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EDITORIAL

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A New Approach for the Classification of Mechanisms of Chronic Spontaneous Urticaria

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Mast cells have the largest receptor repertoire in our body and contain many different inhibitor and activator receptors (1). The most potent activator receptor on mast cells is the high-affinity IgE receptor (FcεRI), of which activation leads to cell degranulation by releasing various mediators such as histamine, PAF, cytokines, leukotrienes, and prostaglandins (2). These mediators cause disease-related symptoms such as itching, swelling, or angioedema.

Chronic spontaneous urticaria (CSU) is no doubt a mast-cell mediated disease (1,3). However, in order to understand the underlying mechanisms of this disease and to optimize the treatment, we believe the existing classification of CSU endotypes need to be revised. Currently, two different autoimmune endotypes that may cause mast cell degranulation in CSU have been demonstrated (4). The type-1 autoimmune (autoallergic) endotype, found in approximately 50% of patients with CSU, is characterized by the formation of IgE antibodies against self-antigens (e.g., IL-24, thyroid peroxidase, dsDNA). In type-2b autoimmune endotype, the formation of autoantibodies mainly in IgG1 or IgG3 structure against FcεRI receptors on mast cells or IgE antibodies bound to these receptors and stimulation of mast cells by these autoantibodies ends up with mast cell degranulation (5). This classification provides a useful framework for understanding the heterogeneous nature of CSU. However, ignoring non-FcεRI-mediated mechanisms leaves this model incomplete.

Omalizumab has been the only targeted therapy option approved for the treatment of CSU for many years and shows its efficacy by binding to free IgE. In this way, it causes FcεRI down-regulation on mast cells in the long term. Although omalizumab has been shown to markedly relieve symptoms of CSU, it is not effective in all patients. Thus, there is an unmet need for more effective treatments; currently multiple different new treatment targets and biologics are under investigation for the treatment of CSU and most of them target molecules other than FcεRI (6). Mast cells have the potential to be stimulated and degranulated by both receptor stimulations other than FcεRI and cell-cell interactions such as eosinophil-mast cell (e.g. stem cell factor ligand and c-kit receptor interaction) or nerve cell-mast cell (e.g., substance P ligand and MRGPRX2 receptor interaction) (1,7). Therefore, it may be a more logical approach to categorize the underlying mechanisms in CSU as FcεRI-mediated and non-FcεRI-mediated as described below instead of type-1 or type-2b only.

Keywords: Chronic spontaneous urticaria, IgE-receptor, FcεRI, endotype

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Proposed underlying mechanisms in CSU

1) FcεRI-mediated mechanisms

- Type-1: Mechanisms triggered by IgEs specific for self-antigens binding to FcεRI and activating downstream pathways.
- Type-2b: Mechanisms triggered by IgG autoantibodies binding to FcεRI or FcεRI-bound IgE, and activating downstream pathways.

2) Non-FcεRI-mediated mechanisms

- MRGPRX2 receptor: Mechanisms mostly associated with neuropeptides (e.g., substance P) and neuroinflammation.
- Alarmin receptors: Pathways affected by TSLP, IL-33 and IL-25.
- Cytokine receptors: Pathways affected by IL-4, IL-5, IL-17.
- Complement and other receptors: Pathways affected by C5aR, PAR2 and CysLT1.

A broader classification of the mechanisms of CSU may better explain both the pathophysiology and therapeutic approaches. Although the proposed classification system is based on some recent findings in the literature (like the potential role of MRGPRX2 in the pathogenesis of CSU has been better understood in recent years) (8), further studies are needed on how to detect non-FcεRI mechanisms in clinical practice and how to optimize them as therapeutic targets. The lack of markers reflecting non-FcεRI pathways leads to the under-recognition of these pathways in clinical classification and treatment targets. The heterogeneous nature of CSU necessitates a broader consideration of mechanisms. The proposed classification based on FcεRI and non-FcεRI mechanisms provides an opportunity to better understand the pathophysiology of this disease and optimize treatment strategies. However, it is essential to accelerate biomarker development to support the applicability of the proposed classification in clinical practice. This classification might both guide the decision-making processes of clinicians and guide future research in the field of CSU.

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