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Inhibiting IL11RA to mitigate hepatic metastasis in skin cutaneous melanoma: Comprehensive insights from in vitro and in vivo investigations

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Abstract

Objective: This study aimed to investigate the role of Interleukin-11 receptor alpha (IL11RA) in skin cutaneous melanoma (SKCM) metastasis to the liver.

Methods: Human SKCM cell lines (A375, A375-MA2, SK-MEL-28, RPMI-7951) and primary dermal fibroblasts (HDFa) were utilized to assess IL11RA expression. IL11RA siRNA was transfected into RPMI-7951 and A375-MA2 cells for Wound healing and Transwell invasion assays. Il11ra knockout (KO) mice and wild-type (WT) mice were injected with B16-F10 cells into the spleen to evaluate hepatic melanoma metastasis. Correlation between IL11RA and MMP family genes was explored using online databases, including LinkedOmics, TIMER (Tumor Immune Estimation Resource), and GEPIA (Gene Expression Profiling Interactive Analysis). RT-qPCR and Western blotting were performed for expression analysis of Mmp2 and Mmp9 in liver tissues of mice. The impact of IL11RA on the STAT3 pathway was investigated in vitro and in vivo.

Results: Elevated expression of IL11RA was observed in SKCM cell lines compared to normal cells. IL11RA downregulation significantly inhibited migratory and invasive capabilities of A375-MA2 and RPMI-7951 in vitro. Il11ra gene knockout in mice demonstrated a substantial reduction in hepatic melanoma metastasis. Correlation analyses revealed associations between IL11RA and MMP2/MMP8. Il11ra gene knockout significantly decreased Mmp2 expression while increasing Mmp8 in liver tissues. IL11RA correlated positively with STAT3, and its inhibition led to a suppressed STAT3 pathway in SKCM cells and mouse liver tissue.

Conclusion: IL11RA plays a crucial role in SKCM metastasis, affecting migratory and invasive abilities. Targeting IL11RA may offer a promising avenue for therapeutic interventions in cutaneous melanoma progression.

KEYWORDS
interleukin-11 receptor alpha, liver metastasis, skin cutaneous melanoma, STAT3 pathway

1 | INTRODUCTION

Melanoma, a malignancy originating from melanocytes, poses a significant global health concern. Among its various subtypes, skin cutaneous melanoma (SKCM) is the most prevalent, typically arising on sun-exposed skin areas.[1,2] Despite constituting only 4% of skin cancers, SKCM is responsible for a staggering 75% of skin cancer-related deaths, underscoring the critical need for early detection and intervention.[3] While advancements have improved outcomes, a subset of patients presents with metastatic disease at diagnosis or later develops metastasis, with the liver being a common site.[4,5] Liver metastases, occurring in 10%—20% of cutaneous melanoma patients, present unique challenges, emphasizing the urgency for innovative treatment strategies.[6,7]

Genetic analyses have identified frequent chromosomal loss at 9p13-p22 in melanoma, implicating Interleukin 11 receptor alpha (IL11RA) as a pivotal player encoded in this region.[8,9] IL11RA, situated in the IL-11/IL11RA signaling pathway, governs various biological processes, making it an attractive therapeutic target.[8] Disrupting IL-11/IL11RA interaction, with potential advantages over IL-6 targeting, has shown promise in preclinical models, particularly in gastrointestinal cancer.[10] The multifaceted role of IL11RA extends to influencing mesothelial-to-mesenchymal transition in ovarian cancer, suggesting its potential in precision therapy, including antibody-drug conjugates.[11] In early melanoma, IL11RA exhibits varied expression, potentially influencing the cytokine profile associated with metastasis to regional lymph nodes.[12] Notably, IL11RA overexpression in melanoma is linked to organ-specific metastasis to the liver, as evidenced by its significantly higher expression in tissues with liver metastasis.[13]

Despite these insights, the precise role of IL11RA in the progression of cutaneous melanoma, particularly its impact on liver metastasis, remains incompletely understood. This study aims to bridge this knowledge gap by investigating the specific contributions of IL11RA to melanoma metastasis, with a focus on its association with liver metastases. We hypothesize that IL11RA, implicated in various stages of melanoma development, plays a crucial role in promoting liver metastasis. The study seeks to unravel the underlying molecular mechanisms, explore potential therapeutic interventions targeting IL11RA, and contribute to the development of more effective treatment strategies for advanced cutaneous melanoma, especially those with liver metastases.

2 | METHODS AND MATERIALS

2.1 | Ethics statement

Approval for animal experiments was obtained from the hospital's Ethics Committee, and the experiments followed the Guide for the Care and Use of Laboratory Animals published by the National Academy of Sciences,[14] ensuring compliance with approved standards for animal care.

2.2 | Online databases

The investigation into the correlation between IL11RA and Matrix Metalloproteinases (MMP) family genes, as well as Signal Transducer and Activator of Transcription 3 (STAT3), in SKCM tissues involved comprehensive analysis through three prominent online databases: LinkedOmics ($n = 103$),[15] Gene Expression Profiling Interactive Analysis (GEPIA) ($n = 461$),[16] and Tumor Immune Estimation Resource (TIMER) with a focus on metastasis patients: $n = 368$).[17]

2.3 | Cell culture

The human A375 (Catalog No. CRL-1619), human A375-MA2 (Catalog No. CRL-3223), and mouse B16-F10 (Catalog No. CRL-6475) cell lines were maintained in Dulbecco's Modified Eagle's Medium (Catalog No. 30–2002). The human SK-MEL-28 cell line and RPMI-7951 (Catalog No. HTB-66) were cultured in Eagle's Minimum Essential Medium (Catalog No. 30–2003). Complete growth media were prepared by supplementing the base medium with fetal bovine serum (FBS) to achieve a final concentration of 10%. Additionally, the base medium for Primary Dermal Fibroblast; Normal, Human, Adult (HDFa, Catalog No. PCS-201-012) was Fibroblast Basal Medium (Catalog No. PCS-201-030). All cell lines and base media were procured from the American Type Culture Collection (ATCC, Manassas, VA, USA). All cells were incubated at 37°C, 95% air, and 5% CO_2.

