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# Phospholipase C epsilon mediates cytokine cascade induced by acute disruption of epidermal permeability barrier in mice

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ABSTRACT

Disruption of epidermal barrier is an important trigger in abnormal cutaneous inflammation. Phospholipase C epsilon (PLCε), a Ras/Rap1 effector, is essential for regulating cytokines production in different types of skin inflammation. Our previous studies have demonstrated that elevated expression of PLCε participates in the psoriasis-like inflammation in PLCε overexpressing transgenic mice model, while the reduction in PLCε expression attenuates inflammatory responses in either TPA- or DNFB-induced cutaneous inflammation. Here, we determined the role of PLCε in cutaneous inflammation induced by acute abrogation of epidermal permeability barrier. In comparison to wild type controls, PLCε KO mice exhibited reduced ear swelling and infiltration of granulocytes after tape-stripping. Moreover, expression levels of pro-inflammatory cytokines (IL-1α, IL-1β), chemokines (CXCL-1, CXCL-2, CCL20), and antimicrobial peptides (S100 proteins, MBD3) were lower in PLCε-deficient versus wild type mice. Likewise, expression levels of cytokines and chemokines were also lower in PLCε deficient keratinocytes and fibroblasts following IL-22 stimulation *in vitro*. Furthermore, knockdown of PLCε with its siRNA decreased expression of IL-1α, CCL20, and S100 proteins, and MBD3 in HEK cultures. Collectively, these results suggested that PLCε mediated cytokine cascade induced by acute barrier disruption. IL-22 is likely the upstream of PLCε-mediated cytokine cascade following acute barrier disruption.

## 1. Introduction

Interleukin (IL)-22, a member of IL-10 superfamily, is involved in the modulation of inflammatory response, immunosurveillance and homeostasis at multiple barrier surfaces [1]. A growing number of evidence suggests that IL-22 participates in skin homeostasis and pathogenesis of various skin diseases, such as psoriasis, atopic dermatitis, and skin cancer [2,3]. The interaction of IL-22 and its receptor IL-22R/IL-10R2 contributes to skin inflammation and immune barrier through modulating the expression of numerous cytokines (IL-1β, TNF-α, IL-6, etc.), chemokines (CXCL-1, CXCL-2, CXCL-5, CXCL-8, etc.), and antimicrobial peptides (S100A family genes, beta-defensin family genes, etc.) [4–6]. These molecules are responsible for recruitment of immune cells to inflammatory site, and innate immune response to pathogen invasion [7]. An aberrant cascade of proinflammatory factors may directly lead to continuous inflammation process, and can contribute to the development of series of inflammatory diseases, including psoriasis. The receptor of IL-22 is highly expressed in both fibroblasts and keratinocytes, and the signal primarily goes by phosphorylation of activating signal transducer and activator of transcription 3 (STAT3) through JAK/STAT pathway [7].

As a member of the phosphoinositide-specific PLC family that is

*Abbreviations:* PLCε, phospholipase C epsilon; TNF, tumor necrosis factor; TGF, transforming growth factor; K1, keratin 1; FLG, filaggrin; LOR, loricrin; IVL, involucrin; SPT1, serine palmitoyltransferase 1; TLR2, toll like receptor 2; SHH, sonic hedgehog; BMP4, bone morphogenetic protein 4; LHX2, LIM homeobox 2; SOX9, SRY-box 9; K15, keratin 15; CXCL, chemokine (C-X-C motif) ligand; CCL20, chemokine (C–C motif) ligand 20; MBD, murine beta defensin; STAT3, transducer and activator of transcription 3; HEK, human epidermal keratinocytes; PMA, Phorbol-12-myristate-13-acetate.

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regulated by Ras and Rap small GTPase, phospholipase C epsilon (PLCε) mediates diverse signals in the development of skin inflammation. Our previous studies have shown that PLCε has similar regulatory role to IL-22 in inducing cutaneous inflammation. For example, overexpression of epidermal PLCε induces psoriasis-like skin lesion, and increases cytokine expression, including IL-22, while PLCε deficiency decreases inflammatory responses, including decreased a panel of cytokine expression, but not IL-22, and neutrophil infiltration in murine dermatitis models [8–10]. Being interested in the relationship of IL-22 and PLCε, and their role in inflammation, we investigated the role of PLCε in cutaneous inflammatory response to acute barrier disruption and the link between IL-22 and PLCε.

