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ORIGINAL RESEARCH

Interleukin-1 Receptor Antagonist as a Potential Mediator Linking Psoriasis and Non-Alcoholic Fatty Liver Disease: Insights From Mendelian Randomization and Experimental Evidence

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Background: Epidemiological studies have revealed a close association between psoriasis and non-alcoholic fatty liver disease (NAFLD), but the causal relationship and underlying mechanisms remain unclear.

Materials and Methods: In this study, we used genome-wide association study (GWAS) data from the MRC Integrative Epidemiology Unit (MRC-IEU) to investigate the causal relationship between psoriasis and NAFLD, as well as potential mediators. Two-sample and two-step MR analyses were conducted, followed by bulk and single-cell transcriptomic analyses to validate our MR findings. In vivo validation was performed using Enzyme-Linked Immunosorbent Assay (Sample of patients (n=10)), immunohistochemistry, and liver bulk transcriptomic analysis.

Results: The two-sample MR analysis revealed that genetically predicted psoriasis significantly increased the risk of NAFLD (OR = 1.07, 95% CI = 1.03–1.12, $p = 0.001$). Mediation analysis suggested that psoriasis was associated with elevated plasma Interleukin-1 receptor antagonist protein (IL-1RA) levels (OR = 1.02, 95% CI = 1.00–1.05, $p = 0.031$), which in turn raised the risk of NAFLD (OR = 1.15, 95% CI = 1.04–1.27, $p = 0.006$). In vivo experiments demonstrated elevated IL-1RA levels in the skin and plasma of psoriasis patients. Similarly, imiquimod (IMQ)-induced psoriasis mouse models exhibited increased IL-1RA levels in plasma and liver, accompanied by liver inflammation. MR and colocalization analysis indicated a positive correlation between IL-1RA, apolipoprotein B, and cholesterol.

Conclusion: Our study demonstrates that genetically predicted psoriasis increases the risk of NAFLD, and plasma IL-1RA may serve as a potential mediator between psoriasis and NAFLD.

Keywords: psoriasis, non-alcoholic fatty liver disease, mendelian randomization, imiquimod-induced mouse model

Introduction

Psoriasis is an incurable disease characterized by recurrent lesions after the cessation of treatment, affecting 0.1–1.5% of the global population.[1] Increasing evidence suggests that patients with psoriasis are at higher risk for comorbidities including type 2 diabetes,[2] cardiovascular disease,[3] metabolic syndrome,[4] and non-alcoholic fatty liver disease,[5] which lead to reduced quality of life, increased economic burdens, and even depression and suicidal tendencies.[6,7] Therefore, addressing both psoriasis and the its associated systemic comorbidities is particularly important.

Non-alcoholic fatty liver disease (NAFLD) is characterized by excessive triglyceride accumulation in the liver and has a complex pathogenesis involving genetic factors, liver inflammation, insulin resistance in skeletal muscle and adipose tissue, and gut microbiota alterations.[8] Its prevalence is rising globally, with rates exceeding 30% in major regions.[9] Among individuals with NAFLD, 7–20% progress to cirrhosis or end-stage liver disease within 7–12 years.[10] There is a bidirectional association between

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psoriasis and NAFLD. Cohort studies have demonstrated that young patients with NAFLD exhibit a significantly increased risk of developing psoriasis.[11] However, the inherent limitations of confounding and reverse causality have led to results that are inconsistent with Mendelian randomization (MR) analyses.[12] Epidemiological studies indicate that psoriasis increases the risk of NAFLD, with its association being independently of psoriasis.[13,14] However, common medications used to treat psoriasis may cause liver toxicity, and it remains unclear whether the association between psoriasis and NAFLD is caused by psoriasis itself or by the medications.[15]

Unlike traditional observational studies, Mendelian randomization (MR) analysis minimizes confounding and reverse causality,[16,17] making it a robust method to explore causal relationships and underlying mechanisms between diseases. Given that psoriasis is a systemic condition,[18] we focused on circulating proteins to explore the association between psoriasis and NAFLD. By a two-step MR analysis, transcriptomic analysis, and experimental validation, we identified plasma IL-1RA as a potential biomarker for NAFLD in psoriasis patients.

Materials and Methods

Human Subjects

This study included 10 participants with psoriasis who had not received systemic psoriasis treatments for at least 12 weeks prior to enrollment, as well as healthy controls. Participants, aged 18 years or older, were recruited between January 1, 2024, and August 1, 2024, at Shanghai Ruijin Hospital. Psoriasis was diagnosed by an expert dermatologist. Exclusion criteria included hepatic steatosis (mild, moderate, or severe) confirmed by ultrasound, other causes of hepatic steatosis, positive hepatitis B or C viral infection, excessive alcohol consumption (≥30 g/day for males and ≥20 g/day for females), BMI ≥24, current lipid-lowering treatment, diabetes, cardiovascular diseases (eg, coronary heart disease, hypertension), autoimmune or inflammatory diseases (eg, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease) or any active infection within the past month. Written informed consent was obtained from all participants. The study was conducted with the approval of the Ruijin Hospital Ethics Committee (Confidential Agreement No.2021[285]), and adhered to the ethical principles outlined in the 1964 Declaration of Helsinki and its subsequent amendments. Informed consent was obtained from each patient.

Mouse Model

All mice were housed in the animal facility at Shanghai Jiao Tong University School of Medicine. The mice were of the C57BL/6J strain and 7–8 weeks old. A total of 25 mg of imiquimod (IMQ) cream was applied to ears for 5 consecutive days, followed by a 2-week rest period, repeated for 3 cycles. Plasma was collected from the inner canthus vein using heparinized tubes. All animal experiments were approved by the Institutional Animal Care and Use Committee of Shanghai Jiao Tong University School of Medicine.