2.4 | Cell transfection with IL11RA siRNA

During the logarithmic growth phase of RPMI-7951 and A375-MA2 cells, the cells were categorized into the mock group (cells cultured normally, no transfection), control siRNA group (cells transfected with control siRNA, Catalog No. sc-37007, Santa Cruz Biotechnology, Inc., Shanghai, China), and IL11RA siRNA group (cells transfected with IL-11RA siRNA, Catalog No. sc-35647, Santa Cruz Biotechnology, Inc., Shanghai, China). To optimize siRNA transfection efficiency, siRNA Transfection Reagent (Catalog No. sc-29528), siRNA Transfection Medium (Catalog No. sc-36868), and siRNA Dilution Buffer (Catalog No. sc-29527) recommended by Santa Cruz Biotechnology, Inc. (Shanghai, China) were employed.

2.5 | Wound healing and transwell invasion assays

Following 48 h of transfection, Wound healing and Transwell invasion assays were conducted. In the wound healing assay, cells were treated to allow adherent growth, creating a distinct wound. Subsequently, free cells were removed by washing, and the cells were incubated for 24 h in serum-free medium. At 0 h and 24 h, the width of lines in each well was observed and photographed using an inverted microscope. The cell migration rate was calculated. In the Transwell invasion assay,

TABLE 1 Primer sequences in reverse transcription quantitative polymerase chain reaction (RT-qPCR).

Genes	GenBank accession	Species	Forward primer (5′ → 3′)	Reverse primer (5′ → 3′)
IL11RA	NM_004512	Human	CTGGGCTAGGGCATGAACTG	CTGGGACTCCAAGTGCAAGA
GAPDH	NM_001256799	Human	CTGGGCTACACTGAGCACC	AAGTGGTCGTTGAGGGCAATG
Mmp8	NM_008611	Mouse	TCTTCCTCCACACACAGCTTG	CTGCAACCATCGTGGCATTC
Mmp2	NM_008610	Mouse	CAAGTTCCCCGGCGATGTC	TTCTGGTCAAGGTCACCTGTC
Gapdh	NM_008084	Mouse	AGGTCGGTGTGAACGGATTTG	TGTAGACCATGTAGTTGAGGTCA

after treatment, cells were seeded into the upper chamber of Transwell plates with serum-free medium, while the lower chamber was filled with an appropriate medium containing serum. The plates were incubated in a cell culture incubator for 24 h. Subsequently, the Transwell inserts were removed, and the upper membrane was fixed and stained, followed by microscopic observation and counting of invasive cells. The experiments were repeated three times.

2.6 | Animals

Il11ra knockout (KO) mice (Strain #:004621), exhibiting normal hematopoiesis, and Wild type (WT, Strain #:000664) mice on a C57BL/6J background were obtained from The Jackson Laboratory (Bar Harbor, ME, USA). For 11 weeks, WT and Il11ra KO female mice were injected with B16-F10 cells (1.5×10^5 cells) into the spleen. Subsequently, they were bred consecutively for 2 weeks. On Day 14, mice were euthanized, and liver resection was performed for metastatic analysis. The number of macroscopic visible hepatic metastases was quantified in mice.

2.7 | Reverse transcription quantitative polymerase chain reaction (RT-qPCR)

Total RNA was extracted from cells and mouse liver tissue using the TRIzol Plus RNA Purification Kit (12183555, Thermo Fisher Scientific Inc., Shanghai, China). Subsequently, RNA was reverse-transcribed into cDNA using SuperScript® IV Reverse Transcriptase (18090050, Thermo Fisher Scientific Inc., Shanghai, China). The SuperScript™ III Platinum™ One-Step qRT-PCR Kit (Catalog No. 11732-020) was used for RNA detection and quantification. IL11RA and MMP genes (MMP2 and MMP1) were normalized using the reference gene GAPDH, and relative expression levels were calculated using the 2-ΔΔCt method. The primer sequences are listed in Table 1. The experiments were repeated three times.

2.8 | Western blotting

Total protein was extracted from cells and mouse liver tissue using a protein extraction kit (Catalog No. 89901, Thermo Fisher Scientific Inc., Shanghai, China). Protein concentration was determined using the Pierce BCA Protein Assay Kit (Catalog No. 23225, Thermo Fisher Scientific Inc., Shanghai, China). Twenty micrograms of protein samples were separated by SDS-PAGE gel electrophoresis. Subsequently, proteins were transferred to a PVDF membrane, and primary antibodies, including rabbit monoclonal to IL-11RA (Catalog No. 23225, ab125015) at 1/1000 dilution, rabbit monoclonal phospho-STAT3 antibody (Catalog No. 23225, ab76315) at 1/20000 dilution, rabbit monoclonal to STAT3 (ab68153) at 1/1000 dilution, rabbit monoclonal to GAPDH-Loading Control (Catalog No. 23225, ab181602) at 1/10000 dilution, were added. Afterward, the membranes were reacted with the corresponding Goat Anti-Rabbit IgG H&L (HRP) (Catalog No. 23225, ab97051) at 1/20000 dilution. Finally, the ECL staining method was used to detect the luminescent signal of proteins, and the relative expression levels of target proteins were analyzed by imaging the membrane. The experiments were repeated three times.

