Psoriasis: Targets and Therapy

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ORIGINAL RESEARCH

TYK2 rs34536443 (P1104A) Variant Suppresses ICAM1-Mediated Inflammation: Insights From Mendelian Randomization and Functional Analyses

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Background: Genetic susceptibility to psoriasis involves multiple loci, including TYK2 (Tyrosine Kinase 2), which is associated with various autoimmune diseases. However, its specific role and mechanisms in psoriasis remain unclear. This study aimed to identify psoriasis-associated proteins using Summary-based Mendelian Randomization (SMR) and to explore their regulatory mechanisms.
Methods: SMR analysis integrating pQTL data was conducted to identify proteins linked to psoriasis, revealing ICAM1 (Intercellular Adhesion Molecule 1) as a potential pathogenic factor. A key SNP, rs34536443 (P1104A), located in TYK2, was found to regulate ICAM1. To assess its function, THP-1 cells carrying the TYK2-P1104A mutation were generated, and ICAM1 and cytokine expression were analyzed following LPS stimulation. The effect of the TYK2 inhibitor Deucravacitinib was tested in an imiquimod (IMQ)-induced psoriasis mouse model.
Results: SMR identified ICAM1 as a causal protein for psoriasis, regulated by the TYK2 SNP rs34536443. In TYK2-P1104A mutant THP-1 cells, LPS-induced ICAM1 expression was significantly reduced, with ICAM5 unaffected. The mutation also suppressed IL-1β, TNF-α, IL-6, and IL-18 expression, suggesting anti-inflammatory effects. Single-cell RNA-seq revealed enrichment of TYK2, ICAM1, and ICAM5 in dendritic cells and monocytes. In vivo, Deucravacitinib significantly downregulated ICAM1 in the IMQ-induced psoriasis model, with minimal effect on ICAM5.
Conclusion: This study identifies ICAM1 as a key mediator in psoriasis via SMR analysis and implicates the TYK2 SNP rs34536443 in its regulation. The TYK2-P1104A variant attenuates ICAM1 and cytokine expression, and Deucravacitinib downregulates ICAM1 in vivo. These findings provide mechanistic insights into the TYK2-ICAM1 axis and support the therapeutic potential of TYK2 inhibitors for psoriasis.
Keywords: TYK2, GWAS, pQTL, ICAM1

Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disease characterized by abnormal keratinocyte proliferation and excessive infiltration of immune cells.[1] Psoriasis has a strong genetic basis, with heritability estimated at approximately 66%.[2] Meta-analyses of genome-wide association studies (GWAS) have identified 65 genomic loci associated with psoriasis susceptibility in individuals of European ancestry, and 17 additional loci in Asian populations.[3] A substantial portion of genetic risk is attributed to class I major histocompatibility complex (MHC) alleles—particularly HLA-C06:02—and variants affecting antigen processing and presentation. The pathogenic roles of the IL-23/IL-17 immune axis, type I interferons, and NF-κB signaling have been well established.[4] Notably, genetic variation in these pathways closely aligns with the clinical efficacy of biologic agents targeting IL-23 and IL-17, underscoring the translational relevance of GWAS findings.[5] In addition to these well-characterized loci, GWAS have also highlighted

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several susceptibility genes encoding therapeutic targets, including susceptibility variants at loci encoding therapeutic targets such as IL17RA, AHR, and TYK2.[5,6] Tyrosine kinase 2 (TYK2), a member of the Janus kinase (JAK) family, is involved in signaling pathways such as type I interferons (IFN-I), interleukin 12 (IL-12), and interleukin 23 (IL-23). It plays a crucial role in the pathogenesis and progression of psoriasis.[7] Due to its pivotal role in immune regulation, TYK2 has emerged as a potential therapeutic target, leading to the development of selective inhibitors such as Deucravacitinib, which has shown promising therapeutic effects in clinical trials.[8–10]

ICAM1 (Intercellular Adhesion Molecule 1) plays a pivotal role in leukocyte-endothelial adhesion and transendothelial migration, and has been widely studied in the context of inflammatory and cardiovascular diseases. Several single nucleotide polymorphisms (SNPs) in the ICAM1 gene—most notably G241R (rs1799969) and K469E (rs5498)—have been investigated for their clinical relevance.[11] While some studies have found no association between these variants and ischemic heart disease or myocardial infarction, others have reported population-specific links to increased risk of ischemic stroke and coronary artery disease (CAD).[12] Among the various genetic variants of TYK2, rs34536443 (P1104A) is a missense mutation that reduces the kinase activity of TYK2 and weakens the activation of its downstream JAK-STAT signaling pathway, thus preventing the occurrence of autoimmune diseases.[13–15] Some studies have shown that this mutation is associated with a reduced risk of multiple autoimmune diseases, including psoriasis, systemic lupus erythematosus, and inflammatory bowel disease.[16–18] However, how TYK2-P1104A specifically influences psoriasis susceptibility and inflammatory responses remains incompletely understood.[19] During the pathogenesis of psoriasis, the interaction between immune cells and cell adhesion molecules is critical for shaping the inflammatory microenvironment. Therefore, elucidating how TYK2 genetic variants regulate immune-related signaling is essential for a deeper understanding of the disease mechanism.[20]

