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Article

Critical Role for Mast Cell Stat5 Activity in Skin Inflammation

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SUMMARY

Atopic dermatitis (AD) is a chronic inflammatory skin disease. Here, we show that phospholipase C-β3 (PLC-β3)-deficient mice spontaneously develop AD-like skin lesions and more severe allergen-induced dermatitis than wild-type mice. Mast cells were required for both AD models and remarkably increased in the skin of *Plcb3*$^{-/-}$ mice because of the increased Stat5 and reduced SHP-1 activities. Mast cell-specific deletion of *Stat5* gene ameliorated allergen-induced dermatitis, whereas that of *Shp1* gene encoding Stat5-inactivating SHP-1 exacerbated it. PLC-β3 regulates the expression of periostin in fibroblasts and TSLP in keratinocytes, two proteins critically involved in AD pathogenesis. Furthermore, polymorphisms in *PLCB3*, *SHP1*, *STAT5A*, and *STAT5B* genes were associated with human AD. Mast cell expression of PLC-β3 was inversely correlated with that of phospho-STAT5, and increased mast cells with high levels of phospho-STAT5 were found in lesional skin of some AD patients. Therefore, STAT5 regulatory mechanisms in mast cells are important for AD pathogenesis.

INTRODUCTION

Atopic dermatitis (AD) is a chronic or chronically relapsing inflammatory skin disease. Although the etiology of AD is not completely understood, numerous studies suggest that immune dysregulation and impaired skin barrier function underlie the disease (Bieber, 2008; Boguniewicz and Leung, 2011). Epidermal overexpression of thymic stromal lymphopoietin (TSLP), a T_H2-promoting cytokine (Liu, 2006; Ziegler and Artis, 2010), seems to be a major mechanism for AD development (Li et al., 2005; Soumelis et al., 2002; Yoo et al., 2005). Periostin, an α_v integrin-interacting matricellular protein (Hamilton, 2008; Ruan et al., 2009), recently emerged as another mediator for AD that induces TSLP production from keratinocytes (Masuoka et al., 2012). A mouse AD model (Spergel et al., 1998) induced by epicutaneous treatment of ovalbumin revealed the involvement of T_H2, T_H1, and T_H17 cytokines and other factors (Jin et al., 2009a). Another model (Kawakami et al., 2007) induced by allergen (extract of *Dermatophagoides farinae*, Der f) and staphylococcal enterotoxin B (SEB) also showed the requirement of mast cells and T cells as well as TSLP receptor (TSLPR) (Ando et al., 2013).

Phospholipase C (PLC) is a family of enzymes that catalyze the hydrolysis of phosphatidylinositol 4,5-bisphosphate in order to generate diacylglycerol and inositol 1,4,5-trisphosphate (Suh et al., 2008). Independent of its enzymatic activity, PLC-β3 inhibits the proliferation of hematopoietic stem cells (HSCs)

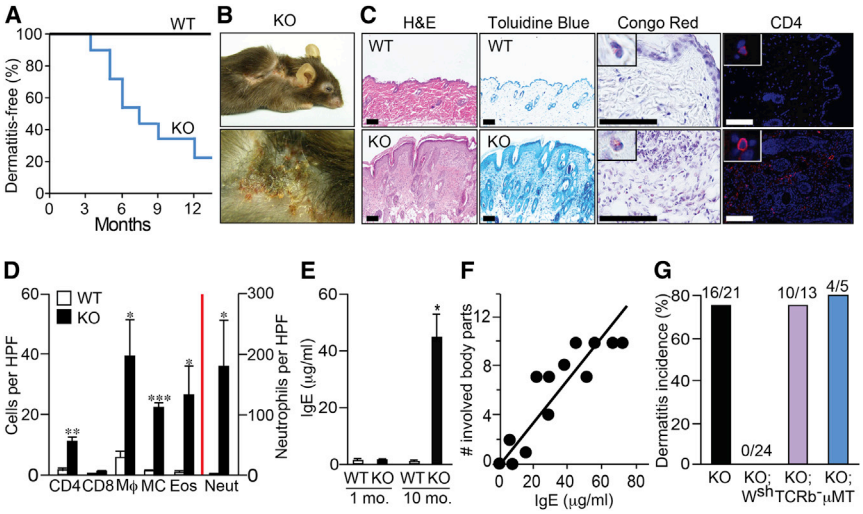

Figure 1. *Plcb3*$^{-/-}$ Mice Spontaneously Develop AD-like Skin Lesions in a Mast Cell-Dependent Manner

(A) Kaplan-Meier plots for dermatitis development in *Plcb3*$^{-/-}$ mice (n = 21).

(B) Note the eczematous skin lesions and hair loss in periocular areas, cheeks, ears, neck, and flanks in a 10-month-old *Plcb3*$^{-/-}$ mouse.

(C) Histology of healthy (WT) and skin lesions (*Plcb3*$^{-/-}$) in ear. Scale bar, 100 μm.

