INTRODUCTION

Intracranial aneurysm (IA) is a cerebrovascular aneurysm-like protrusion caused by pathologically limited expansion of the arterial wall.\(^1,2\) It is a major cerebrovascular disease that threatens people’s health with an incidence rate of 2%-3% in the population. The incidence and mortality of subarachnoid hemorrhage (SAH) caused by IA are high in China, with a mortality rate of 11%-70%.\(^3\) Only 30%-45% of surviving patients’ functions can be restored to their pre-onset state.\(^2,4,5\) Thus, it is of great clinical and social importance to find reasonable treatment.

In the initial formation stage of IA, intravascular hemodynamic changes can damage the vascular endothelium which undergoes inflammatory defense and oxidative stress.\(^6,7\) The secreted by IA are high in China, with a mortality rate of 11%-70%.\(^3\) Only 30%-45% of surviving patients’ functions can be restored to their pre-onset state.\(^2,4,5\) Thus, it is of great clinical and social importance to find reasonable treatment.

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Abstract

As an inhibitor of STAT3, BP-1-102 can regulate the inflammation response caused by vascular smooth muscle cells (VSMCs) by inhibiting the JAK/STAT3/NF-κB pathway, thereby attenuating the symptoms of intracranial aneurysm (IA). IA mouse model was established by stereotactic injection of elastase to evaluate the effect of BP-1-102. The expression levels of smooth muscle markers and matrix metalloproteinases (MMPs) were detected by qRT-PCR, and the levels of inflammatory factors were detected by ELISA and qRT-PCR. The protein levels of the NF-κB signaling pathway factors were examined by Western blot. BP-1-102 reduced blood pressure in aneurysm mice, up-regulated smooth muscle cell markers MHC, SMA, and SM22, and down-regulated the expression of MMP2 and MMP9 in vascular tissues. At the same time, BP-1-102 also down-regulated the expression levels of inflammatory response factors and the NF-κB pathway proteins. In the IA model, BP-1-102 can reduce the expression of inflammatory factors and MMPs bound to NF-κB by inhibiting the activation of the JAK/STAT3/NF-κB pathway proteins, and then restore the vascular wall elastin to reduce blood pressure, thereby treating aneurysm.
inflammatory factors act on vascular smooth muscle cells (VSMCs) through the intercellular cascade reaction. VSMCs undergo phenotypic transformation under the stimulation of inflammatory factors, and further induce the production of downstream inflammatory factors, such as tumor necrosis factor alpha (TNF-α), interleukin 1β (IL-1β), IL-6, monocyte chemoattractant protein-1 (MCP-1), interferon-γ (IFN-γ), and IL-10. VSMCs are characterized by their ability to transform their phenotypes under environmental stimuli. Under physiological conditions, the VSMCs are in a contracted state, which regulate blood flow and maintain the tension of blood vessels. When the vascular environment or blood flow conditions change, VSMCs can undergo an inflammatory response and matrix remodeling, and transform from contractile cells to inflammatory response cells. VSMCs exhibit a strong plasticity during the development of new blood vessels to functional mature blood vessels. Compared with naive VSMCs, mature VSMCs express smooth muscle α22 alpha (SM22α), smooth muscle alpha actin (SM-α-actin), and smooth muscle myosin heavy chain (SM-MHC). The proliferation and apoptosis of VSMCs maintain a dynamic balance under normal physiological environment. IA formation and development are caused by endothelial dysfunction and phenotypic transformation of VSMCs to the pro-inflammatory phenotype. When the intracranial blood vessel wall is abnormally stimulated, VSMCs undergo an inflammatory reaction to proliferate and secrete extracellular matrix to maintain the integrity of vascular function.

Previous studies have shown that the inflammatory response, especially nuclear factor κB (NF-κB)-mediated inflammation, plays a vital role in the pathogenesis of IA. NF-κB is a transcription factor that promotes the expression of pro-inflammatory genes, including cytokines, adhesion molecules, chemokines, growth factors, and some inflammatory-related enzymes, to regulate inflammation. The abnormal activation of JAK2/STAT3/NF-κB is related to the occurrence and development of IA. Studies have shown that NF-κB is activated in the early stage of cerebral aneurysm formation, and up-regulates the expression of downstream genes. A large number of inflammatory cells are attached to the blood vessel wall of the aneurysm, which induce changes in the secretion of smooth muscle cells and endothelial cells, thereby causing damage to the arterial blood vessel wall.

