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Short-term exposure to a Western diet induces psoriasiform dermatitis by promoting accumulation of IL-17A-producing γδ T cells

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Abstract

A Western diet (WD)—characterized by its high fat and simple sugar content—is thought to predispose individuals to inflammatory skin diseases such as psoriasis, through the development of obesity. This scenario, however, is being challenged by emerging data suggesting that dietary components, rather than obesity itself, may exacerbate psoriasis. We herein show that short-term feeding with a diet analogous to the WD in mice leads to Th1/Th17-biased skin inflammation before significant body weight gain. Feeding for as little as 4 weeks with WD promoted mild dermatitis and accumulation of IL-17A-producing γδ T cells in the skin. Strikingly, γδ T cells from WD-fed mice exhibited enriched IL-23 receptor expression and increased potential to produce IL-17A after IL-23 stimulation. In contrast to wild-type mice, WD-fed TCRδ-deficient and CCR6-deficient mice had reduced skin inflammation and IL-17A expression. Supplementation with a bile acid sequestrant, cholestyramine, prevented WD-induced skin inflammation along with

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AUTHOUS CONTRIBUTION

Conceptualization and Methodology: Z Shi, Y Wan and S Hwang

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DATA AVAILABILITY STATEMENT

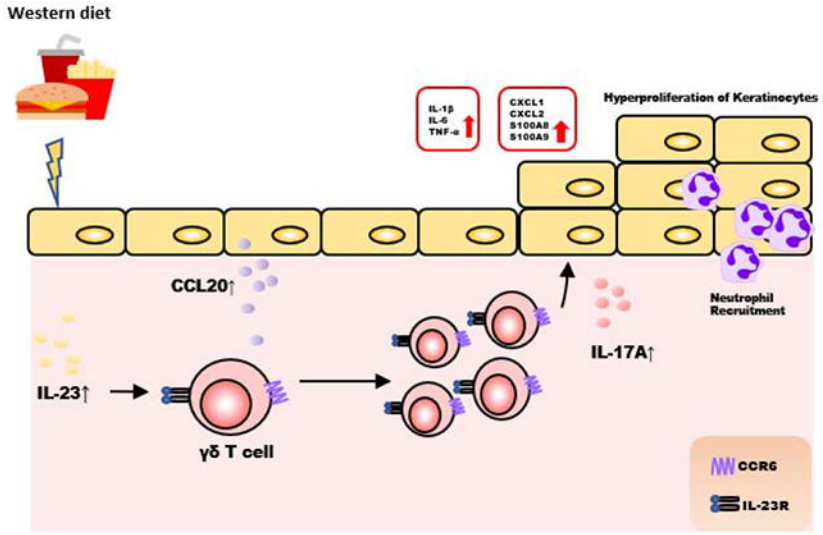
No datasets were generated during the current study, but some data are available from the corresponding author by request.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

a reduction in the infiltration of γδ T cells and the expression of proinflammatory mediators. In summary, our data revealed dietary influences in inflammatory signaling in the skin. The dysregulation of IL-23 pathways and BA pathways may be key to the development of WD-associated psoriasiform dermatitis.

Graphical Abstract



Keywords

Western diet; psoriasis; γδ T cells; IL-17A; bile acid

INTRODUCTION

Psoriasis is an autoimmune disease associated with multiple co-morbidities including cardiovascular diseases, metabolic syndrome, and obesity (Hwang et al., 2017). Mounting evidence suggests that obesity is a risk factor for development or exacerbation of psoriasis, and weight reduction may improve outcomes of anti-psoriatic therapies in overweight individuals (Armstrong et al., 2012, Jensen et al., 2013). Adipokines have been proposed as the pathological link between obesity and psoriatic inflammation (Cao, 2014). In obesity, visceral adipose tissue is a crucial site for the formation of pro-inflammatory adipokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α—both key cytokines implicated in the pathogensis of psoriasis. Recently, the causative relationship between obesity and psoriatic inflammation is being challenged by emerging data implicating that dietary components, rather than obesity itself, may exacerbate psoriasis (Herbert et al., 2018, Nakamizo et al., 2017, Yu et al., 2018).

The Western diet (WD), containing moderate-to-high levels of fat and high levels of simple sugars, contributes to the increased prevalence of obesity in the Western world. We previously found that C57BL/6 mice spontaneously developed dermatitis as they aged and that WD intake substantially increases the incidence after 8 months of continuous feeding

(Jena et al., 2019). Long-term intake of WD leads to dysregulated bile acid (BA) signaling accompanied by dysbiosis, which is implicated in WD-exacerbated dermatitis as well as other metabolically compromised phenotypes (Jena et al., 2017, Sheng et al., 2017). In particular, it is the WD, rather than a high fat diet (HFD), that enhances susceptibility of mice to imiquimod (IMQ)-induced psoriasiform dermatitis (PsD), suggesting obesity alone is not sufficient to promote psoriatic inflammation (Yu et al., 2018).

In our current study, we found that short-term exposure to WD alone is able to induce PsD before significant body weight gain. Additionally, there is an increase in IL-17A-producing γδ T cell in the skin. The IL-23 and BA signaling pathways may be essential mediators in the development of PsD induced by short-term exposure to WD.

RESULTS

Short-term exposure to WD induces skin inflammation

C57BL/6 mice were fed a WD or an otherwise nutritionally matched control diet (CD) after weaning. Ear thickness was continuously measured for up to 3 months after diet change. Modest ear swelling was observed at as early as 2 weeks in WD-fed mice compared to their CD-fed counterparts, but the increased ear swelling at this time point was uncoupled from obvious signs of inflammation, as indicated by a lack of epidermal hyperplasia and neutrophil infiltration (Supplementary Figure 1). The ear thickness peaked at around 1 month and gradually declined thereafter, with minimal differences observed between the two groups at 3 months (Figure 1a). Therefore, we chose to focus on phenotypic changes at the 4 week time point. In the absence of significant differences in body weight (Figure 1b), mice fed a WD for 4 weeks developed a clinically visible dermatitis of the ear skin that was characterized by mild erythema and scaling (Figure 1c). Histological analysis showed greater epidermal hyperplasia in ear skin (Figure 1d) as well as transepidermal water loss (TEWL) (Figure 1e), a marker of barrier dysfunction (Lee et al., 2012), in WD-fed mice compared to CD-fed mice (Figure 1 d). Inflammation was not only localized to skin. Half of mice fed with WD exhibited redness and mild swelling of the paws, which was notably absent in mice fed with CD (Supplementary Figure 2). H&E staining further revealed epidermal hyperplasia and hyperkeratosis in the paw skin from WD-fed mice as compared to those from CD-fed mice. WD-fed mice also showed an increase in cell counts per cervical lymph node (cLN) (Figure 1f). Thus, we observed the development of a clinically measurable dermatitis and epidermal barrier dysfunction after relatively short-term feeding of a WD in the absence of significant weight gain.

