Clinical, Cosmetic and Investigational Dermatology

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ORIGINAL RESEARCH

Influence of Immune Cells and Circulating Inflammatory Cytokines on Pathological Scars: A Mendelian Randomization Study

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Background: Pathological scars are the products of abnormal repair during the wound healing process. Previous researches have demonstrated that immune cells and inflammatory cytokines are closely associated with pathological scars. However, the causality between immune cells, inflammatory cytokines and pathological scars remains unclear.

Methods: After obtaining genome-wide association studies (GWAS) data on immune cells, cytokines, hypertrophic scars, and keloids, we selected appropriate single - nucleotide polymorphisms (SNPs) for Mendelian randomization (MR) analysis. The inverse-variance weighted (IVW) method was used as the main analytical method. Sensitivity analyses were conducted to evaluate reliability of research findings.

Results: Our research results indicated that 10 immunophenotypes can increase risk of hypertrophic scars, 5 immunophenotypes can decrease risk of hypertrophic scars, 3 inflammatory cytokines can increase risk of hypertrophic scars, and 2 inflammatory cytokines can decrease risk of hypertrophic scars. Meanwhile, 5 immunophenotypes can increase risk of keloids, 4 immunophenotypes can decrease risk of keloids, 1 inflammatory cytokine can increase risk of keloids, and 1 inflammatory cytokine can decrease risk of keloids.

Conclusion: This study reveals the roles of immune phenotypes and cytokines in the pathogenesis of pathological scars, and provides valuable references in research areas such as early identification and intervention treatment of pathological scars.

Keywords: Mendelian randomization, pathological scars, immune cells, inflammatory cytokines

Introduction

Pathological scars are the products of abnormal repair during the wound healing process. Abnormal scars, namely hypertrophic scars or keloids, may form during the healing process of some injuries, which are collectively referred to as pathological scars.[1] Pathological scars can occur in any part of the body, affecting approximately 30–90% of the population.[2] Furthermore, pathological scars often cause problems such as pain, itching, and cosmetic defects, bringing severe physical and psychological distress to patients.[3,4] Since there are still problems such as unsatisfactory treatment effects and high recurrence rates in the treatment of pathological scars, there is an urgent need to develop more effective treatment methods.[5]

The specific pathogenesis of pathological changes remains unclear at present. It may be related to genetic factors, immune factors, altered cytokine expression, and environmental factors.[6–8] Both hypertrophic scars and keloids demonstrate genetic susceptibility and familial recurrence. Genetic factors play a significant role in the pathogenesis of pathological scars.[9,10] The pathological scars are closely associated with the immune cells and inflammatory cytokines.[11,12] Compared with normal tissues, the levels of macrophages, T cells, and mast cells are all elevated in scar tissues. In addition, cytokines such as IL - 6, IL - 8, chemokine like factor-1, and prostaglandins produced by cyclooxygenase (COX - 1) are significantly elevated in scar tissue.[13,14] Nishiguchi et al demonstrated that the chemokine CXC chemokine ligand-12 (CXCL12) promotes scar formation in mice, whereas the knockout of CXCL12 inhibits this process.[15] A study demonstrates that IL-10 can mitigate scar formation by decreasing the deposition of extracellular

Received: 2 April 2025
Accepted: 12 July 2025
Published: 29 July 2025

matrix (ECM) proteins and inhibiting the transformation of fibroblasts into myofibroblasts.[16] Mice with a double deficiency of IL - 10 and IL - 4 exhibited an inflammatory response, with significantly aggravated scar formation. In contrast, mice that received recombinant human IL - 10 showed reduced inflammation and scarring.[17] Cytokines serve as crucial mediators through which immune cells perform their functions, and an imbalance in cytokine levels is closely linked to abnormal scar formation. However, the causality between various immune cells, inflammatory cytokines and pathological scars are currently unclear.

We often utilize genetic data to infer causality through Mendelian randomization (MR) analysis. MR analysis can circumvent potential confounding factors and demonstrate a significant causal association. This study is the first to explore the causality among 731 immune cells, 91 inflammatory cytokines, and pathological scars through MR analysis, providing novel directions into the inflammatory immune mechanisms and treatment of pathological scars.

Methods

Study Design

The data were derived from the summary statistics of genome-wide association studies (GWAS). This analysis necessitated the fulfillment of three primary assumptions: (1) Exposure factors are strongly correlated with instrumental variables (IVs); (2) There are no known confounding factors associated with either exposure or outcome; and (3) IVs only affect outcomes when they are associated with exposure factors (Figure 1).

