

Role of Pyroptosis and Immune Infiltration in Keloids: Novel Insights from Bioinformatics Analyses

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Abstract

Keloids are fibroproliferative scars characterized by persistent growth beyond the original wound boundary after skin injury, often causing deformity and functional impairment. Pyroptosis, a pro-inflammatory form of programmed cell death, has been implicated in multiple diseases, but its role in keloids remains unclear. In this study, we investigated pyroptosis-related genes in keloids using integrated bioinformatics and experimental validation. A total of 23 pyroptosis-related differentially expressed genes (PRDEGs) were identified from the GSE145725 dataset. Regulatory network analysis revealed complex PRDEG-associated transcription factor and miRNA interactions. A diagnostic model based on VCAM1, CASP4, CD14, NLRP1, and MALT1 showed good performance, with an area under the curve of 1.000 in the training set and 0.7407 in the external validation set. Immune infiltration analysis showed significantly decreased APC co-inhibition, B-cell abundance, inflammation-promoting signatures, and T-cell co-inhibition, but increased Th1-cell infiltration in keloids. PRDEGs were closely associated with interferon responses and Th1-related immune features. Experimental validation showed that baseline NLRP3 expression was lower in keloid fibroblasts than in normal skin fibroblasts, and that keloid fibroblasts exhibited a weaker pyroptotic response to LPS/nigericin stimulation. Pyroptosis induction increased IL-1 β and IL-18 secretion and inhibited fibroblast proliferation, whereas NLRP3 inhibition produced the opposite effect. In addition, MALT1 and VCAM1 were associated with dendritic cell maturation in a co-culture system. These findings suggest that pyroptosis is dysregulated in keloids and closely associated with immune infiltration. Activation of pyroptosis may suppress keloid fibroblast proliferation and represent a potential therapeutic strategy for keloids.

Introduction

Keloids are fibroproliferative scars characterized by persistent growth beyond the original wound boundary after skin injury [1]. They occur frequently on the face, trunk, and joints and may cause deformity, functional impairment, and recurrent inflammation [2, 3]. Because of their high recurrence rate, surgical excision alone is often ineffective, and current adjuvant therapies such as corticosteroid injection provide limited benefit [3, 4]. The unclear pathogenesis of keloids remains a major obstacle to effective treatment.

Pyroptosis is a pro-inflammatory form of programmed cell death mediated by inflammasome activation, gasdermin cleavage, membrane pore formation, and release of inflammatory cytokines [5, 6]. In addition to the canonical caspase-1 pathway and the non-canonical caspase-11/4/5 pathway, pyroptosis can also be regulated by multiple inflammatory and stress-related signals [7–11]. Because dysregulated cell death contributes to abnormal tissue remodeling, pyroptosis may be involved in fibroproliferative diseases.

Keloids share features of chronic inflammation, immune dysregulation, and tumor-like growth [12–16]. However, the role of pyroptosis in keloid formation remains unclear. In this study, we performed integrated bioinformatics analyses of GEO datasets to identify pyroptosis-related genes in keloids,

construct a diagnostic model, and characterize immune infiltration patterns. We further validated representative genes and explored their potential roles in pyroptosis-associated immune regulation.

Methods

Data acquisition and differential expression analysis

Gene expression datasets related to keloids were downloaded from the GEO database. GSE145725 was used as the training dataset and GSE44270 as the external validation dataset. GSE145725, generated on the GPL16043 platform, included 19 samples, comprising 10 controls and 9 keloids. GSE44270, generated on the GPL6244 platform, was used for external validation. GSE188952 was additionally analyzed to compare keloids with hypertrophic scars. Datasets were included if they contained human samples, available expression matrices and platform annotation, and clearly defined comparison groups.

A pyroptosis-related gene set containing 436 genes was obtained from the GeneCards database. Differential expression analysis of GSE145725 was performed using the “limma” package in R. Genes with $P < 0.05$ and $|\log_2FC| > 0.585$ were considered differentially expressed genes (DEGs). Volcano plots, heatmaps, and Venn diagrams were generated using the “ggplot2”, “pheatmap”, and “VennDiagram” packages, respectively. GEO2R was used to analyze GSE188952.

Identification of pyroptosis-related differentially expressed genes

Pyroptosis-related differentially expressed genes (PRDEGs) were identified by intersecting the DEGs from GSE145725 with the pyroptosis-related gene set. These PRDEGs were used for enrichment analysis, network construction, diagnostic modeling, immune infiltration analysis, and experimental validation.