WD-induced skin inflammation is biased towards a Th1/Th17 response

We previously found that WD predisposes mice to enhanced susceptibility to PsD in an IMQ-induced psoriasis model (Yu et al., 2018), and postulated that the spontaneous skin inflammation observed in WD-fed mice showed features of PsD. Considering the essential role of IL-17 signaling in psoriasis pathogenesis (Blauvelt and Chiricozzi, 2018), we first examined the expression of cytokines associated with T helper (Th) 17 cells in the ear skin. In ear skin from WD-fed mice, quantitative reverse transcriptase PCR (RT-qPCR) showed a substantial increase in Th17-cytokines, including *Il17a* and *Il17f*, as well as other

proinflammatory mediators involved in Th17 cell activation and differentiation (Figure 2a). Within 2 weeks of feeding, WD induced a 60-fold increase in *Il17a* mRNA expression without overt dermatitis, suggesting a pivotal role of IL-17A in priming the skin to WD-induced inflammation. In addition to increased Th17 cytokines, ear skin from WD-fed mice showed upregulated mRNA levels of other key mediators of human psoriasitic disease, including neutrophil chemoattractants, antimicrobial peptides (AMPs) and TNF-α (Figure 2b). Consistent with mRNA expressions, the protein levels of IL-17A and IL-1β, as determined by ELISA, was significantly increased in the cutaneous homogenates from WD mice compared to CD mice (Figure 2c). However, the proteins levels of IL-17A and IL-1β in plasma were comparable between two groups of mice (data not shown), demonstrating that WD did not lead to measurable increases in plasma levels of these cytokines at this time point. Immunochemical (IHC) staining also confirmed a stronger expression of S100A8 in ear skin from WD-fed mice (Figure 2d).

While their role in psoriasis is controversial, Th1 cytokines are also uprelated in psoriatic lesions. By contrast, Th2 cytokines are generally expressed at low levels (Baliwag et al., 2015). In our experiments, Th1-related cytokines were significantly increased in WD-fed mice after 4 weeks (Figure 2e) whereas Th2-related cytokines were not altered (Figure 2f). Of interest, the expression of *Il10*, an immunosuppressive cytokine, was also remarkably increased in the ear skin from mice on WD compared to those on CD (Figure 2g). In sum, our data suggested that the WD-induced skin inflammation was biased toward a Th1/Th17 response and mirrored the cytokine profile observed in human psoriatic lesions.

γδ cells are a major source of IL-17A in WD-induced PsD

There are two distinct subsets of γδ cells in mice skin in terms of the amount of TCR present on their surface, γδ-high expressing T cells (also known as dendritic epidermal T cell, DETC) and γδ-low expressing (GDL) T cells (DETC are TCR-bright whereas the GDL T cell are found to be TCR-intermediate) (Sumaria et al., 2011). We have previously shown that GDL T cells account for the majority of IL-17A production and are required for the development of full-blown skin inflammation in an IL-23 injection PsD model (Mabuchi et al., 2011).

Therefore, we evaluated the role of γδ T cells—particularly GDL T cell in skin—in regard to IL-17A production in our WD-induced PsD model. The frequency and absolute number of γδ T cells, as well as their potential to produce IL-17A, was remarkably increased in the cLNs from WD-fed mice (Figure 3a). In line with our previous study (Mabuchi et al., 2011), GDL T cells, instead of DETC, were present at higher frequencies and with higher expression of IL-17A in ear skin from WD-fed mice (Figure 3b). Concurrently, a marked infiltration of neutrophils was observed in the ear skin from mice fed with WD (Figure 3c). To determine if γδ T cells played a critical functional role in our model, we fed T-cell receptor delta chain knock-out (TCRδ-KO) (lacking all γδ T cells) with WD and compared the skin inflammation with their WT counterparts. TCRδ-KO mice exhibited less erythema and scaling as well as smaller increases in ear swelling compared to WT mice after 4 weeks of feeding with a WD (Figure 3d and e). Histological assessment further revealed that TCRδ-KO mice had reduced epidermal hyperplasia and celluar infiltrates in the ear skin

compared to WT mice (Figure 3f and g). Consistently, flow cytometry revealed that lack of γδ T cells resulted in a reduction in neutrophilic infiltration in the skin (Figure 3h). A marked decrease in the total number of IL-17A-producing CD3+ T cell in both cLN and ear skin was observed in TCRδ-KO mice compared to WT mice (Figure 3i). In accordance with flow cytometry, RT-qPCR analysis confirmed a notable reduction in mRNA expression of several proinflammatory markers including *Il17a, Il6, cxcl1, S100a8 and S100a9*, in ears from TCRδ-KO mice compared to WT mice (Figure 3j). Taken together, our data showed that WD intake led to increased accumulation of IL-17A-producing γδ T cell, which contributed to the development of WD-induced PsD.

IL-17A-producing γδ T cells from WD-fed mice preferentially expand to IL-23 stimulus

Because previous studies showed that IL-23 was critical for the expansion and maintenance of IL-17-secreting T cells (Wilson et al., 2007), we next asked if the IL-23 pathway was essential for the development of WD-induced, IL-17A dominant psoriasiform dermatitis. We first examined the expression of IL-23 and its receptor, IL-23R, in WD-fed mice. Strikingly, ear skin from WD-fed mice exhibited an increase in *Il23* mRNA at 2 weeks, followed by an upregulation of *Il23r* at 4 weeks in constrast to CD-fed mice (Figure 4a). Furthermore, there were more IL-23R positive γδ T cells in cLNs from WD-fed versus CD-fed mice at 4 weeks (Figure 4b). To further study the impact of WD on the expansion potential of γδ T cells, single cell suspensions of cLNs and ear skin were obtained from mice fed with CD or WD for 4 weeks, and further stimulated in vitro with recombinant IL-23 protein. Addition of IL-23 failed to induce a significant increase in the total number or ratio of IL-17A-producing γδ T cells from cLNs of CD-fed mice (Figure 4c and d). In contrast, stimulation with IL-23 resulted in remarkable expansion of IL-17A-producing γδ T cells from cLNs of WD-fed mice. Co-culture with IL-23 also resulted in a significantly higher percentage of IL-17A positivity in GDL T cells from ear skin of WD-fed mice, but not those from CD-fed mice (Figure 4e and f). Together, the data showed that WD activated the IL-23 signaling pathway and further predisposed γδ T cells to increased IL-17A production after IL-23 stimulation.

