

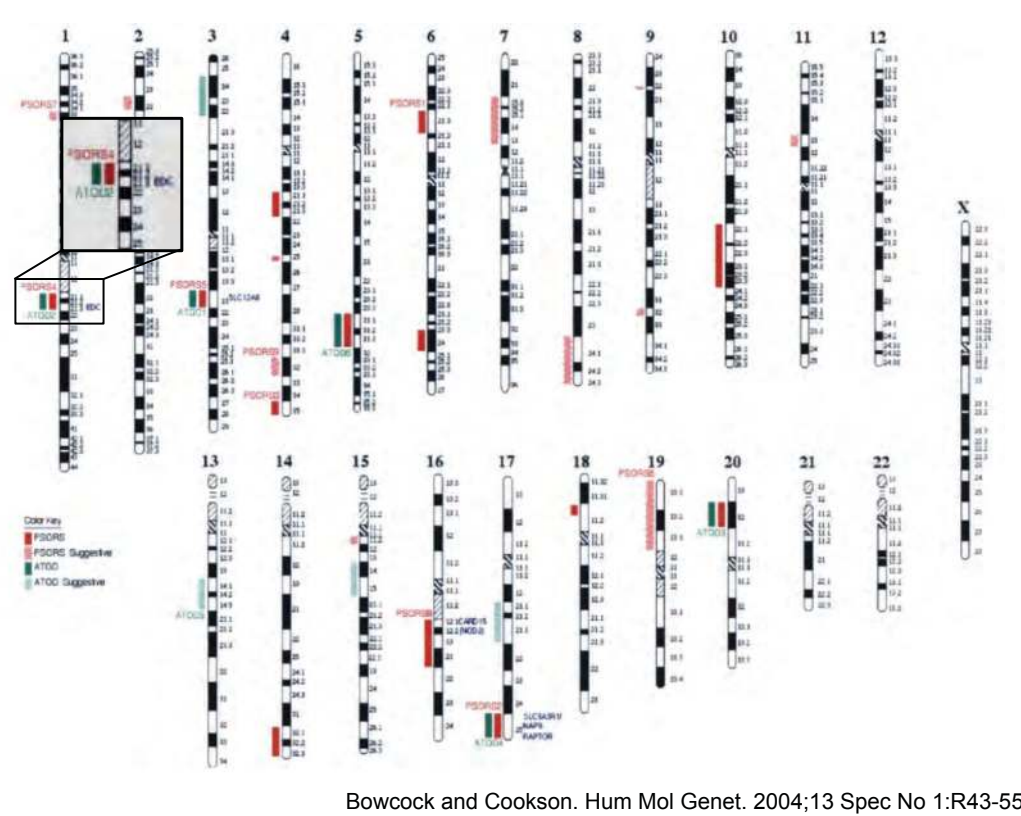
# Loss of Loricrin Exacerbates Psoriasis-like Skin Inflammation Through Altered Dendritic Cell Homeostasis

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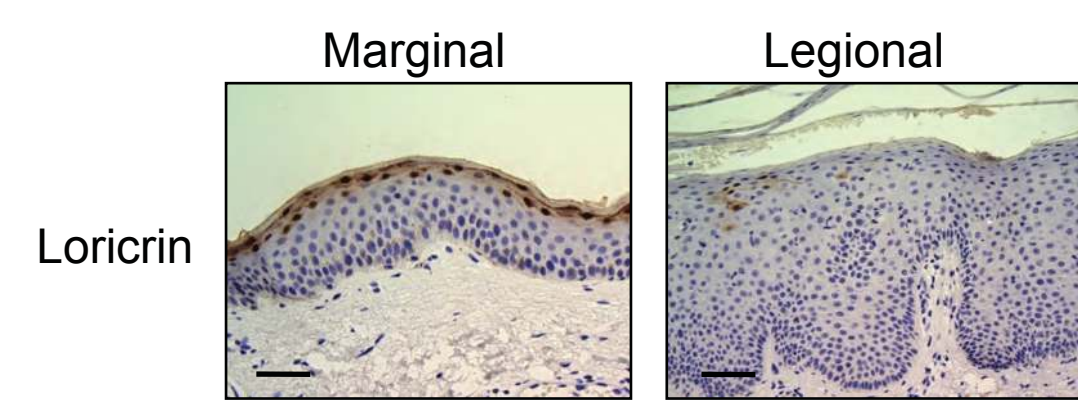
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## Introduction

