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Original Article

SB202190 alleviates endometrial fibrosis by modulating the TGF-β/Smad signaling pathway

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Abstract: The TGF-β/Smad signaling pathway plays important roles in both normal tissue repair and pathological fibrosis of the endometrium. In this study, for *in vivo* mice experiments, SB202190, a p38 MAPK inhibitor, was administered by subcutaneous injection twice daily for 2 consecutive weeks. For *in vitro* experiments, 10 ng/mL TGF-β1 was added into human endometrial epithelial cells (HEECs) for stimulation, followed by co-culture with gradient concentrations of SB202190. The Cell Counting Kit-8 (CCK-8) assay was used to assess cell viability, and TdT-mediated dUTP Nick-End Labeling (TUNEL) staining for apoptosis, and a Transwell assay was used to assess cell migration. We introduced SRI-011381 - a Transforming growth factor β (TGF-β)/Smad pathway agonist - along with SB202190 to intervene in HEECs for mechanistic validation. Our results showed that SB202190 treatment significantly increased the number of endometrial glands, reduced collagen deposition, and alleviated inflammation in Intrauterine adhesion (IUA) mouse models. *In vitro*, SB202190 markedly enhanced HEECs viability, suppressed cell apoptosis, and mitigated inflammatory response, fibrosis progression, and epithelial-mesenchymal transition (EMT). SRI-011381 significantly reversed the effects of SB202190 on fibrosis and EMT in the cell model. These findings suggest that SB202190 alleviates fibrosis and inflammation and inhibits EMT in IUA models by suppressing the TGF-β/Smad signaling pathway.

Keywords: SB202190, endometrial fibrosis, intrauterine adhesion, TGF-β/Smad, EMT

Introduction

Intrauterine adhesion (IUA) results from damage to the endometrial basal layer caused by surgery, infection, or trauma, leading to menstrual disorders, secondary infertility, cyclical pelvic pain, and recurrent miscarriage [1]. Currently, hysteroscopy is the main clinical treatment for IUA, and can separate adhesive tissue to some extent and promote endometrial regeneration [2]. However, this surgical approach has obvious limitations, including poor long-term patient compliance, an elevated postoperative recurrence rate, and a high risk of various perioperative complications [3]. Intrauterine devices (IUDs) such as balloon catheters and stents are often used as adjuvant therapy after surgery, which can physically separate the anterior and posterior uterine walls to reduce re-adhesion [4], but long-term implantation may also increase the risk of a persistent intrauterine inflammatory response [5-7]. Estrogen therapy is commonly used in clinical practice to promote endometrial epithelial proliferation and damage repair, but the optimal dose and treatment duration have not yet been standardized, and there are still controversies about its clinical safety and application scope. In addition, invasive intrauterine operations may cause secondary damage to the uterus, aggravate local irritation, and further promote the progression of endometrial fibrosis [8]. Therefore, it is urgent to develop safe and effective drugs for IUA.

Endometrial fibrosis is widely recognized as the key disease-related mechanism underlying the development and progression of IUA. Extensive research has confirmed that the TGF-β/Smad signaling pathway plays important roles in both normal tissue repair and pathologic fibrosis. Smad proteins act as the main downstream messengers for TGF-β1 [9], carry pro-fibrotic signals and regulate the expression of fibrosis-related factors [10-13]. Furthermore, aberrant activation of epithelial-mesenchymal transition

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(EMT) in endometrial epithelial cells promotes endometrial fibrosis. Sustained activation of the TGF-β/Smad pathway continuously promotes TGF-β1-driven EMT and exacerbates endometrial fibrosis [14-17].

SB202190 is a highly selective inhibitor of the p38 MAPK pathway. Previous studies showed that SB202190 effectively inhibits fibrosis and inflammation in renal tubular cells [18]. The p38 MAPK pathway cross-talks extensively with the TGF-β/Smad pathway in fibrotic diseases. Inhibiting p38 MAPK can indirectly block excessive TGF-β/Smad activation without directly targeting TGF-β receptors, thus reducing off-target effects and improving safety [19]. Thus, we hypothesized that SB202190 may alleviate endometrial fibrosis in IUA by regulating the TGF-β/Smad pathway.

Materials and methods

Animal experiments

Female C57BL/6J mice (6- to 8-weeks old) were housed under specific-pathogen-free (SPF) conditions with free access to sterile food and water. IUA mouse model was established by mechanical curettage combined with lipopolysaccharide (LPS) injection. Briefly, after anesthesia with isoflurane, a 1-1.5 cm longitudinal incision was made in the lower abdomen to expose the uterus. The uterus was gently scratched with a curette until it exhibited congestion. 0.2 mg/kg LPS (HY-D1056, MedChem Express, Monmouth Junction, NJ, USA) was injected into the tail vein after the abdominal cavity was closed layer by layer. The secondary intrauterine procedure was performed on day 3 post primary modeling. Administration of SB202190 or saline was initiated immediately after the primary surgery and continued twice daily for 14 consecutive days, including on the day of the secondary procedure. The sham group underwent the same open procedure but received no uterine scratching or LPS injection [17].