Date Sources

The data concerning immune cell phenotypes were sourced from the GWAS database.[18] The data on 91 circulating cytokines can be found in a GWAS involving 14,824 subjects of European population.[19] The GWAS data of hypertrophic scars were sourced from the latest FinnGen database, including 2068 cases and 465673 controls. The GWAS data of keloids were derived from a previously conducted meta-analysis, including 668 cases and 481,244 controls.[20]

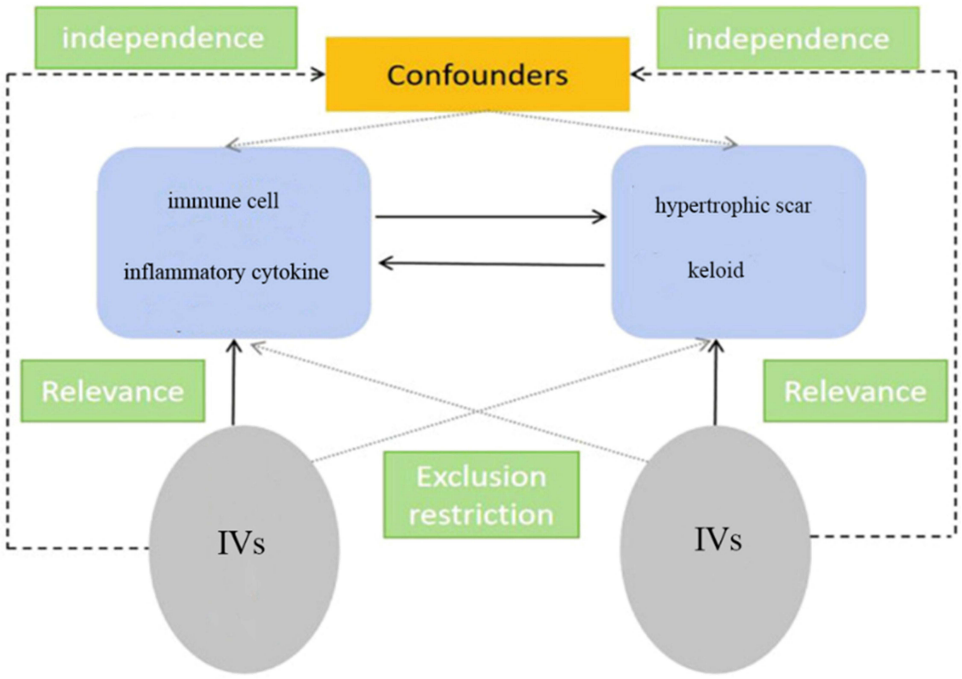

Figure 1 Key assumptions diagram for bidirectional MR analysis.

Selection of IVs

In this study, a significance threshold of $P < 1.0\times10^{-5}$ was set to screen out single - nucleotide polymorphisms (SNPs) that were associated with immune cells.[21] We selected a P - value of $5\times10^{-}$□ as the threshold to screen out SNPs associated with inflammatory cytokines.[22] Furthermore, the analysis of linkage disequilibrium was conducted using the following threshold ($r^2 = 0.001$, kb = 10,000).[23] The palindromic SNPs were excluded, and the IVs was assessed using the F-statistic ($F > 10$) to ensure that the exposure factors were strongly related to the obtained IVs.[24] We employed a threshold of (5×10^{-6}) to screen out SNPs associated with pathological scars ($r^2 = 0.001$ and kb = 10,000).[25]

Statistical Analysis

The inverse-variance weighted (IVW) method was used as a primary analytical method.[26] To control potential false positives, we applied the false discovery rate (FDR) method to perform multiple testing on the results. A p - value < 0.05 suggested a suggestive causality, while an FDR - adjusted p - value < 0.05 indicated a significant causality.[27]

Sensitivity Analysis

The Cochran's Q test was used to identify heterogeneity.[28] Furthermore, horizontal pleiotropy was assessed using MR-Egger regression ($P < 0.05$ considered to indicate horizontal pleiotropy.[29] The leave - one - out method is employed to assess the stability of the research data.[30]

Reverse MR Analysis

Hypertrophic scars and keloids were used as exposure factors, and immune cells and inflammatory cytokines were used as outcome variables. We used the IVW method as the main analytical method to analyze the reverse causality of pathological scars acting on immune cells and inflammatory cytokines.

