

〈シンポジウム I〉

『環境と皮膚免疫』

フィラグリンと皮膚バリア機能

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Filaggrin and Skin Barrier Function

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Abstract

Research in atopic dermatitis (AD) has gained huge momentum after the finding that mutations in filaggrin gene are major predisposing factors. Filaggrin is a structural protein of stratum corneum (SC) and its breakdown products form natural moisturizing factor (NMF). Accumulating reports suggest that filaggrin contributes skin barrier formation, but the precise mechanisms remain unclear. We generated filaggrin knockout (KO) mice to evaluate the impact of filaggrin deficiency on skin barrier function. Filaggrin KO mice exhibited dry and scaly skin, but did not develop any spontaneous dermatitis. Despite of prominent decrease in NMF, water content and transepidermal water loss (TEWL) in SC of filaggrin KO mice was unaffected. Permeability assay using calcein-encapsulating liposomes demonstrated that filaggrin-deficiency allows its penetration through SC. Barrier defect in filaggrin KO mice led to enhanced hapten-induced contact hypersensitivity responses and humoral responses to topically immunized protein antigens. Our filaggrin KO mice will provide a valuable tool to dissect the function of SC, especially in the context of AD. The mammalian skin has another epidermal barrier, tight junctions (TJs). It has been long believed that epidermal Langerhans cells (LCs) acquire foreign antigens encountered in skin, but how such antigens penetrate the epidermal barriers was completely unknown. Using 3D visualization method of epidermal TJs in mouse ear skin, we investigated the behavior of LC dendrites in relation to TJs. In resting state, LCs projected their dendrites upward to the skin surface but stopped short of TJs. Surprisingly, once activated by tape stripping or intra-dermal injection of IL-1 β or TNF α , elongated LC dendrites docked with TJs, and sometimes penetrated through, to reach to the SC. When a protein biotinylation reagent was topically applied on the skin, the endocytic activity was demonstrated to take place at the dendrite tip. Of note, TJ formation was observed between LC dendrites and surrounding keratinocytes. These findings will provide a new fundamental framework for the immunological behavior of dendritic cells at the body surface.

Key words: stratum corneum, filaggrin, skin barrier, tight junction.