

Epithelial TRAF6 drives IL-17-mediated psoriatic inflammation

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Epithelial cells are the first line of defense against external dangers, and contribute to induction of adaptive immunity including Th17 responses. However, it is unclear whether specific epithelial signaling pathways are essential for the development of robust IL-17-mediated immune responses. In mice, the development of psoriatic inflammation induced by imiquimod required keratinocyte TRAF6. Conditional deletion of TRAF6 in keratinocytes abrogated dendritic cell activation, IL-23 production, and IL-17 production by $\gamma\delta$ T cells at the imiquimod-treated sites. In contrast, hapten-induced contact hypersensitivity and papain-induced IgE production were not affected by loss of TRAF6. Loss of psoriatic inflammation was not solely due to defective imiquimod sensing, as subcutaneous administration of IL-23 restored IL-17 production but did not reconstitute psoriatic pathology in the mutant animals. Thus, TRAF6 was required for the full development of IL-17-mediated inflammation. Therefore, epithelial TRAF6 signaling plays an essential role in both triggering and propagating IL-17-mediated psoriatic inflammation.

Introduction

Epithelial tissues provide a physical barrier between the host and the external environment. Epithelial cells are capable of sensing pathogens and environmental factors and produce immunomodulatory factors including a variety of cytokines and chemokines (1). It is now well accepted that epithelial products influence the nature of the innate and adaptive immune responses (2). For example, epithelial cells promote T helper 2-type (Th2-type) immune responses by releasing interleukin 33 (IL-33), thymic stromal lymphopoietin (TSLP), and IL-25 in allergic airway inflammation (3) and atopic dermatitis (4). Similarly, epithelial cells secrete serum amyloid A (SAA) in response to segmented filamentous bacteria (SFB) colonization, promoting Th17-type immune responses in murine intestine (5). Conditional deletion of genes encoding immunomodulatory factors specifically in epithelial cells has established that epithelial cells do shape the immune response in vivo (6–10). However, it is less clear how specific epithelial signaling events are mechanistically linked to qualitative changes in the nature of the immune response (11–13).

Psoriasis is a common, chronic skin disease with histological features of abnormal proliferation and differentiation of keratinocytes accompanied with massive infiltration of immune cells (14, 15). First, environmental factors, such as physical trauma and bacterial products, initiate a cascade of events at the epidermis in genetically predisposed individuals. Second, continuous activation of keratinocytes by IL-17 family cytokines leads to disease maintenance and propagation. Production of IL-17 is driven by the IL-23/IL-17 axis in which dendritic cells (DCs) produce IL-23, which supports Th17-dependent or -independent production of IL-17 in the skin (16, 17). Keratinocytes release multiple factors that contribute to both phases of psoriasis pathogenesis. In response to tissue damage, keratinocytes release the cellular damage-associated molecular patterns (DAMPs) including self-nucleic acids and high-mobility group box 1 protein (HMGB1).

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Keratinocytes also produce inducible proinflammatory transcriptional products, such as chemokine (C-C motif) ligand 20 (CCL20) and chemokine (C-X-C motif) ligand 1 (CXCL1) (15), that act on the immune cells that induce psoriatic inflammation. Consequently, it is suggested that the interplay of keratinocytes and immune cells orchestrates an IL-17–dependent, feed-forward inflammatory loop in psoriasis. However, it is not known whether keratinocytes, or a specific signaling pathway within keratinocytes, are truly required for initiating the IL-23/IL-17 axis in skin.

Tumor necrosis factor (TNF) receptor–associated factor 6 (TRAF6) is a signaling adaptor and E3 ubiquitin ligase that can regulate the activation of nuclear factor- κ B (NF- κ B) and mitogen-activated protein kinase (MAPK) pathways. TRAF6 plays an important role in a variety of immunological functions through the regulation of MAPK and NF- κ B activation (18, 19). Genetic alterations that affect the NF- κ B and MAPK pathways in the epidermis have been associated with genetic predisposition to psoriasis (20–22) and suggest a possible role for TRAF6 in the disease. Specifically, gain-of-function mutations in caspase recruitment domain–containing protein 14 (CARD14), which is predominantly expressed in the epidermis and signals through TRAF6, are related to a familial type of psoriasis (23, 24). Likewise, in animals, the psoriatic phenotype is induced by keratinocyte-specific gene deletion of *Tnfr1* coding A20 binding and inhibitor of NF- κ B-1 (ABIN-1) (12). ABIN-1, which binds to polyubiquitin chains and interacts with the deubiquitinase A20, restricts activation of NF- κ B and MAPK signaling by inhibiting polyubiquitination of TRAF6 (25). In addition, IL-17–mediated psoriatic dermatitis is induced by topical application of imiquimod (IMQ), a ligand for Toll-like receptor 7/8 (TLR7/8), which signals through TRAF6 (26). Based on these studies, which suggest a role for TRAF6 in psoriasis pathogenesis, we set out to use conditional gene deletion to directly assess the contribution of keratinocyte TRAF6 in murine models of cutaneous inflammation.

Here, we show that keratinocyte-specific TRAF6-deficient mice are fully resistant to IMQ-induced psoriatic inflammation. In the absence of epithelial TRAF6, IMQ fails to induce activation of either skin-resident DCs or $\gamma\delta$ T cells. This abrogation of psoriatic dermatitis in mice lacking epithelial TRAF6 results from loss of 2 signaling events. First, TRAF6 in keratinocytes regulates the primary response to external stimuli, and second, TRAF6 is required for the positive feedback loop through the IL-17 receptor (IL-17R). Thus, these findings conclusively demonstrated that TRAF6 signaling in keratinocytes is critical for the establishment of IL-17–dependent psoriatic inflammation in the skin.

Results

TRAF6 in keratinocytes is essential for the development of IMQ-induced psoriatic dermatitis. To address the role of TRAF6-dependent signaling in epithelial cells in cutaneous inflammation, we generated keratinocyte-specific TRAF6-deficient (*K5-Cre; Traf6^{fl/fl}*) mice, hereafter referred to as *Traf6* epithelial knockout (*Traf6EKO*) mice, by crossing keratin 5-Cre (*K5-Cre*) transgenic mice with mice carrying floxed *Traf6* alleles (*Traf6^{fl/fl}*; Supplemental Figure 1A; supplemental material available online with this article; <https://doi.org/10.1172/jci.insight.121175DS1>).

To evaluate the role of epidermal TRAF6 in IL-17–mediated inflammation, we used a well-established model, IMQ-induced dermatitis, which is characterized by an IL-23/IL-17 axis–dependent psoriatic inflammation (16). Consistent with previous reports, repetitive topical application of IMQ to the ears of *Traf6^{fl/fl}* mice induced skin inflammation with marked erythema, scaling, and crust (Figure 1A). In contrast, no obvious inflammation was observed in *Traf6EKO* mice treated with IMQ. Histological examination revealed that IMQ-treated skin of *Traf6^{fl/fl}* mice was characterized by hyperplasia of the epidermis, with massive infiltration of inflammatory cells, recapitulating human psoriatic dermatitis (Figure 1B). On the other hand, *Traf6EKO* mice failed to exhibit these histological changes following IMQ treatment (Figure 1B). The increased ear thickness following IMQ application on WT mice was abrogated in *Traf6EKO* mice during the observation period (Figure 1C). Flow cytometric analysis of the lesional skin infiltrates revealed a profound increase of total living cells and CD45⁺ cells, including neutrophils and CD4⁺ T cells, in *Traf6^{fl/fl}* mice but not in *Traf6EKO* mice (Figure 1, D and E). There was also a striking reduction in infiltrating neutrophils, which are characteristic of psoriatic inflammation in this animal model (27), in *Traf6EKO* mice compared with *Traf6^{fl/fl}* mice following IMQ treatment (Figure 1D). V γ 4⁺ $\gamma\delta$ T cells are the dominant source of IL-17 in IMQ-induced inflammation (28). We observed reduced V γ 4⁺ $\gamma\delta$ T cells and IL-17 production by these cells was significantly decreased in *Traf6EKO* mice compared with *Traf6^{fl/fl}* mice following IMQ treatment (Figure 1, D–F). These results demonstrated that loss of TRAF6 in epithelial cells renders mice resistant to IMQ-induced psoriatic inflammation.

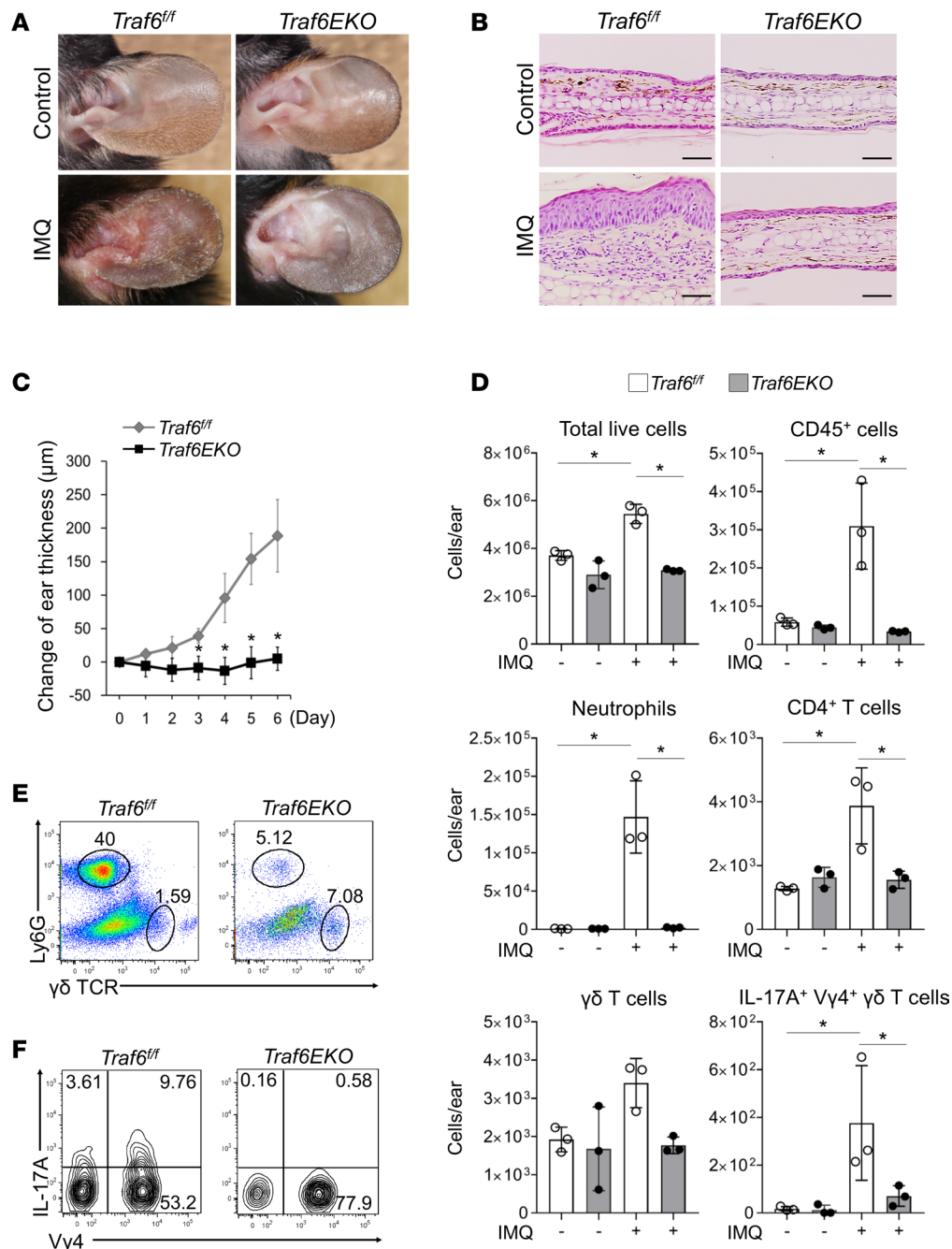


Figure 1. *Traf6EKO* mice are resistant to psoriatic inflammation induced by IMQ. (A) Representative gross appearance of ears from *Traf6^{fl/fl}* and *Traf6EKO* mice treated daily with or without topical IMQ for 6 consecutive days. *Traf6EKO* mice showed no remarkable gross abnormality in the skin except for modest hair reduction in the auricles and postauricular regions. (B) Histology of the ear sections harvested on day 6. H&E staining. Scale bars: 50 μ m. (C) Time course of changes in the ear thickness ($n \geq 4$ per group). The thickness was measured daily before treatment. Values are shown as means $\pm$ SD. * $P < 0.05$ (2-tailed Student's t test). (D) Flow cytometric analyses of total live cells, CD45⁺ cells, CD4⁺ T cells, Ly6G⁺ neutrophils, $\gamma\delta$ TCR⁺ cells, and $\gamma\delta$ TCR⁺V γ 4⁺IL-17A⁺ cells from the ears of individual mice after 3 days of IMQ treatment ($n = 3$). Results are expressed as means $\pm$ SD. * $P < 0.05$ (Tukey's multiple-comparisons test). (E and F) Representative flow cytometry plots of neutrophils and IL-17A-producing $\gamma\delta$ T cells infiltrated in the ear of *Traf6^{fl/fl}* and *Traf6EKO* mice treated with IMQ on day 3 ($n = 3$). Dot plots show Ly6G⁺ neutrophils (E) gated on CD45⁺ cells and V γ 4⁺IL-17A⁺ cells (F) gated on $\gamma\delta$ TCR^{int} cells shown in E. Data are representative of at least 3 independent experiments (A–C) or 2 experiments (D–F).

Traf6EKO mice may exhibit reduced expression of *Traf6* in thymic epithelial cells, as these cells are also known to express keratin 5 (29). Furthermore, mice with *Traf6* deletion in *Foxn1*-expressing thymic epithelial cells are reported to have abnormalities in the negative selection of T cells, leading to abnormal T cell populations including CD4⁺CD8⁺ double-positive populations of T cells in their peripheral tissues (30).

Flow cytometric analysis showed that the absolute numbers of CD4⁺ T cells, CD8⁺ T cells, and CD4⁺CD8⁺ T cells in the thymus and lymph nodes were similar between *Traf6*^{EKO} and *Traf6*^{fl/fl} mice (Supplemental Figure 1B). The numbers of CD4⁺ T cells and $\gamma\delta$ T cells in the skin of *Traf6*^{EKO} mice were higher than those of *Traf6*^{fl/fl} mice, whereas those of V γ 4⁺ $\gamma\delta$ T cells in the skin of both groups were comparable (Supplemental Figure 1B). Nevertheless, despite potentially autoreactive T cells in the *Traf6*^{EKO} skin related to the expected reduction of TRAF6 expression in the thymus (30), there were no obvious signs of cutaneous inflammation (Figure 1, A and B).

Langerhans cells (LCs) are the dominant professional antigen-presenting cells in the epidermis, and our previous work has suggested that LCs produce IL-23 and induce IL-17–producing cells in the IMQ-induced murine psoriatic dermatitis model (31). In contrast to *Traf6*^{EKO} mice, IMQ treatment of *Langerin-Cre; Traf6*^{fl/fl} (*Traf6*^{LCKO}) mice lacking TRAF6 specifically in LCs induced robust inflammation similar to that observed in *Traf6*^{fl/fl} mice (Supplemental Figure 1, C and D). These findings indicated that TRAF6-dependent signaling in keratinocytes, not in LCs, is required for the development of psoriatic inflammation.

IL-17–mediated immunity induced by IMQ depends on TRAF6 in keratinocytes. To more broadly characterize the impact of TRAF6 in keratinocytes on IMQ-induced psoriatic inflammation, we analyzed gene expression in IMQ-treated whole ears of *Traf6*^{EKO} mice and *Traf6*^{fl/fl} mice using a cDNA microarray. At day 2, prior to the prominent skin immune infiltrate evident on day 3 (Figure 1, B–D), increased expression of several proinflammatory genes was detectable. As shown in the heatmap, 406 genes were upregulated more than 2-fold by IMQ treatment in *Traf6*^{fl/fl} mice, and this IMQ-induced upregulation was attenuated in *Traf6*^{EKO} mice (Figure 2, A and B). These genes included many psoriasis signature genes (15), including those coding defensins, *S100a8/a9*, and *Ccl2* (Figure 2B and Supplemental Table 1). Pathway analysis revealed that various immune mediator–related pathways, including the TNF signaling pathway, which is a therapeutic target in psoriasis, were significantly upregulated by IMQ treatment in *Traf6*^{fl/fl} mice compared with *Traf6*^{EKO} mice (Figure 2C and Supplemental Table 2). Differences in the gene expression levels between the untreated *Traf6*^{fl/fl} mice and *Traf6*^{EKO} mice were not annotated to specific pathways. These findings suggest that the IL-17–mediated psoriatic immune response induced by IMQ treatment is dependent on TRAF6 in keratinocytes.

To assess whether the IL-17–related immune response is impaired in *Traf6*^{EKO} mice, we examined the expression of *Il23a* and *Il12b* encoding IL-23p19 and p40, respectively, and Th17 cytokines *Il17a*, *Il17f*, and *Il22*, in the IMQ-treated skin by quantitative reverse transcription PCR (RT-PCR). During IMQ-induced psoriatic dermatitis, IL-23 is produced by DCs to induce an IL-17–mediated immune response (32, 33). Indeed, expression levels of the IL-23 subunit gene transcripts were upregulated in the skin of *Traf6*^{fl/fl} mice by treatment with IMQ (Figure 2D). Similarly, expression of *Il17a*, *Il17f*, and *Il22* were significantly upregulated in *Traf6*^{fl/fl} mice by IMQ treatment (Figure 2D). The expression of other psoriasis-related genes, such as *Saa1*, *Il1a*, *Il1b*, *Il24*, and *S100a8*, was also induced in *Traf6*^{fl/fl} mice (Figure 2D and Supplemental Figure 2). In contrast, the IMQ-induced gene expression of all of these cytokines and chemokines was defective in *Traf6*^{EKO} mice (Figure 2D and Supplemental Figure 2).

We next asked whether *Traf6*^{EKO} mice are selectively deficient in the induction by IMQ of an IL-17–related immune response or are broadly deficient in other cutaneous immune responses. To this end, we evaluated the requirement for keratinocyte TRAF6 in 2 distinct immune responses elucidated by epicutaneous treatments: treatment with 2,4-dinitro-1-fluorobenzene (DNFB) induces a Th1-type contact hypersensitivity, while repetitive papain occlusive dressing treatment induces a Th2 immune response (34, 35). DNFB treatment after sensitization elicited contact hypersensitivity with similar ear swelling in both *Traf6*^{EKO} and *Traf6*^{fl/fl} mice (Supplemental Figure 3A). Although a significant but partial attenuation of *Ifng* expression was observed in the skin of *Traf6*^{EKO} mice compared with that of *Traf6*^{fl/fl} mice, the induction of *Il17a* gene expression was comparable in both groups (Supplemental Figure 3, B and C). In papain-induced skin inflammation, expression of *Il4* mRNA and serum IgE levels were comparable between *Traf6*^{EKO} and *Traf6*^{fl/fl} mice (Supplemental Figure 3, D–F). Taken together, these findings indicate that TRAF6-dependent signaling in murine keratinocytes plays a critical role in the development of IL-17–related inflammation induced by IMQ treatment, but not in hapten-induced Th1-type inflammation or papain-induced Th2-type inflammation.