Mendelian Randomization

We used the "Two Sample MR" package (version 0.6.8) to conduct a two-sample MR analysis to explore the causal relationship between psoriasis and NAFLD. In the MR analysis, psoriasis is the exposure of interest, NAFLD is the outcome, and single nucleotide polymorphisms (SNPs) are the instrumental variables. The two-sample MR analysis is based on the following assumptions: (I) the instrumental variables are strongly associated with the risk of psoriasis; (II) the instrumental variables affect the risk of NAFLD only through their effect on psoriasis risk; (III) the instrumental variables are independent of confounding factors. The two-step MR is used to assess whether intermediate traits mediate the relationship between exposure and outcome.[19] Data on psoriasis, NAFLD, and plasma proteins were obtained from GWAS summary statistics (Table S1). As suggested in previous studies, the threshold for SNPs selection was set at $P < 1e\text{-}05$ and linkage disequilibrium [LD] $r^2 < 0.001$,[20–22] while excluding instrumental variables with F values ($beta^2/se^2$) less than 10 to ensure a strong association between instrumental variables and exposure factors. We employed five MR methods, including MR Egger, weighted median, inverse variance weighting (IVW), simple mode, and weighted mode, to robustly analyze the causal relationship, with $p < 0.05$ using the IVW method indicating statistical significance. We used MR-Egger regression tests and MR-PRESSO to assess pleiotropy, and Cochran's Q test to evaluate heterogeneity. In the two-step MR analysis, the direct

effect of exposure on the outcome was calculated as $\beta 0 - \beta 1 \times \beta 2$.[23] Here, β0 represents the total causal effect of exposure on the outcome, β1 indicates the causal effect of exposure on the mediator, β2 reflects the causal effect of the mediator on the outcome, and $\beta 1 \times \beta 2$ quantifies the mediating effect of exposure on the outcome (Table S2). The analysis was conducted using R software (version 4.2.0).

Colocalization

We used the "coloc" package[24] to quantify the probability of shared causal variation between the exposure and the outcome showing significant causal relationships. Colocalization analysis was performed using all SNPs within ± 500 kb of the top SNP location of Interleukin 1 receptor antagonist protein.

RNA Sequencing and Gene Expression Analysis

Skin RNA-seq datasets were obtained from GSE121212 (healthy controls, psoriasis lesions), GSE178197 (healthy controls, full-thickness biopsies from psoriasis patients). Peripheral blood dataset was obtained from GSE55201 (healthy controls and psoriasis patients at baseline). Liver datasets were obtained from GSE63067 (NAFLD patients and healthy controls). Datasets from different batches were integrated using the R package "sva" (version 3.48.0), and differential gene analysis was performed using the R package "limma" (version 1.40.2). Mouse liver samples were preserved in TRIzol and then sent to Beijing Genomics Institute (BGI) for RNA extraction, library preparation, and sequencing.

Single-Cell Transcriptome Analysis

The skin single-cell RNA-seq data was obtained from the GSE230842. Clustering and dimensionality reduction analyses were conducted using the R package "Seurat" (version 4.4.0), and cell populations were identified based on their highly expressed genes.

Flow Cytometry

Skin samples were obtained from ear lesions and lymph nodes from the cervical region, as described in our previous studies.[25] Flow cytometry gating strategy is provided in the Supplementary Materials. Skin samples were minced and digested for 2 hours in RPMI-1640 containing hyaluronidase, type I collagenase, and DNase I (Sigma-Aldrich). Lymph node samples were ground directly on ice. The resulting suspension was filtered through a 40 μm cell strainer to obtain a single-cell suspension. A total of 1×10^6 cells were stimulated at 37°C for 4 hours using a cell stimulation cocktail (BioLegend). Cells were then blocked with CD16/32 antibodies on ice for 10 minutes, followed by surface staining with PerCP-Cy5.5–CD3, APC–γδT for 20 minutes at 4°C, along with Fixable Viability Dye eFluor 780. After staining, cells were fixed at room temperature for 20 minutes and washed twice with permeabilization buffer (BioLegend). Intracellular staining with BV650–IL-17A was performed at 4°C for 1 hour. After washing, samples were analyzed using a Beckman CytoFLEX flow cytometer. Data were analyzed with FlowJo version 10.8.1.

RT-qPCR

cDNA was synthesized using a reverse transcription kit (Promega) following the manufacturer's instructions. Quantitative PCR (qPCR) was carried out on the Bio-Rad CFX Connect™ Real-Time System. Actb served as the internal control gene. The primer sequences used were as follows: *Il17a* (QT00103278, Qiagen), *Il1b* (tnt5198b, Biotnt), *Il6* (5199e, Biotnt), *Tnf* (tnt5197e, Biotnt), Il23(tnt2434b, Biotnt), *Il1rn* (tnt2829a, Biotnt).

Immunohistochemical Staining

The tissue was embedded in paraffin, sectioned at a thickness of 20 μm, and subsequently deparaffinized. Antigen retrieval was performed using EDTA (pH 9.0) (Solarbio, C1038) under high temperature and pressure for 90 seconds. After cooling to room temperature, the slices were washed three times with TBST (PS103, Shanghai Epizyme Biomedical Technology) and treated with 3% H2O2 in the dark at room temperature for 30 minutes to block endogenous peroxidase, followed by rinsing with distilled water. The slices were then blocked with goat serum for 30 minutes. Primary antibodies, anti-human IL-1RA (ab303490) and anti-mouse IL-1RA (10844-1-AP), diluted 1:1000 in goat serum, were applied and incubated overnight at

4°C. After three washes with TBST, Goat Anti-Rabbit IgG H&L (HRP)(ab205718), diluted 1:2000 in TBST, was added and incubated at 37°C for 45 minutes. Following another three washes with TBST, DAB (Solarbio, DA1010) was used for color development. Finally, the slides were counterstained with hematoxylin for 1 minute, dried, and mounted.

Enzyme-Linked Immunosorbent Assay

The human IL-1RA (CSB-E10396h) and mouse IL-1RA (CSB-E10395m) kits were purchased from CUSABIO (Wuhan, China) and used according to the manufacturer's instructions. Absorbance was measured at 450 nm to generate a standard curve.

