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ORIGINAL RESEARCH

Downregulation of Gbp2 Attenuates LPS-Induced Inflammation in BV2 Microglia Cells Through Inhibition of STAT1

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Introduction: Postoperative cognitive dysfunction (POCD) commonly occurs in around 50% of patients within first few weeks after surgery. Research indicates that the activation of microglia is believed to be closely associated with the decline in POCD. Neuroinflammation has been confirmed as a significant feature of POCD.

Methods: Inflammation-associated differentially expressed genes (DEGs) were screened using GEO databases. Quantitative PCR and Western blot were applied for analysis of mRNA and protein expressions, respectively. Furthermore, the concentrations of IL-6 and TNF-α were measured using ELISA.

Results: Six hippocampal tissues collected from three mice with POCD and three control mice were used for inflammation-associated differential gene expression analysis. In addition, Gbp2 was found to be significantly upregulated, which was associated with the inflammatory responses in patients with POCD. Knockdown of Gbp2 significantly reversed LPS-induced inflammation and apoptosis in mouse microglial BV2 cells. The anti-apoptotic and anti-inflammatory effects of Gbp2 deficiency was mediated by the transcription factors STAT1 and Irf1. Taken together, our findings demonstrated Gbp2 level was highly expressed in POCD patients comparing with that in non-POCD patients post-surgery.

Conclusion: Downregulation of Gbp2 attenuates LPS-induced inflammation in BV2 cells through inhibition of STAT1, which might shed new lights on exploring new strategies against POCD.

Keywords: postoperative cognitive dysfunction, STAT1, Gbp2, neuroinflammation

Introduction

Postoperative cognitive dysfunction (POCD) is a prevalent neurological complication following surgery and systemic anesthesia, particularly in elderly patients.[1,2] POCD is characterized by a decline in cognitive function post-surgery, with impairments in memory, learning, attention, and executive functions that may persist for weeks to several months, or even longer.[3] These complications can significantly diminish the quality of life after surgery, prolong hospitalization, increase mortality rates, and impose a substantial burden on society.[4] As the age of surgical patients increases, the likelihood of developing POCD also rises.

The neuroinflammation triggered by overactive glial cells is a key factor in the occurrence of POCD.[5] Anesthesia, trauma and postoperative pain trigger the interaction between the immune system and the central nervous system, causing hippocampal microglia to transform into an inflammatory phenotype (M1).[6] Then, M1 hippocampal microglia was able to release of inflammatory mediators including tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), thereby leading to cognitive decline.[7] Although there have been advancements in perioperative anesthesia and surgical techniques, the incidence of POCD

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remains high.[8] This phenomenon indicating that in addition to the neuroinflammation, other potential factors may take part in the pathogenesis of POCD.

Microglia serve as the resident macrophages within the central nervous system, playing a crucial role in monitoring and maintaining the stability of the neural environment.[9] These cells frequently activate in response to almost all types of neurological disorders. Upon activation, microglia can release inflammatory cytokines, move towards the site of injury, and phagocytose damaged neurons.[10] Research indicates that the activation of microglia is believed to be closely associated with the decline in patients with POCD after surgery.[11] Thus, investigating microglia may offer invaluable insights into the mechanisms underlying neurological diseases.

Guanylate binding protein 2 (Gbp2), a member of the guanine-binding protein (GBP) family, have a significant role in controlling cell apoptosis and inflammation.[12,13] It is reports that up-regulation of GBP2 is associated with representative brain disorders including Alzheimer's disease.[14] GBP2 was found as one of the highly expressed genes in brain tissue and its high expression is associated with immune responses. In addition, GBP2 was reported to be highly expressed in M1 microglia.[14] This suggests GBP2 is able to act as a gene-inducing immune response in the immune cell of the brain. However, it remained unclear whether the abnormal expression of GBP2 affects the progression of neuroinflammation in POCD.

In this study, we aimed to explore the mechanisms underlying POCD and to develop effective intervention strategies to prevent or mitigate its occurrence.

