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Research paper

The bidirectional role of the JAK2/STAT3 signaling pathway and related mechanisms in cerebral ischemia-reperfusion injury

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ABSTRACT

The Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) signaling pathway, a well-conserved and basic intracellular signaling cascade, is mostly inactivated under basal conditions, although it can be phosphorylated under extracellular stimulation; in addition, it can influence the transcription and expression of multiple genes involved in biological processes such as cellular growth, metabolism, differentiation, degradation and angiogenesis. The inflammatory response, apoptosis, oxidative stress and angiogenesis are the main factors involved in the pathogenesis of ischemic stroke. Numerous studies have confirmed that the JAK2/STAT3 axis can be activated rapidly by ischemic stress, which is closely related to the regulation of these important pathological processes. However, different opinions on the specific role of this signaling pathway remain. In this paper, we review and summarize previous studies on the JAK2/STAT3 pathway in ischemic stroke.

1. Introduction

Stroke is a common clinical cerebrovascular disease that is often caused by arterial embolism after an embolus on the inner wall of the vessels that supply the brain falls off (i.e., ischemic stroke). Although it may happen due to cerebral vascular or thrombus hemorrhage (i.e., hemorrhagic stroke), the former is more common than the latter. Approximately 15 million people worldwide suffer from mild strokes every year (Yu et al., 2020), which becomes increasingly worse as aging accelerates in the population. Because of its sudden occurrence and rapid progression, stroke is still a formidable global problem. The only standard therapeutic drug approved by the Food and Drug Administration (FDA) is recombinant tissue plasminogen activator (rtPA) (i.e., reteplase), which can effectively restore cerebral blood flow perfusion but often fails to ensure the best treatment window in a satisfactory timely manner. Thus, it is far from satisfactory in regard to therapeutic efficacy (Dong et al., 2016). In addition, its complications, such as intracranial hemorrhage, blood-brain barrier damage, and neurotoxicity, are associated with increased mortality within the first week after the onset of cerebral ischemia symptoms (Yu et al., 2020). Therefore, the prevention and treatment of stroke has always been an important factor in healthcare.

Ischemia/reperfusion (I/R) injury is the main pathophysiological process of stroke and involves a sudden decrease in regional cerebral blood flow and internal homeostasis following ischemia, resulting in energy depletion, continuous depolarization of neurons, release of

Abbreviations: JAK2/STAT3, Janus kinase 2/signal transducer and activator of transcription 3; FDA, Food and Drug Administration; rtPA, recombinant tissue plasminogen activator; I/R, ischemia/reperfusion; CIRI, cerebral ischemia-reperfusion injury; JH, Janus homology domain; FERM, four-point-one, ezrin, radixin, moesin; APRF, acute phase response factor; DBD, DNA-binding domain; SH2, Src homology 2; TAD, transcription activation domain TAD; CSFRs, colony-stimulating factor receptor; GPCR, G protein-coupled receptors; VEGFR, vascular endothelial growth factor receptor; EGFR, epithelial growth factor receptor; GHR, growth hormone receptor; EPOR, erythropoietin receptor; NLS, nuclear localization signal; NPCs, nuclear pore complexes; LIF, leukemia inhibitory factor; OSM, oncostatin M; CNTF, ciliary neurotrophic factor; OGD, oxygen glucose development; α7nAChR, α7 nicotinic acetylcholine receptor; SOCS3, suppressor of cytokine signaling 3; Hcy, homocysteine; MDA, malondialdehyde; SOD, superoxide dismutase; AS-IV, astragaloside IV; APN, adiponectin; VEGF, vascular endothelial growth factor; EPO, erythropoietin.

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excitatory amino acids from the presynaptic membrane, increase in Ca2+ inflow and obstruction of Ca2+ efflux, which in turn leads to intracellular Ca2+ overload and gradual neuronal death (Eltzschig and Eckle, 2011; Horn and Limburg, 2001). During the reperfusion period, the previously described scenario is aggravated because the function of the energy pump is not restored. Excessive deposition of Ca2+ further damages mitochondria, promotes the production of oxygen free radicals, and stimulates the secretion of inflammatory cytokines and chemokines to recruit inflammatory cells to infiltrate the area of cerebral ischemia; the recruited inflammatory cells then release more inflammatory mediators, form inflammatory cascade reactions, and finally initiate neuronal death and apoptosis (Li et al., 2015; Liu and Savtchouk, 2012).

Overall, the released cytokines and other messengers trigger a variety of signaling pathways by binding to their receptors, interrelating with each other and weaving into a complex network of mechanisms. Janus kinase 2 (JAK2)/signal transduction and activator of transcription 3 (STAT3) is a signal transduction pathway localized to the cytoplasm. Cytokine receptors activate JAK2 phosphorylation, which is followed by activation of cytoplasmic STAT3, and STAT3 transfers to the nucleus to control the transcription of target downstream genes (Fig. 1). Studies on ischemia-reperfusion injury of the heart (Lan et al., 2019), liver (Zhang et al., 2019), kidney (Liu et al., 2017) and intestines (Zhang et al., 2020a) have been performed and report that JAK2/STAT3 is considered a key membrane-to-nucleus signaling pathway that responds to diverse