Statistical Analyses

Prism 9.0 (GraphPad Prism, GraphPad Software) was used for statistical analyses in this study. Data are presented as mean ± standard deviation (SD). Differences between groups with normally distributed data were analyzed using Student's *t*-test, while those with non-normally distributed data were compared using the Mann–Whitney *U*-test.

Results

Genetically Predicted Psoriasis Increases the Risk of NAFLD Through Plasma IL-1RA

In a two-sample MR analysis, SNPs were used as instrumental variables, with the psoriasis as the exposure and NAFLD as the outcome (Tables S1 and S3). The MR analysis showed a positive causal effect between genetically predicted psoriasis and NAFLD (Inverse variance weighted: OR = 1.07, 95% CI = 1.03–1.12, $p = 0.001$) (Figure 1A and Table S4). Although the Cochran's Q test indicated heterogeneity in the results, the IVW method employed a random-effects model, ensuring the reliability of the results. The MR-Egger intercept test suggested minimal influence from pleiotropy (Table S4). Leave-one-out analysis confirmed that no single SNP significantly influenced the main results (Figure S1A).

To explore the potential plasma proteins mediating the relationship between psoriasis and NAFLD, we performed a two-step MR analysis using plasma proteins as mediators (Table S4). In the first step, seven plasma proteins were identified as having causal relationships with psoriasis: Heme oxygenase 1 ($OR_{IVW} = 0.97$, 95% CI = 0.95–1.00, $p = 0.026$), Vitamin K-dependent protein C ($OR_{IVW} = 0.98$, 95% CI = 0.95–1.00, $p = 0.037$), Antithrombin-III ($OR_{IVW} = 0.98$, 95% CI = 0.95–1.00, $p = 0.049$), Plasminogen ($OR_{IVW} = 0.97$, 95% CI = 0.95–0.99, $p = 0.003$), Interleukin-1 receptor antagonist protein ($OR_{IVW} = 1.02$, 95% CI = 1.00–1.05, $p = 0.031$), Fibroblast growth factor 5 ($OR_{IVW} = 0.87$, 95% CI = 0.79–0.95, $p = 0.002$), and EN-RAGE ($OR_{IVW} = 1.10$, 95% CI = 1.01–1.21, $p = 0.035$) (Figure 1B and Table S4). Among these, only IL-1RA showed a positive causal relationship with NAFLD (Figure 1C), with a mediating effect value of 0.052 (Table S2). The analysis revealed no significant heterogeneity or pleiotropy (Table S4), and leave-one-out analysis indicated that no single SNP significantly affected the main results (Figure S1B-I). These findings suggest that genetically predicted psoriasis increases the risk of NAFLD, with elevated plasma IL-1RA levels partially mediating this relationship.

IL-1RA Levels are Elevated in Both Psoriasis and NAFLD Patients

We analyzed transcriptomic data from the skin of psoriasis patients and healthy controls using datasets GSE121212 and GSE178197, as well as peripheral blood data from dataset GSE55201. The analysis revealed elevated *IL1RN* expression in the skin and peripheral blood of psoriasis patients compared to healthy controls (Figure 2A and B). Similarly, transcriptomic data from the liver of NAFLD patients and healthy controls in dataset GSE63067 showed a significant increase in *IL1RN* expression in the liver of NAFLD patients (Figure 2C).

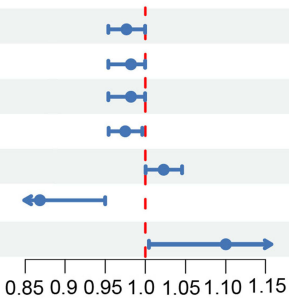
To validate these findings at the protein expression level, we collected skin and plasma samples from psoriasis patients and healthy controls. Consistent with the transcriptomic data, immunohistochemistry revealed higher IL-1RA expression in the skin of psoriasis patients compared to healthy controls, with positive signals observed in both the epidermis and dermis (Figure 2D). Furthermore, plasma IL-1RA levels were elevated in psoriasis patients, corroborating the results of the MR analysis (Figure 2E). To further investigate the source of elevated IL-1RA in psoriasis, we analyzed single-cell transcriptomic data from the skin of psoriasis patients and healthy controls using dataset GSE230842. The

A

Exposure	Outcome	Method	nSNPs	p-value	OR(95%CI)
psoriasis	NAFLD	MR Egger	94	0.058	1.07(1.00 to 1.16)
psoriasis	NAFLD	Weighted median	94	0.003	1.10(1.03 to 1.16)
psoriasis	NAFLD	Inverse variance weighted	94	0.001	1.07(1.03 to 1.12)
psoriasis	NAFLD	Simple mode	94	0.374	1.07(0.93 to 1.23)
psoriasis	NAFLD	Weighted mode	94	0.014	1.08(1.02 to 1.15)

B

Exposure	Outcome	nSNPs	p-value	OR(95%CI)
psoriasis	Heme oxygenase 1	94	0.026	0.97(0.95 to 1.00)
psoriasis	Vitamin K-dependent protein C	94	0.037	0.98(0.95 to 1.00)
psoriasis	Antithrombin-III	94	0.049	0.98(0.95 to 1.00)
psoriasis	Plasminogen	94	0.003	0.97(0.95 to 0.99)
psoriasis	Interleukin-1 receptor antagonist	94	0.031	1.02(1.00 to 1.05)
psoriasis	Fibroblast growth factor 5	87	0.002	0.87(0.79 to 0.95)
psoriasis	EN-RAGE	87	0.035	1.10(1.01 to 1.21)



C

Exposure	Outcome	nSNPs	p-value	OR(95%CI)
Heme oxygenase 1	NAFLD	37	0.252	1.15(0.91 to 1.45)
Vitamin K-dependent protein C	NAFLD	35	0.351	0.95(0.88 to 1.04)
Antithrombin-III	NAFLD	34	0.202	0.93(0.84 to 1.04)
Plasminogen	NAFLD	26	0.913	1.00(0.92 to 1.07)
Interleukin-1 receptor antagonist protein	NAFLD	30	0.006	1.15(1.04 to 1.27)
Fibroblast growth factor 5	NAFLD	14	0.104	1.04(0.99 to 1.09)
EN-RAGE	NAFLD	7	0.052	1.06(1.00 to 1.12)

Figure 1 MR analysis shows a positive causal relationship between genetically predicted psoriasis and NAFLD, with IL-1RA as a mediator. (**A**) The causal relationship between genetically predicted psoriasis and NAFLD. (**B**) Plasma proteins that have causal associations with psoriasis calculated using the IVW method ($p < 0.05$). (**C**) Associations of seven proteins in (**B**) with NAFLD calculated using the IVW method.
Abbreviations: OR, odds ratio; CI, confidence interval.

analysis revealed that *IL1RN* is predominantly expressed in myeloid cells and keratinocytes in the skin and is significantly upregulated in psoriasis (Figure 2F–G).