Materials and Methods

Data Collection

The dataset numbered GSE115440 was retrieved from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/) and comprises six hippocampal tissues collected from three mice with POCD (POCD group) and three control mice (control group). Additionally, 854 inflammation-related genes were sourced from the Molecular Signatures database (https://www.gsea-msigdb.org/gsea/msigdb/mouse/collections.jsp?targetSpeciesDB=Mouse) and were detailed in Table S1. The detailed parameters how the 854 inflammation-related genes were selected was set as following: 1) the keyword: inflammatory; 2) collection: all collection; 3) source species: Mus musculus; 4) contributor: Gene Ontology Consortium.

Differential Expression Analysis

Utilizing the "limma" function package (version 3.52.4) in the R language, differentially expressed mRNAs (DEGs) were identified between POCD and control groups utilizing the applying thresholds of $|Log2FC| > 0.5$ and P value < 0.05.[15]

Functional Analyses

Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analyses were conducted to investigate the functional pathways of DEGs utilizing the "clusterProfiler" package in R language (version 4.7.1.2).[16] The significantly enriched GO terms and KEGG pathways were identified with a p.adjust value of below 0.05, applying the Benjamini and Hochberg (BH) correction method.

Prediction of Transcription Factors (TFs)

Using the TRRUST database (http://www.grnpedia.org/trrust/), the TFs of Gbp2 were predicted.

Cell Culture and Transfection

Mouse microglial BV2 cells (CL-0493) were sourced from Procell, and grown in DMEM medium containing 10% FBS and 1% penicillin-streptomycin (P/S). BV2 cells were maintained at 37°C with 5% CO_2. For transient transfection, the BV2 cells were treated with siRNA negative control (siRNA-NC), Gbp2 siRNA1, Gbp2 siRNA2, STAT1 siRNA1, and STAT1 siRNA2 using the Lipo2000 Transfection Reagent (Thermo Fisher).

Reverse Transcription Quantitative Real-Time PCR (RT-qPCR)

Total RNA extraction was carried out with Trizol (Invitrogen), followed by cDNA synthesis utilizing the PrimeScript II First Strand cDNA Synthesis Kit (TaKaRa). Next, quantitative PCR was conducting employing the SYBR Green Master Mix Kit (Takara). The mRNA levels of Gbp2 and STAT1 were normalized against the β-actin expression by using the $2^{-\Delta\Delta Ct}$ method.

Western Blot

Proteins were extracted from BV2 cells using with RIPA (Sigma Aldrich) and the protein concentration was quantified with BCA kit (ASPEN Biotechnology). Next, 10% SDS-PAGE was used to separate protein. Proteins were separated by 8% SDS-PAGE and transferred to PVDF membranes. The membranes were blocked with 5% non-fat milk for 1 h at room temperature and incubated overnight at 4°C with the primary antibodies against Gbp2 (1:1000 dilution), STAT1 (1:1000 dilution), IRF1 (1:1000 dilution) and GAPDH (1:1000 dilution). The primary antibodies were purchased form Abcam. After that, the membranes were incubated with the secondary antibody (1:3000 dilution) for 2 h at room temperature. Finally, proteins were detected with ECL reagent (ASPEN Biotechnology), and the densitometry was quantified by using ImageJ software (version 1.8.0).

Enzyme Linked Immunosorbent Assay (ELISA)

ELISA kits (ASPEN Biotechnology) was used to measure the levels of IL-6 and TNF-α in cell supernatants. The procedure was performed according to the manufacturer's instruction.

Immunofluorescence

Cells were fixed in 4% paraformaldehyde (Sigma Aldrich) for 20 min at room temperature. After permeabilization, the cells were incubated in blocking buffer 5% BSA for 1 h at room temperature. Next, the cells were incubated with primary antibody against Cleaved caspase 3 (Abcam) for 24 h at 4°C. Subsequently, cells were incubated with secondary antibody (goat anti-rabbit IgG, Abcam) for 1 h at room temperature. The cells were then washed with PBS for three times. The coverslips were overlaid on 50% glycerol in PBS and fluorescent images were observed by the microscope (Olympus).

Statistical Analysis

Data are presented as the mean ± SD. One-way ANOVA with Tukey's post hoc test was used to conduct multiple comparisons using GraphPad Prism 8 (Dotmatics). $P<0.05$ means a statistically significant difference.