Mice were randomly divided into 4 groups (n = 12 per group): Sham, IUA, and two SB202190 groups (5 mg/kg/d and 10 mg/kg/d). Six mice in each group were used for histopathological analysis, and six for molecular assays. SB202190 (HY-10295, MedChem Express) was subcutaneously injected twice daily for 2 weeks. Sham and IUA groups received equal volume of saline. The doses of 5 mg/kg/d and 10 mg/kg/d were selected based on previous studies and preliminary exploratory experiments. SB202190 shows effective anti-fibrotic activity and good safety at 5-10 mg/kg/d in multiple fibrotic disease models [19, 20].

At the end of the experiments, mice were euthanized by cervical dislocation under deep anesthesia in accordance with animal welfare guidelines.

Histopathologic analysis

Mouse uterine tissue was fixed in 4% paraformaldehyde, then dehydrated, embedded in paraffin, and sliced. The sections were stained with H&E and Masson's kits (C0105s, C0189S, Beyotime, Shanghai, China), and histopathological changes were examined under a light microscope.

ELISA assay

The expression levels of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) in mouse serum and cell culture supernatant were measured by using ELISA kits (ab181421, ab208348, ab214025, ab197742, ab178013, ab222503, Abcam, Cambridge, MA, USA) following the manufacturers' instructions.

Cell culture and treatment

Human endometrial epithelial cells (HEECs) were cultured in DME/F12 complete medium (Gibco, Thermo Fisher Scientific, Waltham, MA, USA) at 37°C with 5% CO_2. Groups were designed as follows: 1. Control group: HEECs cultured in complete medium without any intervention; 2. TGF-β1 group: HEECs exposed to 10 ng/mL TGF-β1 (HY-P70543, MedChem Express) for a period of 48 h; 3. SB202190 5/10 μM: HEECs processed with 10 ng/mL TGF-β1 combined with SB202190 (5 μM, 10 μM) for 48 h; 4. SB202190 10 μM + DMSO/SRI-011381: HEECs processed with 10 ng/mL TGF-β1, 10 μM SB202190 and DMSO or 10 μM SRI-011381 (HY-100347, MedChem Express) for a period of 48 h. The concentration of SRI-011381 (10 μM) was selected based on preliminary cytotoxicity tests and the manufactur-

Table 1. RT-qPCR primers

Gene	Forward Primer (5'-3')	Reverse Primer (5'-3')
TGF-β1-mus	AAACTAAGGCTCGCCAGTCC	CATAGATGGCGTTGTTGCGG
Smad2-mus	CCCCAACATGACAGGAGACC	TCACGTGCCCCACTTACAAA
Smad3-mus	AGGCTGAGAAGGCTCTAGCT	ACAGGAGGAGCGAGCTCTAA
β-actin-mus	GTGCTTCTAGGCGGACTGTT	ATCCTGAGTCAAAAGCGCCA
TGF-β1-Homo	GACTTTTCCCCAGACCTCGG	ATAGGGGATCTGTGGCAGGT
Smad2-Homo	GCTGGCCTGATCTTCACAGT	CCAGAGGCGGAAGTTCTGTT
Smad3-Homo	CAAGTGGCCGCGTGTAAAAA	AGTCCAGAACAGCCGAGTTG
β-actin-Homo	CACCATTGGCAATGAGCGGTTC	AGGTCTTTGCGGATGTCCACGT

Note: TGF-β1, transforming growth factor beta 1; Smad2, mothers against decapentaplegic homolog 2; Smad3, mothers against decapentaplegic homolog 3; β-catenin, beta-actin; mus, Mus musculus (mouse); Homo, Homo sapiens (human).

er's recommended effective concentration range.

CCK-8 assay

HEECs were seeded at 5 × 10^3 cells/well in 96-well plates. CCK-8 solution (CK04, Dojindo Laboratories, Japan) was added and incubated at 37°C for 2 h, Absorbance at 450 nm was measured.

TUNEL assay

HEECs (1 × 10^5) were suspended in PBS and processed following the instructions provided with the TUNEL assay kit (ab66108, Abcam). Apoptosis was observed under a fluorescence microscope (LSM700B, Zeiss, Oberkochen, Germany).

Transwell assay

HEECs were centrifuged and resuspended in a FBS-free medium. A suspension containing 2 × 10^4 cells was added to the upper transwell chamber (Corning, USA), and complete medium containing 10% FBS was added to the lower chamber. After 24 hours of incubation, the migrating cells on the lower chamber membrane were fixed and stained.