Chronic Psoriasis-Like Inflammation in Mice Leads to Increased Hepatic Inflammation, Lipogenesis, and Circulating and Hepatic IL-1RA Levels

The occurrence of comorbidities is positively correlated with the duration of psoriasis.[26,27] To investigate the effects of chronic psoriatic inflammation on the liver, mice were treated with a topical application of 25 mg IMQ on the ears for five consecutive days, followed by a two-week rest period, repeated three times (Figure 3A). Chronic IMQ treatment induced marked scaling and epidermal thickening in mouse ears (Figure 3B and C). Pro-inflammatory cytokines such as *Il1b, Il17a, Il6, Tnf*, and *Il23* exhibited significantly increased mRNA expression levels, accompanied by a notable elevation in *Il1rn* expression (Figure 3D). Given that γδT cells are the primary source of IL-17A in the IMQ-induced psoriasis model,[28] we analyzed the number of IL-17A + γδT cells in skin lesions and draining lymph nodes. The results showed that chronic psoriasis significantly increased the proportion of IL-17A+ γδT cells in both ear skin lesions and draining lymph nodes (Figures 3E and F, S2A and B).

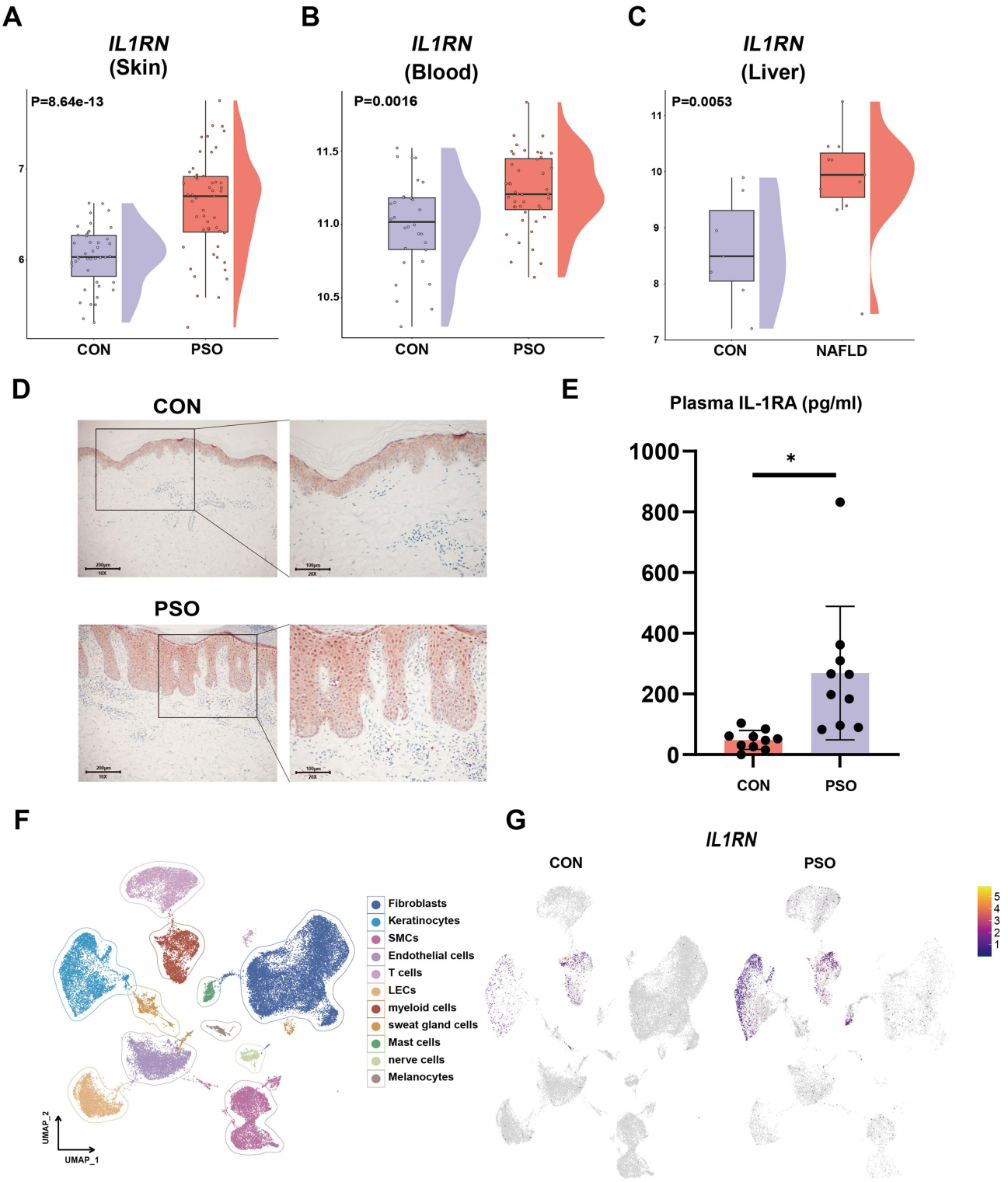


Figure 2 IL-1RA (*IL1RN*) levels are elevated in the skin and peripheral blood of psoriasis patients, and the liver of NAFLD patients. (**A**) *IL1RN* mRNA levels in the skin of psoriasis patients and healthy controls. (**B**) *IL1RN* mRNA levels in the whole-blood of psoriasis patients and healthy controls (**C**). *IL1RN* mRNA levels in the liver of NAFLD patients and healthy controls (**D**) Representative immunohistochemical staining of IL-1RA in skin biopsy samples from psoriasis patients and healthy controls. Scale bars, 200μm. (**E**) IL-1RA levels in the plasma of psoriasis patients and healthy controls (n=10). (**F**) UMAP plot of single-cell RNA sequencing data from skin samples of psoriasis patients and healthy controls. (**G**) Feature plot depicting *IL1RN* expression in the skin of psoriasis patients and healthy controls. *$p < 0.05$.