Functional enrichment and regulatory network analyses

GO and KEGG enrichment analyses were performed using the “clusterProfiler” package in R, with $P < 0.05$ considered statistically significant. Protein–protein interaction data for PRDEGs were obtained from the STRING database and visualized in Cytoscape.

To explore upstream regulatory mechanisms, transcription factor-related regulatory relationships were obtained from the TRRUST, hTFtarget, and RegNetwork databases. Gene–transcription factor and gene–miRNA interaction networks were visualized using Cytoscape.

Construction and validation of the diagnostic model

The GSE145725 dataset was used as the training set, and GSE44270 was used as the external validation set. The 23 PRDEGs were subjected to least absolute shrinkage and selection operator (LASSO)

regression for feature selection and diagnostic model construction. A risk score was calculated based on gene expression values and regression coefficients. Receiver operating characteristic (ROC) curve analysis was performed to evaluate diagnostic performance in the training and external validation datasets. ElasticNet regression was additionally used for comparison. MALT1 and VCAM1 were selected for further validation because they had the largest absolute coefficients in the diagnostic model and showed strong associations with Th1-related immune features.

Immune infiltration analysis

Single-sample gene set enrichment analysis (ssGSEA) was performed to estimate the relative abundance of immune cells and immune-related functions in each sample. Correlations among immune cell populations and between key genes and immune infiltration signatures were evaluated using Spearman's correlation and visualized in R.

Cell culture and pyroptosis induction

Mouse keloid fibroblasts (MKFBs) and DC2.4 cells were purchased from Guangzhou Novel Biotechnology Co., Ltd. Human keloid fibroblasts (KFBs) and normal skin fibroblasts (NSFBs) were obtained from Wuhan Pricella Biotechnology Co., Ltd. and the National Collection of Authenticated Cell Cultures, respectively. Cells were cultured at 37°C in 5% CO₂.

MKFBs were identified by immunofluorescence staining with an anti-vimentin antibody (Proteintech, 10366-1-AP), followed by Alexa Fluor 488-conjugated secondary antibody (Abcam, ab150077) and DAPI staining. To induce pyroptosis, cells were treated with LPS followed by nigericin. For inhibition experiments, cells were pretreated with NLRP3-IN-13 for 24 h before LPS/nigericin stimulation.

Plasmid transfection and co-culture assay

MALT1 knockdown and VCAM1 overexpression were performed in MKFBs using the corresponding plasmids and Lipofectamine 3000 (Invitrogen, L3000015) according to the manufacturer's instructions. After transfection, cells were exposed to LPS/nigericin and then co-cultured with DC2.4 cells at 1×10^5 /mL for 24 h.

For flow cytometry, cells were stained with FITC anti-mouse CD11c antibody (Elabscience, E-AB-F0991C) and PE-conjugated CD86 antibody. Blank and single-stain controls were included. Samples were analyzed using a CytoFLEX S flow cytometer (Beckman Coulter).

Quantitative real-time PCR

Total RNA was extracted using TRIzol reagent (Invitrogen), and cDNA was synthesized using the PrimeScript RT Reagent Kit (Takara Bio, Japan). Quantitative real-time PCR was performed using a 20 µL

reaction system, with GAPDH as the internal control. Relative gene expression levels were calculated using the $2^{-\Delta\Delta C_t}$ method. All experiments were performed in triplicate.

Primer sequences (5'–3') were as follows: MALT1-F, CACAGAACTGAGCGACTTCCT; MALT1-R, CAGCCAACACTGCCTTGGA; VCAM1-F, AGTTGGGGATTTCGGTTGTTCT; VCAM1-R, CCCCTCATTCTTACCACCC; GAPDH-F, TGTAGACCATGTAGTTGAGGTCA; GAPDH-R, AGGTCGGTGTGAACGGATTTG.

Western blotting, ELISA, and cell proliferation assay

For western blotting, equal amounts of protein were separated by SDS-PAGE, transferred onto PVDF membranes, and incubated with primary antibodies against NLRP3, caspase-1, GSDMD, and GAPDH, followed by appropriate secondary antibodies. IL-1 β and IL-18 levels in cell culture supernatants were measured using ELISA kits according to the manufacturers' instructions. Cell proliferation was assessed using an MTT assay kit (Solarbio, Beijing, China). Cells were seeded into 96-well plates at a density of 3×10^3 cells per well. At the indicated time points, MTT solution was added, followed by DMSO, and absorbance was measured at 490 nm.

Statistical analysis

Statistical analyses were performed using R software and GraphPad Prism 8.0. Data are presented as mean $\pm$ SD. Student's t-test was used for comparisons between two groups, and one-way ANOVA was used for comparisons among multiple groups. Spearman's correlation analysis was used to evaluate associations between variables. A two-sided $P < 0.05$ was considered statistically significant.