CCR6 is required for the development of WD-induced PsD

CC chemokine receptor 6 (CCR6) is involved in the trafficking of IL-17 producing cells and is essential for the development of skin inflammation in both IL-23 injection and IMQ murine PsD model (Campbell et al., 2017, Mabuchi et al., 2013). We next sought to evaluate whether CCR6 also played a key role in the PsD induced by short-term feeding of WD. After 4 weeks of feeding, WD-fed mice had increased mRNA expression of *Car6* and its sole chemokine ligand, *Ccl20*, in ear skin (Figure 5a). Prominent upregulation of CCL20 was seen in acanthotic epidermis from WD-fed mice (Figure 5b), consistent with what has previously been described in human psoriatic skin (Homey et al., 2000) and IL-23-injected mouse skin (Hedrick et al., 2009). Of interest, staining of CCL20 was also found in cells within Munro microabscesses and infiltrated neutrophils in ear skin from WD-fed mice. Increased numbers of CCR6+ γδ T cells in the cLN were also observed in ear skin from WD-fed mice as compared to CD-fed mice (Figure 5c). To further explore the role of CCR6 in this model, we fed CCR6-deficient (CCR6-KO) mice and WT mice with WD and compared the degree of skin inflammation. At 4 weeks, WD-fed CCR6-KO mice developed little inflammation compared to WT mice, as evidenced by decreased erythema and scaling

(Figure 5d). Histological assessment revealed less epidermal hyperplasia and inflammatory cell infiltration in the ear skin of CCR6-KO mice compared to those of WT mice (Figure 5e). Diminished ear swelling (Figure 5f) and reduced epidermal thickness (Figure 5g) was observed in CCR6-KO mice. In accordance with clinically and histologically reduced skin inflammation, neutrophilic infiltration was profoundly impaired in CCR6-KO mice (Figure 5h). Most proinflammatory mediators previously shown to be elevated by WD were markedly suppressed in the ear skin from CCR6-KO mice compared to WT mice (Figure 5i). Together, these findings demonstrated that CCR6 is required for full expression of WD-induced skin inflammation.

Effect of cholestyramine (CSM) in WD-fed mice

We previously showed that long-term WD intake leads to dysregulated BA signaling, which may play a significant role in inducing cutaneous inflammation (Jena et al., 2019). To monitor BA signaling, we first investigated the expression and downstream signaling of two major BA receptors: TGR5 (Takeda G protein receptor 5) and S1PR2 (sphingosine-1-phosphate receptor 2) in this short-term WD model (Supplementary Figure 3). Short-term intake of WD failed to affect TGR5 signaling but resulted in dysregulation of the S1PR2 pathway in ear skin, including S1PR2, phingosine kinase isoenzymes (Sphk1, Sphk2), S1P phosphatase (Sgpp1) and S1P binding protein, i.e., prohibitin 2 (Phb2).

CSM is a BA sequestrant that reduces serum cholesterol and improves cholestatic pruritus associated with liver disease or other conditions (Ala et al., 2019). To further determine if BAs were critical for the skin inflammation following short term WD, we supplemented WD-fed mice with 2% CSM. Strikingly, compared to WD-fed mice, CSM-supplemented mice had reduced erythema and scaling (Figure 6a). H&E staining further revealed that CSM reduced epidermal hyperplasia and cellular infiltrates (Figure 6b). In addition, CSM also reduced WD-associated ear swelling (Figure 6c) and epidermal thickness (Figure 6d), infiltration of γδ T cells and neutrophils, (Figure 6e and f), and the expression of almost all inflammatory markers measured, with the exception of TNF-α (Figure 6g). Moreover, mRNA expression of *Ccl20* and *Il23r* was significantly downregulated by CSM feeding. In summary, CSM supplementation had an anti-inflammatory effect in WD-induced PsD, suggesting dysregulated BA signaling due to WD intake likely contributes to skin inflammation.

DISCUSSION

Herein, we demonstrate that a WD can, even in as little as one month, result in clinically and molecularly significant proinflammatory changes in the skin of mice. The relationship between diet and skin immunity is complicated and may be influence by the host microbiome. Cumulative evidence has demonstrated an intimate, reciprocal network between the gut and skin microbes (Salem et al., 2018). For example, some microbial metabolites such as short chain fatty acids (SCFAs), were found to play a pivotal role in determining the predominance of certain skin microbiome profiles, which subsequently influence cutaneous immune defense mechanisms. Because the WD can cause rapid shifts in the composition of gut microbiota (Jena et al., 2018), the gut-skin microbial axis may

contribute to WD-induce dermatitis. In line with this hypothesis, we found that treatment with an antibiotic cocktail attenuated the dermatitis induced by short-term exposure to WD (Supplementary Figure 4).

Other possible mediators in the gut-skin axis are bile acids (BA). Produced in the liver from cholesterol and metabolized in the intestine by the gut microbiota, BA not only play a pivotal role in dietary lipid absorption and cholesterol homeostasis, but are increasingly recognized as important signaling molecules in the regulation of immune homeostasis (Wahlstrom et al., 2016). WD intake causes dysbiosis and dysregulation in BA synthesis, accompanied by increased inflammation involving multiple organs (Jena et al., 2018, Jena et al., 2019). At high cellular concentrations, bile acids have been suggested to cause a calcium-dependent activation of NLRP3 inflammasome and promote the production of IL-1β (Fiorucci et al., 2018). Consistent with a recent finding that WD potentiates NLRP3-dependent inflammation (Christ et al., 2018),we had found that WD-fed mice have higher gene expression of NLRP3 and IL-1β upon IMQ stimulation (Yu et al., 2018). We previously showed that long-term intake of WD increased the incidence of dermatitis in C57BL/6 mice and altered the BA profile in comparison to CD-fed mice. Herein, we showed that short-term WD-mediated PsD is blocked by dietary supplementation with CSM, a BA sequestrant, suggesting a potential association between dysregulated BA signaling and psoriasis (Figure 6).

