26.Primary ceramide deficiency in keratinocytes leads to gene alterations linked to dermatitis

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Impaired skin barrier is associated with inflammatory skin disorders including atopic dermatitis (AD). We have studied the role of epidermal ceramide by using keratinocytes-specific Sptlc deficient mice (K5.SPT-KO mice), which lack serine palmytoltransferase (SPT), a rate-limiting enzyme for ceramide biosynthesis. K5.SPT-KO mice exhibited barrier disruption from two weeks of age and developed skin lesions with hyperkeratosis, epidermal hyperplasia, and dermal infiltration. To examine whether ceramide deficiency itself affected gene expression within keratinocytes, we performed an array analysis on primary cultured keratinocytes of newborn K5.SPT-KO mice. Transcriptional profiling revealed that increased expression of thymic stromal lymphopoietin (TSLP, ration=4.2), amphiregulin (Areg, 3.2), and aqaporin 3 (AQP3, 3.0). Interestingly, these three molecules are associated with the pathogenesis of AD. Since no skin lesion expect for skin dehydration was found in newborn KO mice, the up-regulation of these genes in keratinocytes was primary consequences of constitutive ceramide deficiency. AQP3, AR and TSLP were increased in the lesional skin of K5.SPT KO mice. Langerhans cells (LCs) in the epidermis of K5.SPT KO mice appeared mature and increased numbers of langerin+dendritic cells were found in the skin-draining lymph nodes of K5.SPT KO mice. This may be consistent with recent notion that local increase of TSLP was directly associated with LC activation. Strikingly, acute barrier disruption by tape stripping led to up-regulation of AQP3, AR and TSLP as well as activation of LCs in hairless mice. We suggested that primary ceramide deficiency in keratinocytes and barrier disruption resulted in increased expression of AQP3, AR, and TSLP, which may contribute to development of atopic dermatitis.