TRAF6 in keratinocytes is required for the activation of skin-resident DCs. Skin-resident DCs are reported to be the main source of IL-23 in the IMQ animal model (31, 33) and we, therefore, expected that the attenuated expression of IL-23 in the lesional skin of *Traf6*^{EKO} mice (Figure 2D) was due to the impaired DC activation. We examined DC activation markers in both *Traf6*^{fl/fl} and *Traf6*^{EKO} mice treated with IMQ. Skin-resident

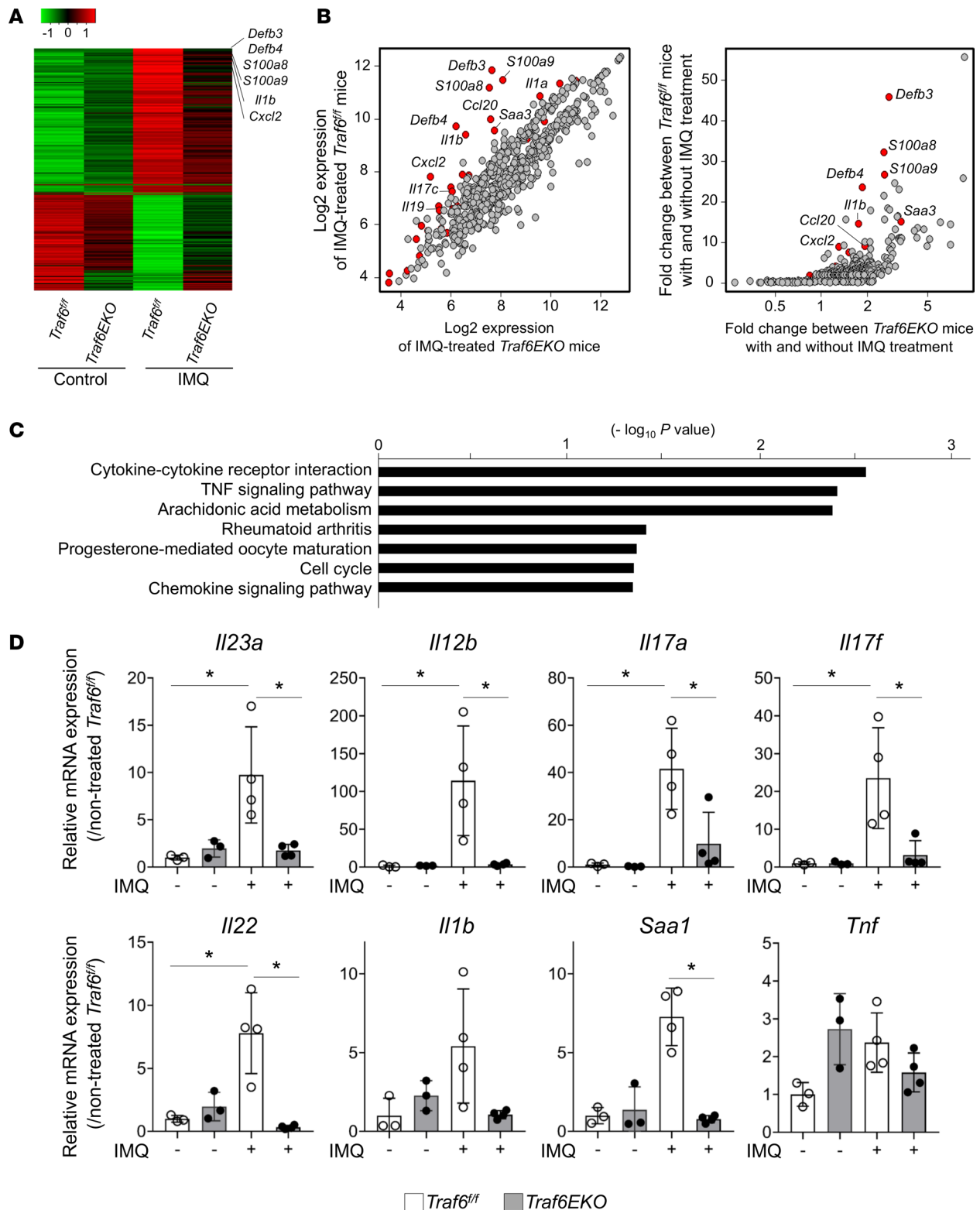


Figure 2. IL-17-mediated gene expression was impaired in *Traf6EKO* mice. (A) Heatmap of differentially expressed genes in *Traf6EKO* mice and *Traf6^{fl/fl}* mice with or without IMQ treatment. Genes differentially expressed more than 2-fold by IMQ treatment in either mouse group (674 genes) were analyzed. Representative psoriasis-related genes are indicated. (B) Scatter plots of gene expression in *Traf6EKO* mice and *Traf6^{fl/fl}* mice. Left panel shows correlation of gene expression between IMQ-treated *Traf6EKO* mice and IMQ-treated *Traf6^{fl/fl}* mice. Right panel shows correlation between fold changes in gene expression induced by IMQ treatment in *Traf6EKO* mice and in *Traf6^{fl/fl}* mice. Representative psoriasis-related genes are indicated by red plots accompanied with their names. (C) Pathways enriched in genes upregulated by IMQ treatment in *Traf6^{fl/fl}* mice compared with *Traf6EKO* mice. Pathways with $P < 0.05$ are shown. (D) qPCR analysis of mRNA levels in the epidermis of the IMQ-treated mouse ears on day 2 ($n \geq 3$). The results were normalized to *Gapdh* expression and are shown as means $\pm$ SD. * $P < 0.05$ (Tukey's multiple-comparisons test). Data are representative of 3 experiments (D) or 1 experiment (A-C).

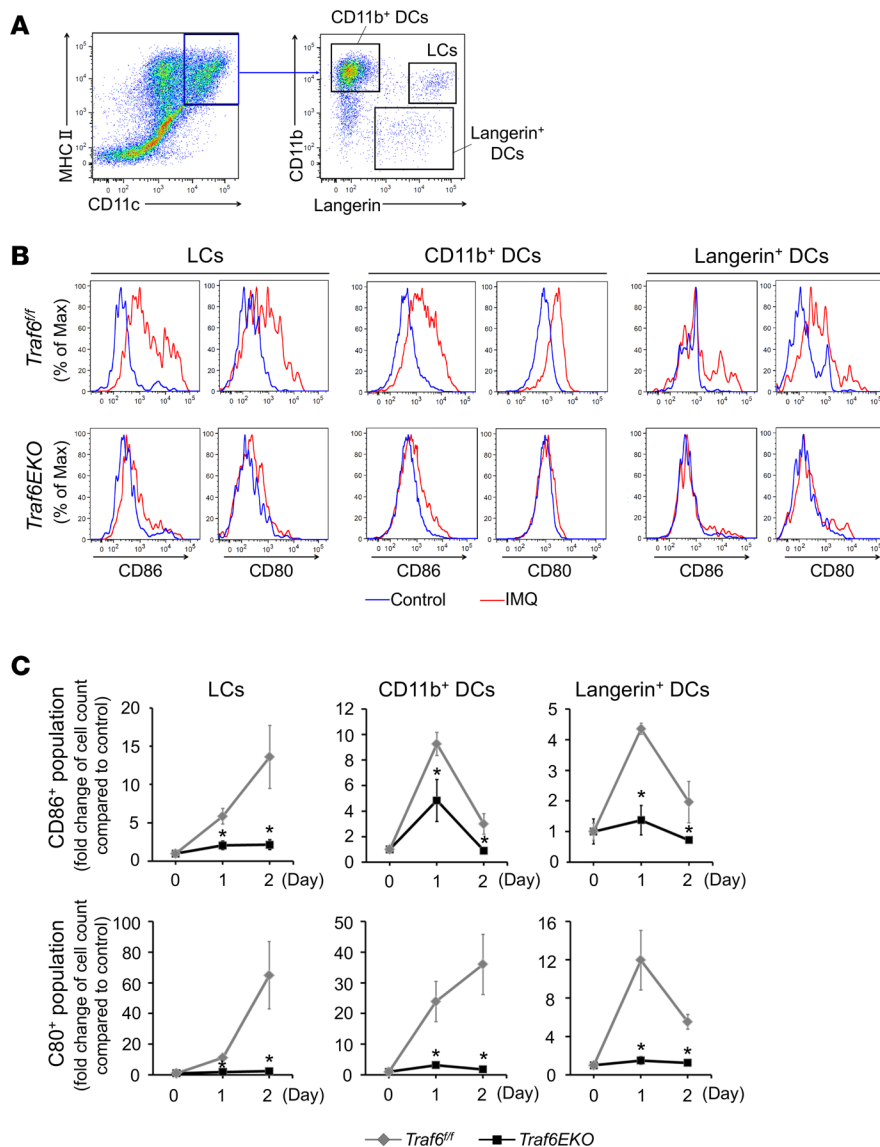


Figure 3. TRAF6 in keratinocytes is required for the activation of skin-resident DCs. (A) Flow cytometric analyses of skin-resident DCs. Gating strategies of Langerhans cells, langerin⁺ DCs, and CD11b⁺ DCs in the IMQ-treated ears are shown. (B) Expression of activation markers in cutaneous DCs after IMQ treatment. Expression of CD86 and CD80 in cutaneous DCs was analyzed using the IMQ-treated ears from *Traf6*^{EKO} mice and *Traf6*^{fl/fl} mice harvested on day 2 (n = 3). Representative single-parameter histograms of each DC subset in the ear treated with or without IMQ are shown in a red and blue line, respectively. (C) Time course of the rates of CD86⁺ and CD80⁺ populations in each DC subset after IMQ treatment (n = 3). Results are shown as means ± SD. *P < 0.05 (2-tailed Student's t test). Data are representative of 2 experiments (A–C).

DCs including LCs, langerin⁺ DCs, and CD11b⁺ DCs (Figure 3A), exhibited high expression of CD80 and CD86 at the early (≤2 days) after IMQ treatment in *Traf6*^{fl/fl} mice, but not in *Traf6*^{EKO} mice (Figure 3, B and C). These results suggested that TRAF6-dependent keratinocyte signaling is required for the activation of DCs in vivo. Previous studies suggested that IMQ directly activates skin-resident DCs and that this activation of DCs is associated with IL-23 production and subsequent IL-17 responses (17, 33). However, taken together with the marked decrease in the number of activated DCs and IL-17-producing $\gamma\delta$ T cells in the lesional skin of *Traf6*^{EKO} mice (Figure 1, D and F), our results suggest that TRAF6-dependent keratinocyte signaling events are required for the skin-resident DC activation and induction of IL-17-producing $\gamma\delta$ T cells in IMQ-induced inflammation, independent of the ability of IMQ to directly activate resident DCs.

Keratinocytes produce psoriasis-related mediators via TRAF6-dependent signaling in vitro. The results of cell death assays demonstrated that the susceptibility of keratinocytes to cell death did not depend on TRAF6 and that altered keratinocyte survival could not account for the defective inflammatory response of *Traf6*^{EKO} mice (Supplemental Figure 4, A and B). We therefore hypothesized that loss of TRAF6 directly impairs signaling leading to transcription of psoriasis-related genes in keratinocytes, and that this loss of keratinocyte transcriptional responses abrogates development of IL-17-mediated inflammation. To confirm the function of TRAF6 in murine keratinocytes, we first evaluated IL-1 β signaling in these cells. Consistent with observations made in the human keratinocyte cell line HaCaT (36), primary-cultured keratinocytes derived from *Traf6*^{fl/fl} mice exhibited I κ B degradation

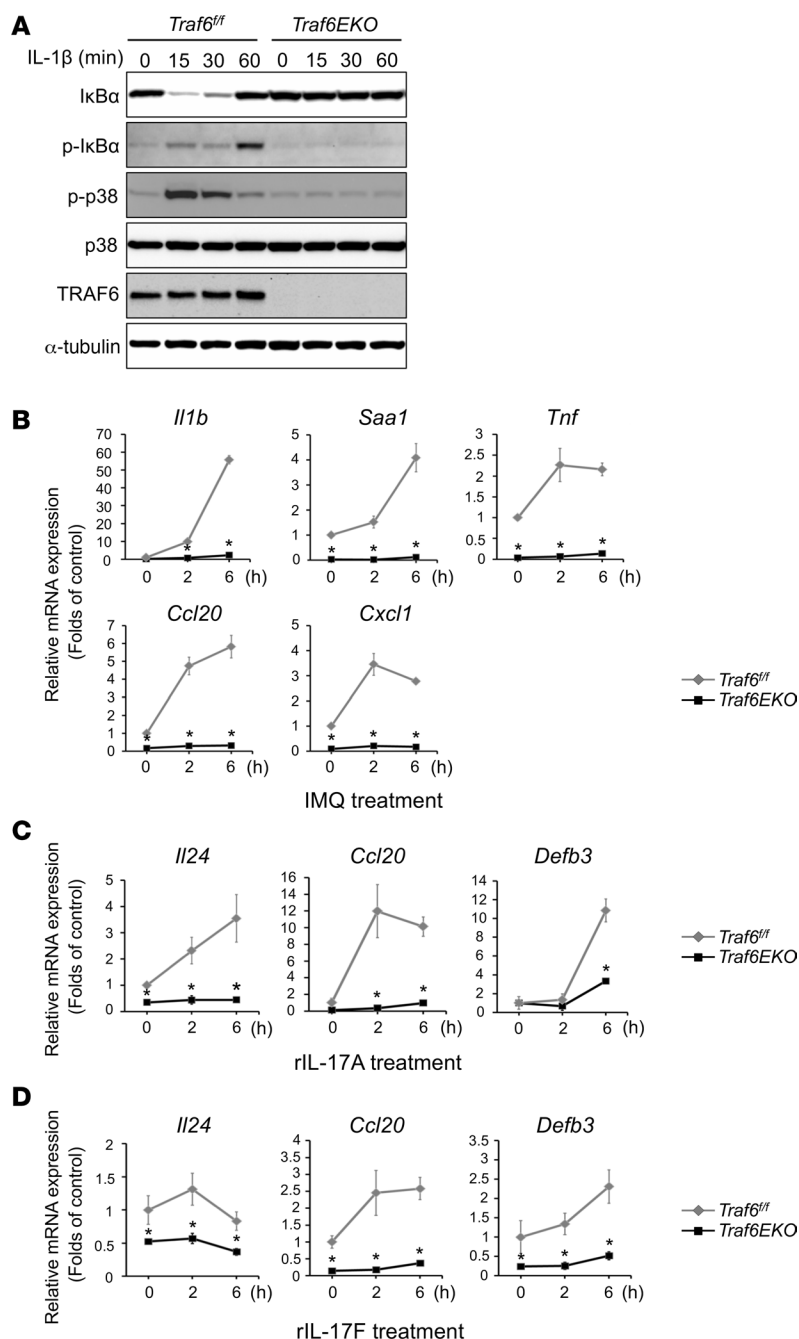


Figure 4. IMQ enhanced psoriasis-related gene expression in keratinocytes via TRAF6-dependent signaling pathway. (A) Western blot analysis of keratinocytes from *Traf6EKO* mice and *Traf6^{fl/fl}* mice stimulated with rIL-1 β at the indicated time points. Total cell lysates were resolved by SDS-PAGE followed by immunoblotting. (B) qPCR analysis of mRNA levels in the primary cultured keratinocytes from *Traf6EKO* mice and *Traf6^{fl/fl}* mice stimulated with IMQ for 0–6 hours ($n = 3$). (C and D) qPCR analysis of mRNA levels in the primary cultured keratinocytes from *Traf6EKO* mice and *Traf6^{fl/fl}* mice treated with IL-17A (100 ng/ml) (C) and IL-17F (100 ng/ml) (D) for 0–6 hours ($n = 3$). These results were normalized to *Gapdh* expression and are shown as means $\pm$ SD. * $P < 0.05$ (2-tailed Student's t test). Data are representative of 3 experiments (B) or 2 experiments (A, C, and D).

and the phosphorylation of IkB and p38 in response to recombinant IL-1 β (rIL-1 β) treatment, whereas those signaling events were not detected in TRAF6-deficient keratinocytes (Figure 4A).

We next investigated whether TRAF6 in keratinocytes is also required for the direct transcriptional activation by IMQ stimulation in vitro. Consistent with in vivo results (Figure 2D and Supplemental Figure 2), IMQ-treated *Traf6^{fl/fl}* keratinocytes showed significant upregulation of the expression levels of psoriasis-related genes, such as *Il1b*, *Saa1*, *Tnf*, *Ccl20*, and *Cxcl1* in vitro. However, the induction of all these genes was abrogated by the lack of TRAF6 (Figure 4B), despite intact phosphorylation of p38 without detectable activation of NF- κ B in both groups (Supplemental Figure 5).

TRAF6 is required for the IL-17R signaling pathway in mouse embryonic fibroblasts (37). Therefore, we examined the potential role of epithelial TRAF6 in the IL-17R signaling pathway in keratinocytes. As expected, *Traf6^{fl/fl}* keratinocytes produced *Il24*, *Ccl20*, and *Defb3* by stimulation with IL-17A or IL-17F in vitro, whereas the expression of these genes in *Traf6EKO* keratinocytes was significantly

impaired (Figure 4, C and D). Taken together, these results suggest that direct activation of epithelial cells by IMQ may be necessary for IL-17–mediated inflammation, and that TRAF6 is required for the transcriptional response of keratinocytes: both the primary response to external stimuli, such as IMQ, and the secondary response to IL-17.

IL-23 administration reconstitutes IL-17 production in Traf6EKO mice. The development of IMQ-induced psoriatic dermatitis and the expression of IL-17 is almost completely blocked in mice deficient for *Il23a* (16). Therefore, the reduced keratinocyte transcriptional responses accompanied by impaired activation of DCs and IL-17⁺ $\gamma\delta$ T cells in *Traf6EKO* mice could be attributable to decreased IL-23 production. This further suggests that induction of IL-23 production by skin DCs and other immune cells depends on the activation of TRAF6 signaling in keratinocytes in this animal model. However, the defect we observed in the responses of TRAF6-deficient keratinocytes to IL-17 in vitro suggests there may be an additional function for TRAF6 downstream of IL-23 production. To directly test whether the requirement for TRAF6-dependent signaling in keratinocytes is predominantly for the induction of IL-23 production, *Traf6^{fl/fl}* and *Traf6EKO* mice were subcutaneously injected with rIL-23, which induces psoriatic dermatitis by directly inducing dermal $\gamma\delta$ T cells to produce IL-17 and IL-22 (38). Consistent with previous reports, *Traf6^{fl/fl}* mice developed psoriasis-like disease, as determined by ear thickness and histopathology (Figure 5, A and B). In contrast, IL-23 injection into *Traf6EKO* mice induced a more limited psoriatic inflammation (Figure 5, A and B), despite inducing comparable levels of expression of genes encoding IL-17A/F and IL-22, mainly produced by $\gamma\delta$ T cells (38), in both groups (Figure 5, C and D). These results demonstrated that the T cell repertoire in the skin of *Traf6EKO* mice was fully competent to mediate an IL-17 response. Furthermore, given that IL-17 production is fully reconstituted by IL-23 administration, these results suggest that IL-23 is a major downstream effector of the TRAF6-dependent keratinocyte response to external stimuli.

The unexpectedly less severe phenotype in the IL-23–treated *Traf6EKO* mice suggested that further activation of the IL-17R signaling, which is required for psoriatic inflammation following IL-23 production (38), depends on TRAF6 in keratinocytes. In fact, the increase in expression of genes mainly transcribed in keratinocytes, such as *Ccl20* and *Defb3*, was significantly impaired in *Traf6EKO* mice (Figure 5C). This blunted response is potentially explained by defective IL-17R signaling in *Traf6EKO* keratinocytes (Figure 4, C and D). Moreover, the impaired expression of both *Il24* and *Il19* in *Traf6EKO* (Figure 5C) mice might also be responsible for the impaired phenotype, because of the essential role of these cytokines in IL-23–induced inflammation (39).

Taken together, these results demonstrated that TRAF6 in keratinocytes plays an important role in the full development of psoriatic skin inflammation. Keratinocyte TRAF6 is a necessary primary, triggering event for the induction of the IL-23/IL-17 axis and for induction of fulminant psoriatic dermatitis as a key mediator of IL-17–driven keratinocyte-positive feedback pathways.

Discussion

In the present study, we demonstrated that mice lacking TRAF6 specifically in keratinocytes do not develop psoriatic inflammation in response to topical treatment with IMQ. Consistent with the known role of TRAF6 in TLR signaling (26) and IL-17R signaling (11, 39), we find that IMQ or IL-17 directly induced the expression of psoriasis-related genes in keratinocytes in a TRAF6-dependent manner. However, we also found that TRAF6-dependent keratinocyte responses were crucial for the activation of DCs, IL-17–producing $\gamma\delta$ T cells, and the initiation of IL-17–mediated immunity. In addition, even when the primary responses of keratinocytes or DCs to IMQ were bypassed by direct administration of IL-23, development of psoriatic dermatitis was blunted in the absence of keratinocyte TRAF6. This reduction in IL-23/IL-17–driven psoriatic pathology likely reflects the role of TRAF6 in regulating epidermal IL-17R signaling. These findings indicate that TRAF6-dependent signaling in keratinocytes plays critical roles in the initiation as well as the propagation of IL-17–mediated immunity.