2.9 | Statistical analysis

GraphPad Prism 8 (La Jolla, CA) was used for performing statistical analysis. The graphs represent the mean ± standard deviation (SD). Unpaired, two tailed *t*-test or One way ANOVA were applied for statistical testing. A p-value < 0.05 was regarded as statistically significant.

3 | RESULTS

3.1 | Elevated expression of IL11RA in cutaneous melanoma cells

IL11RA expression levels were evaluated in various human cutaneous malignant melanoma cell lines (A375, A375-MA2, SK-MEL-28, and RPMI-7951) through RT-qPCR (Figure 1A) and Western blotting (Figure 1B-C). The results revealed a significant increase in IL11RA mRNA and protein expression in cutaneous melanoma cell lines compared to normal cells (human dermal fibroblasts HDFa) (all $p < 0.05$). Due to its relatively higher expression in RPMI-7951 and A375-MA2 cells, they were selected for subsequent experiments.

3.2 | Impact of IL11RA on invasive and migratory capabilities of cutaneous melanoma cells

To minimize off-target effects, IL11RA siRNA was transfected into RPMI-7951 and A375-MA2 cells, both resulting in a marked

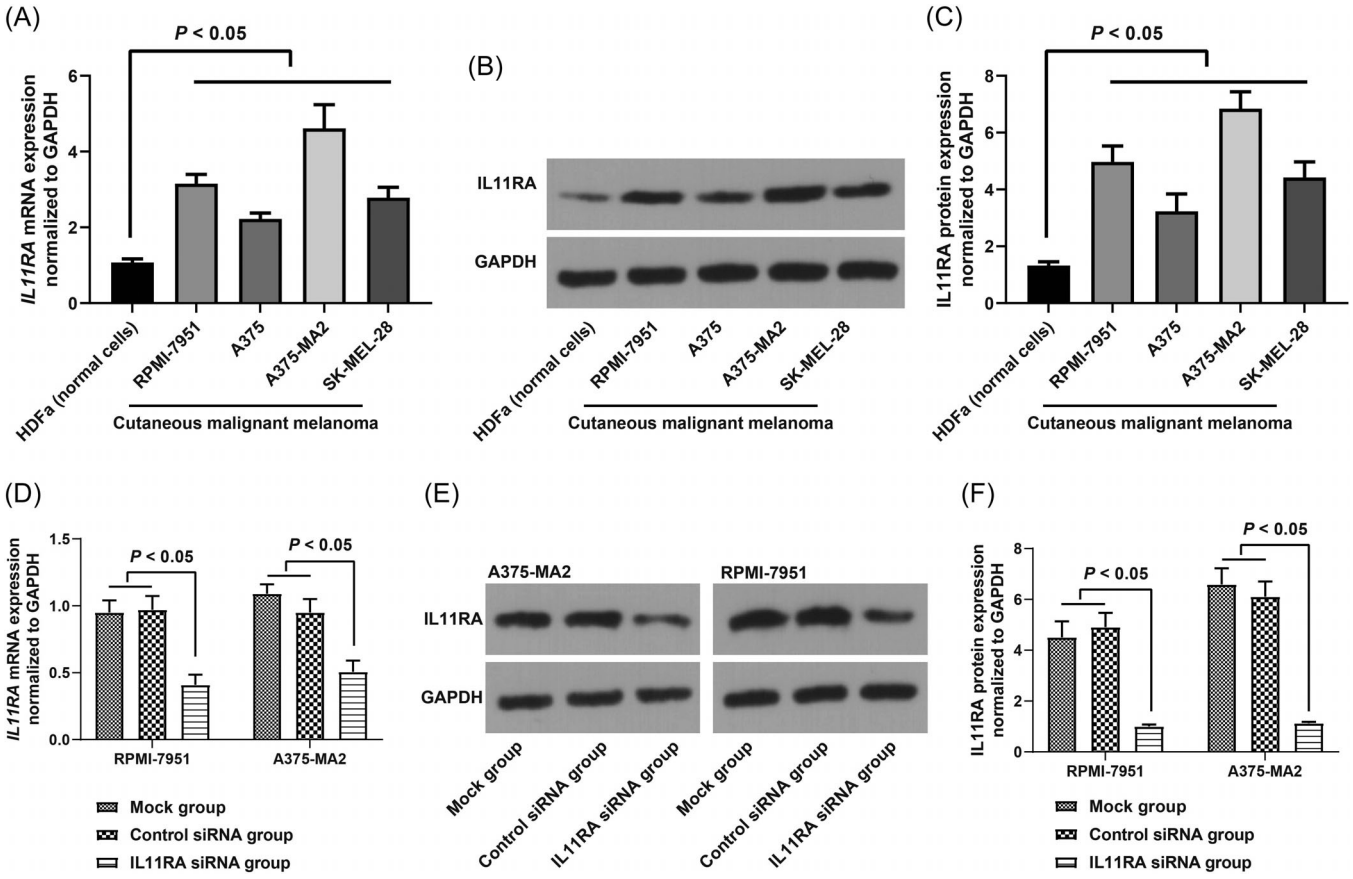

FIGURE 1 elevated expression of interleukin-11 receptor alpha (IL11RA) in cutaneous melanoma cells. Note: A-C: Reverse Transcription Quantitative Polymerase Chain Reaction (RT-qPCR) (A) and Western blotting (B-C) reveal a significant increase in IL11RA mRNA and protein expression in cutaneous melanoma cell lines compared to normal cells (human dermal fibroblasts HDFa); D-F: RT-qPCR (D) and Western blotting (E-F) demonstrate a pronounced suppression of IL11RA expression following the transfection of IL11RA small interfering RNA (siRNA) into RPMI-7951 and A375-MA2 cells.

