et al., 2001; McAllister-Lucas et al., 2001). Whereas the CARD and CC domains are necessary for NF-κB activation and self-oligomerization, the linker region might exert an auto-inhibitory function (Bertin et al., 2001; Howes et al., 2016; Matsumoto et al., 2005; Sommer et al., 2005; Tanner et al., 2007). The MAGUK domain targets proteins to the membrane and is involved in various processes, such as signal transduction, tight junction formation, cell proliferation, apoptosis, and differentiation (te Velthuis et al., 2007). However, its specific role in CARD14-mediated signaling is still unclear.

The *CARD14* gene gives rise to several splice variants. In addition to the full-length form (CARD14fl), a shorter splice variant (CARD14sh), which lacks a part of the membrane-associated guanylate kinase domain, has been described (Scudiero et al., 2011). The functional differences between CARD14fl and CARD14sh have remained elusive thus far, as they seem equally potent in mounting an NF-κB response (Afonina et al., 2016). A third splice variant, CARD14cardless, lacks the CARD domain as well as part of the CC domain and the SH3 and GUK domains. Because of the missing CARD domain, CARD14cardless is not able to activate NF-κB and may function as a dominant-negative regulator of CARD14 signaling (Scudiero et al., 2011).

The three CARD14 splice variants are predominantly expressed in placenta and skin tissue (Jordan et al., 2012b). In healthy skin, CARD14 is primarily expressed in the keratinocytes of the basal layer of the epidermis. In contrast, psoriatic skin lesions show increased levels of CARD14 in the upper layers of the epidermis and reduced CARD14 levels in the basal layer (Jordan et al., 2012b). This expression pattern might reflect the deregulated differentiation of keratinocytes