Results

Screening of Inflammation-Associated DEGs Between POCD and Control Groups

Based on the data from the GSE115440 dataset, DEGs was screened between POCD and control groups using the "limma" package in R language. A total of 236 DEGs were identified in the POCD group compared to the control group (Figure 1A, B and Table S2). Specifically, 38 genes were significantly upregulated, while 198 genes were downregulated in the POCD group relative to the control group (Figure 1A, B and Table S2). By intersecting the 236 DEGs with 854 inflammation-related genes, we identified a total of 7 intersecting genes (Trpv4, Pla2g5, Gbp2, Itgb6, Serpina1b, Lbp, Gbp5), which were designated as candidate genes (Figure 1C).

Subsequently, GO and KEGG enrichment analyses were conducted on these seven genes. As shown in Table S3, these genes exhibited significant enrichment in 331 GO-BP, 41 GO-MF, and 20 GO-CC terms, as well as in 5 KEGG pathways. Figure 1D presents the five KEGG pathways, while the top 10 GO-BP, GO-MF, and GO-CC terms are displayed in Figure 1E.

Downregulation of Gbp2 Decreased Inflammatory Response and Increased Cell Proliferation in LPS-Stimulated BV2 Cells

Among these 7 candidate genes, Gbp2 was found significantly upregulated in POCD patient and associated with inflammatory responses, but its role in POCD remains unclear.[17] To investigate the role of Gbp2 in POCD in vitro, we downregulated Gbp2 expression in BV2 cells by using with Gbp2 siRNAs. As shown in Figure 2A, Gbp2 siRNA1 and siRNA2 notably decreased