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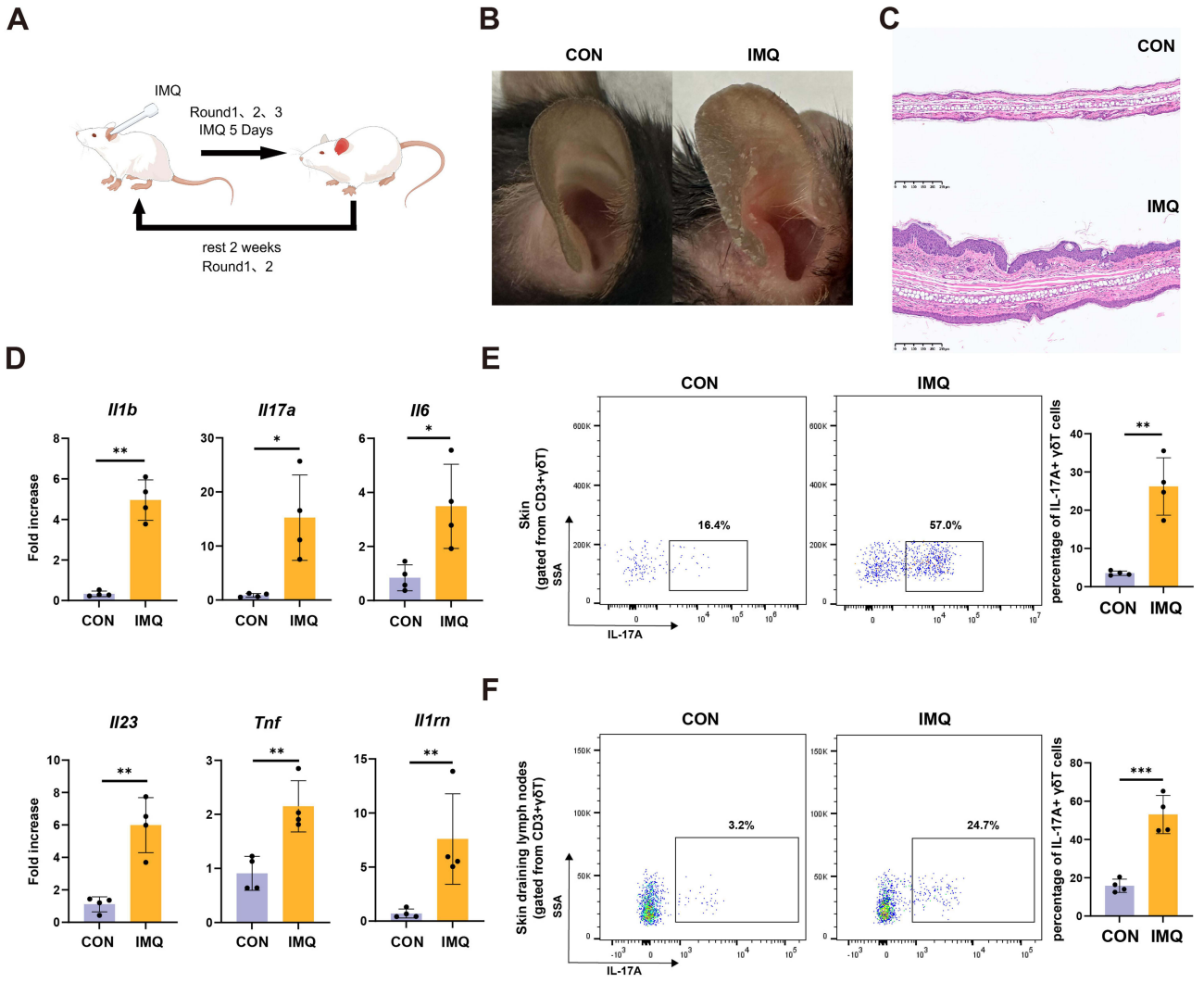

Figure 3 Topical application of imiquimod (IMQ) on mouse ears induces psoriasis-like skin inflammation. (**A**) Diagram illustrates the process of imiquimod application to induce psoriasis-like inflammation in mice. (**B**) Representative photographs of skin lesions on mouse ears. (**C**) Representative hematoxylin and eosin (H&E) stained images of skin lesions on mouse ears. Scale bars, 50μm. (**D**) mRNA levels of cytokines in mouse ears (n=4). (**E**) The proportion of IL-17A+ γδT cells in mouse ear skin lesions (n=4). (**F**) The proportion of IL-17A+ γδT cells in the draining lymph nodes of mouse ears (n=4). *$p < 0.05$; **$p<0.01$; ***$p<0.001$.