suppression of IL11RA expression (both $p < 0.05$, Figure 1D-F). Transwell invasion and wound healing assays revealed that the down-regulation of IL11RA significantly impeded the migratory and invasive capabilities of cutaneous melanoma RPMI-7951 and A375-MA2 cells. This was evident through a decreased cell migration rate and a reduced number of invasive cells (all $p < 0.05$, Figure 2).

3.3 | Il11ra gene knockout suppressed hepatic melanoma metastasis

Il11ra gene knockout resulted in a notable suppression of hepatic melanoma metastasis, as demonstrated by a significant decrease in liver colonization at day 14 upon intrasplenic injection of B16-F10 cells in Il11ra KO mice compared to WT mice ($p < 0.05$, Figure 3A-B). This reduction in hepatic metastatic foci was further validated by a significant decrease in the total macroscopic tumor area in Il11ra KO mice with B16-F10 metastases after spleen injection ($p < 0.05$, Figure 3C).

3.4 | Effects of Il11ra gene knockout on MMP family genes in mouse liver tissue

The exploration of the correlation between MMP family genes and IL11RA in melanoma occurrence and development utilized three online databases (Table 2): LinkedOmics (SKCM patients: 103), GEPIA (SKCM patients: 461), and TIMER (SKCM metastasis patients: 368). Illustrated in Figure 4A-B, MMP2 exhibited a positive correlation with IL11RA in LinkedOmics ($p = 0.011$), a correlation supported by GEPIA ($p = 0.001$) and TIMER ($p = 0.046$) databases. Conversely, MMP8 displayed a negative correlation with IL11RA in LinkedOmics ($p = 2.03E-05$), confirmed in GEPIA ($p = 2.30E-06$) and TIMER ($p = 5.10E-05$) databases. These findings suggest a potential regulatory association between IL11RA and MMP2 as well as MMP8 in melanoma progression. Subsequently, following qRT-PCR analysis of gene expression in mouse liver tissue, it was observed that Il11ra gene knockout significantly decreased *Mmp2* expression while increasing *Mmp8* (all $p < 0.05$, Figure 4C), and these results were corroborated at the protein level through Western blotting (Figure 4D-E).

