Synopsis of Original Research Paper

Expression, functions, and lipid metabolomics of phospholipase A_2 enzymes in the skin.

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Phospholipase A_2 (PLA_2) enzymes catalyze the hydrolysis of glycerophospholipids to fatty acids and lysophospholipids and have been implicated in a wide variety of biological events. Of more than 30 PLA_2 enzymes identified in mammals, the secreted PLA_2 ($sPLA_2$) family contains 10 catalytically active enzymes (IB, IIA, IIC, IID, IIE, IIF, III, V, X, and XIIA). Although $sPLA_2$s have been implicated in various biological events such as gastrointestinal phospholipid digestion, inflammation, host defense and atherosclerosis, precise functions of individual $sPLA_2$s remain largely unknown. In an effort to elucidate the possible in vivo functions of $sPLA_2$s, we generated transgenic mice that overexpressed individual $sPLA_2$ isozymes. We found that transgenic mice overexpressing group X $sPLA_2$ under the control of the β-actin promoter displayed notable skin abnormalities characterized by alopecia, epidermal hyperplasia, hyperkeratosis and sebaceous gland hyperplasia during a period corresponding to the late stage of the initial hair cycle. However, endogenous expression of group X $sPLA_2$ was rather low and confined only to hair follicles entering the anagen phase in wild-type mouse skin. Moreover, K14 promoter-directed, skin-specific transgenic overexpression of group X $sPLA_2$ did not cause skin defects, suggesting that the epidermal abnormality resulting from overexpression of group X transgenic mice in the whole body might result from a secondary effect and not reflect the intrinsic function of this enzyme. We found that another $sPLA_2$ with unknown function, group IIF $sPLA_2$, was highly expressed in the epidermis of wild-type mice and that its expression was markedly elevated in the thickened epidermis of group X $sPLA_2$ transgenic mice, of TPA-treated wild-type mice, and of patients with skin disorders harboring epidermal hyperplasia. Notably, transgenic overexpression of group IIF $sPLA_2$ under either the β-actin or the K14 promoter led to marked skin abnormalities. The alopecic skins of group IIF and X $sPLA_2$ transgenic mice displayed an identical gene expression profile, with increased expression of genes related to terminal differentiation of epidermis and sebaceous glands as well as reduced expression of genes related to hair development. Lipid mass spectrometry revealed that group IIF $sPLA_2$ hydrolyzed particular phosphatidylethanolamine molecular species containing docosahexaenoic acid, which was further converted to the docosanoid protectin D1, in the transgenic skin. These results underscore an unexplored aspect of group IIF $sPLA_2$ as an epidermal $sPLA_2$ participating in skin biology and also suggest that protectin D1, a major group IIF $sPLA_2$ product, is a novel regulator of epidermal homeostasis and pathogenesis.