Next, we examined the effects of chronic psoriasis on the liver in mice. Consistent with findings in humans, IMQ-treated mice exhibited significantly elevated plasma IL-1RA protein levels compared to controls (Figure 4A). Liver transcriptome Gene Set Enrichment Analysis (GSEA) revealed that psoriasis significantly upregulated inflammatory pathways, including the "NF-κB signaling pathway", "Leukocyte Transendothelial Migration" and "Apoptosis", while "Oxidative Phosphorylation" was notably downregulated (Figure 4B). Specifically, the expression of *Il1rn*, inflammatory genes (*Il1b, Tnf, S100a8, S100a9*), chemokines (*Ccl*2, *Ccl3, Ccl4, Ccl5*), and the macrophage marker gene (*Adgre1*) was increased (Figure 4C). Notably, in the liver, NAFLD-related lipid transport genes (*Cd36, Fabp4*),[29,30] the lipogenesis gene (*Pparg*),[31] and cholesterol metabolism genes (*Nr1h3, Abcg1, Abca1*)[32,33] were also upregulated following psoriasis dermatitis induction (Figure 4C). Immunohistochemistry further confirmed an increase in hepatic IL-1RA protein levels in IMQ-treated mice (Figure 4D). These findings suggest that psoriasis-like inflammation elevates IL-1RA levels in the circulation and liver of mice, accompanied by hepatic inflammation and lipid metabolism disorders associated with fatty liver.

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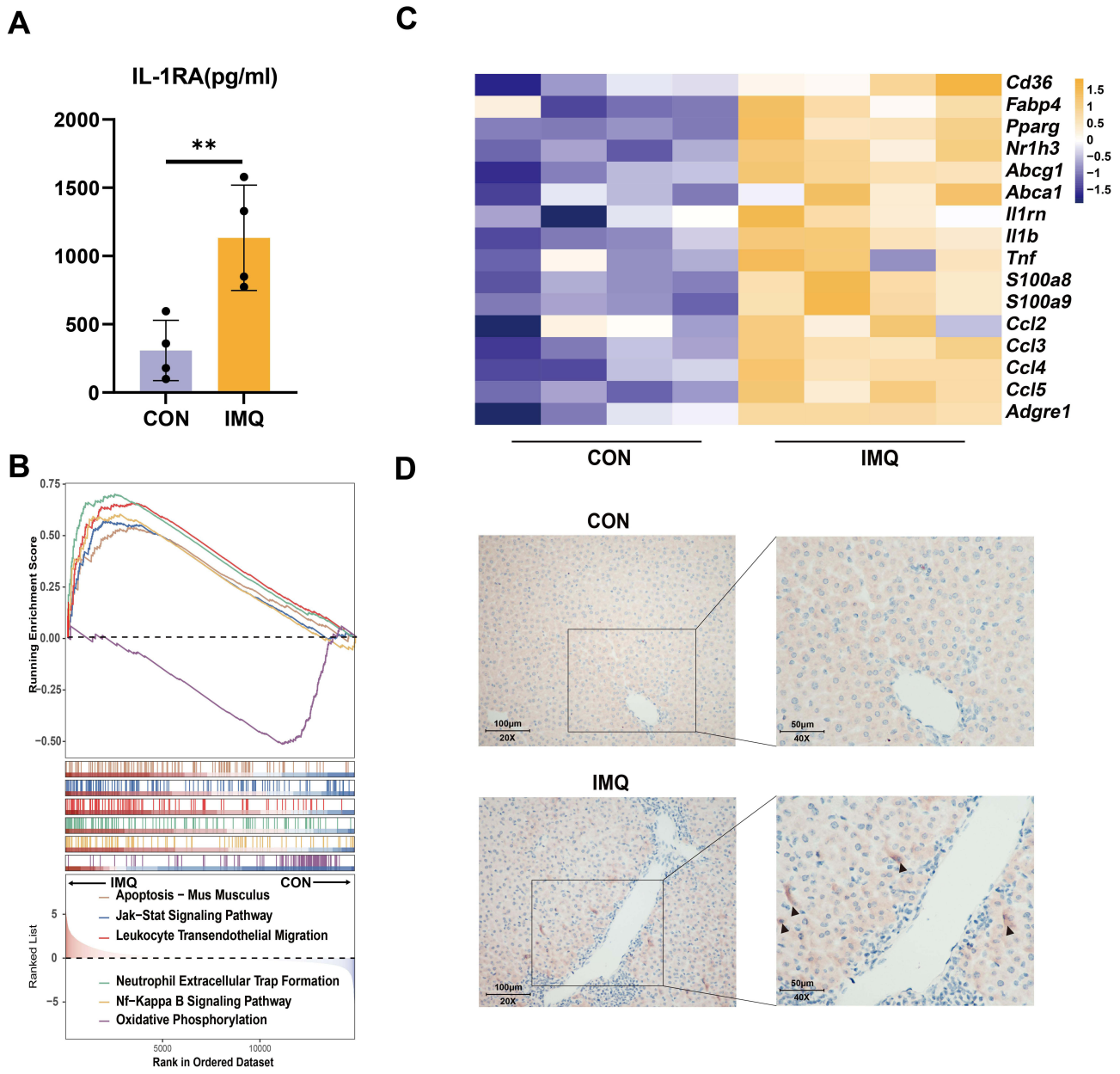

Figure 4 Chronic psoriasis-like inflammation in mice leads to increased hepatic inflammation, lipogenesis, and circulating and hepatic IL-1RA levels. (**A**) Plasma IL-1RA levels in mice with recurrent psoriasis and control mice (n = 4). (**B**) GSEA of KEGG pathways showing alterations of "Apoptosis", "Jak-Stat Signaling Pathway", "Leukocyte Transendothelial Migration", "Neutrophil Extracellular Trap Formation", "NF-Kappa B Signaling Pathway", "Oxidative Phosphorylation" genes. (**C**) Heatmap showing the expression of genes related to lipid metabolism and inflammation in the livers of control and psoriasis mice (n = 4). (**D**) Representative immunohistochemical staining of liver IL-1RA in mice with recurrent psoriasis and control mice. Scale bars, 200μm. $^{**}p < 0.01$.