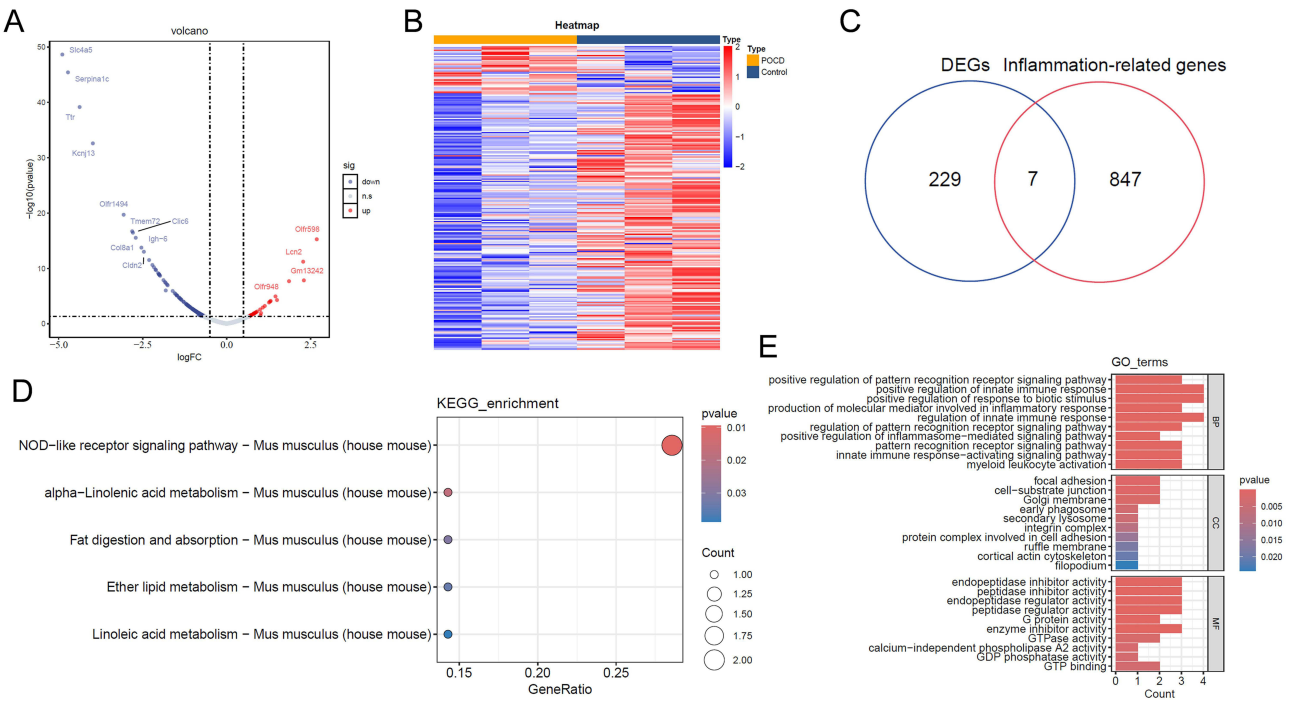

Figure 1 Screening of inflammation-associated DEGs between POCD and control groups. (**A**) Volcano plot and (**B**) heat map plot of DEGs between POCD and control groups. (**C**) Venn diagram of common genes between DEGs and inflammation-related genes. (**D**) KEGG and (**E**) GO analyses.

the levels of Gbp2 in BV2 cells compared to the siRNA-NC group. Significantly, LPS notably elevated Gbp2 levels in BV2 cells; however, Gbp2 downregulation reduced Gbp2 levels in LPS-treated BV2 cells (Figure 2B–D).

Furthermore, LPS markedly elevated IL-6 and TNF-α levels in BV2 cells; conversely, Gbp2 downregulation led to a notable decrease in IL-6 and TNF-α levels in BV2 cells exposed to LPS (Figure 2E and F). Meanwhile, LPS remarkably reduced the number of EdU-positive cells in BV2 cells; however, Gbp2 deficiency reversed this effect (Figure 2G). These results suggested that downregulation of Gbp2 could affect cell proliferation and inflammatory response in LPS-stimulated BV2 cells.

Downregulation of Gbp2 Inhibited Cell Apoptosis in LPS-Stimulated BV2 Cells

Next, we explored the effect of Gbp2 on the apoptosis of BV2 cells following exposed to LPS. As indicated in Figure 3A, LPS remarkably upregulated cleaved caspase 3 expression in BV2 cells; however, Gbp2 deficiency notably reduced cleaved caspase 3 expression in LPS-stimulated BV2 cells. Additionally, LPS remarkably upregulated the number of TUNEL-positive cells in BV2 cells; however, Gbp2 deficiency notably reduced the number of TUNEL-positive cells in LPS-stimulated BV2 cells (Figure 3B). Collectively, downregulation of Gbp2 could inhibit cell apoptosis in LPS-stimulated BV2 cells.

The Anti-Apoptotic and Anti-Inflammatory Effects of Gbp2 Deficiency Is Mediated by the TFs STAT1 and Irf1

To further understand the upstream regulation mechanism of Gbp2 in POCD, TRRUST database was applied to predict the upstream regulatory TFs of Gbp2. The results showed that Irf1 and STAT1 are potential TFs that regulate Gbp2 (Table 1 and Figure 4A). Subsequently, to explore whether STAT1 can affect the POCD progression through the expression of Gbp2, we downregulated STAT1 expression in BV2 cells by transfection with STAT1 siRNAs. As shown in Figure 4B, STAT1 siRNA1 and siRNA2 notably decreased the levels of STAT1 in BV2 cells. Notably, downregulation of STAT1 decreased LPS-induced apoptosis in BV2 cells (Figure 4C). Additionally, downregulation of STAT1 notably reduced IL-6 and TNF-α levels in BV2 cells exposed to LPS compared to LPS treatment group