Given that epithelial cells are directly exposed to the external environment, it is reasonable to consider that upon external stresses, epithelial cells might trigger immune cell activation (15). Keratinocytes' contributions to the onset of psoriasis have been proposed to occur via cell death–dependent mechanisms (40); nucleic acid and antimicrobial peptide LL-37/RNA complexes released by injured keratinocytes have been shown to activate DCs or surrounding keratinocytes resulting in IL-23 production (15, 41, 42). However, our in vitro studies showed that TRAF6 does not affect IMQ-induced cell death (Supplemental Figure 4, A and B), but is nevertheless required for induction of DC activation and IL-23 production. Of note, our results suggest that

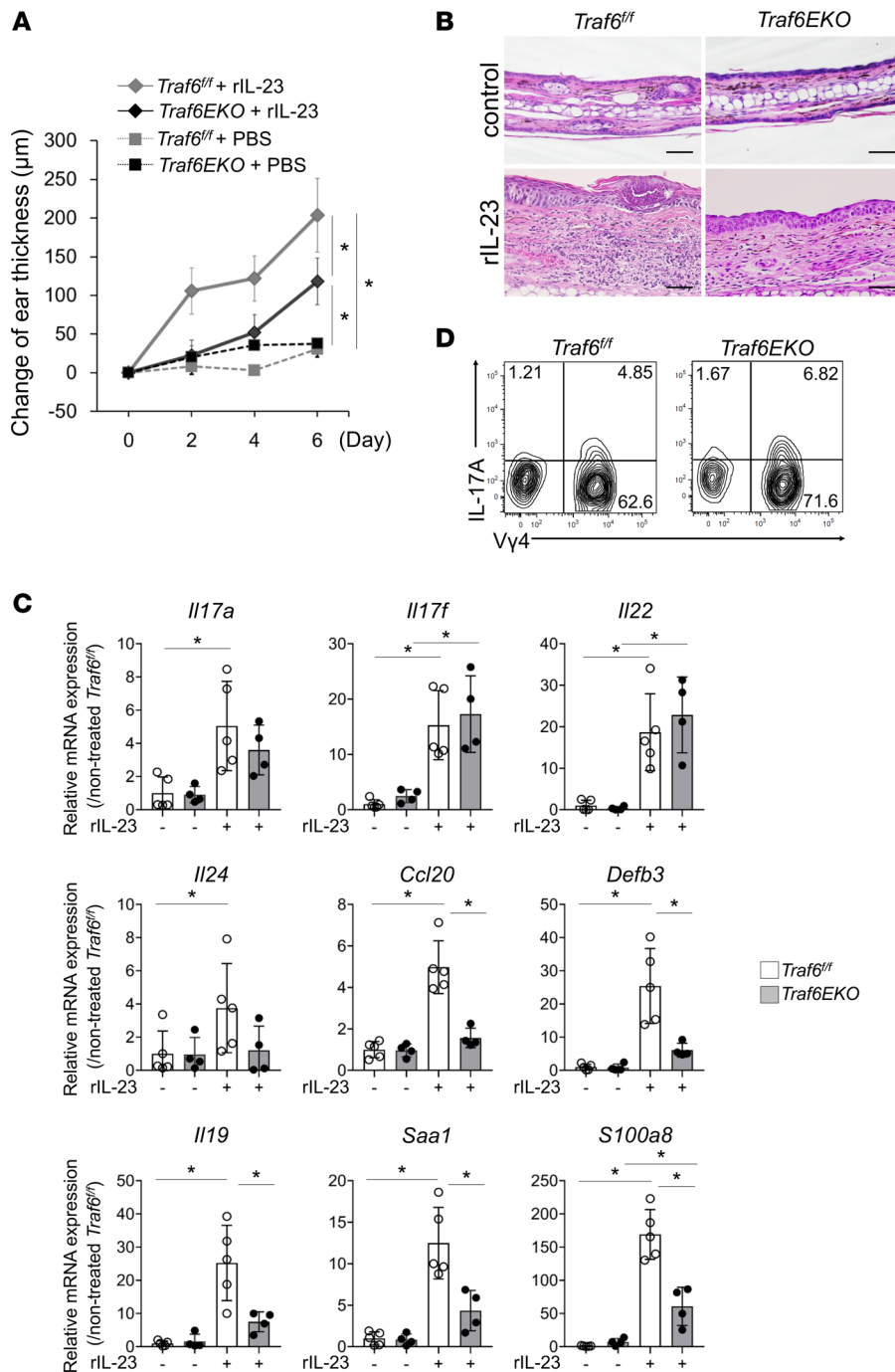


Figure 5. IL-23 partially restored the inflammation in *Traf6EKO* mice. (A) Time course of changes in ear thickness. *Traf6^{fl/fl}* and *Traf6EKO* mice ($n \geq 4$) were treated with rIL-23 every other day for 6 days and the ear thickness was measured before every treatment. Values are shown as means $\pm$ SD. * $P < 0.05$ (2-tailed Student's t test). (B) Histology of ear sections from the rIL-23-treated mice on day 6. H&E staining. Scale bars: 50 μ m. (C) qPCR analysis of mRNA levels in the ears from each group of mice on day 6 ($n \geq 4$). The results were normalized to *Gapdh* expression and are shown as means $\pm$ SD. * $P < 0.05$ (Tukey's multiple-comparisons test). (D) Representative flow cytometry plots of IL-17A-producing $V\gamma 4^+ \gamma\delta$ T cells in the ears of *Traf6^{fl/fl}* and *Traf6EKO* mice after 4 days of rIL-23 treatment. The plots show $\gamma\delta$ TCR $^+ V\gamma 4^+ IL-17A^+$ cells gated on $CD45^+$ cells. Data are representative of 3 experiments (A and B) or 2 experiments (C and D).

TRAF6 in keratinocytes regulates the transcriptional expression of proinflammatory genes in the unstimulated state (Figure 4, B–D), and that epidermal keratinocytes might affect the local, steady-state cutaneous immune system even under nonpathological conditions. Thus, our work inspires questions and follow-up investigations about whether epithelial TRAF6 signaling is also involved in the physiological and pathological responses, such as to commensal microorganisms (e.g., candida species and *Staphylococcus aureus*) (13).

The pathogenic mechanisms by which immune cells are initially activated in psoriasis are still under debate (15). We found that TRAF6 in LCs was dispensable for IMQ-induced inflammation (Supplemental Figure 1C), consistent with results obtained when LCs were deleted (43). Our work does not contradict the possibility of the direct activation of immune cells by external stimuli in psoriatic inflammation. Nevertheless, we demonstrated that the primary response of keratinocytes is required to activate immune cells in IMQ-induced inflammation. However, the key TRAF6-dependent products from keratinocytes have not

been identified. It has been demonstrated that IL-1R signaling also plays an important role in the development of psoriatic inflammation (44). We demonstrated that both the expression of IL-1 cytokines and the IL-1R signaling pathway depend on TRAF6 in keratinocytes (Figure 2, A, B and D; Figure 4A; and Supplemental Figure 2). These results may explain, in part, the impaired activation of skin immune cells and the abolishment of psoriatic inflammation in *Traf6*^{EKO} mice.

In human psoriasis, the upstream signaling events that lead to TRAF6 activation in keratinocytes remain controversial. Although IMQ is a ligand for TLR7/8, several studies have demonstrated that IMQ induces TLR7/MyD88-independent signaling in keratinocytes (45, 46), and in vivo (47). Thus, it is conceivable that TLR7-independent TRAF6 signaling in keratinocytes would take part in the initial wave of psoriatic inflammation. CARD14, predominantly localized in the epidermis, is one of the candidate mediators of the TLR7-independent keratinocyte signaling pathways in psoriatic inflammation. Gain-of-function mutations in CARD14 induce the formation of signalosomes that activate TRAF6 (24, 48, 49), and these mutations are found in familial-type psoriasis (50). Moreover, A20 encoded by another psoriasis susceptibility gene, *Tnfrsf3*, also regulates the TRAF6 pathway (51). Therefore, these genetic susceptibilities may be in part related to the homeostatic imbalance in the epidermal TRAF6 signaling. After all, abolishment of psoriatic inflammation in *Traf6*^{EKO} mice strongly suggests that the pathogenic signals in keratinocytes require TRAF6 regardless of their upstream signaling pathways.

Previous studies have suggested contributions of epithelial cells to immune divergence in several types of inflammation. However, to what extent, and by what principles epithelial cells are involved in shaping each response remains largely unknown. Here, we demonstrated that epithelial TRAF6 signaling is hardly involved in Th1 or Th2 responses: epicutaneous hapten-induced contact hypersensitivity or papain-induced dermatitis, respectively. Considering the requirement for epithelial TRAF6 for IMQ-induced IL-17-mediated inflammation, our results suggest a selective role for this specific epithelial signaling pathway. It is of great interest whether the TRAF6-independent epithelial signaling events are analogously restricted to induction of Th2 responses. Elucidation of such a pathway would be of particular interest given the protective role of the Th2 system in responses to helminths, arthropods, and toxins and the established role of keratinocytes in cutaneous Th2 response (7, 8).

It is noteworthy that studies using mice lacking TRAF6 in intestinal epithelial cells showed a critical role for intestinal epithelial TRAF6 for preventing propagation of dextran sodium sulfate-induced (DSS-induced) colon inflammation (52). Intestinal barrier integrity is maintained by IL-17 cytokines (53, 54). Thus, it is a plausible idea that epithelial TRAF6 is uniquely involved in local, IL-17-mediated, protective responses despite its pathogenetic role in IL-17-mediated psoriatic inflammation.

There are a few limitations to the current study. First, we could not fully rule out indirect effects of defective epithelial development or changes in the organization of immune cells in *Traf6*^{EKO} mice. TRAF6 is involved in the development of epithelial appendages (55, 56), although we did not observe marked defects in epidermal development or keratinocyte proliferation. Second, we could not detect direct evidence of elevated TRAF6 E3 ubiquitin ligase activity in psoriasis, by the experiments with existing techniques or by analyzing the published human transcriptome.

In summary, we demonstrated that epithelial TRAF6-dependent signaling is essential for the initiation of IL-17-mediated inflammation induced by IMQ treatment in mice. In this animal model, epithelial cells respond to the extrinsic agent in a TRAF6-dependent manner, engaging a transcriptional program that programs resident immune cells, leading to the induction and promotion of cutaneous psoriatic inflammation. These findings raise further questions about whether epithelial cells sense microbes directly and how they orchestrate immune cells to induce the appropriate immune response, in the gut, in the lung, and in the skin. This work also underscores the importance of considering epithelial signaling pathways in efforts to identify new treatments for chronic inflammatory diseases and develop effective vaccination strategies for infectious agents.

Methods

Mice. Eight- to 12-week-old female mice were used in this study. All animals used were of the C57BL/6 genetic background. *Traf6*^{fl/fl} mice have been reported previously (18). To prepare keratinocyte-specific TRAF6-deficient (*Traf6*^{EKO}) mice, male mice bearing the *Cre* recombinase transgene, under the control of the keratin 5 promoter (*K5-Cre*), were mated with female *Traf6*^{fl/fl} mice (18). The *K5-Cre; Traf6*^{fl/fl} mice were born at expected Mendelian frequency, fertile, and developed normally without gross abnormality, and displayed impaired expression of *Traf6* mRNA (Supplemental Figure 1A) and TRAF6 protein in keratinocytes (Figure 4A).

The male *Langerin-Cre* mice were crossed with the female *Traf6^{fl/fl}* mice to create *Langerin-Cre; Traf6^{fl/fl}* (*Traf6LCKO*) mice, in which deletion of *Traf6* should be limited to epidermal LCs (57). All animals were maintained under specific pathogen-free conditions.

Skin inflammation models. For the IMQ-induced psoriasis model, a daily dose of 10 mg of IMQ-containing cream, Aldara (Beselna Cream 5%, Mochida Pharmaceuticals), was applied onto the mouse ear for 2–6 consecutive days. In this study, the abbreviation IMQ always means “IMQ-containing cream, Aldara” unless otherwise indicated. Ear thickness was measured for each mouse every day using a thickness gauge (Teclok), and the difference from day 0 was expressed as the change in ear thickness. For DNFB-induced contact hypersensitivity, mice were sensitized on shaved abdominal skin with 25 μ l 0.5% (w/v) DNFB in acetone/olive oil (4:1). Five days after sensitization, the ears were challenged with an application of 20 μ l 0.3% DNFB. For the papain occlusive dressing technique, 100 μ g of papain (Calbiochem) diluted in 10 μ l PBS was applied on shaved and tape-stripped dorsal skin and fixed. Each mouse had a total of three 4-day exposures to the patch, separated by 3-day intervals. Mice were euthanized at the end of the third cycle of sensitization. The clinical severity was scored according to the macroscopic diagnostic criteria (58). For the IL-23–induced psoriatic dermatitis model, mouse rIL-23 (500 ng in 20 μ l of PBS) (Wako Pure Chemicals) was subcutaneously injected into one ear of each mouse using a 30-gauge needle every other day for 6 days.

Histological analyses. For histological analyses, skin tissues were fixed with 10% formalin in PBS and then embedded in paraffin. Sections with a thickness of 5 μ m were prepared and stained with hematoxylin and eosin (H&E).

Flow cytometry. Flow cytometric analysis was performed by the following methods. Briefly, a split ear sample was incubated for 60 minutes at 37°C with a solution of complete RPMI containing 100 μ g/ml DNase I (Sigma-Aldrich) and 2 mg/ml Liberase TL (Roche) to obtain a homogeneous cell suspension. The cell suspensions were filtered using a 40- μ m cell strainer and stained. For analysis of intracellular cytokine production, cell suspensions were obtained in the presence of 10 μ g/ml brefeldin A (Sigma-Aldrich) and were fixed with Cytofix Buffer and permeabilized with Perm/Wash Buffer according to the manufacturer's protocol (BD Biosciences). The following antibodies were used: antibody against mouse CD4-FITC (RM4-5), anti-CD8a-PerCP-Cy5.5 (53-6.7), anti-CD11c-BV605 (N418), anti-MHC class II-FITC (M5/114.15.2), anti-TCR- β -PE-Cy7 (H57-597), anti- $\gamma\delta$ TCR-FITC/PB (GL3), anti-V γ 2-PE/APC (UC3-10A6), and anti-Ly6G-FITC (1A8) (all from BioLegend); anti-CD11b-PE-Cy7 (M1/70), anti-CD45-PE-Cy7/PB (30-F11), anti- $\gamma\delta$ TCR-FITC (GL3), and anti-IL-17A-PE (TC11-18H10) (all from BD Biosciences); anti-CD80-PE (16-10A1), anti-CD86-PE (GL1), and anti-langerin-APC (CD207) (RMUL.2) (all from eBioscience). Flow cytometry was done with an LSR Fortessa (BD Biosciences) and data were analyzed with FlowJo software (Tree Star).

RNA isolation and quantitative RT-PCR analysis. Total RNA was isolated using TRIzol (Invitrogen) or RNeasy kits (Qiagen) according to the manufacturers' protocol. Complementary DNA was reverse transcribed using the Prime Script RT reagent kit (Takara Bio). Quantitative RT-PCR was performed as reported previously (34). All primers were obtained from Greiner Japan. Primer sequences are provided in Supplemental Table 3.

Microarray analysis. Total RNAs prepared from the ears of *Traf6EKO* mice and *Traf6^{fl/fl}* mice treated with IMQ for 2 consecutive days ($n = 2$) were analyzed by microarray. Total RNA from skin samples was immediately isolated with TRIzol according to the manufacturer's protocol. An amplified sense-strand DNA product was synthesized with the Ambion WT Expression Kit (Life Technologies), was fragmented and labeled by the WT Terminal Labelling and Controls Kit (Affymetrix), and hybridized to a Mouse Gene 1.0 ST Array (Affymetrix). We used the robust multiarray average algorithm for log transformation ($\log_2$) and normalization of the GeneChip data. Z-score transformation followed by generation of a heatmap was performed using R software. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis was performed using DAVID v6.8 bioinformatics resources (<https://david.ncifcrf.gov/>). *P* values < 0.05 were considered to be significant (adjusted by the Benjamini–Hochberg method), whereas false discovery rates of only the top 2 pathways were < 0.1. Microarray data were deposited in the NCBI's Gene Expression Omnibus database (GEO GSE101077).

Cell culture. Mouse primary keratinocytes were harvested from newborn epidermis and were cultured in low-calcium medium (0.05 mM Ca^{2+}), using EMEM (Lonza) with chelated FCS as reported previously (59). In general, full-thickness skin was obtained from newborn mice. The skin samples were floated and incubated in Dispase II (1 U/ml; Roche) overnight at 4°C. The epidermis was then separated from the

dermis, cut into pieces, and incubated in 0.05% trypsin for 5 minutes. Cells were cultured in low-calcium medium (0.05 mM Ca^{2+}), using EMEM with chelated FCS. Cells were seeded on 12-well plates at a density of 3×10^5 cells per well for RNA extraction and lactate dehydrogenase (LDH) assay. For cell-signaling experiments, cells were serum starved for 24 hours prior to stimulation. A total of 60 mg IMQ (Aldara cream) was dissolved in 1 ml dimethylsulfoxide (DMSO), which was further diluted with cell-culture medium at the indicated dilution, and used for cell stimulation. IMQ (30 $\mu\text{g}/\text{ml}$), rIL-17A and IL-17F (100 ng/ml; R&D Systems), and rIL-1 β (20 ng/ml, R&D Systems) were used to stimulate primary keratinocytes. LDH assay was performed using a Pierce LDH cytotoxicity assay kit (Thermo Fisher Scientific) according to the manufacturer's protocol.

Cell death assay. We treated primary cultured murine keratinocytes with or without IMQ and analyzed the release of LDH in the supernatants. The levels of LDH release were comparable between *Traf6^{fl/fl}* and *Traf6^{EKO}* mice at all tested doses of IMQ, and nuclear morphology was indistinguishable in both at the lower doses of IMQ (Supplemental Figure 4, A and B).

Western blotting. Cells were lysed with cell lysis buffer (Abcam, ab152163) and protease inhibitor cocktail (Sigma-Aldrich, P8340). The lysates were centrifuged at 13,000 g for 5 minutes at 4°C and the supernatant was used in the following steps. Samples were resolved by SDS-PAGE and transferred to nitrocellulose membranes (Bio-Rad, 162-0168). After blocking with 5% (wt/vol) nonfat dry milk or bovine serum albumin, the membranes were incubated with primary antibodies for 16 hours at 4°C, followed by incubation with horseradish peroxidase-conjugated secondary antibodies for 1 hour at room temperature. Signals were detected using ECL Prime Western Blotting Detection Reagent (GE Healthcare, GE-RPN2024). Images were captured and density of the bands was measured using the ChemiDoc Touch Imaging System (Bio-Rad).

Antibodies recognizing the following proteins were used: TRAF6 (Santa Cruz Biotechnology, 7221), α -tubulin (Sigma-Aldrich, T5168), I κ B α (Cell Signaling Technology, 9242), p-I κ B α (Cell Signaling Technology, 2859), p38 (Cell Signaling Technology, 9212), and p-p38 (Cell Signaling Technology, 9211).

Statistics. Unless otherwise indicated, data are presented as means $\pm$ standard deviations. Two-tailed Student's *t* test and Tukey's multiple comparison test were performed to assess statistical significance. *P* values < 0.05 were considered to be significant and are marked by an asterisk in the figures.

Study approval. In this study, all procedures for animal experiments were reviewed and approved by Animal Research Committee, Graduate School of Medicine, Kyoto University (approval Med Kyo 17282) and were performed in accordance with institutional guidelines.

Author contributions

RM and TD designed the studies. RM performed experiments and analyzed data. TD advised on execution of experiments, and interpretation of results. ST and YS performed microarray. KJI, MT, and TK provided animals and research ideas. TN generated animals. AK, TH, GE, AO, and SN reviewed the draft. MSH, KS, and YN contributed to discussion and interpretation of the results. RM, TD and MSH wrote and edited the manuscript. KK supervised and financed the work.