Genetically Predicted Elevated Plasma IL-1RA Levels Causally Contribute to Increased NAFLD-Related Lipid Metabolic Risk Factors, with SNP Colocalization

As previous studies have indicated a correlation between the *IL1RN* gene and lipid metabolic traits,[34] and hyperlipidemia is known to be an important pathogenic factor for NAFLD.[35,36] To explore the causal relationship between IL-1RA and lipid metabolism, We utilized GWAS data related to cholesterol, triglycerides, and fatty acids[37] (Table S1). MR analysis revealed a positive causal relationship between plasma IL-1RA levels and several lipid metabolic risk factors, including total free cholesterol (OR_{IVW} = 1.03, 95% CI = 1.01–1.06, p = 0.016), total cholesterol (OR_{IVW} = 1.03, 95% CI = 1.00–1.05, p = 0.041), LDL cholesterol (OR_{IVW} = 1.03, 95% CI = 0.95–1.00, p = 0.016), total triglycerides (OR_{IVW} = 1.02, 95% CI = 1.00–1.04,

A

Exposure	Outcome	nSNPs	p-value	OR(95%CI)
Interleukin-1 receptor antagonist	Total free cholesterol levels	26	0.016	1.03(1.01 to 1.06)
Interleukin-1 receptor antagonist	Total cholesterol levels	27	0.041	1.03(1.00 to 1.05)
Interleukin-1 receptor antagonist	LDL cholesterol levels	26	0.016	1.03(1.01 to 1.05)
Interleukin-1 receptor antagonist	Total triglycerides levels	28	0.034	1.02(1.00 to 1.04)
Interleukin-1 receptor antagonist	Apolipoprotein A1 levels	28	0.068	1.02(1.00 to 1.04)
Interleukin-1 receptor antagonist	Total esterified cholesterol levels	28	0.118	1.02(0.99 to 1.05)
Interleukin-1 receptor antagonist	Total fatty acid levels	26	0.001	1.04(1.01 to 1.06)
Interleukin-1 receptor antagonist	Apolipoprotein B levels	26	0.049	1.02(1.00 to 1.05)

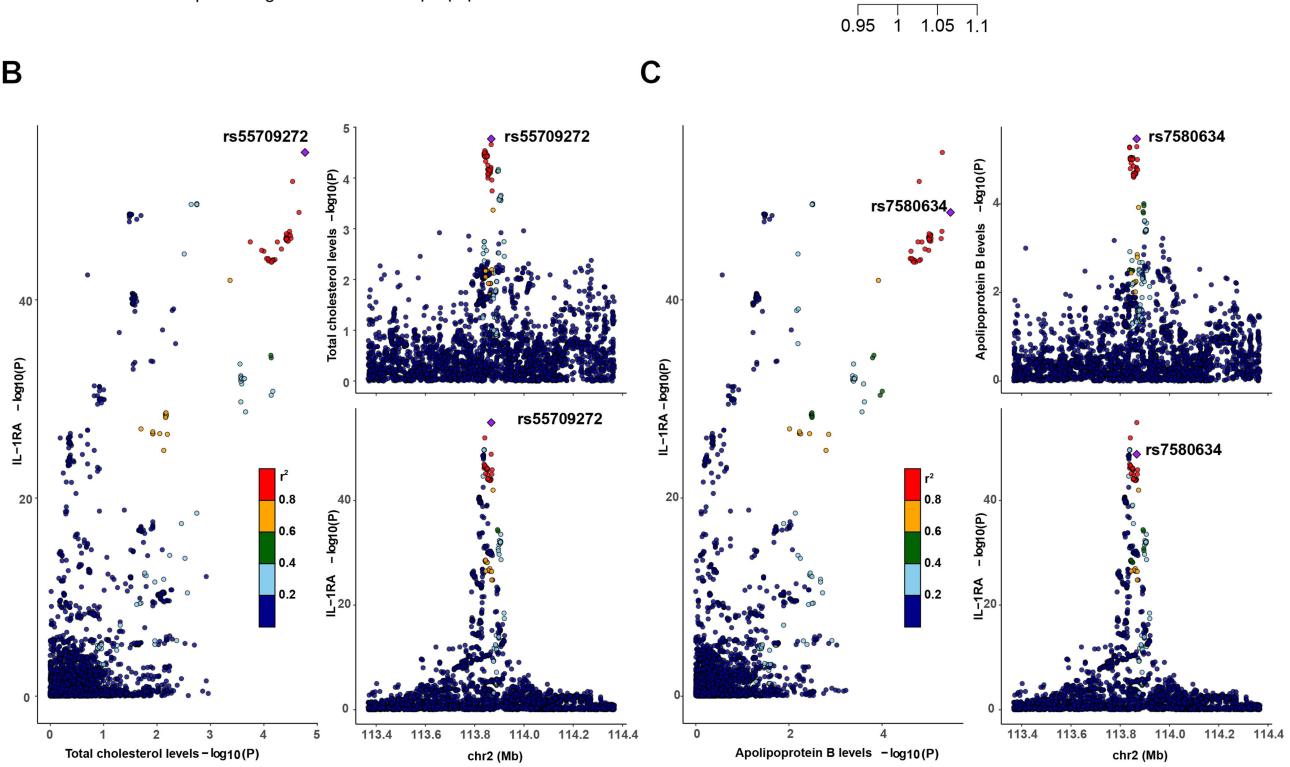

Figure 5 MR and colocalization evidence suggest that genetically predicted IL-1RA levels are positively associated with apolipoprotein B and cholesterol levels. (**A**) MR analysis using IVW method showing the causal relationship between genetically determined plasma IL-1RA levels and lipid metabolites levels. (**B**) Colocalization analysis between total cholesterol and IL-1RA. (**C**) Colocalization analysis between Apolipoprotein B and IL-1RA.

p = 0.034), total fatty acids (OR_{IVW}=1.04, 95% CI=1.01–1.06, p = 0.001) and Apolipoprotein B (OR_{IVW} = 1.02,95% CI = 1.00–1.05, p = 0.049) (Figure 5A and Table S5). The results showed no heterogeneity or pleiotropy (Table S5), and leave-one-out analysis confirmed that no single SNP influenced the findings (Figure S3A-F). Colocalization analysis further supported this findings, with high posterior probabilities for the overlap bwteen IL-1RA and lipid traits: (total cholesterol: PPH4=0.948, Apolipoprotein B: PPH4=0.970, total free cholesterol: PPH4=0.960, LDL cholesterol: PPH4=0.981) (Figures 5B and C and S4A-F,Table S6). These results suggest that elevated IL-1RA levels are causally associated with increased lipid metabolic risk factors for NAFLD.