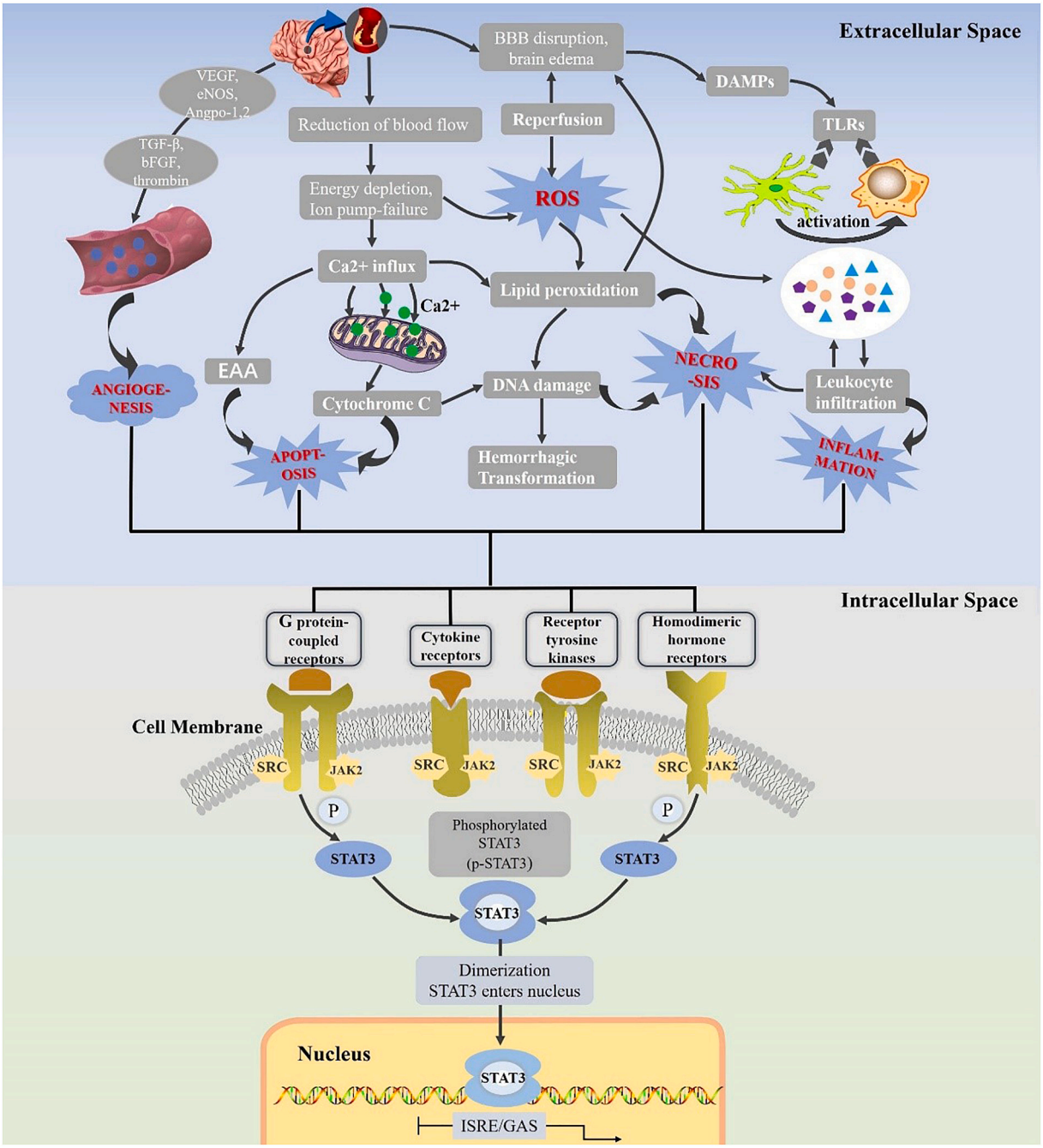

Fig. 1. Cerebral ischemia-reperfusion injury activates JAK2/STAT3 pathway. After cerebral ischemia, on the one hand, energy deficiency leads to excitotoxicity, mitochondrial damage, lipid peroxidation and oxidative stress, while peripheral and central inflammation is stimulated, causing neuronal apoptosis and necrosis, on the other hand, vascular regeneration is initiated, which promotes the formation of collateral circulation. The above pathways release a variety of cytokines to bind to membrane receptors and phosphorylate JAK2 and STAT3. The phosphorylated STAT3 dimer then enters the nucleus to regulate the expression of downstream genes.

stresses, and the brain is no exception. Accumulating evidence (Chen et al., 2017a; Oliva Jr. et al., 2012) shows that significant changes in phosphorylated JAK2 and STAT3 in the ipsilateral cortex and striatum were detected in the early stage of reperfusion after middle cerebral artery occlusion (MCAO) in rodents, but these measures have not yet been determined. Some studies (Dong et al., 2016; Zhu et al., 2013; Zhou and Yu, 2013) suggest that p-STAT3 can promote angiogenesis, regulate cell proliferation and antagonize apoptosis, but other studies propose (Chen et al., 2017a; Wang et al., 2017) that activated STAT3 can promote the production and secretion of proinflammatory mediators and induce oxidative stress injury caused by hydrogen peroxide, delaying recovery of the brain.

Hence, in this review, we aim to comprehensively explain the role and possible mechanism of the JAK2/STAT3 signal transduction pathway in cerebral ischemia-reperfusion injury (CIRI) to offer help for follow-up research and contribute to novel approach studies, even delving into the molecular targets that might be crucial for modulating CIRI.

2. Structure and transcriptional function of the JAK2/STAT3 signaling pathway

The JAK/STAT pathway is a newly discovered signal transduction pathway shared by multifarious cytokines, and can specifically respond to almost all extracellular regulatory signals. It involves tyrosine kinase-associated receptors and two protein families, JAKs and STATs. Currently, four kinds of JAK (JAK1, JAK2, JAK3 and TYK2) and seven kinds of STATs (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6) have been confirmed (Rane and Reddy, 2000). Among them, JAK2 and STAT3 are regarded to be the oldest and most conserved isomers and the most important isomers that widely affect the adaptability of cells to environmental stimulation or stress.

2.1. Janus kinase 2

JAK2 is a non-cross-model tyrosine kinase that can be found in every cell (Dawson et al., 2009). Unlike other tyrosine kinases, JAK2 has only a catalytic domain without an Src homology 2 (SH2) domain, which enables it to phosphorylate not only the cytokine receptors that bind to it but also multiple signaling molecules containing SH2 domains. JAK2 has seven JH (Janus homology) domains, and it is mainly divided into three parts (Lafave and Levine, 2012; Wallweber et al., 2014; Ungureanu et al., 2011). These are the four-point-one, ezrin, radixin, moesin (FERM) domain (JH5 ~ JH7); the SH2 domain (JH3 and 4), which together with FERM forms half of the N-terminus, also known as the receptor binding domain, connecting JAK with the Box1 and Box2 regions that exist in the cytoplasm of cytokine receptors; a C-terminal tyrosine kinase domain (JH1), responsible for most of the transcriptional activity of JAKs phosphate groups; and a pseudokinase or kinase-like domain (JH2), located upstream of the JH1, which is necessary for JAK2 to maintain normal activity and negatively controls tyrosine kinase activity in the basal scenario. Specifically, JH1 catalyzes the transphosphorylation process of two tyrosine residues of JAK2 (Tyr1007 and Tyr1008) in the kinase reaction ring, which is a key step in JAK activation.

