Anti-IL-23 exerted protective effects on cerebral ischemia–reperfusion injury through JAK2/STAT3 signaling pathway

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Abstract
Ischemia–reperfusion frequently occurs in ischemic cerebral vascular disease, during which the inflammatory signaling plays essential roles. The aim of this study was to discover the efficacy of the antibody to a key immune cytokine IL-23 (anti-IL-23) for the therapy of cerebral ischemia–reperfusion injury. We established the cerebral ischemia–reperfusion injury model by middle cerebral artery occlusion (MCAO). Anti-IL-23 injection attenuated lesions indicated by histology study. RT-PCR and Western blot were employed to detect the mRNA and protein expression of JAK2 and STAT3 after anti-IL-23 treatment. ELISA was utilized to measure the levels of MDA (malondialdehyde) and superoxide dismutase (SOD). Moreover, curcumin and IL-6 were implicated in the endogenous intervention of IL-23 signaling in vivo. Our data demonstrated that the treatment of anti-IL-23 might transcriptionally activate the classic immune pathway in the brain. Anti-IL-23 augmented phosphorylation levels of both JAK2 and STAT3, suggesting the amplification signaling of JAK/STAT after exogenous IL-23 intervention. Anti-IL-23 reduced ROS molecules of STAT downstream in the serum and brain. It also alleviated the injury by bringing down levels of MDA and SOD in the serum. JAK2 inhibitor could abolish the effect of anti-IL-23 whereas JAK3i ameliorated the injury. The combination of anti-IL-23 and JAK3i could reduce infarct volume more effectively. In summary, this study indicated that anti-IL-23 had protective effects against cerebral ischemia–reperfusion injury by targeting the immune specific JAK2-STAT3 in JAK/STAT pathway.

Keywords Anti-IL-23 · Cerebral ischemia–reperfusion injury · JAK/STAT pathway

Background
Cerebral vascular diseases, such as cerebral hemorrhage and cerebral ischemia are severe neural diseases which could result in disability and mortality [1, 2]. It is well known that deficient blood supply in brain vessels could cause ischemia induced injury [3]. Multiple molecular mechanisms are involved in the ischemia induced injury caused by insufficient blood supply in brain vessels, including the neural apoptosis, DNA damage, neurotransmitter release, oxidative stress and hypoxia [4].

Accumulative evidence has implied that inflammation plays a major role in neural damage or repair through diverse signaling pathways [5, 6]. For example, C1-inhibitor, a complement and contact-kinin systems inhibitor, are neuroprotective in cerebral ischemia by decreasing the pro-inflammatory cytokines such as TNF and IL-18 and increasing the protective cytokines such as IL-6 and IL-10 gene expression [7, 8]. C1-inhibitor exerted an anti-inflammatory and anti-apoptotic function on ischemia–reperfusion injury, which indicated that inflammation played a role in nerve injury [9–11]. Neuroprotective agents derived from natural herbs with anti-inflammatory and anti-oxidant activities could alleviate neural damage nerve injury after cerebral ischemia–reperfusion injury through inhibiting necrosis and inflammation [12–14]. Besides the chemical inhibitors or natural compound, agents such as pure proteins or targeted antibodies might contribute to the protection against cerebral ischemia–reperfusion injury [15, 16].

Apoptosis has been proved to be the main pathogenic factor in the pathogenesis of ischemic stroke, which involved several important signaling pathways. The Janus kinase/activator of transcription (JAK) signaling pathway family was an important pathway through which most cytokines

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exerted their biological functions, was normally expressed in the brain and played a vital role in neuronal apoptosis [17]. Brain ischemia impairs NK-cell-mediated immune defense at least partially via the JAK-STAT3 pathway [18]. Extracellular vesicles from Mesenchymal stem cells (MSCs-EVs) may be used to treat MCAO injured rats by regulating AMPK and JAK2/STAT3/NF-κB signaling pathway [19].

