cells of HFD-fed mice and propose that SFAs sensitize myeloid cells to produce proinflammatory cytokines, thereby exacerbating dermatitis. However, the cell populations that are affected by SFAs have not been identified. In addition, although Herbert et al. performed in vitro experiments that relate to the in vivo findings, the cells used in the culture systems were myeloid "peritoneal" cells. It is therefore uncertain if the in vitro findings can be directly translated to the skin myeloid cells. The concentrations and localization of SFAs in the skin after HFD feeding also need to be defined.

The reasons for the discrepancy between the results of Herbert et al. (2018) and those of previous studies are also unclear. For example, it has been reported that skin T cells and macrophages are increased by feeding mice an HFD (Nakamizo et al., 2017; Vasseur et al., 2016; Zhang et al., 2015), yet no changes in skin cell composition were observed in this study. This may relate to different HFDs that were used in different studies. The HFD used in the study by Herbert et al. was made from coconut oil, whereas other studies have used HFDs derived from lard (Nakamizo et al., 2017; Zhang et al., 2015) and cocoa butter (Vasseur et al., 2016). Differences in environmental factors, such as the microbiomes in the skin or in the gut, may also affect the phenotypes of HFD-fed mice. Additional investigation of these issues will provide new insights into the pathogenesis of psoriasis and the role of SFAs in it.

The proposal by Herbert et al. (2018) that dietary SFAs exacerbate psoriasis and that alternation of the diet may lead to the improvement of psoriasis is important. Although further experiments are required to confirm the applicability of their findings to human psoriasis and to elucidate the mechanisms of action of SFAs in skin, dietary changes may become an important therapeutic strategy for psoriasis.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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See related article on pg 2010

Psoriasis Plays a Wild CARD

Elien Van Nuffel[1,2], Inna S. Afonina[1,2] and Rudi Beyaert[1,2]

Rare autosomal mutations in *CARD14* have previously been linked to psoriasis susceptibility in humans, but their pathogenic role had not been shown. Mellett et al. generated mice harboring the patient-derived gain-of-function *Card14ΔE138* mutation and showed that hyperactivation of CARD14 alone is sufficient to induce immunopathogenic mechanisms that are responsible for psoriasis, which is driven by the IL-17/IL-23 axis.

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Psoriasis is a common chronic inflammatory skin disease that has a serious impact on the quality of life of affected patients. Plaque psoriasis, which is the most common type of psoriasis and is also known as psoriasis vulgaris, is characterized by the emergence of red, scaly, and sharply demarcated plaques that result from the pathogenic interplay between hyperproliferative keratinocytes and activated immune cells. Less common types of psoriasis include pustular, inverse, erythrodermic, and guttate psoriasis. Genome-wide association studies have shown that genetic factors play an important role in the etiology of psoriasis. Rare highly penetrant mutations in *CARD14* have been associated with plaque psoriasis, and *CARD14* accounts for the elusive *PSORS2* locus association (Jordan et al., 2012b). *CARD14* mutations have also been linked to clinically related conditions such as psoriatic arthritis, generalized pustular psoriasis, and pityriasis rubra pilaris (reviewed by Van Nuffel et al., 2017). CARD14 is an intracellular

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scaffold protein that is prominently expressed in keratinocytes and mediates NF-κB activation through the formation of a CBM (CARD14-BCL10-MALT1) signaling complex. Gain-of-function mutations in *CARD14* enhance CBM complex formation and downstream NF-κB signaling, leading to production of psoriasis-associated cytokines and chemokines by cultured keratinocytes (Afonina et al., 2016; Howes et al., 2016; Jordan et al., 2012a). However, follow-up studies have been limited, so the functional and physiological effects of *CARD14* mutations in vivo were unknown. Mellett et al. (2018) show that heterozygous expression of a gain-of-function *CARD14* mutation that was originally identified in patients led to spontaneous psoriasiform inflammation in mice (Mellett et al., 2018).