Intercellular adhesion molecules (ICAMs) play a pivotal role in immune cell chemotaxis and inflammatory responses.[21] Among them, ICAM1 is highly expressed in psoriatic lesions and contributes to dendritic cell infiltration, T cell activation, and the secretion of pro-inflammatory cytokines.[22–24] Beyond leukocyte trafficking, ICAM1 also serves as a critical costimulatory ligand for LFA-1, promoting $CD8^+$ T cell activation and formation of immunological synapses with antigen-presenting cells.[25] Recent studies have shown that mature DCs require ICAM1 to establish stable interactions with naïve $CD8^+$ T cells, which are essential for effective priming, IFN-γ production, and memory formation. Moreover, ICAM1 engagement can modulate MHC-I clustering at the immunological interface, enhancing antigen presentation efficiency. ICAM1 is not only a structural adhesion receptor but also acts as a biosensor, capable of transducing outside-in signaling via interactions with the actin cytoskeleton, thereby influencing cell survival, migration, and immune responses.[26,27] Previous studies have suggested that TYK2 may regulate inflammation by modulating ICAM1 expression,[28,29] however, the underlying mechanisms remain unclear. Moreover, it is not yet known whether the therapeutic efficacy of TYK2 inhibitors in psoriasis is partly mediated through ICAM1-related signaling pathways. Therefore, elucidating the role of the TYK2–ICAM1 axis in psoriasis may provide new mechanistic insights for TYK2-targeted therapies.

In this study, we integrated genetic analysis, single-cell RNA sequencing, and both in vivo and in vitro experiments to investigate the impact of the TYK2-P1104A mutation on ICAM1 expression and psoriasis pathogenesis. We also assessed the potential of TYK2 inhibition to suppress ICAM1 expression and downstream inflammatory signaling. These findings not only enhance our understanding of the pathophysiology of psoriasis but also provide a novel theoretical basis for TYK2-targeted therapeutic strategies.

Materials and Methods

Animal Experiments

Animal experiments were performed in accordance with our previously published protocol.[30] This experimental protocol was approved by the Animal Research Ethics Committee of Shanghai University of TCM (Approval no.: PZSHUTCM191108013). All the animal care and experimental procedures follow the Guidelines for the Care and Use of Laboratory Animals developed by the Ministry of Science and Technology of China, and the Animal Research Ethics Committee of Shanghai University of TCM, and all methods are reported in accordance with ARRIVE guidelines for the reporting of animal experiments. Briefly, specific pathogen-free (SPF) BALB/c mice (6–8 weeks old, 18–22 g) were

purchased from Jihui Laboratory Animal Co., Ltd. (Shanghai, China). Mice were randomly assigned to control, IMQ, and Deucravacitinib treatment groups. Psoriasis-like lesions were induced by topical application of 62.5 mg imiquimod cream (Aldara, 3M Pharmaceuticals) on the shaved dorsal skin for 7 consecutive days. Mice were bred in a normal facility (room temperature of 20 °C–26 °C, relative humidity of 40%–70%, and 12 h light/12 h dark cycle) and fed with normal diets.After 1 week of acclimation, 30 mice were randomly divided into 3 groups (n = 5 per group): control group (WT), IMQ model group (IMQ), and Deucravacitinib Treatment group (IMQ+ Deucravacitinib). Deucravacitinib was applied following the protocol in the past.[31] At the end of the experiment, mice were euthanized, and skin samples (3 cm × 3 cm) were collected for further analysis. All procedures were approved by the Institutional Animal Care and Use Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine (Approval No. 2025210).

SMR Analysis

SMR analysis was performed using pQTL data for psoriasis patients from the Finngen-R11 database. SNP information was based on the GRCh38 reference genome, and only SNPs located within exon regions were selected for further analysis. Corresponding pQTL-associated proteins were identified and analyzed to explore their potential involvement in the pathogenesis of psoriasis.[32]

scRNA-Seq Analysis

The scRNA-seq dataset GSE220116, which includes psoriasis and normal epidermal samples, was used for analysis.[33] Only psoriasis samples were selected. Cells were clustered into seven major cell types, followed by subcluster identification. ICAM1, ICAM5, and TYK2 expression across cell types and subclusters was analyzed, and pathway enrichment analysis was performed using GO and KEGG. Cell-cell interactions were inferred using CellChat and CellPhoneDB.

Machine Learning

The selection of feature genes to build the diagnostic predictor is crucial. In the present study, we used the "Random Forest" to narrow the list of potential genes of interest.

For formal modeling, the whole AMI merged dataset was randomized and then separated into a training set and a test set at a ratio of 7.5:2.5. In the present study, 20 machine-learning algorithms were compared and evaluated.[34]

qPCR

Quantitative PCR (qPCR) was performed using 2×Universal Blue SYBR Green qPCR Master Mix (Servicebio, G3326-15). Total RNA was extracted from THP-1 cells using the Magnetic Bead Method Total RNA Extraction Kit for Cells (Pre-packaged 48T) (Servicebio, G3694-48T), and reverse transcription was carried out using the SweScript RT II First Strand cDNA Synthesis Kit (With gDNA Remover) (Servicebio, G3333-100) according to the manufacturer's instructions. Specific primers (listed in Supplementary Table 1) were used to quantify mRNA expression levels of ICAM1, ICAM5, IL1β, TNFα, IL23, IL6, and IL18. Relative gene expression was calculated using the $2^{-\Delta\Delta Ct}$ method, with β-actin as the internal reference gene.

ELISA

To induce monocyte-to-macrophage differentiation, cells were plated at a density of 2×10^5 cells/mL in 12-well plates. Differentiation was achieved by treating the cells with 10 ng/mL phorbol 12-myristate 13-acetate (PMA) for 72 hours in culture medium supplemented with 2.5% fetal bovine serum (FBS, v/v). For cytokine quantification, THP-1 cells were stimulated with lipopolysaccharide (LPS) LPS (1 mg/L) from Escherichia coli O111:B4 (Sigma-Aldrich, Cat# L4391) at the indicated concentrations. After stimulation, cell culture supernatants were collected and analyzed using commercial ELISA kits for TNFα, IL1β, and IL23 (EpiZyme, HJ110, HJ060, and HJ078, respectively), following the manufacturer's instructions.[35] Absorbance was measured at 450 nm using a microplate reader (BioTek Synergy HTX), and cytokine concentrations were calculated from the standard curves.