Results

Identification of differentially expressed genes and pyroptosis-related genes

Using the GSE145725 dataset, which included 10 control samples and 9 keloid samples, we performed differential expression analysis with the "limma" package in R using a threshold of $P < 0.05$ and $|\log_2 FC| > 0.585$. A total of 1,061 differentially expressed genes were identified, including 520 upregulated and 541 downregulated genes (Fig. 1A, B). Intersecting these DEGs with the pyroptosis-related gene set yielded 23 pyroptosis-related differentially expressed genes, including 10 upregulated and 13 downregulated genes (Fig. 1C, Table 1).

Table 1
23 pyroptosis-related differentially expressed genes

Up-regulated Gene			Down-regulated Gene		
Gene Symbol	LogFC	P value	Gene Symbol	LogFC	P value
NLRP1	0.672114	2.60E-08	VCAM1	-4.37634	2.69E-15
MALT1	1.09485	1.44E-06	CD14	-2.10897	2.62E-07
VDR	0.745595	2.94E-06	CASP4	-0.59364	6.07E-05
MIR21	1.962424	0.000114	ATF6	-0.59857	0.000226
CITED2	0.937568	0.000155	PANX1	-0.7873	0.004697
ADORA1	0.724492	0.000588	MELK	-0.7059	0.005634
CHI3L1	1.090604	0.011351	SLC16A4	-1.34907	0.007781
XIST	1.845384	0.011728	IRF1	-0.761	0.01007
IL13RA2	2.243281	0.012008	FGF5	-0.94181	0.012875
IL1B	0.749899	0.021651	CDK1	-0.70269	0.013602
			BIRC3	-1.08331	0.027797
			VTN	-1.0003	0.035978
			GJA1	-0.92464	0.041427

Functional enrichment and regulatory network analyses

Functional enrichment analysis of the 23 PRDEGs showed that these genes were mainly involved in response to lipopolysaccharide, positive regulation of NIK/NF- κ B signaling, and T-cell proliferation. KEGG analysis indicated significant enrichment in the NF- κ B signaling pathway, NOD-like receptor signaling pathway, and TNF signaling pathway (Fig. 1D–E). A protein–protein interaction network was constructed using the STRING database and visualized in Cytoscape (Fig. 1F).

To further investigate upstream regulatory mechanisms, transcription factor-related regulatory networks were constructed using the TRRUST, hTFtarget, and RegNetwork databases. These analyses identified multiple gene–transcription factor and gene–miRNA regulatory relationships involving the PRDEGs, suggesting a complex regulatory landscape associated with pyroptosis in keloids (Fig. 2).

Construction and validation of a diagnostic model

To identify characteristic genes associated with keloids, the 23 PRDEGs were subjected to LASSO regression using GSE145725 as the training set. Five genes were retained in the final model: VCAM1, CASP4, CD14, NLRP1, and MALT1 (Fig. 3A–C). The risk score formula was as follows:

Risk score = VCAM1 $\times$ (– 0.322472926985684) + CASP4 $\times$ (– 0.0577799583890575) + CD14 $\times$ (– 0.0276913153496275) + NLRP1 $\times$ 0.00364998517640558 + MALT1 $\times$ 0.0754397665558227.

The model showed excellent diagnostic performance in the training set, with an AUC of 1.000 (Fig. 3D). External validation using GSE44270 demonstrated acceptable stability, with an AUC of 0.7407 (Fig. 3E).

To further assess the clinical relevance of the model, we analyzed GSE188952 to compare keloids with hypertrophic scars. Among the five model genes, CD14 was significantly downregulated in keloids relative to hypertrophic scars, with a log2 fold change of – 1.877. Because differentiation between keloids and hypertrophic scars is important in clinical practice, this finding further supported the diagnostic value of the model.

We also compared LASSO with ElasticNet regression. Although ElasticNet achieved an AUC of 1.000 in the training set, its performance in the external validation set decreased to 0.56, indicating that the LASSO-based model was more robust (Fig. 3F, G).

Association between PRDEGs and immune infiltration

To explore the immune landscape of keloids, ssGSEA was used to estimate immune cell infiltration in each sample. Significant correlations were observed among multiple immune cell populations (Fig. 4A,B). Compared with the control group, the keloid group showed significantly lower levels of APC co-inhibition, B cells, inflammation-promoting signatures, and T-cell co-inhibition, but a significantly higher level of Th1 cells (Fig. 4C).