Anti-IL-23 is an antibody to a novel immune related cytokine of IL-23. IL-23 has been demonstrated to exert pro-inflammatory functions in a series of brain diseases such as stroke [20], aneurysmal subarachnoid hemorrhage [21], as well as cerebral ischemia/reperfusion inflammatory injury [9, 22]. In our preliminary experiment, we found that the proliferation and expansion of Th17 cells with potent pro-inflammatory cytokine IL-17 production are dictated by IL-23. Moreover, IL-23 can drive the IL-17 signaling which is associated with the IL-17 producing CD8 T cells. Although IL-23 is functionally implicated in host defense responses against acute infection and chronic autoimmune diseases, the effect of IL-23 antibody (anti-IL-23) on the neural vascular diseases remains uncertain. Here, we aimed to apply anti-IL-23 in the cerebral ischemia–reperfusion injury model to analyze its therapeutic features in the nerve damage in cerebral vascular diseases.

Materials and methods

Rat MCAO model

Seventy-five male adult Sprague–Dawley rats (250 g) were purchased from Sparford, China. 6 rats were randomly selected as Sham operation group. The remaining 69 are used for modeling. The experiments were approved by the Animal Use Committee of Beijing Chaoyang Hospital, Capital Medical University. The model was established using middle cerebral artery occlusion (MCAO). Rats were anesthetized with 2% isoflurane for 2 h, followed by 24 h of reperfusion. We separated the right internal carotid and internal carotid arteries (ICA) and common carotid artery (CCA). Then, the right external carotid artery (ECA) and CCA were ligated to the distal and proximal ends. We inserted a piece of nylon suture from the ECA in ICA until it reached the middle cerebral artery (MCA). The diameter of thread was about 0.235 mm, and the thread was inserted from the CCA to the right ICA until it passed the MCA origin (approximately 20 mm). Reperfusion was established after 90 min by removing the suture. Rats were scored 24 h after regaining consciousness and before neurological dysfunction was recorded. The assigned scores were as follows: 0 point (no symptoms of nerve damage were identified), 1 point (the contralateral forelimbs could not be fully extended when the tail of the animals was lifted), 2 points (turned to the temporal side when walking), 3 points (rats fell to the opposite side of the lesion when walking) and 4 points (rats could not walk spontaneously and lost their consciousness). 3 rats failed in the model establishment. 66 rats were successfully modeled. After reperfusion for 24 h, the rats were sacrificed, and the brains were harvested. The rats were anesthetized with 10% chloral hydrate intraperitoneally (300 mg/kg, i.p.). The cerebral infarct volume was evaluated by using 2% 2,3,5-triphenyltetrazolium chloride (TTC) staining. Other specimens were homogenized in ice-cold normal saline by 1:9 (w/v) for the future experiments.

Drug administration

Rats were randomly divided into seven groups. There are 6 rats in each group: (1) Sham operation group: Rats received sham operation and equal volume of 0.9% NaCl. (2) MCAO + anti-IL-23 group treatment with anti-IL-23 Apteramer intravenously with a dose of 4 μg from day 3 until day 10. (3) MCAO group which had brain inflammation, but had been treated with anti-IgG. (4) MCAO group had been treated with JAK2 inhibitor (30 mg/kg × 3 wk WP1066). (5) MCAO group had been treated with anti-IL-23 and WP1066 (Calbiochem, La Jolla, CA, USA). (6) MCAO group had been treated with JAK3 inhibitor (20 mg/kg × 3 wk JANEX-1). (7) MCAO group had been treated with anti-IL-23 and JANEX-1 (Calbiochem, La Jolla, CA, USA). (8) MCAO + Cum group had been treated with 10 μm × 3 wk Curcumin (Sabinsa Corp, East Windsor, NJ, USA). (9) MCAO + IL-6 group had been treated with 1 μg 2 μg/mL IL-6(R&D System Inc., Minneapolis, MN). (10) MCAO + Cum + IgG group had been treated with Curcumin and 10 μg control IgG (Abcam, Cambridge, MA). (11) MCAO + Cum + IL-23 group had been treated with anti-IL-23 and Curcumin. (12) MCAO + IL-17 group had been treated with 100 μg IL-17 (Pharmingen, San Diego, CA, USA). Both anti-IL-23 and anti-IgG antibodies were special ordered from Santa Cruz to be diluted in PBS only so that they could be used in vivo.