Studies have shown that the extracellular matrix degradation process involving matrix metalloproteinases (MMPs) is implicated in the formation of IA. MMPs can destroy and degrade the elastic fibers of blood vessels, leading to aneurysms. MMP-9 and MMP-2 are two members of the MMP family mainly produced by epithelial cells and macrophages, and play an important role in the formation of IA. Up-regulated expression of MMP2 and MMP9 can destroy the extracellular matrix, weaken the integrity of the arterial wall, leading to the occurrence and development of IA.

Taking all of the above literature into consideration, we hereby hypothesized that BP-1-102, a novel and potent STAT3 inhibitor, could regulate the contraction of smooth muscle cells by interrupting the JAK2/STAT3/NF-κB signaling pathways, thereby regulating the expression of MMPs and inflammatory factors, and eventually restore blood pressure and relieve the rupture of aneurysms.

## 2 METHODS AND MATERIALS

### 2.1 Animal model

Nine-week-old male C57BL/6 mice were kept in SPF animal house. IA was induced according to the previously described methods involving induced hypertension and stereotactic elastase injection. First, we perform unilateral nephrectomy on the animal, where the left stiff artery and the left renal artery were ligated under general anesthesia using pentobarbital sodium injection (50 mg/kg). Elastase (Sigma-Aldrich) of 35 mU was then injected stereotactically into the cerebrospinal fluid of the basal cistern 1 week later. In the second operation, subcutaneous injection of deoxycorticosterone acetate (50 mg; 21-day release, American Innovative Research) was also performed. All the procedures complied with the guidelines approved by the Administrative Committee of Experimental Animal Care and Use of Quanzhou First Hospital Affiliated to Fujian Medical University. All surgeries were performed under anesthesia and efforts were made to minimize the suffering and number of animals used in this study.

Animals were monitored for changes in body weight and neurological function by observers blind to group assignment every day, and animals that lost more than 2.0 g in weight within 24 h or exhibited significant loss of nerve function were euthanized and autopsied to confirm the occurrence of SAH, using the neurological symptom scoring criteria described previously. To detect aneurysmal rupture, two observers blind to group assignment performed neurological examination daily as previously described. Neurological symptoms were scored as follows: 0: normal function; 1: reduced eating or drinking activity demonstrated by a weight loss >2 grams of body weight (<10% weight loss) for 24 h; 2: flexion of the torso and forelimbs on lifting the whole animal by the tail; 3: circling to one side with a normal posture at rest; 4: leaning to one side at rest; and 5: no spontaneous activity. When mice were found to show neurological symptoms associated with aneurysmal rupture (neurological score, 1–5), they were euthanized immediately (within 4 h). A total of 150 mice were employed in this study. Each group of 30 mice was then modeled and observed for 21 days after modeling. Aneurysm was defined as the wall of blood vessel larger than the diameter of the aorta and partially dilated outward. If symptoms of ruptured aneurysm appeared, the animal was euthanized and verified for intracranial hemorrhage within 4 h. Mice that did not show symptoms after 21 days were euthanized, and then confirmed the occurrence of aneurysm. Then, the artery tissue where the aneurysm occurred was obtained, and then the circles of Willis of the obtained artery tissue were used to perform PCR, ELISA, and Western blot experiments.

### 2.2 Drug treatments

BP-1-102 (dissolved in 0.1% DMSO in PBS; Selleck Chemical), the STAT3 inhibitor, was administrated via oral gavage every other day...
to mice at the dose of 1, 2, and 5 mg/kg, respectively, starting from the IA induction to 21 days after.

2.3 | Blood pressure measurement

We measured the blood pressure of animals without symptoms of ruptured aneurysm at Week 0 (before the operation started), the first week, the second week, and the third week after the operation (Kent Industries Co.). The specific method used followed previously established protocol, as follows: water and food was deprived 2 h before the measurement, and the animals were placed in a 37°C preheated incubator for 10 min to adapt to the environment. Blood pressure was measured after adjusting the instrument and stabilizing the mice’ beating after clamping the mouse tail. The blood pressure of mice was tested three times to obtain the average value of blood pressure.

