Molecular link between itch and atopic dermatitis

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Atopic dermatitis (AD) is a relapsing inflammatory skin disease often associated with intractable chronic itch. The sensation of itch depends on the activity of pruriceptive sensory neurons whose nerve fibers innervate the dermis and epidermis. These fibers can respond to factors secreted by keratinocytes (e.g., thymic stromal lymphopoietin) and immune cells (e.g., IL-31, histamine, and proteases) (1). However, the pathogenesis of chronic itch and inflammation in AD is not well understood, and therapeutic options are limited. In PNAS, Emrick et al. (2) perform an elegant study in which they determine the cellular and molecular mechanisms by which the AD-associated gene Tmem79 drives skin inflammation and itch. Emrick et al. find that Tmem79 acts as a putative glutathione transferase to decrease oxidative stress in keratinocytes to prevent mast cell activation and histamine-driven neuronal activation and itch (Fig. 1). This study is an important advance in our understanding of the molecular and cellular mechanisms of AD.

AD affects ∼20% of children in the developed world and 2 to 8% of adults, with 87 to 100% of these patients experiencing chronic itch (3, 4). It is generally thought that AD is caused by a combination of skin barrier dysfunction and immune dysregulation. Several genetic predispositions have been linked to AD. The most common mutations in AD patients are loss-of-function mutations in the filaggrin (FLG) gene (5). FLG encodes for profilaggrin, a protein at the skin barrier necessary to maintain epidermal hydration and low pH. Tmem79 is another gene recently linked to AD in animals and humans (5–7). Mutations in the Tmem79 gene are responsible for the matted hair and AD-like phenotypes observed in flaky tail (ma/ma Flgft/ft) mice, characterized by skin lesions, dermal thickening, and inflammation (5–7). In humans, a missense mutation in the Tmem79 gene was recently discovered and associated with AD patients (6). Tmem79 encodes a protein with five transmembrane domains, found to be expressed in the outermost layers of the stratum granulosum in the epidermis (7). However, the molecular functions of TMEM79 and how its deficiency drives AD are not clear.

Emrick et al. (2) used transgenic and knockout mouse studies to determine the role of Tmem79 in skin inflammation and itch. They generated Tmem79−/− mice, which developed spontaneous itch, dermal thickening, and immune cell accumulation in the skin. Tmem79−/− mice showed significant expansion of mast cells and IL-17–expressing γδ T cells. Next, to determine the cell types in which Tmem79 was specifically expressed and that mediated its function, Emrick et al. generated a Tmem79-knockin GFP reporter mouse with an inverted floxed cassette, allowing the analysis of Tmem79 promoter-driven gene expression and subsequent targeted deletion of this gene from specific cell types via Cre recombination. The authors found that Tmem79 was expressed both by keratinocytes and dorsal root ganglion sensory neurons. A majority of Tmem79+ neurons also expressed histamine receptor 4 (H4R) (80%) and peripherin (74%), which marks small-diameter C-fiber sensory neurons. Using keratinocyte-specific (K14-Cre) and sensory neuron-specific (Prph-Cre) deletion of Tmem79, Emrick et al. show that both cell types contribute to itch. While keratinocyte ablation of Tmem79 induced significant itch, Tmem79 deletion from both keratinocytes and neurons induced greater itch and skin inflammation to levels that phenocopied Tmem79−/− mice.

To investigate the molecular function of TMEM79, Emrick et al. (2) performed homology analysis and found that TMEM79 shared 30% amino acid sequence homology with microsomal glutathione transferases [i.e., membrane-associated proteins in eicosanoid and glutathione metabolism (MAPEGs)], a family of detoxification enzymes that protect cellular macromolecules from attack by reactive species (RS) (8). This led Emrick et al. (2) to hypothesize that TMEM79 could act as a glutathione transferase to decrease oxidative stress in cells. The authors found that Tmem79−/− keratinocytes had greater accumulation of RS when challenged with the oxidant 3-morpholinosydnonimine (SIN-1), and that HEK293T cells overexpressing TMEM79 better reduced RS in response to SIN-1. These data demonstrate...
that TMEM79 is necessary and sufficient to regulate RS. The protective effect against RS was lost when two putative active sites were mutated in the Tmem79 region homologous with MAPEG family members.