RT-qPCR

Total RNA was extracted using RNAsimple (4992858, TIANGEN Biotech, Beijing, China). cDNA was synthesized using cDNA Synthesis SuperMix (11141ES60, YEASEN, Shanghai, China). qPCR was performed using the Premix Ex Taq (RR309A, Takara, Tokyo, Japan) with β-actin as internal control. Relative expression was calculated by $2^{-\Delta\Delta Ct}$ method [21]. Primer sequences are shown in **Table 1**.

Western blot experiment

Total protein was extracted using a protein extraction kit (PP123-01, Beyotime). Proteins were separated by 10% SDS-PAGE and transferred to PVDF membranes. Membranes were incubated with primary antibody overnight at 4°C, then with HRP-conjugated secondary antibody (1:10000, ab6721, Abcam) for 1 h. Bands were visualized using ECL chemiluminescence kit (ab65623, Abcam).

Primary antibody information: TGF-β1 (1:2000, ab215715), Smad2 (1:1000, ab33875), Smad3 (1:2000, ab84177), α-SMA (1:1000, ab108-424), Collagen I (1:2000, ab260043), Collagen III (1:2000, ab184993), E-cadherin (1:1000, ab231303), N-cadherin (1:2000, ab76011), GAPDH (1:2500, ab9485), all purchased from Abcam.

Statistical analysis

Data were analyzed using GraphPad Prism 9.0 and presented as mean ± SD. Comparisons between two groups were performed using t-test. Multiple-group comparisons were performed using One-way ANOVA (for single factor) or Two-way ANOVA (for multiple factors), followed by Tukey's *post-hoc* test. $P < 0.05$ was considered significant.

Results

SB202190 attenuates endometrial damage and fibrosis in IUA mice

H&E and Masson staining showed that the sham group had intact uterine cavity structure, clear endometrium with evenly distributed glands, and no obvious collagen deposition.