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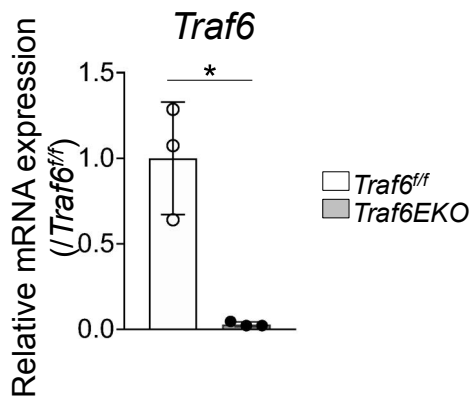
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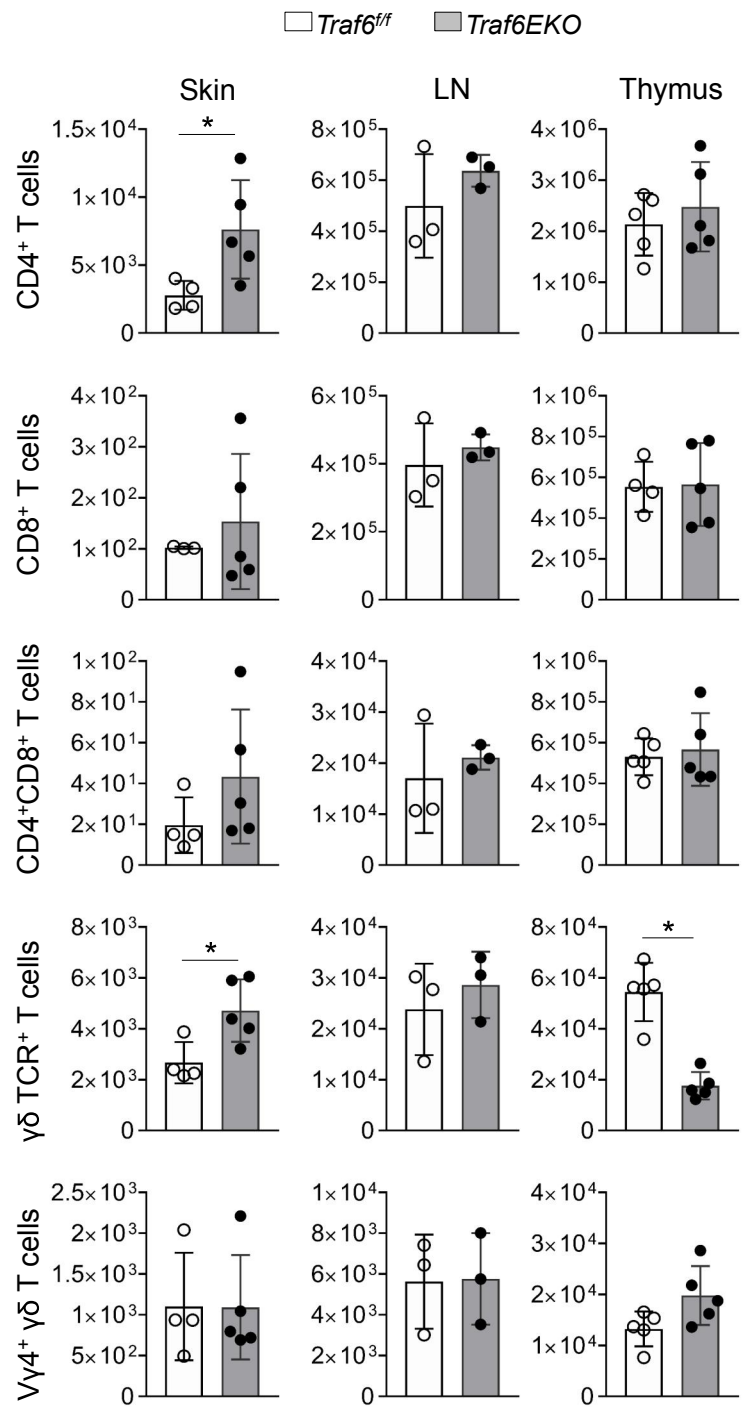
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Figure S1.

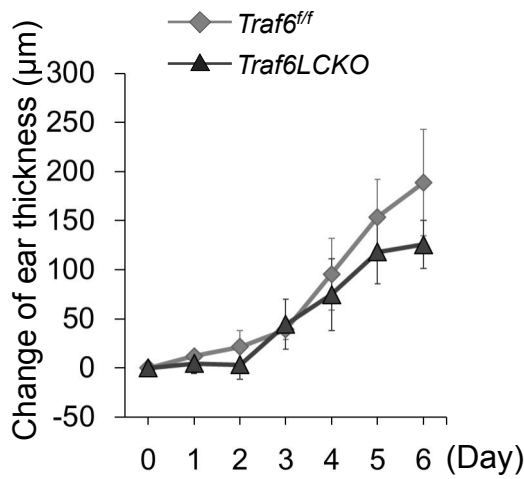
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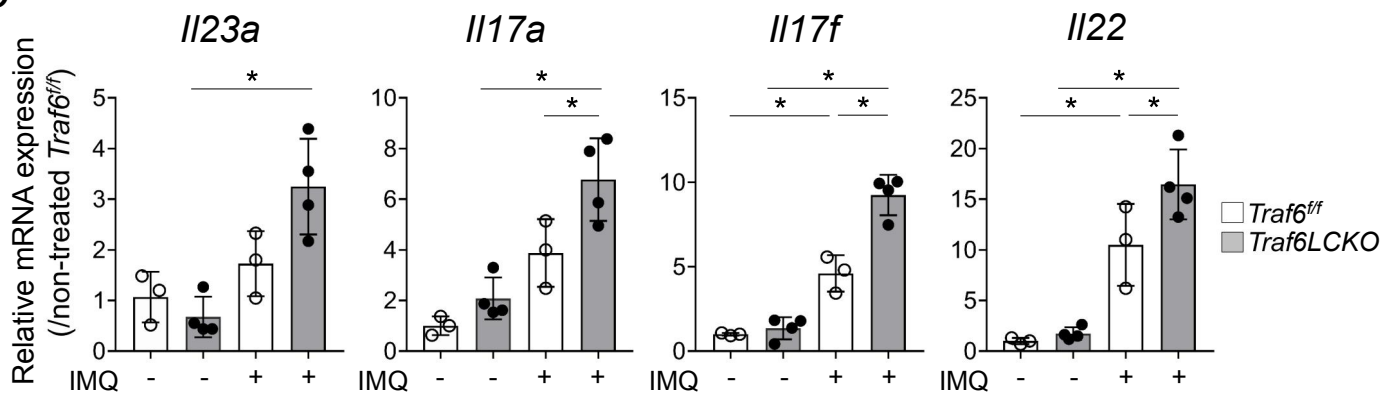
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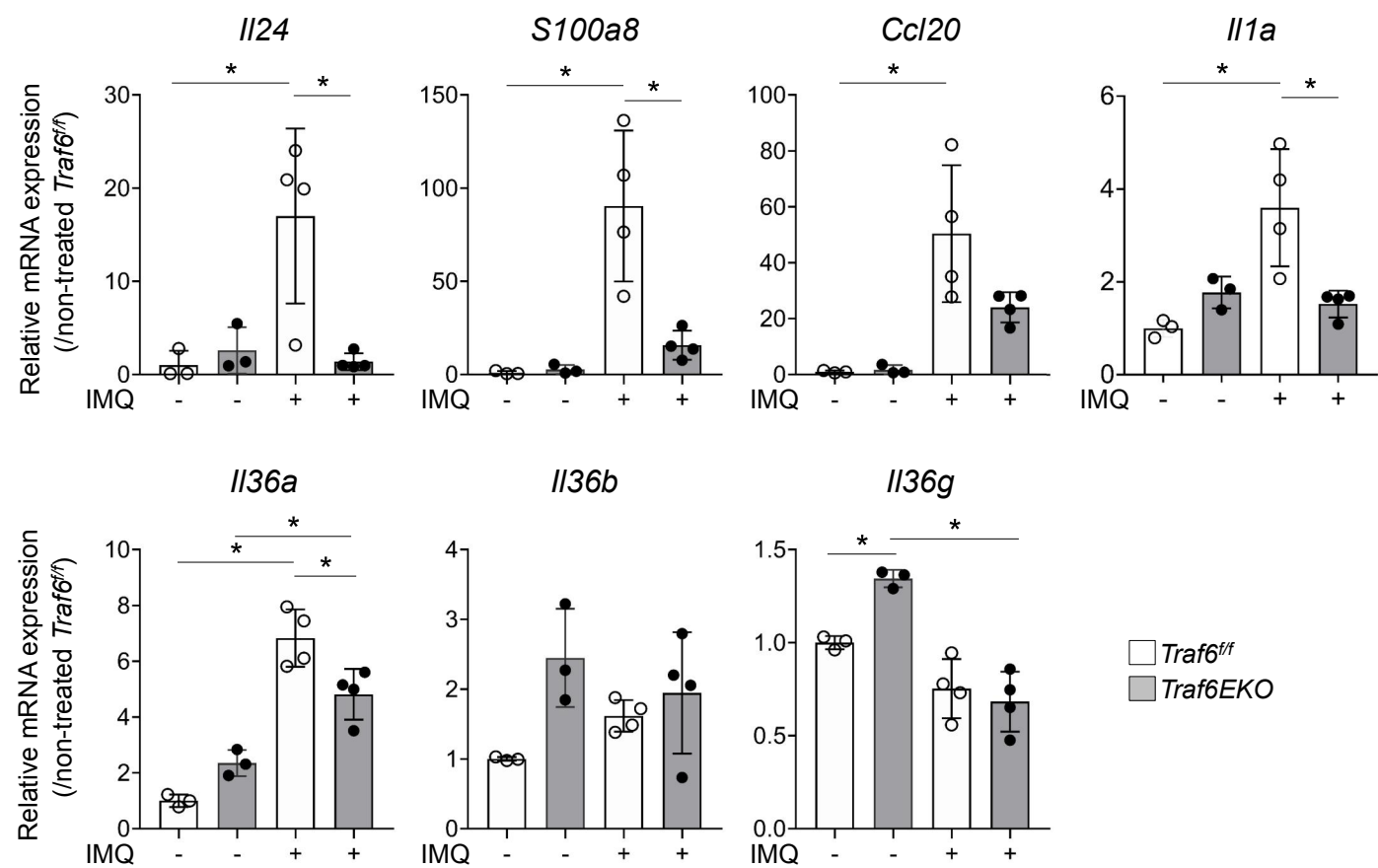
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Supplemental Figure 1. The effect of keratinocyte-specific deletion of TRAF6 and the retained response in *Traf6LCKO* mice treated with IMQ.

(A) *Traf6* mRNA levels in keratinocytes from *Traf6^{ff}* mice and *Traf6EKO* mice (n = 3 per group). Results are shown as means $\pm$ SD, * $P < 0.05$ (two-tailed Student's *t*-test). The deletion efficiency of TRAF6 protein in keratinocytes from *Traf6EKO* mice was demonstrated by Western blot analysis (**Figure 4A**) (B) Flow cytometric quantification of CD4⁺ T cells, CD8⁺ T cells, CD4⁺ CD8⁺ T cells, $\gamma\delta$ TCR⁺ cells, $\gamma\delta$ TCR⁺ V γ 4⁺ cells from ear, lymph node and thymus in *Traf6^{ff}* mice and *Traf6EKO* mice (n $\geq$ 3 per group). Results are shown as means $\pm$ SD, * $P < 0.05$ (two-tailed Student's *t*-test). (C) Time course of changes in ear thickness. *Traf6^{ff}* and *Traf6LCKO* mice (n $\geq$ 4 per group) were treated with IMQ for 6 consecutive days and ear thickness was measured daily before treatment. Results are shown as means $\pm$ SD, * $P < 0.05$ (two-tailed Student's *t*-test). (D) qPCR analysis of mRNA levels in the ear of *Traf6^{ff}* and *Traf6LCKO* mice treated with IMQ for 6 days (n $\geq$ 3). The results were normalized to *Gapdh* expression and are shown as means $\pm$ SD, * $P < 0.05$ (Tukey's multiple comparison test). Data are representative of five experiments (A), three experiments (B), or two experiments (C and D).

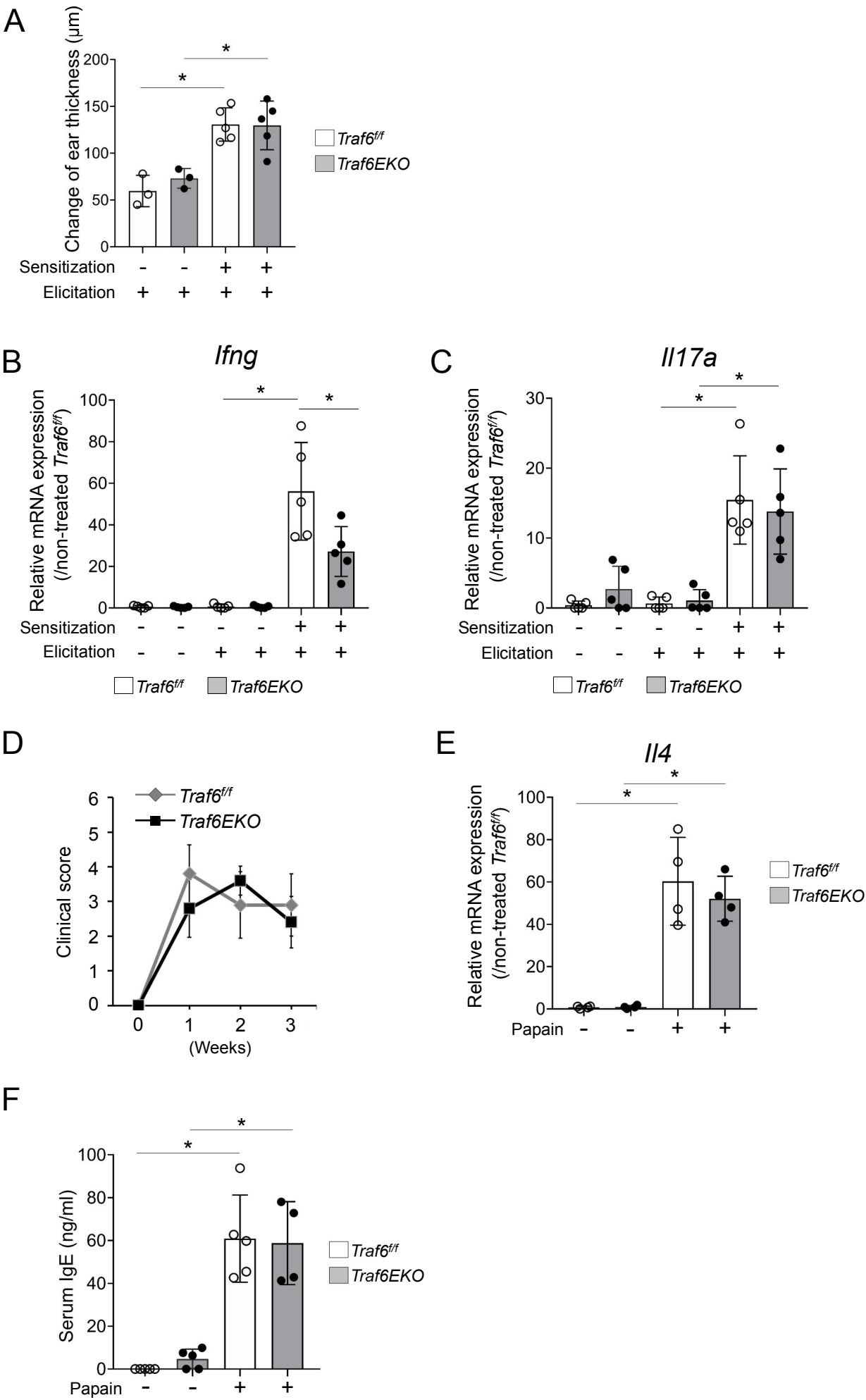
Figure S2.



Supplemental Figure 2. Additional gene expression analysis of IMQ-treated epidermis in *Traf6*^{EKO} mice.

qPCR analysis of psoriasis-related gene expression levels in the epidermis of the IMQ-treated mouse ear on day 2 (n ≥ 3 per group). The results were normalized to *Gapdh* expression and are shown as means ± SD, * $P < 0.05$ (Tukey's multiple comparison test). Data are representative of three experiments.

Figure S3.

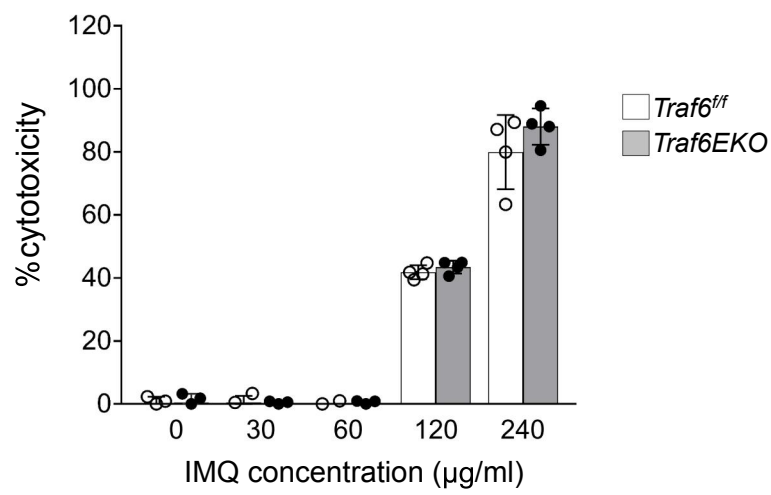


Supplemental Figure 3. Additional response of *Traf6*^{EKO} mice in several types of skin inflammation.

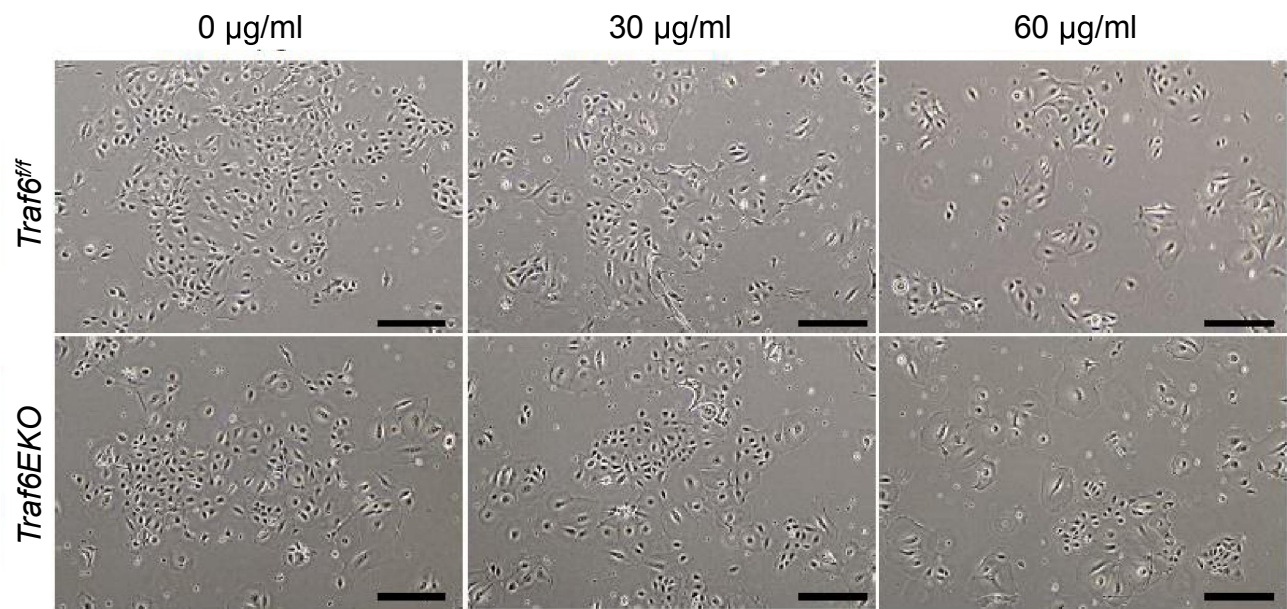
(A) Changes in ear thickness in a DNFB-induced contact hypersensitivity (CHS) model. *Traf6*^{f/f} and *Traf6*^{EKO} mice (n ≥ 3) were sensitized with DNFB or vehicle, and the ear thickness was measured 24 h after elicitation. (B and C) qPCR analysis of mRNA levels of *Ifng* (B) and *Il17a* (C) in the CHS-elicited ears of *Traf6*^{f/f} and *Traf6*^{EKO} mice (n ≥ 4). (D) Clinical severity scores of *Traf6*^{f/f} and *Traf6*^{EKO} mice treated with papain (n ≥ 4). (E) qPCR analysis of mRNA levels of *Il4* in the draining lymph nodes of *Traf6*^{f/f} and *Traf6*^{EKO} mice 5 days after epicutaneous administration with papain (n ≥ 4). (F) Serum IgE levels of *Traf6*^{f/f} and *Traf6*^{EKO} mice were determined by enzyme-linked immunosorbent assay after 3-week treatment with papain (n ≥ 4). Results are shown as means ± SD, * *P* < 0.05 (Tukey's multiple comparison test). Data are representative of three experiments (A–F).

Figure S4.

A



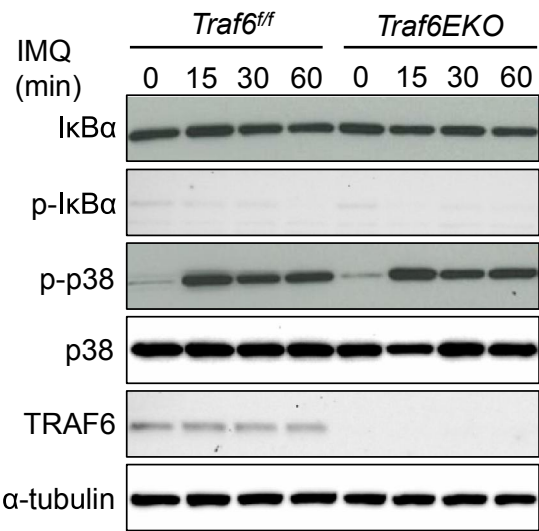
B



Supplemental Figure 4. The impact of TRAF6 deficiency on keratinocyte cell death.