Correlation analysis further showed that the five model genes were closely associated with immune infiltration patterns (Fig. 4D–H). CD14 expression was positively correlated with the type II IFN response, inflammation-promoting signatures, B cells, APC co-inhibition, T-cell co-inhibition, APC co-stimulation, checkpoint activity, plasmacytoid dendritic cells, and CD8 + T cells. MALT1 expression was positively correlated with Th1 cells, tumor-infiltrating lymphocytes, neutrophils, CCR, parainflammation, and the type I IFN response, but negatively correlated with B cells. NLRP1 expression was positively correlated with neutrophils, CCR, tumor-infiltrating lymphocytes, and Th1 cells, but negatively correlated with the type II IFN response. VCAM1 expression was positively correlated with B cells, APC co-inhibition, T-cell co-inhibition, and CD8 + T cells, but negatively correlated with Th1 cells. CASP4 expression was positively correlated with B cells, T-cell co-inhibition, APC co-inhibition, and the type II IFN response.

Because MALT1 and VCAM1 had the largest absolute coefficients in the diagnostic model and showed close associations with Th1-related immune features, they were selected for experimental validation.

Experimental validation of MALT1- and VCAM1-mediated immune regulation

To validate the bioinformatics findings, MALT1 was knocked down and VCAM1 was overexpressed in mouse keloid fibroblasts (MKFBs) (Fig. 5A,B). The transfected MKFBs were then treated with LPS and

nigericin to induce pyroptosis and subsequently co-cultured with DC2.4 dendritic cells. The experimental groups were as follows: DC2.4 alone; DC2.4 + MKFBs; DC2.4 + MKFBs + LPS/nigericin; DC2.4 + MKFBs + LPS/nigericin + sh-NC; DC2.4 + MKFBs + LPS/nigericin + sh-MALT1; DC2.4 + MKFBs + LPS/nigericin + OE-vector; and DC2.4 + MKFBs + LPS/nigericin + OE-VCAM1.

Flow cytometry was used to detect CD11c+CD86 + cells as an indicator of dendritic cell maturation (Fig. 5C). Compared with DC2.4 cells cultured alone, co-culture with MKFBs promoted dendritic cell maturation. This effect was further enhanced after pyroptosis induction in MKFBs. However, MALT1 knockdown markedly reduced the proportion of mature dendritic cells, whereas VCAM1 overexpression also inhibited dendritic cell maturation. These results suggest that pyroptosis-related genes may modulate the immune microenvironment of keloids by influencing dendritic cell activation.

Validation of pyroptosis activation and inhibition in fibroblasts

To further explore the role of pyroptosis in keloids, human normal skin fibroblasts (NSFBs) and keloid fibroblasts (KFBs) were cultured and compared. No obvious morphological differences were observed between the two cell types under routine culture conditions (Fig. 6A).

After treatment with LPS and nigericin, as well as pretreatment with NLRP3-IN-13, the expression of NLRP3, caspase-1, and GSDMD was assessed by western blotting (Fig. 6B–E). Baseline NLRP3 expression was lower in KFBs than in NSFBs. LPS/nigericin stimulation increased pyroptosis-related protein expression in both cell types, whereas NLRP3-IN-13 reduced this effect. Overall, NSFBs showed a stronger response to pyroptosis induction than KFBs.

ELISA showed no significant baseline differences in IL-1 β or IL-18 levels between NSFBs and KFBs (Fig. 6F). However, LPS/nigericin treatment significantly increased IL-1 β and IL-18 secretion in both cell types, with a greater increase observed in NSFBs. These increases were attenuated by NLRP3-IN-13.

MTT assays showed no significant difference in baseline proliferation between NSFBs and KFBs (Fig. 6G). Pyroptosis induction inhibited proliferation in both cell types, whereas NLRP3-IN-13 promoted proliferation, with a more pronounced effect in KFBs. NSFBs were more sensitive than KFBs to LPS/nigericin-induced growth suppression.

Discussion

Pyroptosis is a caspase-dependent inflammatory form of programmed cell death originally described in immune cells [17]. It is generally classified into canonical and non-canonical pathways [18]. In the canonical pathway, inflammasomes such as NLRP3, NLRC4, AIM2, and pyrin activate caspase-1, which cleaves GSDMD to form membrane pores and trigger cell lysis. Caspase-1 also processes pro-IL-1 β into mature IL-1 β , thereby amplifying inflammatory signaling [19–21]. In the non-canonical pathway, caspase-4/5/11 directly senses LPS and initiates pyroptotic signaling, often with secondary activation of NLRP3

[23]. Although pyroptosis has been widely studied in inflammatory and neoplastic diseases, its role in keloids has remained unclear.