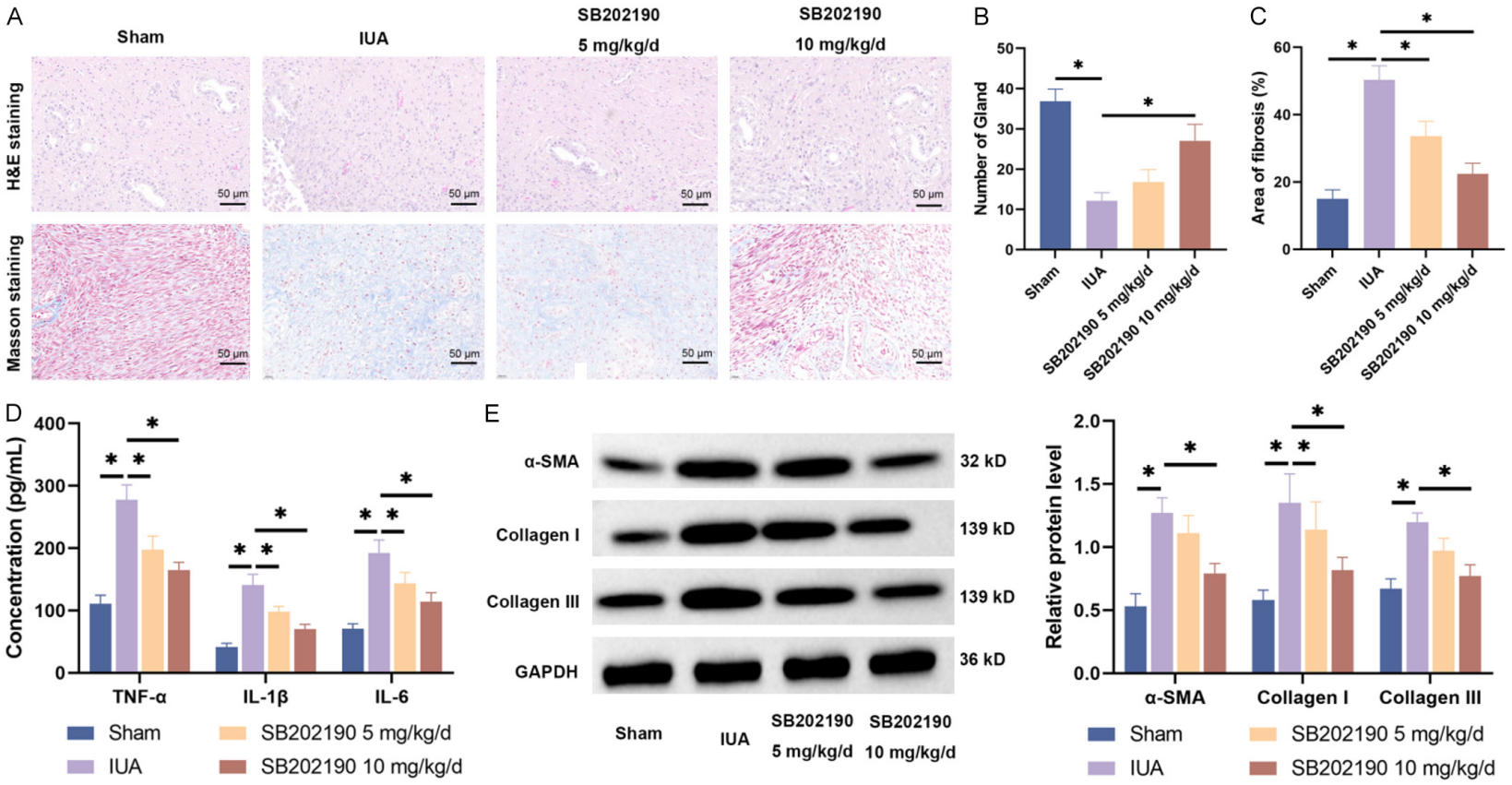

Figure 1. SB202190 alleviates endometrial fibrosis in IUA mice. An IUA (intrauterine adhesion) mouse model was established by mechanical curettage and inflammatory stimulation. SB202190 (5, 10 mg/kg) was administered subcutaneously twice daily for two weeks. (A) H&E (hematoxylin and eosin) and Masson staining were used to detect the histologic structure of mouse endometrium (scale bar = 50 μm, ×200); (B) Number of glands in the mouse endometrium (scale bar = 50 μm, ×200); (C) Endometrial fibrotic area in mice; (D) ELISA (enzyme-linked immunosorbent assay) was used to detect the levels of inflammatory factors TNF-α (tumor necrosis factor-alpha), IL-1β (interleukin-1 beta), and IL-6 (interleukin-6) in mouse serum; (E) Western blot was used to detect the expression of fibrosis-related proteins α-SMA (alpha-smooth muscle actin), Collagen I, and Collagen III in mouse endometrial tissue; n = 6 per group, three independent replicate experiments were performed. Data are presented as mean ± standard deviation. One-way ANOVA was used for (B, C), two-way ANOVA for (D, E), *post-hoc* test using Tukey's multiple comparisons test, * indicates $P < 0.05$.

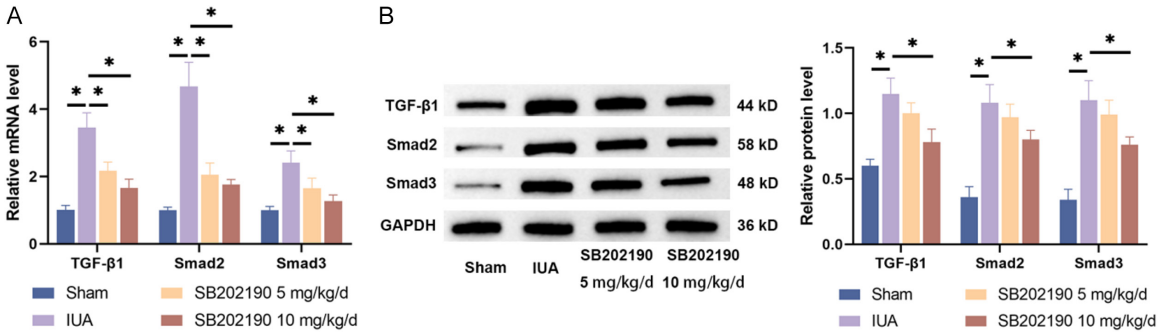

Figure 2. SB202190 inhibits the TGF-β/Smad signaling pathway in the endometrium of IUA mice. (A, B) RT-qPCR and western blot were used to detect the expression of TGF-β1 (transforming growth factor beta 1), Smad2 (mothers against decapentaplegic homolog 2), and Smad3 (mothers against decapentaplegic homolog 3) in mouse endometrial tissues; n = 6 per group, three independent replicate experiments were performed. Data are presented as mean ± standard deviation. Two-way ANOVA was used for (A, B), *post-hoc* test using Tukey's multiple comparisons test, * indicates $P < 0.05$.

The IUA group exhibited narrowed uterine cavity, significant stromal edema, reduced gland count, and massive collagen deposition. Compared to the IUA group, the SB202190 intervention groups had significantly enlarged uterine cavity, alleviated stromal edema (**Figure 1A**), increased gland number (**Figure 1B**, F = 72.33, P < 0.05), and decreased collagen deposition (**Figure 1C**, F = 102.60, P < 0.05), with better effects at 10 mg/kg/d. Meanwhile, SB202190 intervention significantly downregulated the protein expression of fibrosis-related markers α-SMA, Collagen I and III in the endometerial tissue of IUA mice (**Figure 1E**, F = 98.58, P < 0.05) and reduced the level of inflammatory factors in serum (**Figure 1D**, F = 218.40, P < 0.05).

