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ORIGINAL RESEARCH

A Novel Chronic Psoriasis Mouse Model via Optimized Imiquimod Dosing and Machine Learning Evaluation

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Scope: Imiquimod (IMQ)-induced psoriasis-like mouse models are widely used for psoriasis research, but existing methods fail to sustain disease manifestation over time. This study explores the effect of different IMQ dosing frequencies on maintaining psoriasis symptoms in mice.

Methods and Results: We compared a general IMQ model (General Model) with models that used spaced dosing (D-D Model) or 5–6 doses per week (3D-D Model) over a 28-day duration. Each experimental group consisted of eight mice (n=8) to ensure statistical significance. Both the D-D and 3D-D models maintained classic pathological features of psoriasis, including immune cell accumulation in skin and sustained levels of psoriasis-related inflammatory factors in the blood, compared to the control and General Model groups. Transcriptomic analysis revealed that D-D Model and 3D-D models mice exhibited more severe psoriasis-like lesions and significantly increased expression of IL-17 and IL-23 signaling genes (IL-17A, IL-17F, S100A9) compared to the General Model. Furthermore, adjusted dosing frequencies influenced the metabolic profile, with higher regulation of TRP channels and 2-oxocarboxylic acid metabolism in the skin of D-D mice. Subsequent, Identification and validation of a conserved psoriasis biomarker signature via machine learning and cross-species analysis.

Conclusion: Adjusting the dosing frequency of conventional imiquimod-induced psoriasis-like mouse models to alternate-day administration (D-D) or three days on followed by one day off (3D-D) maintained long-term psoriasis symptoms. enhancing IL-17/IL-23 signaling pathways. This modification resulted in a model exhibiting biological characteristics more closely resembling those in humans, thereby providing a more clinically relevant model for chronic psoriasis. Despite these advantages, the current model has not yet fully recapitulated the complex seasonal and cyclical nature of clinical psoriasis.

Keywords: psoriasis, imiquimod, chronic mouse model, transcriptomics, machine learning

Introduction

Psoriasis is a chronic skin disease characterized by abnormal keratinocyte proliferation and infiltration of immune cells, leading to the development of scaling skin plaques.[1] This difficult-to-treat illness has a significant adverse impact on patients' quality of life, with an estimated 2–3% of the world population affected.[2] Current pharmaceutical treatments are ineffective and often provide only temporary relief, increasing the need to further understand the disease pathogenesis and develop better treatment strategies.[3] Due to ethical concerns and the difficulty of obtaining human samples, research on psoriasis is largely dependent on animal models, which provide researchers with a better perception of the disease model, pathophysiology processes, and evaluation of different therapeutic options.[4] A number of approaches have been

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used to model the characteristics of psoriasis in animals, with each having distinct advantages and limitations. These models may be chemically induced, xenograft based or genetically driven.[5]

However, current animal models of psoriasis still face numerous challenges; in particular, the specific staging characteristics of psoriasis are difficult to replicate in these models.[6] The pathological features of psoriasis exhibit significant differences between the acute flare-up phase and the chronic stable phase in terms of clinical characteristics, genetic background, natural disease course, and molecular expression profiles.[7] Specifically, acute psoriasis is often characterized by intense inflammation and rapid proliferation of keratinocytes, with the potential for spontaneous remission, whereas chronic plaque psoriasis presents with persistent epidermal hyperplasia and immune activation, featuring a more complex inflammatory infiltration.[8] Therefore, it is essential to explicitly distinguish between acute and chronic phase psoriasis at both the clinical and experimental levels. The imiquimod (IMQ)-induced psoriasis model is one of the most widely used chemically induced models. It is very widely used due to its relative simplicity, the ease of dosing and controlling the experimental process, and its ability to reproduce key features of human psoriasis, including erythema, scaling, and epidermal thickening.[9] The traditional regimen of continuous IMQ administration for approximately one week serves as typical acute model, but these symptoms are not quite congruent with the chronic characteristics of psoriasis since they are transient.[10] Moreover, high doses and long-running daily use of IMQ produce profound acute inflammatory reactions and can even kill the mice, which is not analogical to the natural, persistent immunological mechanisms of the chronic disease.[5,11] Animal models that more closely resemble chronic psoriasis often require genetic interventions through various means. For instance, the spontaneously mutated asebia mice, which have been used for many years,[12,13] are gradually deviating from current research needs due to their systemic, multi-organ complex pathological changes. Meanwhile, transgenic mice that closely mimic chronic psoriasis manifestations, such as those overexpressing TGF-β1[14] or with IL-25 knockout,[15] often fail to fully replicate the complex immune environment of human psoriasis. Correspondingly, genetic interventions frequently lead to a decline in animal welfare (eg, severe pruritus, pain) and an increase in research costs. Therefore, the improved application and design of IMQ-induced psoriasis-like mouse models remain a pressing research need today.

Despite previous efforts to modify IMQ administration frequencies and durations, a critical knowledge gap remains, as there is a lack of rigorously validated chronic IMQ models that demonstrate long-term molecular and transcriptomic comparability to human psoriasis.[16,17] To overcome this challenge and establish a more clinically representative model, we optimized the IMQ dosing frequency (utilizing alternate-day (D-D) or three days on followed by one day off (3D-D) regimens) to sustain chronic inflammation. Furthermore, to quantitatively validate the molecular fidelity of these models, we employed a machine-learning-based approach. By deriving a conserved biomarker signature from human clinical transcriptomic datasets using multiple machine-learning algorithms, we were able to cross-validate our novel mouse models against genuine human disease profiles. Ultimately, this integration of optimized in vivo modeling and computational validation provides a more biologically and pathologically relevant platform for investigating psoriasis pathogenesis and novel therapeutic interventions.

Subjects and Methods

Study Design

The study was designed according to ARRIVE guideline, as well as the national standard GB/T 35892–2018 Guidelines for the Ethical Review of Laboratory Animal Welfare and relevant regulations. All experiments were approved by the Animal Ethics Committee of the Beijing Institute of Traditional Chinese Medicine (No. BJTCM-M-20220601).

Six-week-old male C57BL/6J mice were obtained from Spearfish (Beijing) Biotechnology Co. Mice were housed in specific pathogen-free (SPF) facility at the Beijing Institute of Traditional Chinese Medicine (No. SYXK Jing 2018–0006) with access to food and water ad libitum. Housing conditions were on a 12 h light—dark cycle. After being adapted for a certain time, mice were randomly divided into the following groups: Control group ("Ctrl"), model group with imiquimod intervention for 7 days continuously ("General Model"), model group with imiquimod intervention on every other day ("D-D Model"), and model group with imiquimod intervention every three days on condition of one withdrawal ("3D-D Model"), and model group with imiquimod intervention every other week ("W-W Model").

Psoriasis-like lesions were induced with varying frequencies of imiquimod treatment (IMQ) in the different experimental groups, and were assessed by different approaches, including disease progression and immune responses.

DOSE INFORMATION: Mice received imiquimod (IMQ) topically according to the schedule indicated in the experimental groups indicated in order to standardize the experimental parameters amongst groups. In detail, to induce a psoriasis-like lesion model for when intervention was needed, 5% IMQ cream (Sichuan Mingxin, Sichuan, China) with a dosage of 62.5 mg was applied to the skin of the mice daily. This dose and route of administration were chosen according to common protocols used to induce psoriasis-like lesions in mice. C57BL/6J male mice aged six weeks were obtained from Spearfish (Beijing) Biotechnology Co., one of the laboratory animal suppliers, and used to establish an IMQ-induced psoriasis-like mouse model. The mice were put into the Specific Pathogen-Free (SPF) animal laboratory of the Beijing Institute of Traditional Chinese Medicine once they were arrived.

