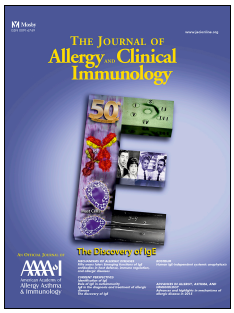
Accepted Manuscript



New pathways for itching in atopic dermatitis?

Jennifer Heimall, MD, Jonathan M. Spergel, MD, PhD

PII: S0091-6749(17)31021-7

DOI: 10.1016/j.jaci.2017.06.004

Reference: YMAI 12886

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 7 April 2017

Revised Date: 31 May 2017

Accepted Date: 5 June 2017

Please cite this article as: Heimall J, Spergel JM, New pathways for itching in atopic dermatitis?, *Journal of Allergy and Clinical Immunology* (2017), doi: 10.1016/j.jaci.2017.06.004.

New pathways for itching in atopic dermatitis?

Jennifer Heimall[1], MD and Jonathan M. Spergel[1], MD, PhD

The Children's Hospital of Philadelphia

[1]Division of Allergy and Immunology

Department of Pediatrics

Perelman School of Medicine at University of Pennsylvania

[*]Correspondence Author:

Jonathan M. Spergel MD, PhD

The Children's Hospital of Philadelphia

Division of Allergy and Immunology

Wood 3552D

3401 Civic Center Boulevard

Philadelphia, PA 19104

spergel@email.chop.edu

Acknowledgements:

JMS is funded by Stuart Starr Endowed Chair, JMS and JH are funded by The Children's Hospital of Philadelphia Funds for Food Allergy Research and Eosinophilic Esophagitis.

Atopic dermatitis has been described as the itch that rashes. Indeed, the itching associated with the condition often considered to be the most challenging features of the disease to control. In addition, itching has been cited as the symptom most associated with impact on quality of life in atopic dermatitis (1). The sensation of itching is mediated by complex signaling from the skin through the dorsal root ganglion to the spine and brain and is mediated by may different neurologically active molecules including substance P. In this issue, the following 3 articles address the potential for novel mechanisms underlying the vexing symptom of itching and demonstrate early proof of concept for novel treatment options. Azimi et al (2) describe the role of Substance P mediated activation of Mas-related G-protein coupled receptors (Mrgprs) in inducing itching in a mouse model, while Cevikbas et al (3) describe a synergistic role for GABA-A and GABA-B agonists for addressing symptoms of itching in murine atopic dermatitis. Finally, Luo et (4) describe the how transient receptor potential vanilloid receptor 4 (TRPV4) contributes to the sensation of itching.

Substance P is known to have an association with mediating the sensation of itching in patients with atopic dermatitis, but the best known receptor family associated with substance P signaling pathways are the neurokinin receptors (NK-1R). NK-1R antagonists have had variable results in controlling itch in humans. In the article by Azimin, it is demonstrated that Substance P can activate Mrgprs as well as neurokinin receptor. Mrgprs are known to be associated with sensory neurons of the dorsal root ganglion, leading to itch and nociception, and in humans are also expressed on mast cells in the form of MRGPRX2. In Mrgprs knock out mice, substance P mediated itching was decreased. The investigators then demonstrated that a Mrgprs antagonist, QWF (antagonist of NK-R1, as well as the murine receptors MrgprB2, MrgprA1), was able to decrease Substance P induced itch, including Substance P induced degranulation from mast cells more effectively than an isolated NK-R1 antagonist in a mouse model. A tissue culture model was used to demonstrate that substance P was able to activate cultured dorsal root ganglia cells from NK-1R knock out mice; this effect was able to be blocked with QWF. Since mouse MrgprA1 is considered equivalent to the human MRGPRX2, it is postulated that MRGPRX2 could be a target for mast cell mediated disease and non-histamine mediated itching. This presents an intriguing therapeutic option to address the troubling itching experienced by atopic dermatitis patients. Although QWF was administered systemically in the reported studies, QWF is known to be rapidly hydrolyzed in plasma, therefore this therapy may be most practical for development as a novel topical agent specifically aimed to reduce itching.