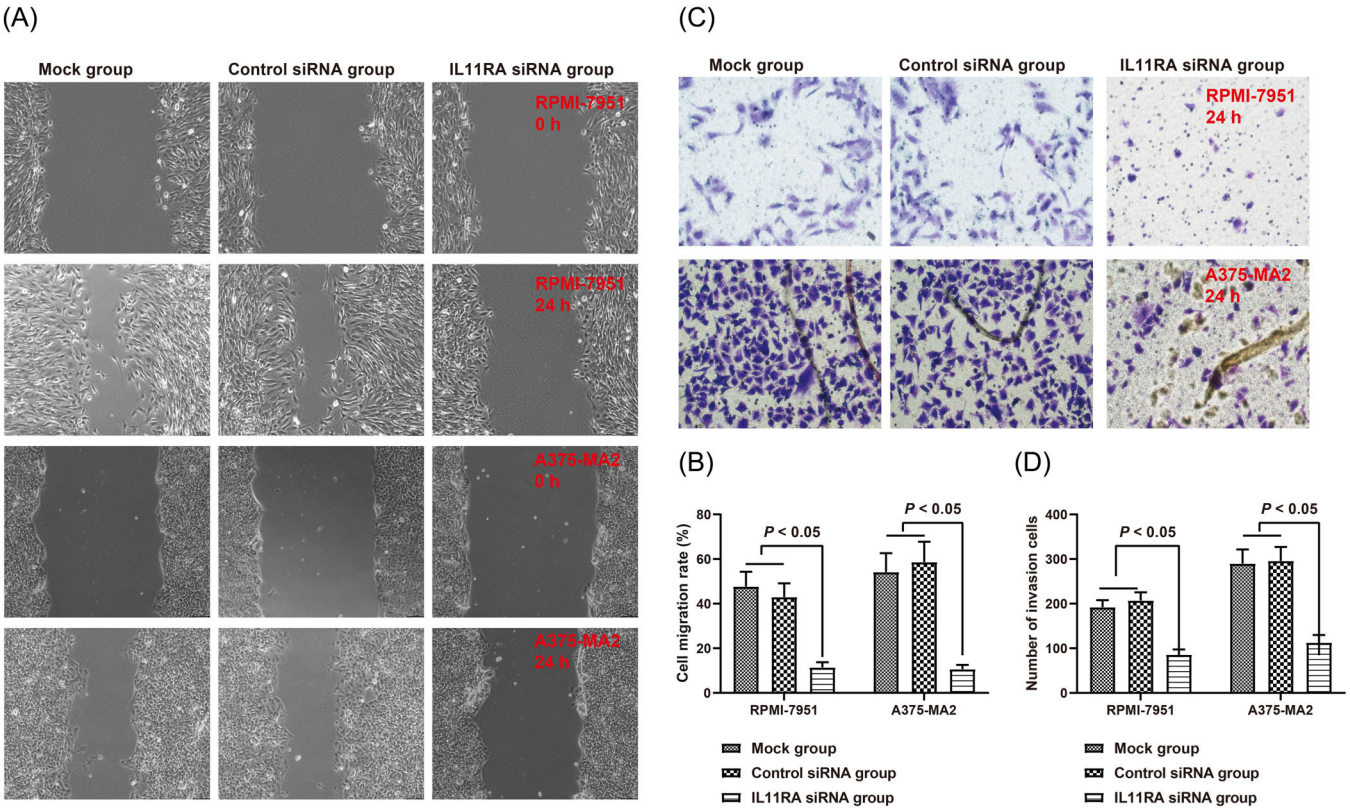

FIGURE 2 Impact of IL11RA on invasive and migratory capabilities of cutaneous melanoma cells. Note: A-D: Transwell invasion (A-B) and Wound healing assays (C-D) indicated that IL11RA downregulation inhibited the migratory and invasive capacities of cutaneous melanoma RPMI-7951 and A375-MA2 cells.

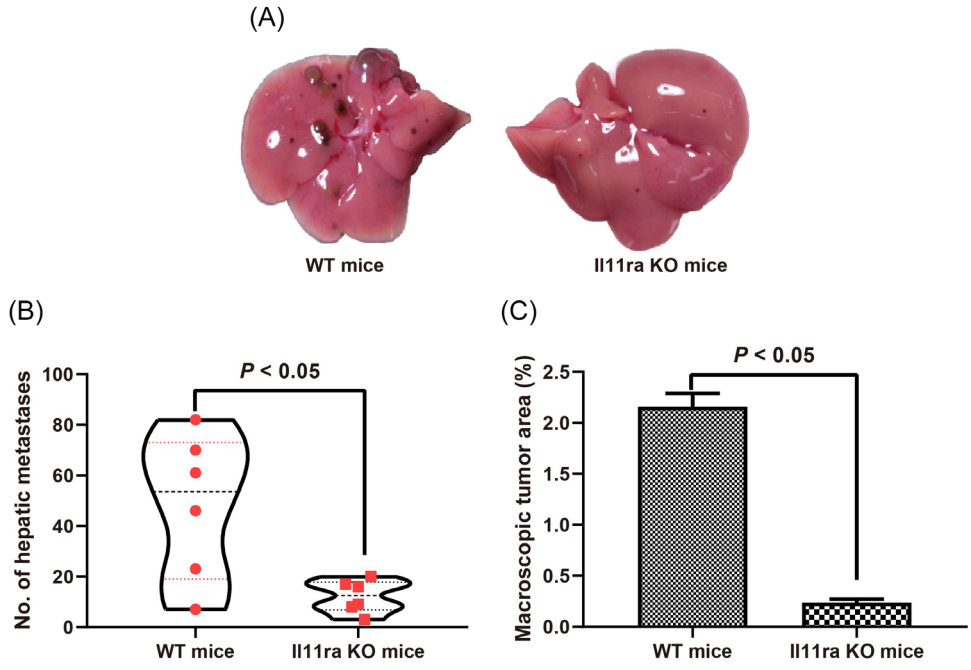

FIGURE 3 Il11ra gene knockout suppressed hepatic melanoma metastasis. Note: A: Representative photographs depicted livers with metastases. B-C: Following spleen injection of B16-F10 cutaneous melanoma cells on day 14, Il11ra KO mice ($n = 6$) exhibited fewer visible hepatic metastases (B) and a reduced macroscopic tumor area (%, C) compared to WT mice ($n = 6$).

TABLE 2 Correlation between IL11RA and MMP family genes in SKCM occurrence and development using LinkedOmics, TIMER, and GEPIA databases.

	LinkedOmics database		GEPIA database		TIMER	
MMPs	**R**	***p*-value**	**R**	***p*-value**	**R**	***p*-value**
MMP1	−0.231	0.019	−0.068	0.150	−0.048	0.359
MMP2	**0.250**	**0.011**	**0.150**	**0.001**	**0.104**	**0.046**
MMP3	−0.082	0.412	−0.015	0.750	0.002	0.962
ILF3	0.191	0.053	0.240	1.30E-07	0.204	8.29E-05
MMP7	0.116	0.242	0.057	0.220	0.023	0.657
MMP8	**-0.407**	**2.03E-05**	**-0.220**	**2.30E-06**	**-0.210**	**5.10E-05**
MMP9	0.171	0.085	0.070	0.130	0.034	0.513
MMP10	−0.025	0.802	−0.053	0.250	−0.084	0.107
MMP11	0.100	0.314	0.120	0.011	0.115	0.028
MMP12	0.033	0.739	−0.038	0.420	−0.087	0.094
MMP13	−0.034	0.731	0.036	0.440	0.063	0.227
MMP14	−0.180	0.069	−0.120	0.010	−0.170	0.001
MMP15	0.117	0.239	0.230	3.90E-07	0.230	8.83E-06
MMP16	−0.015	0.880	0.160	4.70E-04	0.134	0.010
MMP17	−0.046	0.646	−0.037	0.420	−0.019	0.714
MMP19	0.219	0.026	0.028	0.550	0.082	0.116
MMP20	−0.023	0.820	0.039	0.400	0.001	0.984
MMP21	0.176	0.075	0.220	1.10E-06	0.190	2.42E-04
MMP23A	0.016	0.870	0.047	0.310	0.019	0.712
MMP23B	0.203	0.040	0.007	0.890	−0.035	0.497
MMP24	0.107	0.282	0.120	0.009	−0.059	0.262
MMP25	0.050	0.615	−0.067	0.150	−0.119	0.022
MMP27	−0.066	0.509	−0.037	0.430	0.018	0.733
MMP28	0.021	0.836	0.039	0.400	0.053	0.307
TIMP1	−0.020	0.843	−0.072	0.120	−0.124	0.018
TIMP2	−0.047	0.636	0.041	0.370	0.023	0.659
TIMP3	−0.072	0.468	0.140	0.002	0.124	0.017
TIMP4	0.188	0.057	0.190	3.90E-05	0.173	0.001

