Epidermal Barrier Function Is Impaired in Langerhans Cell-Depleted Mice


TO THE EDITOR

Langerhans cells (LCs) are members of dendritic cell lineage located in the epidermis and are the outermost antigen-presenting cells to encounter pathogens at the skin surface (Merad et al., 2008). The functional role of LCs has been widely studied in the context of immunological settings. It seems that LCs are capable of eliciting both productive immunity and tolerance, depending on the type of immune models tested (Romani et al., 2010). It has been shown that the number of epidermal LCs is reduced in certain skin conditions such as aged skin, UV-irradiated skin (Cerimele et al., 1990), and sarcoidosis (Fox et al., 1983). Those circumstances commonly show the signs of delayed barrier recovery, with impaired epidermal permeability barrier function including xerosis, scale, erythema, and pruritus. Because of the pivotal role of LCs in the inflammatory response of the skin, we assumed that there might be a link between LCs and the permeability barrier function of the skin. Indeed, Proksch et al. (1996) showed that the abrogation of the permeability barrier led to a lower density of LCs than intact barrier (Proksch et al., 1996). Kubo et al. (2009) showed that disruption of the stratum corneum (SC) resulted in LC activation and that activated LCs extended their dendrites through the weakened tight junctions (TJs) and uptake allergens. Although this evidence elegantly showed that dysfunctional epidermal permeability barrier stimulates LCs, there is lack of knowledge about whether LCs regulate epidermal barrier function. In this study, we aimed to test whether epidermal barrier function is impaired in LC-depleted mice. All animal studies were approved by the Department of Laboratory Animal Resources Committee of Yonsei University College of Medicine.

We first examined transepidermal water loss (TEWL), an indicator for epidermal permeability barrier function from wild-type (WT) and human langerin-diphtheria toxin (DT) active subunit A (HuLang-DTA) transgenic mice, which selectively lack epidermal LCs (Kaplan et al., 2005; Lee et al., 2018). Tape stripping did not induce a difference in clinical erythema between WT and HuLang-DTA mice (data not shown). HuLang-DTA mice showed significantly increased levels of TEWL, both at baseline and after 6 hours of recovery from acute barrier injury (Figure 1a and b). Because HuLang-DTA mice are constitutively devoid of epidermal LCs, which might result in long-term LC-depleted effects, we next tested whether acute LC ablation also imitated barrier dysfunction. Barrier recovery after tape stripping was significantly decreased in Langerin-DT receptor (Lang-DTR) mice at 7 days after DT treatment (when LCs were depleted), and barrier recovery at 14 days after DT treatment (when LCs were recovered) was comparable (Figure 1a and b). Because HuLang-DTA mice showed a significantly increased level of surface pH (Elias and Wakefield, 2014; Enjoji et al., 2014; Hachem et al., 2006). We found that LC-deficient epidermis had an increased expression of PAR2 compared with WT epidermis (Figure 1f and g). Because one of the key mechanisms for PAR2 activation is increased protease activity of kallikreins mediated by the elevated level of SC pH (Elias and Wakefield, 2014), we next measured SC surface pH. The SC of HuLang-DTA mice showed a significantly increased level of surface pH compared with WT mice (Figure 1h). Consequently, the gene expression level of Tslp, a downstream target of activated PAR2, was significantly increased in LC-deficient skins. However, gene expressions of Klk5 and Klk7 were comparable between the skin of WT and HuLang-DTA mice (Figure 1i, Supplementary Table S1 online).

Because HuLang-DTA mice showed a delayed permeability barrier recovery after acute barrier injury, we examined epidermal differentiation recovery in this process. Six hours after tape stripping, recovery of the expression of the epidermal differentiation marker filaggrin was significantly attenuated in HuLang-DTA mice compared with WT (Figure 2a). In addition, the thickness of the cornified envelope is significantly decreased in...
HuLang-DTA mice compared with that of WT mice at 6 hours after tape stripping (Figure 2b). Maintenance of high extracellular concentration of calcium in the granular layer is essential to the initial trigger of barrier recovery after perturbation (Elias and Wakefield, 2014). Electron microscopy study showed that the granular layer in HuLang-DTA epidermis had significantly decreased baseline calcium level compared with that in WT mice (Figure 2c). Although WT mice showed a rapid recovery of calcium gradient within 6 hours after barrier injury, HuLang-DTA mice did not show significant calcium deposition in the granular layer.
Moreover, HuLang-DTA mice had an increased density of LBs compared with WT mice at baseline and at 6 hours after tape stripping (Figure 2c).

Although several reports have shown that barrier disruption can induce functional maturation of LCs and trigger adaptive immunity, it has not been investigated so far whether LCs inversely control epidermal barrier functions. Disruption of the permeability barrier stimulates a homeostatic repair response in the underlying viable epidermis that leads to a rapid restoration of permeability barrier function (Proksch et al., 1993). Based on our results, we found that LCs have a potential role in maintaining and recovering epidermal barrier integrity.

However, further studies are definitely needed regarding whether and how epidermal barrier functions are directly or indirectly regulated by LCs, which belong to an immunological barrier component of the skin. Future strategies to enhance the number and/or function of LCs would be novel approaches for restoring barrier function in diverse barrier-related skin conditions.
Development of a Pigmented Facial Lesion Scale Based on Darkness and Extent of Lesions in Older Veterans


TO THE EDITOR

Pigmented facial lesions (PFLs), including ephelides, pigmented actinic keratoses, seborrheic keratoses, and solar lentigines, are often perceived as a sign of photoaging and can increase in darkness and extent with sun exposure. Although benign, patients often seek treatment for these lesions due to their undesirable appearance. Topical medications, liquid nitrogen, chemical peels, and laser or light-based devices can all be used to clinically lighten these lesions.

Although several validated grading scales exist for photoaging, the majority of these focus on a global photoaging score, such as the Griffiths scale (Griffiths et al., 1992). Scales specific to facial rhytides also exist, where the majority of scored participants were middle-aged and female (Carruthers et al., 2008a, 2008b, 2008c; Carruthers et al., 2016a, 2016b). There remains a lack of validated scales to evaluate the darkness and extent of facial pigmented lesions, particularly in older male participants. Prior studies examining the role of topical tretinoin in fading facial pigmented lesions used non-validated scales (Rafal et al., 1992). Studies of laser treatment of facial pigmented lesions also use non-validated scales (Imhof et al., 2016). Thus, this study aims to develop and validate a facial pigmented lesion scale using data from 4 of the 12 participating VA Keratinocyte Carcinoma (VAKCC) trial sites. These sites were chosen because, unlike at the other eight sites, actinic keratoses (AKs) were clinically marked and photographed by board-certified dermatologists at each study visit. There were 348 participants enrolled at baseline, of which 206 either lacked solar lentigines or demonstrated numerous papular seborrheic keratoses. Of the remaining 124 participants...