Measurement of infarct volume

The rats received an overdose of chloral hydrate and decapitated. Brains were quickly removed, rinsed in cold normal saline, placed at −80 °C for 3 min, and sliced into 2 mm-thick coronal sections. Tissue sections were incubated for 30 min at 37 °C in a solution of 2% TTC in normal saline in the dark. The borders of the infarct in each brain slice were outlined and the area quantified using Image J, a NIH image software. To correct it for brain swelling, the infarct area was determined by subtracting the area of undamaged tissue in the left hemisphere from that of the intact contralateral hemisphere. The infarct volume was calculated by using the
slice thickness and the measured area of the lesion. Infarct area = Contralateral hemisphere area − healthy area of the ipsilateral hemisphere. Infarct volume = Infarct area × thickness of slice. Data was expressed as a percentage of the total hemisphere.

RNA isolation and quantitative real-time PCR (RT-PCR)

Total RNA was extracted from tissues using TRIzol reagent (Invitrogen, San Diego, CA, USA) in accordance with the manufacturer’s instructions. Reverse transcription and quantitative real-time PCR using SYBR Green were performed to compare the relative expression levels of specific mRNAs, as described previously [23]. Real-time PCR measurements were performed to obtain a mean CT value for each sample. The values of the different samples were compared using the $2^{-\Delta\Delta CT}$ method, and actin expression levels served as an internal reference.

Western blot

The cerebral tissues were homogenized in the ice-cold buffer. Then, total proteins were lysed. We performed SDS-PAGE electrophoresis and sent the proteins to polyvinylidene fluoride membranes (Millipore, USA). Then sealed with Tris-buffered saline-Tween 20 containing 5% bovine serum albumin. The membrane was incubated at 4 °C overnight, together with the following diluted anti-rabbit primary antibodies against β-actin (1: 1000, ab8226,37 kDa, abcam), JAK2 (1: 500, ab108596, 131 kDa, abcam), p-JAK2(1: 200, ab32101,120 kDa, abcam), JAK3 (1: 100, ab203611, 125 kDa, abcam), p-JAK3 (1: 200, ab61102, 106 kDa, abcam),STAT3(1: 1000, ab68153, 88 kDa, abcam), p-STAT3(1: 200, ab76315, 88kD, aabcam). The proteins were treated by primary antibodies. After washing, the membrane was treated by the corresponding IgG-HRP secondary antibody (1:2000, sc-2004, Santa Cruz) for an hour. GelDoc-2000 Imagine system was used to measure chemiluminescence to visualize and quantify signal bands. The protein level was normalized to β-actin.

Oxidative stress

Brain tissues isolated from rats were homogenized in normal saline and centrifuged at 3000×g at 4 °C for 10 min. Supernatants were collected and the levels of malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) were detected according to the manufacturer’s protocol of the corresponding detection kits (Nanjing Jiancheng Bioengineering Institute) using the UV/Vis Spectrophotometer (Beijing Lab Tech Instrument Co., Beijing, China). The absorbance was measured at a wavelength of 532, 420 and 340 nm for MDA, SOD and GSH-Px, respectively.

H&E staining

Three brain sections for each case taken from the injury area were stained with H&E (Sigma-Aldrich). The brain tissue was fixed with 4% paraformaldehyde for 24 h and embedded in paraffin. Then, the tissue was cut into slices, dewaxed in xylene and dehydrated in alcohol. The sections were then counterstained in eosin solution for 25 s, quickly dipped in 95% alcohol four times, dehydrated in 95% alcohol, with two changes of absolute alcohol for 5 min each, and followed by clearing with two changes of xylene for 5 min each. The sections were cover-slipped using PermounTM Mounting Medium (0909129, Shanghai Zhanyun Chemical Co., Ltd., Shanghai, China).