Immunohistochemistry (IHC)

Paraffin-embedded skin sections (4 µm) were deparaffinized, rehydrated, and subjected to antigen retrieval in sodium citrate buffer (10 mM, pH 6.0) by boiling for 20 min). After blocking endogenous peroxidase and non-specific binding with 5% BSA, sections were incubated overnight at 4 °C with primary antibodies against ICAM1 (GB11106-100, Servicebio, Wuhan, China) or ICAM5 (Proteintech, 12759-1-AP). After washing with PBS, sections were incubated for 1 hour at room temperature with fluorophore-conjugated secondary antibodies (eg, Alexa Fluor 488- or 594-conjugated goat anti-rabbit IgG, Thermo Fisher Scientific), diluted 1:500 in blocking buffer. Nuclei were counterstained with DAPI (1 µg/mL) for 5 min. Finally, sections were mounted using anti-fade fluorescence mounting medium (eg, ProLong™ Gold Antifade Mountant, Thermo Fisher Scientific) and imaged using a fluorescence microscope.[30]

Immunofluorescence Staining

Fresh skin tissues were fixed in 4% paraformaldehyde (Sigma-Aldrich) for 30 min at 25 °C, followed by graded ethanol dehydration, paraffin embedding, sectioning (6 µm), and dewaxing. After antigen retrieval (eg, in sodium citrate buffer, pH 6.0, at 95–100 °C for 20 min) and blocking with immunohistochemical blocking solution (Beyotime, China) at 37 °C for 30 min, sections were incubated with primary antibodies against p-STAT3 (Y705) (GB150001-100, Servicebio, Wuhan, China), ICAM1 (GB11106-100, Servicebio, Wuhan, China), or ICAM5 (12,759-1-AP, Proteintech, Wuhan, China) at 37 °C for 45 min. After washing with PBS, sections were incubated with fluorophore-conjugated secondary antibodies (eg, Alexa Fluor 488- or 594-conjugated goat anti-rabbit IgG, Thermo Fisher Scientific, 1:500 dilution) at 37 °C for 45 min. Nuclei were counterstained with DAPI (1 µg/mL, Sigma-Aldrich) for 5 min, and sections were mounted using ProLong™ Gold Antifade Mountant (Thermo Fisher Scientific) prior to imaging with a fluorescence microscope.[30]

Statistical Analyses

All statistical analyses were performed using GraphPad Prism software (version 8.0, GraphPad Software Inc., San Diego, CA, USA). Data are presented as the mean ± standard error of the mean (SEM) from at least three independent experiments. Comparisons between two groups were performed using an unpaired two-tailed Student's *t*-test, while multiple group comparisons were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. A p-value of < 0.05 was considered statistically significant.

Result

Summary-Based Mendelian Randomization Combined with Machine Learning Reveals That rs34536443 Mutation Affects ICAM1 and ICAM5 Protein Expression and Promotes Psoriasis Development

To investigate the genetic characteristics of psoriasis, we performed Summary-based Mendelian Randomization (SMR) analysis using pQTL data from the Finngen-R11 database to identify psoriasis-associated genes (Supplementary Table 2). Next, we extracted the chromosomal location of all SNPs from the GRCh38 reference genome and filtered for those located within exonic regions. The corresponding pQTL protein information was compiled (Figure 1A, Supplementary Table 3). To further assess differential gene expression in psoriasis patients, we conducted a forest plot analysis based on the GSE121212 dataset. The top five genes identified were ARPC1B, GALNT16, ICAM1, MIA, and FGF2 (Figure 1B). The calibration curve demonstrated that the bias-corrected line closely aligned with the ideal line, indicating good calibration of the prediction model and further supporting the potential pathogenic relevance of these genes in psoriasis (Figure 1C).

Subsequently, we evaluated the diagnostic potential of these 11 candidate genes using 20 different machine learning algorithms. With the exception of the Naïve Bayes model, the remaining models achieved high performance in terms of accuracy (ACC), F1 score, precision, and recall (Figure 1D). Receiver Operating Characteristic (ROC) curve analysis further confirmed that these genes exhibited strong predictive power across all machine learning models for psoriasis risk (Figure 1E). Among them, the ElasticNet model achieved the highest prediction accuracy. Based on this model, we calculated the relative importance of each gene and ranked them using both feature importance and permutation importance methods (Figure 1F).