Clinically, CSM is used to treat pruritus (mediated by bile acids) secondary to biliary obstruction (Scaldaferri et al., 2013). Cholestyramine binds bile acids in the intestine and increases excretion of bile acids in the stool, promoting conversion of cholesterol into bile acids in the liver and, ultimately, lowering the level of cholesterol in the blood as well as bile acids in the skin and other organs. Although CSM alone is not as effective as statins in lowering low-density lipoprotein (LDL) cholesterol, we wanted to demonstrate that the diminished inflammation in CSF-treated WD mice was not a result of a reduction in hypercholesterolemia. Therefore, we treated the WD-fed mice with atorvastin and assessed its effect on skin inflammation. In contrast to CSM, atorvastatin (20 mg/kg/day in drinking water) did not have a significant effect on reducing ear thickness (data not shown). Therefore, we believe that the effect of CSM on WD-induced PsD is unlikely to be mediated strictly through its effect on cholesterol levels. Of note, an early clinical study reported an improvement of psoriasis after oral administration of CSM resin in five patients with psoriasis (Skinner et al., 1982). Given these findings, larger clinical studies should be conducted to assess the therapeutic potential of CSM or other BA sequestrants in psoriatic patients, particularly in those who regularly eat a WD.

Short-term exposure to WD significantly increased the expression programmed cell death protein 1 (PD-1) on GDL T cells in ear skin and γδ T cells in cLNs (Supplementary Figure 5), suggesting a mechanism by which WD-induced skin inflammation spontaneously diminishes over time since PD-1 is a well known suppressor of T cell activation. Moreover, the levels of PD-1 was increasingly over-expressed on GDL T cells after 3 month feeding with WD (data not shown). The overexpression of PD-1 in WD-fed mice is a possible self-regulatory mechanism for the subsequent spontaneous regression of dermatitis in this mouse model.

High sugar consumption has been suggested to be a potential environmental risk factor for the increasing incidence of several diseases including autoimmune disorders (Hu et al., 2014). Recent studies showed high sugar intake in mice exacerbates autoimmunity in experimental models of T cell-transfer colitis and experimental autoimmune encephalomyelitis (EAE) by promoting Th17 cell differentiation (Cao et al., 2017, Zhang et al., 2019). Based on our experimental findings and that of others, we postulate that the WD-induced inflammation is due to a combination of excessive fat and sugars. To test this hypothesis, we fed mice with CD, WD, HFD, HFD plus 12.5% sucrose-sweetened water or high sugar diet (HSD, containing same amount of sugar as WD but normal in fat) for 4 weeks and measured the ear thickness. WD-fed mice had significantly increased ear swelling compared to CD-fed mice and HFD-fed mice, but exhibited comparable ear thickness versus mice fed with HFD plus sweetened water (Supplementary Figure 6c). Of note, HSD-fed mice had identical ear thickness compared with CD-fed mice. In sum, these data suggest that high sugar alone is not enough to initiate grossly observable skin inflammation. A diet containing both high fat and high sugar is required to reach the maximum effect on inducing skin inflammation. Therefore, health education for obese patients with psoriasis may focus on weight loss as well as a reduction in certain dietary components, including fat and sugar.

In conclusion, our study shows that a relatively short-term exposure to WD leads to development of CCR6-dependent, psoriasis-like inflammation through accumulation of IL-17A-producing γδ T cells. These data support the hypothesis that dietary components, rather than obesity, may render the skinto mild but clinically significant Th17/Th1-dominant inflammation. Further studies are warranted to investigate the mechanism behind diet-induced skin inflammation with special attention to the interaction between metabolism, microbes, and immunity.

MATERIALS AND METHODS

Mice and diets

Female C57BL/6 mice and TCR δ-deficient mice (B6.129P2-*Tcrd*^{tm1Mom}/J) between 8 and 12 week-old were purchased from The Jackson Laboratory. C57BL/6 CCR6-KO mice were generated at the NIH and bred at Univ. of CA, Davis. Animal protocols were approval by the Institutional Animal Care and Use Committee at the Univ. of CA, Davis. WD and matched chow was purchased from Envigo Teklad animal laboratory diets (Madison, WI, USA; catalog numbers, WD: TD.140414, CD: TD.140415).

Flow cytometry

Anti–mouse γδ-TCR (clone GL3), CD45 (30-F11), CCR6 (29-2L17), CD11b (M1/70), Ly6G (IA8), IL-23R (12B2B64), PD-1(29F.1A12) antibodies were purchased from BioLegend (San Diego, CA,USA). Anti–IL-17A (eBio17B7) antibodies was purchased from eBioscience (San Diego, CA,USA). Intracellular staining for IL-17A was done after incubating cells for 2 hours with cell stimulation cocktail (eBioscience, San Jose, CA, USA). Flow cytometry was performed and analyzed using an Accuri C6 (BD Biosciences, San Jose, CA, USA).

Quantitative real-time PCR

Total RNA of mouse ear skin was extracted by using an RNeasy Fibrous Tissue Kit (Qiagen, Hilden, Germany). Quantitative real-time PCR was performed using Quant Studio 3 real-time PCR system (Applied Biosystems, Foster City, CA, USA). The primers were obtained from Integrated DNA Technologies, Inc (Skokie, IL, USA). Detailed Catalogue number is available in supplementary documents.

Statistical analysis

All data are shown as mean±SEM. Data were analyzed using GraphPad Prism version 6 (GraphPad Software, San Diego, CA, USA). For two-group comparisons, a two-sided Student's t-test was used. A *p*-value less than 0.05 was considered to be statistically significant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AMPs	antimicrobial peptides
BA	bile acid
CCR6	CC chemokine receptor 6
CD	control diet
CCL20	C-C motif chemokine ligand 20
CSM	cholestyramine
IL	interleukin
cLN	cervical lymph node
GDL	γδ-low
H&E	hematoxylin and eosin
HFD	high-fat diet
IMQ	imiquimod
PsD	psoriasiform dermatitis