The design of experiments required not only allocation of eight mice in each group, a total of 32 mice, but also that mice in each group were assigned randomly. Mouse group sizes (n=8 per group) were chosen based on standard research and were sufficient to demonstrate statistically significant and biologically consistent differences in the biomarker signature scores between disease models and controls, as shown in our results. To minimize potential confounding factors, all cages across different experimental groups were randomly relocated and dispersed on the racks weekly. All routine procedures (weighing, monitoring) and experimental treatments (induction, sample collection) were performed in a randomized sequence across groups daily to avoid temporal bias. To allow for the consistent and direct administration of the IMQ cream, the dorsal hair of all mice was shaved after an acclimatization period in which the mice were allowed to acclimatize to their new environment. To prevent mice from ingesting additional imiquimod cream while grooming each other's back skin or fur, they must be housed individually in separate cages during the treatment period. The Control group mice underwent skin preparation without further intervention. Mice in the General Model group underwent modeling synchronously with other model groups starting on day 21, for a continuous period of 6 days. The application of IMQ was in accordance with each of the intervention models; for the W-W model (week-week), IMQ was applied for seven consecutive weeks with one suspension week; for the D-D model (day-day), IMQ was administered every day; and for the 3D-D model, IMQ was given for one day every three days with a suspension for another three days.

Animal Inclusion Criteria: Mice were included in the study only if they: 1) belonged to the specified C57BL/6J genetic background; 2) were of the same sex and age cohort; 3) successfully completed the entire modeling protocol without severe welfare complications (eg., excessive weight loss >20%, severe ulceration).

Data Point Exclusion Criteria: During bioinformatic analysis, data points (samples) were excluded only for technical reasons: 1) poor RNA quality (RIN < 7.0); 2) outliers identified via principal component analysis (PCA) that were attributed to clear sample handling or sequencing batch artifacts.

All groups were dosed with their respective treatment for 28 days of continuous exposure for each experimental model. IMQ cream was gently patted onto the skin and allowed to absorb completely over the course of the interventions to ensure efficacy. During the intervention period, the mice were individually housed to minimize scratching behavior that could disrupt the intervention application site or introduce variance in the results. At the end of the intervention period on day 28, reaching a stage of relatively stable skin condition, animals were euthanized according to ethical guidelines, and dorsal skin tissues and serum were obtained for analysis thereafter. These samples were processed for biochemistry, histology, and molecular analyses in response to the different dosing regimens for the treatment of psoriasis-like conditions.

Euthanasia or Anesthesia Method

Throughout the experiment, we administered isoflurane anesthesia using the RWD (RWD Life Science Co., Ltd) small animal anesthesia system (TAIJI-IE Compact Small Animal Anesthesia Machine) during the pre-shaving sedation phase and at the experimental endpoint for tissue collection Prior to dorsal shaving, mice were placed in an induction chamber connected to the anesthesia machine and rapidly induced using oxygen containing 3% isoflurane (flow rate 1 L/min). Following successful induction, mice were immediately removed from the induction chamber and fitted with an appropriately sized anesthesia mask. The isoflurane concentration was then reduced to 1.5%, and the oxygen flow rate adjusted to 0.5 L/min. The mouse was maintained under these conditions until the plantar reflex disappeared and

adequate body temperature was ensured, at which point dorsal shaving was performed. At the experimental endpoint on Day 29, mice were anesthetized under the same conditions prior. Once deep anesthesia was achieved, mice were euthanized by decapitation, followed by tissue harvesting.

Blinding During the Experiment

During the allocation phase, researchers responsible for animal grouping and model induction were necessarily aware of group assignments, as the treatment method determined group identity. But results evaluation phase (data collection), blinding was implemented for key molecular indicators. Personnel performing tissue collection, RNA extraction, library preparation, and sample sequencing submission received only samples labeled with unique identifiers.

Psoriasis Area and Severity Index Score (PASI)

The PASI score was calculated according to the three clinical scoring criteria used to score skin lesions (erythema (redness), scaling (flakiness), and infiltration (thickness)) on a 0–4 scale. The individual scores were summed to obtain the PASI score. The PASI score was graphically represented to allow for time zero data, as PASI evaluations would show changes in skin lesions over time.

Histopathology and Immunofluorescence Staining

Skin samples were collected and fixed in formalin to preserve the structural integrity of the cells, followed by embedding in paraffin. Tissue was cut into 5 μm slices followed by hematoxylin and eosin (H&E) staining for tissue and cellular morphology. Stained sections were scanned using Aperio CS2 Leica scanner and epidermis thickness was measured and analyzed in ImageScope software. Immunofluorescence staining of tissue sections was performed using an anti-ki67 antibody (ab15580, Abcam, UK) for proliferating cells. Subsequently, an Alexa 488-conjugated secondary antibody was used for fluorescence detection. Sections were then mounted with a medium containing DAPI, which stains cell nuclei. The slides were then analyzed by Zeiss confocal microscope. For quantitative analysis, the number of positive cells was manually counted in three randomly selected fields per slide beneath a 200× magnification.

Serum Cytokine Measurements

Serum samples collected from mice were isolated by centrifugation. Later, these processed samples were assayed according to the provided protocol of Th1/Th2/Th9/Th17/Th22/Treg Cytokine 17-Plex Mouse ProcartaPlex™ Panel (Invitrogen, USA, EPX170-26,087-901). This analysis enabled serum cytokine detection and quantification. The concentration levels for each cytokine were measured using a Luminex instrument. The results were then analyzed, and cytokine concentrations were determined by interpolation in a standard curve. Ninety-five percent confidence limits are shown and the curve was derived using a five-parameter nonlinear regression model.

Transcriptome Sequencing

Total RNA was respectively extracted using TRIzol reagent according to the manufacturer's protocol. The purity and concentration of the extracted RNA were estimated using a NanoDrop 2000 spectrophotometer (Thermo Scientific, USA), whereas the integrity was evaluated with an Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA). These procedures allowed the RNA to be of high enough quality to be analyzed. Following the instructions of the kit, transcriptome libraries were prepared using the VAHTS Universal V5 RNA-seq Library Prep Kit. Shanghai Ouyi Biotechnology Co. subsequently performed transcriptome sequencing and associated data analysis.

Flow Cytometry

10× diluted Hanks balanced salt solution was added to 1× suspension buffer that contained HEPES solution, DNase I, collagenase A, DTT, calcium chloride, l-glutamine, and penicillin-streptomycin to create single-cell suspensions. The solution kept at 4°C until use. The skin was cut into small pieces and placed in a 50-milliliter tube. Add 2 mL of digestion buffer and incubate for 1 hour at 37 °C with shaking 220 rpm. The suspension was then filtered before being centrifuged, and the microspheres were resuspended in 1 mL of cold staining buffer. CD45 APC/CY7 (103116,

BioLegend, USA); CD3 FITC-A (35–0031-U025, USA); Ly6G PerCP-cy-5-5A (127605, BioLegend, USA); CD11B BV605-A (562127, USA); TCR-γδ PE-A (118108, USA). These were incubated for 15 minutes under light-avoidance conditions. After washing twice with PBS, data were collected over 10 min in centrifugation at 1500 rpm using a BD LSR II and analysed with FACSDiVa 8.0 software.