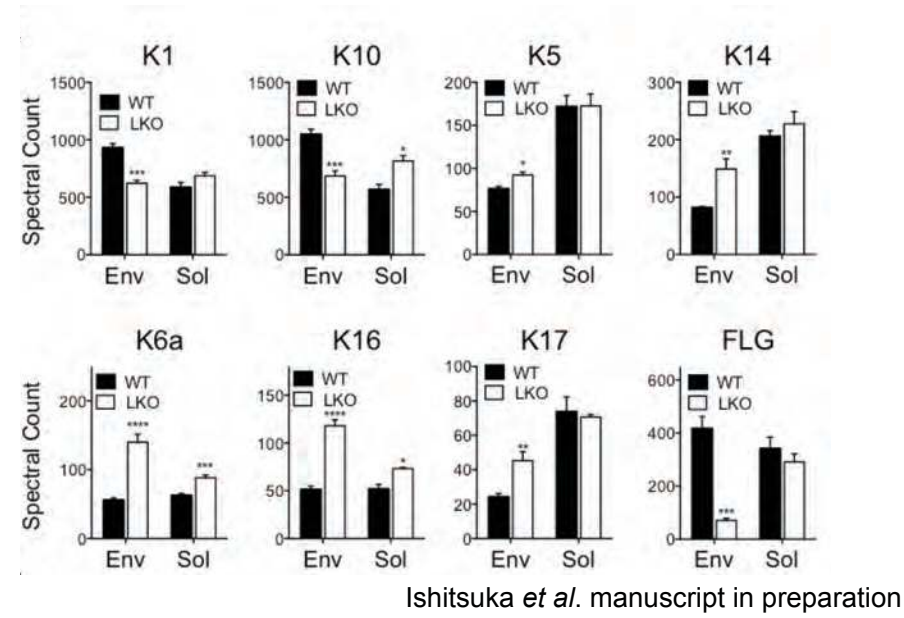
### Epidermal Differentiation Complex And Psoriasis



### Decreased Loricrin Expression In Psoriatic Epidermis



### Loricrin Knockout Mice (LKO) Epidermis Has Impaired Keratin Cross-linking That Leads To Increased Mechanical Susceptibility



