Progress in Understanding Atopic Dermatitis

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Introduction
Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, and its realm of basic mechanisms and predisposing factors is similarly wide. The Journal of Investigative Dermatology (JID) has recently published a surprisingly numerous collection of articles, comments, and reviews that scan the universe of basic information about AD. This review is directed toward using the JID Collections to provide a background and melding of research focuses in the current setting. This online commentary will attempt to consolidate and interweave some of the featured studies that have emerged. In the past century, most efforts to explain AD reflected allergic and immune mechanisms. With the 2006 revelation of a clear association between FLG deficiency and AD (Palmer et al., 2006), that focus began to shift to inclusion of epidermal barrier defects and their interaction with immune and inflammatory factors. This broadened approach has provided further fresh insights to genetic aspects, microbiome factors, and neural associations of skin pruritus and pain.

Epidermal barrier
Cellular and molecular abnormalities associated with AD have been detected during the past two decades, providing more detailed understanding beyond the clinical domains of allergy or neurodermatitis (Eyerich et al., 2018). A major advance came with the genetic demonstration that significant numbers of AD patients had FLG deficiency that compromises the epidermal barrier, allowing penetration of bacteria, allergens, and environmental chemicals and pollutants. Increases of these xenobiotics in urban regions combined with barrier access has been shown to act on keratinocytes to trigger the transcription factor PXR (Elentner et al., 2018) and the aryl hydrocarbon receptor, both of which can work to cause AD worsening and even downstream release of TSLP and activation of the Th2 helper (Th) type 2 pathway (Hidaka et al., 2017).

Inflammation mediated by Th2 reactivity is seen as a prime pathway to AD. Subsequent studies have shown that epidermal barrier defects are generated by many factors, including bacteria (Nakatsui et al., 2016), increased skin pH (Jang et al., 2016), keratinocyte cytokines, and Th2-generated inflammation (Honzke et al., 2016). Also, many other deficient/defective barrier components may well predispose to skin inflammation. These include claudin-1 (Furuse et al., 2002), corneodesmosin (Oji et al., 2010), LECTI (Igawa et al., 2017), small proline-rich proteins (Kelsell and Byrne, 2011), and lipid components (Kim et al., 2017). Studies in mice have suggested that mast cells may even have a beneficial role in regulating epidermal barrier function and reducing inflammation (Sehra et al., 2016). Likewise, other studies have provided evidence of a two-way street for filaggrin-associated effects in AD, showing that inflammatory factors can act to reduce barrier function (Elentner et al., 2018; Traidl et al., 2018).

Cellular and molecular inflammatory mechanisms
Through many decades, prominent AD comorbidities such as asthma, food allergy, and rhino-conjunctivitis have steered research toward immunological mechanisms, with the preponderant focus on IgE-related factors. It has been difficult, however, to find associations with the oft-noted but inconsistent presence of allergen-specific IgE, eosinophils, or mast cells in tissue and blood. During the past two decades, investigations of Th2 cells that secrete IL-4 and IL-13 have predominated. The practical benefits of these studies have been recently realized through the development of new agents that provide confirmation of the Th2 pathway.

Another outgrowth of epidermal barrier studies was the realization that keratinocyte cytokines such as TSLP could act on dendritic cells and Th2 cells to augment immune and inflammatory responses in the skin and other organs, potentially influencing AD and asthma. A similar effect on Th2 cells contributes to increased pruritus via IL-31 effects (Meng et al., 2018). Conversely, TSLP has been shown to act on keratinocytes to impair expression of antimicrobial proteins via a JAK/STAT mechanism, potentially contributing to infections in AD skin (Lee et al., 2016).

TSLP regulates a distinct group of immune cells in the skin called innate lymphoid cells (ILCs) that are enriched in the skin of AD patients and promote skin inflammation (Kim et al., 2013). ILCs reside in the upper dermis near the epidermis, in proximity to T lymphocytes, and distinct population subtypes have been described in AD (Bruggen et al., 2016). Trm32, an innate antiviral protein associated with ILCs, has been found at low levels in AD skin, suggesting another possible pathway to explain AD patients’ susceptibility to herpes and other viral infections (Gao et al., 2015; Liu et al., 2017).

