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.


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
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 autoinhibitory 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.
CARD14 variants in psoriasis

In 2012, Jordan et al. described several common and rare variants of CARD14 that are directly associated with psoriasis in familial and nonfamilial cases (Jordan et al., 2012a). Since then, several studies have reported associations of CARD14 variants with psoriasis vulgaris, psoriatic arthritis, generalized pustular psoriasis, and palmoplantar pustular psoriasis (Ammar et al., 2013, 2016; Eskin-Schwartz et al., 2016; Feng et al., 2016; Gonzalez-Lara et al., 2013; Inoue et al., 2016; Korber et al., 2013; Mossner et al., 2015; Qin et al., 2014; Sugiura et al., 2014, 2015; Zhu et al., 2016). Furthermore, CARD14 variants have also been associated with pityriasis rubra pilaris, a distinct inflammatory skin disease characterized by keratotic follicular papules and salmon-colored erythematous plaques (Eytan et al., 2014; Fuchs-Telem et al., 2012; Has et al., 2016; Inoue et al., 2016; Li et al., 2015). An overview of all CARD14 variants identified in patients with psoriasis and pityriasis rubra pilaris is listed in Table 1.

Most of the observed CARD14 missense variants are heterozygous. Interestingly, exon 4, which encodes part of the CC domain, seems to be a hotspot for missense variants (Table 1). In addition, the CARD14 variants that were shown to be most pathogenic, such as p.Glu138Ala, p.Glu142Lys, and p.Glu142Gly, are also encoded by exon 4 (Jordan et al., 2012a). Another strongly pathogenic variant, p.Gly117Ser, is encoded by exon 3 and leads to altered splicing of CARD14, resulting in the insertion of 22 additional amino acids between exons 3 and 4 (Jordan et al., 2012b). Overexpression of the pathogenic missense CARD14 variants in primary keratinocytes resulted in enhanced NF-κB activation and increased production of several psoriasis-associated chemokines, such as CXCL8 and CCL20 (Afonina et al., 2016; Jordan et al., 2012b). Therefore, it is generally believed that excessive activation of NF-κB and expression of NF-κB-responsive genes in keratinocytes by psoriasis-associated CARD14 variants can initiate an inflammatory reaction that attracts immune cells to the skin and culminates in psoriasis development. However, not all CARD14 variants that have been identified in patients with psoriasis and pityriasis rubra pilaris lead to excessive NF-κB activation. For instance, the variant p.Arg69Trp reduces NF-κB activation sevenfold compared with wild-type CARD14 (Ammar et al., 2016). These ambiguous effects on NF-κB suggest that CARD14 could be involved in additional signaling pathways or that basal NF-κB levels might be crucial to preserve skin homeostasis. Finally, p.Arg820Trp, a common polymorphism of CARD14 that is associated with psoriasis susceptibility, was shown to be enriched in patients who responded well to anti-TNF therapy, indicating that CARD14 variants might be used to stratify patients for optimal treatment strategies (Coto-Segura et al., 2016; Feng et al., 2016; Gonzalez-Lara et al., 2013; Jordan et al., 2012a; Sugiura et al., 2015). Although further research is necessary to identify pathogenic CARD14 variants and their effects on CARD14 function, recent studies have provided some insight into CARD14-induced signaling events and how psoriasis-associated CARD14 variants may affect NF-κB activation.