Keloids are characterized by persistent fibroblast proliferation, excessive extracellular matrix deposition, and chronic inflammation. Current treatments, including surgery, corticosteroids, and 5-fluorouracil, are limited by recurrence, incomplete efficacy, and restricted use in some patient groups. Therefore, identifying cell death-related mechanisms that suppress keloid growth may provide new therapeutic opportunities.

Our findings suggest that pyroptosis is relatively suppressed in keloids. Bioinformatics analysis showed dysregulation of multiple pyroptosis-related genes, including decreased expression of several pro-pyroptotic factors such as VCAM1, CASP4, and PANX1. Although NLRP1 and IL1B were upregulated at the transcript level, experimental validation did not show a corresponding increase in IL-1 β secretion in keloid fibroblasts under basal conditions. In addition, key terminal markers of pyroptosis, including GSDMD and IL-18, were not significantly elevated in keloid fibroblasts compared with normal skin fibroblasts (NSFBs). After LPS/nigericin stimulation, keloid fibroblasts (KFBs) showed a weaker pyroptotic response than NSFBs, further supporting the possibility that pyroptosis is inhibited in keloids.

These observations may help explain why KFBs maintain excessive proliferative capacity. If pyroptosis is impaired, abnormal fibroblasts may evade inflammatory cell death and continue to accumulate, contributing to scar overgrowth. Consistent with this interpretation, induction of pyroptosis by activating the NLRP3 pathway increased the expression of pyroptosis-related proteins and inflammatory cytokines and suppressed fibroblast proliferation. In contrast, inhibition of this pathway alleviated these effects. These results indicate that restoring pyroptotic signaling may represent a potential strategy to limit keloid progression.

We also developed a diagnostic model based on five pyroptosis-related genes: VCAM1, CASP4, CD14, NLRP1, and MALT1. The model showed excellent performance in the training dataset and acceptable performance in the external validation dataset, supporting the potential diagnostic value of pyroptosis-related signatures in keloids. Because keloids and hypertrophic scars can present similarly in clinical practice, such molecular models may assist in diagnosis, although further validation in larger cohorts and direct modeling against hypertrophic scars are still needed.

Another important finding of this study was the association between pyroptosis-related genes and immune infiltration. Enrichment analysis indicated that these genes were related to T-cell proliferation and inflammatory signaling. Immune infiltration analysis further showed altered Th1 cells, T-cell co-inhibition, and other immune signatures in keloids. The five model genes, especially MALT1 and VCAM1, were closely associated with Th1-related immune features and interferon responses. Because Th1 cells and IFN- γ are known to influence collagen synthesis and fibrotic remodeling [25], these data suggest that pyroptosis-related genes may contribute to keloid development not only by regulating fibroblast death but also by shaping the immune microenvironment.

Based on both the model coefficients and immune correlation analyses, MALT1 and VCAM1 were selected for experimental validation. Functional assays showed that modulation of these genes influenced dendritic cell maturation in the co-culture system, further supporting a link between pyroptosis-related gene expression and immune regulation in keloids. These findings suggest that pyroptosis-related pathways may affect both fibroblast behavior and local immune responses during keloid formation.

This study has several limitations. The public datasets were relatively small, and the diagnostic model requires validation in larger independent cohorts. In addition, although our experiments support a suppressive role of impaired pyroptosis in KFBs, the precise molecular mechanisms linking pyroptosis, fibroblast proliferation, and immune infiltration remain to be clarified. Further in vivo studies and mechanistic experiments are needed.

Conclusion

In conclusion, our study indicates that pyroptosis is dysregulated and likely suppressed in keloids. Pyroptosis-related genes are associated with diagnostic potential and immune infiltration patterns, and activation of pyroptosis can inhibit KFB proliferation. These findings provide new evidence that pyroptosis-related pathways may serve as potential biomarkers and therapeutic targets in keloids.

Declarations

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Availability and Implementation

The data supporting the findings of this study are available from the corresponding author, Hang

Ji, upon request. The R studio software was downloaded from <https://www.rstudio.com/categories/rstudio-ide/>.

Competing interests

1. The authors declare that they have no competing interests.
2. All authors disclosed no relevant relationships
3. The authors declared no potential conflicts of interest with respect to the research, author- ship, and/or publication of this article.

Authors' contributions

Yeltai Nurzat and **Aybota Ahemet** conducted the experiments and wrote the manuscript with the support of **Hang Ji**, **Hang Ji** helped supervise the project and conceived the original idea. **All authors** discussed the results and contributed to the final manuscript.

Ethics approval and consent to participate

Ethics approval or specific consent procedures were not required for this study. All the data is from the public database.

Consent for publication

No identifying patient details are contained within this manuscript.

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