Neural aspects
Pruritus is perhaps the most important clinical feature associated with AD. Although this is obvious today, pruritus was often not included in severity assessments two decades ago. The recognition and study of itch has revealed a variety of factors that initiate and perpetuate itch in AD. However, as with immune and inflammatory pathways, progress tends to be piecemeal, with evidence of sodium and receptor potential channels and cytokine
receptors, among others, being slowly added (Azimi and Lerner, 2014; Lerner, 2018). Itch in AD is primarily histamine independent (Snyder et al., 2016), a fact that is often ignored by practitioners, who divert patients from proper skin care with endless prescriptions of antihistamines.

Studies in recent years have begun to identify neural pathways that begin with keratinocyte cytokines. TSLP, involved with Th2 immune pathways, also communicates with cutaneous sensory neurons to promote itch through activation of ion channels such as TRPV1 and TRPA1 (Wilson et al., 2013). These studies have led to identification of other TRP channels and sodium channels in nerves carrying itch responses (Akiyama et al., 2016). A prominent histamine-independent mediator of itch in AD is IL-31, which forms a neuroimmune link between the Th2 pathway and sensory nerves. A recent study showed that IL-31, binding to its receptor in dorsal root ganglion cells, not only caused itch but also increased brain-derived neurotropic peptide (i.e., BNP) synthesis and release, which in turn can mediate release of chemokines and cytokines from keratinocytes and dendritic cells (Meng et al., 2018). In chronic itch, neuronal IL-4Rx and JAK signaling mediates itch sensation, a discovery that has led to effective therapeutic interventions (Oetjen et al., 2017).

Some of the emerging therapies for AD highlight benefits on cells in the Th2 and IL-31 pathways. Nemolizumab, a monoclonal antibody, can block the IL-31 receptor and reduce itch independently. The newly approved monoclonal antibody dupilumab blocks the IL-4Rx receptor, reducing both itch and inflammation (Simpson et al., 2016). Another pathway that may influence itch in AD has been unexpectedly suggested by recent clinical trials. Past studies of mononuclear leukocytes had shown reduced cyclic adenosine monophosphate control, due to overactive intracellular phosphodiesterase activity (Chan et al., 1993), and this led to development of topical phosphodiesterase inhibitors, which can have benefits in mild to moderate disease. A surprising observation has been the fairly rapid reductions in itch, possibly even preceding evidence of reduced skin inflammation (Garcia et al., 2016). Genetic studies are also indicating distinct patterns of expression in pruritic AD skin that contrast with psoriasis (Nattkemper et al., 2018).

Infections and microbiome associations with AD
The realm of infections and skin colonization is complex and multifaceted. Studies over many decades showed impaired delayed hypersensitivity and increased frequency of viral and bacterial infections (Gao et al., 2015; Traidl et al., 2018). The association between AD and staphylococcal infections has also been known for decades and, although the incidence of colonization on children may be lower, it may occur earlier and tends to affect patients with more severe disease (Simpson et al., 2018). Certainly, the association is strong and of genetic interest for both bacteria and host (Harkins et al., 2018). Current prevention studies of Staphylococcus aureus are increasing our understanding of the relationship with AD. A recent prospective study from Europe showed that S. aureus can preclude development of infant AD, with increased colonization even 2 months earlier than appearance of AD, and that onset was earlier in S. aureus—positive infants (Meylan et al., 2017). This contrasted with an earlier study indicating that S. aureus colonized after AD onset but suggesting that different staphylococcal variants might be causal (Kennedy et al., 2017). Studies assessing the interaction between S. aureus and the epidermis have shown proinflammatory and barrier-damaging effects on keratinocytes (Williams and Gallo, 2017) and have suggested possible target avenues for new therapies.

Overview
AD continues to be a complex disease, very difficult to define and delineate. This review has considered some of the main areas of research focus at the present time. In the 12 years since the revelation of the connection between AD and FLG deficiency initiated the intense focus on the epidermal barrier, a wide range of studies has provided new reflections on inflammatory and immune pathways, neural interactions, and genetic features that relate to multiple aspects (Blunder et al., 2017; Chen et al., 2017; Miyaj et al., 2016). All of those segments have generated fresh ideas aimed at therapeutic possibilities (Johnston, 2017), and some new and highly beneficial products have begun to enter a realm of much-needed patient care with products for both milder childhood disease and for patients with severe AD.

CONFLICT OF INTEREST
The author states no conflict of interest.

REFERENCES