## 2. Material and methods

### 2.1. Animals and acute barrier disruption

Mice with inactivated PLCε allele were established and validated as described previously [11,12]. For acute disruption of the skin barrier, 8-week old PLCε KO and wild type mice were tape-stripped for 3 times with a cellophane tape. Afterward skin samples of 2 $cm^2$ were obtained at the indicated time points for qRT-PCR. According to our prior studies, a minimum of three animals are required to achieve statistical comparison.

All the animals were housed in a pathogen-free animal facility with temperature of 22 ± 1 °C, relative humidity of 50 ± 1% and a light/dark cycle of 12/12 h. All animals had free access to regular solid chow and drinking water. All animal studies (including the mice euthanasia procedure) were done in compliance with the regulations and guidelines of Tianjin Medical University institutional animal care and conducted according to the AAALAC and the IACUC guidelines.

### 2.2. Histology

The skin samples were obtained from the ears 24 and 48 h after tape-stripping, and fixed in 4% PFA for H&E staining, as described previously [13].

### 2.3. Isolation, culture, and stimulation of mouse fibroblasts and keratinocytes

Primary dermal fibroblasts and epidermal keratinocytes were isolated from new born PLCε KO and wild type mice, and cultured as described previously [9]. Both fibroblasts and keratinocytes were stimulated with IL-22 (50 ng/ml, 582-ML/CF, R&D Systems) for 0, 3, 6, 12, 24 h, followed by harvest of cells for qRT-PCR analysis.

### 2.4. Culture, silencing and stimulation of human epidermal keratinocytes

Primary human epidermal keratinocytes (HEK) were purchased from Lifeline Cell Technology in America and cultured in Defined Keratinocyte-SFM supplemented with growth factors (Lifeline, MD, USA). HEK were transfected with PLCε siRNA (Santa Cruz Biotechnology, CA, USA) using previously described approach [13]. Cells were stimulated with medium containing IL-22 (10 ng/ml, 782-82-ML/CF, R&D Systems).

### 2.5. qRT-PCR analysis

Total RNA was isolated from excised tissue and cells using Trizol reagent (Invitrogen, Carlsbad, CA) and RNeasy Mini kit (Qiagen, Duesseldorf, Germany), following the manufacturer's instructions. cDNA synthesis was performed with TaqMan Reverse Transcription kit (Applied Biosystems, CA, USA). The qRT-PCR was performed with 7500 Real-Time PCR system. Relative mRNA levels of each sample were determined by the ΔΔCt method with GAPDH. Primers are listed in Supplementary Table 1.

### 2.6. Statistical analyses

Data were presented as means ± SD. One-tailed Student's t-test was performed for determination of *P* values. *P* value $< 0.05$ was considered statistically significant.

## 3. Results

### 3.1. Ablation of PLCε decreases skin inflammation induced by acute disruption of epidermal permeability barrier

Our prior study showed that PLCε ablation suppresses skin inflammatory response in various dermatitis models [8,9,14]. To explore whether PLCε is also involved in the inflammatory response to disruption of the skin barrier, first we compared the inflammatory reactions by H&E staining. As shown in Fig. 1, the ears of PLCε KO mice displayed moderate swelling and less granulocyte infiltration compared to wild type controls both 24 h and 48 h after tape-stripping. We further examined the inflammatory cytokine, proliferation and differentiation factor, antimicrobial peptide levels in the whole skin of PLCε KO and CON mice after acute disruption of epidermal permeability barrier (Fig. 2a and b). In parallel, expression levels of mRNA for a number of inflammatory cytokines and chemokines were lower in the whole skin of PLCε KO than in that of wild type mice after acute disruption of epidermal permeability barrier. Notably, expression levels of IL-22 was significantly increased in both PLCε KO and wild type with a PLCε-independent manner after barrier disruption (Fig. 2b). These results indicate that PLCε deficiency reduces inflammatory response to inflammation induced by disruption of epidermal permeability barrier.

### 3.2. IL-22 increases expression levels of cytokines and chemokines in fibroblast and keratinocyte cultures

Because IL-22 is a well-known upstream regulator of cytokine cascade in inflammatory response, we assessed next whether PLCε deficiency-associated reduction in inflammatory response is mediated by IL-22 [1]. Previous study showed that both fibroblasts and keratinocytes are cellular targets for IL-22 [15]. We first evaluated the impact of IL-22 on inflammation in fibroblasts from PLCε KO and wild type mouse skin *in vitro*. Our results showed that IL-22 markedly increased expression levels of mRNA for cytokines, chemokines and antimicrobial peptides in fibroblasts from wild type mice, while minimally increased in fibroblasts from PLCε KO mice (Fig. 3a). These results suggest a crucial role of PLCε in IL-22-induced inflammation in fibroblasts.