2.4 | ELISA

Interleukin-1α, IL-6, and TNF-α ELISA kits (purchased from R&D System) were performed to detect the expression of inflammatory cytokines of vascular tissues of circles of Willis. Tissues were treated according to the manufacturer’s protocols, and the supernatant was added into 96-well plates coated with primary antibodies. After washing four times, biotinylated antibodies were added into each well for 30 min at 37°C, and detected using horseradish peroxidase (HRP)-conjugated streptavidin and chromogen reagent. Absorbance at 570 nm was immediately determined using an ELISA reader (Molecular Devices).

2.5 | Reverse transcription-quantitative polymerase chain reaction

We measured the expression levels of smooth muscle cell markers (MHC, SMA, and SM22) and MMPs (MMP2 and MMP9), IL-1β, IL-6, and TNF-α in vascular tissues of circles of Willis by qRT-PCR (Table 1). Total RNA was extracted using TRIzol (Life Technologies), then cDNA was synthesized using the Reverse Transcription Kit (Qiagen). Primers were designed by Primer 5.0 and sequences as follows: MHC (F): ATTGCGCAAGGAAATGGGG, MHC (R): GCACATACAGCCTGTCACC; SMA (F): GAGGAGCAAGTATCATGGC, SMA (R): ATCCGGAACCTGACATTAC; SM22 (F): GCCTCAACATGGGCAACAG, SM22 (R): TCAGCAAGGGTTACTCACAC; MMP2 (F): ATTGGCAGCCGGTTTTCTCTAA, MMP2 (R): GGTCTGCTTCTCTCTCTC; MMP9 (F): TTTTCCATTGGATGGAGTCA, MMP9 (R): TAAAGCAGTTCAGAAGCCT; IL-1β (F): TCTCAAGGTTACTCAGC; IL-1β (R): TTGTTGCGCTGCTGATG; IL-6 (F): GGTGCTTCTCTGTTGTT, IL-6 (R): ACTGCAAGGGCTTGTACCT; TNF-α (F): TTGGTCATGGGAGCTCAG, TNF-α (R): TTGGTTCAGCCGTCTCAGC; GAPDH (F): CTTTTAGGAGGTAATTG, GAPDH (R): CTGAGCAGTCAGGCTTGTAGT. The amplification protocol for the reaction was as follows: preincubation at 95°C for 4 min, followed by 35 cycles at 95°C for 40 s, 56°C for 30 s, and 72°C for 30 s. The relative mRNA expression levels of targeted genes were calculated using the comparative 2ΔΔCt method. GAPDH was used as the internal standard.

2.6 | Western blot

The protein levels of JAK2, p-STAT3, STAT3, p-NF-κB (p-p65), NF-κB (p65), and GAPDH were determined by Western blot. Samples were extracted on ice using RIPA buffer supplemented with 1% protease inhibitor cocktail Complete Mini (Roche). BCA method was used to determine the protein concentration. Protein samples of 40 μg were loaded on 10% SDS-PAGE at 100 volts and then transferred to a nitrocellulose membrane at 220 mA current for 1.5 h. Membranes were probed overnight at 4°C with primary antibodies against JAK2 (1:1000, #3265; Cell Signaling Technology, Rabbit mAb), p-STAT3 (1:1000, sc-8059; Santa Cruz), STAT3 (1:1000, #9132; Cell Signaling Technology, Mouse mAb), p-NF-κB (p-p65) (1:1000, #3033; Cell Signaling Technology, Rabbit mAb), NF-κB (p65) (1:1000, #8242; Cell Signaling Technology, Rabbit mAb), and GAPDH (1:2000, sc-47724; Santa Cruz), respectively. The membrane was incubated