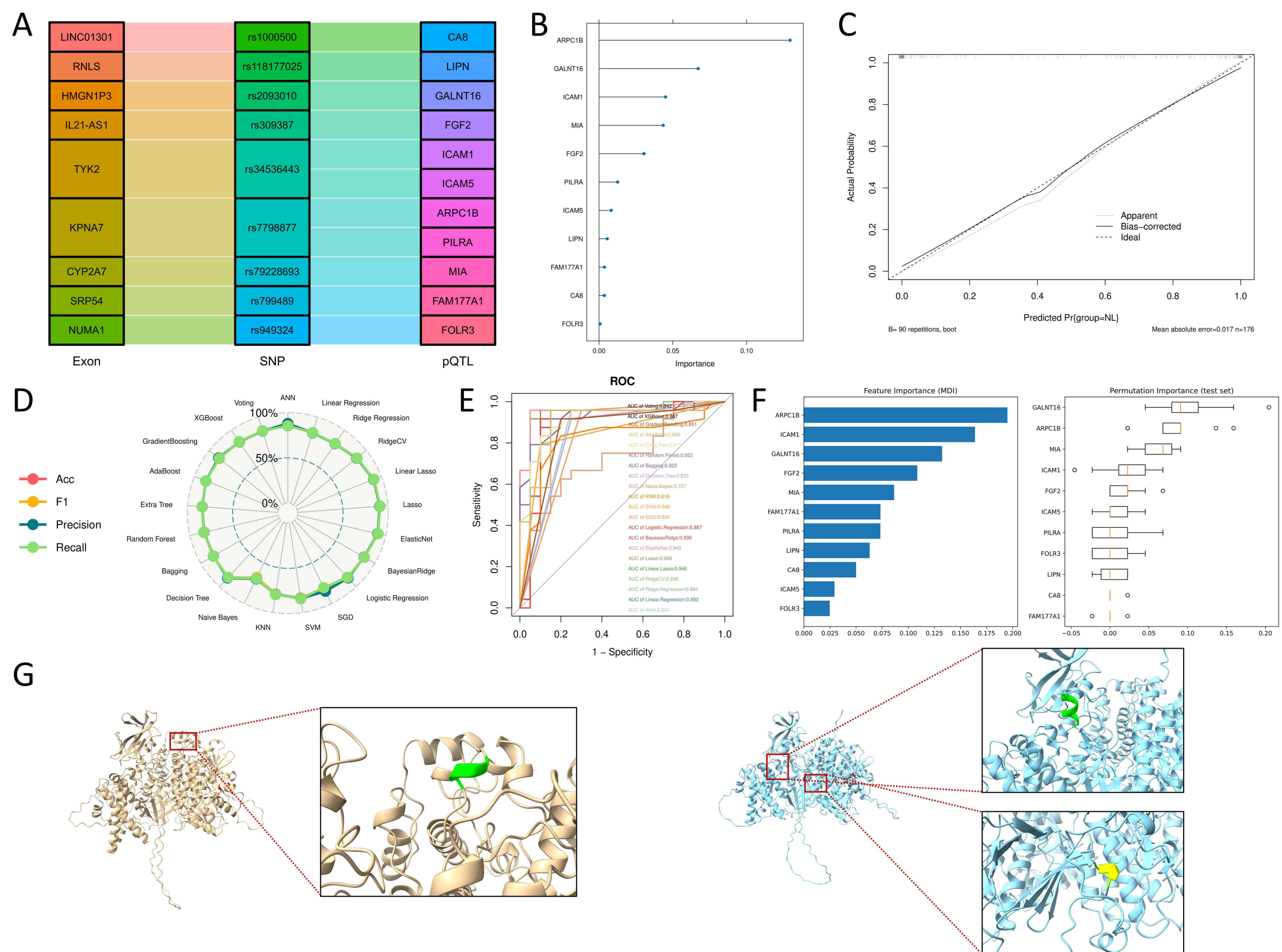

Figure 1 Identification of TYK2 as a potential psoriasis-related gene using SMR analysis and machine learning. (**A**) Workflow of SMR analysis based on pQTL data to identify key genes and locate SNPs within coding regions (CDS). (**B**) Forest plot highlighting differentially expressed key genes. (**C**) Calibration curve assessing the goodness-of-fit of the prediction model. (**D**) Evaluation of the diagnostic potential of candidate genes using multiple machine learning models. (**E**) ROC curve analysis comparing the performance of different models in predicting psoriasis risk. (**F**) Gene importance ranking derived from the ElasticNet model. (**G**) Structural prediction of TYK2 protein before and after mutation using AlphaFold3. (The red box indicates the parts of the β-sheet structure that changed before and after the mutation).

Integrating these findings with prior literature, we ultimately identified ICAM1 as a key gene, whose protein expression was found to be regulated by a missense mutation (rs34536443) in the TYK2 gene. To further explore the impact of this mutation on protein structure, we utilized AlphaFold3 to predict conformational changes in TYK2 before and after the mutation. The results indicated that the wild-type allele (rs34536443-C) promoted the formation of a β-sheet structure at residues ANS (788–790), while the mutant allele (rs34536443-G) abolished this structure and instead induced new β-sheet formations at DQTAQGM (135–141) and QAE (285–287) (Figure 1G). We hypothesize that these structural alterations may impair TYK2 function, leading to dysregulation of ICAM1 expression and thereby contributing to psoriasis pathogenesis.

Single-Cell Transcriptomic Analysis Reveals the Functional Roles of TYK2, ICAM1, and ICAM5 in Psoriatic Epidermal Cells

To elucidate the cell type–specific roles of TYK2, ICAM1, and ICAM5 in psoriatic skin, we analyzed single-cell RNA-sequencing data from GSE220116, which includes epidermal samples from both psoriasis patients and healthy individuals. We focused on psoriasis patient-derived cells to determine the expression patterns and potential functional relevance of these genes across distinct epidermal cell populations. Through clustering analysis, we identified seven major cell types, including dendritic cells (DCs), endothelial cells, keratinocytes, macrophages, monocytes, T cells, and