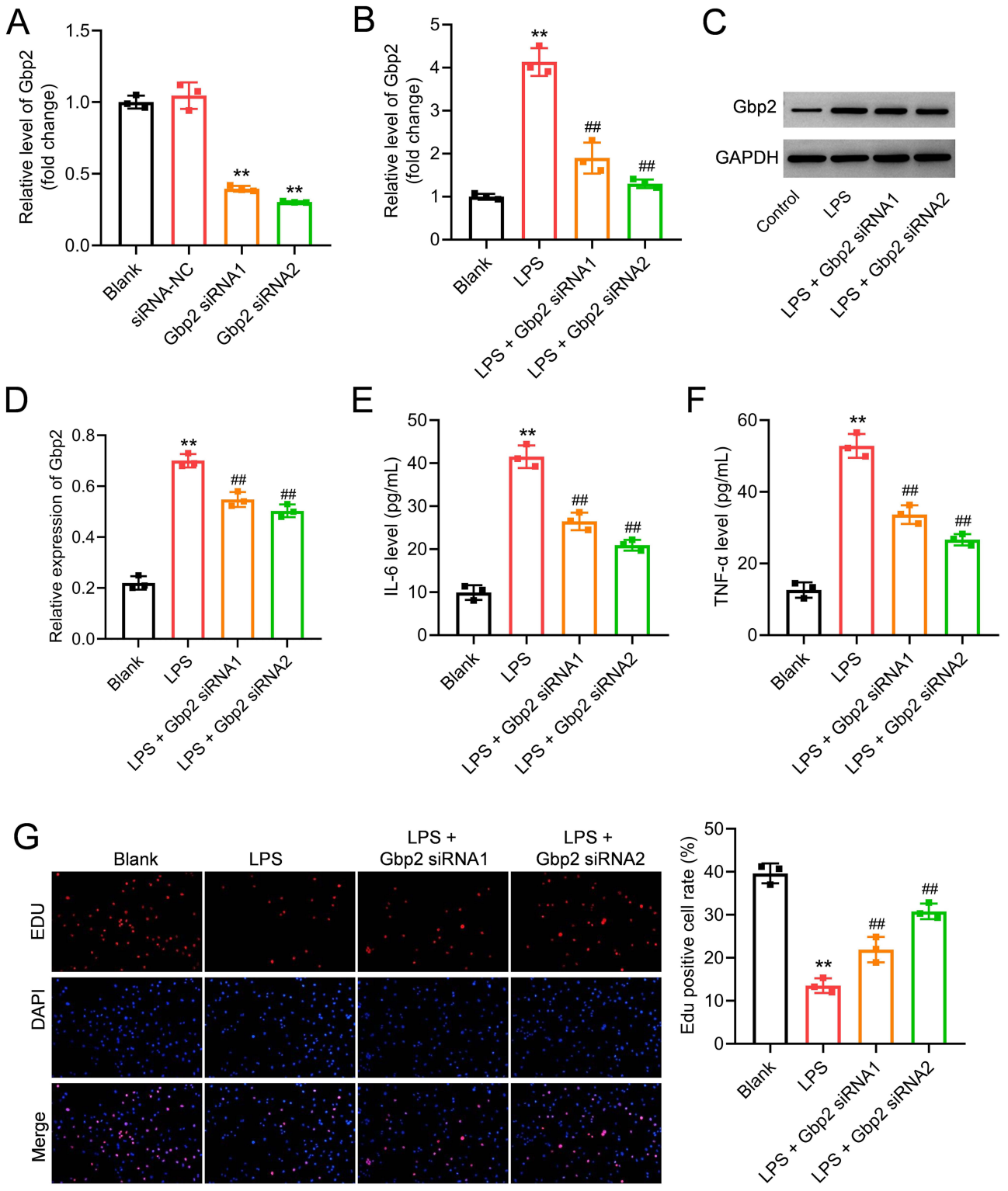

Figure 2 Downregulation of Gbp2 decreased inflammatory response and increased cell proliferation in LPS-stimulated BV2 cells. (**A**) BV2 cells were transfected with Gbp2 siRNA1 and Gbp2 siRNA2. RT-qPCR assay was performed to determine Gbp2 levels in BV2 cells. (**B–D**) BV2 cells were transfected with Gbp2 siRNA1 and Gbp2 siRNA2, followed by exposed to LPS. RT-qPCR and Western blot assays were conducted to determine Gbp2 levels in BV2 cells. (**E** and **F**) ELISA was employed to analyze IL-6 and TNF-α levels in the supernatant of BV2 cells. (**G**) Cell proliferation was determined by the EdU staining assay. **P<0.01 vs Blank group; ##P<0.01 vs LPS group.