Th	T helper
TEWL	Trans-epidermal water loss
WD	Western diet
WT	wild-type

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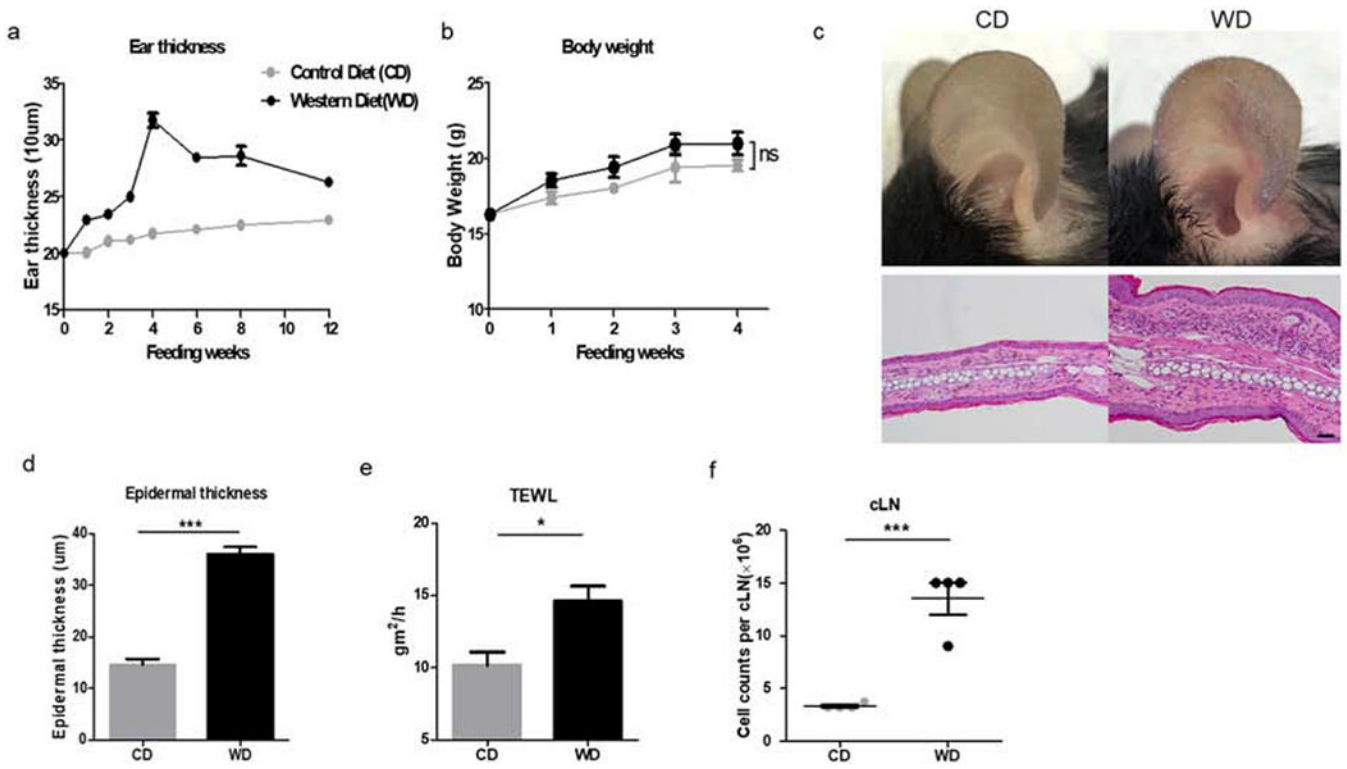

Figure 1. Short-term exposure to Western diet (WD) induces skin inflammation.

(a and b) Time course of ear thickness (a) and body weight (b) from mice fed with WD or a control diet (CD). (c-f) Representative photographs and image of H&E staining (c), epidermal thickness as measured in microscopic fields (d), Trans-epidermal water loss (TEWL) of ear skin (e) and cell counts per cerival lymph node (cLN) (f) from mice fed with WD or CD for 4 weeks. Scale bars, 50 um. Data are presented as mean ± SEM. Four animals per group, ns, no statistical significance. * p<0.05, *** p <0.001.

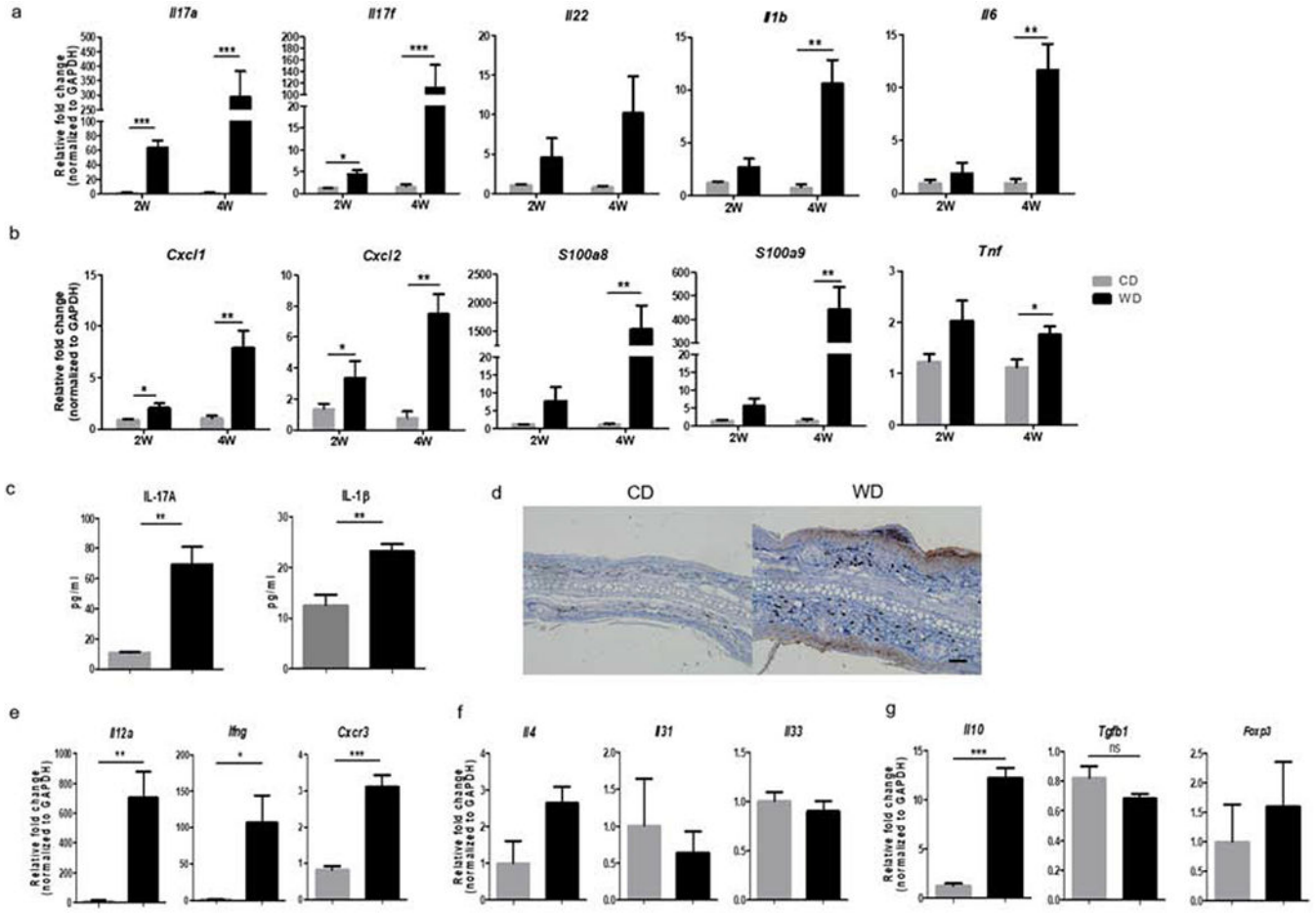

Figure 2. WD-induced skin inflammation is biased toward a Th1/Th17 response.