(A) LDH release assay of cytotoxicity. Culture supernatants of *Traf6^{ff}* and *Traf6EKO* keratinocytes were collected after 2 h exposure to 0–120 µg/ml IMQ (n ≥ 3). Bars indicate means ± SD of the percentiles of cytotoxicity. * $P < 0.05$ (two-tailed Student's *t*-test). (B) Photomicrographs of comparison of cell morphology between *Traf6^{ff}* and *Traf6EKO* keratinocytes at different concentration of IMQ. Primary cultured keratinocytes from *Traf6^{ff}* and *Traf6EKO* mice were stimulated with IMQ (0–60 µg/ml) for 2 h. Data are representative of three experiments (A and B).

Figure S5.



Supplemental Figure 5. Additional Western blot analysis of IMQ-treated TRAF6-deficient keratinocytes.

Western blot analysis of keratinocytes from *Traf6*^{EKO} mice and *Traf6*^{f/f} mice stimulated with IMQ at the indicated time point. Total cell lysates were subjected to SDS-PAGE followed by immunoblotting.

Supplemental Table 1.

Gene symbol	Gene description	Traf6				Expression ratio by		A/B
		f/f control	Traf6EKO control	Traf6 f/f IMQ	Traf6EKO IMQ	IMQ in Traf6 f/f mice (A)	Expression ratio by IMQ in Traf6EKO mice	
Defb3	defensin beta 3	1	0.90	45.96	2.51	45.96	2.78	16.52
Defb4	defensin beta 4	1	1.10	23.59	2.04	23.59	1.86	12.68
S100a8	S100 calcium binding protein A8 (calgranulin A)	1	1.01	32.22	2.59	32.22	2.56	12.57
Sprr2j-ps	small proline-rich protein 2J, pseudogene	1	0.88	15.74	1.28	15.74	1.45	10.84
S100a9	S100 calcium binding protein A9 (calgranulin B)	1	0.98	26.74	2.53	26.74	2.59	10.32
Sprr2f	small proline-rich protein 2F	1	1.05	17.94	2.22	17.94	2.11	8.50
Il1b	interleukin 1 beta	1	1.18	14.69	2.06	14.69	1.75	8.39
Sprr2g	small proline-rich protein 2G	1	1.36	21.54	3.49	21.54	2.57	8.38
Lce3a	late cornified envelope 3A	1	1.29	24.69	3.93	24.69	3.04	8.12
Sprr2e	small proline-rich protein 2E	1	1.03	23.10	3.32	23.10	3.23	7.15
Cxcl2	chemokine (C-X-C motif) ligand 2	1	1.09	8.90	1.43	8.90	1.31	6.80
Gm5416	predicted gene 5416	1	1.16	18.49	3.16	18.49	2.72	6.79
Ptgs2	prostaglandin-endoperoxide synthase 2	1	2.26	9.38	3.17	9.38	1.40	6.68
Trem1	triggering receptor expressed on myeloid cells 1	1	1.01	7.24	1.12	7.24	1.11	6.54
Slc7a11	family 7 (cationic amino acid transporter, y+ system)	1	1.52	18.18	4.27	18.18	2.81	6.47
Lce3e	late cornified envelope 3E	1	3.75	55.71	32.43	55.71	8.65	6.44
Epgn	epithelial mitogen	1	1.55	15.76	4.01	15.76	2.59	6.08
Uox	urate oxidase	1	1.00	6.17	1.06	6.17	1.05	5.88
Slfn4	schlafen 4	1	1.32	10.22	2.55	10.22	1.93	5.30
Sprr1b	small proline-rich protein 1B	1	4.09	16.49	12.94	16.49	3.17	5.21
Sprr2b	small proline-rich protein 2B	1	0.98	16.30	3.09	16.30	3.15	5.17
Defb14	defensin beta 14	1	1.84	7.52	2.79	7.52	1.52	4.95
Slpi	secretory leukocyte peptidase inhibitor	1	1.12	7.83	1.78	7.83	1.60	4.89
Has3	hyaluronan synthase 3	1	1.23	10.13	2.56	10.13	2.08	4.87
Ccl20	chemokine (C-C motif) ligand 20	1	0.88	9.14	1.71	9.14	1.94	4.71
Saa3	serum amyloid A 3	1	1.28	15.14	4.28	15.14	3.33	4.54
Sprr2i	small proline-rich protein 2I	1	0.85	6.07	1.15	6.07	1.35	4.52
Sprr2d	small proline-rich protein 2D	1	1.20	13.21	3.65	13.21	3.05	4.33
Hbegf	heparin-binding EGF-like growth factor	1	1.22	6.53	1.98	6.53	1.62	4.02
Prss27	protease, serine, 27	1	1.52	8.36	3.20	8.36	2.11	3.97
Lce3c	late cornified envelope 3C	1	2.76	11.38	7.97	11.38	2.89	3.94
Ccl3	chemokine (C-C motif) ligand 3	1	1.12	7.00	2.01	7.00	1.79	3.91
BC117090	cDNA sequence BC117090	1	1.09	10.34	2.98	10.34	2.74	3.77
Lcn2	lipocalin 2	1	0.92	6.25	1.55	6.25	1.68	3.71
Il1f6	interleukin 1 family, member 6	1	1.87	6.30	3.18	6.30	1.70	3.71
Slc5a1	carrier family 5 (sodium/glucose cotransporter), mem	1	1.59	5.22	2.27	5.22	1.43	3.66
Klk13	kallikrein related-peptidase 13	1	1.74	11.09	5.59	11.09	3.21	3.46
Gjb2	gap junction protein, beta 2	1	1.26	11.13	4.13	11.13	3.28	3.39
Klk6	kallikrein related-peptidase 6	1	2.23	11.13	7.40	11.13	3.32	3.35
Timp1	tissue inhibitor of metalloproteinase 1	1	1.12	5.49	1.84	5.49	1.64	3.35
Alox8	arachidonate 8-lipoxygenase	1	0.83	3.92	0.98	3.92	1.18	3.31
Il1a	interleukin 1 alpha	1	1.36	4.11	1.69	4.11	1.24	3.31
LOC100862551	late cornified envelope protein 3C-like	1	1.13	11.10	3.81	11.10	3.37	3.30
Cxcr2	chemokine (C-X-C motif) receptor 2	1	1.90	6.77	3.95	6.77	2.07	3.26
Gyk	glycerol kinase	1	1.05	5.47	1.77	5.47	1.69	3.23
Gsta4	glutathione S-transferase, alpha 4	1	1.37	13.66	5.83	13.66	4.26	3.21
Stfa2	stefin A2	1	1.17	12.87	4.74	12.87	4.05	3.17
Sprr2h	small proline-rich protein 2H	1	1.76	10.43	5.80	10.43	3.30	3.16
Serpina9	peptidase inhibitor, clade A (alpha-1 antiproteinase, an	1	1.28	6.06	2.49	6.06	1.95	3.11
Cyp7b1	cytochrome P450, family 7, subfamily b, polypeptide 1	1	1.03	3.92	1.31	3.92	1.28	3.07
Krt16	keratin 16	1	1.83	25.82	15.57	25.82	8.50	3.04
Gjb6	gap junction protein, beta 6	1	1.36	8.39	3.84	8.39	2.82	2.98
Irg1	immunoresponsive gene 1	1	0.98	4.21	1.40	4.21	1.43	2.94
Pi15	peptidase inhibitor 15	1	0.77	4.70	1.24	4.70	1.60	2.93
Pla2g4e	phospholipase A2, group IVE	1	1.22	8.15	3.48	8.15	2.85	2.86
Lpo	lactoperoxidase	1	1.34	13.34	6.30	13.34	4.70	2.84
Slc5a8	solute carrier family 5 (iodide transporter), member 8	1	0.96	5.11	1.75	5.11	1.82	2.81
Il33	interleukin 33	1	1.19	3.07	1.31	3.07	1.10	2.79
Lce3b	late cornified envelope 3B	1	1.42	3.71	1.89	3.71	1.33	2.79
Bcl3	B cell leukemia/lymphoma 3	1	1.06	4.79	1.84	4.79	1.73	2.77
2310042E22Rik	RIKEN cDNA 2310042E22 gene	1	1.70	4.45	2.75	4.45	1.62	2.75
Chi3l1	chitinase 3-like 1	1	1.15	4.68	1.96	4.68	1.71	2.75
Phlda1	pleckstrin homology-like domain, family A, member 1	1	1.07	3.02	1.21	3.02	1.13	2.67
Gm5593	predicted gene 5593	1	1.83	5.37	3.73	5.37	2.04	2.63
Stfa2l1	stefin A2 like 1	1	1.32	11.13	5.62	11.13	4.24	2.62
Areg	amphiregulin	1	1.01	3.33	1.30	3.33	1.29	2.58
Gm12248	predicted gene 12248	1	1.03	4.22	1.71	4.22	1.67	2.53
Clec4d	C-type lectin domain family 4, member d	1	1.11	3.13	1.37	3.13	1.24	2.53
Pglyrp3	peptidoglycan recognition protein 3	1	0.87	4.10	1.41	4.10	1.63	2.52
Ankrd1	ankyrin repeat domain 1 (cardiac muscle)	1	0.88	2.61	0.92	2.61	1.04	2.51
Bub1	ng uninhibited by benzimidazoles 1 homolog (S. cerevi	1	1.61	5.32	3.44	5.32	2.13	2.50
Ect2	ect2 oncogene	1	1.86	4.28	3.19	4.28	1.72	2.49
LOC101055986	uncharacterized LOC101055986	1	1.12	2.50	1.13	2.50	1.01	2.48
Stfa3	stefin A3	1	1.77	14.94	10.64	14.94	6.01	2.48
Degs2	rative spermatocyte homolog 2 (Drosophila), lipid desa	1	1.69	7.27	4.97	7.27	2.93	2.48
Slc26a9	solute carrier family 26, member 9	1	1.49	4.39	2.68	4.39	1.80	2.44
Gm10871	predicted gene 10871	1	1.11	6.32	2.87	6.32	2.59	2.44
Tnfrsf25	tumor necrosis factor, alpha-induced protein 2	1	1.08	2.90	1.29	2.90	1.19	2.43
Hist1h2bb	histone cluster 1, H2bb	1	1.63	3.46	2.32	3.46	1.42	2.43
Ccl2	chemokine (C-C motif) ligand 2	1	0.97	3.36	1.34	3.36	1.39	2.41
Hs3st1	heparan sulfate (glucosamine) 3-O-sulfotransferase 1	1	1.04	2.22	0.96	2.22	0.93	2.40
Csf3r	colony stimulating factor 3 receptor (granulocyte)	1	1.10	2.74	1.28	2.74	1.16	2.35
Prss22	protease, serine, 22	1	0.90	3.37	1.29	3.37	1.44	2.34
Hist1h2bm	histone cluster 1, H2bm	1	1.81	3.19	2.47	3.19	1.36	2.34

Fos1	fos-like antigen 1	1	1.24	3.36	1.80	3.36	1.45	2.32
Fgfbp1	fibroblast growth factor binding protein 1	1	1.24	3.39	1.82	3.39	1.46	2.32
Plk1	polo-like kinase 1	1	1.76	4.91	3.74	4.91	2.12	2.32
Rbp2	retinol binding protein 2, cellular	1	1.68	6.20	4.53	6.20	2.70	2.30
Pla2g4b	phospholipase A2, group IVB (cytosolic)	1	1.19	4.21	2.21	4.21	1.86	2.26
Gm10872	predicted gene 10872	1	1.00	2.55	1.14	2.55	1.14	2.23
Ank1	ankyrin repeat and kinase domain containing 1	1	1.14	2.15	1.11	2.15	0.98	2.20
Mmp13	matrix metalloproteinase 13	1	1.18	2.69	1.45	2.69	1.23	2.19
Gm9944	predicted gene 9944	1	0.93	3.32	1.42	3.32	1.52	2.18
Serpinb6c	serpin (or cysteine) peptidase inhibitor, clade B, member 6	1	1.36	6.22	3.88	6.22	2.86	2.17
Klk9	kallikrein related-peptidase 9	1	1.63	4.50	3.37	4.50	2.07	2.17
Tgm3	transglutaminase 3, E polypeptide	1	1.37	3.07	1.94	3.07	1.42	2.17
Aqp3	aquaporin 3	1	1.60	4.51	3.32	4.51	2.08	2.16
Ccr1	chemokine (C-C motif) receptor 1	1	0.87	2.65	1.07	2.65	1.23	2.16
Clec7a	C-type lectin domain family 7, member a	1	0.81	2.14	0.80	2.14	0.99	2.16
1190003J15Rik	RIKEN cDNA 1190003J15 gene	1	1.41	3.28	2.15	3.28	1.52	2.15
Asf1b	SF1 anti-silencing function 1 homolog B (S. cerevisiae)	1	1.56	3.85	2.80	3.85	1.80	2.14
Ccna2	cyclin A2	1	1.77	4.34	3.59	4.34	2.03	2.13
Stom	stomatin	1	1.14	2.70	1.45	2.70	1.27	2.13
Cdk1	cyclin-dependent kinase 1	1	1.48	3.58	2.48	3.58	1.68	2.13
Nlrp3	NLR family, pyrin domain containing 3	1	0.94	2.18	0.97	2.18	1.03	2.12
Tubb6	tubulin, beta 6 class V	1	0.95	2.76	1.24	2.76	1.30	2.12
Krt6b	keratin 6B	1	1.77	10.78	9.09	10.78	5.13	2.10
Tnc	tenascin C	1	1.15	3.44	1.89	3.44	1.64	2.10
Socs3	suppressor of cytokine signaling 3	1	1.32	2.03	1.28	2.03	0.97	2.09
Slc1a1	neuronal/epithelial high affinity glutamate transporter, 1	1	0.74	2.10	0.75	2.10	1.01	2.09
Dsg3	desmoglein 3	1	1.22	2.63	1.54	2.63	1.26	2.08
Zc3h12a	zinc finger CCCH type containing 12A	1	1.24	2.73	1.63	2.73	1.31	2.08
Fetub	fetuin beta	1	1.06	2.33	1.19	2.33	1.12	2.08
Cdc20	cell division cycle 20	1	1.49	3.98	2.85	3.98	1.92	2.08
Lamc2	laminin, gamma 2	1	1.27	2.28	1.40	2.28	1.10	2.07
Krt6a	keratin 6A	1	1.09	14.47	7.63	14.47	7.02	2.06
Klk12	kallikrein related-peptidase 12	1	1.11	2.39	1.29	2.39	1.16	2.05
Akr1b8	aldo-keto reductase family 1, member B8	1	1.10	3.43	1.85	3.43	1.68	2.04
Ccl7	chemokine (C-C motif) ligand 7	1	0.97	3.41	1.61	3.41	1.67	2.04
Ccnb2	cyclin B2	1	1.77	4.23	3.67	4.23	2.07	2.04
Clcf1	cardiotrophin-like cytokine factor 1	1	1.11	2.28	1.24	2.28	1.12	2.04
Cd44	CD44 antigen	1	1.29	2.91	1.84	2.91	1.43	2.03
Crabp2	cellular retinoic acid binding protein II	1	1.32	2.86	1.87	2.86	1.42	2.02
Hist1h1b	histone cluster 1, H1b	1	1.72	3.69	3.14	3.69	1.83	2.02
Ptges	prostaglandin E synthase	1	1.27	2.61	1.65	2.61	1.30	2.01
Enah	enabled homolog (Drosophila)	1	1.21	2.88	1.74	2.88	1.43	2.01
Tmem97	transmembrane protein 97	1	1.54	3.01	2.31	3.01	1.50	2.01
Kif4	kinesin family member 4	1	1.51	2.60	1.96	2.60	1.30	2.01
Ifi202b	interferon activated gene 202B	1	1.02	2.06	1.05	2.06	1.03	2.00
Cdca3	cell division cycle associated 3	1	1.65	3.60	2.98	3.60	1.81	2.00
Tgm1	transglutaminase 1, K polypeptide	1	1.40	2.36	1.66	2.36	1.18	1.99
Klk10	kallikrein related-peptidase 10	1	0.75	4.39	1.66	4.39	2.21	1.98
Gsdmc	gasdermin C	1	1.53	5.37	4.14	5.37	2.71	1.98
Psors1c2	psoriasis susceptibility 1 candidate 2 (human)	1	0.95	2.92	1.41	2.92	1.48	1.98
Cks2	CDC28 protein kinase regulatory subunit 2	1	1.52	3.31	2.55	3.31	1.68	1.97
Il17c	interleukin 17C	1	0.85	2.23	0.96	2.23	1.13	1.97
Pbk	PDZ binding kinase	1	1.30	2.69	1.80	2.69	1.38	1.95
Ppif	peptidylprolyl isomerase F (cyclophilin F)	1	1.23	2.49	1.57	2.49	1.28	1.94
Smc2	structural maintenance of chromosomes 2	1	1.28	2.92	1.92	2.92	1.50	1.94
Itga3	integrin alpha 3	1	1.28	2.36	1.55	2.36	1.22	1.94
Mfsd7c	major facilitator superfamily domain containing 7C	1	1.42	2.28	1.67	2.28	1.18	1.94
Odc1	ornithine decarboxylase, structural 1	1	1.03	2.05	1.09	2.05	1.06	1.93
Srm	spermidine synthase	1	1.30	2.28	1.53	2.28	1.18	1.93
Stfa1	stefin A1	1	1.36	4.56	3.23	4.56	2.37	1.93
Uck2	uridine-cytidine kinase 2	1	1.44	2.71	2.04	2.71	1.41	1.92
Nucb2	nucleobindin 2	1	1.03	2.40	1.28	2.40	1.25	1.92
Duox1	dual oxidase 1	1	1.19	2.23	1.38	2.23	1.16	1.92
Tpx2	microtubule-associated protein homolog (Xenopus laevis)	1	1.37	3.46	2.48	3.46	1.81	1.92
Ak4	adenylate kinase 4	1	1.41	2.10	1.55	2.10	1.10	1.92
Gm12891	predicted gene 12891	1	1.42	3.27	2.44	3.27	1.71	1.91
Avp1	arginine vasopressin-induced 1	1	1.53	2.83	2.27	2.83	1.48	1.91
4933413G19Rik	RIKEN cDNA 4933413G19 gene	1	1.61	2.94	2.49	2.94	1.55	1.90
Cenpe	centromere protein E	1	1.49	3.96	3.09	3.96	2.08	1.90
Kif20a	kinesin family member 20A	1	1.43	3.71	2.78	3.71	1.95	1.90
Adam8	a disintegrin and metalloproteinase domain 8	1	1.25	2.57	1.70	2.57	1.35	1.90
Rrm2	ribonucleotide reductase M2	1	1.28	3.06	2.07	3.06	1.62	1.89
Trex2	three prime repair exonuclease 2	1	1.55	3.27	2.68	3.27	1.73	1.89
Cdca5	cell division cycle associated 5	1	1.59	2.64	2.22	2.64	1.40	1.89
Mki67	antigen identified by monoclonal antibody Ki 67	1	1.60	3.74	3.17	3.74	1.98	1.89
Kif11	kinesin family member 11	1	1.43	3.74	2.87	3.74	2.00	1.87
Galnt6	phenyl-beta-D-galactosamine:polypeptide N-acetyl-galactosaminyl transferase 6	1	1.29	3.18	2.19	3.18	1.70	1.87
Bnc1	basonuclin 1	1	1.15	2.36	1.45	2.36	1.26	1.87
Kif15	kinesin family member 15	1	1.39	2.83	2.11	2.83	1.52	1.87
Htr1b	5-hydroxytryptamine (serotonin) receptor 1B	1	0.98	2.04	1.07	2.04	1.09	1.87
Sult2b1	sulfotransferase family, cytosolic, 2B, member 1	1	1.47	3.20	2.51	3.20	1.72	1.87
Top2a	topoisomerase (DNA) II alpha	1	1.47	3.63	2.87	3.63	1.95	1.86
Tk1	thymidine kinase 1	1	1.68	2.97	2.68	2.97	1.59	1.86
Ngf	nerve growth factor	1	1.09	2.76	1.61	2.76	1.49	1.86
Slc7a5	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5	1	1.26	2.68	1.82	2.68	1.44	1.86
S100a7a	S100 calcium binding protein A7A	1	0.83	2.07	0.92	2.07	1.12	1.85
Fgf23	fibroblast growth factor 23	1	0.98	2.03	1.07	2.03	1.09	1.85
Cpxm1	carboxypeptidase X 1 (M14 family)	1	0.94	2.33	1.19	2.33	1.27	1.84
Sh2d5	SH2 domain containing 5	1	1.08	2.09	1.23	2.09	1.14	1.84