Note: Matrix Metalloproteinase (MMP); Interleukin-11 Receptor Alpha (IL11RA); Skin Cutaneous Melanoma (SKCM); LinkedOmics ($n = 103$ SKCM patients), TIMER (Tumor Immune Estimation Resource, $n = 368$ SKCM metastasis patients); GEPIA (Gene Expression Profiling Interactive Analysis, $n = 461$ SKCM patients).
Bold values indicate a significant correlation between IL11RA and MMP2/MMP8 in SKCM tissues, with consistent correlations observed across three online databases.

3.5 | Impact of IL11RA on STAT3 pathway in cutaneous melanoma

Cytokines of the IL6 family, such as IL-6 and IL-11, utilize the gp130 receptor to activate downstream STAT3 signaling, contributing to the activation of genes associated with cancer hallmarks.[18] Notably, the activation of STAT3 signaling by IL11RA is linked to an adverse prognosis in various human cancers.[19,20] Analysis of the GEPIA database (461 SKCM patients, Figure 5A) and TIMER database (368 SKCM metastasis patients, Figure 5B) indicated a significant positive correlation between IL11RA and STAT3 (both $p < 0.001$). Subsequent Western blotting confirmed that IL11RA siRNA markedly inhibited p-STAT3/total STAT3 in RPMI-7951 and A375-MA2 cells (all $p < 0.05$, Figure 5C). Furthermore, to validate in vitro findings regarding the impact of IL11RA on STAT3 in cutaneous melanoma, the STAT3 pathway activity in liver tissue was assessed, demonstrating that Il11ra gene knockout markedly inhibited p-Stat3/total Stat3 expression ($p < 0.05$, Figure 5D).

4 | DISCUSSION

In recent years, IL11RA has emerged as a significant player in various cancers, being implicated in gastric tumorigenesis, colorectal