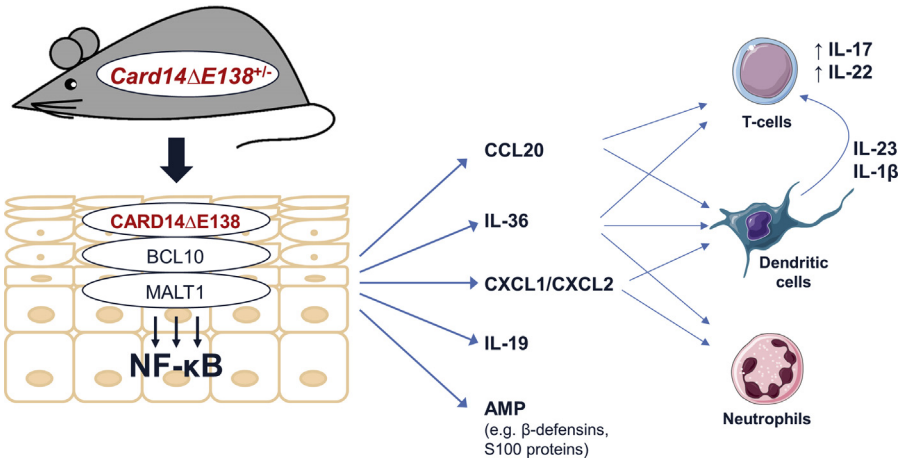

Figure 1. CARD14 mutation in mice induces immunological responses, which culminate in psoriasiform inflammation. Heterozygous expression of the gain-of-function mutation *Card14ΔE138* in mice strongly enhances CARD14-BCL10-MALT1 complex formation in keratinocytes and, in this way, drives hyperactivation of NF-κB. This leads to transcription of several chemokines (CCL20, CXCL1, and CXCL2), cytokines (IL-36 and IL-19), and antimicrobial peptides, followed by recruitment and activation of neutrophils, dendritic cells, and T cells. Activated dendritic cells release IL-23, which drives expression of IL-17 and IL-22 in T cells. AMP, antimicrobial peptides.

> Mice expressing a gain-of-function mutant of CARD14 are a novel mouse model for human psoriasis.

A CARD14 mutation is sufficient to induce psoriasiform inflammation in mice

To investigate the pathological role of a *CARD14* mutation, Mellett et al. (2018) used CRISPR/Cas-mediated genome editing to generate mice expressing CARD14 with a deletion of residue E138 (Figure 1). This variant was originally described in a patient suffering from pityriasis rubra pilaris type V. Additional mutations affecting the same residue—CARD14E138A and CARD14E138K—have been linked to generalized pustular psoriasis and pityriasis rubra pilaris. Mice that expressed one *Card14ΔE138* allele developed spontaneous psoriasiform disease that was characterized by scaling skin lesions and mainly affected the ears and tail. Histological analysis of affected skin showed typical hallmarks of human psoriasis such as epidermal acanthosis, hyperkeratosis, parakeratosis, hyperproliferating keratinocytes, and immune cell infiltration. Analysis of the infiltrating immune cells in involved ears showed marked increases in neutrophils, myeloid antigen-presenting cells, and αβ and γδ T cells (Mellett et al., 2018).

Mellett et al. (2018) also showed that transcriptomic profiles of affected ear tissue of *Card14ΔE138*-expressing mice strongly resembled those of human plaque psoriasis skin. Several cytokines that are central in the IL-17/IL-23 axis of psoriasis pathogenesis (e.g., *Il17f, Il19, Il22,* and *Il23p19*) were strongly upregulated. Chemokines (e.g., *Ccl20, Cxcl1*, and *Cxcl2*), antimicrobial peptides (e.g., *Defb4, S100a7*, and *Lcn2*), and proinflammatory cytokines (e.g., *Il36γ* and *Il17c*) that are typically produced by activated keratinocytes to sustain and amplify skin inflammation during psoriasis were also induced. Selected molecules that are involved in the formation of the cornified envelope and the skin barrier were also increased (e.g., *Ivl, Lce3b, Lce3c,* and *Flg1*), which is consistent with the intact skin barrier observed in *Card14ΔE138* mice. Mechanistically, Mellet et al. expanded on previous studies that reported that psoriasis-associated *CARD14* mutants drove enhanced CBM complex formation and activation of MALT1 proteolytic activity (Afonina et al., 2016; Howes et al., 2016). Mellett et al. point out that the CBM complex was hyperactivated in keratinocytes that were isolated from *Card14ΔE138*-expressing mice (Mellett et al., 2018). Taken together, these data show that heterozygous expression of the gain-of-function mutant *Card14ΔE138* is sufficient to drive the immunological and clinical phenotype of plaque-type psoriasis in mice (Mellett et al., 2018), further strengthening the hypothesis that CARD14 signaling is part of a pivotal pathway in psoriasis pathogenesis. Consistent with this, mice deficient in CARD14 were recently shown to be partially protected from imiquimod- and IL-23–induced "psoriasis" (Tanaka et al., 2018), suggesting that CARD14 signaling can be activated in the absence of *CARD14* mutations.