Nppb	natriuretic peptide type B	1	0.86	2.92	1.37	2.92	1.59	1.84
Lrg1	leucine-rich alpha-2-glycoprotein 1	1	0.91	2.27	1.12	2.27	1.24	1.83
Slc16a1	arrier family 16 (monocarboxylic acid transporters), me	1	1.32	2.56	1.84	2.56	1.40	1.83
Slc35f2	solute carrier family 35, member F2	1	1.24	2.56	1.74	2.56	1.40	1.83
Nt5dc2	5'-nucleotidase domain containing 2	1	1.57	2.92	2.51	2.92	1.60	1.82
Cirrh1a	cirrhosis, autosomal recessive 1A (human)	1	1.12	2.22	1.36	2.22	1.22	1.82
Pde12	phosphodiesterase 12	1	1.53	2.54	2.13	2.54	1.59	1.82
Mastl	microtubule associated serine/threonine kinase-like	1	1.43	2.83	2.22	2.83	1.56	1.82
Bak1	BCL2-antagonist/killer 1	1	1.21	2.08	1.38	2.08	1.15	1.82
Endou	endonuclease, polyU-specific	1	1.27	3.31	2.31	3.31	1.82	1.82
E2f8	E2F transcription factor 8	1	1.41	3.00	2.34	3.00	1.66	1.81
Tagln2	transgelin 2	1	1.18	2.38	1.55	2.38	1.32	1.81
Kif23	kinesin family member 23	1	1.58	2.70	2.37	2.70	1.49	1.81
Cdh3	cadherin 3	1	1.17	2.55	1.66	2.55	1.42	1.80
Ereg	epiregulin	1	1.84	2.08	2.12	2.08	1.16	1.80
Epha2	Eph receptor A2	1	1.21	2.15	1.46	2.15	1.20	1.79
Prep	prolyl endopeptidase	1	1.37	2.18	1.67	2.18	1.22	1.79
Scnn1g	sodium channel, nonvoltage-gated 1 gamma	1	1.22	2.71	1.86	2.71	1.52	1.78
Ckap2	cytoskeleton associated protein 2	1	1.66	2.84	2.65	2.84	1.60	1.78
Dusp6	dual specificity phosphatase 6	1	1.19	2.21	1.48	2.21	1.24	1.78
Aurkb	aurora kinase B	1	1.48	3.19	2.65	3.19	1.80	1.78
Fpr1	formyl peptide receptor 1	1	1.04	3.22	1.89	3.22	1.82	1.77
Ptpnz1	tein tyrosine phosphatase, receptor type Z, polypeptid	1	0.84	2.15	1.02	2.15	1.22	1.77
Klk8	kallikrein related-peptidase 8	1	1.80	3.38	3.44	3.38	1.91	1.77
Sox15	SRY-box containing gene 15	1	1.43	2.40	1.95	2.40	1.36	1.76
Rhof	ras homolog gene family, member f	1	1.20	2.57	1.75	2.57	1.46	1.76
Selp	selectin, platelet	1	0.97	2.22	1.23	2.22	1.27	1.76
Slc10a6	rier family 10 (sodium/bile acid cotransporter family), i	1	1.29	2.14	1.57	2.14	1.22	1.75
Mad2l1	MAD2 mitotic arrest deficient-like 1	1	1.31	3.08	2.31	3.08	1.76	1.75
Ceacam19	cinoembryonic antigen-related cell adhesion molecule	1	1.48	2.18	1.85	2.18	1.25	1.75
Dusp7	dual specificity phosphatase 7	1	1.27	2.06	1.50	2.06	1.18	1.74
Ripk3	receptor-interacting serine-threonine kinase 3	1	1.14	2.27	1.49	2.27	1.31	1.74
Impdh2	inosine 5'-phosphate dehydrogenase 2	1	1.62	2.01	1.87	2.01	1.16	1.74
Mab21l3	mab-21-like 3 (C. elegans)	1	1.14	2.13	1.40	2.13	1.22	1.74
Smpd13b	sphingomyelin phosphodiesterase, acid-like 3B	1	1.21	2.32	1.61	2.32	1.34	1.73
Phlda2	pleckstrin homology-like domain, family A, member 2	1	1.11	3.15	2.02	3.15	1.82	1.73
Tmem125	transmembrane protein 125	1	1.21	2.54	1.77	2.54	1.47	1.73
LOC101056658	adenosylhomocysteinase-like	1	1.27	2.60	1.92	2.60	1.51	1.73
Sfn	stratigin	1	1.40	2.26	1.83	2.26	1.31	1.73
Mcm3	inichromosome maintenance deficient 3 (S. cerevisiae)	1	1.38	2.45	1.95	2.45	1.42	1.72
Ier3	immediate early response 3	1	1.50	2.32	2.01	2.32	1.34	1.72
Glrx	glutaredoxin	1	1.27	3.13	2.31	3.13	1.82	1.72
Ddx39	DEAD (Asp-Glu-Ala-Asp) box polypeptide 39	1	1.12	2.63	1.71	2.63	1.53	1.72
Vstm5	V-set and transmembrane domain containing 5	1	1.20	2.16	1.51	2.16	1.26	1.72
Sgol1	shugoshin-like 1 (S. pombe)	1	1.44	2.67	2.23	2.67	1.56	1.72
Stil	Scf/Tal1 interrupting locus	1	1.31	3.17	2.43	3.17	1.85	1.72
C330027C09Rik	RIKEN cDNA C330027C09 gene	1	1.25	2.37	1.73	2.37	1.38	1.71
Kif14	kinesin family member 14	1	1.34	2.76	2.16	2.76	1.61	1.71
Cad	phate synthetase 2, aspartate transcarbamylase, and	1	1.13	2.28	1.51	2.28	1.33	1.71
Slc2a1	carrier family 2 (facilitated glucose transporter), mem	1	1.24	2.55	1.85	2.55	1.49	1.71
Casc5	cancer susceptibility candidate 5	1	1.39	3.20	2.59	3.20	1.87	1.71
Ckap4	cytoskeleton-associated protein 4	1	1.21	2.21	1.56	2.21	1.29	1.71
Gm3601	predicted gene 3601	1	1.28	4.65	3.48	4.65	2.72	1.71
Shmt2	serine hydroxymethyltransferase 2 (mitochondrial)	1	1.31	2.63	2.02	2.63	1.54	1.71
Atp12a	Pase, H+/K+ transporting, nongastric, alpha polypepti	1	0.94	2.73	1.50	2.73	1.60	1.70
Sell	selectin, lymphocyte	1	0.97	2.47	1.40	2.47	1.45	1.70
Slc7a1	r family 7 (cationic amino acid transporter, y+ system)	1	1.26	2.29	1.70	2.29	1.35	1.70
Hist1h2bl	histone cluster 1, H2bl	1	1.51	2.23	1.98	2.23	1.32	1.70
Shb	c homology 2 domain-containing transforming protein	1	1.14	2.11	1.43	2.11	1.25	1.69
Il1f8	interleukin 1 family, member 8	1	1.50	2.67	2.37	2.67	1.58	1.69
Il1f9	interleukin 1 family, member 9	1	1.25	2.10	1.56	2.10	1.24	1.69
Ncaph	non-SMC condensin I complex, subunit H	1	1.31	2.81	2.18	2.81	1.67	1.69
Troap	trophinin associated protein	1	1.42	2.02	1.70	2.02	1.20	1.69
Entpd7	ectonucleoside triphosphate diphosphohydrolase 7	1	1.20	2.29	1.64	2.29	1.36	1.68
Tripl3	thyroid hormone receptor interactor 13	1	1.21	2.26	1.62	2.26	1.34	1.68
LOC101056577	ndrial import inner membrane translocase subunit Timl	1	0.98	2.33	1.37	2.33	1.39	1.68
Hist1h4c	histone cluster 1, H4c	1	1.27	2.17	1.64	2.17	1.29	1.68
Hist1h2bh	histone cluster 1, H2bh	1	1.44	2.32	2.00	2.32	1.38	1.68
Knstrn	kinetochore-localized astrin/SPAG5 binding	1	1.68	2.68	2.69	2.68	1.60	1.67
Hspd1	heat shock protein 1 (chaperonin)	1	1.05	2.03	1.27	2.03	1.21	1.67
Cnfn	cornifelin	1	1.37	2.30	1.88	2.30	1.38	1.67
Kpna2	karyopherin (importin) alpha 2	1	1.26	2.55	1.93	2.55	1.53	1.67
Hist1h2bk	histone cluster 1, H2bk	1	1.47	2.27	2.01	2.27	1.36	1.67
LOC100047753	nucleoside diphosphate kinase A-like	1	1.14	2.44	1.68	2.44	1.47	1.67
Cenpn	centromere protein N	1	1.41	3.02	2.55	3.02	1.81	1.66
Capg	capping protein (actin filament), gelsolin-like	1	1.29	2.19	1.70	2.19	1.32	1.66
Il1rn	interleukin 1 receptor antagonist	1	1.11	2.11	1.40	2.11	1.27	1.66
Tmem40	transmembrane protein 40	1	1.49	2.40	2.16	2.40	1.45	1.65
Idi1	isopentenyl-diphosphate delta isomerase	1	1.04	2.45	1.55	2.45	1.49	1.65
Ptk6	PTK6 protein tyrosine kinase 6	1	1.29	2.02	1.58	2.02	1.23	1.65
Dsg1b	desmoglein 1 beta	1	1.52	2.20	2.04	2.20	1.34	1.65
Lypd3	Ly6/Plaur domain containing 3	1	1.38	2.16	1.82	2.16	1.32	1.64
Mfsd2a	major facilitator superfamily domain containing 2A	1	1.43	2.81	2.44	2.81	1.71	1.64
Rad18	RAD18 homolog (S. cerevisiae)	1	1.15	2.08	1.46	2.08	1.27	1.64
Hist1h2ak	histone cluster 1, H2ak	1	1.49	2.29	2.08	2.29	1.40	1.64
Blmh	bleomycin hydrolase	1	1.43	2.65	2.30	2.65	1.62	1.64
Ovol1	OVO homolog-like 1 (Drosophila)	1	1.50	2.16	1.99	2.16	1.32	1.64
Hist1h2bf	histone cluster 1, H2bf	1	1.44	2.20	1.94	2.20	1.35	1.63
Hist1h1a	histone cluster 1, H1a	1	1.29	2.91	2.32	2.91	1.79	1.62

Rps6ka4	ribosomal protein S6 kinase, polypeptide 4	1	1.34	2.23	1.84	2.23	1.38	1.62
Aldh1l2	aldehyde dehydrogenase 1 family, member L2	1	1.37	2.25	1.91	2.25	1.39	1.62
Slc16a6	arrier family 16 (monocarboxylic acid transporters), me	1	1.17	2.01	1.46	2.01	1.25	1.61
Nop58	NOP58 ribonucleoprotein	1	1.02	2.06	1.30	2.06	1.28	1.61
Scnn1b	sodium channel, nonvoltage-gated 1 beta	1	1.18	2.64	1.93	2.64	1.64	1.61
Dkc1	dyskeratosis congenita 1, dyskerin	1	1.02	2.04	1.30	2.04	1.27	1.61
Cwh43	ll wall biogenesis 43 C-terminal homolog (S. cerevisiae)	1	1.30	3.23	2.62	3.23	2.01	1.61
Fscn1	nolog 1, actin bundling protein (Strongylocentrotus pur	1	1.01	3.03	1.91	3.03	1.89	1.60
Slc34a2	solute carrier family 34 (sodium phosphate), member 2	1	1.48	3.02	2.79	3.02	1.89	1.60
Dbf4	DBF4 homolog (S. cerevisiae)	1	1.09	2.81	1.90	2.81	1.75	1.60
Spag5	sperm associated antigen 5	1	1.30	2.78	2.26	2.78	1.73	1.60
Cdca8	cell division cycle associated 8	1	1.19	2.95	2.21	2.95	1.85	1.60
Asns	asparagine synthetase	1	1.21	2.03	1.54	2.03	1.27	1.60
Slfn1	schlafen 1	1	0.91	2.13	1.21	2.13	1.33	1.60
Degs1	degenerative spermatocyte homolog 1 (Drosophila)	1	1.27	2.14	1.70	2.14	1.34	1.60
Fam162a	family with sequence similarity 162, member A	1	1.18	2.68	1.99	2.68	1.68	1.59
C330005M16Rik	RIKEN cDNA C330005M16 gene	1	1.27	2.23	1.78	2.23	1.40	1.59
Slc37a2	arrier family 37 (glycerol-3-phosphate transporter), me	1	1.25	2.79	2.18	2.79	1.75	1.59
Ckap2l	cytoskeleton associated protein 2-like	1	1.45	2.33	2.13	2.33	1.47	1.59
Arc	activity regulated cytoskeletal-associated protein	1	1.24	2.72	2.13	2.72	1.71	1.59
Hist1h2ab	histone cluster 1, H2ab	1	1.53	3.78	3.65	3.78	2.38	1.59
Cdhr1	cadherin-related family member 1	1	1.10	2.17	1.50	2.17	1.37	1.59
Gsdmc2	gasdermin C2	1	0.98	2.94	1.82	2.94	0.85	1.59
Eif6	eukaryotic translation initiation factor 6	1	1.30	2.02	1.66	2.02	1.28	1.58
Tcf23	transcription factor 23	1	1.08	2.10	1.43	2.10	1.33	1.58
Tmem79	transmembrane protein 79	1	1.43	2.30	2.07	2.30	1.45	1.58
Aldh18a1	aldehyde dehydrogenase 18 family, member A1	1	1.31	2.16	1.79	2.16	1.37	1.58
Erh	enhancer of rudimentary homolog (Drosophila)	1	1.10	2.06	1.43	2.06	1.31	1.58
Hmgcr	3-hydroxy-3-methylglutaryl-Coenzyme A reductase	1	1.18	2.38	1.79	2.38	1.51	1.58
Trdn	triadin	1	1.31	0.70	0.58	0.70	0.44	1.57
Hn1l	hematological and neurological expressed 1-like	1	1.25	2.04	1.61	2.04	1.29	1.57
Casp14	caspase 14	1	1.94	2.99	3.72	2.99	1.92	1.56
Aurka	aurora kinase A	1	1.20	2.39	1.84	2.39	1.53	1.56
Bdh1	3-hydroxybutyrate dehydrogenase, type 1	1	1.34	2.03	1.73	2.03	1.30	1.56
Ccnf	cyclin F	1	1.28	2.75	2.25	2.75	1.76	1.56
Rad51	RAD51 homolog	1	1.29	2.32	1.93	2.32	1.49	1.56
Dnase1l2	deoxyribonuclease 1-like 2	1	1.40	2.36	2.12	2.36	1.51	1.56
Hist1h2ba	histone cluster 1, H2ba	1	1.34	2.08	1.79	2.08	1.34	1.56
Maoa	monoamine oxidase A	1	1.17	2.02	1.52	2.02	1.30	1.55
Hist2h2ab	histone cluster 2, H2ab	1	1.43	2.06	1.89	2.06	1.32	1.55
Cks1b	CDC28 protein kinase 1b	1	1.11	2.52	1.79	2.52	1.62	1.55
Lrrc59	leucine rich repeat containing 59	1	1.07	2.12	1.46	2.12	1.37	1.55
Uhrf1	iquitin-like, containing PHD and RING finger domains,	1	1.24	2.36	1.89	2.36	1.53	1.55
Uchl3	itin carboxyl-terminal esterase L3 (ubiquitin thiolester	1	1.19	2.08	1.61	2.08	1.35	1.55
Tyro3	TYRO3 protein tyrosine kinase 3	1	1.34	2.19	1.91	2.19	1.42	1.55
Fhl2	four and a half LIM domains 2	1	1.17	2.45	1.86	2.45	1.59	1.54
Mthfd2	e dehydrogenase (NAD+ dependent), methenyltetrahy	1	1.14	2.27	1.68	2.27	1.47	1.54
Hsd17b7	hydroxysteroid (17-beta) dehydrogenase 7	1	1.04	2.62	1.76	2.62	1.70	1.54
Hist1h3i	histone cluster 1, H3i	1	1.33	2.15	1.85	2.15	1.40	1.54
Cers3	ceramide synthase 3	1	1.10	2.04	1.46	2.04	1.33	1.54
Prr11	proline rich 11	1	1.36	3.24	2.88	3.24	2.11	1.54
Car12	carbonic anhydrase 12	1	1.46	2.63	2.50	2.63	1.71	1.54
Hilpda	hypoxia inducible lipid droplet associated	1	0.93	2.12	1.28	2.12	1.38	1.54
Ces2g	carboxylesterase 2G	1	1.44	2.22	2.08	2.22	1.44	1.54
Pno1	partner of NOB1 homolog (S. cerevisiae)	1	1.13	2.01	1.47	2.01	1.31	1.53
Epn3	epsin 3	1	1.30	2.30	1.95	2.30	1.50	1.53
2610528J11Rik	RIKEN cDNA 2610528J11 gene	1	1.43	2.44	2.27	2.44	1.59	1.53
Hist2h3c2	histone cluster 2, H3c2	1	1.35	2.09	1.85	2.09	1.37	1.52
Gm13310	predicted gene 13310	1	1.25	2.49	2.04	2.49	1.64	1.52
Hist1h3f	histone cluster 1, H3f	1	1.31	2.12	1.82	2.12	1.40	1.52
Cd24a	CD24a antigen	1	1.07	2.08	1.46	2.08	1.37	1.52
Bysl	bystin-like	1	1.09	2.19	1.58	2.19	1.45	1.51
Nkpd1	NTPase, KAP family P-loop domain containing 1	1	1.25	2.20	1.82	2.20	1.46	1.51
S100a16	S100 calcium binding protein A16	1	1.21	2.06	1.66	2.06	1.37	1.51
Bop1	block of proliferation 1	1	1.28	2.03	1.73	2.03	1.35	1.50
Nbeal2	neurobeachin-like 2	1	1.25	2.03	1.68	2.03	1.35	1.50
lh2ap // Hist1f	histone cluster 1, H2ap // histone cluster 1, H2ao	1	1.31	2.08	1.81	2.08	1.38	1.50
Tlr13	toll-like receptor 13	1	0.91	2.17	1.32	2.17	1.45	1.50
Hist1h3a	histone cluster 1, H3a	1	1.33	2.06	1.84	2.06	1.38	1.49
Ccne1	cyclin E1	1	1.07	2.20	1.58	2.20	1.48	1.49
Ticrr	DPBP1-interacting checkpoint and replication regulatc	1	1.17	2.67	2.10	2.67	1.80	1.49
Bub1b	uninhibited by benzimidazoles 1 homolog, beta (S. cer	1	1.38	2.50	2.34	2.50	1.69	1.48
Sqle	squalene epoxidase	1	1.21	2.37	1.94	2.37	1.60	1.48
Cyp51	cytochrome P450, family 51	1	1.11	2.16	1.62	2.16	1.46	1.48
Cdkn3	cyclin-dependent kinase inhibitor 3	1	1.38	2.44	2.27	2.44	1.65	1.48
Hist1h3d	histone cluster 1, H3d	1	1.32	2.03	1.81	2.03	1.38	1.47
Dlgap5	discs, large (Drosophila) homolog-associated protein 5	1	1.40	2.56	2.43	2.56	1.74	1.47
Ran	RAN, member RAS oncogene family	1	1.14	2.20	1.71	2.20	1.50	1.47
Gja1	gap junction protein, alpha 1	1	1.15	2.94	2.30	2.94	2.00	1.47
Tdh	L-threonine dehydrogenase	1	1.88	4.11	5.27	4.11	2.81	1.47
Incenp	inner centromere protein	1	1.37	2.22	2.08	2.22	1.51	1.47
Slc9a3r1	ier family 9 (sodium/hydrogen exchanger), member 3 r	1	1.26	2.11	1.81	2.11	1.44	1.46
Kctd11	otassium channel tetramerisation domain containing 1	1	1.38	2.03	1.91	2.03	1.39	1.46
Ncapd2	non-SMC condensin I complex, subunit D2	1	1.41	2.56	2.47	2.56	1.75	1.46
Slc25a48	solute carrier family 25, member 48	1	1.22	2.23	1.86	2.23	1.53	1.46
Rrm1	ribonucleotide reductase M1	1	1.16	2.31	1.85	2.31	1.59	1.46
Chit1	chitinase 1 (chitotriosidase)	1	1.27	2.15	1.90	2.15	1.49	1.44
Atp1a1	ATPase, Na+/K+ transporting, alpha 1 polypeptide	1	1.20	2.03	1.70	2.03	1.41	1.44
Mkl	mixed lineage kinase domain-like	1	0.82	2.05	1.17	2.05	1.43	1.44

