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〈シンポジウム II〉

『香粧品の『未来に続く最先端科学』』

オートファジー関連分子による皮膚上皮細胞の分化調節・形態維持

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Roles of Autophagy-Related Gene in Differentiation and Maintenance of Epidermis

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Abstract

The skin epidermis is a stratified epithelium. Recent studies have clarified a numerous number of molecules involved in epidermal development, although it remains elusive how these molecules are coordinated to undergo proper stratification of the epidermis. Autophagy, a lysosomal degradation pathway, is involved in differentiation of erythrocytes, lymphocytes, and adipocytes. Keratinocyte differentiation is also going along with activation of lysosomal enzymes and organelle clearance, expecting the contribution of autophagy in this process. Previously, we show multiple roles of Notch signaling in the regulation of transit amplifying cells in epidermal layers. Notch signaling induces differentiation of suprabasal cells *via* Hes1 independent manner, whereas Hes1 is required for maintenance of the immature status of suprabasal cells by preventing premature differentiation. In this study, we found that Hes1 directly suppressed the expression of Bnip3, whose expression is sufficient to induce terminal differentiation of keratinocytes by induction of autophagy. We found that HES1 could directly bind to *BNIP3* promoter to suppress the expression. BNIP3 was expressed in the granular layers, just above the layers where Hes1 expression was observed. Consistent with the BNIP3 expression, autophagosome formation was observed in the granular layer of the epidermis. Forced expression of BNIP3 in human primary epidermal keratinocytes（HPEK）resulted in induction of autophagy and mitophagy, followed by keratinocyte differentiation. Intriguingly, addition of an inhibitor of autophagy significantly suppressed the BNIP3-stimulated differentiation of keratinocytes. These data clearly indicate that BNIP3 plays a crucial role in keratinocytes differentiation by inducing autophagy. Furthermore, we also found that suppression of BNIP3 expression induced by UVB irradiation caused a further increase of the cleaved caspase3 protein level, suggesting that BNIP3 also has a protective effect against UVB-induced apoptosis in keratinocytes. Overall, our data shed light on functions of BNIP3, regulated by Notch signaling, in both differentiation and maintenance of epidermal keratinocytes.

Key words: autophagy, apoptosis, differentiation, stress response, Notch signal.