### Mechanical Stress As A Trigger For Psoriatic Eruption

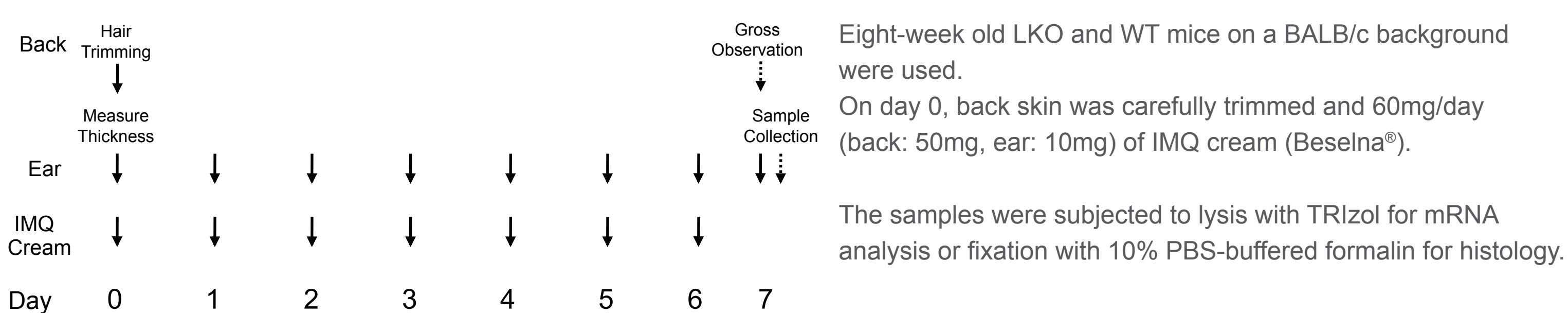


## Hypothesis

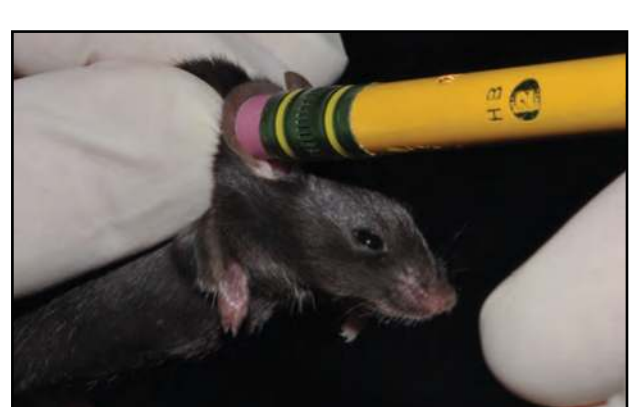
Increased Mechanical Susceptibility Due To The Loss Of Loricrin  