2.2. Signal transducer and activator of transcription 3

STAT3, the substrate of JAK2, was first discovered more than 20 years ago, when it was considered to be one of the components of the acute phase response factor (APRF) complex that reacted to IL-6 (Su et al., 2020). The STAT3 gene is situated on chromosome 17q21 and encodes an 89 kDa-length protein (You et al., 2015). There are three isomers of the STAT3 protein: STAT3 α, STAT3 β and STAT3 γ, which usually refer to the first isomer. Similar to other members of the STAT3 family, STAT3 can be distributed into six categories according to its structure and function (You et al., 2015; Hillmer et al., 2016): a first point of amino-terminal coiled-coil domain (residues 1–130), followed by a central DNA-binding domain (DBD, residues 320–490), a linker domain extension (residues 490–580), a conservative Src homology 2 (SH2) domain (residues 580–680), and a carboxy-terminal transcription activation domain (TAD, residues 680–770). In these six functional regions, the amino-terminal domain is structurally independent and can bind the two adjacent STAT3 dimers more closely. Studies have indicated that this domain cooperates with the DNA-binding domain to bind to the tandem γ-interferon activated sequence (GAS) elements in the process of nuclear transport and the coiled-coil domain consisting of a 4-α-helical bundle, which provides a large number of hydrophilic surfaces for transcription factors and regulatory proteins while serving as binding sites. The DNA-binding domain is composed of a β-immunoglobulin fold formation, with a sequence specific to the active IFN-gamma palindromic sequence (GAS) element, and it can directly bind to the GAS family of enhancers. The linker domain affects the stability of the DBD. The SH2 domain is the most conservative and functionally important segment in the sequence; it has the core sequence “GTFLLRFSS”, which is identical to the SH2 domain of the tyrosine kinase Src, and can directly bind to the tyrosine phosphorylated region of the cytokine receptor, thus mediating the link between the two molecules and determining the specificity of cytokine binding to STAT3. TAD consists of C-terminal residues, where there are two tyrosine phosphorylation sites (Y701 and Y705) and a serine phosphorylation site at Ser727, which is a modification to enhance transcriptional activity (Levy and Darnell Jr, 2002).

2.3. Tyrosine kinase-associated receptors

Cytokine receptors are a type of transmembrane receptor that may be the most prevalent family related to the activation of JAK (Bousoik and Montazeri Aliabadi, 2018). Many cytokines and growth factors transfer signals through JAK2-STAT3 signaling pathways, which can be roughly divided into three categories: interferon (IFN) receptors, interleukin (IL) receptors and colony-stimulating factor receptors (CSFRs) (Bousoik and Montazeri Aliabadi, 2018). It has been reported that the gp130 subunits IL-2, IL-6, IL-11, IL-12, IL-13, IL-23, IL-27, and IL-31 and the leptin receptor can trigger the activation of JAK2 and IFN-γ. G-CSFR can also trigger the activation of JAK2 (Bousoik and Montazeri Aliabadi, 2018; Liao et al., 2013). The common feature of these receptors is that they do not have kinase activity, but there is a homologous region near the cytoplasmic membrane, which is the functional region that binds to tyrosine kinase JAK and includes two highly conserved structures found in various cytokine receptors; one is proline-rich “box 1”, the other is “box 2”, and both are located near the cell membrane, which determines the coupling between cytokine receptors and JAK kinase. When the receptor binds to the ligand, activated JAK binds to the tyrosine residues of various target proteins and phosphorylates them to transfer signals from the extracellular space to the intracellular space. The dimerization of receptors can be homologous or heterogeneous. When homologous dimerization occurs, only JAK2 is activated; instead, heteroreceptor dimerization is composed of different subunits that can activate a variety of JAKs. In addition to cytokine receptors, the JAK2 protein can be the site of action of other types of receptors in order to expand the scope of signals that are capable of triggering this signaling pathway, for instance, CCR2 (Mellado et al., 2001) and CXCR4 (Bousoik and Montazeri Aliabadi, 2018) of G protein-coupled receptors (GPCR), vascular endothelial growth factor receptor (VEGFR) (Zhu and Zhou, 2015) and epithelial growth factor receptor (EGFR) (Andl et al., 2004) of receptor tyrosine kinases, growth hormone receptor (GHR) (Brooks et al., 2014) and erythropoietin receptor (EPOR) (Bousoik and Montazeri Aliabadi, 2018) of the homodimeric hormone receptors.

2.4. Transduction of the JAK2/STAT3 axis

Tyrosine phosphorylation is the canonical pathway of JAK2/STAT3,

and it is also the key activation mechanism for stimulating the transcriptional function of STAT3. Once the extracellular signal is sensed, the cytokine binds to its receptor, which initiates the dimerization of the receptor molecule and brings the receptor-coupled JAKs close to each other, initially converting to p-JAK2 through interactive tyrosine phosphorylation. The activated JAKs in turn catalyze the continued phosphorylation of the tyrosine residues on p-JAK2 in the cytoplasm to form a corresponding STAT docking site. At the same time, the STAT protein containing the SH2 domain is recruited to this site, leading to the presence of a single tyrosine residue between SH2 and TAD phosphorylation, namely, Tyr705, as well as to the homo or heterodimerization of two STAT3 units via reciprocal phosphotyrosine interactions within the SH2 domains of 2 monomers (Yu et al., 2009). However, owing to the existence of the nuclear membrane barrier, macromolecules such as STAT that are transported into the nucleus usually require a specific transport receptor that is widely known as importin and contains α and β subunits, that is, importin α and β, respectively. The conformationally altered STAT3 protein is guided to combine with importin α through an active and specific motif on the protein, namely, the nuclear localization signal (NLS), which is constitutively but not conditionally expressed (You et al., 2015). Subsequently, importin β interrelates and interacts with importin α, joining the protein/importin compound together at nuclear pore complexes (NPCs). The whole process of active transport is powered by NPC-related GTPase (RAN) (Hulsmann et al., 2012). STAT3, which is activated, then binds to the specific promoter sequence and regulates a series of target genes, but some of the triggered reactions are even opposing.