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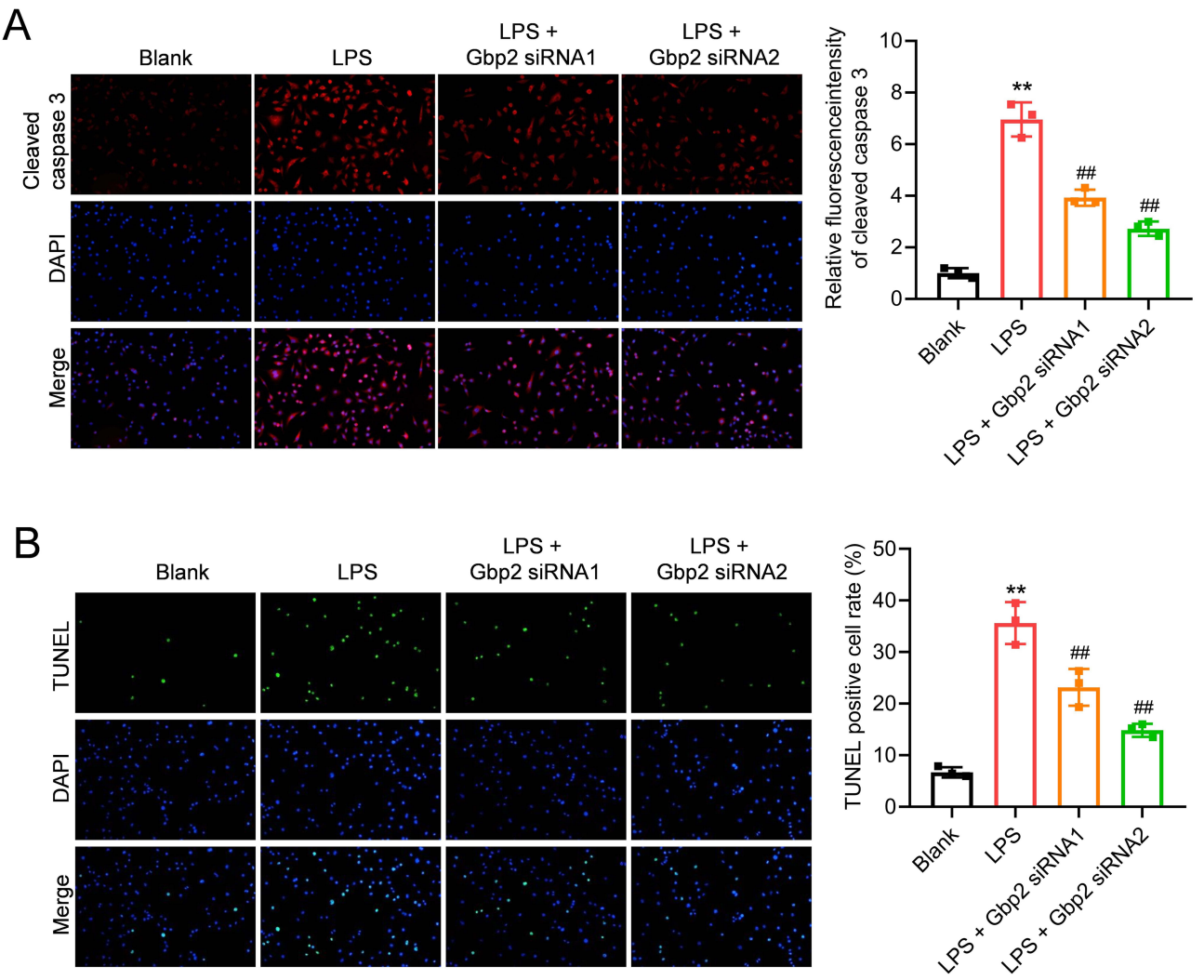

Figure 3 Downregulation of Gbp2 inhibited cell apoptosis in LPS-stimulated BV2 cells. BV2 cells were transfected with Gbp2 siRNA1 and Gbp2 siRNA2, followed by exposed to LPS. (**A**) IF staining assay was conducted to detect the expression of cleaved caspase 3 in BV2 cells. (**B**) Cell apoptosis was determined by the TUNEL staining assay. **P<0.01 vs Blank group; ##P<0.01 vs LPS group.

(Figure 4D and E). Meanwhile, downregulation of STAT1 remarkably reduced the levels of STAT1, Irf1 and Gbp2 in LPS-treated BV2 cells (Figure 4F and G). To sum up, the anti-apoptotic effects of Gbp2 deficiency is regulated by the TFs STAT1 and Irf1.