Statistical Processing

SPSS 20.0 software was employed to conduct the statistical analysis, and GraphPad Prism 9 was used for graphical representation. Data with a normal distribution were described as mean ± standard deviation (x ± s). Intergroup comparison: One-way ANOVA was used for comparison between the two groups, and Tukey's method was used for two-way comparison between groups. P-value < 0.05 were considered statistically significant.

Results

Frequency of IMQ Treatment Effects on Psoriasis-Like Inflammation in Mice

Here, we sought to determine the effects of different IMQ treatment frequencies on the onset and the course of psoriasis-like skin inflammation in mice. Therefore, we compared differences in the frequency of treatment to further assess the relationship between the frequency of dosage and the degree or duration of inflammation. The study also focused primarily on the development of an improved mouse model for chronic psoriasis. The new model that the scientists formed reflects the chronic, relapsing nature of psoriasis in humans more accurately. It captures specifically the persistent inflammation, and immune-related features, which are hallmarks of the disease.[2]

It is well-described that topical IMQ (imiquimod) application induces an acute inflammatory response within six days of treatment.[18] Thus, one week of treatment cycle is often used as a standard to develop acute psoriasis mouse model verifying key symptoms of psoriasis,[19] including epidermal thickening (hyperplasia), scaling, and erythema (Figure 1a). To establish a more suitable model of chronic psoriasis, the authors tested multiple doses of IMQ (Figure 1b). We now tried to expand the treatment duration of IMQ by repeating the dosing cycle detailed above. However, the mortality rate of the mice significantly increased after feeding IMQ for more than 12 days, which constituted a serious barrier for long-term observation in the model.

In fact, when the IMQ was applied at the frequency described above but on even and odd Weeks (the W-W model), while mortality was lower this was not sufficient to maintain the lesions of the skin. Day 28: macroscopic examination demonstrated very thin and wet skin in the mice (Figure 1d), which ever more differential from normal psoriasis pathology, they also had virtually lost the scaly look typical of psoriasis.[20] In contrast, decreasing the number of IMQ administrations, in the form of administering the medication three to four times per week (the D-D model) or five to six times per week (the 3D-D model), effectively prolonged the inflammatory process without stimulating excessively severe short-term reactions (Figure 1c). Mice that received IMQ doses at a low frequency exhibited a more chronic type of inflammation characterized by sustained keratinocyte hyperproliferation and moderate immune cell infiltration. This pattern of staining is suggestive of a chronic pathological process, as shown in skin tissue staining (Figure 1e–i). These results indicate a more stable disease progression and delayed onset of skin inflammation in the mouse model upon lower frequency IMQ administration with longer cycles. In contrast, this approach takes a longer period for disease maintenance, better reflecting the chronic, migratory nature of the symptoms seen in human psoriasis before the onset of proinflammatory factors in humans.[21]

IMQ Administration Frequency Affects Immune Responses in Psoriasis Models

Their aim was to determine whether altering the timing of medication delivery would make the mice's inflammatory responses more regulated and sustained. Furthermore, key inflammatory cytokines were evaluated by flow cytometry and the novel model epidermis was examined for immune cell infiltration, thereby further establishing the pathophysiology of the model.[22]

When the frequency of IMQ administration was altered, flow cytometric analysis demonstrated a marked change in the immune cell population composition in more proximal layers of the epidermis (Figure 2a). Significantly enhanced

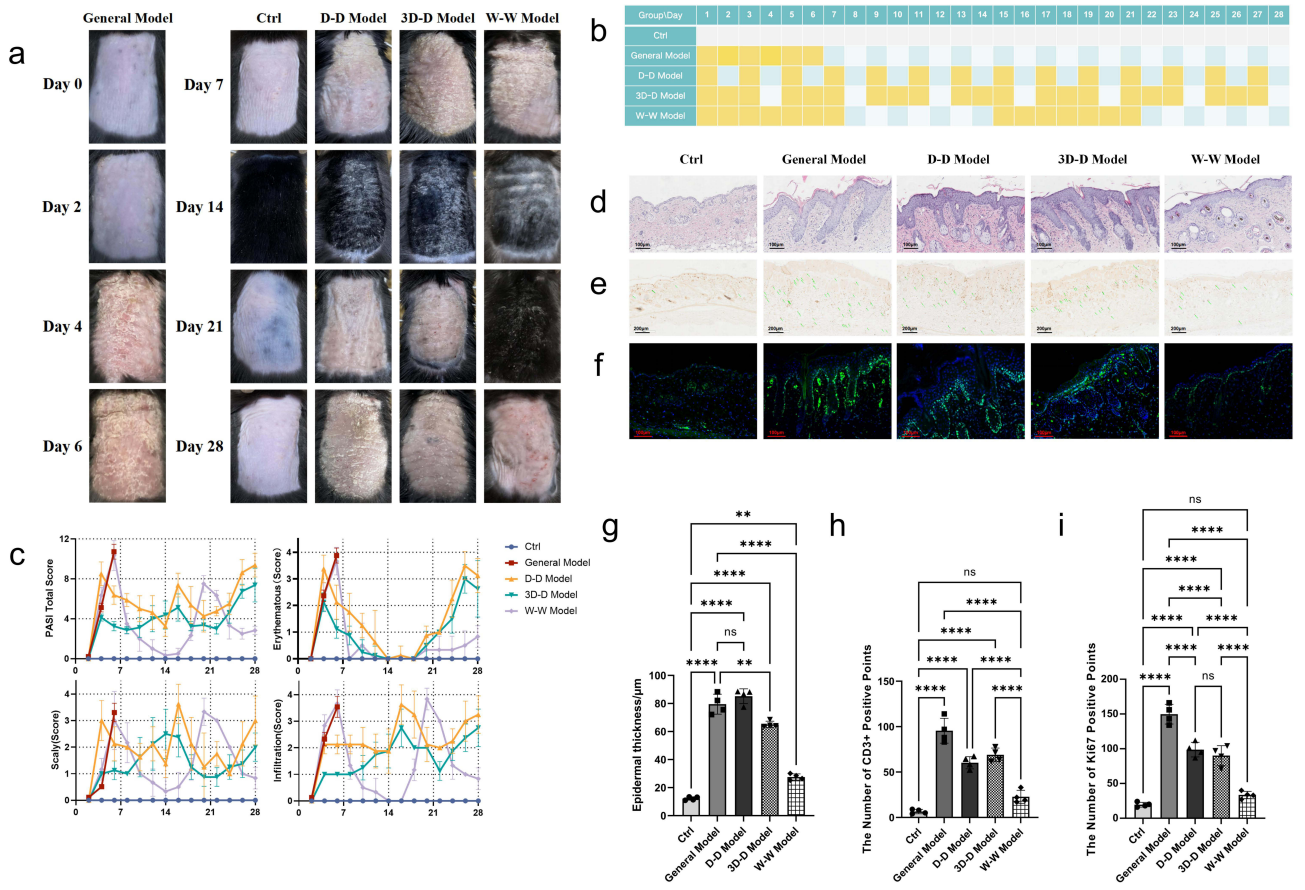

Figure 1 Frequency of IMQ Treatment Effects on Psoriasis-like Inflammation in Mice. (**a**) Psoriasis lesion manifestations in each cycle after different frequencies of imiquimod cream interventions. (**b**) Different schedules of topical application of imiquimod cream in each group. (Yellow: administration of imiquimod cream). (**c**) Erythema, scaling, infiltration, and total scores of PASI (n =8). (**d**) Hematoxylin and eosin (H&E) staining of the skin lesions. Scale bar = 100 μm. (**e**) Immunofluorescence staining for CD3 (brown). Scale bar = 200 μm. (**f**) Immunofluorescence staining for Ki67 (green) and DAPI (blue). Scale bar = 100 μm. (**g**) Epidermal thickness change (n = 4). (**h**) The number of CD3-positive cells in the skin (n = 4). (**i**) The number of Ki67-positive cells in the skin (n = 4). **p < 0.01, ****p < 0.0001.
Abbreviation: ns, not significant.