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 Exaggerated Inflammatory Phenotype In Imiquimod (IMQ)-induced Skin Inflammation

## Methods

### 1. IMQ-induced Skin Inflammation Model



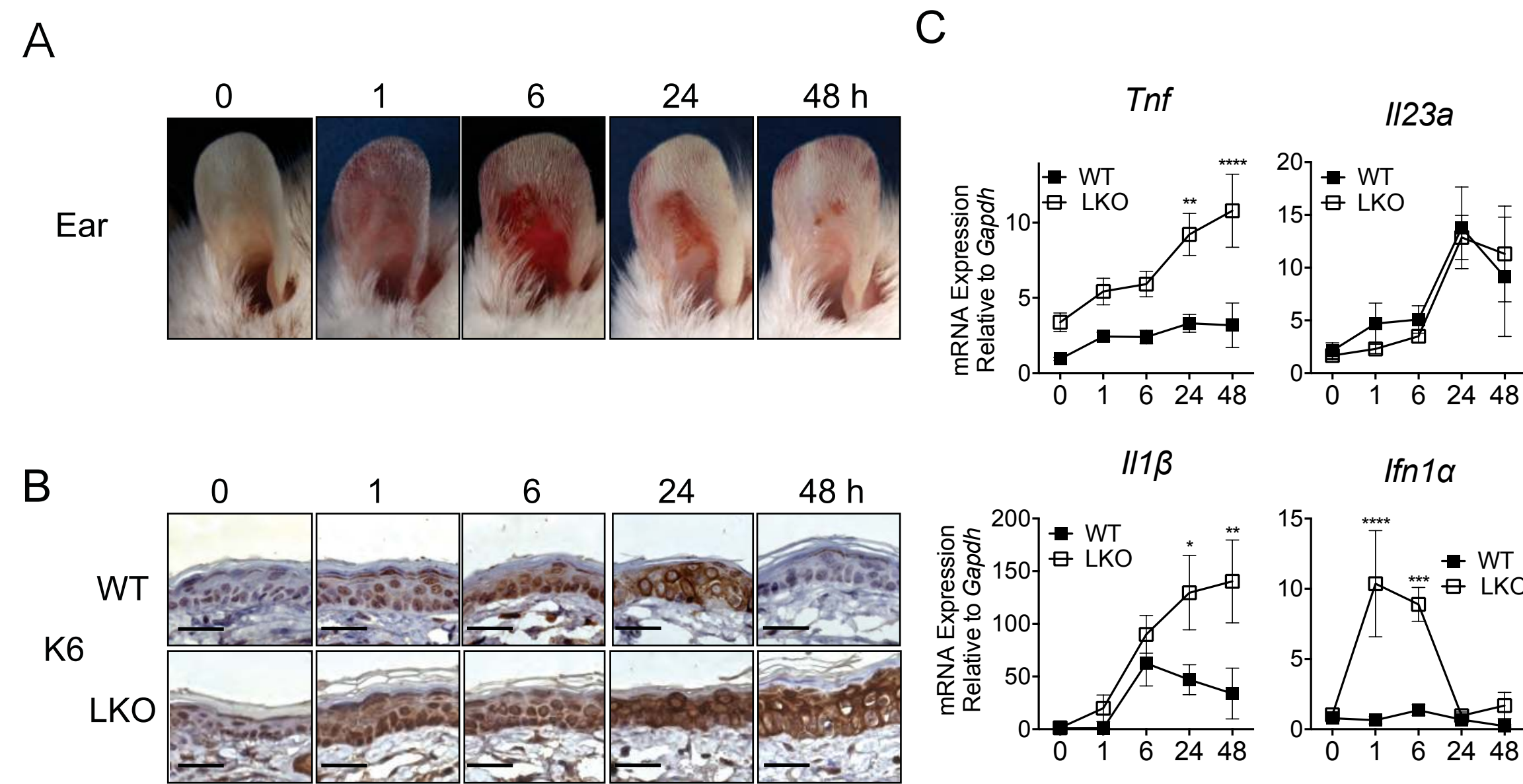
### 2. Irritation Of Ear Skin By Mechanical Stress



