Epidermal phospholipase A₂–driven lipid metabolism regulates skin barrier homeostasis and atopic dermatitis

Yoshitaka Taketomi

Department of Biochemistry and Molecular Biology, Graduate School of Medicine, The University of Tokyo

Epidermal lipids are important for skin homeostasis. However, the overall view of the roles of lipids, particularly nonceramide lipid species, in epidermal biology still remain obscure. Here we show that epidermal sPLA₂ (Ep-PLA₂), a functionally phospholipase A₂ expressed in the stratum granulosum of the mouse and human epidermis, regulates epidermal permeability barrier homeostasis and protects against atopic dermatitis through mobilization of polyunsaturated fatty acids (PUFAs). In a survey of knockout mouse lines of the various PLA enzymes, global and keratinocyte-selective Ep-PLA₂ knockout mice has a defect of the epidermal barrier, due to reduced synthesis of natural moisturizing factor, combined with abnormal type 2 immune responses and showed exacerbated antigen-induced atopic dermatitis. Primary keratinocytes from Ep-PLA₂-null mice had signs of aberrant cell proliferation, differentiation, and activation in association with skin barrier defect. Several screening approaches by lipidomics analysis of mouse skin, phenotypic analyses of mouse lines deficient in various lipid receptors and biosynthetic enzymes, and gene expression profiling in keratinocytes revealed that Ep-PLA₂ is coupled with the production of a large pool of cutaneous PUFA-derived lipid mediators. The constitutive levels of PUFAs and their metabolites in the skin were lower in Ep-PLA₂-null than in wild-type mice. Actually, an abnormality in epidermal permeability barrier observed in mice lacking Ep-PLA₂ were phenocopied in lipid X receptor-deficient mice. The expression of Ep-PLA₂ and the lipid receptor are upregulated during keratinocyte differentiation. Treatment with the lipid receptor agonist restored defective differentiation and/or activation of Ep-PLA₂-null keratinocytes. In human atopic dermatitis lesions, the expression levels of Ep-PLA₂ was inversely correlated with the severity of atopic dermatitis. Thus, our results underscore a previous unrecognized role of nonceramide lipid species in skin allergy, and the novel role of a particular Ep-PLA₂-driven lipid metabolism in epidermis.