Interdependence of Sebaceous Lipids and the Microbiome in Atopic Dermatitis

Samia Almoughrabie1 and Richard L. Gallo1

Journal of Investigative Dermatology (2022) 142, 2845–2847; doi:10.1016/j.jid.2022.07.004

Dysfunction of the skin barrier, immune system, and microbiome all occur in atopic dermatitis (AD), but a single cause for this disease has not been clearly identified for all patients. Evidence supporting that AD is a multistep process that can involve lipid synthesis has been provided in a recent publication by Morimoto et al. (2022). In Tmem79−/− mice used in this study, previous work of Ito et al. (2021) showed that skin inflammation occurs in a biphasic pattern, with a first phase of dermatitis that occurs independently of the microbiota and a second phase that is microbiota dependent. In their study, Morimoto et al. (2022) show that a deletion of Tmem79 first results in abnormalities in lipid synthesis sufficient to trigger dermatitis, although the microbiome is required to trigger the final development of the disease (Figure 1).

Animal models are essential to understanding human disease, and mouse models have been key to unraveling the complex interactions that lead to AD. For example, the Flaky Tail mouse model has been used extensively because this mouse has AD-like skin disease and has alterations in the sequence in genes for both Flg and Tmem79 (also known as matted). Mice with single mutations in Flg do not develop spontaneous dermatitis but are highly susceptible to T helper (Th)2 inflammation when they are sensitized with an allergen and exposed to the bacterium Staphylococcus aureus (Nakatsuji et al., 2016). However, mutation of Tmem79 results in spontaneous disease as well as an abnormal hair coat. Because mutation in Flg or Tmem79 can occur in the human population, Morimoto et al. (2022) use Tmem79−/− mice to investigate the factors that could help to understand AD. They show that these mice have hyperplasia of the sebaceous gland, and through RNA sequencing, they highlight an upregulation of fatty acid (FA) genes and sebocyte differentiation genes in chin skin. Such findings suggest an alteration in lipid metabolism. Indeed, when they performed thin-layer chromatography, it revealed an increase in wax esters, cholesterol (CHOL) esters, and fatty alcohols. Moreover, they observed an increase of long- to very-long-chain FAs. These findings imply that an increase in sebaceous lipid synthesis is responsible for the skin disease in Tmem79−/− mice.

Alterations of skin lipid composition in AD

CHOL, ceramides (CERs), FAs, and triglycerides (TGs) are the main lipids present in the skin, and the regulation of their synthesis in the epidermis is essential for the maintenance of the permeability barrier. Several different lipid classes have been shown to be abnormal in AD, although these changes do not all align with the observations made in Tmem79−/− mice. For example, an analysis of the stratum corneum of patients with AD revealed a decrease in long-chain CERs, sphingomyelins, and lysophosphatidylcholines compared with that in healthy controls (Berdyshev et al., 2018). This shift suggested that an alteration in FA elongation is essential for the synthesis of the main long-chain lipids. Indeed, RNA-sequencing analysis revealed decreased expression of FA elongases ELOVL3 and ELOVL6 in the stratum corneum of patients with AD, a finding in contrast to that reporting increased expression of these genes in Tmem79−/− mice. Moreover, the Th2 cytokines IL-4 and IL-13 will downregulate ELOVL3 and ELOVL6 in human keratinocytes (KCs), but Tmem79−/− mice had no significant change in Th2 pathway–related genes. These differences between this mouse model and human AD do not negate the importance of the mouse observations. The Tmem79−/− mouse shows how primary lipid barrier changes can result in inflammation and may reflect the changes that occur in humans before the onset of disease, which are driven by bacterial dysbiosis before allergic inflammation.

Other lipid abnormalities were found from analysis of the transcriptome of Tmem79−/− mice that may further inform the biology of this system. Changes were seen in genes related to the biosynthesis of unsaturated FAs, and this was supported by gas chromatography–mass spectrometry analysis that found an increase in polyunsaturated FAs. That multiple lipid species can be involved is also consistent with studies in humans that have shown increases in CHOL-3-sulfate in patients with
Clinical Implications

- Mice without Tmem79−/− spontaneously develop dermatitis and may model an early phase of atopic dermatitis.
- Tmem79−/− mice have abnormal sebaceous gland-specific lipid production.
- Alteration of epidermal lipid production may result in inflammation that permits microbes to further establish chronic disease.

AD that correlated to an increase in transepidermal water loss (TEWL), suggesting that CHOL-3-sulfate may contribute to impairment of the epidermal barrier (Li et al., 2017). Patients with AD also exhibit an alteration of TGs, with an accumulation of long-chain TGs. TGs are important in the epidermis because their breakdown will provide the FAs needed for the synthesis of long-chain lipids, including CERs. The Tmem79−/− mouse also showed an increase in the expression of enzymes involved in CHOL metabolism (SOAT1) and in TG metabolism (CIDEA). Combined, abnormal epidermal lipid content are associated with skin inflammation in this mouse model and in human AD but more extensive studies need to be performed to fully determine how specific changes in lipid metabolism influence the inflammatory response of AD in humans. Is it only a defect in the barrier properties of the epidermis or also an influence on the immune response and the microbiome?