Keratinocytes respond to oxidative stress by producing eicosanoids, including prostaglandin E2 (PGE2) (9). Emrick et al. (2) hypothesized that elevated oxidative stress in Tmem79−/− mice could result in increased PGE2 and downstream inflammation. PGE2 levels were indeed increased in keratinocytes from Tmem79−/− mice, which may relate to increased levels of PGE2 observed in skin plaques from AD patients (10). Blocking prostaglandin production using a cyclooxygenase inhibitor or blocking EP3 receptors to recruit dermal mast cells. Mast cell degranulation results in the release of histamine, which acts on H1R and H4R expressed by C-fiber sensory neurons to drive itch. Potential strategies to inhibit itch in AD suggested by this study include the use of antioxidants, EP3 receptor antagonists, and histamine receptor (H4R/H1R) antagonists.

In AD, the molecular mechanisms involved in linking itch, inflammation, and barrier dysfunction remain poorly understood. Current hypotheses concerning these mechanisms include increased transepidermal water loss (TEWL), with subsequent epidermal pH rise and protease activation, which could explain how TEWL is correlated with itch intensity in patients (4). Dysfunction of the barrier could also allow irritants and allergens to enter more easily, including bacterial products and proteases that directly or indirectly activate sensory neurons to mediate itch. Another promising hypothesis is an underlying role for oxidative stress in AD. For the last 15 y, studies have shown that AD patients showed evidence of oxidative stress (e.g., nitrite/nitrate and lipid peroxidation) and decreased antioxidant capability (e.g., lower levels of vitamins A, C, and E) (12). A polymorphism in GST was recently associated with increased AD susceptibility (13). With this study, Emrick et al. (2) contribute to the emerging concept that oxidative stress could mediate AD, by showing that TMEM79 belongs to a protective system against oxidative stress in keratinocytes and potentially in sensory neurons, and that loss of this protection leads to mast cell activation, dermatitis, and chronic itch. Therapeutic options are limited to effectively treat AD, especially for the chronic itch that remains a huge burden on the quality of life for many patients. In recent years, there has been a push to translate several therapies specifically targeting immune cell signaling and cytokines to treat AD (e.g., dupilumab, an IL-4/IL-13 signaling blocker; and nemolizumab, an IL-31 receptor inhibitor) (14). The findings by Emrick et al. (2) provide arguments for several targeted strategies to block itch in AD (Fig. 1). While it remains to be determined whether these mechanisms apply more broadly to AD or mainly to patients bearing a Tmem79 mutation, potential strategies include reducing oxidative stress, blocking the PGE2/EP3 pathway, or blocking histamine signaling in neurons.
using an H4R antagonist or a combination of H4R/H1R antagonists. A recent trial showed promising, although not conclusive, results using an H4R inhibitor in alleviating pruritus in AD patients (15). While the trial was terminated because of off-target effects of the inhibitor, H4R antagonists without side effects are currently under investigation (16). As well as being a relevant model of human disease, the Tmem79−/− mouse may be a useful preclinical tool for development of novel therapeutics to treat inflammation and itch in AD.

In addition to therapeutic implications, the study by Emrick et al. (2) provides insights into the function of TMEM79 that merit future investigation. Biochemical studies are needed to define the exact protein domains and molecular mechanisms by which TMEM79 mediates RS reduction. Previous studies have shown that loss-of-function mutations in Tmem79 induced abnormal function of lamellar granules, including reduced protein secretion and impaired stratum corneum formation (7). It would be interesting to determine whether the role of Tmem79 in oxidative stress also impacts lamellar granule secretion. It would also be informative to determine whether TMEM79 reduces oxidative stress in sensory neurons. Emrick et al. (2) make the interesting observation that γδ T-cells and IL-17 production were significantly elevated in Tmem79−/− mice. AD has potential links with IL-17–driven pathology (17). It would be interesting in future work to determine whether γδ T-cells or IL-17 signaling also drives skin thickening or itch induction in Tmem79−/− mice.

In summary, the Emrick et al. (2) study is a tour de force, establishing a molecular link between chronic itch and AD. It shows that loss of the AD-associated gene Tmem79 in keratinocytes and neurons results in skin inflammation and itch. The study demonstrates a protective role of TMEM79 against oxidative stress, which prevents keratinocyte-mediated PGE2 induction, mast cell accumulation, and histaminergic itch. It also introduces exciting research questions about the TMEM79 protein and highlights potential therapeutic avenues for AD.

Acknowledgments

The authors’ research is supported by National Institutes of Health Grants R01 AI30019 and DP2 AT009499 (to I.M.C.)