concluded that high dietary fats exacerbate IMQ-induced psoriasis-like dermatitis in mice (Higashi et al., 2018). Despite being termed high-fat diets by their authors, these two studies used diets that were not only rich in fat, but also had a high content of simple sugars, bearing considerable similarity to the WD used in our studies (Supplementary Table 1 online). Based on our findings and their results, we propose that dietary content, beyond just the ability to induce obesity, plays a crucial role in the predisposition to psoriasisform inflammation. In conclusion, it is a WD, but not a HDF alone, that predisposes mice to enhanced susceptibility to IMQ-induced PsD. Although we cannot say that higher than standard levels of fat in the WD are dispensable for increased PsD susceptibility, our data do suggest that sucrose/sugar content of the WD is a critical factor for the enhanced susceptibility to IMQ-mediated PsD.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

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REFERENCES


Disinhibition of Touch-Evoked Itch in a Mouse Model of Psoriasis


Abbreviations: IMQ, imiquimod; LTMR, low-threshold mechanoreceptors; NFH, neurofilament H; QX-314, N-ethyl-lidocaine; TLR5, toll-like receptor 5; VH, vehicle

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TO THE EDITOR

Alloknesia, itch due to light mechanical stimulation, is frequently associated with dry skin and inflammatory skin disorders (e.g., atopic dermatitis, psoriasis). Recent studies have shown that mechanical itch is...
regulated by neuropeptide Y-positive spinal inhibitory interneurons that are innervated by low-threshold mechanoreceptors (LTMRs) (Bourane et al., 2015). LTMRs are divided into subtypes based on their action potential conduction velocities and their rates of adaptation to sustained mechanical stimulus (Woo et al., 2015; Zimmerman et al., 2014). In hairy skin, Aβ-slowly adapting type I LTMRs and Merkel cells compose touch domes to detect skin identification. In dry skin and aged skin, a reduction of the sustained firing of Aβ-slowly adapting type I LTMRs due to a loss of Merkel cells relates to alloknesis (Feng et al., 2018). We investigated whether the number of Merkel cells or innervation of Merkel cells by Aβ-fibers is decreased in the imiquimod (IMQ)-induced psoriatic mouse model. In addition, we tested whether the targeted silencing of Aβ-fibers is sufficient to produce alloknesis.

To develop the mouse model for psoriasis, IMQ cream was applied on the rostral back skin for 7 consecutive days. For further information on materials and methods, see the Supplementary Materials online. All experimental procedures were approved by the University of Miami Institutional Animal Care and Use Committee. In naïve mice, myelinated A-fibers labeled with neurofilament H (NFH) contacted keratin 8-positive Merkel cells in the epidermis (Figure 1a). In IMQ-treated mice, the alloknesis score was markedly increased compared with vehicle.
(VH)-treated mice (control) (Figure 1b). Although the loss of Merkel cells in aged skin and dry skin was reported (Feng et al., 2018), the number of keratin 8-positive Merkel cells was comparable between the IMQ and VH groups (Figure 1c and d). NFH-positive epidermal nerve fiber density was decreased in the IMQ group compared with the VH group (VH, 19.6 ± 0.9 nerve fiber counts/mm; IMQ, 9.7 ± 2.1 counts/mm) (Figure 1e and f).