(a and b) Gene expression of Th17-related (a) and other psoriasis-related proinflammatory cytokines (b) in ear skin at 2 weeks and 4 weeks after feeding with CD or WD. (c and d) protein levels of IL-17A and IL-1β in homogenates (c) and immunochemical staining of S100a8 (d) of ear skin at 4 weeks after feeding with CD or WD.(e-f) Gene expression of Th1- (e) ,Th2- (f) and Treg-related markers (g) in ear skin at 4 weeks after feeding with CD or WD. All of the data are presented as mean± SEM. Four animals per group. Data are representative of two independent experiments. * $p<0.05$, ** $p<0.01$. *** $p<0.001$, as calculated by two-tailed, unpaired Student's t test.

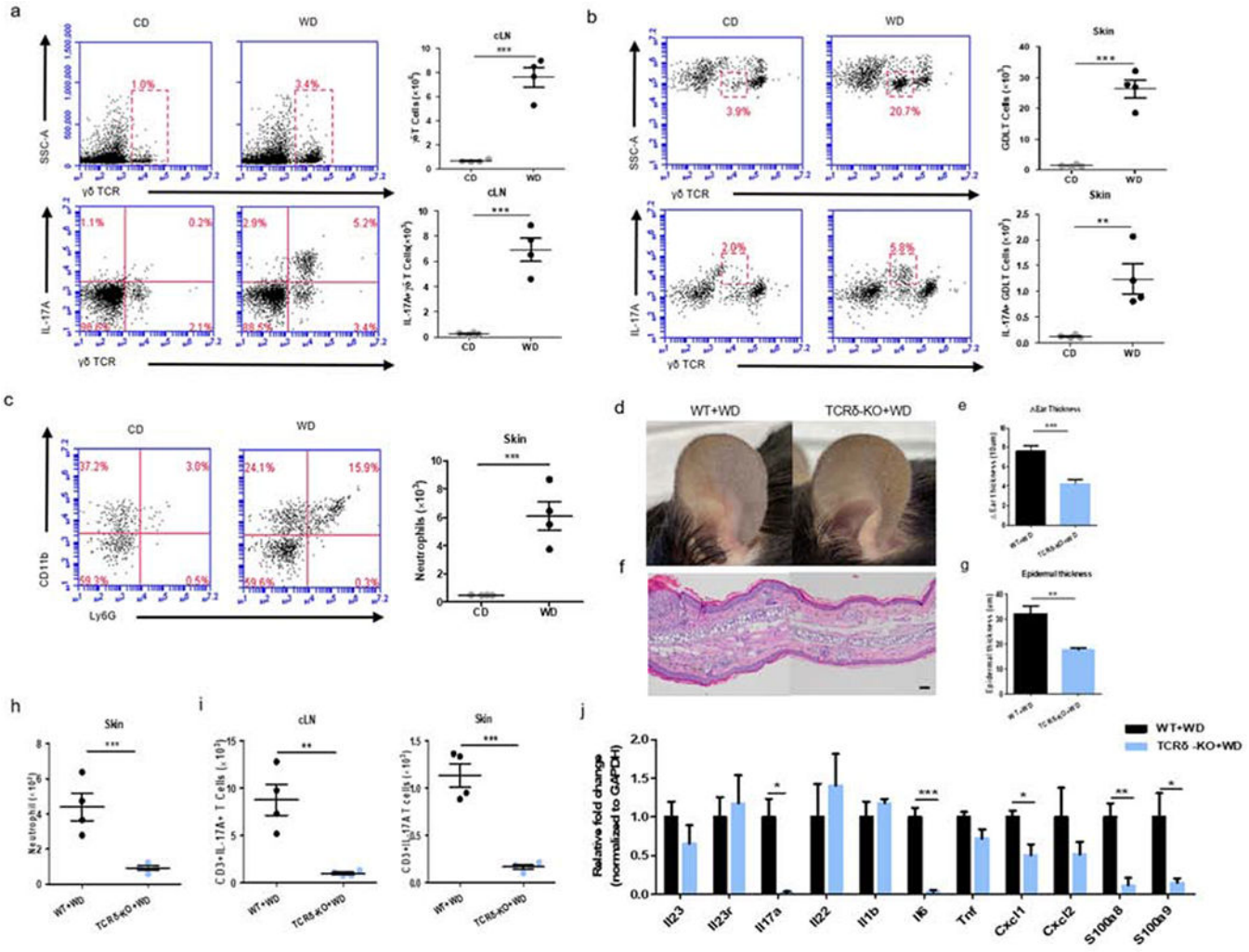

Figure 3. γδ T cells are the predominant source of IL-17A in WD-induced psoriasiform dermatitis (PsD).

(a-c) Total and IL-17A-producing γδ T cells in the cLN (a) or GDL T cells in the ear skin (b) and neutrophils (c) in ear skin from WT mice fed with CD or WD for 4 weeks. (d-j) Representative photographs (d) and H&E staining (f), ear thickness change (e), epidermal thickness (g), absolute number of total neutrophil per ear (h), absolute number of IL-17A-producing CD3+ T cells per cLN and per ear (i), gene expression of psoriasis-related cytokines in ear skin (j) from WT mice and TCRδ-KO mice on a WD for 4 weeks. Data are presented as mean ± SEM. Scale bars, 50 um. Four animals per group. * p <0.05, ** p <0.01. *** p <0.001.