infiltration of CD8+ T cells[23] (Figure 2b) and γδ T cells[24] (Figure 2c), two key players in the pathophysiology of psoriasis, was noted in both chronic models (D-D and 3D-D) after IMQ exposure. The chronic models remarkably exhibited the presence of neutrophils and macrophages remaining in the chronic inflammatory milieu whereas this is usually shown to only occur by an immediate influx of such cells in acute models[25] (Figure 2d). During the progression of psoriasis, dendritic cells (DCs) are activated or stimulated to mature,[26] both chronic model groups exhibited an increased proportion of DCs, while the 3D-DModel group maintained a higher proportion of CD11c-positive DCs (Figure 2e). The mouse spleen flow cytometry results (Figure 3a–e). This chronic inflammatory state is more representative of clinical psoriasis with chronic, persistent immune activation that lacks the acute flares seen in many more severe models.

Compared to the blank control group, both new and conventional model displayed an elevated immune response, like Granulocyte-macrophage colony-stimulating factor (GM-CSF) an immune factor produced by activated T lymphocytes, myeloid cells, endothelial cells, macrophages, fibroblasts, and keratinocytes in psoriasis, exhibits significantly elevated levels in the acute model while maintaining relatively low levels in the chronic model[27] (Figure 3f). Cytokines such as IL-1β often proliferate rapidly and exert their effects in the early stages of psoriasis, while the corresponding two chronic models also exhibit relative downregulation compared to the standard model[28] (Figure 3g). Importantly, however, only the D-D model exhibited Intermediate levels of IL-17A, IL-22, and IL-23—all three major mediators of psoriasis—compared with all other models[29,30] (Figure 3i–k), unlike high IMQ frequency administration where peak levels of inflammatory factor expression usually reached a high state, the 3D-D Model even remained at relatively low levels,

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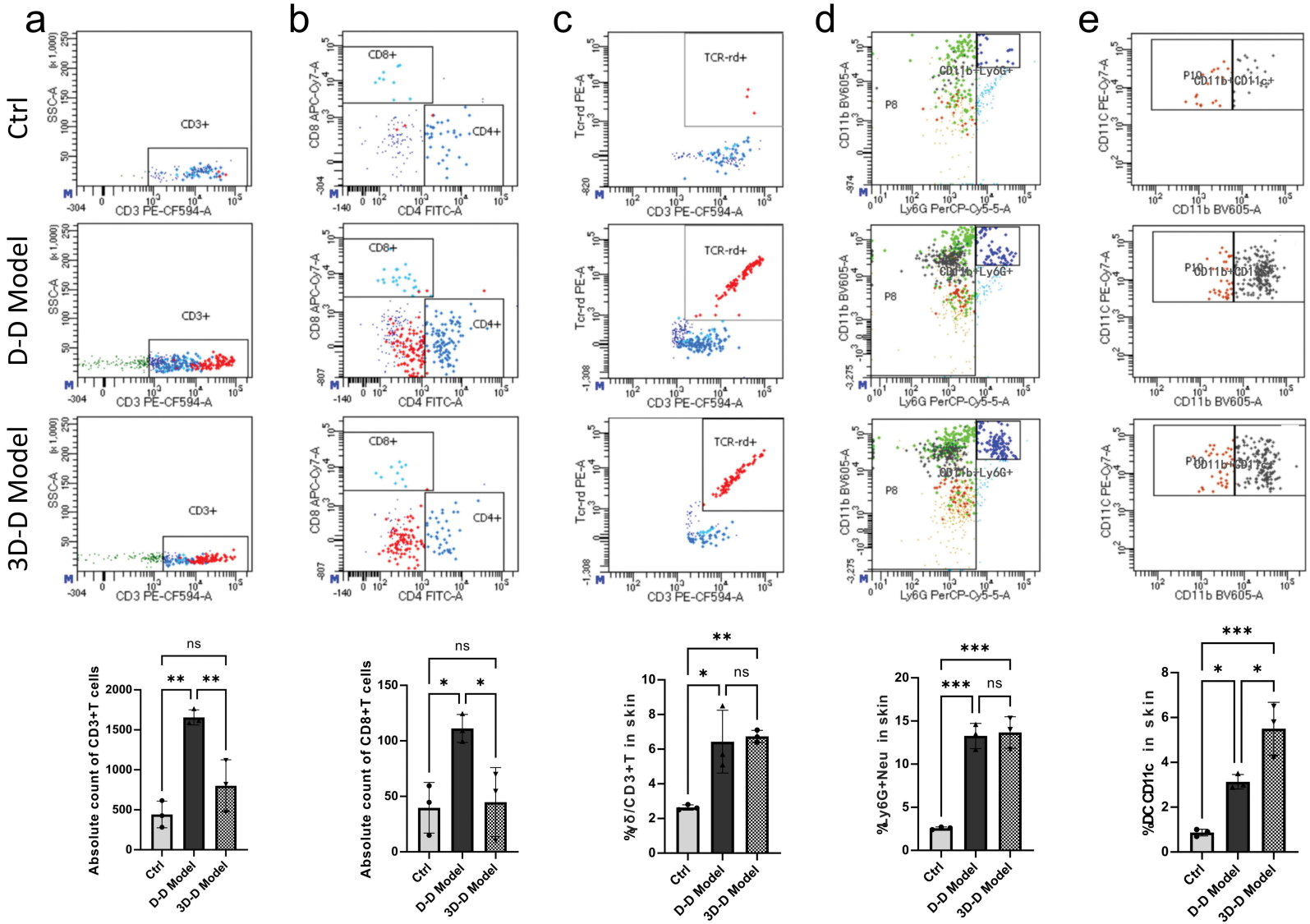

Figure 2 CD3+ T cells, CD4+ T cells,CD8+ T cells, γδ T cells, neutrophils, and DC cells are accumulated in the skin of D-D Model mice. (**a**) The absolute count of CD3+T cells. (**b**) The absolute count of CD8+T cells. (**c**) The percentage of γδ T cells. (**d**) The percentage of neutrophils. (**e**) The percentage of DC cells (n = 3). *p < 0.05, **p < 0.01, ***p < 0.001.
Abbreviation: ns, not significant.