Results

Causal Effect of Immune Cells and Inflammatory Cytokines on Hypertrophic Scars

Our analysis showed that 15 of these immune cells were suggestively associated with hypertrophic scars, including 10 risk factors and 5 protective factors. Our research findings revealed that Resting CD4 regulatory T cell %CD4 regulatory T cell, CD25++ CD4+ T cell %T cell, CD25 on CD45RA- CD4 not regulatory T cell, HLA DR on CD14+ CD16+ monocyte, CD45RA on naive CD4+ T cell, T cell Absolute Count, CD25 on transitional B cell, CD27 on IgD+ CD38- unswitched memory B cell, SSC-A on Natural Killer, and CD16-CD56 on Natural Killer show a positive correlation with the risk of hypertrophic scars, while CD20 on IgD+ CD38+ B cell, HLA DR on CD14+ CD16- monocyte, HLA DR++ monocyte %monocyte, CD8+ T cell %T cell, and HLA DR on CD14+ monocyte show a negative correlation with the risk of hypertrophic scars (Figure 2) (Table S1).

Our analysis showed that 5 inflammatory cytokines were suggestively associated with hypertrophic scars, including 3 risk factors and 2 protective factors. Programmed cell death 1 ligand 1 (PD-L1) levels, Stem cell factor (SCF) levels and Glial cell line-derived neurotrophic factor (GDNF) levels may increase the risk of hypertrophic scars, while TNF-related apoptosis-inducing ligand (TRAIL) levels and Eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) levels may reduce the risk of hypertrophic scars (Figure 3) (Table S2).

Causal Effect of Immune Cells and Inflammatory Cytokines on Keloids

Our analysis showed that 9 of these immune cells were suggestively associated with keloids, including 5 risk factor and 4 protective factors. Our research findings revealed that CD19 on naive-mature B cell, CD86 on CD62L+ myeloid Dendritic Cell, CD45 on Natural Killer T, CD25 on CD39+ CD4 regulatory T cell, and CD45RA on resting CD4 regulatory T cell show a positive correlation with the risk of keloids, while Plasmacytoid Dendritic Cell Absolute Count, Activated & secreting CD4 regulatory T cell Absolute Count, CD25 on unswitched memory B cell, CD3 on Central Memory CD8+ T cell show a negative correlation with the risk of keloids (Figure 4) (Table S3).