3. JAK2/STAT3 signaling pathway in the CIRI

Cerebral ischemia-reperfusion injury is a complex dynamic process that includes initial injury in the early phase of ischemia and secondary injury after reperfusion. Decreased blood flow brings about an insufficient supply of both glucose and oxygen and promoting an inability to sustain normal metabolism in brain tissue, evoking intracellular calcium overload, oxidative stress, neurotoxicity of excitatory amino acids and inflammation, and eventually nerve cell necrosis/apoptosis or neurological abnormalities (Radak et al., 2017). Abundant studies confirm that the JAK2/STAT3 signaling pathway has a neuron-specific function in the central nervous system (CNS), which is mostly dormant under physiological conditions and participates in the development of the CNS, such as nerve cell proliferation, survival, and differentiation (Bjorbaek and Kahn, 2004; Amantea et al., 2011). It is activated under ischemic stimulation and continues to be highly expressed in neurons and nerve cells around the infarction, responding to a variety of pathogenic factors that include apoptosis, inflammatory response, vascular remodeling, oxidative stress and autophagy (Li et al., 2003). However, there are still critical questions as to what are the exact roles, i.e., activation or inhibition, of the JAK2-STAT3 signaling pathway in ischemic stroke (Table 1).

3.1. Expression features of STAT3 in CIRI

Normally, in rodents in sham-operated groups, the STAT3 protein is primarily diffused in the cytoplasm of cortical and striatal neurons (Stromberg et al., 2000). When driven by ischemic stroke, especially through a general receptor subunit of a family of neurotrophic factors called neurokines, which is composed of IL-6, IL-11, leukemia inhibitory factor (LIF), cardiotrophin-1, oncostatin M (OSM), ciliary neurotrophic factor (CNTF), STAT3 translocates into the nuclei concurrently with phosphorylation and should be discussed in two stages. During the ischemic period, activated microglia, astrocytes, and endothelial cells clearly expressed STAT3 in the ischemic region, in contrast to weak STAT3 staining in shrunken neurons (Justicia et al., 2000); however, after reperfusion, STAT3 immunoreactivity in neurons regained its strength and reached a peak at 24 h (You et al., 2015). Moreover, there

Table 1
Summary of the role of JAK2/STAT3 signaling pathway in the researches of ischemic stroke.

	Upstream stimulations	STAT3 activation	Downstream effects
Beneficial	SMND-309[1]	Promotion	Promoting angiogenesis
	Epidermal growth factor receptor[2]	Promotion	Inhibiting apoptosis
	Diosmin[3]	Promotion	Inhibiting apoptosis
	Catalpol[4]	Promotion	Promoting angiogenesis
	Adiponectin[5]	Promotion	Attenuating apoptosis and mitochondrial oxidation
	Leptin[6, 7]	Promotion	Attenuating apoptosis and mitochondrial damage
	Curcumin[8]	Promotion	Anti-inflammation, reducing brain edema
	Sevoflurane[9]	Promotion	Inhibiting apoptosis
	Melatonin[10]	Promotion	Promoting microglia/macrophage phenotype to M2 polarity
	SH2B1[11]	Promotion	Inhibiting apoptosis
	Astragaloside IV[12]	Promotion	Reducing oxidative stress and apoptosis
	Gap19[13]	Promotion	Specific blocking of Cx43 hemichannels, inhibiting apoptosis
	Electroacupuncture	Promotion	Inhibiting apoptosis
	S14G-humanin[14]	Promotion	Inhibiting apoptosis and oxidative stress
	IL-6[15]	Promotion	Inhibiting apoptosis
	Secretoneurin[16]	Promotion	Inhibiting apoptosis, enhancing neurogenesis and angiogenesis
	Imatinib[17]	Promotion	Improving locomotor activity and memory
	Resveratrol[18]	Promotion	Inhibiting apoptosis
	a7nAchR[19]	Promotion	Anti-inflammation
	Leukemia inhibitory factor[20]	Promotion	Inhibiting apoptosis
	Oncostatin-M[21]	Promotion	Promoting postischemic neuronal survival
	Delayed recanalization[22]	Promotion	Anti-apoptotic
	MEPO[23]	Promotion	Shifting microglial polarization to M2 phenotype
	iMSC-sEV[24]	Promotion	Promoting angiogenesis 7 days after MCAO
	Estradiol[25]	Promotion	Promoting neuronal survival
	Erythropoietin[26]	Promotion	Promoting neuronal survival and neuroregeneration
	Salvianolic acids[27]	Promotion	Promoting cerebral angiogenesis and neurological recovery
	Azithromycin[28]	Promotion	Neuroprotective
	PDGFRβ[29]	Promotion	Promotes astrogliosis, oligodendrogenesis, and functional recovery
Detrimental	Ginkgetin aglycone[30]	Inhibition	Reducing oxidative stress, apoptosis and inflammation
	Oncostatin-M[31, 32]	Promotion	Inducing blood-brain barrier impairment
	Remote ischemia preconditioning[33]	Inhibition	Reducing inflammation and apoptosis
	Homocysteine[34, 35]	Promotion	Pro-inflammation; aggravating apoptosis and mitochondrial injury
	SOCS1[36]	Inhibition	Neuroprotective
	MiR-216a[37]	Inhibition	Reducing inflammation and apoptosis
	AG490 and STAT3-siRNA[38]	Inhibition	Reducing inflammation and apoptosis

(continued on next page)