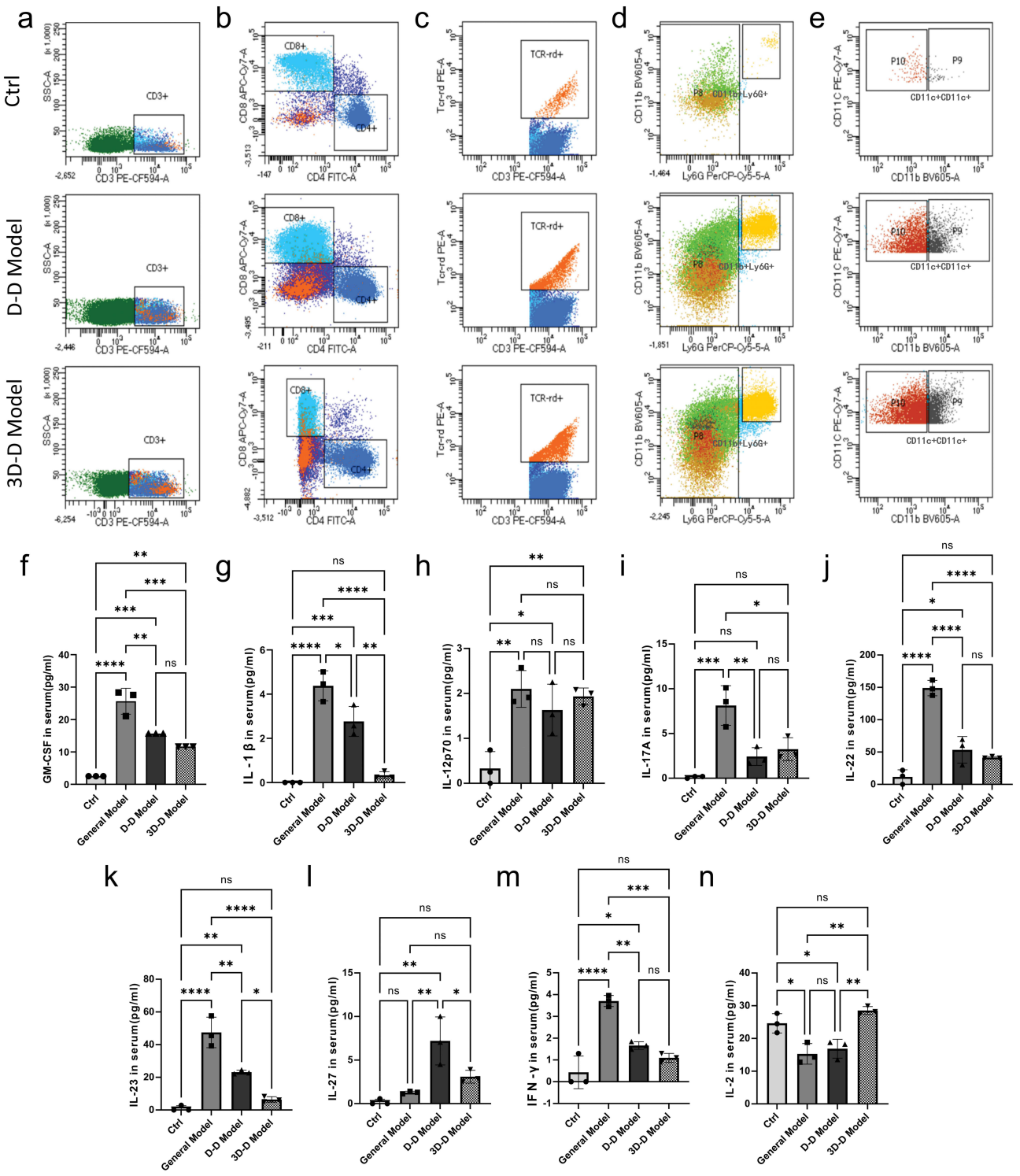

Figure 3 CD3+ T cells, CD4+ T cells,CD8+ T cells, γδ T cells, neutrophils,and DC cells are accumulated in the spleen of D-D Model mice, various inflammatory factors remained relatively low in D-D Model. (**a**) The percentage of CD3+T cells. (**b**) The percentage of CD4+/CD8+T cells. (**c**) The percentage of γδ T cells. (**d**) The percentage of neutrophils. (**e**) The percentage of DC cells. (**f–n**) GM-CSF, IL-1β, IL-12p70, IL-17A, IL-22, IL-23, IL–27, IFN-γ, IL-2 levels in serum (n = 4).*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

Abbreviation: ns, not significant.

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consistent with the results suggested by flow cytometry. IL-12p70, IFN-γ levels also showed similar patterns[31,32] (Figure 3h and m). IL-27, also a member of the IL-12 family, exhibited a distinct upregulation in the serum of the D-D Model group, far exceeding the performance of the General model[33] (Figure 3l).Th1 dominated acute but transitioning to a more balanced chronic inflammation driven by Th17 and Th22 cells.[34] In particular, the results suggest that since these T-cell subsets are typically engaged in the pathogenesis of human psoriasis, this alteration is in agreement with the chronic characteristics of the disease. In addition, IL-2, an anti-inflammatory cytokine, was also decreased in the D-D model as it was in the traditional model (Figure 3n), suggesting that the D-D model mimics changes in immune modulation in the chronic stages of human psoriasis, as well as induces a more protracted inflammatory trajectory. In summary, the findings support the hypothesis that the D-D and 3D-D model, with its lower frequency of drug administration compared to General models of psoriasis, is a better reflection of the complexities of the chronic inflammatory response found in psoriasis.

The results provided here imply that IMQ delivery frequency can be adjusted to achieve a long-lasting CrISE, which is much closer to the human aspects of chronic and recurrent manifestation of psoriasis in mice. Psoriasis reflects the invasion of immune cells and the cytokine alterations that characterize the normal chronic immune response process, as it more closely mimics the chronic immune response that occurs in psoriasis than do traditional high-frequency dosing models and therefore affordably recapitulates the psoriasis immune phenotype.

Gene Expression Response to Acute Versus Chronic IMQ Treatment

Following previous adjustments and observations, transcriptome analysis was performed in this study to uncover molecular mechanisms that may lead to the phenotypic changes. We hope to further explore this approach to provide a stronger theoretical basis to guide the research of pathophysiology of psoriasis by exploring the molecular differences in acute and chronic IMQ treatment models.

The transcriptome analysis showed that the gene expression profiling was very different between the acute and chronic IMQ treatment models. Unsupervised principal component analysis (PCA) revealed distinct separation among the Ctrl, General Model, D-D Model and 3D-D Model groups (Figure 4a). Heatmaps reveal high correlations among samples within groups (most >0.97), while some groups exhibit moderate or negative correlations (as low as −0.84). This indicates both strong covariation and inverse association patterns exist between different conditions (Figure 4b). For example, the core psoriasis pathways were still notably activated in the chronic animal model of psoriasis, including pathways related to keratinocyte differentiation, immune response, and epidermal barrier function. Therefore, these pathways, which are critical in the pathogenesis of psoriasis, highlight the chronic inflammatory milieu, as demonstrated in the chronic model. Moreover, IL-17 and IL-23 signaling pathway associated genes are continuously expressed at high levels in the chronic model (Figures 4c and d). On the contrary, the acute model showed a burst of expression which increased rapidly, but dropped steeply soon thereafter. This demonstrates the differential immunological dynamics between acute and chronic models, and provides insight into the long-term inflammatory mechanisms that drive chronic psoriasis.