Female 14-week-old FvB WT (Charles River) and LKO mice were restrained manually, and a pencil eraser (Laddie No. 2; Dixon, Heathrow, FL) was rubbed perpendicularly on the anterior of the ear. Mechanical stress was applied by rotating the pencil with light pressure for 3 minutes. Vasodilation was observed immediately following the irritation. Half pieces from each ear were collected at the time points (1, 6, 24 and 48 hours after the procedure). The samples were subjected to lysis with TRIzol for mRNA analysis or fixation with 10% PBS-buffered formalin for histology.

## Results

### Mechanical Stress Induced Pro-inflammatory Conditions In LKO Mice

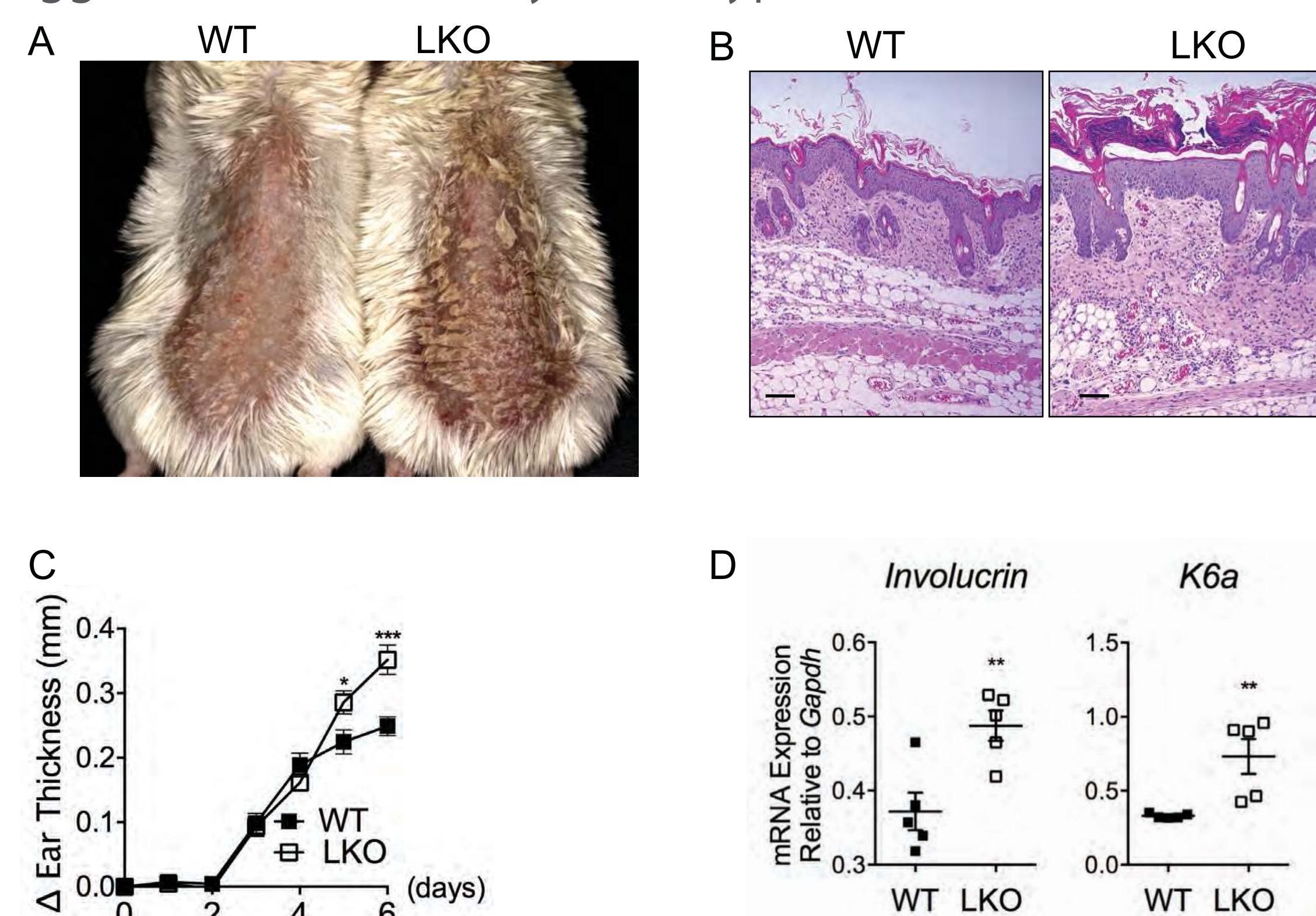


A. Time course of ear skin gross appearance after mechanical irritation. Mild skin immediate erythema formation followed by skin erosion occurs.

B. Histological findings of irritated ear skin. Note enhanced and sustained expression of keratin 6 (K6) in LKO epidermis, suggesting more stressed condition.