Exposure	Outcome	Methods	nSNP	OR (95% CI)	P
Resting CD4 regulatory T cell %CD4 regulatory T cell	hypertrophic scars	Inverse variance weighted	29	1.038 (1.004 to 1.073)	0.029
		MR Egger	29	1.055 (1.011 to 1.100)	0.020
		Simple mode	29	1.045 (0.969 to 1.126)	0.263
		Weighted median	29	1.040 (0.995 to 1.086)	0.081
		Weighted mode	29	1.039 (0.999 to 1.080)	0.065
CD25++ CD4+ T cell %T cell	hypertrophic scars	Inverse variance weighted	19	1.099 (1.015 to 1.189)	0.020
		MR Egger	19	1.076 (0.965 to 1.198)	0.204
		Simple mode	19	1.097 (0.922 to 1.305)	0.309
		Weighted median	19	1.074 (0.960 to 1.203)	0.213
		Weighted mode	19	1.092 (0.976 to 1.223)	0.143
CD25 on CD45RA− CD4 not regulatory T cell	hypertrophic scars	Inverse variance weighted	26	1.101 (1.043 to 1.162)	0.001
		MR Egger	26	1.087 (1.013 to 1.166)	0.029
		Simple mode	26	1.071 (0.952 to 1.205)	0.265
		Weighted median	26	1.071 (0.994 to 1.155)	0.072
		Weighted mode	26	1.075 (1.012 to 1.142)	0.027
HLA DR on CD14+ CD16+ monocyte	hypertrophic scars	Inverse variance weighted	19	1.042 (1.005 to 1.080)	0.025
		MR Egger	19	1.042 (0.994 to 1.092)	0.107
		Simple mode	19	1.036 (0.961 to 1.116)	0.372
		Weighted median	19	1.048 (0.997 to 1.101)	0.067
		Weighted mode	19	1.041 (0.997 to 1.086)	0.085
CD45RA on naive CD4+ T cell	hypertrophic scars	Inverse variance weighted	32	1.052 (1.003 to 1.105)	0.039
		MR Egger	32	1.060 (0.994 to 1.129)	0.085
		Simple mode	32	1.074 (0.938 to 1.229)	0.309
		Weighted median	32	1.046 (0.979 to 1.118)	0.183
		Weighted mode	32	1.046 (0.984 to 1.111)	0.156
T cell Absolute Count	hypertrophic scars	Inverse variance weighted	17	1.156 (1.053 to 1.270)	0.002
		MR Egger	17	1.062 (0.906 to 1.244)	0.471
		Simple mode	17	1.172 (0.918 to 1.495)	0.220
		Weighted median	17	1.179 (1.025 to 1.356)	0.021
		Weighted mode	17	1.142 (0.966 to 1.349)	0.140
CD25 on transitional B cell	hypertrophic scars	Inverse variance weighted	22	1.106 (1.013 to 1.208)	0.025
		MR Egger	22	1.087 (0.950 to 1.243)	0.240
		Simple mode	22	1.014 (0.833 to 1.234)	0.895
		Weighted median	22	1.028 (0.903 to 1.170)	0.678
		Weighted mode	22	1.033 (0.897 to 1.189)	0.657
CD27 on IgD+ CD38− unswitched memory B cell	hypertrophic scars	Inverse variance weighted	23	1.067 (1.008 to 1.129)	0.026
		MR Egger	23	1.105 (0.998 to 1.225)	0.069
		Simple mode	23	1.060 (0.936 to 1.201)	0.369
		Weighted median	23	1.131 (1.041 to 1.228)	0.004
		Weighted mode	23	1.131 (1.047 to 1.221)	0.005
CD25 on CD45RA− CD4 not regulatory T cell	hypertrophic scars	Inverse variance weighted	26	1.101 (1.043 to 1.162)	0.001
		MR Egger	26	1.087 (1.013 to 1.166)	0.029
		Simple mode	26	1.071 (0.952 to 1.205)	0.265
		Weighted median	26	1.071 (0.994 to 1.155)	0.072
		Weighted mode	26	1.075 (1.012 to 1.142)	0.027
CD16−CD56 on Natural Killer	hypertrophic scars	Inverse variance weighted	28	1.096 (1.023 to 1.174)	0.009
		MR Egger	28	1.091 (0.944 to 1.260)	0.249
		Simple mode	28	1.019 (0.875 to 1.187)	0.808
		Weighted median	28	1.035 (0.938 to 1.142)	0.490
		Weighted mode	28	1.023 (0.908 to 1.153)	0.715
HLA DR on CD14+ CD16− monocyte	hypertrophic scars	Inverse variance weighted	22	0.911 (0.854 to 0.972)	0.005
		MR Egger	22	0.934 (0.826 to 1.056)	0.286
		Simple mode	22	0.901 (0.753 to 1.079)	0.271
		Weighted median	22	0.941 (0.865 to 1.024)	0.158
		Weighted mode	22	0.940 (0.870 to 1.016)	0.132
HLA DR++ monocyte %monocyte	hypertrophic scars	Inverse variance weighted	21	0.899 (0.830 to 0.974)	0.009
		MR Egger	21	0.827 (0.716 to 0.955)	0.018
		Simple mode	21	0.898 (0.763 to 1.056)	0.206
		Weighted median	21	0.871 (0.779 to 0.975)	0.016
		Weighted mode	21	0.867 (0.776 to 0.969)	0.020
CD8+ T cell %T cell	hypertrophic scars	Inverse variance weighted	22	0.911 (0.844 to 0.984)	0.018
		MR Egger	22	0.914 (0.809 to 1.033)	0.164
		Simple mode	22	0.879 (0.715 to 1.080)	0.233
		Weighted median	22	0.919 (0.821 to 1.029)	0.142
		Weighted mode	22	0.915 (0.827 to 1.013)	0.102
HLA DR on CD14+ monocyte	hypertrophic scars	Inverse variance weighted	21	0.911 (0.853 to 0.973)	0.006
		MR Egger	21	0.930 (0.819 to 1.056)	0.276
		Simple mode	21	0.867 (0.726 to 1.036)	0.131
		Weighted median	21	0.939 (0.863 to 1.021)	0.143
		Weighted mode	21	0.938 (0.865 to 1.018)	0.139
CD20 on IgD+ CD38+ B cell	hypertrophic scars	Inverse variance weighted	26	0.912 (0.855 to 0.974)	0.006
		MR Egger	26	0.960 (0.873 to 1.055)	0.402
		Simple mode	26	0.958 (0.823 to 1.117)	0.592
		Weighted median	26	0.949 (0.860 to 1.046)	0.292
		Weighted mode	26	0.953 (0.875 to 1.038)	0.279