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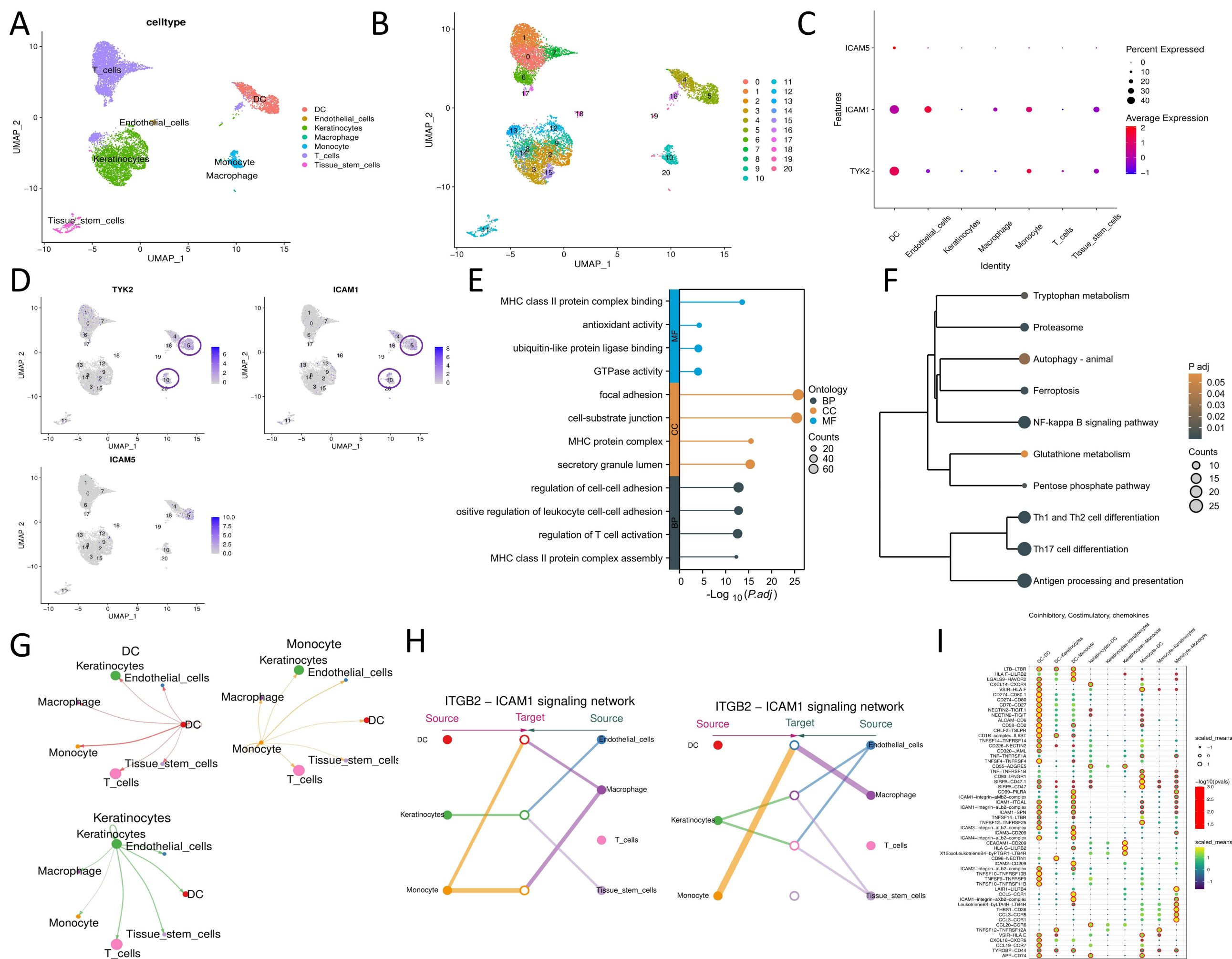

Figure 2 Single-cell transcriptomic analysis of TYK2, ICAM1, and ICAM5 expression in psoriasis epidermal cells. (**A**) Single-cell clustering identifies seven major cell types in the epidermis of psoriasis patients. (**B**) Subcluster analysis reveals 20 distinct cellular subtypes. (**C**) Expression distribution of TYK2, ICAM1, and ICAM5 across different cell types. (**D**) Enrichment of TYK2, ICAM1, and ICAM5 expression among cellular subtypes. (**E**) GO enrichment analysis of Type 5 cells, showing related molecular functions (MF), cellular components (CC), and biological processes (BP). (**F**) KEGG pathway analysis highlights the major signaling pathways enriched in Type 5 cells. (**G**) CellChat analysis reveals intercellular communication among DCs, monocytes, keratinocytes, and T cells in psoriatic epidermis. (**H**) ITGB-ICAM1 signaling network illustrates interactions between monocytes/macrophages and DCs or endothelial cells. (**I**) CellPhoneDB analysis uncovers ICAM1-mediated intercellular interaction networks.

tissue stem cells (Figure 2A). Subclustering revealed 20 distinct cell subtypes (Figure 2B). Expression profiling demonstrated that ICAM1, ICAM5, and TYK2 were predominantly enriched in DCs. Additionally, ICAM1 and TYK2 were also highly expressed in monocytes, endothelial cells, and tissue stem cells (Figure 2C). At the subtype level, all three genes were most enriched in Type 5 cells, with TYK2 and ICAM1 also expressed in Type 10 cells (Figure 2D).

To gain further insight into the functional properties of Type 5 cells, we conducted Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses. GO analysis revealed that, at the molecular function (MF) level, the genes were primarily involved in MHC class II protein complex binding and antioxidant activity. For the cellular component (CC) category, genes were enriched in focal adhesion and cell-substrate junctions, while the biological processes (BP) were mainly associated with regulation of cell–cell adhesion and T cell activation (Figure 2E). KEGG analysis highlighted the activation of key pathways including the NF-κB signaling pathway, tryptophan metabolism, and autophagy (Figure 2F).

Given that DCs function as professional antigen-presenting cells (APCs) and rely heavily on intercellular communication, we performed CellChat analysis to map the interaction networks between DCs and other cell types. The results showed that DCs and monocytes primarily interact with keratinocytes and T cells, while keratinocytes were mainly

regulated by DCs and T cells (Figure 2G). In the ITGB–ICAM1 signaling network, monocytes were found to target DCs, themselves, and endothelial cells via this pathway. Similarly, macrophages interacted with monocytes, DCs, and endothelial cells through the same signaling axis (Figure 2H). Complementary CellPhoneDB analysis further uncovered ICAM1-mediated cell–cell interaction patterns: interactions such as ICAM1–ITGAL, ICAM1–SPN, and the ICAM1–integrin-αLβ2 complex were primarily involved in DC–DC and DC–monocyte communications, whereas the ICAM1–integrin-αMβ2 complex was predominantly responsible for DC–monocyte interactions (Figure 2I).