Discussion

Microglia function as a crucial component of the central nervous system (CNS), serving as the primary defense mechanism against potential pathogens and cellular damage.[18] They can eliminate pathogens and cellular debris through phagocytosis, thereby mitigating the impacts of injury and infection.[19,20] Importantly, within the CNS, microglia is crucial in modulating inflammatory responses.[21] Under conditions of chronic inflammation, the activation of microglia

Table 1 Transcription Factors Regulating Gbp2

Transcription Factors	Target	Type	Reference
Irf1	Gbp2	Activation	17293456
Stat1	Gbp2	Activation	17293456

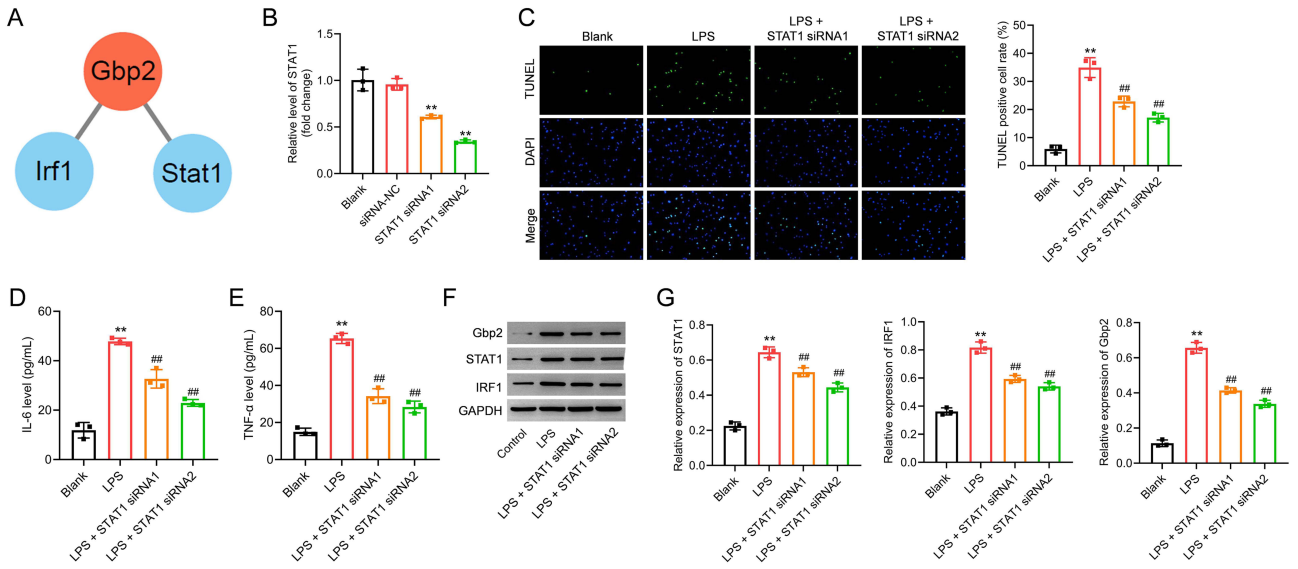

Figure 4 The anti-apoptotic and anti-inflammatory effects of Gbp2 deficiency is mediated by the TFs STAT1 and Irf1. (**A**) Network of Gbp2 and its transcription factors STAT1 and Irf1. (**B**) BV2 cells were transfected with STAT1 siRNA1 and STAT1 siRNA2. RT-qPCR assay was performed to determine STAT1 levels in BV2 cells. (**C**) BV2 cells were transfected with STAT1 siRNA1 and STAT1 siRNA2, followed by exposed to LPS. Cell apoptosis was determined by the TUNEL staining assay. (**D** and **E**) ELISA was employed to analyze IL-6 and TNF-α levels in the supernatant of BV2 cells. (**F** and **G**) Western blot assay was conducted to measure STAT1, Irf1 and Gbp2 levels in BV2 cells. **P<0.01 vs Blank group; ##P<0.01 vs LPS group.

leads to a persistent release of pro-inflammatory factors.[22,23] This continuous release can exacerbate neuroinflammation and contribute to neurotoxicity, ultimately leading to cell death.[22,23] These findings indicate that microglia play a dual role-both beneficial and detrimental-in neurological diseases, depending on environmental conditions. In this study, we observed that LPS notably triggered an inflammatory response in BV2 cells; however, downregulation of Gbp2 notably attenuated this inflammatory response in LPS-treated BV2 cells. This suggests that Gbp2 may represent a potential target for the treatment of POCD.