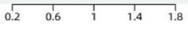

Figure 2 Association of immune cells with the risk of hypertrophic scars in MR analyses.
Abbreviations: CI, confidence intervals; OR, odds ratio.

Exposure	Outcome	Methods	nSNP	OR (95% CI)	P
Programmed cell death 1 ligand 1 levels	hypertrophic scars	Inverse variance weighted	26	1.327 (1.096 to 1.607)	0.004
		MR Egger	26	1.390 (0.886 to 2.182)	0.165
		Simple mode	26	1.324 (0.803 to 2.184)	0.282
		Weighted median	26	1.282 (0.965 to 1.704)	0.086
		Weighted mode	26	1.313 (0.868 to 1.985)	0.208
Stem cell factor levels	hypertrophic scars	Inverse variance weighted	45	1.157 (1.012 to 1.323)	0.032
		MR Egger	45	1.074 (0.843 to 1.369)	0.567
		Simple mode	45	1.050 (0.708 to 1.557)	0.810
		Weighted median	45	1.043 (0.860 to 1.264)	0.671
		Weighted mode	45	1.002 (0.802 to 1.253)	0.983
Glial cell line–derived neurotrophic factor levels	hypertrophic scars	Inverse variance weighted	21	1.006 (1.516 to 0.693)	0.044
		MR Egger	21	0.713 (1.434 to 0.996)	0.950
		Simple mode	21	0.684 (2.078 to 1.000)	0.541
		Weighted median	21	0.863 (1.437 to 0.895)	0.408
		Weighted mode	21	0.838 (1.406 to 0.974)	0.543
TNF–related apoptosis–inducing ligand levels	hypertrophic scars	Inverse variance weighted	37	0.846 (0.760 to 0.941)	0.002
		MR Egger	37	0.866 (0.728 to 1.030)	0.114
		Simple mode	37	0.745 (0.552 to 1.006)	0.063
		Weighted median	37	0.804 (0.684 to 0.945)	0.008
		Weighted mode	37	0.796 (0.660 to 0.961)	0.023
Eukaryotic translation initiation factor 4E–binding protein 1 levels	hypertrophic scars	Inverse variance weighted	18	0.749 (0.601 to 0.933)	0.010
		MR Egger	18	0.761 (0.427 to 1.357)	0.369
		Simple mode	18	0.739 (0.459 to 1.189)	0.229
		Weighted median	18	0.768 (0.563 to 1.047)	0.095
		Weighted mode	18	0.744 (0.514 to 1.077)	0.136

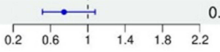

Figure 3 Association of inflammatory cytokines with the risk of hypertrophic scars in MR analyses.
Abbreviations: CI, confidence intervals; OR, odds ratio.

Our analysis showed that 2 inflammatory cytokines were suggestively associated with keloids, including 1 risk factor and 1 protective factor. Our research findings revealed that Urokinase-type plasminogen activator (uPA) levels may increase the risk of keloids, while Osteoprotegerin (OPG) levels may reduce the risk of keloids (Figure 5) (Table S4).

Causal Effect of Pathological Scars on Immune Cells and Inflammatory Cytokines

In the reverse causal analysis, the findings indicated that there was no significant causality between hypertrophic scars and 15 immune cells, and there was also no significant causality between hypertrophic scars and 5 inflammatory cytokines. In addition, there was no significant causality between keloids and 9 types of immune cells, nor was there a notable causality with 2 inflammatory cytokines (Tables S5–S6).

Sensitivity Analysis

The MR-Egger intercept indicated no significant horizontal pleiotropy ($p > 0.05$). IVW and MR-Egger results indicated the absence of heterogeneity ($p > 0.05$) (Table S7). The leave-one-out analysis, scatter plots and funnel plots also supported these findings (Figures S1–S12).