Table 1 (*continued*)

	Upstream stimulations	STAT3 activation	Downstream effects
	Hydroxysafflor Yellow A[39]	Inhibition	Promotes neurological and functional recovery
	Nicotiflorin[40]	Inhibition	Reducing apoptosis
	Ginkgo biloba extract[41]	Inhibition	Suppressing astrogliosis and neuroinflammation
	Rapamycin, curcumin[42]	Inhibition	Reducing the inflammatory response
	Stachydrine[43]	Inhibition	Down-regulation of inflammation and oxidation
	SC99[44]	Inhibition	Shifting microglial polarization to M2 phenotype
	Yes-associated protein (YAP)[45]	Inhibition	Reducing the inflammatory response of astrocytes
	BCL6[46]	Promotion	Aggravating oxidative stress-induced neuronal damage
	Atractylenolide III[47]	Inhibition	Alleviating neuroinflammation
	Electroacupuncture[48]	Inhibition	Improving cognitive deficits
	Bradykinin[49]	Promotion	Aggravating neuroinflammation
	M2 microglial small extracellular vesicles[50]	Inhibition	Reducing glial scar formation
	Folic Acid Deficiency[51]	Promotion	Aggravating neuron degeneration and mitochondrial injury
	MSCs-EVs[52]	Inhibition	Reducing neuronal apoptosis
	Combination of Xuesaitong, aspirin and clopidogrel[53]	Inhibition	Reducing oxidative stress and inflammation
	Knockdown of the lncRNA NEAT1[54]	Inhibition	reduces microglial M1 polarization and cell apoptosis

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are particular chronological features of STAT3 phosphorylation in each region. In the ischemic core, STAT3 was partially phosphorylated at approximately 3.5 h after reperfusion, which disappeared gradually; in the ischemic penumbra, STAT3 phosphorylation lasted from 3.5 h to 96 h after focal ischemia, and more importantly, neurons could still maintain normal morphology (Suzuki et al., 2001), so saving the ischemic penumbra is always considered the foundation in recovery of ischemic stroke.

3.2. JAK2/STAT3 in neuroinflammation

3.2.1. Anti-inflammation effect

Overall, inflammatory signals involve all stages of the cerebral ischemia cascade, and overwhelming evidence shows that the JAK2/STAT3 signaling pathway is also largely related to the regulation of inflammation (Yi et al., 2007). In the early stage of infarction, the activation of this pathway is clearly noticeable (Guo et al., 2008). To some extent, the increase in JAK2/STAT3 phosphorylation in the acute phase of cerebral ischemia can be explained as an automatic protective mechanism. Resident microglia in the brain and macrophages from peripheral sources, collectively known as microglia/macrophages, are the key regulators of the brain immune response and have a dual function, either protective or detrimental, according to the characteristics of different subtypes (Patel et al., 2013). Changing the phenotype of microglia/macrophages is expected to be one of the treatment strategies for stroke. STAT3 is considered to be of great significance in regulating microglial polarization and inflammation. p-STAT3 increases the level of M2 expression markers, meaning that increased levels of neurotrophic factors and anti-inflammatory cytokines are conducive to tissue repair and remodeling (Jiang et al., 2016). STAT3 knockdown significantly reduced the production of CD163 and IL-10 and nevertheless induced the production of IL-12 and NO. (Ning et al., 2018) Another study (Wang et al., 2010) on the polarization of macrophages induced by IL-6 in vitro also found that macrophages differentiated into the M2 type and that the level of phosphorylated STAT3 increased under IL-6 stimulation. After silencing the STAT3 gene with siRNA, the level of phosphorylated STAT3 and the expression of M2 markers decreased. Non-erythropoietic mutant erythropoietin (MEPO) facilitates microglial polarization toward the protective M2 phenotype by regulating the JAK2/STAT3 signaling pathway, which contributes to white matter repair after ischemic stroke (Wang et al., 2020). This is also a possible mechanism of many potential neuroprotective agents. Melatonin treatment directly suppresses the proinflammatory state in BV2 cells cocultured with neural cell lines under oxygen glucose development (OGD) challenge to reduce neurotoxicity in a STAT3-dependent manner (Liu et al., 2019). Resveratrol can simultaneously activate STAT6 and STAT3 via PGC-1α to inhibit the M1 phenotype and promote the M2 phenotype to show antineuritis activity and improve neuroinflammation (Yang et al., 2017). Furthermore, propofol prevents further neuronal damage by inhibiting Ca2+ overload, regulating extracellular-signal-regulated kinase (ERK) and NF-κB phosphorylation and activating the JAK1/STAT3 pathway to maintain anti-inflammatory microglial polarization (Lu et al., 2017). The α7 nicotinic acetylcholine receptor (α7nAChR) is a pivotal mediator in the endogenous cholinergic anti-inflammatory pathway, whose anti-inflammatory function is also at least associated with an increased ratio of p-JAK2/JAK2 and p-STAT3/STAT3; moreover, α7nAChR activation plays a decisive role in the production and quantity of anti-inflammatory factors such as IL-10 by microglia in wild-type mice, and its agonist PHA-543613 or AG490 augments and attenuates this effect (Krafft et al., 2017).