Taken together, these findings suggest that ICAM1, ICAM5, and TYK2 are primarily enriched in DCs and monocytes, with monocytes displaying higher intercellular activity. These two cell populations likely play a crucial role in psoriasis pathogenesis through dynamic and complex intercellular communication networks.

TYK2-P1104A Mutation Alters Inflammatory Response Patterns and ICAM1 Expression in THP-1 Cells

The rs34536443 variant corresponds to the P1104 residue of TYK2. To investigate the functional consequences of this mutation, we constructed a plasmid encoding the TYK2-P1104A mutant and transfected it into THP-1 cells alongside an empty vector control. Cells were subsequently stimulated with LPS, and inflammatory responses were assessed. qPCR analysis revealed no significant difference in ICAM1 or ICAM5 mRNA levels between the TYK2-P1104A and control groups under basal conditions. Upon LPS stimulation, ICAM1 expression was markedly upregulated in the pcDNA-TYK2 group but remained unchanged in the TYK2-P1104A group, suggesting that the P1104A mutation impairs LPS-induced ICAM1 transcription. In contrast, ICAM5 expression was not significantly altered in either group (Figure 3A).To further evaluate the inflammatory response, ELISA assays were performed. In the absence of LPS, IL-1β and IL-23 levels did not differ significantly between the two groups, although TNF-α levels were slightly reduced in the TYK2-P1104A group. After LPS stimulation, IL-1β and TNF-α levels were significantly lower in the TYK2-P1104A group compared to controls, while IL-23 remained unchanged (Figure 3B). Consistently, qPCR analysis confirmed that mRNA levels of IL-1β, TNF-α, IL-6, IL-18, and IL-23 were all significantly downregulated in the TYK2-P1104A group following LPS exposure (Figure 3C), indicating a potential anti-inflammatory role for this mutation. Immunofluorescence staining supported these findings at the protein level. Under unstimulated conditions, ICAM1 expression was lower in the TYK2-P1104A group compared to the control (pcDNA-TYK2) group (~17% vs ~25% positive cells), and this difference was further accentuated following LPS stimulation (~38% vs ~45%, respectively). In contrast, ICAM5 protein levels remained low and showed no significant differences across conditions, with positivity ranging from ~2.5% to ~6.3% (Figure 3D).

Given the known role of TYK2 in the JAK-STAT pathway, we examined whether the P1104A mutation affects STAT3 phosphorylation. Immunofluorescence analysis demonstrated that LPS stimulation significantly increased p-STAT3 levels in the control group, whereas this induction was markedly attenuated in the TYK2-P1104A group (Figure 4A), suggesting that the mutation may inhibit LPS-triggered STAT3 activation and its downstream inflammatory signaling. Deucravacitinib, a selective TYK2 inhibitor currently under clinical investigation, has not been previously evaluated for its effects on ICAM expression in psoriatic lesions. Using an imiquimod (IMQ)-induced psoriasis-like mouse model, we found that Deucravacitinib treatment significantly reduced ICAM1 expression in lesional skin, while ICAM5 expression remained unchanged (Figure 4B).

Discussion

This study integrates SMR analysis, single-cell RNA sequencing (scRNA-seq), and in vitro experiments to investigate the potential role of the TYK2 rs34536443 (P1104A) variant in psoriasis, and further elucidates the mechanism of action of the TYK2 inhibitor Deucravacitinib. The results suggest that the P1104A mutation may attenuate psoriasis progression by downregulating ICAM1 expression and subsequently suppressing proinflammatory cytokine secretion.

In recent years, genome-wide association studies (GWAS) have repeatedly identified genetic variants in TYK2 associated with psoriasis.[6] Among them, the P1104A mutation has been shown to reduce TYK2 kinase activity, thereby impairing activation of the JAK-STAT signaling pathway.[18,36] In parallel, the expression of ICAM1 is markedly