Discussion

Our research indicated that 15 immunophenotypes and 5 inflammatory cytokines exhibit potential causal relationships with hypertrophic scars. 10 immunophenotypes, including Resting CD4 regulatory T cell %CD4 regulatory T cell, CD25++ CD4+ T cell %T cell, etc., are identified as risk factors for hypertrophic scars. 5 immunophenotypes, including CD20 on IgD+ CD38+ B cell, HLA DR on CD14+ CD16- monocyte, etc., are identified as protective factors for hypertrophic scars. In addition, our research revealed that 9 immunophenotypes and 2 inflammatory cytokines exhibit potential causal relationships with keloids. 5 immunophenotypes, including CD19 on naive-mature B cell, CD86 on CD62L+ myeloid Dendritic Cell, etc., are identified as risk factors for keloids. 4 immunophenotypes, including Plasmacytoid Dendritic Cell Absolute Count, Activated & secreting CD4 regulatory T cell Absolute Count, etc., are identified as protective factors for keloids.

Inflammatory cytokines play a vital role in the formation of scars. We explored the effects of 91 circulating cytokines on pathological scars. The finds showed that the PD-L1 levels, SCF levels and GDNF levels were risk factors for

Exposure	Outcome	Methods	nSNP	OR (95% CI)	P
CD19 on naive–mature B cell	keloids	Inverse variance weighted	28	1.089 (1.021 to 1.161)	0.009
		MR Egger	28	1.082 (0.998 to 1.173)	0.068
		Simple mode	28	1.053 (0.893 to 1.243)	0.542
		Weighted median	28	1.047 (0.962 to 1.140)	0.289
		Weighted mode	28	1.061 (0.984 to 1.144)	0.134
CD86 on CD62L+ myeloid Dendritic Cell	keloids	Inverse variance weighted	23	1.130 (1.023 to 1.249)	0.016
		MR Egger	23	1.224 (1.043 to 1.435)	0.022
		Simple mode	23	1.201 (0.963 to 1.498)	0.118
		Weighted median	23	1.148 (0.997 to 1.322)	0.056
		Weighted mode	23	1.168 (0.997 to 1.368)	0.068
CD45 on Natural Killer T	keloids	Inverse variance weighted	22	1.124 (1.026 to 1.230)	0.012
		MR Egger	22	1.113 (0.954 to 1.299)	0.189
		Simple mode	22	1.030 (0.825 to 1.285)	0.799
		Weighted median	22	1.153 (1.010 to 1.316)	0.036
		Weighted mode	22	1.158 (0.973 to 1.377)	0.113
CD25 on CD39+ CD4 regulatory T cell	keloids	Inverse variance weighted	17	1.173 (1.033 to 1.332)	0.014
		MR Egger	17	1.323 (1.033 to 1.695)	0.043
		Simple mode	17	1.061 (0.824 to 1.365)	0.653
		Weighted median	17	1.096 (0.919 to 1.307)	0.306
		Weighted mode	17	1.069 (0.870 to 1.314)	0.532
CD45RA on resting CD4 regulatory T cell	keloids	Inverse variance weighted	28	1.074 (1.013 to 1.139)	0.016
		MR Egger	28	1.108 (1.017 to 1.208)	0.027
		Simple mode	28	1.085 (0.962 to 1.225)	0.195
		Weighted median	28	1.084 (0.997 to 1.178)	0.060
		Weighted mode	28	1.090 (1.002 to 1.186)	0.055
Plasmacytoid Dendritic Cell Absolute Count	keloids	Inverse variance weighted	30	0.930 (0.874 to 0.989)	0.021
		MR Egger	30	0.928 (0.854 to 1.008)	0.088
		Simple mode	30	0.973 (0.829 to 1.143)	0.745
		Weighted median	30	0.919 (0.842 to 1.004)	0.061
		Weighted mode	30	0.941 (0.870 to 1.017)	0.134
Activated & secreting CD4 regulatory T cell Absolute Count	keloids	Inverse variance weighted	22	0.946 (0.900 to 0.995)	0.032
		MR Egger	22	0.935 (0.879 to 0.995)	0.046
		Simple mode	22	0.949 (0.848 to 1.061)	0.366
		Weighted median	22	0.927 (0.863 to 0.995)	0.036
		Weighted mode	22	0.930 (0.871 to 0.992)	0.038
CD25 on unswitched memory B cell	keloids	Inverse variance weighted	23	0.932 (0.875 to 0.993)	0.028
		MR Egger	23	0.957 (0.882 to 1.039)	0.308
		Simple mode	23	0.826 (0.703 to 0.970)	0.030
		Weighted median	23	0.941 (0.853 to 1.038)	0.225
		Weighted mode	23	0.947 (0.870 to 1.031)	0.224
CD3 on Central Memory CD8+ T cell	keloids	Inverse variance weighted	18	0.845 (0.740 to 0.965)	0.013
		MR Egger	18	0.727 (0.554 to 0.954)	0.035
		Simple mode	18	0.674 (0.479 to 0.948)	0.037
		Weighted median	18	0.890 (0.734 to 1.079)	0.235
		Weighted mode	18	0.895 (0.731 to 1.096)	0.298