Epidermal keratinocytes can also produce and release cytokines in response to various stimuli. Next, we investigated the effect of PLCε in IL-22-induced inflammation in keratinocytes. As shown in Fig. 3b, treatment of keratinocytes with IL-22 increased expression levels of mRNA for cytokines, chemokines and antimicrobial peptide starting as early as 3 h after addition of IL-22 to control keratinocytes. In contrast, IL-22 only induced a minimal increase in expression levels of these mRNA at 12 and 24 h in PLCε KO keratinocytes. These results indicate a requirement of PLCε for IL-22-induced inflammation in keratinocytes.

To further confirm the role of PLCε in IL-22-induced inflammation, we assessed expression levels of mRNA for cytokines and chemokines in HEK transfected with PLCε siRNA, followed IL-22 treatment. As shown in Fig. 3c, expression levels of mRNA for IL-1α, IL-8, and CCL20 were significantly higher in the controls than in HEK-treated with PLCε siRNA 3 h after IL-22 stimulation. In addition, mRNA levels of S100A8, S100A12, and beta-defensin were also higher in the controls than in HEK-treated with PLCε siRNA 12 h after IL-22 stimulation. These results implicated that IL-22-induced productions of pro-inflammatory cytokines, chemokines, and antimicrobial peptides are mediated by PLCε in keratinocytes.

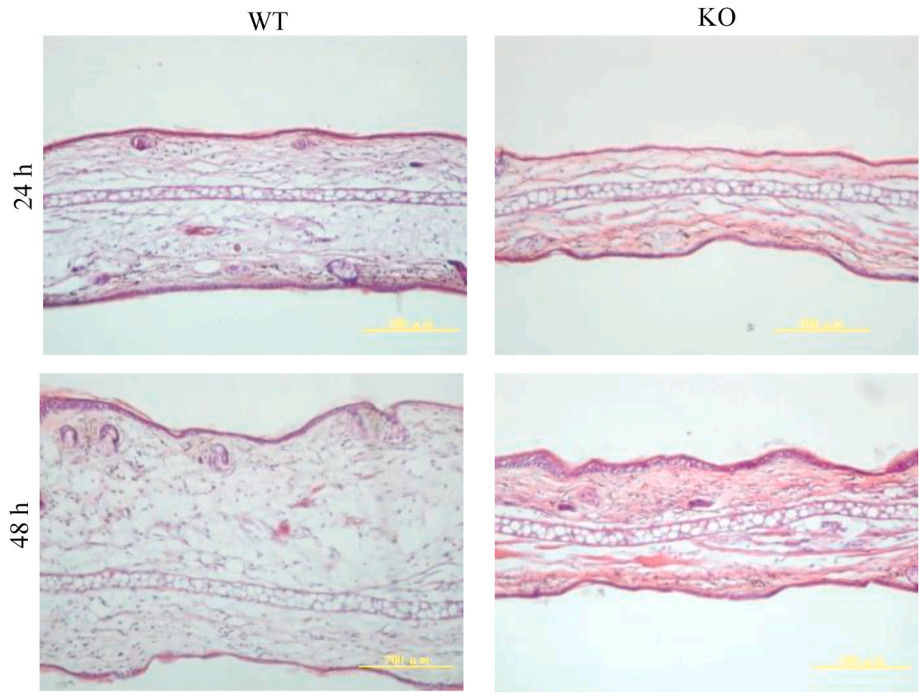


**Fig. 1.** Effects of PLCε on the whole skin after acute barrier disruption. Both PLCε deficient mice and their littermates were tape-stripped for 3 times. Representative H&E staining images of ear skin 24 h and 48 h after tape-stripping (Bars = 200 μm).