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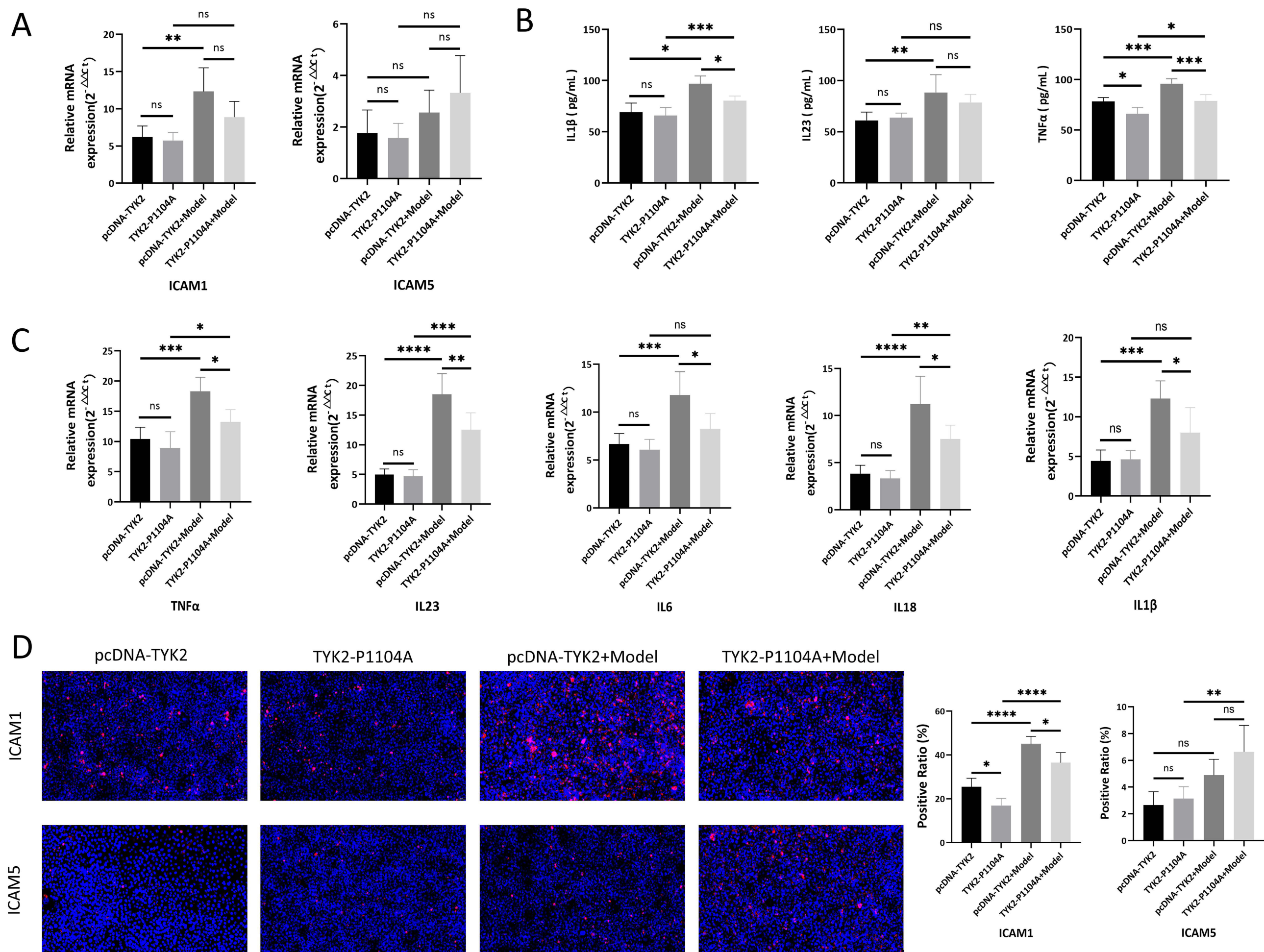

Figure 3 Effect of TYK2 P1104A mutation on LPS-induced inflammation and ICAM1 expression. (**A**) qPCR analysis of the impact of TYK2 P1104A mutation on LPS-induced mRNA expression of ICAM1 and ICAM5 (n = 5). (**B**) ELISA quantification of IL-1β, TNF-α, and IL-23 secretion before and after LPS treatment (n = 5). (**C**) qPCR analysis of LPS-induced mRNA expression of pro-inflammatory cytokines including IL-1β, TNF-α, IL-23, IL-6, and IL-18 (n = 5). (**D**) Immunofluorescence staining to assess the effects of TYK2 P1104A mutation on protein expression of ICAM1 and ICAM5 (magnification, 200×; scale bar, 50 μm). Significant differences were denoted by ^{ns} (not significant) (n = 5), * (P < 0.05), ** (P < 0.01), *** (P < 0.001) and **** (P < 0.0001).

upregulated in psoriatic lesions, suggesting its potential involvement in cutaneous inflammation and T cell infiltration.[37,38] In this study, we performed a summary-data-based Mendelian randomization (SMR) analysis and, for the first time, identified ICAM1 as a potentially pathogenic protein in psoriasis. We further found that the key regulatory SNP rs34536443 is located within the TYK2 gene, indicating that TYK2 may modulate psoriasis pathogenesis by regulating ICAM1 expression—an observation consistent with the clinical efficacy of TYK2 inhibitors in psoriasis. Single-cell RNA sequencing analysis revealed that ICAM1, ICAM5, and TYK2 are primarily enriched in monocytes and dendritic cells (DCs), which are key players in the psoriatic immune response.[39–41] Additionally, ICAM1 expression was significantly upregulated in the epidermis of psoriasis patients, whereas ICAM5 expression remained largely unchanged. These findings align with previous reports on the role of ICAM1 in T cell recruitment and inflammatory spread, further supporting the hypothesis that TYK2 mediates psoriatic inflammation primarily via ICAM1 regulation.[42]

Further in vitro experiments demonstrated that the TYK2-P1104A mutation attenuates ICAM1 expression in LPS-stimulated THP-1 cells and downregulates the secretion of pro-inflammatory cytokines, including IL-1β, TNF-α, IL-6, and IL-18. This suggests that the P1104A variant may impair TYK2's pro-inflammatory signaling functions, thereby exerting a protective anti-inflammatory effect. Previous studies have established a central role for TYK2 in the IL-23/IL-17 axis—a core pathogenic pathway in psoriasis.[7,43] Notably, the P1104A variant also significantly inhibited LPS-induced STAT3 phosphorylation, indicating that it may suppress inflammation through inhibition of the TYK2–STAT3 signaling axis.