Discussion

Recent observational studies have indicated that psoriasis may increase the risk of NAFLD.[5,13] However, the causal relationship and mediating factors remain unclear. MR analysis, which uses SNPs as instrumental variables, minimizes confounding factors and is a robust tool for investigating causal relationships.[16,17] Our study found that psoriasis increases the risk of NAFLD, with IL-1RA acting as a mediator. By transcriptomics, plasma testing and histopathological examination, we confirmed that IL-1RA expression is elevated in patients with psoriasis. In a psoriasis-like mouse model, we demonstrated that skin inflammation in psoriasis upregulates IL-1RA expression in skin, plasma and liver, along with

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liver inflammation. MR and colocalization analyses revealed that IL-1RA levels are associated with lipid metabolic risk factors for NAFLD.

Psoriasis leads to elevated circulating IL-1RA levels. Psoriasis-like inflammation induces keratinocytes to release IL-1RA,[38] and peripheral blood mononuclear cells from psoriasis patients produce higher IL-1RA in vitro,[39] consistent with elevated IL-1RA levels observed in their skin and plasma.

Excessive IL-1RA is also implicated in non-alcoholic steatohepatitis (NASH), a severe form of NAFLD.[40] Additionally, other studies have shown that elevated circulating IL-1RA levels are associated with increased risk of diseases related to lipid disorders, such as coronary heart disease and diabetes.[41,42] Mechanistically, it remains unclear whether IL-1RA directly regulates these diseases or merely serves as an indicator of IL-1 signaling activation status. On one hand, a genetic study of IL-1RA identified that increased IL-1RA concentrations are associated with a reduced risk of rheumatoid arthritis, but with elevated risk lipid levels and coronary heart disease.[43] Similarly, a recent study found that the expression of *IL1RN*, the gene encoding IL-1RA, is significantly negatively correlated with inflammatory markers and positively correlated with lipid biomarkers.[34] An animal experiment revealed that excessive IL-1RA reduces insulin sensitivity in mouse skeletal muscle.[44] Our results also identify SNP colocalization between IL-1RA and NAFLD-related risk lipids such as apolipoprotein B and cholesterol,[45–47] suggesting a complex role for IL-1RA in modulating cellular inflammation and metabolic processes. However, metabolic diseases such as NAFLD and diabetes involve chronic inflammation,[48] and IL-1RA itself lacks agonist activity in humans, functioning only through competitive binding to IL-1R1 to block IL-1β binding and downstream signaling.[49] Therefore, IL-1RA is more likely to be considered a marker reflecting systemic inflammatory status with protective effects. Notably, a study found plasma IL-1RA levels to be significantly elevated six years prior to diabetes diagnosis, indicating its potential as a predictive biomarker.[50] Taken together, elevated circulating IL-1RA levels induced by psoriasis might serve as a potential biomarker for NAFLD. Nonetheless, whether excessive IL-1RA directly modulates lipid levels to promote NAFLD requires future interventional studies for confirmation.

Additionally, a mouse model of chronic psoriasis-like dermatitis demonstrated increased hepatic expression of monocyte/macrophage chemokines *Ccl2, Ccl3, Ccl4*, and *Ccl5*, as well as the macrophage marker gene *Adgre1*. Monocyte-derived macrophages plays an important role in the pathogenesis of NAFLD.[51] Liver-derived chemokines recruit monocytes into the liver via CCR2- and CCR5-dependent pathways, where they differentiate into inflammatory macrophages that produce IL-1β, TNF, and other pro-inflammatory factors, thereby contributing to hepatic steatosis and fibrosis.[52] In this study, psoriasis-induced inflammation also resulted in increased hepatic expression of genes involved in lipid transport (*Cd36, Fabp4*), synthesis (*Pparg*), and cholesterol metabolism (*Nr1h3, Abcg1, Abca1*). These lipid-related genes were previously reported to be elevated in NAFLD livers.[29–33] This suggests that chronic inflammation in psoriasis can induce hepatic lipid metabolism dysregulation and inflammatory responses, which are key factors in the pathogenesis of NAFLD.

This study has limitations. First, to screen for as many potential mediating factors as possible, we did not apply multiple testing correction and set the SNP threshold to 1e-5, which increases the risk of false positives. Second, although we identified IL-1RA as a mediator between psoriasis and NAFLD, further research is needed to determine whether it functions solely as a biomarker and predictor, or if it directly regulates the metabolism of cholesterol and other lipid metabolites. Third, the sample sizes of both psoriasis patients and animal experiments in this study were relatively small. Future studies should increase the sample size of animal experiments and utilize additional psoriasis animal models, such as skin-specific transgenic models, to compensate for the limitations of the IMQ-induced model. In addition, larger cohorts of psoriasis patients should be recruited and prospective analyses conducted to investigate the association between IL-1RA levels and the incidence of NAFLD. Fourth, it remains to be clarified whether IL-1RA levels in psoriasis patients correlate positively with the incidence and severity of NAFLD, and whether circulating IL-1RA levels are higher in patients with both psoriasis and NAFLD compared to those with either condition alone.

Conclusion

In conclusion, we demonstrated that psoriasis increases the risk of developing NAFLD, with IL-1RA identified as a potential biomarker.

Data Sharing Statement

Data generated during this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

All animal experiments were approved by the Institutional Animal Care and Use Committee of Shanghai Jiao Tong University School of Medicine (approval number: JUMC2023-195-B) and were conducted in accordance with the Laboratory animal—Guideline for ethical review of animal welfare, GBT 35892-2018. Sample acquisitions were approved by the ethics review committees of Ruijin Hospital Affiliated to The Shanghai Jiao Tong University School of Medicine (approval number: No.2021[285]).

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

All of the authors declare that they have no relevant conflicts of interest in this work.

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