a

| KO/CON | 0h | 3h | 6h | 12h | 24h | 48h |
|---|---|---|---|---|---|---|
| TNFα | 1.71 | 0.93 | 0.77 | 0.53 | 0.68 | 0.74 |
| TGFβ1 | 1.07 | 0.56 | 1.67 | 0.91 | 1.17 | 0.18 |
| IL-1α | 0.96 | 0.58 | 1.05 | 0.51 | 0.51 | 0.55 |
| IL-1β | 1.27 | 0.44 | 0.52 | 0.23 | 0.55 | 0.39 |
| IL-6 | 0.53 | 0.81 | 0.94 | 0.71 | 1.14 | 0.67 |
| IL-17 | 0.35 | 0.16 | 1.48 | 1.26 | 2.58 | 1.93 |
| IL-22 | 0.27 | 0.74 | 1.29 | 1.29 | 1.30 | 1.13 |
| IL-23 | 0.66 | 0.48 | 0.84 | 0.75 | 1.43 | 1.19 |
| IL-24 | 0.72 | 0.65 | 1.00 | 1.23 | 0.29 | 0.25 |
| KRT1 | 1.11 | 0.90 | 1.53 | 1.92 | 2.67 | 2.15 |
| FLG | 0.74 | 1.09 | 2.27 | 2.18 | 2.70 | 1.18 |
| LOR | 0.81 | 1.53 | 1.60 | 1.74 | 3.25 | 1.69 |
| IVL | 1.78 | 2.48 | 1.26 | 3.10 | 1.93 | 5.93 |
| SPT1 | 0.26 | 0.72 | 2.76 | 0.88 | 1.17 | 0.83 |
| TLR2 | 0.53 | 0.90 | 2.52 | 1.04 | 1.47 | 2.99 |
| SHH | 1.70 | 0.99 | 1.32 | 0.94 | 1.51 | 0.67 |
| BMP4 | 0.76 | 0.58 | 1.29 | 1.13 | 1.19 | 1.45 |
| LHX2 | 0.48 | 0.50 | 1.14 | 1.03 | 3.50 | 3.02 |
| SOX9 | 0.62 | 0.52 | 1.54 | 1.15 | 1.08 | 1.08 |
| K15 | 0.32 | 1.84 | 1.95 | 0.59 | 0.61 | 0.33 |
| CD34 | 0.52 | 0.41 | 0.66 | 0.56 | 0.90 | 0.52 |
| CXCL1 | 0.62 | 1.04 | 0.97 | 0.27 | 0.19 | 0.31 |
| CXCL2 | 0.70 | 0.62 | 0.93 | 0.61 | 0.20 | 0.20 |
| CCL20 | 0.60 | 0.60 | 1.36 | 0.50 | 0.41 | 2.09 |
| S100A7 | 1.26 | 2.52 | 3.04 | 0.43 | 0.76 | 0.24 |
| S100A8 | 0.65 | 0.72 | 0.91 | 0.26 | 0.72 | 0.34 |
| S100A12 | 0.67 | 0.67 | 0.97 | 1.03 | 0.68 | 0.48 |
| PCNA | 0.44 | 2.72 | 1.27 | 0.63 | 1.71 | 1.18 |
| CylinD1 | 0.91 | 0.81 | 0.94 | 1.79 | 3.84 | 1.43 |
| MBD3 | 1.11 | 0.74 | 2.10 | 1.42 | 1.72 | 0.11 |