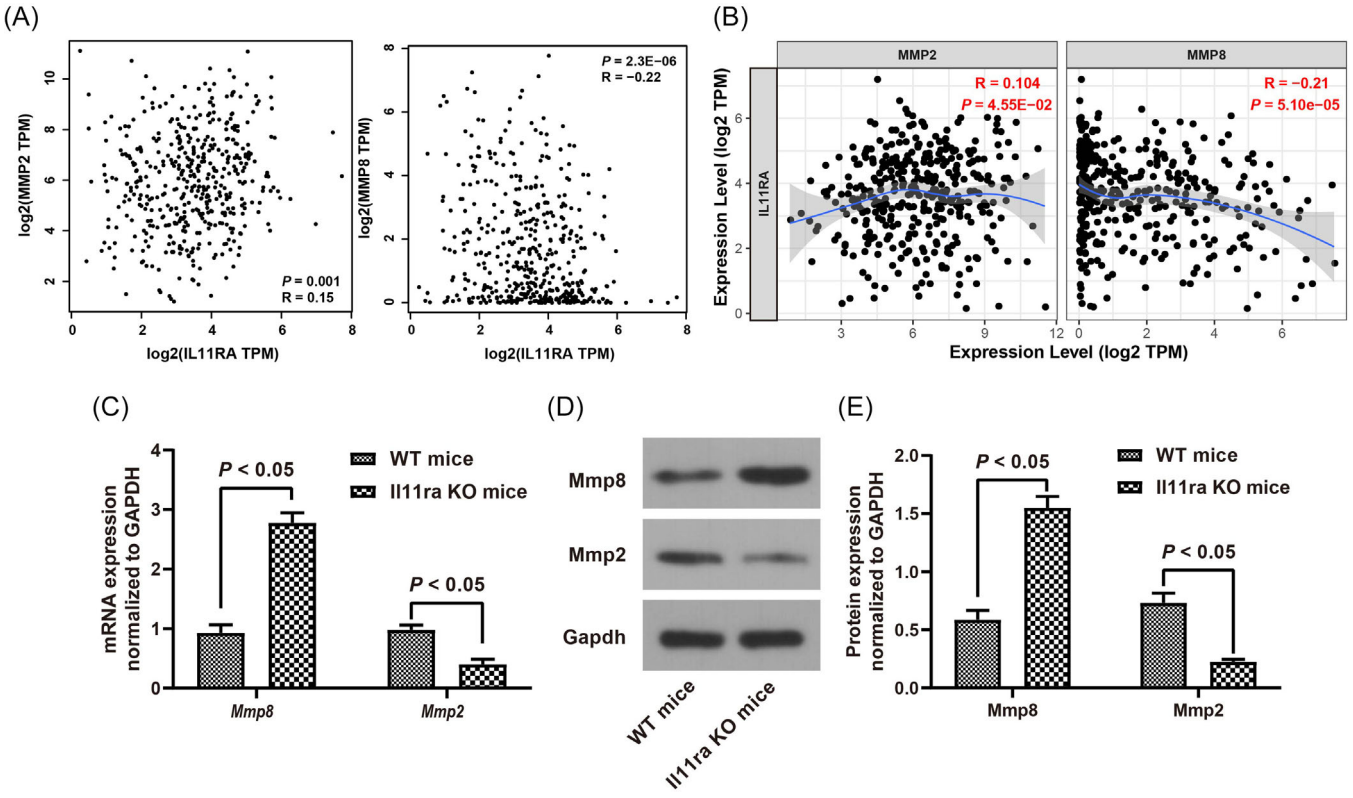

FIGURE 4 Effects of Il11ra gene knockout on Mmp2 and Mmp8 in mouse liver tissue. Note: A-B: The correlation between IL11RA and MMP2 as well as MMP8 based on GEPIA (SKCM patients = 461, A) and TIMER (SKCM metastasis patients = 368, B). C-E: RT-qPCR (C) and Western blotting (D-E) demonstrate Mmp2 and Mmp8 expression in Mouse Liver Tissue.

cancer development, and suppression of antitumor responses in colon cancer.[20–22] It has also been identified as a potential therapeutic target in osteosarcoma, with studies suggesting its involvement in tumor growth and metastases.[23,24] A cytokine profile analysis revealed lower expression of IL-11RA in tumor-positive sentinel nodes compared to tumor-negative sentinel nodes in melanoma.[12] However, a previous study emphasized the overexpression of the IL11RA gene in the organ-specific metastasis of primary melanoma cells to the liver, indicating its involvement in the interaction between liver endothelial and melanoma cells.[13] Our study found elevated IL11RA expression in various human SKCM cell lines compared to normal cells. IL11RA downregulation significantly inhibited the migratory and invasive capabilities of SKCM cells. Il11ra gene knockout in mice demonstrated a substantial reduction in hepatic melanoma metastasis, emphasizing the pivotal role of IL11RA in driving metastatic behavior.

Correlation analyses of online databases revealed associations between IL11RA and MMP2/MMP8. In vivo studies revealed that Il11ra gene knockout significantly decreased Mmp2 expression while increasing Mmp8 in liver tissues, suggesting that IL11RA influences the expression of these matrix-degrading enzymes and, consequently, plays a role in SKCM progression. MMPs are a family of zinc-dependent endopeptidases collectively capable of degrading essentially all extracellular matrix components.[25] During cutaneous melanoma progression, tumor cells must cross the dermal-epidermal junction and invade the dermis, involving the essential degradation of matrix proteins by serine proteinases and MMPs.[26] MMP-8 plays a protective role against metastasis by modulating tumor cell adhesion and invasion, as observed in mouse models and breast cancer patients, where its expression correlates with a lower incidence of lymph node metastasis and a favorable prognosis.[27] In Marfan syndrome, elevated IL11RA and MMP2/MMP9 levels contribute to ERK-mediated thoracic aortic pathology.[28] In a mouse model of injury-induced plaque development, therapeutic inhibition of IL-11 using X203 reduced vessel thickness, neointimal hyperplasia, and MMP2 levels, preserving the contractile VSMC phenotype, suggesting a potential therapy for arterial stenosis post-revascularization.[29]

Binding of ligands to IL-11RA induces the phosphorylation of associated JAK kinases, leading to the recruitment of STAT family transcription factors, particularly STAT3.[30] The study further explores the impact of IL11RA on the STAT3 pathway, a signaling cascade associated with cancer hallmarks. Colitis-induced IL11 triggers STAT3 activation through IL11RA, fostering colon carcinogenesis.[31] IL11RA is implicated in breast cancer bone metastasis-induced osteolysis, activating osteoclastogenesis via JAK1/STAT3 independently of RANKL.[32] Blocking IL11RA with an antibody, combined with doxorubicin, inhibits high-grade endometrioid cancer growth by reducing STAT3 phosphorylation, suggesting a dual therapeutic strategy targeting IL11RA and STAT3.[33] Anti-human IL11RA antibody inhibits endometrial cancer cell proliferation, invasion, and promotes apoptosis in vitro, while also reducing tumor growth and metastasis in vivo, potentially through

