Synopsis of Original Research Paper

Elucidation of mechanism of skin homeostasis and disease regulation by plasmalogen-type lysophospholipid pathway

Kei Yamamoto

Division of Bioscience and Bioindustry, Graduate School of Technology, Industrial and Social Sciences, Tokushima University

Epidermal lipids play important roles in skin homeostasis and diseases. We herein report that lysoplasmalogen (P-LPE), preferentially produced by group IIF secreted phospholipase A_2 (sPLA$_2$-IIF; an "epidermal sPLA$_2$") that is expressed in the suprabasal epidermis, promotes epidermal hyperplasia. In both mice and humans, the expression of sPLA$_2$-IIF is increased in inflamed skin in correlation with that of several inflammatory markers such as *S100A9* and TNF. *Pla2g2f* $^{-/-}$ mice had a fragile stratum corneum and were strikingly protected against psoriasis, atopic dermatitis. Conversely, global and keratinocyte-specific *Pla2g2f*-transgenic mice developed psoriasis-like epidermal hyperplasia spontaneously. Primary keratinocytes from *Pla2g2f* $^{-/-}$ mice showed defective differentiation and activation. sPLA$_2$-IIF was induced by calcium or Th17 cytokines (IL-17A and IL-22) in keratinocytes and preferentially hydrolyzed ethanolamine plasmalogen secreted from keratinocytes to give rise to P-LPE. Treatment with P-LPE restored defective activation of *Pla2g2f* $^{-/-}$ keratinocytes both *in vitro* and *in vivo*, while forcible degradation of P-LPE by topical application of recombinant lysophospholipase D from *Thermocrispum*, a lysoplasmalogen-specific hydrolase, prevented psoriasis and atopic dermatitis by in wild-type skin. Moreover, P-LPE markedly facilitated upward proliferation and differentiation of human primary keratinocytes in three-dimensional culture. Diagnostically, the increase of several P-LPE species, but not other lysophospholipids, was readily detectable in the tape-stripped stratum cormeum obtained from psoriatic and atopic skins. Overall, our results highlight P-LPE as a previously unrecognized bioactive lysophospholipid and point to the sPLA$_2$-IIF/P-LPE axis as a novel drug or biomarker target for psoriasis and atopic dermatitis and possibly other epidermal-hyperplasic diseases.