### Table 1: Oligonucleotide primer sequences for qRT-PCR

| Gene      | Primer direction | Sequence (5’-3’) |
|-----------|------------------|-----------------|
| IFN-γ     | Forward          | GTATTGCCAAGTGGAGTCT |
|           | Reverse          | AATCAGGAGCCCTCTCCTT |
| IL-10     | Forward          | CTTACTGACTGCTAGGATCTCA |
|           | Reverse          | GCACCTCTGAGCAGCATGTTG |
| MCP-1     | Forward          | CCAGCCTTCTACTTTGGAGG |
|           | Reverse          | CCAGCCTTCTACTTTGGAGG |
| TNF-α     | Forward          | CCAACGCCGTGATCTCAAGACA |
|           | Reverse          | AGATACGAAATGGGGATGG |
| IL-1β     | Forward          | CTACAGGTCTCGAGATGAC |
|           | Reverse          | TTCAATGGGAGAGGCTT |
| IL-6      | Forward          | TCCCAGGCTTCTTGAGGAGT |
|           | Reverse          | GAGGTGCCTCTGAGGAGT |
| SM-MHC    | Forward          | CAGCTTTGTCAGAGGAAATA |
|           | Reverse          | TGACAGAACCTTTCTACCT |
| SMA       | Forward          | CTTTCATTGGAGTGGAGTCA |
|           | Reverse          | GGGCTGTGATCCCTCTTG |
| SM22      | Forward          | GTGTCAGACTGTGAGGACC |
|           | Reverse          | AGTTTGCTGCTGCTGAGG |
| MMP2      | Forward          | GGAGCAAGTTCTGGGAGG |
|           | Reverse          | GGTTACAGGGATGGGATT |
| MMP9      | Forward          | GACATCTTTCCGAGGAAAG |
|           | Reverse          | CCACCTGTTCACCTCAT |
| GAPDH     | Forward          | GTGCCATCTGGCTTGTTG |
|           | Reverse          | GGAGTGGTGCGGAAATGCTGTA |
with HRP-conjugated secondary antibodies (1:3000, Bioworld) for 2 h at room temperature. Proteins were detected by the Odyssey® Infrared Imaging System. Densitometric analysis was calculated using the Scion Imaging application (Scion Corporation), using GAPDH as the internal reference.

2.7 | Statistical analysis

Rates of IA formation and rupture were evaluated by a Fisher’s exact test. Other data were analyzed by the analysis of variance (one or two-way) and a post hoc test. All data are expressed as mean ± SD, and \( p \leq .05 \) is considered statistically significant.

3 | RESULTS

3.1 | Effects of BP-1-102 on the development of aneurysmal rupture in mice

In order to verify the effect of BP-1-102 on IA rupture, we treated four groups of aneurysm model mice (30 male mice in each group) with different concentrations of BP-1-102 (1, 2, and 5 mg/kg). The incidence of aneurysm rupture in the 5 mg/kg BP-1-102 treatment group was significantly lower than that in the vehicle control group (Figure 1A). In the survival analysis, the number of asymptomatic surviving mice increased significantly in the 2 and 5 mg/kg group compared to vehicle control (Figure 1B), therefore, 5 mg/kg BP-1-102 dose was chosen for the subsequent experiments. These above results showed that BP-1-102 treatment could effectively prevent the rupture of aneurysms.

3.2 | BP-1-102 could attenuate blood pressure caused by IA

The underlying mechanism responsible for the formation of cerebral aneurysms may be attributed to multiple factors, in which hypertension and increased activity of MMPs play an important role. Therefore, we first monitored the blood pressure at Weeks 0, 1, 2, and 3 of the operation and found that, compared with the control group, the blood pressure of the vehicle control group increased significantly over time. While the 5 mg/kg BP-1-102 treatment group displayed significantly lowered blood pressure (by nearly 40 mmHg) compared to the vehicle control group (Figure 2A). MMPs are mainly secreted proteolytic enzymes produced by smooth muscle cells in a non-enzymatic form, so we next measured the expression of...
smooth muscle cell markers (MHC, SMA, and SM22) and MMPs (MMP2 and MMP9). We found that BP-1-102 treatment significantly inhibited the increased expression of smooth muscle cell markers (Figure 2B). Moreover, the 5 mg/kg BP-1-102 treatment group showed significantly inhibited MMP protein levels compared to the vehicle control group (Figure 2C). These results suggested that BP-1-102 treatment inhibited the expression of MMPs.