Moreover, the chronic model exhibited a differential expression of genes related to the regulation of Th17 cells and other immune effector cells, demonstrating an ongoing chronic inflammatory state. Th17 cells are pivotal in the pathophysiology of psoriasis and sustain a state of chronic inflammation through the dysregulated expression of the genes associated with them.[35] These cells not only portray dynamic behaviors, but also maintain a consistent pattern of immune activation in the tissue (Figure 4e), as they provide a continuously stimulatory environment via chronic IMQ treatment similar to the long-lasting immune dysregulation displayed in psoriasis patients. Eg., the upregulation of genes such as S100A9 and DEFB4 is believed to be a key marker of innate immune activation.[36] The chronic model also showed significantly increased expression of genes associated with tissue remodeling and fibrosis including MMP9 and TGF-β,[37] suggesting the model may reflect long-term changes to the tissue during multiple chronic flares of psoriasis. The aforementioned overexpressed genes indicate a persistent immune response, coupled with progressive structural modifications of skin tissues during the chronic phase of psoriasis, which may lead to impaired skin barrier function.[38] And with this as a cue, we were equally curious: whether the chronic IMQ treatment model was altered at the metabolic level. The metabolomics results suggest that the skin of D-D Model mice is higher than that of conventional model mice

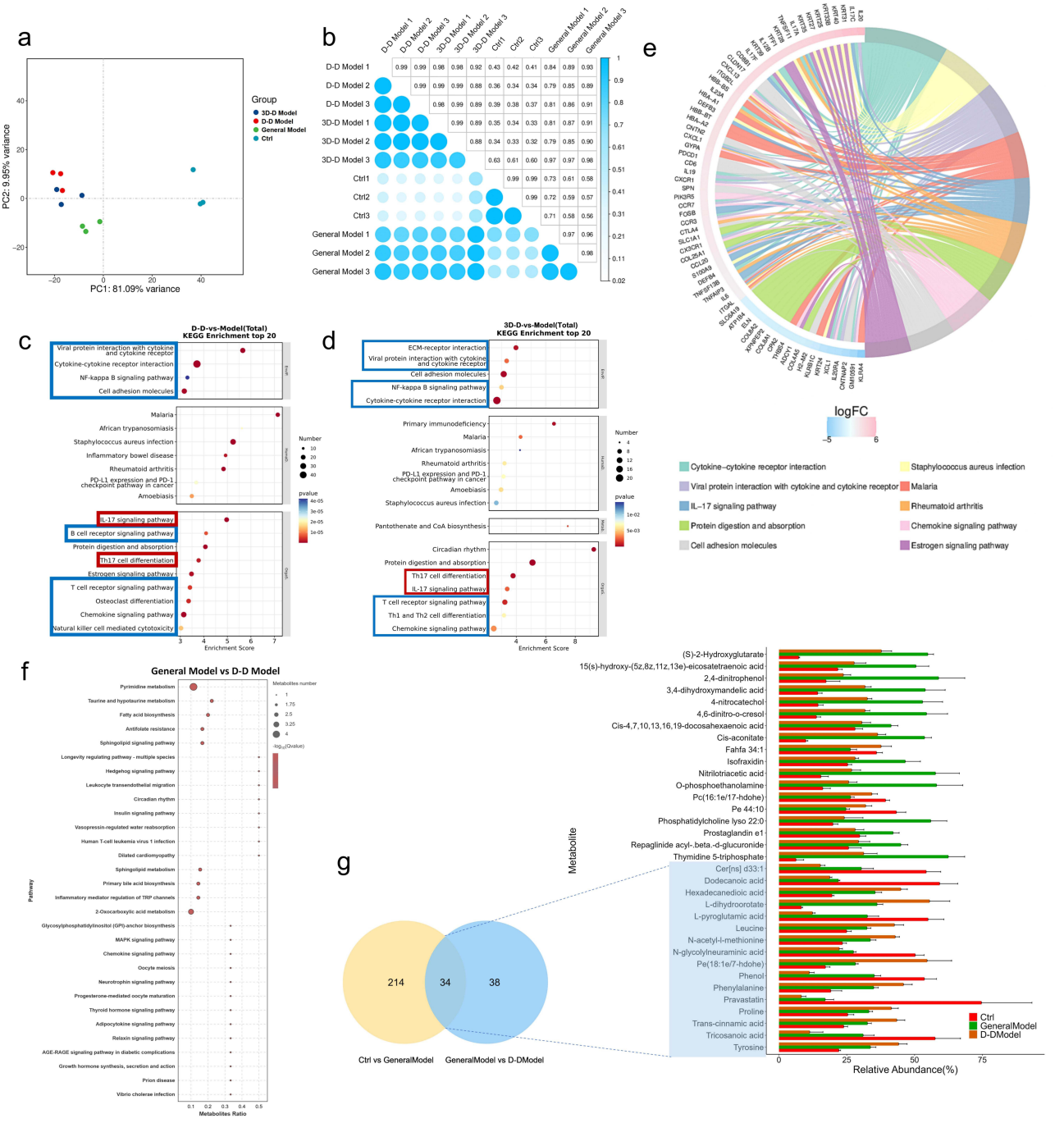

Figure 4 Gene Expression and metabolite response to acute versus Chronic IMQ treatment. (**a**) PCA of Ctrl, General Model, D-D Model, and 3D-D Model groups. (**b**) The coefficient matrix heatmap of Ctrl, General Model, D-D Model, and 3D-D Model groups. (**c**) KEGG enrichment total analysis top 20 of General Model vs D-D Model. (**d**) KEGG enrichment total analysis top 20 of General Model vs 3D-D Model. (**e**) Reactome chord of General Model vs D-D Model. (**f**) KEGG enrichment analysis of differential metabolites in serum. (**g**) Expression levels of differential metabolite intersections (n=3).

in pathways such as inflammatory mediator regulation of TRP channels and 2-Oxocarboxylic acid metabolism (Figures 4f and g).[39]

In summary, the transcriptome analysis demonstrated that the molecular signature of the acute and chronic IMQ treatment models differed significantly. The sustained activation of major psoriasis-ish pathways in the chronic model indicates long-term immune dysregulation and inflammatory response, consistent with the chronic recurring features of human psoriasis.[8,40] Thus, the differential regulation of genes involved in immune response and tissue remodeling across

chronic models highlights the complexity of chronic inflammatory development in psoriasis. So, these results provide critical clues that allow us to understand the molecular mechanisms of psoriasis and theoretical rationale for developing more personalized treatment plans.

A Machine Learning-Derived Biomarker Signature for Psoriasis Validated in Human and Mouse Models

Based on transcriptomic data from six cohorts of psoriasis patients (from GSE59029/GSE78097/GSE106992), we identified differentially expressed genes, with a focus on upregulated genes as candidate biomarkers.[41] To pinpoint the most predictive gene signatures, we employed ten machine-learning algorithms,Included: SVM (Support Vector Machine), LASSO (Least Absolute Shrinkage and Selection Operator), GLM (Generalized Linear Model), DT (Decision Tree), XGB (XGBoost), KNN (K-Nearest Neighbors), NNET (Neural Network), RF (Random Forest), GBM (Gradient Boosting Machine), C50 (C5.0 Decision Tree), for feature selection and evaluated their performance on the training set. Residual analysis indicated high fitting accuracy across all models, with SVM and RF showing the smallest root mean square of residuals (Figure 5a). The reverse cumulative distribution of absolute residuals further confirmed that most samples exhibited small residual values (Figure 5b). ROC curve analysis revealed that all models achieved AUC values above 0.92, with RF and SVM demonstrating the highest AUC (0.987 and 0.989, respectively), indicating excellent classification performance (Figure 5c). Decision curve analysis suggested favorable clinical net benefit across a wide threshold probability range (0.1–0.8) (Figure 5d). These results support the good fitting accuracy, classification capability, and clinical utility of our prediction models.