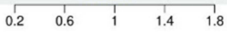

Figure 4 Association of immune cells with the risk of keloids in MR analyses.
Abbreviations: CI, confidence intervals; OR, odds ratio.

hypertrophic scars. In contrast, TRAIL levels and 4E-BP1 levels were protective factors for hypertrophic scars. Meanwhile, uPA levels was a risk factor for the occurrence of keloids, and OPG levels was a protective factor for the occurrence of keloids. We comprehensively explore the immune cells and inflammatory cytokines associated with pathological scars, aiming to provide references for future in - depth studies on the roles of immune cells and inflammatory cytokines in pathological scars.

The proportion of T regulatory (Treg) cells in keloid tissue was considerably higher.[31] Treg can inhibit effector T cells and M1 macrophages and impede the differentiation of M1 macrophages into M2 macrophages, thereby promoting a persistent inflammatory response.[32] We revealed that CD25 on CD39+ CD4 regulatory T cell and CD45RA on resting CD4 regulatory T cell might increase the risk of keloids, while Resting CD4 regulatory T cell might increase the risk of hypertrophic scars. During the wound - healing process, the proliferation and differentiation of fibroblasts, along with the massive deposition of collagen, jointly contribute to the formation of scars.[33,34] An in vitro experiment revealed that

Exposure	Outcome	Methods	nSNP	OR (95% CI)	P
Urokinase–type plasminogen activator levels	keloids	Inverse variance weighted	46	1.231 (1.048 to 1.446)	0.012
		MR Egger	46	0.994 (0.724 to 1.365)	0.972
		Simple mode	46	1.425 (0.976 to 2.081)	0.073
		Weighted median	46	1.157 (0.875 to 1.531)	0.306
		Weighted mode	46	1.214 (0.951 to 1.551)	0.126
Osteoprotegerin levels	keloids	Inverse variance weighted	30	0.701 (0.544 to 0.903)	0.006
		MR Egger	30	0.554 (0.324 to 0.946)	0.039
		Simple mode	30	0.544 (0.323 to 0.916)	0.029
		Weighted median	30	0.689 (0.507 to 0.936)	0.017
		Weighted mode	30	0.703 (0.527 to 0.939)	0.024

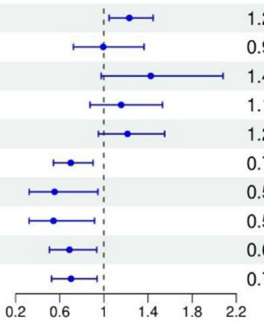

Figure 5 Association of inflammatory cytokines with the risk of keloids in MR analyses.
Abbreviations: CI, confidence intervals; OR, odds ratio.

CD4+ T cells from burn patients with scarring tendency could promote the proliferation of fibroblasts and the synthesis of collagen.[35] We revealed that CD25++ CD4+ T cell and CD45RA on naive CD4+ T cell might increase the risk of hypertrophic scars. The levels of CD28, CD80 and CD8+ T cell in the skin tissues of keloid patients are higher than those in healthy individuals. The binding of CD28 to its ligand CD80 further induces the activation and differentiation of T cells.[36] CD8+ T cells may inhibit keloid by suppressing fibroblast proliferation. It is noteworthy that we revealed that CD8+ T cell might decrease the risk of hypertrophic scars and CD3 on Central Memory CD8+ T cell might decrease the risk of keloids. CD8+ T cells may serve as a protective factor in inhibiting scar hyperplasia, but the specific mechanism of action remains to be further explored.