3.3 | BP-1-102 suppressed IA-induced inflammatory responses

In order to explore the inflammatory response after IA rupture in the brain, we conducted an ELISA assay on the level of inflammatory factors (TNF-α, IL-1β, IL-6, MCP-1, IFN-γ, and IL-10) in the tissue. In the aneurysm model control group (VC), the expression levels of inflammatory factors increased significantly, and were then significantly reduced by BP-1-102 treatment (Figure 3A–E), while IL-10, an anti-inflammatory cytokine, showed an opposite expression profile (Figure 3F). The synthesis of new proteins caused by STAT activation is necessary for the anti-inflammatory effect of IL-10 on monocytes, further indicating that the anti-inflammatory ability was weakened with the elevated expression of inflammatory factors. Subsequently, we conducted qRT-PCR on the expression of these inflammatory factors, and the results were the same as ELISA (Figure 4A–F). This result indicated that BP-1-102 inhibited the inflammatory response caused by ruptured aneurysm.

3.4 | BP-1-102 reduced the expression of inflammation signaling pathway-related proteins

In view of the above results, ruptured aneurysm could cause an inflammatory response that was inhibited by BP-1-102 administration, mediated by an unknown mechanism. In order to explore the mechanism responsible, we performed Western blot for the NF-κB pathway proteins that play an important role in immune and inflammatory responses. The results showed that in the aneurysm model group (VC), the expression levels of JAK, STAT3, and NF-κB total, and phosphorylated proteins were all up-regulated (Figure 5A–F), all of which were significantly reduced by BP-1-102 treatment. These results indicated that...
BP-1-102 could suppress the phosphorylation/activation of the JAK/STAT3/NF-κB pathway proteins, thereby inhibiting the inflammation response and the expression of MMPs bound to NF-κB, and eventually reduce blood pressure and relieve aneurysm rupture.

**DISCUSSION**

Intracranial aneurysm is a disease that seriously threatens human life and health, with a high incidence rate second only to cerebral
thrombosis and high-pressure cerebral hemorrhage in cerebral tube disease, and its mortality rate is as high as 70%. To date, the treatment methods of IA mainly include intravascular interventional therapy and surgical clamping, both of which inevitably also result in complications and mortality. The disease is more common in middle-aged people, which has no obvious symptoms in the early stage. With the development of IA, once the tumor suddenly ruptures and bleeds, the patient condition will quickly deteriorate. Therefore, the investigation searching for novel IA treatment is of great clinical significance.

In previous studies, ruptured aneurysm was found to be related to dysfunction of VSMCs. VSMCs have the ability to deform under the stimulation of injury and inflammatory response. As shown in Figure 2B, the expression levels of the smooth muscle marker genes were significantly down-regulated in the aneurysm model mice, and the deformation of blood vessels led to changes in blood flow rate and affected the stability of blood pressure, which could be rescued by the treatment of BP-1-102 (Figure 2A).

**FIGURE 5** BP-1-102 reduced the expression of inflammation signaling pathways-related proteins in mice models with intracranial aneurysm. Western blotting was applied to analyze inflammation signaling pathways-related proteins expressions including JAK2, p-STAT3, STAT3, p-NF-κB (p-p65), and NF-κB (p65). (A) Representative blots and (B–F) the expressions were normalized to NC. N = 3 for each group in each panel and the results have been confirmed by repeated experiments for three times. Data were presented as mean ± SD. #p < .01 and ###p < .001 compared to NC group. *p < .05, **p < .01, and ***p < .001 compared to VC group. NC, normal control; VC, vehicle control.
Studies have shown that MMPs can compromise the elasticity of blood vessel walls and are related to the formation of IA. The main substrates of MMPs include gelatin, colloid, and elastic protein, which destroy and degrade the inner layer of the tube and lead to the development of aneurysms, and the high expression of MMPs in aneurysm model mice disrupts the tension in the blood vessel wall.\textsuperscript{22,31} We assessed the expression levels of MMP-9 and MMP-2, which have been implicated in aneurysm formation, and found that both of them showed high expression levels in the aneurysm model mice, which could be reduced by BP-1-102 treatment (Figure 2C). This result is consistent with the speculation that the high expression of MMPs in aneurysm model mice disrupted the tension in the blood vessel wall, resulting in changes in blood pressure, while BP-1-102 effectively restored the increased blood pressure as a result of the IA. Therefore, monitoring the changes in MMP levels during the formation of cerebral aneurysms could provide a basis for finding preventive measures for cerebral aneurysms.