SB202190 inhibits the TGF-β/Smad signaling pathway in the endometrium of IUA mice

The mRNA (**Figure 2A**, F = 195.80, P < 0.05) and protein (**Figure 2B**, F = 159.30, P < 0.05) expression levels of TGF-β1, Smad2, and Smad3 were significantly upregulated in IUA mice. After SB202190 intervention, the levels of the above key molecules were significantly decreased (**Figure 2A**, **2B**, P < 0.05), suggesting that SB202190 may improve the recovery of endometrial damage and fibrosis in IUA mice by inhibiting the activity of the TGF-β/Smad pathway.

SB202190 attenuates TGF-β1-induced fibrosis and EMT in HEECs

HEECs were induced by 10 ng/mL TGF-β1 and co-cultured with 5 μM and 10 μM SB202190 for 48 h. The results showed that TGF-β1 induction reduced the viability of HEECs (**Figure 3A**, F = 23.33, P < 0.05), promoted cell apoptosis (**Figure 3B**, F = 64.36, P < 0.05), and upregulated inflammatory-factor levels in the cell supernatant (**Figure 3C**, F = 63.81, P < 0.05). TGF-β1 markedly increased the protein expression of α-SMA, Collagen I, Collagen III, and interstitial marker N-cadherin, while decreasing the expression of epithelial marker E-cadherin (**Figure 3D**, F = 77.35, P < 0.05), and enhanced migration ability (**Figure 3E**, F = 43.10, P < 0.05). In contrast, SB202190 intervention significantly reversed the above changes (**Figure 3A-E**, P < 0.05). These results demonstrate that SB202190 mitigates TGF-β1-induced fibrosis and EMT progression in HEECs.

SB202190 blocks TGF-β1-induced activation of TGF-β/Smad signaling pathway in HEECs

The mRNA (**Figure 4A**, F = 194.30, P < 0.05) and protein (**Figure 4B**, F = 158.60, P < 0.05) expression levels of TGF-β1, Smad2, and Smad3 were significantly upregulated in TGF-β1-induced HEECs, while SB202190 intervention significantly downregulated the expression of these key molecules (**Figure 4A**, **4B**, P < 0.05), indicating that SB202190 may alleviate TGF-β1-induced cellular fibrosis and EMT by inhibiting the activation of the TGF-β/Smad signaling pathway.

SRI-011381 reverses the effects of SB202190 on fibrosis and EMT

To further verify the regulatory mechanism of SB202190, we added the TGF-β/Smad specific

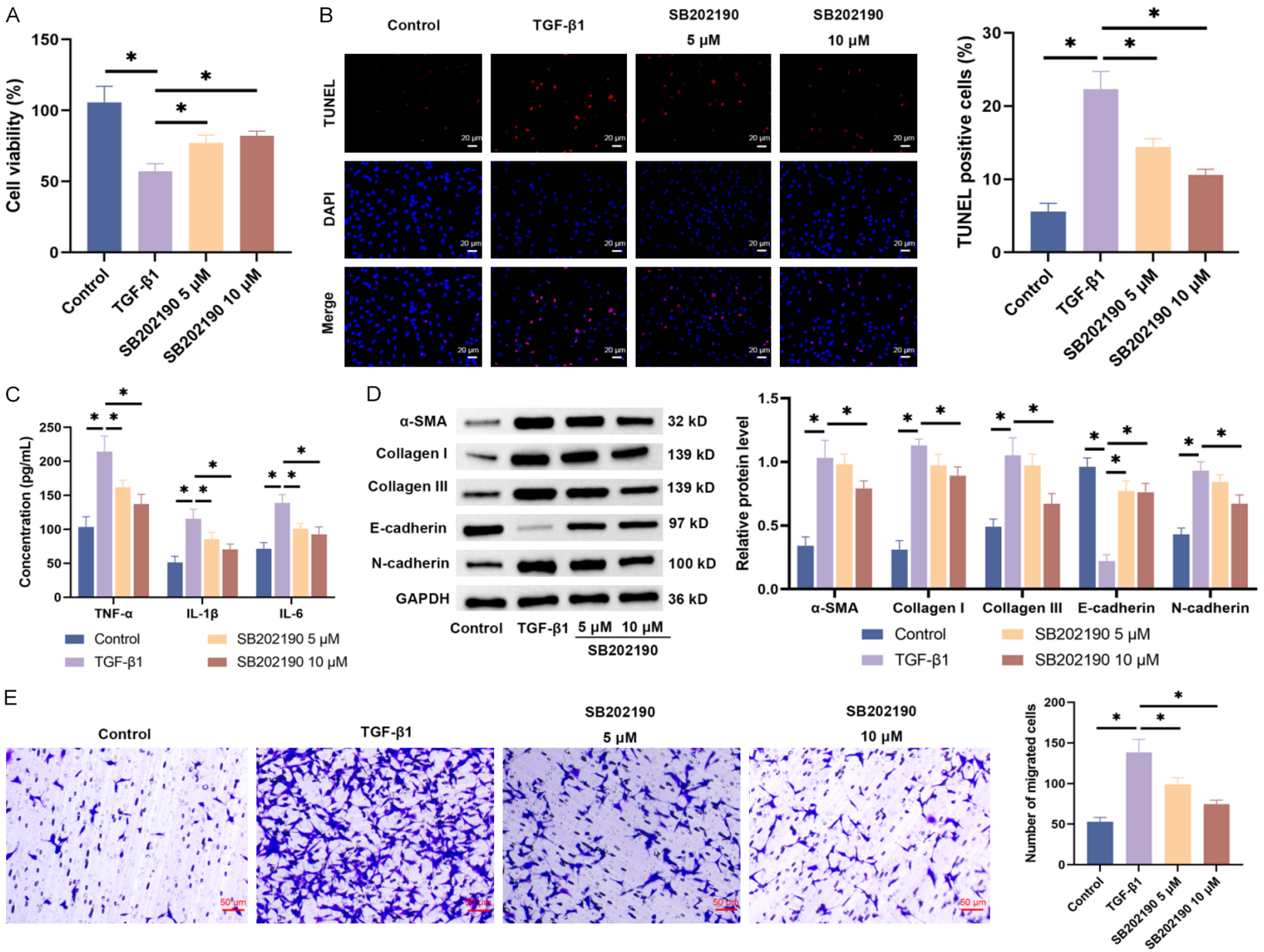
A
Cell viability (%)
Control
TGF-β1
SB202190 5 μM
SB202190 10 μM
B
Control
TGF-β1
SB202190 5 μM
SB202190 10 μM
TUNEL
DAPI
Merge
TUNEL positive cells (%)
C
Concentration (pg/mL)
TNF-α
IL-1β
IL-6
D
α-SMA
Collagen I
Collagen III
E-cadherin
N-cadherin
GAPDH
32 kD
139 kD
139 kD
97 kD
100 kD
36 kD
Relative protein level
E
Number of migrated cells