0.0 0.5 1.0 2.0

b

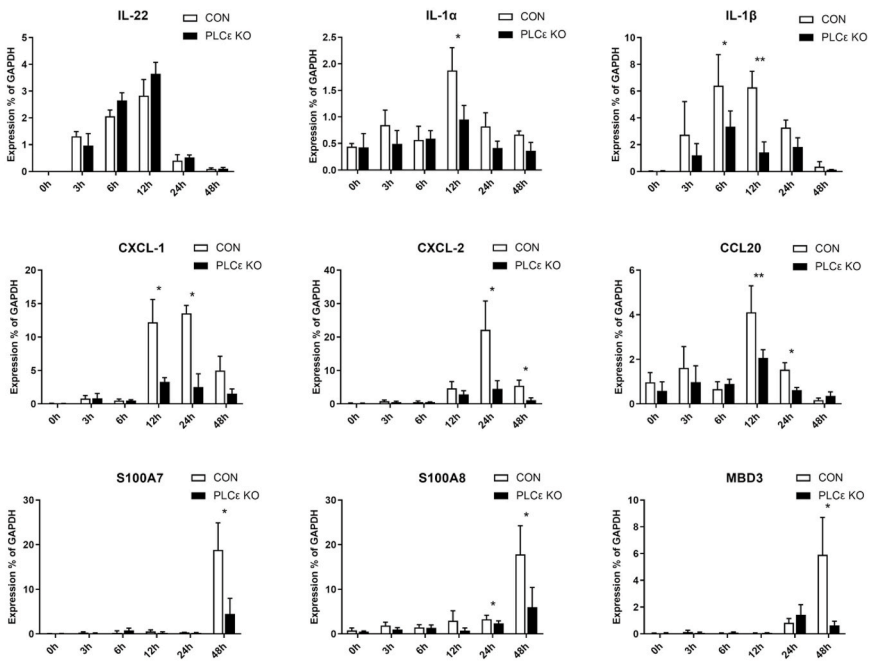


**Fig. 2.** PLCε-KO leads to the abnormal expression of inflammatory Cytokines after acute disruption of epidermal permeability barrier. The mRNA Expression of factors relevant to proliferation, differentiation, inflammation, antimicrobial activity at different time points was detected 0, 3, 6, 12, 24, 48 h after tape stripping. (a) The mRNA levels of the listed genes relative to control GAPDH were measured by qRT-PCR. (b) A detailed expression at different time points for IL-22, IL-1α, IL-1β, CXCL-1, CXCL-2, CCL20, S100A7, S100A8, MBD3. The data are presented as mean ± SD. *$P < 0.05$, **$P < 0.01$.

## 4. Discussion

Regulatory role of epidermal permeability barrier in keratinocyte proliferation, differentiation and antimicrobial peptide production is well appreciated [16]. Disruption of epidermal permeability barrier can provoke cutaneous inflammation, predisposing to the development of