Mis18bp1	MIS18 binding protein 1	1	1.20	2.56	2.13	2.56	1.77	1.44
Sprr2a3	small proline-rich protein 2A3	1	1.26	3.17	2.78	3.17	2.20	1.44
Nek2	MA (never in mitosis gene a)-related expressed kinase	1	1.23	2.54	2.17	2.54	1.77	1.44
Nav3	neuron navigator 3	1	1.17	2.16	1.76	2.16	1.50	1.44
2810417H13Rik	RIKEN cDNA 2810417H13 gene	1	1.19	3.53	2.93	3.53	2.46	1.43
Serinc2	serine incorporator 2	1	1.07	2.87	2.14	2.87	2.01	1.43
Klk11	kallikrein related-peptidase 11	1	1.33	2.34	2.18	2.34	1.64	1.43
Spc24	DC80 kinetochore complex component, homolog (S. cerevisiae)	1	1.15	2.01	1.63	2.01	1.41	1.42
Elovl3	very long chain fatty acids (FEN1/Elo2, SUR4/Elo3, y)	1	0.81	2.96	1.71	2.96	2.10	1.41
Cdca2	cell division cycle associated 2	1	1.31	2.14	2.00	2.14	1.53	1.40
Ttk	Ttk protein kinase	1	1.25	2.04	1.83	2.04	1.47	1.39
Esco2	establishment of cohesion 1 homolog 2 (S. cerevisiae)	1	1.33	2.53	2.43	2.53	1.83	1.38
Tyms	thymidylate synthase	1	1.22	2.21	1.95	2.21	1.60	1.38
Ephx3	epoxide hydrolase 3	1	1.31	2.16	2.05	2.16	1.57	1.38
Gsdmc3	gasdermin C3	1	1.11	2.13	1.71	2.13	1.55	1.38
Ska3	spindle and kinetochore associated complex subunit 3	1	1.22	2.45	2.18	2.45	1.79	1.37
Mcm5	ome maintenance deficient 5, cell division cycle 46 (S. cerevisiae)	1	1.21	2.25	2.00	2.25	1.65	1.37
Eno1	enolase 1, alpha non-neuron	1	1.33	2.09	2.04	2.09	1.53	1.36
Parpbp	PARP1 binding protein	1	1.09	2.18	1.75	2.18	1.60	1.36
4632434I11Rik	RIKEN cDNA 4632434I11 gene	1	1.13	2.16	1.81	2.16	1.59	1.36
Spink7	serine peptidase inhibitor, Kazal type 7 (putative)	1	1.86	9.49	13.06	9.49	7.03	1.35
E2F7	E2F transcription factor 7	1	0.99	2.13	1.56	2.13	1.58	1.35
Hmmr	hyaluronan mediated motility receptor (RHAMM)	1	1.15	2.49	2.12	2.49	1.85	1.35
Hist1h4f	histone cluster 1, H4f	1	1.17	2.21	1.91	2.21	1.64	1.35
Etv4	is variant gene 4 (E1A enhancer binding protein, E1AF)	1	1.07	2.16	1.72	2.16	1.60	1.34
Aadac	arylacetamide deacetylase (esterase)	1	0.96	2.25	1.61	2.25	1.68	1.34
Fancd2	Fanconi anemia, complementation group D2	1	1.11	2.02	1.68	2.02	1.52	1.33
BC030867	cDNA sequence BC030867	1	1.15	2.07	1.79	2.07	1.56	1.33
Slc39a2	solute carrier family 39 (zinc transporter), member 2	1	1.10	2.11	1.76	2.11	1.60	1.33
Awat1	acyl-CoA wax alcohol acyltransferase 1	1	0.65	2.04	0.99	2.04	1.54	1.32
Iqgap3	IQ motif containing GTPase activating protein 3	1	1.22	2.07	1.90	2.07	1.56	1.32
Ear11	osinophil-associated, ribonuclease A family, member 1	1	1.23	0.45	0.42	0.45	0.34	1.32
Chaf1b	chromatin assembly factor 1, subunit B (p60)	1	1.33	2.09	2.11	2.09	1.59	1.31
Depdc1a	DEP domain containing 1a	1	1.29	2.44	2.39	2.44	1.86	1.31
Rdh9	retinol dehydrogenase 9	1	1.05	2.07	1.68	2.07	1.60	1.29
Ttc22	tetratricopeptide repeat domain 22	1	1.30	2.29	2.30	2.29	1.77	1.29
Cenpm	centromere protein M	1	1.18	2.23	2.04	2.23	1.73	1.29
Tacc3	transforming, acidic coiled-coil containing protein 3	1	1.21	2.06	1.95	2.06	1.61	1.28
Taf1d	x binding protein (Tbp)-associated factor, RNA polymerase II	1	1.07	2.08	1.75	2.08	1.63	1.28
Spc25	DC80 kinetochore complex component, homolog (S. cerevisiae)	1	1.22	2.03	1.94	2.03	1.59	1.28
Dio2	deiodinase, iodothyronine, type II	1	1.24	3.04	2.95	3.04	2.38	1.28
Tgm5	transglutaminase 5	1	1.14	2.48	2.22	2.48	1.95	1.27
Hist2h2bb	histone cluster 2, H2bb	1	1.06	2.15	1.80	2.15	1.69	1.27
Cgref1	cell growth regulator with EF hand domain 1	1	1.08	2.12	1.89	2.12	1.75	1.21
Krt17	keratin 17	1	0.80	2.26	1.52	2.26	1.89	1.20
Serpinb11	-cysteine) peptidase inhibitor, clade B (ovalbumin), member 11	1	0.74	2.91	1.85	2.91	2.49	1.17
Sox7	SRY-box containing gene 7	1	1.14	2.23	2.18	2.23	1.91	1.16
Gad1l	glutamate decarboxylase-like 1	1	1.35	3.12	3.71	3.12	2.75	1.14
Defb6	defensin beta 6	1	0.68	2.54	1.54	2.54	2.26	1.13
Itgam	integrin alpha M	1	0.88	2.12	1.69	2.12	1.91	1.11
Slc13a3	family 13 (sodium-dependent dicarboxylate transporter)	1	1.12	2.44	2.55	2.44	2.29	1.07
Wfdc12	WAP four-disulfide core domain 12	1	1.13	2.46	2.63	2.46	2.32	1.06
Gm5150	predicted gene 5150	1	0.92	2.60	2.25	2.60	2.45	1.06
Plac8	placenta-specific 8	1	0.73	2.43	1.76	2.43	2.40	1.01
Krt79	keratin 79	1	0.75	2.08	1.61	2.08	2.14	0.97
Olah	oleoyl-ACP hydrolase	1	1.04	2.02	2.21	2.02	2.13	0.95
Trim12a	tripartite motif-containing 12A	1	1.10	0.41	0.53	0.41	0.48	0.86
Nmu	neuromedin U	1	1.61	2.07	3.97	2.07	2.47	0.84
Lect1	leukocyte cell derived chemotaxin 1	1	0.91	0.44	0.49	0.44	0.54	0.81
Pinlyp	pholipase A2 inhibitor and LY6/PLAUR domain containing 1	1	0.68	1.73	1.48	1.73	2.19	0.79
Wif1	Wnt inhibitory factor 1	1	0.98	0.49	0.62	0.49	0.63	0.78
Gucy1b3	guanylate cyclase 1, soluble, beta 3	1	0.82	0.47	0.50	0.47	0.61	0.77
Npr3	natriuretic peptide receptor 3	1	0.89	0.46	0.53	0.46	0.60	0.77
Angptl7	angiopoietin-like 7	1	0.97	0.47	0.60	0.47	0.62	0.76
D7Ert443e	DNA segment, Chr 7, ERATO Doi 443, expressed	1	1.00	0.48	0.65	0.48	0.65	0.74
Ppp1r3c	protein phosphatase 1, regulatory (inhibitor) subunit 3C	1	0.88	0.45	0.54	0.45	0.61	0.73
Ablim3	actin binding LIM protein family, member 3	1	0.90	0.46	0.58	0.46	0.64	0.73
Emr4	odule containing, mucin-like, hormone receptor-like subunit 4	1	0.84	0.43	0.50	0.43	0.59	0.73
Ucma	er zone of growth plate and cartilage matrix associated protein 1	1	0.93	0.45	0.58	0.45	0.63	0.72
Ecm2	ellular matrix protein 2, female organ and adipocyte specific	1	0.85	0.49	0.58	0.49	0.68	0.72
Arhgap20	Rho GTPase activating protein 20	1	0.84	0.50	0.59	0.50	0.70	0.71
Igfbp6	insulin-like growth factor binding protein 6	1	0.85	0.50	0.60	0.50	0.70	0.71
Cd82	CD82 antigen	1	1.02	0.45	0.64	0.45	0.63	0.71
Tppp	tubulin polymerization promoting protein	1	1.17	0.49	0.80	0.49	0.68	0.71
Slc43a1	solute carrier family 43, member 1	1	0.99	0.43	0.62	0.43	0.62	0.70
LOC100041516	protein FAM205A-like	1	1.06	0.46	0.71	0.46	0.66	0.70
Ppil6	peptidylprolyl isomerase (cyclophilin)-like 6	1	0.95	0.34	0.47	0.34	0.49	0.70
Slc6a4	ier family 6 (neurotransmitter transporter, serotonin), member 4	1	1.04	0.43	0.64	0.43	0.61	0.70
9330159F19Rik	RIKEN cDNA 9330159F19 gene	1	0.83	0.48	0.57	0.48	0.69	0.69
Sparcl1	SPARC-like 1	1	0.90	0.45	0.59	0.45	0.66	0.69
Gabbr1	gamma-aminobutyric acid (GABA) B receptor, 1	1	0.81	0.47	0.56	0.47	0.69	0.69
Gm21093	redicted gene, 21093	1	1.04	0.49	0.74	0.49	0.71	0.69
Pik3r1	ylinositol 3-kinase, regulatory subunit, polypeptide 1 (gamma)	1	0.95	0.47	0.65	0.47	0.68	0.69
Chrdl1	chordin-like 1	1	0.73	0.50	0.53	0.50	0.72	0.69
Sult5a1	sulfotransferase family 5A, member 1	1	0.81	0.47	0.56	0.47	0.70	0.68
Pdk2	pyruvate dehydrogenase kinase, isoenzyme 2	1	1.03	0.50	0.76	0.50	0.74	0.68
Tmem182	transmembrane protein 182	1	0.87	0.46	0.59	0.46	0.68	0.67
Agbl1	ATP/GTP binding protein-like 1	1	0.86	0.46	0.59	0.46	0.68	0.67
Ptpn14	protein tyrosine phosphatase, non-receptor type 14	1	1.00	0.43	0.64	0.43	0.64	0.66

Sgce	sarcoglycan, epsilon	1	0.83	0.48	0.60	0.48	0.72	0.66
Mrgprg	MAS-related GPR, member G	1	1.07	0.46	0.75	0.46	0.70	0.66
Sgcg	rcoglycan, gamma (dystrophin-associated glycoprotein	1	0.87	0.43	0.57	0.43	0.65	0.66
Mxipl	MLX interacting protein-like	1	0.81	0.50	0.61	0.50	0.75	0.66
Mrap	melanocortin 2 receptor accessory protein	1	0.69	0.48	0.51	0.48	0.74	0.66
Dpt	dermatopontin	1	0.91	0.49	0.68	0.49	0.75	0.65
Il20ra	interleukin 20 receptor, alpha	1	0.97	0.43	0.64	0.43	0.66	0.65
Fzd4	frizzled homolog 4 (Drosophila)	1	0.82	0.48	0.60	0.48	0.74	0.65
Klhl38	kelch-like 38	1	0.93	0.45	0.65	0.45	0.70	0.65
Cyp2d22	cytochrome P450, family 2, subfamily d, polypeptide 22	1	0.84	0.48	0.62	0.48	0.74	0.65
Aldh1a7	aldehyde dehydrogenase family 1, subfamily A7	1	0.91	0.48	0.67	0.48	0.74	0.65
Slco2b1	solute carrier organic anion transporter family, member 2	1	0.81	0.46	0.58	0.46	0.72	0.65
Naaladl2	N-acetylated alpha-linked acidic dipeptidase-like 2	1	0.60	0.34	0.31	0.34	0.52	0.65
Tcap	titin-cap	1	0.98	0.49	0.74	0.49	0.75	0.65
Tcea3	transcription elongation factor A (SII), 3	1	1.04	0.46	0.74	0.46	0.71	0.64
Sesn1	sestrin 1	1	0.96	0.45	0.68	0.45	0.71	0.64
Cped1	cadherin-like and PC-esterase domain containing 1	1	0.73	0.50	0.57	0.50	0.78	0.64
Clec10a	C-type lectin domain family 10, member A	1	0.78	0.36	0.44	0.36	0.56	0.64
Ttn	titin	1	0.79	0.48	0.59	0.48	0.75	0.64
Myh4	myosin, heavy polypeptide 4, skeletal muscle	1	0.88	0.49	0.67	0.49	0.76	0.64
Crebrf	CREB3 regulatory factor	1	0.87	0.46	0.63	0.46	0.72	0.64
Irs1	insulin receptor substrate 1	1	1.02	0.46	0.73	0.46	0.72	0.63
Arrdc3	arrestin domain containing 3	1	0.85	0.48	0.65	0.48	0.76	0.63
Islr	immunoglobulin superfamily containing leucine-rich repeat	1	0.87	0.48	0.66	0.48	0.75	0.63
F830045P16Rik	RIKEN cDNA F830045P16 gene	1	0.89	0.43	0.60	0.43	0.68	0.63
Plscr4	phospholipid scramblase 4	1	0.93	0.44	0.65	0.44	0.69	0.63
Fbxo32	F-box protein 32	1	0.99	0.42	0.66	0.42	0.67	0.63
Mme	membrane metallo endopeptidase	1	0.84	0.44	0.59	0.44	0.70	0.63
Ppm1k	protein phosphatase 1K (PP2C domain containing)	1	0.75	0.50	0.60	0.50	0.79	0.62
Cox8b	cytochrome c oxidase subunit VIIIb	1	0.83	0.42	0.56	0.42	0.67	0.62
Cmya5	cardiomyopathy associated 5	1	0.87	0.45	0.64	0.45	0.73	0.62
Nkd2	naked cuticle 2 homolog (Drosophila)	1	0.90	0.45	0.64	0.45	0.72	0.62
Klf9	Kruppel-like factor 9	1	0.86	0.48	0.66	0.48	0.77	0.62
Fitm1	fat storage-inducing transmembrane protein 1	1	0.94	0.49	0.74	0.49	0.79	0.62
Ebf1	early B cell factor 1	1	0.82	0.49	0.65	0.49	0.79	0.62
Tnnc2	troponin C2, fast	1	0.88	0.49	0.70	0.49	0.79	0.62
Ephx2	epoxide hydrolase 2, cytoplasmic	1	0.66	0.47	0.50	0.47	0.76	0.62
Aldh6a1	aldehyde dehydrogenase family 6, subfamily A1	1	0.83	0.42	0.57	0.42	0.69	0.61
Sncg	synuclein, gamma	1	0.79	0.41	0.52	0.41	0.66	0.61
Asb12	ankyrin repeat and SOCS box-containing 12	1	0.87	0.46	0.65	0.46	0.75	0.61
Apcdd1	adenomatous polyposis coli down-regulated 1	1	0.97	0.48	0.77	0.48	0.79	0.61
Txnip	thioredoxin interacting protein	1	0.85	0.41	0.57	0.41	0.68	0.61
Trf	transferrin	1	0.75	0.43	0.53	0.43	0.71	0.60
Skint7	selection and upkeep of intraepithelial T cells 7	1	0.88	0.41	0.61	0.41	0.69	0.60
Tshr	thyroid stimulating hormone receptor	1	0.81	0.44	0.60	0.44	0.74	0.60
Slc22a4	solute carrier family 22 (organic cation transporter), member	1	1.06	0.49	0.87	0.49	0.82	0.60
Rab30	RAB30, member RAS oncogene family	1	1.01	0.42	0.70	0.42	0.69	0.60
Hmcn1	hemicentin 1	1	0.82	0.49	0.67	0.49	0.82	0.60
Sema3d	semoglobulin domain (Ig), short basic domain, secreted,	1	1.09	0.46	0.84	0.46	0.77	0.60
Cyp27a1	cytochrome P450, family 27, subfamily a, polypeptide 1	1	0.87	0.41	0.61	0.41	0.70	0.59
Serpina3c	serpin (or cysteine) peptidase inhibitor, clade A, member	1	0.72	0.41	0.50	0.41	0.69	0.59
Dpep1	dipeptidase 1 (renal)	1	0.88	0.47	0.70	0.47	0.80	0.59
Gstt1	glutathione S-transferase, theta 1	1	0.82	0.49	0.67	0.49	0.82	0.59
Cyp2f2	cytochrome P450, family 2, subfamily f, polypeptide 2	1	0.81	0.43	0.59	0.43	0.73	0.59
Adssl1	adenylosuccinate synthetase like 1	1	0.92	0.49	0.76	0.49	0.83	0.59
Cttnbp2	cortactin binding protein 2	1	0.94	0.49	0.77	0.49	0.82	0.59
Hnmt	histamine N-methyltransferase	1	0.80	0.49	0.67	0.49	0.84	0.59
Angptl1	angiopoietin-like 1	1	0.90	0.42	0.65	0.42	0.72	0.59
A530099J19Rik	RIKEN cDNA A530099J19 gene	1	0.85	0.39	0.57	0.39	0.67	0.59
Slc36a2	solute carrier family 36 (proton/amino acid symporter), member	1	0.74	0.41	0.52	0.41	0.70	0.59
Slc24a3	solute carrier family 24 (sodium/potassium/calcium exchanger),	1	0.93	0.39	0.62	0.39	0.67	0.59
Pfkfb3	phosphofructo-2-kinase/fructose-2,6-bisphosphatase	1	0.82	0.49	0.69	0.49	0.84	0.59
Jph1	junctophilin 1	1	0.86	0.47	0.69	0.47	0.81	0.59
Bche	butyrylcholinesterase	1	0.70	0.43	0.51	0.43	0.73	0.59
Abca5	ATP-binding cassette, sub-family A (ABC1), member 5	1	0.80	0.27	0.37	0.27	0.47	0.59
Kcnj16	potassium inwardly-rectifying channel, subfamily J, member	1	1.20	0.43	0.89	0.43	0.74	0.59
Gm4787	predicted gene 4787	1	0.73	0.47	0.60	0.47	0.81	0.58
Cd36	CD36 antigen	1	0.66	0.46	0.53	0.46	0.79	0.58
Apol6	apolipoprotein L 6	1	0.68	0.47	0.54	0.47	0.80	0.58
Myh2	myosin, heavy polypeptide 2, skeletal muscle, adult	1	1.02	0.48	0.85	0.48	0.82	0.58
Ano5	anoctamin 5	1	0.72	0.43	0.53	0.43	0.74	0.58
Slc16a7	solute carrier family 16 (monocarboxylic acid transporters), member	1	0.74	0.44	0.56	0.44	0.76	0.58
Mgl2	mannose-6-phosphate galactose N-acetyl-galactosamine specific lectin	1	0.72	0.26	0.32	0.26	0.45	0.58
Casq1	calcineurin 1	1	0.82	0.40	0.57	0.40	0.69	0.58
Zbtb16	zinc finger and BTB domain containing 16	1	0.96	0.35	0.58	0.35	0.60	0.58
Gm2012	predicted gene 2012	1	1.01	0.47	0.82	0.47	0.81	0.58
Gm5934	predicted gene 5934	1	1.01	0.47	0.82	0.47	0.81	0.58
Lrrc39	leucine rich repeat containing 39	1	0.73	0.48	0.61	0.48	0.84	0.58
Lce1m	late cornified envelope 1M	1	1.07	0.47	0.88	0.47	0.82	0.58
Atp1a2	ATPase, Na+/K+ transporting, alpha 2 polypeptide	1	0.87	0.47	0.71	0.47	0.81	0.57
Vnn1	vanin 1	1	0.51	0.49	0.44	0.49	0.86	0.57
Aspa	aspartoacylase	1	0.78	0.49	0.68	0.49	0.86	0.57
Gm4836	predicted gene 4836	1	1.00	0.50	0.86	0.50	0.87	0.57
Gpr125	G protein-coupled receptor 125	1	0.74	0.42	0.54	0.42	0.73	0.57
Pvalb	parvalbumin	1	0.76	0.37	0.49	0.37	0.64	0.57
Acss3	acyl-CoA synthetase short-chain family member 3	1	0.72	0.40	0.51	0.40	0.71	0.57
Ryr1	ryanodine receptor 1, skeletal muscle	1	0.91	0.47	0.76	0.47	0.83	0.57
Ccl27a	chemokine (C-C motif) ligand 27A	1	0.77	0.35	0.48	0.35	0.62	0.56
Nova1	neuro-oncological ventral antigen 1	1	0.87	0.50	0.77	0.50	0.88	0.56