Figure 3. SB202190 attenuates TGF-β1-induced cellular fibrosis and EMT. HEECs (human endometrial epithelial cells) were induced with 10 ng/mL TGF-β1 (transforming growth factor beta 1) to establish an IUA (intrauterine adhesion) cell model and co-cultured with SB202190 (5, 10 μM) for 48 h. (A) CCK-8 (Cell counting Kit-8) assay for cell viability; (B) TUNEL (TdT-mediated dUTP Nick-End Labeling) staining for cell apoptosis (scale bar = 20 μm, ×200); (C) ELISA (enzyme-linked immunosorbent assay) for levels of inflammatory factors TNF-α (tumor necrosis factor-alpha), IL-1β (interleukin-1 beta), and IL-6 (interleukin-6); (D) Western blot for expression of fibrosis and EMT (epithelial-mesenchymal transition)-related proteins; (E) Transwell assay for cell migration (scale bar = 50 μm, ×200); Three independent replicate experiments were performed. Data are presented as mean ± standard deviation. One-way ANOVA was used for (A, B, E), two-way ANOVA for (C, D), *post-hoc* test using Tukey's multiple comparisons test, * indicates $P < 0.05$.

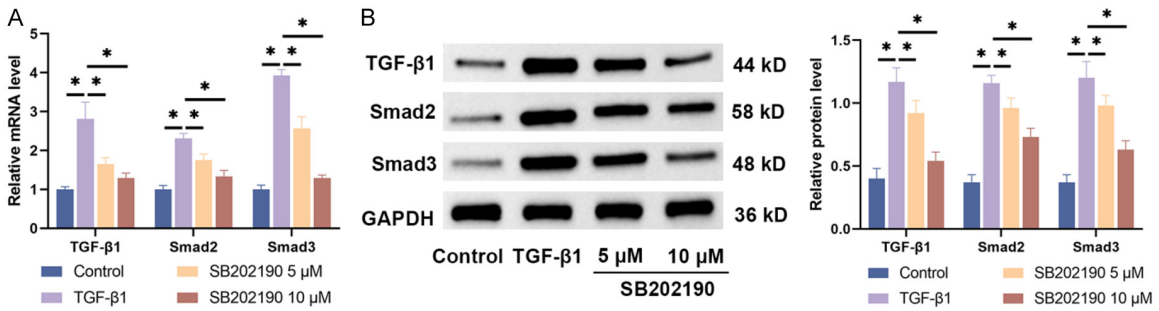

Figure 4. SB202190 inhibits the TGF-β/Smad signaling pathway in TGF-β1-induced HEECs. (A, B) RT-qPCR and western blot were used to detect the expression of TGF-β1 (transforming growth factor beta 1), Smad2 (mothers against decapentaplegic homolog 2), and Smad3 (mothers against decapentaplegic homolog 3) in HEECs (human endometrial epithelial cells); Three independent replicate experiments were performed. Data are presented as mean ± standard deviation. Two-way ANOVA was used for (A, B), *post-hoc* test using Tukey's multiple comparisons test, * indicates $P < 0.05$.