3.2.2. Proinflammation effect

Paradoxically, many reports have raised objections that inhibiting STAT3 nuclear translocation can reduce neuroinflammation damage. Unlike a previous study, Qin et al. (Qin et al., 2012) illustrated that stimulation of JAK2/STAT3 after ischemic stroke skewed microglia/

macrophage transformation toward a proinflammatory M1 phenotype, and there may be a two-way connection between the two. Long-term overactivated microglia release inflammatory mediators such as TNF-α and IL-6 to induce gp130 dimerization, which conversely triggers the activation of more JAK2/STAT3. Activated STAT3 further initiates the transcription and expression program of genes encoding proinflammatory-related elements, including cytokines, chemokines, adhesion molecules and matrix metalloproteinases, forming a vicious circle of the inflammatory response chain, constantly spreading and amplifying the role of proinflammatory factors, resulting in pathological damage (Satriotomo et al., 2006). After using homocysteine to activate microglia, Chen et al. (Chen et al., 2017a) observed a strong inflammatory response and increased the expression of pSTAT3, and immunohistochemistry showed that ischemia-induced phosphorylated STAT3 was mainly localized in microglia. In addition, suppressor of cytokine signaling 3 (SOCS3) (Raghavendra Rao et al., 2002), SC99 (Ding et al., 2019), sesquiterpene dimer, dasatinib (Ryu et al., 2019), schizandrin A (SchA) (Zeng et al., 2014) and other proteins or compounds exert anti-inflammatory and neuroprotective effects by limiting microglia-mediated neuroinflammation injury by inhibiting the JAK2-STAT3 signaling pathway. Astrocytes are also vital activation sites of STAT3. After cerebral ischemia, STAT3 phosphorylation in GFAP+ astrocytes catalyzes the proliferation of reactive astrocytes, and the formation of astrocyte scars has the potential to aggravate postischemic neuroinflammation, exacerbating neuronal death (Qiu et al., 2005). Activating the JAK2/STAT3 signaling pathway can also induce the overexpression of HMGB1 (an important endogenous damage-associated molecular pattern (DAMP)), promoting the production and delivery of inflammatory factors (TNF-α, IL-1, IL-6) in addition to activating astrocytes in ischemic areas to secrete MMP-9 and destroying brain tissue and the blood-brain barrier. However, blocking this signal transduction with astrocytic nuclear yes-associated protein (YAP) (Huang et al., 2020), rapamycin, curcumin or AG490 suppresses astrogliosis, and the pathological inflammatory response is also alleviated (Wu et al., 2018). In contrast to drugs that stimulate STAT3 transcription and relieve inflammation, other compounds that inhibit the JAK2/STAT3 pathway exhibit anti-inflammatory effects on cerebral ischemic injury, and stachydrine (Li et al., 2020) and linagliptin (Elbaz et al., 2018) cause blockage of both JAK2/STAT3 and p65, reducing the concentrations of TNF-α and IL-1β, which is beneficial for the reduction in inflammation.

3.3. JAK2/STAT3 in oxidative stress

3.3.1. Alleviation of oxidative stress injury

Mitochondria are the main source of reactive oxygen species (ROS), which are extremely vulnerable to hypoxia and ischemia (Wang et al., 2018). Under normal physiological conditions, the level of intracellular ROS is controlled by antioxidants in vivo, but with cerebral ischemia, mitochondria become seriously damaged and undergo changes in morphology and function, resulting in superoxide anions and ROS production greatly exceeding that of free radical scavengers, proceeding to the next step, provoking the generation of H_2O_2 to give rise to cytotoxicity by changing the cell signal transduction pathway (Ham 3rd and Raju, 2017). Malondialdehyde (MDA) is the final product of free radicals acting on lipid peroxidation, which results in cross-linked polymerization of proteins, nucleic acids and other biological macromolecules, affecting the activities of mitochondrial respiratory chain complexes and key enzymes in mitochondria. Superoxide dismutase (SOD) is an antioxidant metalloenzyme in organisms that possesses the ability to scavenge some ROS and maintain the balance between oxidation and antioxidation (Kanzaki et al., 2017). A reduction in SOD and an increase in MDA in brain tissues are typical signs of oxidative stress after CIRI. Recent studies have proven (Xu et al., 2020) that astragaloside IV (AS-IV), a natural product purified from *Astragalus membranaceus*, has potential antioxidative pharmacological activities through experimentation in vitro and in vivo. The activities of SOD and glutathione peroxidase are enhanced, while MDA and ROS are reduced at the rate of AS-IV application, despite oxidative harm and prominent increases in the expression of p-JAK2 and p-STAT3. Furthermore, AG490, a specific pharmacological inhibitor of JAK2, eliminates JAK2/STAT3 signaling pathway activity to restrict the observed protective effects on oxidative stress in the presence of AS-IV. Therefore, whether activation of JAK2 and the subsequent phosphorylation of STAT3 are beneficial in enhancing the survivability of neurons under conditions of increased ROS levels remains to be elucidated.

3.3.2. Aggravate oxidative stress

As more studies start to have an extensive and in-depth focus on the suppression of oxidative stress, general opinions have changed. It has been well documented that crosstalk occurs between ROS and pSTAT3, and the profile of STAT3 activation seems similar to that of ROS generation in stroke. The production of ROS precedes the activation of STAT3; in homocysteine (Hcy)-treated cells, ROS levels began to increase at 5 min, and p-STAT3 levels increased later at approximately 30 min (Chen et al., 2017a). Thus, the activation of STAT3 may be a downstream event generated by ROS. For other implementations, H2O2 treatment significantly increased the levels of p-STAT3 in human peripheral blood lymphocytes, fibroblasts, A-431 tumor cells and human umbilical vein endothelial cells (Chen et al., 2017b). Moreover, STAT3 phosphorylation could be completely blocked by the ROS inhibitor *N*-acetyl-L-cysteine in a dose-dependent manner, but the relationship between them is not unidirectional. The JAK2-STAT3 pathway could also upregulate oxidative stress and the level of ROS through a feedback effect (Chen et al., 2017b; Duan et al., 2013). P-STAT3 has a decisive function in H2O2-induced oxidative stress, and AG490 or JAK2 siRNA treatment blocks not only STAT3 activation but also Neuro-2a cell (N2a) damage (Sun et al., 2020). Notably, the STAT3 protein basically dwells in the cytoplasm, and a small pool of STAT3, approximately one-tenth of the total STAT3 in the cytosol, also localizes to mitochondria (mitoStat3) and accumulates with the appearance of various stimuli, such as ischemia (Szczepanek et al., 2012). Chen et al. (Chen et al., 2017a) verified this finding and clarified that in addition to inducing inflammation, Hcy increases oxidative stress under elevated plasma levels, the degree of mito-Stat3 activation parallels mitochondrial damage in the cerebral cortex and hippocampus, and the intensity of these effects was positively correlated with the concentration of Hcy administered. Similarly, stachydrine treatment can also promote the activity of SOD and lower the level of MDA by inhibiting the phosphorylation of P65/JAK2 and STAT3 (Kim et al., 2017).