THE CARD14-BCL10-MALT1 COMPLEX IN KERATINOCYTES

Activated CARD14 and its homologues are known to bind the adapter protein B-cell lymphoma 10 (BCL10) via a CARD-CARD-mediated interaction (Bertin et al., 2001; McAllister-Lucas et al., 2001; Wang et al., 2001). BCL10 is constitutively bound to mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) and has recently been shown to recruit MALT1 to activated CARD14, resulting in the formation of a CBM (CARD14-BCL10-MALT1) complex (Afonina et al., 2016; Howes et al., 2016; Lucas et al., 2001; Uren et al., 2000) (Figure 1). CARD14-induced CBM complex formation further culminates in the activation of NF-κB as well as of the MAP kinases p38 and JNK (Afonina et al., 2016). The formation of a CARD14-BCL10-MALT1 signaling complex in keratinocytes is reminiscent of the well-described CARD11-BCL10-MALT1 signaling complex that is formed in antigen receptor-stimulated lymphocytes. CBM complex assembly in lymphocytes leads to the recruitment of the ubiquitin ligase TRAF6, which mediates K63-linked polyubiquitination of itself, MALT1 and BCL10 (Deng et al., 2000; Oeckinghaus et al., 2007; Sun et al., 2004). These polyubiquitin chains serve as docking sites for the inhibitor of κB kinase complex (IKK), the linear ubiquitin chain assembly complex, and a TAK1-containing complex, resulting in the optimal activation of the IKK complex (Afonina et al., 2015; Thome, 2008). The activated IKK complex phosphorylates IκB, which is subsequently degraded by the proteasome, thus releasing NF-κB subunits into the nucleus to activate the transcription of target genes. Although the molecular signaling events downstream of the CARD14-BCL10-MALT1 signaling complex have not yet been described in keratinocytes, it can be expected that they are similar to those downstream of the CARD11-induced signaling described above (Figure 1).

The molecular events that lead to the formation of a CARD14-BCL10-MALT1 signaling complex are still largely unclear. It has been suggested that, in unstimulated cells, CARD14 is kept in an autoinhibitory conformation by the inhibitory linker domain located between the CC and the PDZ domains (Howes et al., 2016). Removal of the inhibitory domain of CARD14 abrogates the effect of psoriasis-associated activating point mutations on NF-κB induction (Howes et al., 2016). Compared to wild-type CARD14 expression, overexpression of the p.Glu138Ala and p.Gly117Ser mutants enhances CBM complex formation, leading to increased NF-κB activation (Afonina et al., 2016; Howes et al., 2016). Collectively, these data indicate that single point mutations in the CC domain of CARD14 result in
conformational changes that affect inter- or intramolecular interactions crucial for CBM assembly.

It has been shown that MALT1 can be activated by treatment of keratinocytes with the fungal cell wall component zymosan. Moreover, silencing of the zymosan-detecting C-type lectin receptor dectin-1, but not of TLR2 or its adaptor MyD88, strongly reduces MALT1 activity in keratinocytes (Schmitt et al., 2016). Interestingly, stimulation of dectin-1 in myeloid cells leads to the formation of a CARD9-containing CBM complex that is crucial for antifungal immune responses (Gross et al., 2006), suggesting the potential formation of a related CARD14-containing CBM complex in dectin-1-stimulated keratinocytes. How exactly dectin-1 activates the CBM complex in keratinocytes is thus far unclear. Dectin-1, like other immune receptors (e.g., T cell receptor, B cell receptor, and NKG2D), employs immunoreceptor tyrosine-based activation motifs (ITAMs) to initiate downstream signaling via Src kinases (Thome, 2008).