agonist SRI-011381 to HEECs in combination with 10 μM SB202190 for intervention. The results demonstrated that SRI-011381 significantly reactivated the TGF-β/Smad signaling pathway (**Figure 5A**, **5B**, $F = 155.30$, 35.25, $P < 0.05$), decreased cell viability (**Figure 5C**, $t = 5.16$, $P < 0.05$), promoted cell apoptosis (**Figure 5D**, $t = 9.15$, $P < 0.05$) and inflammation (**Figure 5E**, $F = 34.33$, $P < 0.05$), upregulated fibrosis and EMT markers (**Figure 5F**, $F = 20.93$, $P < 0.05$), and enhanced migration (**Figure 5G**, $t = 8.62$, $P < 0.05$). These results confirmed that SB202190 functions by inhibiting TGF-β/Smad signaling.

Discussion

Intrauterine adhesion (IUA) is characterized by endometrial basal layer damage and endometrial fibrosis [22]. Current evaluation of IUA mouse models mainly focuses on endometrial morphology, gland number, and collagen deposition [23, 24]. Endometrial structure was severely damaged in IUA mice, with fewer glands and excessive collagen deposition, consistent with the typical clinicopathologic features. SB202190 treatment significantly improved endometrial morphology, increased gland number, and reduced collagen deposition, confirming its ability to alleviate endometrial fibrosis in IUA.

Inflammation is critical in IUA progression. Although simple inflammatory stimulation cannot directly induce IUA, it has a pivotal influence on the onset, progression, and postoperative recurrence of the condition [16, 25]. Persistent chronic inflammation promotes abnormal tissue repair and progressive fibrosis. Furthermore, repeated tissue damage and repair processes have been shown to exacerbate fibrosis, ultimately leading to the loss of normal tissue function [26-28]. The NF-κB signaling pathway exerts a pivotal regulatory role in the inflammatory response in IUA. The activation of this pathway has been shown to modulate the equilibrium of Th17/Treg cells, promote the pro-inflammatory-factor secretion such as IL-17, and subsequently trigger the upregulation of IL-6, TNF-α, and other inflammatory mediators, forming a positive feedback inflammatory loop [28, 29]. IUA models showed elevated levels of TNF-α, IL-1β, and IL-6 levels, which were markedly reduced by SB202190, indicating effective suppression of local inflammation.

