

Aberrant metabolism of epidermal barrier lipids causes inflammation

Tetsuya Hirabayashi

Tokyo Metropolitan Institute of Medical Science

Epidermal lipids play an essential role for skin barrier function. Especially, the linoleate-containing ω -O-acylceramide is required for formation of both corneocyte lipid envelope (CLE) and the long periodicity phase with a repeat distance of ~13 nm present in the intercellular multilamellar lipid layers of the stratum corneum. Disturbances in epidermal ceramide metabolism contribute to dry sensitive skin, dermatitis, atopic dermatitis, and ichthyosis, but how they affect skin conditions including inflammation is not yet fully understood. In the process of identifying PNPLA1 as an enzyme responsible for ω -O-acylceramide biosynthesis, and SDR9C7 as a dehydrogenase essential for the formation of CLE, we noticed that keratinocyte activation and induced expression of proinflammatory cytokines and chemokines occur only in mice lacking the former, even though both knockout mice are models for congenital ichthyosis with significantly reduced permeability barrier function. This implies that impaired permeability barrier function does not necessarily lead to the induction of inflammatory responses, suggesting the existence of a mechanism that induces activation of keratinocytes and resident immune cells such as Langerhans cells in response to specific metabolic abnormalities of barrier lipids. In this study, we sought to identify metabolic abnormalities of epidermal barrier lipids that trigger proinflammatory responses and to elucidate the molecular mechanisms by which immune cells are activated in recognition of these metabolic abnormalities. ω -Hydroxyceramide, a precursor for ω -O-acylceramide biosynthesis, was accumulated in the epidermis of *Pnplal*-deficient mice, and stimulated the keratinocyte expression of BMP7 and GM-CSF, which can facilitate the maturation and activation of epidermal Langerhans cells, consequently initiating inflammatory responses. Our findings can be applied to new skin care strategies to maintain beautiful skin by retaining moisture, strengthening barrier function and preventing from inflammation, thereby contributing to further advances in cosmetology.