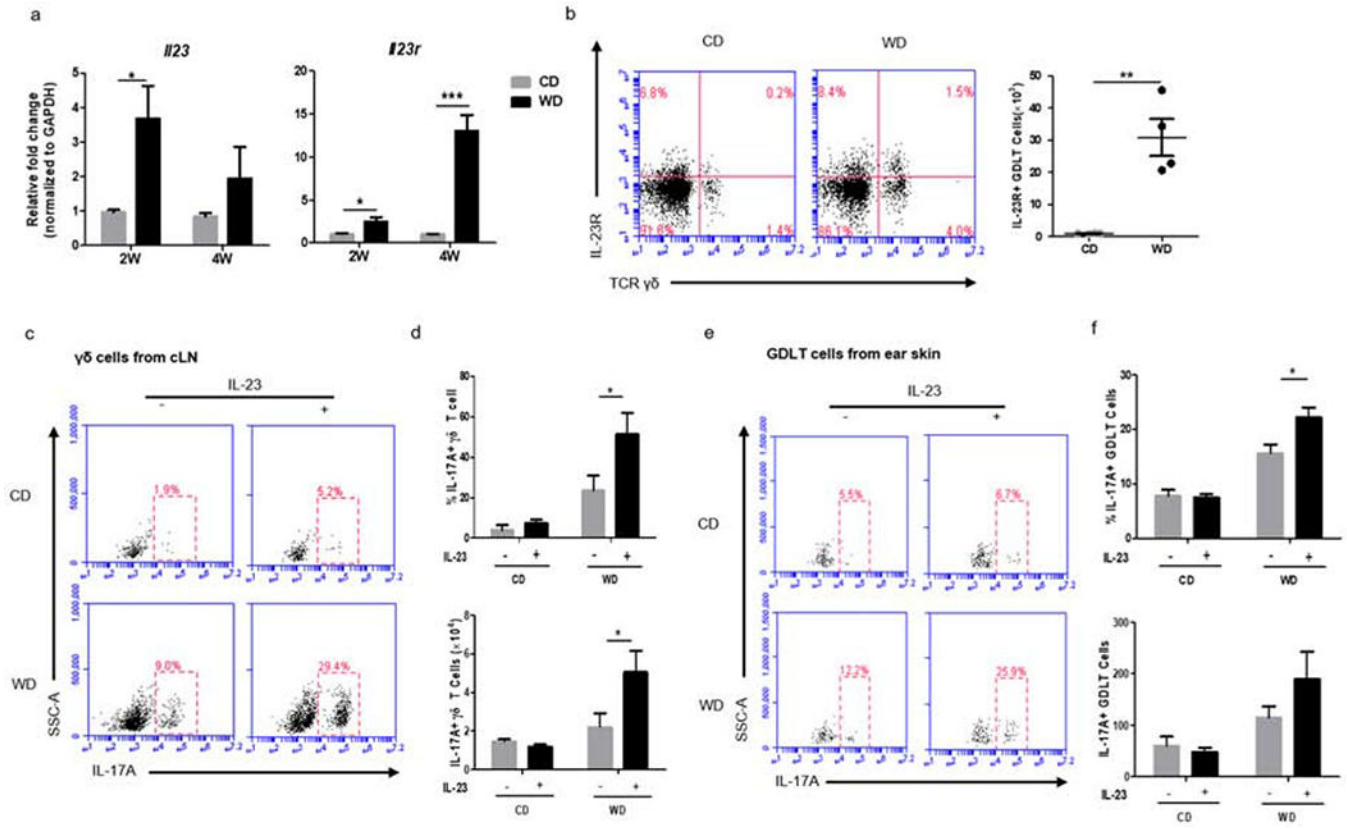

Figure 4. IL-17A-producing γδ T cells of WD-fed mice preferentially expand to IL-23 stimulation.

(a) Gene expression of *Il23* and *Il23r* in ear skin at 2 weeks and 4 weeks after feeding with CD or WD. (b) γδ T cells expressing IL-23R in the cLN at 4 weeks after feeding with CD or WD. (c-e) percentage and absolute number of γδ T cells from cLN (c and d) or GDL T cells from ear skin (e and f) expressing IL-17A of mice fed with CD or WD for 4 weeks, 24 hours incubation in the absence or presence of IL-23 (100ng/ml). Data are presented as mean± SEM. Three to four animals per group. * p <0.05, ** p <0.01, *** p <0.001.