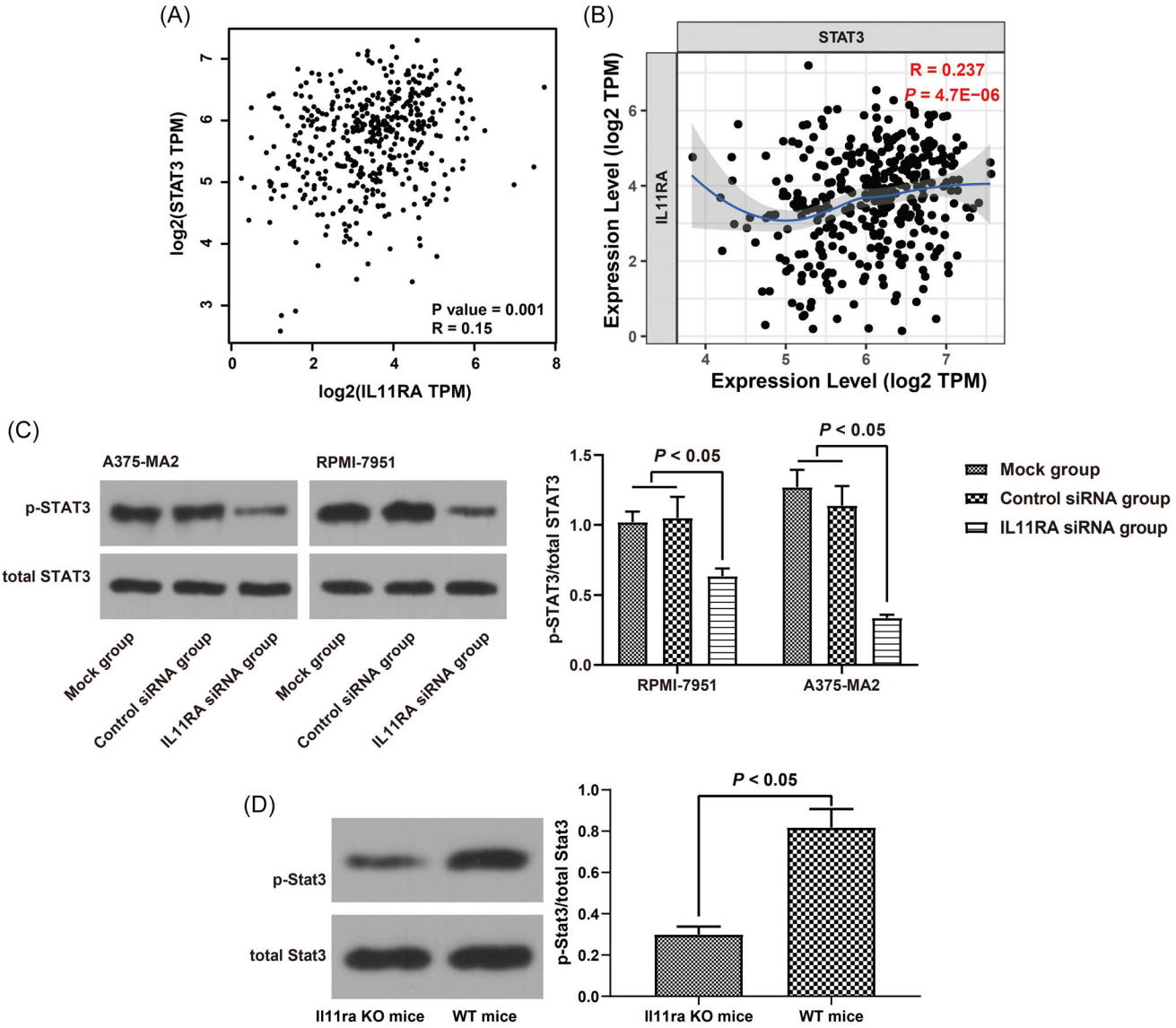

FIGURE 5 Impact of IL11RA on STAT3 pathway in cutaneous melanoma. Note: A-B: Analysis of the GEPIA database (461 SKCM patients, A) and TIMER database (368 SKCM metastasis patients, B) indicated a significant positive correlation between IL11RA and STAT3; C: Western blotting demonstrated a suppression of p-STAT3/total STAT3 following the transfection of IL11RA small interfering RNA (siRNA) into RPMI-7951 and A375-MA2 cells; D: Western blotting demonstrated a suppression of p-STAT3/total STAT3 in liver tissues at day 14 upon intrasplenic injection of B16-F10 cells in Il11ra KO mice compared to WT mice.

STAT3 pathway modulation.[19] In our study, IL11RA's positive correlation with STAT3 is affirmed in both in vitro and in vivo settings, indicating its potential role in cancer-related signaling pathways. Inhibiting IL11RA decreases p-STAT3/total STAT3 in melanoma cells and mouse liver tissue, offering a potential therapeutic target for disrupting the STAT3 pathway.

Moreover, the study extends its implications to the clinical context by exploring IL11RA's potential as a therapeutic target. The significant reduction in hepatic melanoma metastasis in Il11ra knockout mice suggests that targeting IL11RA may offer a promising avenue for therapeutic interventions in cutaneous melanoma progression. The study's findings contribute to the growing body of evidence supporting IL11RA as a potential target for precision-based therapy in various cancers. Despite the valuable insights our study provides into the role of IL11RA in SKCM metastasis to the liver, certain limitations should be acknowledged. Firstly, the translation of our findings into clinical applications necessitates rigorous clinical trials. The observed associations between IL11RA and MMP2/MMP8 indicate potential regulatory roles, but the precise mechanisms remain to be fully elucidated.

5 | CONCLUSION

Our study highlights the significant role of IL11RA in SKCM progression. Elevated IL11RA expression in SKCM cell lines suggests its

relevance in melanoma development, and its downregulation hampers cell migration and invasion. Il11ra gene knockout in a mouse model reduces hepatic melanoma metastasis. Correlation analyses indicate associations between IL11RA and MMP2/MMP8, suggesting potential regulatory roles in matrix degradation during SKCM progression. Additionally, IL11RA shows a positive correlation with STAT3, and its inhibition suppresses the STAT3 pathway in SKCM cells and mouse liver tissue, suggesting IL11RA as a promising therapeutic target in SKCM.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The animal experiments were approved by the Ethics Committee of Lishui People' s Hospital. All experiments were performed following the guidelines outlined in the Guide for the Care and Use of Laboratory Animals published by the National Academy of Sciences.

CONSENT FOR PUBLICATION

Not applicable.

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