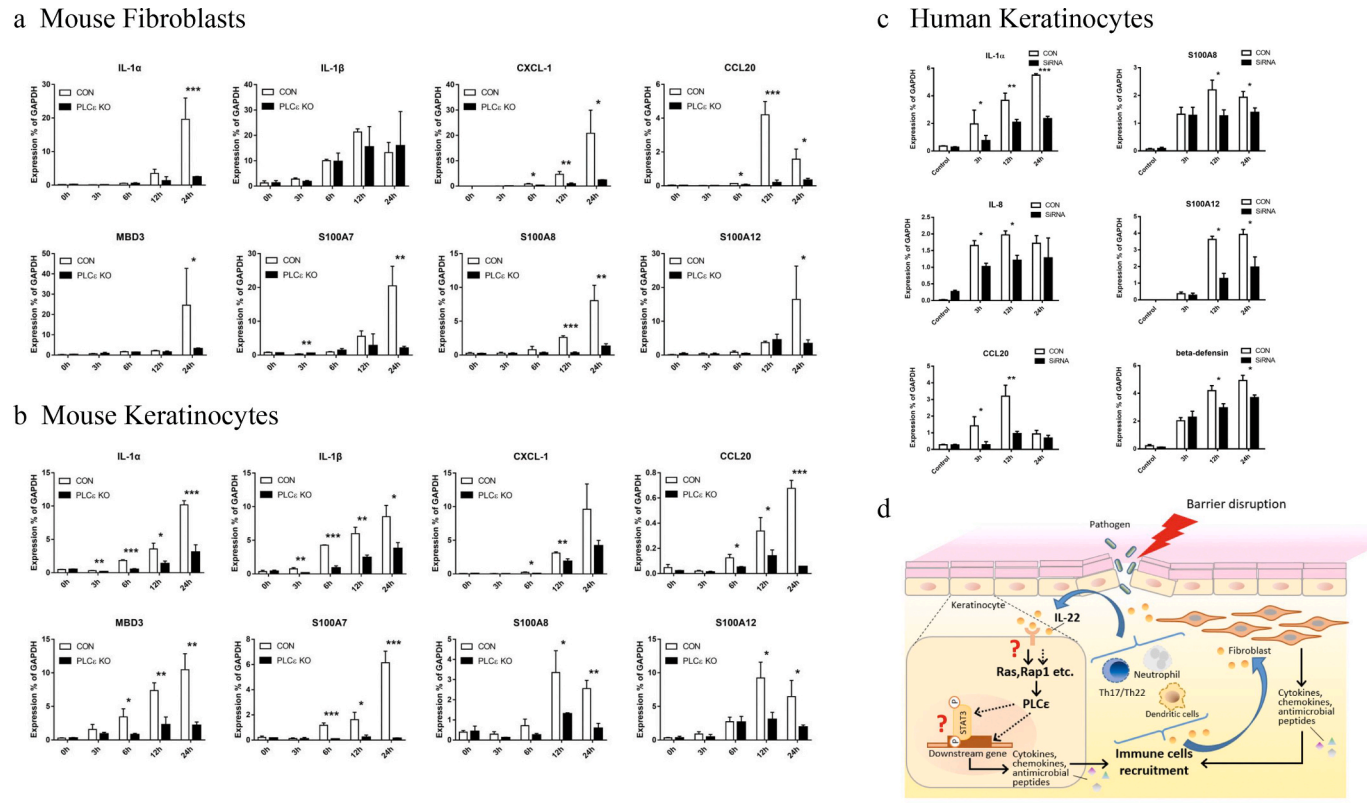


**Fig. 3.** IL-22 induces cytokine cascades in fibroblasts and keratinocytes mediated by PLCε. The mRNA levels of cytokine, chemokines, and antimicrobial peptides induced by IL-22 (50 ng/ml) for 0, 3, 6, 12, 24 h in primary cultured fibroblasts (a) and keratinocytes (b) from newborn PLCε KO and CON mice. (c) HEK were transfected with PLCε siRNA (siRNA) and control siRNA (CON). The mRNA levels of cytokines, chemokines and antimicrobial peptides in HEK 0, 3, 12, 24 h after treatment of IL-22 (10 ng/ml) were detected. The data are presented as mean ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. (d) A model figure of IL-22-induced inflammatory reaction after skin barrier disruption. Abrogation of epidermal permeability barrier leads to acute inflammation response initiated by inflammatory factors including IL-22. We hypothesize that the release of IL-22 probably activates PLCε and induces downstream cytokine cascade, which consequently elicits the new psoriatic lesion.

some inflammatory dermatoses, such as psoriasis, contact dermatitis and cutaneous infections [17–19]. However, the underlying mechanisms how barrier disruption induces cutaneous inflammation are unknown. The present study demonstrated that acute disruption of epidermal permeability barrier dramatically increased expression levels of several cytokines, chemokines and antimicrobial peptides in wild type mice, but only IL-22 was increased in PLCε KO mice. Interestingly, silence of PLCε with its siRNA also lowered expression levels of cytokine and chemokines following stimulation of keratinocytes with IL-22. Collectively, the present study demonstrates that 1) PLCε mediates, at least in part, the induction of cutaneous inflammation by barrier disruption; 2) IL-22 is likely the upstream of cytokine cascades in cutaneous inflammation induced by barrier disruption.

Although the mechanisms by which barrier disruption induces IL-22 expression are unknown, the results of the present study suggest that the pathogenic role of IL-22 in psoriasis could be mediated by PLCε. Previous studies showed that expression levels of IL-22 is higher in psoriatic lesion and the blood of psoriatic patients [5,20]. Either overexpression of IL-22 or administration of IL-22 to the skin induces psoriatic lesion [21]. Conversely, mice with IL-22 deficiency or anti-IL-22 antibody treatment do not develop psoriasis-like lesion after imiquimod treatments [22,23]. Mice with overexpression of PLCε also develop psoriasis-like inflammation phenotypes, driven by aberrant expression of proinflammatory molecules represented by IL-22 and IL-23 [10]. Coupling the results of the present study, IL-22/PLCε signaling pathway is possibly involved in the pathogenesis of psoriasis. Because psoriasis vulgaris preferably occurs on the body sites vulnerable to superficial trauma, e.g., disruption of barrier by scratch or abrasion, and the Köbner phenomenon, we hypothesize that disruption of epidermal permeability barrier induces the release of IL-22, resulting in cytokine cascade mediated by PLCε, consequently leading to the development of psoriasis (Fig. 3d).

This study still exists some limitations. First, as we found the possibility of IL-22 directly activating PLCε in keratinocytes, we still need to show the engagement of the IL-22R and the subsequent signal transduction, such as Ras/Rap and STAT3 signaling, required for activation of PLCε and downstream cytokine cascade induction. Second, a mouse model simulating psoriatic inflammation in PLCε KO mice is required for further evidence to confirm the participation of PLCε and IL-22 in psoriasis.

## 5. Conclusions

The present study demonstrate that PLCε is also required for the development of cutaneous inflammation induced by acute disruption of epidermal permeability barrier, and the regulator role of IL-22 in cutaneous inflammation is mediated, at least in part, by PLCε, suggesting a pathogenic role of IL-22/PLCε signaling pathway in psoriasis.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrep.2020.100869.

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