Microbial dysbiosis: a key component of AD that is linked to the barrier and inflammation

Observations that lipid abnormalities lead to skin inflammation do not negate the importance of microbes in the development of AD. Studies have shown a reduction in bacterial diversity in AD that reflects changes in the growth of specific

Figure 1. Skin lipid alterations in Tmem79−/− mice and AD as a first phase of dermatitis before microbial dysbiosis and chronic skin inflammation.

Comparison of changes of skin lipid composition in Tmem79−/− mice and in patients with AD. Although the specific changes in lipid composition differ between AD and this mouse model, both are associated with barrier defects and inflammation. After a change in the skin microenvironment, the development of microbial dysbiosis such as the overgrowth of Staphylococcus aureus triggers a second phase of inflammation and disruption of the skin barrier, leading to chronic disease. Figure was created with BioRender.com. AD, atopic dermatitis; TEWL, transepidermal water loss; WT, wild-type.
species of *Streptococcus*, *Corynebacterium*, and *Cutibacterium*. In particular, AD is associated with a high prevalence of *S. aureus*. Even in the absence of inherent barrier defects in the host, phenol-soluble modulins from *S. aureus* stimulate the secretion of kallikreins (KLK6, KLK13, and KLK14) by KCs, and combined with the direct effects of bacterial proteases and other toxins, they will directly lead to barrier defects and inflammation (Williams et al., 2017). The importance of the microbiome as a primary driver of AD is further supported by early clinical studies showing that topical application of anti-inflammatory drugs (Nakatsuji et al., 2021).

An important mechanistic link between the microbiome and barrier defects in AD is the Th2 immune response and expression of IL-4 and IL-13. These two Th2 cytokines can inhibit the expression of antimicrobials peptides in the skin (cathelicidin and β-defensin 2) and downregulate the expression of FLG. This facilitates the colonization and penetration of *S. aureus* or other bacteria into deeper layers of the skin, thus promoting skin inflammation. Recent work also shows that the commensal *S. cohnii* can inhibit skin inflammation in *Tmem79*−/− mice by inducing anti-inflammatory and glucocorticoid-related genes that inhibit type 2 and type 17 immune responses (Ito et al., 2021). These data support the hypothesis that some microbiota plays important roles in the regulation of skin inflammation, although these actions are likely specific to bacterial strains as well as species.

Several mechanisms explain how bacteria interact with the lipids of the skin barrier. One recent example is the commensal bacterium *S. epidermis*, which was found to secrete sphingomyelinase that is used by the host for the CER synthesis (Zheng et al., 2022). A study by Li et al. (2017) has also reported a decrease in CERs CER[AH]C48, CER[EOH]C66, CER[EOH] C68, and CER[EOS]C70; TGs TG46:2, TG48:2, TG50:2, and TG50:3, and free FAs FFA16:1 and FFA18:1 in patients with AD colonized by *S. aureus* and show a correlation with a higher TEWL. This decrease of lipids in patients with AD could be the result of the loss of the beneficial effects of some bacteria to assist in the production of epithelial lipids as well as the damage caused by *S. aureus*. Furthermore, *C. acnes* secretes a triacylglycerol lipase GehA that is capable of breaking down the triacylglycerols present in sebum into short-chain FAs (SCFAs). The most abundant SCFA produced by *C. acnes* is propionic acid, and one of its functions is to maintain the acidic pH on the skin surface. Because many enzymes required for lipid synthesis are pH dependent, this could also explain the reduction of some lipids that are observed in patients with AD (Danby and Cork, 2018).

**Epithelial–immune–microbiota cross-talk and the holobiome**

Holobiome theory recognizes that cells from the host as well as different species living on or around it cooperate to make the functioning ecological unit (Bordenstein and Theis, 2015). This theory permits us to put the currently available information on AD into a single comprehensive model. AD results from the dysfunction of three major systems within the holobiont that influence each other: (i) skin barrier, (ii) immune response, and (iii) the skin microbiota. No studies have identified which one of these factors is the primary cause of AD and likely never will. However, accumulating evidence has made it clear that a cycle of multiple and diverse genetic predispositions in the host combine with triggers from the environment to alter the microbiome, then resulting in skin inflammation. Further studies are required to fully understand the interplay between epithelial cells, the microbiota, and the immune system to design better and safer treatments for patients suffering from AD.

**ORCIDs**

Samia Almoughrabie: http://orcid.org/0000-0003-0334-1866

Richard L. Gallo: http://orcid.org/0000-0002-1401-7861

**CONFLICT OF INTEREST**

RLG is a consultant for and has an equity interest in MatriSys Bioscience. SA states no conflict of interest.

**REFERENCES**