The number of monocytes increase significantly during the wound - healing process, and they further differentiate into macrophages and fibroblasts.[37] A study found that CD14+ monocytes promoted the proliferation of fibroblasts by releasing monocyte chemoattractant protein-1 (MCP-1), which in turn contributes to keloid formation.[38] HLA-DR is frequently utilized as a marker to assess the activation or maturation status of monocytes.[39] We revealed that HLA DR on CD14+ CD16- monocyte, HLA DR++ monocyte, and HLA DR on CD14+ monocyte might decrease the risk of hypertrophic scars. Natural killer (NK) cells can defend against viral infections and the development of malignancies by destroying target cells.[40] We revealed that SSC-A on Natural Killer and CD16-CD56 on Natural Killer might increase the risk of hypertrophic scars. However, high-quality relevant studies are still necessary to further confirm these research findings.

PD-L1 can inhibit the inflammatory and accelerate wound healing by regulating the expression of fibroblast-like cells.[41] This study reveals that there is an interaction between PD-L1 and fibroblast-like cells, but the impact on scars still needs further research. SCF is important in the wound healing process. The level of SCF is notably increased in keloid tissues and fibroblasts.[42,43] We revealed that SCF can increase the risk of hypertrophic scars. SCF may serve as a potential therapeutic target for pathological scars. GDNF is a neurotrophic factor. A previous study showed that GDNF can promote hair follicle neogenesis and skin regeneration by regulating dermal fibroblasts. However, the relationship between GDNF and scar formation still needs further exploration.

uPA and its receptor play vital regulatory roles in cellular processes such as tissue remodeling and cell migration. A study found that uPA receptor is highly expressed in the extracellular matrix of keloid tissue.[44] The results of another trial conducted on patients with hypertrophic scars showed that the level of uPA in scars was notably increased.[45] We revealed that uPA can increase the risk of keloids, and uPA is closely related to scar formation. However, further relevant clinical studies are still needed to confirm the above results. A previous study suggested that the content of OPG increased during the process of culturing keloid fibroblasts.[46] OPG is associated with the formation of keloids. We revealed that OPG can decrease the risk of keloids. Conversely, there is still a lack of studies on the correlation between OPG and keloids to confirm the conclusion of this study.

PD- L1 is expressed on T cells following stimulation of the T-cell receptor.[47] Another research result indicated that following co-activation with human dendritic cells, human naive CD4+ effector T cells and CD4+ regulatory T cells exhibit elevated PD-L1 expression.[48] The expression of PD-L1 on activated CD4+ T cells facilitates its interaction with

ligands such as PD-1 and CD80.[49,50] The proliferation and differentiation of CD8+ T cells into effector and memory states are energy-intensive processes that involve significant changes in cellular metabolism. The 4E-BP1 protein plays a crucial role in the proliferation of murine CD8+ T cells and in the development of antiviral effector functions.[51] CD8+ T cells eliminate abnormal cells and maintain homeostasis by mediating TRAIL-induced apoptosis in target cells. uPA plays a crucial role in cell activation, adhesion, and migration, and is highly expressed in macrophages and dendritic cells.[52] Immune cells and inflammatory cytokines exhibit complex interactions in pathological scars, further in-depth research on the underlying mechanisms is necessary.

This research investigates the causality between 731 immune cells, 91 inflammatory cytokines and pathological scars. However, this article still has a few drawbacks. The GWAS data is originated solely from European populations, the generalizability of the conclusion of this study to patients of other ethnicities is limited. After FDR correction, our research results showed no statistically significant differences. The findings presented in this paper should be interpreted with caution. The pathogenesis of pathological scars remains unclear. Therefore, large-scale, multicenter studies are necessary in the future to validate the findings of this study.

Conclusion

This study reveals the roles of immune phenotypes and cytokines in the pathogenesis of pathological scars, and emphasizes the complex interactions among the immune system, cytokines, and pathological scars. The research findings of this paper offer a novel direction for future in - depth exploration of the pathogenesis of pathological scars and offers valuable references in research areas such as early identification and intervention treatment of pathological scars.

Ethics Statement

According to Article 32 of the Ethical Review Measures for Life Science and Medical Research Involving Human Beings of the People's Republic of China, the data used in this study will not cause any form of harm to human beings, nor will it touch sensitive personal privacy or trade secrets, so the ethical review can be exempted. The database used in this study was publicly available and legally available.

Funding

There is no funding for this study.

Disclosure

The authors declare no conflicts of interest.

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