(D) Graphic representation of histological analysis of ear skin lesions of 8- to 10-month-old WT and *Plcb3*$^{-/-}$ mice. Neutrophils (Neut), eosinophils (Eos), and mast cells (MC) were enumerated in H&E-, Congo-red- and Toluidine-blue-stained preparations, respectively. Immunofluorescence staining was performed to detect CD4^{+}, CD8^{+}, and F4/80^{+} (Mϕ) cells. Data represent mean ± SEM. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ versus WT mice by Student's t test. Similar results were obtained in lesional skin in cheeks and neck (data not shown). HPF, high-power field.

(E) Serum IgE levels were increased in 8- to 10-month-old *Plcb3*$^{-/-}$ mice. Data represent mean ± SEM.

(F) Correlation between serum IgE levels and numbers of body parts with skin lesions (see the legend for B for eczematous body parts). $r^2 = 0.78$, $p < 0.0001$, Pearson's correlation.

(G) Incidence of skin lesions in *Plcb3*$^{-/-}$ (KO), *Plcb3*$^{-/-}$;*Kit*$^{W\text{-}sh/W\text{-}sh}$ (KO;W^{sh}), *Plcb3*$^{-/-}$;*TCRb*$^{-/-}$ (*KO;TCRb*$^{-}$) and *Plcb3*$^{-/-}$;*μMT/μMT* (*KO;μMT*) mice for 12 months.

Results in (E) and (F) are representative of two independent experiments using three to six mice per group. See also Figure S1.

and myeloid cells by interacting with SH2-domain-containing protein phosphatase 1 (SHP-1) and signal transducer and activator of transcription 5 (Stat5) and augmenting the dephosphorylating activity of SHP-1 toward Stat5, leading to the inactivation of Stat5 (Xiao et al., 2009).

The present study demonstrated that PLC-β3-deficient mice spontaneously develop AD-like skin lesions. We investigated the cellular and molecular mechanisms for spontaneous and allergen-induced AD-like dermatitis in *Plcb3*$^{-/-}$ mice and their clinical relevance to human AD.

RESULTS

PLC-β3-Deficient Mice Spontaneously Develop Mast Cell-Dependent AD-like Dermatitis

Young (4- to 10-week-old) *Plcb3*$^{-/-}$ mice displayed no obvious abnormalities in their phenotype. By contrast, a majority of older mice developed eczematous skin lesions and hair loss in their periocular areas, cheeks, ears, neck, and trunk (Figures 1A and 1B). The lesions showed hyperkeratosis, thickened epidermis and dermis, and infiltration of T cells, mast cells, macrophages, eosinophils, and neutrophils in the dermis (Figures 1C and 1D). Eczematous *Plcb3*$^{-/-}$ mice had high levels of serum immunoglobulin (Ig) E and IgG1, whereas dermatitis-free young *Plcb3*$^{-/-}$ mice had low IgE levels (Figures 1E and S1A). There was a good correlation between IgE levels and numbers of the involved body parts (Figure 1F). Transepidermal water loss (TEWL) increased only after dermatitis development (Figure S1B), suggesting that skin barrier function was not primarily impaired in *Plcb3*$^{-/-}$ mice.

No *Plcb3*$^{-/-}$;*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice (n = 24) deficient in mast cells developed skin lesions during an observation period of 12 months (Figure 1G). By contrast, skin lesions were observed in a majority of αβ T cell-deficient *Plcb3*$^{-/-}$ (*Plcb3*$^{-/-}$;*TCRb*$^{-/-}$) mice and B cell-deficient *Plcb3*$^{-/-}$;*μMT/μMT* mice. These results suggest that mast cells, but not αβ T or B cells, are indispensable for the spontaneous development of skin lesions in *Plcb3*$^{-/-}$ mice.

Plcb3$^{-/-}$ Mice Develop Severe Allergen-Induced Dermatitis

Der f/SEB-induced dermatitis is dependent on mast cells and T cells, but not B cells or eosinophils (Ando et al., 2013). Epicutaneous treatment with Der f and SEB of young (5- to 11-week-old) *Plcb3*$^{-/-}$ mice, which did not show any skin lesions before experiment, induced more severe skin lesions with thicker epidermis and dermis and higher levels of mast cell and neutrophil infiltration, compared to WT mice (Figures 2A–2E). Although Der f/SEB treatment increased serum levels of IgE and IgG1, some of which recognized Der f antigens, their levels were comparable in WT and *Plcb3*$^{-/-}$ mice (Figures S2A and S2B). As shown previously (Ando et al., 2013), mast cell-deficient *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice showed less severe Der f/SEB-induced skin lesions than did WT mice. Mast cell deficiency also resulted in less severe skin lesions in Der f/SEB-treated *Plcb3*$^{-/-}$;*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice, compared to *Plcb3*$^{-/-}$ mice (Figures 2F and 2G). Moreover, engraftment of *Plcb3*$^{-/-}$ bone-marrow-derived mast cells (BMMCs) into the back skin of *Plcb3*$^{-/-}$;*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice restored the severity of Der f/SEB-induced dermatitis to levels in *Plcb3*$^{-/-}$ mice (Figures 2F–2H). Therefore, similar to spontaneous dermatitis in *Plcb3*$^{-/-}$ mice, mast cells contribute substantially to the development of Der f/SEB-induced dermatitis in these mice. Consistent with increased Der f-specific IgE levels in WT and *Plcb3*$^{-/-}$ mice, FcεRI-deficient mice exhibited

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