Fsd2	fibronectin type III and SPRY domain containing 2	1	1.01	0.45	0.81	0.45	0.80	0.56
Cdo1	cysteine dioxygenase 1, cytosolic	1	0.70	0.34	0.43	0.34	0.61	0.56
Ampd1	adenosine monophosphate deaminase 1	1	0.98	0.39	0.67	0.39	0.69	0.56
Abca6	ATP-binding cassette, sub-family A (ABC1), member 6	1	0.79	0.42	0.60	0.42	0.76	0.56
Txlnb	taxilin beta	1	0.83	0.40	0.60	0.40	0.72	0.56
Slc38a3	solute carrier family 38, member 3	1	0.90	0.43	0.70	0.43	0.78	0.56
Cd209e	CD209e antigen	1	0.67	0.29	0.35	0.29	0.53	0.56
Olfir920	olfactory receptor 920	1	0.78	0.42	0.59	0.42	0.75	0.56
Klhl31	kelch-like 31	1	0.89	0.39	0.63	0.39	0.71	0.55
Fabp4	fatty acid binding protein 4, adipocyte	1	0.66	0.44	0.52	0.44	0.80	0.55
Cd209d	CD209d antigen	1	0.79	0.26	0.37	0.26	0.46	0.55
Art3	ADP-ribosyltransferase 3	1	0.81	0.38	0.56	0.38	0.69	0.55
Paqr7	progesterone and adipoQ receptor family member VII	1	0.54	0.37	0.37	0.37	0.68	0.55
Gm5431	predicted gene 5431	1	0.57	0.39	0.41	0.39	0.72	0.55
Irf4	interferon regulatory factor 4	1	0.73	0.49	0.65	0.49	0.89	0.55
Prkaa2	protein kinase, AMP-activated, alpha 2 catalytic subunit	1	0.83	0.46	0.69	0.46	0.84	0.55
Rtn2	reticulon 2 (Z-band associated protein)	1	0.90	0.48	0.78	0.48	0.87	0.55
Mil1	MHC I like leukocyte 1	1	0.55	0.39	0.40	0.39	0.72	0.54
Lpin1	lipin 1	1	0.88	0.42	0.69	0.42	0.78	0.54
Rorc	RAR-related orphan receptor gamma	1	1.01	0.38	0.70	0.38	0.70	0.54
Fmo1	flavin containing monooxygenase 1	1	0.76	0.41	0.58	0.41	0.76	0.54
Phka1	phosphorylase kinase alpha 1	1	0.79	0.38	0.56	0.38	0.71	0.54
Tusc5	tumor suppressor candidate 5	1	0.75	0.49	0.68	0.49	0.91	0.54
Hfe2	hemochromatosis type 2 (juvenile) (human homolog)	1	0.96	0.42	0.76	0.42	0.79	0.53
Car5b	carbonic anhydrase 5b, mitochondrial	1	0.64	0.42	0.51	0.42	0.79	0.53
Aox1	aldehyde oxidase 1	1	0.77	0.41	0.60	0.41	0.78	0.53
Serpina3b	serpin (or cysteine) peptidase inhibitor, clade A, member 3	1	0.62	0.14	0.17	0.14	0.27	0.53
Padi2	peptidyl arginine deiminase, type II	1	0.90	0.49	0.83	0.49	0.93	0.53
Lep	leptin	1	0.79	0.25	0.37	0.25	0.47	0.53
Glb1l2	galactosidase, beta 1-like 2	1	0.76	0.36	0.53	0.36	0.69	0.53
Pla2g16	phospholipase A2, group XVI	1	0.92	0.33	0.59	0.33	0.64	0.52
Alox12e	arachidonate lipoxygenase, epidermal	1	1.03	0.43	0.85	0.43	0.83	0.52
Aldh1a1	aldehyde dehydrogenase family 1, subfamily A1	1	0.74	0.33	0.46	0.33	0.63	0.52
Sult1a1	sulfotransferase family 1A, phenol-preferring, member 1	1	0.81	0.35	0.54	0.35	0.67	0.51
Cfd	complement factor D (adipsin)	1	0.59	0.39	0.45	0.39	0.76	0.51
Pygm	muscle glycogen phosphorylase	1	0.91	0.42	0.76	0.42	0.83	0.50
Skint4	selection and upkeep of intraepithelial T cells 4	1	1.01	0.37	0.75	0.37	0.74	0.50
Acvr1c	activin A receptor, type IC	1	0.64	0.44	0.57	0.44	0.89	0.50
Slc27a1	luteal carrier family 27 (fatty acid transporter), member 1	1	0.73	0.43	0.63	0.43	0.87	0.50
Ear2	erythrocyte-associated, ribonuclease A family, member 2	1	0.59	0.30	0.36	0.30	0.60	0.50
Lgals12	lectin, galactose binding, soluble 12	1	0.66	0.36	0.48	0.36	0.72	0.49
Myoz1	myozenin 1	1	0.84	0.35	0.60	0.35	0.71	0.49
Agmo	alkylglycerol monooxygenase	1	0.64	0.35	0.46	0.35	0.72	0.49
Lyz1	lysozyme 1	1	0.96	0.25	0.51	0.25	0.52	0.48
Slc7a10	solute carrier family 7 (cationic amino acid transporter, y+ system)	1	0.63	0.32	0.42	0.32	0.67	0.48
Pfkfb1	phosphofructo-2-kinase/fructose-2,6-bisphosphatase 1	1	0.65	0.41	0.56	0.41	0.85	0.48
Fcrls	Fc receptor-like 5, scavenger receptor	1	0.73	0.45	0.68	0.45	0.94	0.48
Cidec	cell death-inducing DFFA-like effector c	1	0.68	0.37	0.52	0.37	0.77	0.48
Abca8a	ATP-binding cassette, sub-family A (ABC1), member 8a	1	0.72	0.36	0.54	0.36	0.75	0.48
Slc15a2	solute carrier family 15 (H+/peptide transporter), member 2	1	0.78	0.47	0.77	0.47	0.99	0.48
Gstz1	glutathione transferase zeta 1 (maleylacetoacetate isomerase)	1	0.68	0.38	0.54	0.38	0.80	0.48
Slc2a12	solute carrier family 2 (facilitated glucose transporter), member 12	1	0.97	0.36	0.73	0.36	0.75	0.47
Cd209a	CD209a antigen	1	0.81	0.19	0.32	0.19	0.39	0.47
Plin1	perilipin 1	1	0.72	0.34	0.52	0.34	0.72	0.47
Btc	betacellulin, epidermal growth factor family member 3	1	0.78	0.42	0.69	0.42	0.88	0.47
Amy1	amylase 1, salivary	1	0.66	0.36	0.50	0.36	0.76	0.47
Abca9	ATP-binding cassette, sub-family A (ABC1), member 9	1	0.73	0.39	0.60	0.39	0.83	0.47
Prkar2b	protein kinase, cAMP dependent regulatory, type II beta	1	0.67	0.35	0.50	0.35	0.76	0.47
Ppp1r3a	protein phosphatase 1, regulatory (inhibitor) subunit 3A	1	0.74	0.31	0.50	0.31	0.67	0.46
Cmb1	carboxymethylglutaryl-CoA lyase-like (Pseudomonas)	1	0.64	0.35	0.49	0.35	0.76	0.46
Gpd1	glycerol-3-phosphate dehydrogenase 1 (soluble)	1	0.68	0.39	0.59	0.39	0.87	0.46
Mrgprb2	MAS-related GPR, member B2	1	0.79	0.34	0.60	0.34	0.77	0.45
Retn	resistin	1	0.71	0.30	0.48	0.30	0.67	0.45
Serpina3b	serpin (or cysteine) peptidase inhibitor, clade A, member 3	1	0.49	0.27	0.30	0.27	0.62	0.44
Tmod4	tropomodulin 4	1	0.78	0.27	0.48	0.27	0.62	0.44
Mybpc2	myosin binding protein C, fast-type	1	0.76	0.40	0.68	0.40	0.90	0.44
Actn3	actinin alpha 3	1	0.70	0.35	0.55	0.35	0.79	0.44
Aoc3	amine oxidase, copper containing 3	1	0.72	0.33	0.54	0.33	0.75	0.43
Bbox1	beta-oxoglutarate dioxygenase 1 (gamma-butyrobetaine dioxygenase)	1	0.87	0.29	0.59	0.29	0.68	0.43
Ear12	erythrocyte-associated, ribonuclease A family, member 12	1	0.59	0.26	0.35	0.26	0.60	0.43
Scgb1a1	secretoglobulin, family 1A, member 1 (uterglobin)	1	1.08	0.20	0.51	0.20	0.47	0.43
Rbp4	retinol binding protein 4, plasma	1	0.71	0.27	0.46	0.27	0.64	0.42
Tgtp2	T cell specific GTPase 2	1	0.54	0.50	0.63	0.50	1.17	0.42
Scgb1b27	secretoglobulin, family 1B, member 27	1	1.91	0.43	2.00	0.43	1.05	0.41
BC023105	cDNA sequence BC023105	1	0.41	0.45	0.45	0.45	1.09	0.41
Krt15	keratin 15	1	0.81	0.26	0.52	0.26	0.64	0.40
Aqp7	aquaporin 7	1	0.62	0.36	0.57	0.36	0.91	0.40
Adipoq	adiponectin, C1Q and collagen domain containing	1	0.61	0.26	0.40	0.26	0.66	0.40
Ces1f	carboxylesterase 1F	1	0.64	0.28	0.46	0.28	0.73	0.38
Fam13a	family with sequence similarity 13, member A	1	0.62	0.28	0.46	0.28	0.74	0.38
Cornn	cornulin	1	0.57	0.46	0.72	0.46	1.27	0.37
Mrgprb3	MAS-related GPR, member B3	1	0.77	0.24	0.51	0.24	0.66	0.36
Thrsp	thyroid hormone responsive	1	0.76	0.24	0.51	0.24	0.68	0.36
Nnat	neuronatin	1	0.62	0.23	0.40	0.23	0.64	0.36
Ces1d	carboxylesterase 1D	1	0.59	0.21	0.35	0.21	0.60	0.35
Gm11555	predicted gene 11555	1	0.46	0.45	0.59	0.45	1.29	0.35
Krtap13-1	keratin associated protein 13-1	1	0.55	0.43	0.69	0.43	1.26	0.34
Krtap9-3	keratin associated protein 9-3	1	0.59	0.49	0.85	0.49	1.44	0.34
Krtap1-3	keratin associated protein 1-3	1	0.43	0.49	0.63	0.49	1.47	0.33

Scd3	stearoyl-coenzyme A desaturase 3	1	0.26	0.22	0.18	0.22	0.68	0.33
Mstn	myostatin	1	0.67	0.25	0.52	0.25	0.78	0.32
Krtap5-4	keratin associated protein 5-4	1	0.55	0.45	0.79	0.45	1.44	0.31
Inmt	indolethylamine N-methyltransferase	1	0.89	0.17	0.50	0.17	0.56	0.31
Krt26	keratin 26	1	0.47	0.45	0.68	0.45	1.44	0.31
Gm10318	predicted gene 10318	1	0.66	0.49	1.04	0.49	1.57	0.31
Krtap4-6	keratin associated protein 4-6	1	0.46	0.47	0.70	0.47	1.52	0.31
Krt72	keratin 72	1	0.55	0.50	0.90	0.50	1.63	0.31
Gm17535	predicted gene, 17535	1	0.66	0.38	0.82	0.38	1.24	0.31
Lrrc15	leucine rich repeat containing 15	1	0.48	0.46	0.72	0.46	1.50	0.31
Gm11564	predicted gene 11564	1	0.34	0.37	0.42	0.37	1.24	0.30
Gm10229	predicted gene 10229	1	0.51	0.45	0.80	0.45	1.56	0.29
Retnla	resistin like alpha	1	0.71	0.11	0.28	0.11	0.40	0.28
Krtap19-3	keratin associated protein 19-3	1	1.08	0.48	1.87	0.48	1.74	0.28
Krtap5-5	keratin associated protein 5-5	1	0.50	0.47	0.86	0.47	1.72	0.28
Mylk4	myosin light chain kinase family, member 4	1	0.67	0.23	0.56	0.23	0.84	0.27
Krtap4-1	keratin associated protein 4-1	1	0.44	0.45	0.73	0.45	1.66	0.27
// Gm11938 // 11937 //	predicted gene 11938 // keratin associat	1	0.49	0.43	0.79	0.43	1.61	0.27
Krtap4-7	keratin associated protein 4-7	1	0.48	0.41	0.73	0.41	1.51	0.27
Krtap1-4	keratin associated protein 1-4	1	0.41	0.37	0.58	0.37	1.41	0.26
Gm11938	predicted gene 11938	1	0.48	0.43	0.78	0.43	1.63	0.26
Krtap2-4	keratin associated protein 2-4	1	0.48	0.43	0.78	0.43	1.64	0.26
Krtap24-1	keratin associated protein 24-1	1	0.52	0.53	1.06	0.53	2.03	0.26
Krtap19-5	keratin associated protein 19-5	1	1.10	0.44	1.90	0.44	1.73	0.26
Krt25	keratin 25	1	0.60	0.35	0.84	0.35	1.40	0.25
Krtap9-1	keratin associated protein 9-1	1	0.38	0.35	0.54	0.35	1.42	0.25
Krtap1-5	keratin associated protein 1-5	1	0.56	0.38	0.87	0.38	1.57	0.24
Krt71	keratin 71	1	0.58	0.43	1.03	0.43	1.79	0.24
Krt86	keratin 86	1	0.53	0.43	0.96	0.43	1.81	0.24
Krtap4-13	keratin associated protein 4-13	1	0.34	0.33	0.47	0.33	1.38	0.24
Gm11563	predicted gene 11563	1	0.41	0.34	0.61	0.34	1.49	0.23
Gm11567	predicted gene 11567	1	0.29	0.24	0.30	0.24	1.05	0.23
Gm11569	predicted gene 11569	1	0.34	0.32	0.48	0.32	1.42	0.23
Cyp2e1	cytochrome P450, family 2, subfamily e, polypeptide 1	1	0.62	0.16	0.43	0.16	0.70	0.22
Krtap6-2	keratin associated protein 6-2	1	0.48	0.39	0.85	0.39	1.77	0.22
Krtap19-1	keratin associated protein 19-1	1	1.16	0.45	2.39	0.45	2.06	0.22
Krtap4-2	keratin associated protein 4-2	1	0.41	0.34	0.67	0.34	1.61	0.21
Krt27	keratin 27	1	0.54	0.37	0.96	0.37	1.78	0.21
Gm10228	predicted gene 10228	1	0.44	0.33	0.72	0.33	1.62	0.20
Car6	carbonic anhydrase 6	1	0.86	0.23	0.99	0.23	1.15	0.20
Krt28	keratin 28	1	0.58	0.34	0.99	0.34	1.70	0.20
Tchh	trichohyalin	1	0.51	0.41	1.06	0.41	2.08	0.19
Krtap15	keratin associated protein 15	1	0.82	0.29	1.22	0.29	1.49	0.19
Prr9	proline rich 9	1	0.32	0.24	0.39	0.24	1.24	0.19
Krtap11-1	keratin associated protein 11-1	1	0.57	0.32	0.94	0.32	1.64	0.19
Gprc5d	protein-coupled receptor, family C, group 5, member I	1	0.49	0.28	0.71	0.28	1.45	0.19
Krtap21-1	keratin associated protein 21-1	1	0.45	0.41	0.98	0.41	2.20	0.19
Krtap3-3	keratin associated protein 3-3	1	0.43	0.25	0.60	0.25	1.39	0.18
Krt33a	keratin 33A	1	0.56	0.32	1.04	0.32	1.85	0.18
Krtap6-5	keratin associated protein 6-5	1	0.49	0.31	0.85	0.31	1.75	0.17
Krtap6-3	keratin associated protein 6-3	1	0.25	0.28	0.40	0.28	1.63	0.17
Krtap4-16	keratin associated protein 4-16	1	0.33	0.29	0.57	0.29	1.73	0.17
Krtap7-1	keratin associated protein 7-1	1	0.55	0.29	0.95	0.29	1.74	0.17
Gm11559	predicted gene 11559	1	0.34	0.25	0.55	0.25	1.62	0.16
Krtap8-1	keratin associated protein 8-1	1	0.54	0.25	1.16	0.25	2.15	0.12
Krtap6-1	keratin associated protein 6-1	1	0.39	0.17	0.69	0.17	1.75	0.09

Supplemental Table 2. KEGG pathways on genes which were upregulated by IMQ treatment in *Traf6^{ff}* mice compared to *Traf6EKO* mice.

ID	Description	Gene count	P value	Genes
mmu04060	Cytokine-cytokine receptor interaction	10	2.9E-03	<i>Ccl3, Ccl2, Ccl20, Clcf1, Ccr1, Il1b, Csf3r, Cxcr2, Ccl7, Il1a</i>
mmu04668	TNF signaling pathway	7	4.1E-03	<i>Ccl2, Ptgs2, Ccl20, Socs3, Cxcl2, Bcl3, Il1b</i>
mmu00590	Arachidonic acid metabolism	5	4.2E-02	<i>Ptgs2, Ptges, Pla2g4b, Alox8, Pla2g4e</i>
mmu05323	Rheumatoid arthritis	5	4.4E-02	<i>Ccl3, Ccl2, Ccl20, Il1b, Il1a</i>
mmu04914	Progesterone-mediated oocyte maturation	5	4.5E-02	<i>Cdk1, Ccnb2, Plk1, Bub1, Ccna2</i>
mmu04110	Cell cycle	6	4.6E-02	<i>Cdk1, Ccnb2, Plk1, Bub1, Cdc20, Ccna2</i>
mmu04062	Chemokine signaling pathway	7	4.6E-02	<i>Ccl3, Ccl2, Ccl20, Ccr1, Cxcl2, Cxcr2, Ccl7</i>

Supplemental Table 3. Primer sequences used for quantitative RT-PCR analyses.

Gene Symbol	Forward primer (5'>3')	Reverse primer (5'>3')
<i>Gapdh</i>	GGCCTCACCCCATTTGATGT	CATGTTCCAGTATGACTCCACTC
<i>Il1b</i>	TTGACGGACCCCAAAAGATG	TGGACAGCCCAGGTCAAAG
<i>Il4</i>	GGTCTCAACCCCAAGCTAGT	GCCGATGATCTCTCTCAAGTGAT
<i>Il6</i>	CACTTCACAAGTCGGAGGCT	TGCCATTGCACAACCTCTTTTCT
<i>Il12b</i>	GGTGTAAACCAGAAAGGTGCG	TAGCGATCCTGAGCTTGAC
<i>Il23a</i>	GACCCACAAGGACTCAAGGA	CATGGGGCTATCAGGGAGTA
<i>Il17a</i>	CTCCAGAAGGCCCTCAGACTAC	GGGTCTTCATTGCGGTGG
<i>Il17f</i>	AATCCTGGTCCTTCGGAGGG	GCCAACTTTTAGGAGCATCTTCT
<i>Il19</i>	GCCAACTCTTTCCTCTGCGT	GGTGGCTTCCTGACTGCAGT
<i>Il22</i>	ATGAGTTTTTCCCTTATGGGGAC	GCTGGAAGTTGGACACCTCAA
<i>Il24</i>	GAGCCTGCCCAACTTTTTGTG	TGTGTTGAAGAAAGGGCCAGT
<i>Saa1</i>	GCGAGCCTACACTGACATGAAG	CCCCCGAGCATGGAAGTATT
<i>Il36a</i>	AGCAGCATCACCTTCGCTTAG	GTGTCCAGATATTGGCATGGG
<i>Il36b</i>	CTTCGATCCCAGAGACAAGACT	ATTCGGTTCCCACATTTGAA
<i>Il36g</i>	CAGGTGTGGATCTTTCGTAATCA	CATGGGAGGATAGTCACGCTG
<i>Ccl20</i>	GCCTCTCGTACATACAGACGC	CCAGTTCTGCTTTGGATCAGC
<i>Tnf</i>	CTGGGACAGTGACCTGGACTGT	ACTCTCCCTTTGCAGAACTCAGG
<i>Cxcl1</i>	ACTGCACCCAAACCGAAGTC	TGGGGACACCTTTTAGCATCTT
<i>Defb3</i>	ATTTCTCCTGGTGCTGCTGT	GGAACCTCCACAACCTGCCAAT
<i>S100a8</i>	AAATCACCATGCCCTCTACAAG	CCCACTTTTATCACCATCGCAA
<i>S100a9</i>	GCACAGTTGGCAACCTTTATG	TGATTGTCCTGGTTTGTGTCC
<i>Ifng</i>	GAACTGGCAAAAGGATGGTGA	TGTGGGTTGTTGACCTCAAAC