3.4. JAK2/STAT3 in apoptosis

3.4.1. Antiapoptosis

Both inflammation and oxidative stress can further induce apoptosis. Apoptosis is the main form of cell death in CIRI and is reversible until a few hours after cerebral ischemia (Hu et al., 2017). Therefore, saving apoptotic cells is an opportunity for therapeutic intervention in ischemic stroke. Apoptosis is achieved by endoplasmic reticulum stress, death receptors and the mitochondrial pathway (Venderova and Park, 2012). Many apoptosis-related genes and signaling pathways participate in this process. Among them, the proapoptotic protein Bax and the antiapoptotic protein Bcl-2 are the most closely associated with apoptosis and interact with Truncated Bid. The balance between these two is crucial, and an increased Bax/Bcl-2 ratio is an important sign of neuronal apoptosis. There are overwhelming indications (Kim et al., 2017; Werner et al., 2017) that activation of the JAK2/STAT3 signaling pathway significantly reduces apoptosis by regulating the expression of apoptotic and antiapoptotic genes after CIRI. Epidermal growth factor receptor (EGFR) penetrates the cell membrane and exerts intrinsic tyrosine kinase activity. Activation of EGFR has an important neuroprotective effect on brain I/R injury, which is inseparable from

activation of the JAK2/STAT3 pathway (Tang et al., 2018). After EGF preconditioning, the expression of Bcl-2, Bcl-xL and TIMP-1 was upregulated, the level of Bax was downregulated, and the abnormal opening of the connexin 43 half channel was also suppressed, which could significantly reduce the infarct volume and improve neurological impairment. AG1478, an antagonist of EGFR, or AG490, an inhibitor of JAK2, destroyed this protective effect. JAK2/STAT3 is also the basis of leptin's neurotrophic and neuroprotective effects (Zhang et al., 2020b). When leptin binds to the functional leptin receptor Ob-Rb, JAK2 and STAT3 are phosphorylated to inhibit the release of mitochondrial cytochrome *c* and mitochondrial-mediated apoptosis. Bcl-2 and Bax jointly dominate the opening of mitochondrial membrane channels. After the activation of apoptosis, oligomerized Bax transfers from the cytoplasm to the outer mitochondrial membrane and increases its interaction with voltage-dependent anion channels, thus opening the channel and releasing apoptotic factors, such as cytochrome *c*, into the mitochondrial matrix, leading to cell death (Chaturvedi et al., 2010). In delayed recanalization after MCAO, hepatocyte growth factor (HGF) binds to the c-Met receptor, and STAT3 and its downstream target, Bcl-2, are activated, contributing to the antiapoptotic mechanism (Tang et al., 2020). In a septic encephalopathy model (Zhou and Yu, 2013), Zhou and Yu discovered that the antiapoptotic effect of recombinant human erythropoietin was eliminated by AG490. Kim and colleagues demonstrated (Kim et al., 2017) that sevoflurane postconditioning induced a significant reduction in the proportion of apoptotic cells by increasing the expression of p-JAK2, P-STAT3, and Bcl-2 and decreasing that of Bax. In vitro experiments carried out by Wang et al. (Wang et al., 2018) showed that oxygen glucose deprivation could induce oxidative stress and apoptosis of mitochondria, while adiponectin (APN) could protect hippocampal HT22 cells from apoptosis by activating the JAK2/STAT3 signaling pathway. In addition, JAK2/STAT3 can also be traced in the exploration of the antiapoptotic mechanisms of diosmin 17 (Liu et al., 2014a), β-estradiol (E2) (Bjornstrom and Sjoberg, 2002), and Src homology-2 (SH2) B adaptor protein-1 (SH2B1) (Yuan et al., 2018). Behavioral studies also determined that improvements in learning and memory disorders are mainly attributed to a reduction in neuronal apoptosis and that JAK2/STAT3 signaling can regulate hippocampal synaptic plasticity by affecting nerve cell survival, which may be related to the recovery of cognitive dysfunction (Zhou and Yu, 2013).

3.4.2. Proapoptosis

Even though most previous studies have reported the benefits of the JAK2-STAT3 pathway after CIRI, a few studies have reported contradictory results indicating that blockade of the JAK2-STAT3 pathway produces improved neurological outcomes and decreased infarct size. SOCS1 is a member of the cytokine signal transduction inhibition (SOCS) protein family. It not only is the target gene of STATs but also acts as a negative feedback monitor to inhibit JAK signal transduction. Activated STATs stimulate SOCS gene transcription to bind SOCS proteins and subsequently phosphorylate JAKs and receptors, thus shutting down the pathway. When SOCS1 silences the JAK2-Stat3 signaling pathway, the mRNA and protein expression levels of Caspase-3 and Bax decrease, while the mRNA and protein expression levels of Bcl-2 increase (Wang et al., 2017). Caspase-3 is a homologous cysteine protease that cleaves the target protein and is the junction during the initiation of the apoptosis pathway. Increased concentrations of Bax activate caspase-3 and indirectly restrain the expression of Bcl-2 through the formation of Bax/Bcl-2 heterodimers, ultimately promoting neuronal apoptosis (Kretz et al., 2005). Ischemia-induced ROS and inflammatory responses are usually treated as triggers and participants that are principally responsible for regulating subsequent apoptosis (Jin et al., 2013) and probably occur via the JAK2/STAT3 pathway; thus, anti-inflammatory and antiapoptotic effects often occur together through inhibition of the JAK2/STAT3 pathway. Moreover, overexpression of miR-216a, which targets JAK2, mitigated cell viability as well as inhibiting the inflammatory mediators (Tian et al., 2018). Nicotiflorin, a traditional Chinese medicine that is effective against neuroinflammation and pathological factors such as hypoxia-, glutamate- or oxidative stress-induced cell death, strongly inhibited both the expression of Bax or caspase-3 and postischemic JAK2 and STAT3 phosphorylation in the ischemic cortex (Hu et al., 2017; Yu et al., 2013).