The slices from anterior to posterior, with left hemisphere on the left, were lined up on a piece of blue plastic. Excess water was removed on and around the slices with a paper towel. A ruler was placed alongside the slices. Photos were taken with a digital camera (Olympus BX 53 microscope, Tokyo, Japan).

TUNEL staining

Apoptotic cells were detected using a TUNEL kit (Zhongshan Bio., China). Tissues of the normal and the model groups were de-waxed and dehydrated. After washing, tissues were treated with proteinase K in a wet chamber at 37 °C for 30 min. Cell nuclei were stained with DAPI (1 lg/ml, Roche Applied Science). Cell counting was performed in the ipsilateral basal cortex under a fluorescent microscope (Olympus). The total number of cells (DAPI +) and the TUNEL-positive cells were counted in 10 separate fields in 5 different slices. The data were expressed as the number of TUNEL-positive neurons per total number of neurons.

Immunohistochemistry staining

The expressions of IL-23 on the brain tissues were immunohistochemically stained. All the brain tissues were fixed in 4% formalin overnight and embedded in paraffin with standard techniques. Hydrogen peroxide was utilized to deactivate intrinsic peroxidase. Antigen retrieval was performed in a water bath using citrate-EDTA buffer (10 mM citric acid, 2 mM EDTA, 0.05% Tween 20, pH 6.2). Sections were incubated with diluted anti-CD68 antibody (1:100; Abcam, UK) or rabbit anti-TNF-a antibody (1:200; Abcam, UK) overnight at 4 °C. The tissues were treated with Chromogen (DakoCytomation, Denmark) and stained with hematoxylin (Sigma, USA). For morphology, tissues were observed by a microscope (Zeiss, Germany) ×400.
Statistical analysis

Statistical analysis was performed using SPSS 22.0 software. Results represent the average of three independent experiments, and data are expressed as mean ± standard deviation (SD). Comparisons between the two groups were analyzed by Student’s t-test. Multiple comparisons between groups were evaluated by one-way analysis of variance, and then Tukey’s multi-range post hoc test was performed. P < 0.05 was considered statistically significant.

Results

The effect of anti-IL-23 on the cerebral infarction induced by reperfusion

The cerebral ischemia–reperfusion injury model was established using MCAO. Anti-IL-23 was injected intravenously. In sham group, no neurological deficits were observed. After 24 h after reperfusion, anti-IL-23 treatment improved the neurological score compared to MCAO rats which displayed severe neural symptoms (Fig. 1a). As shown in Fig. 1b, MCAO showed a dramatic cerebral infarction after reperfusion, which could reduce brain damage by injecting anti-IL-23. The results of RT-PCR experiment showed that compared with the Sham group, IL-23 was highly expressed in the brain of MCAO rats. Compared with the MCAO group, the IL-23 expression level of the MCAO + anti-IL-23 group was reduced. The high expression of IL-23 in the brain of MCAO rats was further confirmed by immunohistochemical staining (Fig. 1c, d). By H&E staining and TUNEL staining, less inflammatory infiltration and apoptosis were consistently observed on the anti-IL-23 treatment group (Fig. 1e, f).

Anti-IL-23 reduces the inflammatory response and oxidative stress

To further evaluate the effects of anti-IL-23 in cerebral ischemia injuries, we evaluated oxidative parameters. MDA, SOD and GSH-Px levels were markedly evaluated especially due to ischemia and the following reperfusion [24]. From Fig. 2, we found that anti-IL-23 also improved series of neural ischemia factors including MDA, SOD and GSH-Px. Anti-IL-23 treatment lowered the MDA content in the MCAO (Fig. 2a). In addition, anti-IL-23 treatment enhanced cerebral SOD (Fig. 2b) and GSH-Px activities caused by ischemia/reperfusion on the rats (Fig. 2c). Our results confirmed that anti-IL-23 lowered the oxidative stress induced by cerebral ischemia–reperfusion injury.