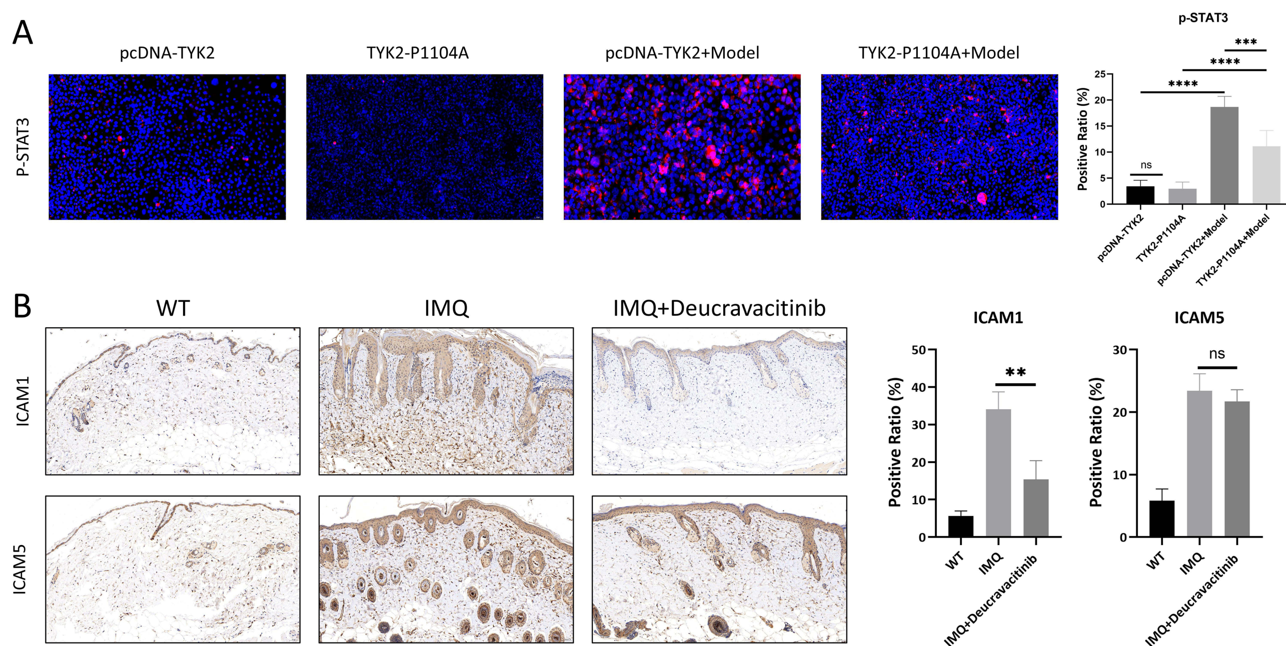

Figure 4 Effect of TYK2-P1104A mutation and Deucravacitinib on STAT3 phosphorylation and ICAM1/ICAM5 expression. (**A**) Immunofluorescence analysis of the effect of TYK2-P1104A mutation on LPS-induced phosphorylation of STAT3 (p-STAT3) (magnification, 200×; scale bar, 50 μm) (n = 5). (**B**) Expression levels of ICAM1 and ICAM5 in lesional skin tissues from IMQ-induced psoriasis-like mouse models following Deucravacitinib treatment. Significant differences were denoted by ^{ns} (not significant), ** ($P < 0.01$), *** ($P < 0.001$) and **** ($P < 0.0001$).

STAT3, a downstream effector of TYK2, plays a crucial role in regulating inflammatory responses.[44] Our data demonstrate that the TYK2-P1104A mutation reduces p-STAT3 expression following LPS stimulation, further corroborating its role in suppressing JAK-STAT signaling, in agreement with prior reports of TYK2's involvement in pro-inflammatory pathways.[45] Finally, treatment with deucravacitinib—a selective TYK2 inhibitor—significantly reduced ICAM1 expression in an imiquimod-induced psoriasis-like mouse model, without affecting ICAM5 levels. These findings further validate the critical role of the TYK2–ICAM1 axis in psoriasis and support the therapeutic potential of TYK2 inhibitors in clinical practice.

The findings of this study not only enhance our understanding of the pathogenic mechanisms underlying psoriasis but also underscore the clinical relevance of TYK2 inhibition from both genetic and functional perspectives. Nevertheless, several limitations should be acknowledged. First, although the SMR analysis revealed an association between TYK2 and ICAM1, it does not establish a direct causal relationship, and further mechanistic studies are required to confirm whether TYK2 regulates ICAM1 expression via specific signaling pathways such as STAT3. Second, our in vitro experiments were conducted exclusively in THP-1-derived macrophages, which may not fully capture the complexity of immune interactions in psoriasis; validation in primary dendritic cells or keratinocyte–immune cell co-culture systems would provide additional insight. Finally, although our in vivo experiments demonstrated that TYK2 inhibition reduces ICAM1 expression in an imiquimod-induced mouse model, clinical evidence from psoriasis patients is still needed to establish the translational relevance of the TYK2–ICAM1 axis.

In conclusion, this study integrates genetic analysis with experimental validation to demonstrate that the TYK2-P1104A variant may contribute to psoriasis pathogenesis by regulating ICAM1 expression. These findings not only clarify a potential mechanism underlying the therapeutic effects of TYK2 inhibition but also suggest that the TYK2–ICAM1 axis may represent an alternative or complementary pathway to the classical TYK2–STAT3 signaling route. This work provides new mechanistic insights for the precision treatment of psoriasis and lays a foundation for the development of future therapeutic strategies targeting this novel axis.

Conclusion

In summary, our integrative analysis combining Mendelian randomization and machine learning identified the TYK2 rs34536443 (P1104A) variant as a functional mutation that regulates ICAM1 and ICAM5 expression and contributes to

psoriasis pathogenesis. Single-cell RNA sequencing revealed their enrichment in dendritic cells and monocytes, implicating them in immune signaling. Functional assays demonstrated that the P1104A variant suppresses LPS-induced ICAM1 expression and proinflammatory cytokine secretion. Moreover, Deucravacitinib treatment reduced ICAM1 levels in an imiquimod-induced mouse model. These findings highlight the anti-inflammatory potential of the TYK2–ICAM1 axis, suggesting that it may function as an alternative or complementary pathway to the classical TYK2–STAT3 signaling axis in mediating the therapeutic effects of TYK2 inhibition. This provides new mechanistic insight into TYK2-targeted therapies and their application in inflammatory skin disorders.

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; 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

The authors declare no competing interest in this work.

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