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Editorial

Neuroimmune interactions in allergic diseases

In Allergy International Vol. 71, Issue 3, we offer a set of four review articles under the title "Neuroimmune interactions in allergic diseases."

The first two focus on the skin and intestine. Both tissues comprise epithelial barriers to protect body tissue and work as sentinels to detect noxious stimuli and pruritogens. The 2021 Nobel Prize in Physiology or Medicine was awarded to David Julius and Ardem Patapoutian for their discoveries of receptors for temperature and touch. The prototype receptor for nociception, transient receptor potential vanilloid 1 (TRPV1), which reacts to capsaicin stimulus, was found by Julius.¹ Then other receptors were discovered that contribute to detecting noxious stimuli by sensory neurons. Among them, transient receptor ankyrin 1 (TRPA1) responds to chemical stress.² Allergic reaction is triggered and exaggerated by nociception and also by pruriception (sense of itch). Pruriception also uses TRPV1 and TRPA1 receptors to detect itch sensations. Recent studies have shown that some of the type 2 inflammatory cytokines (e.g., IL-4, IL-13, TSLP, and IL-31) also can stimulate itch sensing neurons.³ From the clinical point of view, it is quite important to control itch sensation induced by chronic inflammation. Chronic pruritis negatively affects the quality of life of atopic dermatitis patients. It reduces sleeping quality, and it may induce psychological problems.⁴

Tominaga and Takamori's review article focuses on peripheral itch sensitization in atopic dermatitis.⁵ Detailed molecular mechanisms for so-called "itch-scratch cycles" and modifications by type 2 immune reactions are comprehensively described. In these vicious cycles, signals from TRPV1 and TRPA1 receptors have critical roles. They also stress the importance of skin barrier-neuroimmune triadic connectivity to understand peripheral itch sensitization in atopic dermatitis.

Food allergy is a major health problem with wide prevalence, now increasing in some areas of the globe.⁶ Food allergy is a defense mechanism against harmful substances in food, mediated by neuronal and immune mechanisms. Noxious substances in food can induce expulsion of food by activating chemosensory cells in the gut, including entero-endocrine cells, enterochromaffin cells, and tuft cells. Neuropeptides, eicosanoids, and cytokines produced by chemosensory cells can activate mast cells, as well as innate lymphoid cell type 2 (ILC2).⁷ Kadowaki *et al.* offer an excellent review on neuro-immune crosstalk in the intestine, with special reference to mucosal mast cells and neurons.⁸ They

offer anatomical, physiological, and pathological overviews of the nervous and the immune systems in intestine, using a food allergy mouse model. Interaction between mucosal mast cells and neuronal cells are also described in detail, showing how some of the signaling molecules (CGRP, FcεRI, adenosine) work as key molecules for pathologic process.

The second two focus on interaction between two representative allergy-related immune cells (mast cells, ILC2) and nerve systems.

Toyoshima and Okayama's review articles give us an overview of mast cell/nerve loop cross-talks in allergic inflammations in skin, lung, and intestine tissue.⁹ It should be noted that mast cells are located in the perivascular area and adhere directly to the nerves. Histamine released by mast cells react with nerve fibers via histamine receptors, leading to the release of neuropeptides including substance P and CGRP, which in turn elicit histamine release from mast cells through MrgprB2 (substance P receptor). Irie *et al.* provide us a current overview of the role of neuropeptides in ILC2.¹⁰ ILC2-induced type 2 inflammation is now recognized as an aspect of allergic inflammation in lung, nose, skin, eyes, and intestine. ILC2 expressed β2-adrenergic receptors (β2AR) and β2AR agonist used in asthma treatment inhibit ILC2 proliferation in allergic inflammation. Neuromedin U (NMU) released from cholinergic and sensory nerves, epithelial cells, and immune cells activates ILC2 through the NMU receptor in type 2 inflammation models. Although ILC2 did express a CALCRL/RAMP1 heteromeric receptor for CGRP, the effect of CGRP on ILC2 functions is less clear (it may facilitate or suppress ILC2-mediated type 2 inflammation) and is context dependent.

We hope these special review articles will be useful to clinicians and scientists and ultimately to patients awaiting new therapeutic interventions targeting neuroimmune interactions.

Conflict of interest

The author has no conflict of interest to declare.

Akira Matsuda

Associate Editor, Allergy International

Laboratory of Ocular Atopic Diseases, Juntendo University Graduate School of Medicine, Tokyo, Japan

E-mail address: akimatsu@juntendo.ac.jp

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