Anti-IL-23 activated JAK2 and JAK3

To further explore the possible mechanism of anti-IL-23 on the MCAO, we isolated the brain tissues and we found that anti-IL-23 treatment could activate the phosphorylation of JAK2 and STAT3 in vivo. In addition, anti-IL-23 exposure also enhanced the level of phosphorylated JAK3, suggesting that anti-IL-23 triggered JAK/STAT signaling might play an essential role in the immune regulation on neural damage (Fig. 3a). However, anti-IL-23 did not affect the molecules’ transcriptional pattern in this pathway (Fig. 3b). Although anti-IL-23 could activate both JAK2 and JAK3, it was observed that the degree of brain injury was not reduced under the action of JAK2 inhibitor and anti-IL-23, while the JAK3 inhibitor could reduce its severity, and the combination of anti-IL-23 and JAK3i could reduce infarct volume more effectively (Fig. 3c). In short, anti-IL-6 combined with silencing JAK3 had a positive therapeutic effect.
IL-23 suppressor (curcumin) attenuated the effects of IL-23 on cerebral ischemia injury

In addition to the intervention of anti-IL-23, it has been reported that curcumin inhibits the high expression of interleukin-23 and interleukin-17 after retinal ischemia–reperfusion injury in rats [25]. We found in the MCAO model that curcumin treatment directly inhibits the expression of IL-23 during cerebral ischemia–reperfusion (Fig. 4a). IL-23 mRNA expression requires IL-6 [26]. This was also confirmed in the increased expression of IL-23 in brain tissue after IL-6 injection (Fig. 4b). Consistently curcumin treatment also ameliorated the injury (Fig. 4c). In addition, cerebral ischemia–reperfusion injury rats treated with curcumin plus IL-23 showed more severe symptom of neuronal impairment compared with rats which received IgG control antibody (Fig. 4d). However, the injection of pro-inflammatory IL-17 failed to improve the infarction (Fig. 4e) indicating that the effect of anti-IL-23 on cerebral ischemia–reperfusion injury did not depend on its IL-17 induction activity.

Discussion

IL-23 is a heterodimeric cytokine member of the IL-12 cytokine family, which is comprised of IL-23 specific p19 subunit and IL-12p40 subunit, shared with IL-12 [9, 20]. Macrophages and dendritic cells upon activation can express p19 and p40 for the production of IL-23 [27, 28]. The functional IL-23 receptor complex also consists of two receptor subunits including IL-23-specific receptor subunit (IL-23R) as well as IL-12 receptor beta 1 subunit (IL-12R beta 1) [29, 30]. IL-23 and IL-12 are characterized by overlapping but distinct biological functions since IL-12 could drive Th1 type cell development whereas IL-23 is postulated as a cytokine that drives IL-17- and IL-22-producing Th17 cells development. IL-17 could also be produced by IL-23 in NK cells and neutrophils [31, 32]. In addition, IL-23 appeared to be critical for IL-17A-producing γδ T cells especially in experimental arthritis [33]. IL-23 is functionally involved in the pathological process of autoimmune diseases such as psoriasis and rheumatoid [34]. For instance, highly expressed IL-23 in psoriasis can lead to increase in numbers of Th17 cells for the pathogenesis of skin lesions [35]. Moreover, trials with IL-23p40 and p19 blockers indicate that IL-23 is a valid therapeutic target for Crohn’s disease [30].

IL-23 is pleiotropic in diverse immune cells and the dysfunction of the IL-23-IL-17 immune axis plays a crucial role in organ-specific autoimmune inflammatory diseases [36]. However, targeting IL-23 on the cerebral ischemia–reperfusion injury remains less clear. In fact, IL-23 has been implicated in regulating neural inflammation [31, 37]. IL-17-producing γδ T cells were found at high frequency in the brain of rats with experimental autoimmune encephalomyelitis (EAE), forming an amplification loop for IL-17 production by Th17 cells and increasing the susceptibility to EAE [38, 39]. Different from its inflammatory function in EAE, we observed its neural protective effect of anti-IL-23 on the cerebral ischemia–reperfusion injury which is independent of IL-17 production in the present study. Anti-IL-23 could induce IL-17 production in brain. Whereas IL-17 treatment failed to improve the diseases.