### Table 1. Overview of CARD14 variants associated with psoriasis or pityriasis rubra pilaris

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Exon</th>
<th>Domain</th>
<th>Disease</th>
<th>Effect on NF-κB</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>p.Arg38Cys</td>
<td>2</td>
<td>CARD</td>
<td>PsV</td>
<td>0.11</td>
<td>(Jordan et al., 2012a)</td>
</tr>
<tr>
<td>p.Arg62Gln</td>
<td>2</td>
<td>CARD</td>
<td>PsV</td>
<td>1.06</td>
<td>(Ammar et al., 2016; Jordan et al., 2012a)</td>
</tr>
<tr>
<td>p.Arg99Trp</td>
<td>2</td>
<td>CARD</td>
<td>PsV/PA/GPP</td>
<td>0.144</td>
<td>(Ammar et al., 2016)</td>
</tr>
<tr>
<td>p.Gly117Ser</td>
<td>3</td>
<td>Between CARD and CC</td>
<td>PsV/PA/GPP</td>
<td>3.71</td>
<td>(Ammar et al., 2013, 2016; Eskin-Schwartz et al., 2016; Jordan et al., 2012a, 2012b; Korber et al., 2013)</td>
</tr>
<tr>
<td></td>
<td>c.349+5G&gt;C</td>
<td>3</td>
<td>Between CARD and CC</td>
<td>PsV/GPP</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>c.349+1G&gt;A</td>
<td>3</td>
<td>Between CARD and CC</td>
<td>PRP type V</td>
<td>ND</td>
</tr>
<tr>
<td>p.Met119Val</td>
<td>4</td>
<td>Between CARD and CC</td>
<td>GPP</td>
<td>ND</td>
<td>(Qin et al., 2014)</td>
</tr>
<tr>
<td>p.Leu124Pro</td>
<td>4</td>
<td>Between CARD and CC</td>
<td>PRP</td>
<td>ND</td>
<td>(Elyan et al., 2014)</td>
</tr>
<tr>
<td>p.Glu138Ala</td>
<td>4</td>
<td>CC</td>
<td>GPP</td>
<td>8.95</td>
<td>(Jordan et al., 2012a, 2012b)</td>
</tr>
<tr>
<td>p.Glu138Lys</td>
<td>4</td>
<td>CC</td>
<td>PRP type V</td>
<td>ND</td>
<td>(Fuchs-Telel et al., 2012)</td>
</tr>
<tr>
<td>p.Glu142Lys</td>
<td>4</td>
<td>CC</td>
<td>PsV</td>
<td>4.03</td>
<td>(Jordan et al., 2012a)</td>
</tr>
<tr>
<td>p.Glu142Gly</td>
<td>4</td>
<td>CC</td>
<td>PsV</td>
<td>5.00</td>
<td>(Jordan et al., 2012a)</td>
</tr>
<tr>
<td>p.Leu150Arg</td>
<td>4</td>
<td>CC</td>
<td>PsV</td>
<td>1.79</td>
<td>(Ammar et al., 2016; Jordan et al., 2012a)</td>
</tr>
<tr>
<td>p.Arg151Gln</td>
<td>4</td>
<td>CC</td>
<td>PsV</td>
<td>1.766</td>
<td>(Ammar et al., 2016)</td>
</tr>
<tr>
<td>p.Arg151Trp</td>
<td>4</td>
<td>CC</td>
<td>PsV</td>
<td>0.576</td>
<td>(Ammar et al., 2016)</td>
</tr>
<tr>
<td>p.Leu156Pro</td>
<td>4</td>
<td>CC</td>
<td>PRP type V</td>
<td>ND</td>
<td>(Fuchs-Telel et al., 2012)</td>
</tr>
<tr>
<td>p.Arg166His</td>
<td>4</td>
<td>CC</td>
<td>GPP</td>
<td>ND</td>
<td>(Qin et al., 2014)</td>
</tr>
<tr>