Gamma aminobutyric acid (GABA) inhibitory signaling is a key neurologic pathway that can inhibit sensations of pain and itching. In their work, Cevikbas et al describe a synergistic role for GABA-A and GABA-B agonists, muscimol and baclofen respectively, for addressing symptoms of itching in murine atopic dermatitis. Baclofen is a well-known therapy that is employed for treating pain and spasms in human disease such as multiple sclerosis or spinal cord disease. Due to the inhibitory nature of these therapies, the investigators first performed a titration to establish the dose above which motor coordination was impaired and/or sedation occurred. In the experimental model to determine effect on reducing itching, mice were injected with histamine, followed by sub-sedative doses of baclofen and/or muscimol and itch response was observed. Both drugs were found to have a very narrow therapeutic window. Baclofen was found to have onset of action more than 60 minutes after administration with beneficial effect lasting up to 6 hours, whereas muscimol had more rapid onset of action (within 30 minutes) but shorter duration of effect (less than an hour). Of note there was an observed synergistic effect with ineffective doses of baclofen, when paired with subthreshold muscimol had significant anti-

itch properties. In a second set of experiments described in this same report, sustained GABA mediated inhibition of neuronic signaling (achieved with medial gangiolic eminence transplantation to the spinal cord in this mouse model) decreased itching and decreased number and severity of skin lesions. The authors also found that mRNA gastrin releasing peptide (GRP) was increased in segments of spinal cord associated with affected dermatomes in the IL-31 transgenic mouse model, which led to a conclusion that peripheral IL-31 overexpression leads to spinal cord increased production of SP and GRP and decreases expression of GABA-B1 receptor.

At the level of the skin, in addition to histamine, other mediators contribute to initiating the sensation of itch. The activation of TRPV4, an osmreceptor, was demonstrated to promote 5- Hydroxytryptophan signaling of itch in response to dry skin and allergic triggers. Expression of TRPV4 was found to be expressed in higher concentration in the skin from chronic itch patients. Turning to a mouse model, decreased expression of TRPV4 in keratinocytes led to decreased non-allergic itch sensation, while decreased expression of the same receptor in macrophages led to decreased sensation of allergic itching.

These three studies present novel murine models for the treatment of central and histamine mediated itching that is such a vexing challenge for atopic dermatitis patients. Historically, the management of itching in atopic dermatitis has relied heavily upon the use of antihistamines in conjunction with moisturizers and topical immunomodulators (5). Despite their limited efficacy to actually manage the itching associated with the disease, the side effect of sedation associated with some antihistamines gives some patients enough respite from the itching to allow for sleep. While there is potential for sedation with baclofen and muscimol, this was a side effect specifically selected against in these studies and efficacy in a mouse model was still able to be demonstrated in terms of controlling itching. Similarly, the blockade of substance P signaling through Mrgprs is also a promising therapeutic target. Finally the association of the osmoreceptor TRPV4 with the sensation of itch also illustrates an appealing area for potential clinical application. There is clearly a need for additional studies in human tissue for greater evidence to support proof of concept, followed by clinical trials to establish safety and efficacy and safety of the use of these agents for the systemic treatment of itching associated with atopic dermatitis. These proposed agents join a growing list of therapies, including dupilumab (6) systemically, and topical application of phosphodiesterase 4 inhibitors (7), that have recently been explored for a more targeted approach to treatment of both the inflammation and pruritis associated with atopic dermatitis. These and other new and emerging therapies will have the potential to radically change the paradigm of atopic dermatitis as a skin limited disease with barrier dysfunction to one with components of systemic inflammation and neurologic signaling that can be treated to achieve overall remission of this disease that inflicts misery one so many patients.

1. Drucker AM, Wang AR, Li W, Sevetson E, Block J, Qureshi A. The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. Journal of Investigative Dermatology. Volume 137, Issue 1, January 2017, Pages 26–30
2. Azimi E, Reddy VB, Pereira PJ et all. Substance P actives Mas-related G-protein coupled receptors to induce itch. JACI 2017 in press
3. Cevikbas F, Braz JM, Wang X, et all. Synergistic antipruritic effects of GABA-A and GABA-B agonists in a mouse model of atopic dermatitis. JACI 2017 in press
4. Luo J, Feng J, Yu G, et al. TRPV4-expressing Macrophages and Keratinocytes Contribute Differentially to Allergic and Non-allergic Chronic Itch. JACI 2017 in press

5. Schneider L, Tilles S, Lio P, et al. Atopic dermatitis: a practice parameter update 2012. J Allergy Clin Immunol. 2013 Feb;131(2):295-9.
6. Beck LA, Thac_i D, Hamilton JD et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med 2014; 371:130–139.
7. Furue M, Kitahara Y, Akama H et al. Safety and efficacy of topicalE6005, a phosphodiesterase 4 inhibitor, in Japanese adult patients with atopic dermatitis: results of a randomized, vehicle-controlled, multicenter clinical trial. J Dermatol 2014; 41: 577–585.