

The mechanisms of production and action of omega-3-derived fatty acid mediators regulating skin allergy

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Allergic diseases such as atopic dermatitis and asthma are becoming very common in developed countries. Allergy is associated with increased serum IgE levels and mast cell activation. Association of an antigen with IgE on the mast cell surface causes cross-linking of the high-affinity IgE receptor (FcεRI), leading to exocytosis of granule-associated mediators and proteases (degranulation) as well as new synthesis of cytokines and lipid mediators. Therefore, uncovering molecular mechanisms that regulate mast cell activation could provide crucial insights into the pathophysiology of mast cell-associated diseases. We recently found that omega-3 fatty acid epoxides are produced in mast cells dependently of PAF-AH (II), an oxidized phospholipid-selective phospholipase A2 and are critical for proper IgE-mediated mast cell activation. In this study, we demonstrated that PAF-AH (II) preferentially hydrolyzed omega-3 epoxide-containing phospholipids in mast cell membrane to liberate omega-3 epoxides. We also identified Cyp4a12a and Cyp4a12b as enzymes involved in the epoxidation of omega-3 fatty acids in mast cells. We further revealed that the omega-3 epoxides promoted IgE-mediated activation of mast cells by downregulating Srcin1, a Src-inhibitory protein that counteracts FcεRI signaling. Thus, the Cyp4a12-PAF-AH (II)-omega-3 epoxide-Srcin1 axis presents new potential drug targets for allergic diseases.