3.5. JAK2/STAT3 in angiogenesis

However, there are also other cellular responses, such as angiogenesis and functional microvascular remodeling, gradually driven by the body's self-repair mechanism to promote stroke recovery (Zhu et al., 2013). Angiogenesis, that is, the formation of new blood vessels on the basis of existing blood vessels, is a key element in the regeneration of ischemic tissue. Studies have shown that the microvessels in the brain tissue of ischemic stroke rats will gradually grow over time (Liu et al., 2014b). Scanning electron microscopy displayed three-dimensional images of vascular remodeling in the tissues around the infarct in patients with ischemic stroke. Overall, the number of angiogenesis events was proportional to the survival time of patients (Dong et al., 2016). In the ischemic state, angiogenesis is mostly induced by the upregulation of vascular endothelial growth factor (VEGF) expression. Furthermore, the expression of VEGF in the infarcted hemisphere increased 3 h after ischemic injury and lasted for 3 or 7 days (Marti et al., 2000). To date, it has been deemed that the majority of downstream angiogenic effects of VEGF, comprising microvascular permeability, endothelial cell proliferation, survival, migration and invasion, are largely dependent on EPO and its receptor EPOR to mediate the JAK2/STAT3 and VEGF/Flk-1 pathways to increase the expression of CD31 (Zhu et al., 2013). As a powerful pleiotropic neuroprotective factor, EPO is induced to be expressed after stroke and intensively boosts the karyokinesis and positive chemotaxis of endothelial cells and endothelial progenitor cells (Sola et al., 2005); studies have long shown that the JAK2-STAT3 signaling pathway can regulate the expression of genes related to cell cycle progression and angiogenesis under normal conditions and after injury (Dong et al., 2016). As the EPO/EPOR system binds to cytokine receptors, JAK2 is raised to the cell membrane. Activated JAK2 phosphorylates the tyrosine residues of STAT3. These tyrosine residues are shifted to the nucleus soon afterwards and bind to specific DNA elements, which are located upstream of genes related to regeneration and functional remodeling after stroke. The VEGF gene is exactly a STAT3 recognition site. In this process, STAT3 is phosphorylated and transported to the nucleus and integrates with the VEGF DNA promoter to induce VEGF mRNA transcription, resulting in VEGF expression. VEGF further binds to its endothelial cell surface receptors, triggering a variety of downstream signals and promoting angiogenesis. The benefit of this signal axis was confirmed by systemic or local administration of EPO or indirect administration of SMND-309 (Zhu et al., 2013) and catalpol (Dong et al., 2016) in rats with MCAO. Compared with the vehicle, treatment with AG490 or suramin (Zhu et al., 2013) (a VEGF inhibitor, which can effectively block the activation of STAT3 receptor FLK-1) significantly inhibited the constitutive activation of VEGF and the expression of VEGF and promoted a decrease in angiogenesis and an increase in infarct volume.

The influence of the STAT3 signaling pathway on brain vessels after ischemic stroke is multifaceted. Small extracellular vesicles (sEVs) derived from mesenchymal stem cells (MSCs) promote angiogenesis by inhibiting autophagy, a process that is partially due to STAT3 activation, while a recent paper reported that suppression of STAT3 via Stattic improved blood-brain barrier (BBB) integrity (Xia et al., 2020). Furthermore, STAT3-related neovascularization may be correlated with different periods of cerebral ischemia-reperfusion (Guo et al., 2018). The increase in VEGF in the acute phase will carry a risk of BBB leakage, induce cerebral hemorrhage and aggravate cerebral edema. However, treatment with recombinant pyruvate kinase M2 24 h after stroke could activate the JAK2/STAT3 pathway, increase VEGF production, accelerate angiogenesis, increase vascular permeability, strengthen

neurotrophic support for new neurons and synapses, and promote tissue repair and functional recovery (Chen et al., 2018). Consequently, the increase in VEGF in the early stage is disadvantageous to prognosis. Specific knockout of STAT3 from endothelial cells has no significant effect on the acute stage of ischemic stroke but reduces the expression of angiogenic factors and significantly inhibits vascular regeneration in the recovery phase, which is not conducive to prognosis, indicating that STAT3 may be of great importance for vascular regeneration after CIRI, especially in late repair (Hoffmann et al., 2015).

4. Conclusion

The JAK2/STAT3 signaling pathway has an important impact on the prognosis of cerebral ischemic injury. However, the effect of JAK2/STAT3 is double-edged; some studies suggest that its activation upregulates inflammation, apoptosis, oxidative stress, and angiogenesis, whereas others propose the opposite conclusion. To explain the discrepancy, we consider the following possible reasons: first, pJAK2 phosphorylates both STAT3 and STAT1, and the commonly used inhibitor AG490 inhibits the phosphorylation of both STAT3 and STAT1 (Xuan et al., 2001). It is reasonable to speculate that the neuroprotective or neurotoxic effects of STAT3 are likely to be the superposition of STAT1 and STAT3. Remarkably, these two factors often have no synergistic effect; for example, STAT1 and STAT3 play proapoptotic and antiapoptotic roles in rat myocardial I/R, respectively (Xuan et al., 2001). Second, many studies use only one specific kind of cell as the research object, but this is not sufficient to delineate and evaluate the precise overall effect. Third, studies on JAK2/STAT3 in brain I/R are mostly conducted through drug intervention, and different time windows and doses of administration may cause variation in the results. Finally, the types of upstream stimuli and the biological properties of downstream target genes play a decisive role. Therefore, further investigation to thoroughly elucidate the various functions of STAT3 after ischemic stroke is needed, with the goal of developing new ideas for the diagnosis and treatment of ischemic stroke.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Author's contributions

ZY and YB wrote the initial draft. Figures and forms were prepared by ZY and YYZ. XXX and Omar Y A T Dekhel polished the article. JZH and GLJ are responsible for designing and improving the overall structure and ideas of the article. All authors read and approved the final manuscript.

Declaration of Competing Interest

There are no potential conflicts of interest among the authors.

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