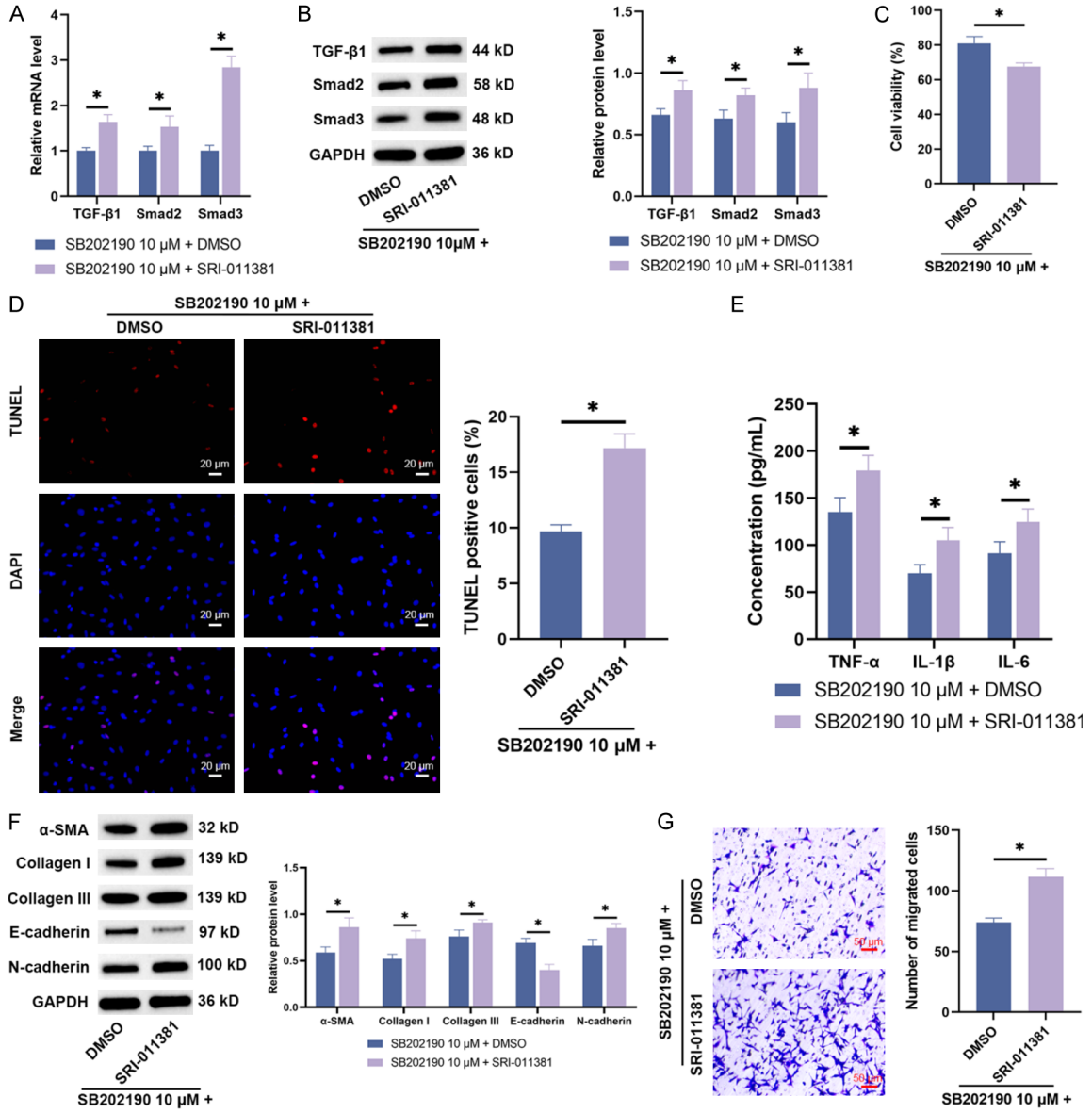

Figure 5. SRI-011381 reverses the inhibitory effects of SB202190 on cellular fibrosis and EMT. HEECs (human endometrial epithelial cells) were treated with 10 μM SRI-011381 (a TGF-β/Smad pathway agonist) in combination with 10 μM SB202190; DMSO served as control. (A, B) RT-qPCR and western blot were used to detect the expression of TGF-β1 (transforming growth factor beta 1), Smad2 (mothers against decapentaplegic homolog 2), and Smad3 (mothers against decapentaplegic homolog 3) in HEECs; (C) CCK-8 (Cell counting Kit-8) assay for cell viability; (D) TUNEL (TdT-mediated dUTP Nick-End Labeling) staining for cell apoptosis (scale bar = 20 μm, ×200); (E) ELISA (enzyme-linked immunosorbent assay) for levels of inflammatory factors TNF-α (tumor necrosis factor-alpha), IL-1β (interleukin-1 beta), and IL-6 (interleukin-6); (F) Western blot for expression of fibrosis and EMT (epithelial-mesenchymal transition)-related proteins; (G) Transwell assay for cell migration (scale bar = 50 μm, ×200); Three independent replicate experiments were performed. Data are presented as mean ± standard deviation. Two-way ANOVA was used for (A, B, E, F), *post-hoc* test using Tukey's multiple comparisons test; t-test was used for (C, D, G), * indicates $P < 0.05$.

EMT is a core mechanism of endometrial fibrosis [30]. The homeostasis of the endometrium is closely related to the normal physiologic function of epithelial cells. Short-term EMT actually contributes to endometrial repair after damage. However, aberrant sustained activation of EMT leads to a series of changes - stromal cells transform into myofibroblasts; epithelial cells lose their normal shape and function, and the extracellular matrix is remodeled. The

classical TGF-β/Smad signaling pathway is the core pathway regulating EMT and tissue fibrosis [29, 31]. TGF-β1, as a key pro-fibrotic cytokine, exerts its biological function by activating the downstream Smad family proteins [32]. Uterine cavity injury induces the release of TGF-β1, which subsequently leads to the phosphorylation of Smad2 and Smad3. This further promotes the expression of pro-fibrotic proteins, regulates extracellular matrix deposition, and induces fibroblast activation [32-34]. Levels of TGF-β1, Smad2, and Smad3 were increased in both IUA mice and TGF-β1-induced HEECs, accompanied by elevated fibrotic and EMT markers and reduced E-cadherin. These changes were consistent with previous reports [35]. SB202190 intervention significantly inhibited the activated TGF-β/Smad pathway and reversed fibrosis and EMT changes. However, addition of the pathway agonist SRI-011381 reversed the protective effect of SB202190 on HEECs. Therefore, these results indicate that SB202190 attenuates endometrial fibrosis, inflammation, and EMT in IUA by inhibiting the TGF-β/Smad signaling pathway. p38 MAPK is a promising target for fibrotic diseases. SB202190 has good inhibitory specificity and low toxicity in preclinical models. Future studies will focus on its pharmacokinetic characteristics, including bioavailability, *in vivo* stability, tissue distribution, and long-term safety to support clinical translation.

Several limitations should be noted. Findings from animal and cellular models cannot be directly extrapolated to human patients. Future studies using clinical endometrial samples will be performed to verify the efficacy and mechanism of SB202190 in human IUA, providing more reliable evidence for clinical application.

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Disclosure of conflict of interest

None.

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