From the ten algorithms, eight selected five key genes each, while LASSO and SVM included all relevant genes based on their inherent model properties (Figure 5e). A comprehensive candidate biomarker gene set was derived by taking the union of all algorithm-selected genes (Figure 5f). To further validate the applicability of this biomarker set in psoriasis models, we intersected it with genes expressed in a mouse model to establish a "mouse-conserved gene set" (Figure 5g). Predictive models constructed using human training data were then validated on an independent human cohort and mouse experimental data. Clustering heatmap analysis showed that in the human validation set, most control and psoriasis samples clustered correctly, with only a few misclassified, indicating high discriminative accuracy of the model (Figure 5h). In the mouse model, despite one sample from the 3D–D Model group deviating from expected clustering, the overall expression trend remained consistent with human disease status, suggesting that the biomarker set retains conservativity and predictive value in murine models. Scores were calculated based on the expression of the conserved biomarker gene set identified in this study. Human samples include healthy controls (HumanControl) and psoriasis patients (HumanPsoriasis). Mouse samples comprise control (mouseControl), general model (mouseGeneralModel), and two disease stages (mouseD-DModel and mouse3D-DModel). There is no doubt that both the new model groups, whether the 3D-D Model or the D-D Model achieved superior scoring results compared to conventional models (Figure 5i). Among these, the 3D-D Model demonstrated near-perfect alignment with the human psoriasis gene set.

To further validate these bioinformatic findings and the machine-learning-derived biomarker signatures at the protein level, in situ expression of TMPRSS11D, which a gene that frequently appears in the intersection of database and transcriptomic results, in the skin lesions was evaluated using immunofluorescence staining (Supplementary Figure S1). Consistent with the biomarker scoring trends, TMPRSS11D exhibited minimal expression in the control group. Following IMQ administration, the relative fluorescent intensity of TMPRSS11D was significantly elevated across all model groups compared to the Ctrl group ($p < 0.001$ for the General Model; $p < 0.0001$ for the D-D and 3D-D Models). Notably, while the D-D Model showed an expression level comparable to the General Model (ns), the 3D-D Model exhibited the most robust protein accumulation. The TMPRSS11D expression in the 3D-D Model was significantly higher than that observed in both the General Model ($p < 0.01$) and the D-D Model ($p < 0.05$). These in situ protein expression patterns provide strong spatial and quantitative validation of the transcriptomic alterations, further reinforcing that the 3D-D Model most closely recapitulates the pathophysiological characteristics of human psoriasis.

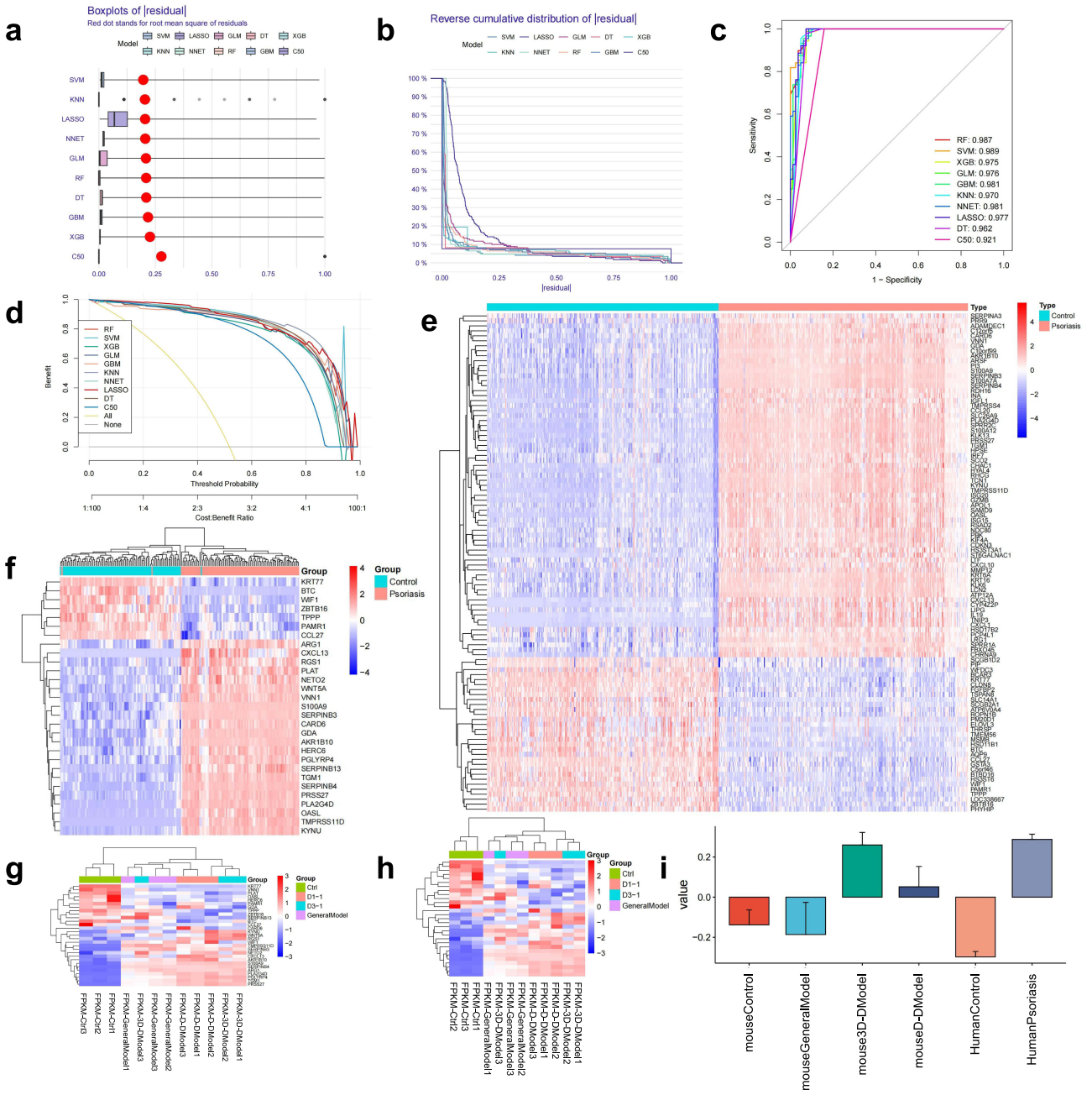

Figure 5 Machine Learning and Evaluation of Gene Sets in Chronic Disease Models. (**a**) Boxplots of absolute residuals for ten machine learning models. (**b**) Reverse cumulative distribution of absolute residuals. (**c**) Receiver operating characteristic (ROC) curves of ten machine learning models. (**d**) Decision curve analysis (DCA) for ten machine learning models. (**e**) Human Signature Gene Clustering Heatmap. (**f**) Heatmap of biomarker gene expression in the human validation cohort. (**g**) Heatmap of biomarker gene expression in mouse models of psoriasis. (**h**) Hierarchical clustering of mouse samples based on biomarker gene expression. (**i**) Comparison of biomarker signature scores between human and mouse samples.