LPS has been utilized to create an in vitro model for POCD.[24] LPS not only decreases the proliferation of BV2 cells, but also trigger an inflammatory response in these cells,[25,26] with our results aligning with these findings. Recent investigations have revealed a close interaction between inflammation and apoptosis.[27,28] Cell death can contribute to inflammatory responses; various pathways of cell death, such as apoptosis, lead to the loss of cell membrane integrity, which subsequently heightens inflammation through the uncontrolled release of cellular components.[27,29] Conversely, excessive inflammation can also trigger cell apoptosis.[28,30] For instance, TNF-α serves as a critical pro-inflammatory cytokine that induces apoptosis via its interaction with TNF-receptor 1.[31] Research indicates that neuroinflammation could contribute to the advancement of POCD.[32] Therefore, the interplay between inflammation and apoptosis might play essential roles in the progression of POCD. Our results demonstrated that LPS notably elevated the cleaved caspase 3 expression and increased IL-6 and TNF-α levels in BV2 cells, suggesting that LPS could simultaneously trigger cell apoptosis and inflammation in BV2 cells. Conversely, deficiency of Gbp2 obviously reduced both cell apoptosis and inflammation in LPS-stimulated BV2 cells. These findings suggest that downregulation of Gbp2 may have the potential to attenuate POCD development through decreasing apoptosis and inflammation in microglia. However, this conclusion necessitates verification through in vivo research in the future. Additionally, the role of Gbp2 in the crosstalk between inflammation and apoptosis remains unclear and warrants further investigation.

Gbp2 is a protein that gets activated in the early stage of inflammatory responses in activated microglia and have a vital role in controlling immune responses.[14] The present results suggested that Gbp2 may serve as a targeted biomarker for diagnosing and the treating of POCD. Based on the data of tissue analysis, we assumed that Gbp2 may induce neuronal damage in LPS-treated microglial cells depending on STAT1 transduction.

Furthermore, we explored the upstream regulatory mechanism of Gbp2 in POCD. Data from the TRRUST database indicated that Irf1 and STAT1 may serve as TFs influencing Gbp2 expression. According to Ramsauer et al, STAT1 and

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Irf1 have the capacity to induce the transcription of the Gbp2 gene.[33] These two TFs, STAT1 and IRF1, are known to regulate genes responsible for immune response and cell survival.[34,35] Additionally, it has been demonstrated that STAT1-IRF1 signaling plays a role in mediating inflammation within microglia.[36,37] In our research, we observed that downregulation of STAT1 led to an obvious decrease in both Irf1 and Gbp2 levels in BV2 cells exposed to LPS. Meanwhile, deficiency of STAT1 considerably diminished cell apoptosis and inflammation in LPS-stimulated BV2 cells. These results indicate that blocking STAT1-IRF1 signaling can alleviate microglial apoptosis and inflammation through downregulating Gbp2, offering a novel strategy for the treatment of POCD.

Indeed, there are some limitations in this research as follows: 1) animal experiments are needed to further explore the function of Gbp2 in POCD; 2) additional database validation is needed to confirm whether the screening results are correct; 3) microglia from aged mice are needed in further analysis; 4) the detailed relations among Irf1, STAT1 and Gbp2 in POCD remain unclear. Thus, more investigations are necessary in coming future.

Conclusion

POCD patients had higher Gbp2 levels than non-POCD patients post-surgery. Downregulation of Gbp2 attenuates neuroinflammation and microglia activation in LPS-stimulated BV2 microglia cells through inhibition of STAT1 pathway. Our findings may help to develop effective intervention strategies to prevent or mitigate the occurrence of POCD.

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Disclosure

Yang Bao, Hongwei Ni and Kai Wang contributed to this study equally and share the first authorship. The authors declare that they have no competing interests.

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