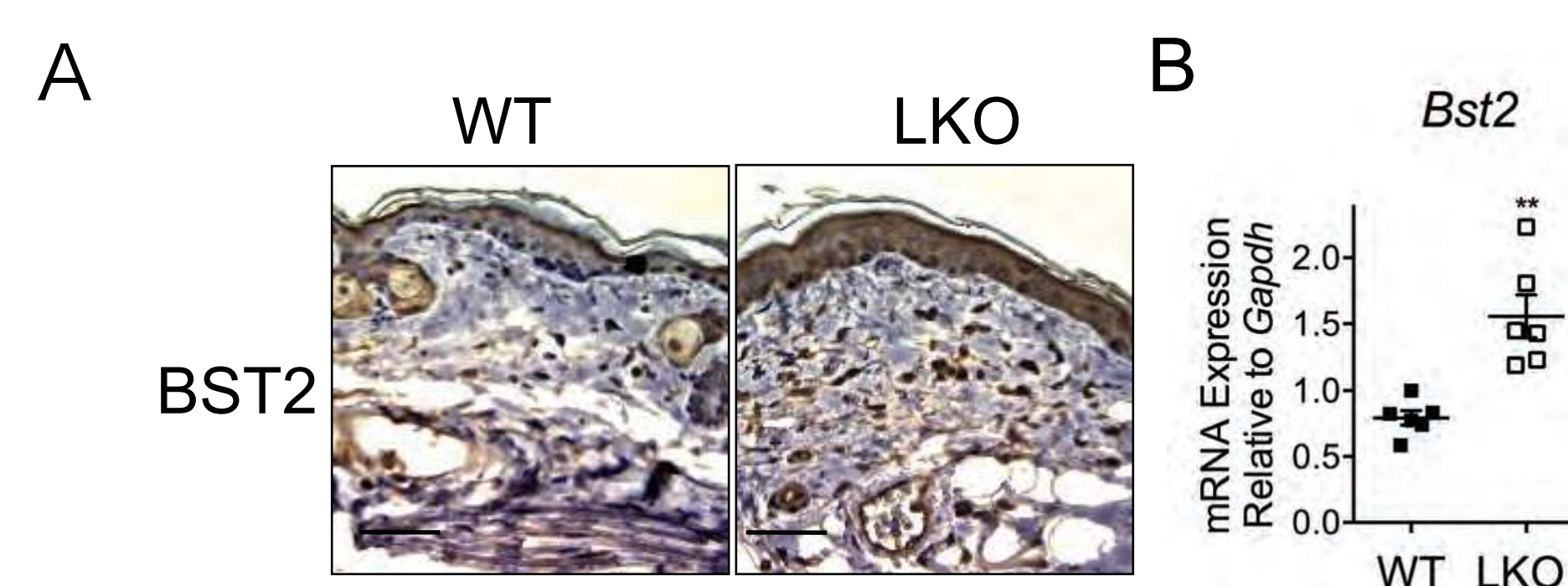
C. Time course of transcriptional expression of inflammatory cytokines associated with psoriasis. Significantly increased expression levels of *Tnf*, *Ifn1α*, *Il1β* in LKO mice. Note that *Il23a* expression levels were comparable between WT and LKO. (\*\* $p < 0.01$ , \*\*\* $p < 0.0005$ , \*\*\*\* $p < 0.0001$  from 2way ANOVA)

### Exaggerated Inflammatory Phenotype In LKO Mice



A. Gross appearance of back skin after 7 consecutive days of IMQ application. Back skin had enhanced erythema and hyperkeratosis.  
 B. Histological findings from IMQ-treated ear skin. Hyperkeratosis admixed with abscess-like structure was more evident in LKO mice.  
 C. Enhanced ear swelling indicated by increased ear thickness in LKO mice.  
 D. Increased transcripts of *Involucrin* and *K6a* in LKO mouse ear skin (\*\* $p < 0.01$ , Student's t-test).

### Enhanced Expression Of A Plasmacytoid Dendritic Cell Marker In LKO Mice In A Steady State



A. Since *Ifnα* expression levels were enhanced in LKO mice after irritation, we suspected that LKO mice have an increased dendritic cell (DC) subset that produces larger amount of IFN- $\alpha$ , plasmacytoid DC (pDC).

A. and B. The expression levels of *Bst2*, a pDC marker, were analyzed in ear skin in a steady state. Immunohistochemistry revealed increased BST2-positive cells with dendritic morphology in LKO mice, accompanied by increased *Bst2* transcripts. (\*\* $p < 0.01$ , Student's t-test)

## Conclusions

- Mechanical stress induced pro-inflammatory conditions in LKO mice.
- LKO mice showed more severe phenotypes in IMQ-induced skin inflammation model.
- Enhanced expression of a pDC marker in LKO mice suggests altered DC-homeostasis associated with skin barrier defect and pro-inflammatory conditions.