<td>p.His171Asn</td>
<td>4</td>
<td>CC</td>
<td>PsV</td>
<td>0.68</td>
<td>(Jordan et al., 2012a)</td>
</tr>
<tr>
<td>p.Asp176His</td>
<td>4</td>
<td>CC</td>
<td>PsV/GPP + PsV/PPP</td>
<td>2.78</td>
<td>(Jordan et al., 2012a; Mossner et al., 2015; Sugura et al., 2014; Zhu et al., 2016)</td>
</tr>
<tr>
<td>p.Arg197His</td>
<td>4</td>
<td>CC</td>
<td>PsV/PPP</td>
<td>1.38</td>
<td>(Jordan et al., 2012a; Mossner et al., 2015)</td>
</tr>
<tr>
<td>p.Val191Ile</td>
<td>4</td>
<td>CC</td>
<td>PsV</td>
<td>1.02</td>
<td>(Jordan et al., 2012a)</td>
</tr>
<tr>
<td>p.Glu197Lys</td>
<td>4</td>
<td>CC</td>
<td>PsV</td>
<td>1.667</td>
<td>(Ammar et al., 2016; Mossner et al., 2015)</td>
</tr>
<tr>
<td>p.Ser200Asn</td>
<td>4</td>
<td>CC</td>
<td>PsV/GPP/PPP</td>
<td>0.67</td>
<td>(Ammar et al., 2016; Jordan et al., 2012a; Korber et al., 2013; Mossner et al., 2015)</td>
</tr>
<tr>
<td>p.Leu209Pro</td>
<td>4</td>
<td>CC</td>
<td>PsV</td>
<td>0.785</td>
<td>(Ammar et al., 2016)</td>
</tr>
<tr>
<td>p.Ala216Thr</td>
<td>4</td>
<td>CC</td>
<td>PsV</td>
<td>0.575</td>
<td>(Ammar et al., 2016; Qin et al., 2014; Zhu et al., 2016)</td>
</tr>
<tr>
<td>p.Asp285Gly</td>
<td>6</td>
<td>None</td>
<td>PsV</td>
<td>1.14</td>
<td>(Jordan et al., 2012a)</td>
</tr>
<tr>
<td>p.Met331Val</td>
<td>7</td>
<td>CC</td>
<td>PsV/GPP/PPP</td>
<td>0.914</td>
<td>(Ammar et al., 2016)</td>
</tr>
<tr>
<td>p.Thr420Ala</td>
<td>9</td>
<td>none</td>
<td>PsV</td>
<td>0.563</td>
<td>(Ammar et al., 2016)</td>
</tr>
<tr>
<td>p.c.1356+5G&gt;C</td>
<td>9</td>
<td>CC</td>
<td>PsV</td>
<td>ND</td>
<td>(Ammar et al., 2016)</td>
</tr>
<tr>
<td>p.Thr591Met</td>
<td>13</td>
<td>PDZ</td>
<td>PsV/GPP/PPP</td>
<td>1.196</td>
<td>(Ammar et al., 2016)</td>
</tr>
<tr>
<td>p.Ile593Asn</td>
<td>13</td>
<td>PDZ</td>
<td>PsV/GPP/PPP</td>
<td>1.30</td>
<td>(Jordan et al., 2012a)</td>
</tr>
<tr>
<td>p.Ser602Leu</td>
<td>13</td>
<td>PDZ</td>
<td>PsV/GPP/PPP</td>
<td>0.95</td>
<td>(Jordan et al., 2012a; Qin et al., 2014)</td>
</tr>
<tr>
<td>p.Gly714Ser</td>
<td>15</td>
<td>SH3</td>
<td>PsV/GPP</td>
<td>1.02</td>
<td>(Jordan et al., 2012a)</td>
</tr>
<tr>
<td>p.Arg820Trp</td>
<td>18</td>
<td>GUK</td>
<td>PsV/PA/GPP</td>
<td>ND</td>
<td>(Feng et al., 2016; Gonzalez-Lara et al., 2013; Jordan et al., 2012a; Sugura et al., 2015)</td>
</tr>
<tr>
<td>p.Asp973Glu</td>
<td>21</td>
<td>GUK</td>
<td>PsV</td>
<td>ND</td>
<td>(Jordan et al., 2012a)</td>
</tr>
</tbody>
</table>