Card14ΔE138 mice as a novel mouse model for psoriasis

The modeling of human psoriasis in vivo through the use of mouse models represents a powerful laboratory tool for investigating the immunological and genetic mechanisms contributing to psoriasis in patients. Although no single psoriasis-like mouse model is likely to replicate the totality of human psoriasis and mice have several obvious cellular and anatomic differences from humans, in vivo systems are indispensable tools for advancing our understanding of the immunological and molecular basis of this inflammatory condition. In this context, the transgenic *Card14ΔE138* mice described by Mellett et al. (2018) display numerous histopathological

features of human psoriasis and exhibit similar gene expression profiles. To determine if psoriasiform inflammation in *Card14ΔE138*-expressing mice responded to an established psoriasis therapy, Mellett et al. treated these mice with an IL-23p19 neutralizing antibody, reducing the psoriatic phenotype and the expression of antimicrobial peptides and proinflammatory cytokines (Mellett et al., 2018). This provides additional support for the clinical relevance of the *Card14ΔE138* transgenic mouse model.

Moreover, the protective effect of IL-23–neutralizing antibodies suggests that targeting IL-23 might be a valid therapeutic approach for psoriasis patients with *CARD14* mutations. Ustekinumab, an IL-12/IL-23 inhibitor, showed beneficial effects in pityriasis rubra pilaris patients with *CARD14* mutations (Lwin et al., 2017). Thus, *Card14ΔE138* transgenic mice are a relevant mouse model for evaluating therapeutic options for patients with genetic defects in CARD14. In this context, because CARD14ΔE138 activates MALT1 proteolytic activity, small compound MALT1 inhibitors might also have beneficial effects. It is also worth mentioning that the role of CARD14 in the pathogenesis of psoriasis may not be limited to cases where *CARD14* gain-of-function mutations are present, as already suggested by the protection of CARD14-deficient mice in imiquimod- and IL-23–inducible murine models of psoriasis (Tanaka et al., 2018). CARD14 expression has also been shown to be up-regulated in lesional psoriatic skin (Jabbari et al., 2012), and a *CARD14* single nucleotide polymorphism was linked to psoriasis susceptibility in a gnome-wide association study (Tsoi et al., 2012). Therefore, *Card14ΔE138* mice will be an interesting mouse model to study the underlying molecular and immunological mechanisms of psoriasis due to uncontrolled CARD14 signaling in general.

Future directions

Even though the report of Mellett et al. (2018) clearly shows a physiological role for *Card14* mutations in the pathogenesis of psoriasis, several open questions remain to be answered. First, the psoriasiform lesions of *Card14ΔE138* mice are mainly restricted to the ears, tail, and around the eyes. Such site-specific differences in skin responses might reflect anatomical, immunological, and microbiological differences in skin from different areas of the body. However, it remains enigmatic why some skin sites are more prone to skin inflammation induced by *Card14ΔE138* expression than others.

Second, it is not yet clear if the psoriasiform skin inflammation in *Card14ΔE138* mice is solely the result of keratinocyte-intrinsic effects or if it might be influenced by the expression of *Card14ΔE138* in other cell types such as immune and endothelial cells. In the study of Mellett et al. (2018), keratinocytes of *Card14ΔE138* mice showed enhanced CBM complex formation and increased transcription of proinflammatory cytokines (*Il17c*, *Il19*, and *Il36γ*). However, it is not known if keratinocyte-intrinsic changes alone can kindle psoriasiform skin inflammation. Furthermore, it has previously been suggested that CARD14 in γδ T cells might play a role in imiquimod-induced psoriasis (Tanaka et al., 2018). It will be important to assess the development of skin inflammation in mice expressing *Card14ΔE138* in specific cell types. In this context, the finding of Mellett et al. that homozygous *Card14ΔE138* mice die soon after birth might point to a role for enhanced CARD14 signaling in other cell types.

Third, although the study of Mellett et al. (2018) shows that a *Card14* mutation is sufficient to drive psoriasiform inflammation, the fact that in humans different *CARD14* mutations are associated with different disease severity or different types of cutaneous inflammation (Van Nuffel et al., 2017) suggests that additional factors may contribute to disease pathogenesis. Relevant factors may include environmental triggers or possibly epigenetic alterations.

Finally, the role of wild-type CARD14 in normal skin, as well as the endogenous or environmental factors that regulate its activity in normal and diseased skin, are still largely unexplored. Defining the role of CARD14 in normal skin homeostasis and finding upstream ligands and receptors may lead to development of alternative therapeutic strategies.

In conclusion, the study of Mellett et al. (2018) not only provides new insights into the physiological consequences of uncontrolled CARD14 signaling, it also provides the scientific community with a valuable new mouse model for further mechanistic studies and the testing of novel therapeutic approaches for human psoriasis.

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