The cytosolic Janus kinases are linked with receptors on the membrane for rapid transduction of signals from the cell surface to the nucleus [40, 41]. So far, four JAKs subtypes including JAK1, JAK2, JAK3 and Tyk2 have been identified in mammals, cytokines as the ligands for receptors cause the activation of JAK and downstream STAT (signal transducers and activators of transcription) [42, 43]. Interestingly, although anti-IL-23 could activate JAK2 and JAK3 at the same time, it was observed that the degree of brain damage did not decrease under the action of JAK2 inhibitor and anti-IL-23. This phenomenon may be that JAK2i eliminated the effect of anti-IL-23, or it may be other reasons worth exploring.

It is known that STATs are a unique class of transcription factors with seven members including STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6 which are essential for regulating genes expression [41, 42]. STATs are initially recruited to receptor signaling complex and phosphorylated by JAKs, forming homodimers or heterodimers which then translocate to the nucleus and bind to gamma-IFN activation site (GAS) motifs for the gene transcription [44, 45]. Thus, cytokines stimulation via receptors is critical for the activation of JAK-STAT. For instance, G-CSF prevented cardiac remodeling after myocardial infarction by activating the Jak-Stat pathway in cardiomyocytes [46]. The IL-10 receptor signaling through the JAK-STAT pathway was also reported [47]. Recently, more evidence also revealed that IL-17/IL-23 axis is associated with the JAK-STAT pathways [48]. Nickel sulfate promotes Th17 cells in an IL-23-dependent manner via JAK-STAT pathways using specific inhibitor (JAK inhibitor) [49]. A plausible mechanism of action of tofacitinib targeting JAKs in psoriatic...
IL-23 suppressor (curcumin) attenuated the effects of IL-23 on cerebral ischemia injury.  

**Fig. 4**

- **a** Relative mRNA level of IL-23 in MCAO rats and MCAO + curcumin rats.  
- **b** Relative mRNA level of IL-23 in MCAO rats and MCAO + IL-6 rats.  
- **c** Infarct volume percentage in MCAO rats and MCAO + curcumin rats.  
- **d** Infarct volume percentage in MCAO + Cum + IgG rats and MCAO + Cum + IL-23 rats.  
- **e** Infarct volume percentage in MCAO rats and MCAO + IL-17 rats.  

Unpaired t-test was utilized for the comparison between two groups. *P < 0.05 compared with MCAO.  
#P < 0.05 compared with MCAO + Cum + IL-23.  
n = 6
arthritis (PsA) is likely to be inhibition of the IL-23/IL-17 cytokine axis via suppressing the anti-IL-23-induced JAK-STAT signaling system [50].

In this study, we investigated the role of anti-IL-23 on cerebral ischemia–reperfusion injury using the establishment of MCAO model. However, further evidence of the mechanism of IL-23 is still required. For instance, although we detected the increasing expression of IL-23R in MCAO, the cell source of IL-23/IL-23R remains unclear. In the future, we would isolate the diverse neural cells including neurons, microglial, or infiltrated immune cells in the CNS to ascertain which cell types could express the molecules targeting IL-23 that are beneficial for the therapy of cerebral ischemia.

Conclusions

In summary, this study indicated that anti-IL-23 had protective effects against cerebral ischemia–reperfusion injury by targeting the immune specific JAK2-STAT3 in JAK/STAT pathway.

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Author contributions LF and LZ designed the study, performed the research, analysed data, and wrote the paper.

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Data availability The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and its supporting information files.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval This study was approved by animal use committee of Beijing Chaoyang Hospital, Capital Medical University and conducted in strict accordance with the national institutes of health guidelines for the care and use of experimental animals.

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