Discussion

By adjusting the IMQ application frequency, this study successfully established a reliable and reproducible chronic psoriasis model. The first thing that we noticed was that when we cut back on the frequency of giving the medicine, the inflammation persisted much longer. This also meant that there were no significant differences that developed between the groups of mice, thereby ensuring that the results were uniform across the board. Second, the model faithfully

mirrored the essential pathogenic characteristics of psoriasis, with sustained keratinocyte hyperplasia, epidermal acanthosis, and immune cell infiltration.[42] These features are important for modelling the chronicity of psoriasis.[43]

Additionally, they found that chronic models are useful, particularly for capturing the immune and molecular dynamics of chronic inflammation. While acute models commonly involve the daily administration of IMQ over 6–7 consecutive days, chronic models lessen the frequency of administration, minimizing the incidence of excessive immune activation and IMQ-induced death due to high-dose IMQ. This prolongs the inflammatory response, thereby making it more similar to the permanent and recurrent characteristics of human psoriasis.[44] In addition, chronic models have been shown to maintain a more stable inflammatory microenvironment, allowing for easier exploration of the immunological mechanisms underlying chronic psoriasis and the development of effective therapeutic strategies.

Transcriptome analysis further showed that, in contrast to the rapid and drastic changes associated with inflammatory response in acute models, psoriasis related signaling pathways, eg., IL-17 and IL-23 pathways, remain constantly activated in chronic models, which represents the features of immune activation in chronic window. Moreover, the status of persistently activated Th17 cells and overexpression of genes related to tissue remodeling in chronic model also demonstrates its advantages for promoting the pathological remodeling of chronic inflammatory diseases. These findings show how chronic models can be used effectively to explore the pathophysiology and immune mechanisms underlying chronic psoriasis.

To provide practical guidance for future preclinical research, it is important to delineate the distinct translational applications of these two chronic models. Because both models establish a prolonged, stable inflammatory window (28 days) while circumventing the high mortality of traditional acute regimens, they are highly advantageous for long-term drug-testing and therapeutic-response studies. They provide an extended timeframe necessary to accurately evaluate the pharmacodynamics of slow-acting systemic biologics (eg., IL-17/IL-23 inhibitors) and novel topical formulations. However, their optimal use cases differ based on their molecular profiles. The 3D-D Model, which demonstrated near-perfect transcriptomic alignment with the human psoriasis biomarker signature and robust in situ protein alterations, serves as the optimal platform for rigorous preclinical drug efficacy evaluation and therapeutic target validation. Conversely, the D-D Model, characterized by a more moderate, steady-state immune activation and unique metabolic shifts, is ideally suited for investigating the mechanistic transition from acute flares to chronic persistence, as well as studying epidermal barrier repair and immune tolerance.

Whereas a distinct cellular and molecular pathway is activated during chronic IMQ treatment. In particular, early transcriptome studies indicate that extended IMQ therapy causes persistently activated IL-17 and IL-23 signaling pathways. Meaning that sustained therapy further maintains long-term immune activation. On the other hand, we also observed significant up-regulation of numerous fundamental immune modulators, such as interferon and TNF-α signalling. In addition, long-term therapy induced a shift in the inflammatory response to Th17 dominance and promoted tissue remodeling processes. Intriguingly, genes associated with fibrosis (eg., TGF-β) and matrix metalloproteinases (MMPs) were also upregulated. It can be observed from this that chronic IMQ treatment not only causes immune-mediated inflammatory responses, but also results in long-term structural changes of the tissue, which is highly consistent with the typical characteristics of chronic psoriasis. As such, chronic models serve as an important research platform to investigate the immune mechanisms and long-term tissue damage of psoriasis. It denotes that chronic cutaneous changes induced by repetitive administration of IMQ are a functional development of the classical aspects of chronic psoriasis and also deduces an added immune component resulting in inflammation.Of particular interest, the machine learning results further revealed that the two novel chronic psoriasis-like mouse models we developed achieved substantially higher biomarker signature scores than those generated by traditional modeling methods. Crucially, this computational alignment was strongly corroborated at the protein level. For instance, the in situ validation of TMPRSS11D demonstrated robust protein accumulation that perfectly mirrored the transcriptomic trends, particularly in the 3D-D Model. Notably, the 3D-D Model exhibited biological characteristics closely resembling those observed in human psoriasis.

Despite the advantages that such a chronic model has shown there are some biases that are an intrinsic part. On the one hand, even though, in this particular model, the inflammatory response is indeed prolonged — the complex seasonal and cyclical nature of clinical psoriasis has not yet been well recapitulated. The model could more faithfully mimic the disease variations by adding additional environmental triggers or other stimulation. However, the potential role of

systemic immunity in the chronic model was not studied in this work as it focused primarily on epidermal immune responses. In addition, genetics variability across strains of mice may have an effect on repeatability of developing the model.[45] Future investigations would need to include the effects of hereditary factors to further enhance the ability of the model to study different human psoriasis subtypes. Furthermore, a notable limitation of the present study is the absence of parallel transcriptomic sequencing using genuine, locally collected clinical human psoriasis tissues. Although we utilized robust machine learning and cross-species analysis with public human datasets, relying primarily on murine tissues for sequencing may limit the direct clinical translation of the specific molecular dynamics observed. Future investigations should prioritize the integration of freshly acquired human biopsies to directly compare against the chronic mouse models.

Conclusions

In conclusion, we successfully established a highly translatable chronic psoriasis mouse model by optimizing the imiquimod dosing frequency (D-D and 3D-D regimens), which effectively maintains long-term immune dysregulation and tissue remodeling. Furthermore, machine-learning-based cross-species validation confirmed that the 3D-D model closely mirrors the molecular signature of human clinical psoriasis. While future studies should incorporate genetic susceptibility factors, this novel platform overcomes the limitations of traditional acute models, providing a more biologically relevant tool for investigating chronic pathogenesis and evaluating targeted therapies. However, to avoid overgeneralization of our findings, it is important to acknowledge that this chemically induced model currently lacks the integration of genetic susceptibility modeling. Future studies should incorporate hereditary factors to comprehensively reflect the diverse genetic backgrounds of clinical psoriasis.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author, upon reasonable request.

Author Contributions

Haoyue Zhu: Conceptualization, Investigation, Data curation, Formal analysis, Writing-original draft. Xiaohan Yu: Data curation, Formal analysis, Software, Writing-original draft. Yazhuo Wang: Data curation, Formal analysis, Writing-original draft. Ning Zhao: Project administration, Validation, Writing-original draft. Baoquan Qu: Data curation, Investigation, Writing-original draft. Huike Ma: Visualization, Investigation, Writing-review and editing. Yujiao Meng: Visualization, Resources, Writing-review and editing. Jingxia Zhao: Resources, Supervision, Investigation, Writing-review and editing, Writing-original draft. Yan Wang: Writing-review and editing, Investigation, Validation, Project administration, Writing-original draft. Ping Li: Funding acquisition, Investigation, Validation, Writing-review and editing, Writing-original draft.

In accordance with the CRediT classification statement, all authors made substantial contributions to this study as described below and contributed to the writing or review of the article.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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