Details on the location of the mutations, their disease occurrence, and their effect on NF-κB activation is shown. The exon sequence was determined using transcript CARD14-201 (ENST000003444227).

Abbreviations: CARD, caspase recruitment domain; CC, coiled coil; GPP, generalized pustular psoriasis; GUK, guanylate kinase-like; ND, not determined; PDZ, postsynaptic density 95/disk large/zona occludens 1; PPP, palmoplantar pustular psoriasis; PsA, psoriatic arthritis; PsV, psoriasis vulgaris; PRP, pityriasis rubra pilaris; SH3, SRC homology 3.

1Fold change compared with unstimulated CARD14 WT.
be prevented by CARD14 silencing (Schmitt et al., 2016), suggesting also a regulatory role for PKC in the activation of CARD14. In addition, Src and PKC inhibition interferes with zymosan-induced MALT1 activation in keratinocytes. It is therefore tempting to speculate that dectin-1 leads to PKC-mediated phosphorylation and activation of CARD14, facilitating the formation of a CBM complex (Figure 1).

PROTEASE ACTIVITY AND SUBSTRATES OF MALT1

Aside from its function as a scaffold protein in the CBM complex, MALT1 also acts as an arginine-specific protease and further fine-tunes the activation of the proinflammatory cascade. Although the caspase-like domain of MALT1 had already been described in 2000 (Uren et al., 2000), its first substrates were only identified in 2008 by two independent groups (Coornaert et al., 2008; Rebeaud et al., 2008). Because of its unique protease activity—MALT1 is the only known human paracaspase (Hulpiau et al., 2016)—it seems to be a promising drug target for dampening excessive inflammatory signaling.

So far, eight substrates of MALT1 have been described in stimulated lymphocytes: A20, BCL10, CYLD, ReLB, regrnase-1, roquin, HOIL-1, and MALT1 itself (Afonina et al., 2015; Hailfinger et al., 2014; Klein et al., 2015). Cleavage of these substrates affects various processes, such as NF-κB (A20, ReLB, HOIL-1) and JNK (CYLD) activation, linear ubiquitination (HOIL-1), mRNA stability (regrnase-1, roquin), and cell adhesion (BCL10). Because MALT1 can regulate inflammatory signaling and immune responses by cleaving these substrates, its proteolytic activity is subject to several regulatory mechanisms. Dimerization and mono-ubiquitination of MALT1 are necessary to adopt and maintain its catalytically active conformation (Cabalzar et al., 2013; Pelzer et al., 2013; Wiesmann et al., 2012). Thus, formation of supramolecular filamentous CBM complexes not only activates NF-κB signaling but also drives MALT1 proteolytic activity through oligomerization of MALT1 (Qiao et al., 2013).

Recently, a distinct role for MALT1 protease activity has emerged in inflammatory signaling in keratinocytes. Certain stimuli, such as zymosan and Staphylococcus aureus, were able to induce MALT1 proteolytic activity in keratinocytes, resulting in the cleavage of CYLD, ReLB, A20, and regnase-1 (Schmitt et al., 2016) (Figure 1). In addition, overexpression of CARD14 in keratinocytes was shown to promote processing of MALT1 substrates (Afonina et al., 2016), which was further enhanced by the psoriasis-associated CARD14 versions p.Gly117Ser and p.Glu138Ala, highlighting the pathological relevance of CARD14 mutations in psoriasis (Afonina et al., 2016; Howes et al., 2016). Inhibition of MALT1 protease activity in keratinocytes reduced the expression of important CARD14-regulated proinflammatory cytokines (e.g., TNF, IL-1β, and IL-17C), chemokines (e.g., CXCL8 and CCL20), and antimicrobial peptides (e.g., HBD-2 and S100A7), pointing to an important role for MALT1 in the immune response in the skin (Afonina et al., 2016; Schmitt et al., 2016). Interestingly, it was also shown that A20 and CYLD, two substrates of MALT1 that have been associated with psoriasis (Nititham et al., 2015; Oudot et al., 2009; Tejasvi et al., 2012), can inhibit CARD14-mediated signaling (Afonina et al., 2016). In this way, the cleavage of these negative regulators by MALT1 may promote optimal CARD14-mediated signaling. These findings imply that the proteolytic activity of MALT1 could contribute to the pathology of psoriasis.