The above results demonstrated that the vascular smooth muscle of the IA model mice was damaged, which could cause inflammatory response. Moreover, researches have found that there could be an severe secondary inflammatory response feedback after the aneurysm rupture.\textsuperscript{19,30} Previous studies have found that the NF-κB-mediated inflammation is linked to IA.\textsuperscript{5,14,17} We therefore evaluated the expression of inflammatory factors, and found that the anti-inflammatory factor IL-10 was down-regulated (Figures 3F and 4F), while the pro-inflammatory factors were all up-regulated (Figures 3A–E and 4A–E), indicating that IA changed the anti-inflammatory status, and STAT3 inhibitor BP-1-102 could reduce the expression of pro-inflammatory factors by up-regulating IL-10.

Based on the above results, we speculate that BP-1-102 can regulate the tension of the blood vessel wall and the level of inflammatory response by reducing the expression levels of MMPs, but the underlying mechanism is still unclear. We are particularly interested in the NF-κB-related inflammatory response, especially the JAK/STAT3/NF-κB pathway, in which the BP-1-102 inhibitor target STAT3 is involved.\textsuperscript{14} We found that the expression levels of total JAK/STAT3/NF-κB proteins and phosphorylation-activated proteins were all up-regulated, and were then repressed by BP-1-102 treatment (Figure 5A–F), suggesting that the therapeutic effect of BP-1-102 on IA is mediated through the JAK/STAT3/NF-κB inflammatory response pathway.

Nuclear factor-κB is a transcription factor, which can induce the expression of pro-inflammatory genes including cell factors, adhesion factors, chemokine factors, growth factors, and inflammation-related enzymes during the inflammatory response.\textsuperscript{13} Intravascular growth factors are the strongest regulators in promoting tube growth, proliferation and migration of vascular endothelial cells, and the progression of atherosclerotic injury, through mechanisms including inflammatory infiltration and neovascularization.\textsuperscript{6} The abnormal expression of MMP-2 and MMP-9 in the cerebrovascular artery wall may be an important reason for the inflammatory reaction and pathological changes during IA. We established the IA mouse model and assessed VSMCs, MMPs, inflammatory response factors and NF-κB pathway proteins after BP-1-102 treatment, and found that BP-1-102 could affect the expression of VSMCs and MMPs through the JAK/STAT3/NF-κB pathway, changing the expression of inflammatory factors and regulating the elasticity of the blood vessel wall, which could provide a theoretical basis for the treatment of IA.

5 | CONCLUSIONS

In summary, using the current mouse IA model, we hereby reported that BP-1-102 regulated the contraction of smooth muscle cells by interrupting the JAK2/STAT3/NF-κB signaling pathways, thereby regulating the expression of MMPs and inflammatory factors, which eventually lead to restored blood pressure and relieved IA rupture.

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DISCLOSURES

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Zhihui Jiang, Jixin Huang, Lingtong You, Jinning Zhang, and Bingyu Li conducted the experiments and analyzed the data. Zhihui Jiang and Zhihui Jiang conceived the study. Bingyu Li coordinated and supervised the study, Zhihui Jiang, Jixin Huang, Lingtong You, Jinning Zhang, and Bingyu Li wrote the manuscript. Zhihui Jiang, Jixin Huang, Lingtong You, Jinning Zhang, and Bingyu Li approved the publication of this study, and are accountable for all aspects of the work and ensure the accuracy or integrity of any part of the work.

ETHICS STATEMENT

All the procedures complied with the guidelines approved by the Administrative Committee of Experimental Animal Care and Use of Quanzhou First Hospital Affiliated to Fujian Medical University.

DATA AVAILABILITY STATEMENT

Data could be obtained upon request to the corresponding author.

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