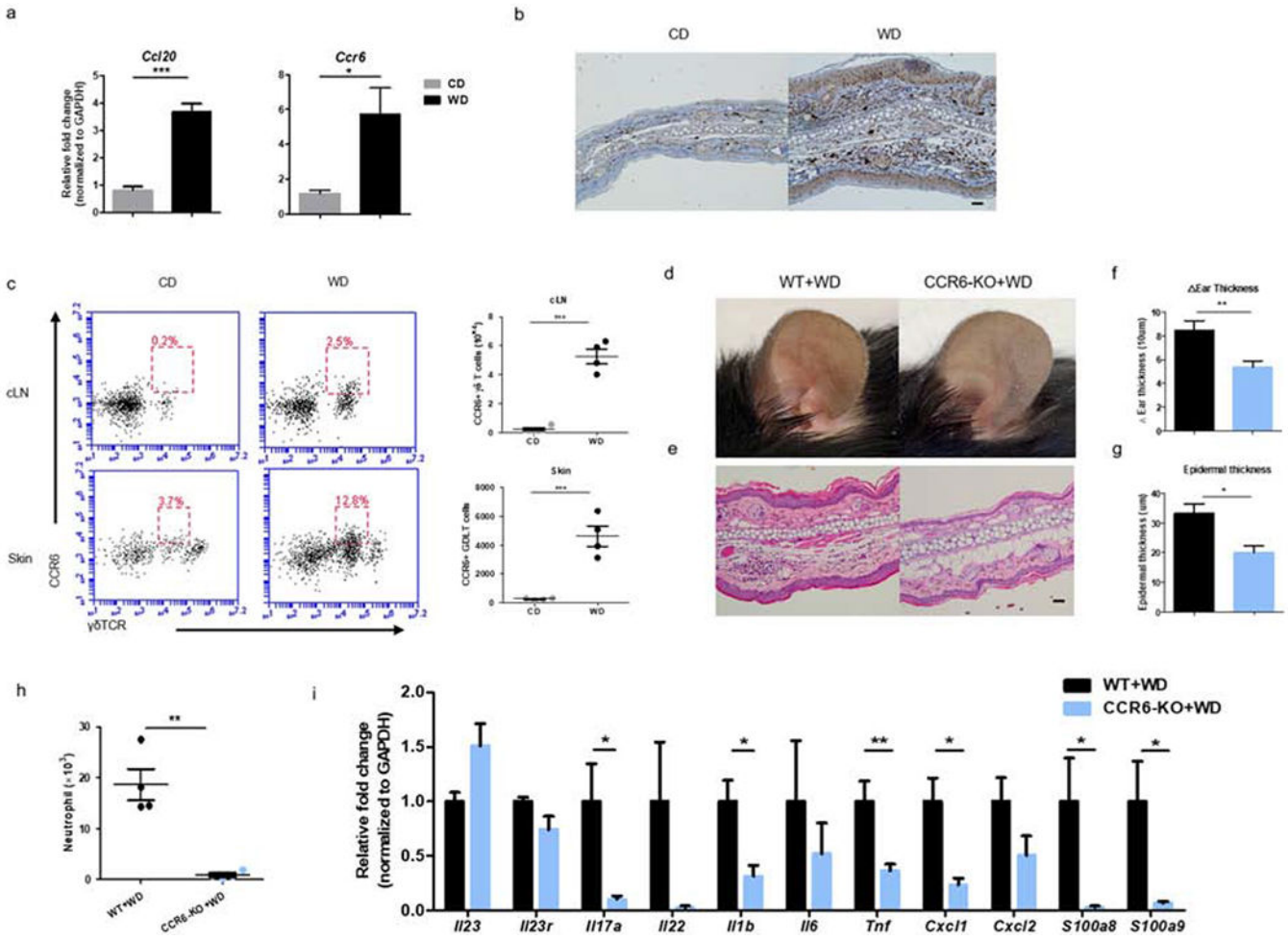

Figure 5. CCR6 is required for the development of a full-blown WD-induced PsD.

(a) Gene expression of Ccr6 and Ccl20 in ear skin from WT mice at 4 week after feeding with WD or CD. (b) immunochemical staining of CCL20 in ear skin. (c) Representative flow cytometry plots and absolute numbers of of CCR6-positive γδ T cells in the cLNs and and GDL T cells in ear skin. (d) Representative photographs and (e) image of H&E staining, (f) change in ear thickness, (g) epidermal thickness, (g) absolute number of total neutrophil per ear, (i) gene expression of psoriasis-related cytokines in ear skin from WT mice and CCR6-KO mice fed with WD for 4 weeks. Scale bars, 50 um. Four to five animals per group. * p<0.05, ** p<0.01. *** p<0.001, two-tailed, unpaired Student's t test.

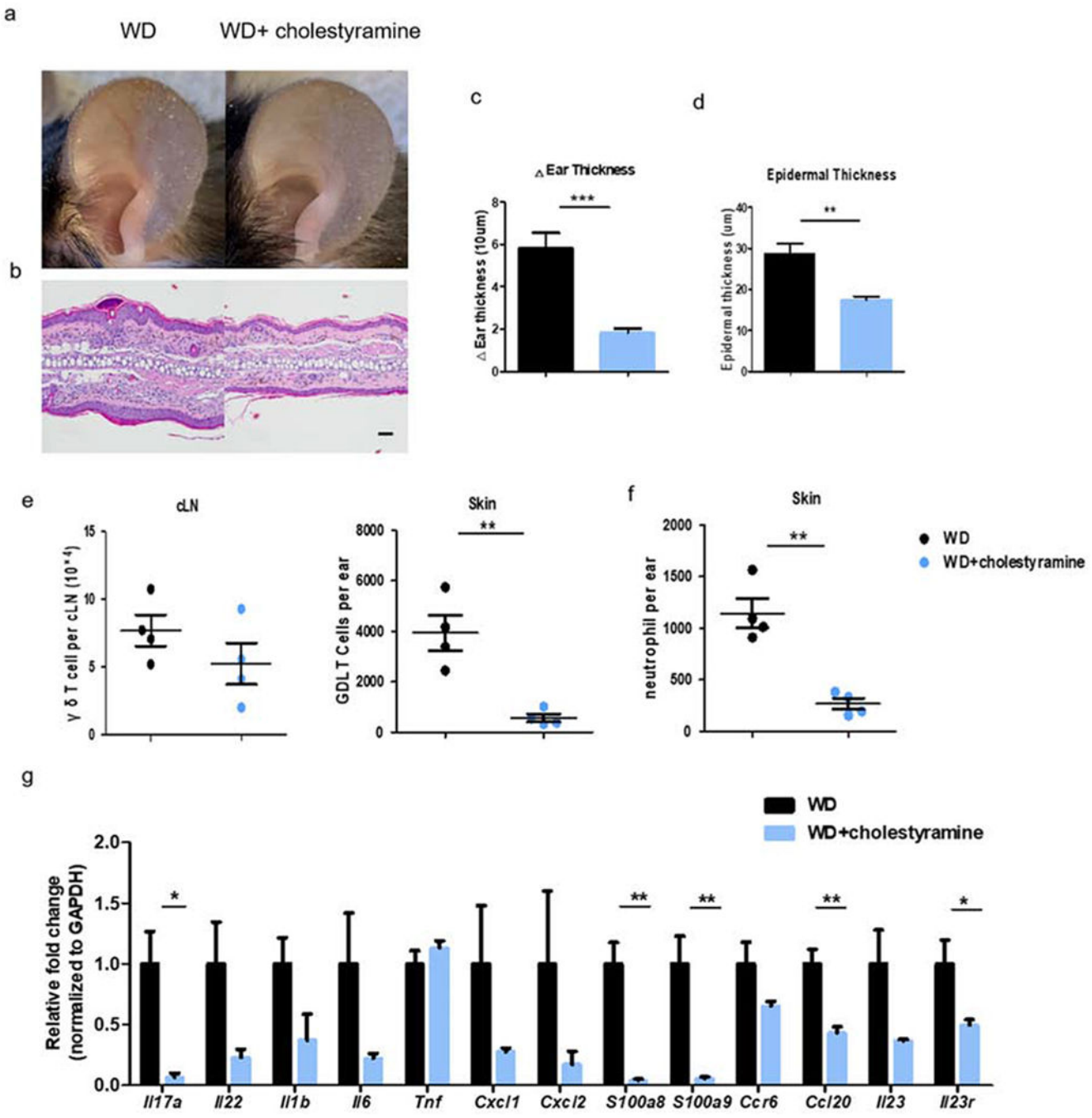

Figure 6. Cholestyramine ameliorates WD-induced PsD

(a) Representative photographs and (b) image of H&E staining of ear skin, (c) change in ear thickness, (d) epidermal thickness, (e) absolute number of total γδ T cell per cLN and GDL T per ear, (f) absolute number of total neutrophil per ear, (g) gene expression of psoriasis-related cytokines in ear skin from mice at 4 week after feeding with WD or WD supplementd with 2% CSM. Data are presented as mean± SEM. Scale bars, 50 um. Four animals per group. * p <0.05, ** p <0.01. *** p <0.001.