THERAPEUTIC POTENTIAL OF MALT1 INHIBITORS IN PSORIASIS AND FUTURE PERSPECTIVES

Currently, there is no cure for psoriasis, but several treatments targeting the immune response and the differentiation status of keratinocytes can alleviate its symptoms. Conventional therapies, including glucocorticoids, fumarates, vitamin D derivatives, and phototherapy, are effective in treating mild cases but often induce unwanted side effects in patients. Recently, biological entities that target central cytokines in psoriasis, such as TNF, IL-17, and IL-12/IL-23, have emerged and often show better efficacy than conventional therapies in severe cases. However, not all patients are responsive to these cost-intensive treatments, highlighting the need for alternative treatment options (Deng et al., 2016).

The ability of CARD14 and particularly its psoriasis-associated mutants to activate the protease function of MALT1 and proinflammatory gene expression in keratinocytes provides a rationale for MALT1 inhibitors in psoriasis treatment (Afonina et al., 2016; Howes et al., 2016). Many CARD14-regulated genes are key players in the pathogenesis of psoriasis and are targets of current standard treatment regimens (e.g., anti-TNF biologics). Although there are at present no MALT1 inhibitors in the clinic, several groups of small molecule inhibitors have been published and patented, thus providing a pool of potential lead structures for further clinical development (Fontan et al., 2012; Lim et al., 2015; Nagel et al., 2012). MALT1 inhibitors have been successfully tested preclinically in vitro and in vivo in the treatment of a subtype of diffuse large B-cell lymphoma and in a mouse model of multiple sclerosis (Fontan et al., 2012; Mc Guire et al., 2014; Nagel et al., 2012). Because CBM activation in keratinocytes leads to MALT1-dependent inactivation of A20, CYLD, ReLB, and the endonuclease regnase-1, MALT1 inhibition will likely result in reduced NF-κB and AP-1 activity and decreased mRNA stability of various proinflammatory target genes.

Potential side effects of MALT1 inhibition can be predicted from MALT1 activity deficient mice. MALT1 knockout mice are viable and develop normally but suffer from severe immunodeficiency, including proliferation and activation defects in B and T cells after antigen receptor stimulation as well as reduced numbers of marginal zone and peritoneal B1 cells (Ruefi-Brasse et al., 2003; Ruland et al., 2003). Surprisingly, mice expressing protease-inactive MALT1 additionally suffer from spontaneous autoimmunity (Bornancin et al., 2015; Gewies et al., 2014; Jaworski et al., 2014; Yu et al., 2015). Whereas T cells from MALT1 knockout mice show no proliferation and IL-2 production upon stimulation, T cells from MALT1 protease-dead knock-in mice still respond partially due to the preserved scaffold function of MALT1. Because the development of regulatory T cells is...
strongly decreased in the knock-in mice, the residual activity of T cells might be enough to drive autoimmunity. Whether the effect on regulatory T cell development is relevant in human patients is unclear but could most likely be circumvented by the topical administration of a therapeutic MALT1 inhibitor. Thus, further studies are needed to validate the potential of MALT1 inhibitors in vivo in psoriasis-like mouse models. New insights could also come from CARD14 knockout or CARD14 mutant-expressing mice or from the keratinocyte-specific expression of a protease-inactive MALT1. In addition, the identification of other receptors driving CBM complex formation will help to further elucidate the role of MALT1 in keratinocytes. Because CARD14 mutations in psoriasis are relatively rare, the analysis of human psoriasis biopsies for active MALT1 will clarify the importance of the CBM pathway in this disease. MALT1 inhibition seems to be a particularly promising treatment strategy because it can tackle psoriasis in two ways: first, by decreasing the expression of proinflammatory target genes in keratinocytes and secondly by blocking the activation of immune cells in the skin.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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