Synopsis of Original Research Paper

Development of a screening method for the identification of molecules that can induce pseudo-allergy in skin

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Recently, it was reported that many cationic drugs (e.g., antibiotics) directly activate connective tissue mast cells, which leads to drug-induced pseudo-allergy via Mas-related G-protein coupled receptor X2 (MRGPRX2) in humans and Mrgprb2 in mice. On the other hand, a variety of cationic peptides/proteins (e.g., host defense peptides and neuropeptides) have been identified as endogenous ligands of MRGPRX2/Mrgprb2. Of these, many show a significantly lower EC50 against MRGPRX2 than against Mrgprb2. Accordingly, we hypothesize that unknown cationic molecules contained in cosmetics or foreign matters which can come into contact with skin could activate connective tissue mast cells via MRGPRX2, resulting in skin pseudo-allergy. The objective of the current study is to develop a screening method for the identification of molecules that can induce pseudo-allergy in skin. For this end, we used newly-bred MRGPRX2 knock-in (MRGPRX2-KI) and Mrgprb2 knock-out (Mrgprb2-KO) mice as well as wild-type (WT) mice. We found that peritoneal mast cells from WT and MRGPEX2-KI mice, but not from Mrgprb2-KO mice, degranulated in response to stimulation with compound 48/80, a known MRGPRX2/Mrgprb2 ligand, although MRGPEX2-KI mast cells more strongly activated than WT mast cells. In addition, WT and MRGPEX2-KI mice, but not Mrgprb2-KO mice, exhibited skin pseudo-allergic reactions in response to intradermal injection of compound 48/80. Moreover, skin pseudo-allergic reactions were stronger in MRGPRX2-KI mice than in WT mice. Thus, we were able to develop both *in vitro* and *in vivo* methods to identify MRGPRX2 ligands, which will help uncover the molecular mechanisms underlying skin pseudo-allergy and test the safety of cosmetics and therapeutic drugs.