Toll-like receptor 5 (TLR5) was recently proposed as a marker for Aβ-fibers (Xu et al., 2015). We observed TLR5 expression in the majority of NFH-positive fibers in the rostral back skin (Figure 2a). Moreover, TLR5 is expressed by NFH-positive fibers innervating the touch dome (see Supplementary Figure S1 online). TLR5-positive epidermal nerve fiber density was decreased in the IMQ group compared with the VH group (VH, 16.8 ± 0.8 nerve fiber counts/mm; IMQ, 8.4 ± 1.2 counts/mm) (Figure 2b). To directly test the contribution of myelinated Aβ-fibers in regulating alloknesis, we used a strategy of the activity-dependent silencing of Aβ-fibers by targeted delivery of a membrane-impermeable lidocaine derivative, N-ethyl-lidocaine (QX-314) (Binshtok et al., 2007; Roberson et al., 2013; Xu et al., 2015). Activation of TLR5 with its ligand flagellin leads to selective QX-314 entry into Aβ-fibers and subsequent blockade of sodium currents in these fibers (Xu et al., 2015). In line with this finding, co-injection of QX-314 and flagellin abolished responses of low-threshold mechanosensitive fibers to brush stimuli without affecting responses of high-threshold mechanosensitive fibers to pinch stimuli (see Supplementary Figure S2 online). Given the decrease in TLR5-positive epidermal nerve fiber density in the mouse model of IMQ-induced psoriasis, we hypothesized that inhibition of TLR5-positive nerves induces a mechanical itch phenotype resembling the alloknesis seen in the psoriasis mice. Intradermal co-application of QX-314 and flagellin produced touch-evoked scratching (Figure 2c). The alloknesis score became increased at 15 minutes, peaked at 0.5–1 hour, was maintained at 3 hours, and recovered at 24 hours. Intradermal injection of either flagellin or QX-314 alone did not induce mechanical itch phenotype in naïve mice (Figure 2c). Touch-evoked scratching was observed only when the mechanical stimulus was delivered to skin adjacent to a site of injection but not skin in the center of the injection site. Consistently, it was
previously reported that touch-evoked scratching was elicited only by stimulation at the skin adjacent to a site of acute itch or the border of the dry skin-treated area on the rostral back (Akiyama et al., 2012; Iwanaga et al., 2018). Therefore, it appears that, although Aβ-fibers innervating the chemical-injected site or the skin within the treatment area drive a circuit for antimechanical itch, a subset of LTMRs innervating the adjacent skin mediates touch-evoked itch.

In summary, we show that alloknesis in an IMQ-induced psoriatic mouse model is associated with a loss of the epidermal nerve endings of Aβ-fibers but not Merkel cells. By contrast, alloknesis in dry skin and aged skin is associated with a loss of Merkel cells (Feng et al., 2018). Considering that the Merkel cells are innervated by Aβ-fibers, the loss of sustained discharge of Aβ-fibers from Merkel cells is essential for alloknesis. Aβ-fibers in hairy skin likely innervate neuropeptide Y-positive inhibitory interneurons in the spinal cord to gate mechanical itch in normal conditions (Bourane et al., 2015).

Our findings suggest that reactivation of Aβ-fibers can reduce alloknesis under chronic itch condition. High-frequency transcutaneous electrical nerve stimulation activates Aβ-fibers and temporarily relieves generalized itch (Wallengren, 2004). Additionally, massage therapy works for certain types of itch (Gürol et al., 2010; Schachner et al., 1998). Although antipruritic effects of those therapies are expected to be temporary, the approach to regain Aβ-fibers could be considered as a novel strategy for treating chronic itch.

CONFLICT OF INTEREST
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SUPPLEMENTARY MATERIAL
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REFERENCES
Gürol AP, Polat S, Akçay MN. Itching, pain, and anxiety levels are reduced with massage therapy in burned adolescents. J Burn Care Res 2010;31:429–32.

Relationship of Chromosome Arm 10q Variants to Occurrence of Multiple Primary Melanoma in the Population-Based Genes, Environment, and Melanoma (GEM) Study


TO THE EDITOR
Using a genome-wide association study of familial melanoma pedigrees (excluding CDKN2A+ pedigrees) and genetically matched controls, Teerlink et al. (2012) identified three single nucleotide polymorphisms (SNPs) in close proximity and high linkage disequilibrium in the 10q25.1 region (rs17119434, rs17119461, and rs17119490) associated with melanoma (Teerlink et al., 2012). These SNPs had low minor allele frequencies of 0.005 among controls utilized by Teerlink et al. (2012), making detection of associations via traditional case–control methods challenging. We sought to confirm the relationship between these SNPs and melanoma...