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# The emerging role of signal transducer and activator of transcription 3 in cerebral ischemic and hemorrhagic stroke

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ABSTRACT

Signal transducers and activators of transcription (STATs) comprise a family of cytoplasmic transcription factors that mediate intracellular signaling. This signaling is typically generated at cell surface receptors, the activation of which results in the translocation of STATs to the nucleus. STATs are involved in biological events as diverse as embryonic development, programmed cell death, organogenesis, innate immunity, adaptive immunity and cell growth regulation in organisms ranging from slime molds to insects to humans. Numerous studies have demonstrated the activation of STAT3 in neurological diseases, particularly in cerebral ischemic and hemorrhagic stroke. Additionally, STAT3 has also been reported to play a critical role in neuroprotective therapies. In light of the pleiotropic effects of STAT3 on the nervous system, we present the elaborate network of roles that STAT3 plays in cerebral ischemia and hemorrhage in this review. First, we introduce basic knowledge regarding STAT3 and briefly summarize the activation, inactivation, and regulation of the STAT3 pathway. Next, we describe the activation of STAT3 following cerebral ischemia and hemorrhage. Subsequently, we discuss the physiopathological roles of STAT3 in cerebral ischemia and hemorrhage. Moreover, we summarize several significant cerebral ischemic and hemorrhagic stroke treatments that target the STAT3 signaling pathway, including

*Abbreviations:* AD, Alzheimer disease; ADC, apparent diffusion coefficient; ADP, adenosine diphosphate; AGEs, advanced glycation end products; Akt, protein kinase B; AT1, angiotensin II type 1 receptors; AT2, angiotensin II type 2 receptors; A2aR, adenosine A2a receptor; ATF6, activating transcription factor 6; BBB, blood brain barrier; Bax, Bcl-2 associated X; Bcl-2, anti-apoptotic protein B cell lymphoma 2; CBV, cerebral blood volume; CLC, cardiotrophin-like cytokine; CNS, central nervous system; CNTF, ciliary neurotrophic factor; COX-2, cyclooxygenase 2; CREB, cAMP response element binding protein; CSF 3, colony-stimulating factor 3; CT-1, cardiotrophin-1; CVA, cerebrovascular accident; CVI, cerebrovascular insult; EGFR, epidermal growth factor receptor; EPO, erythropoietin; EPOR, erythropoietin receptor; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; FGFR, fibroblast growth factor receptor; G-CSF, granulocyte colony-stimulating factor; GDNF, glial cell line-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; gp130, glycoprotein 130; GSH-Px, glutathione peroxidase; GSK3β, glycogen synthase kinase 3; HER2, human epidermal growth factor receptor-2; HGFR, hepatocyte growth factor receptor; HTPI, high-throughput immunoblotting; ICH, intracerebral hemorrhage; IFN, interferon; IGF-1, insulin-like growth factor 1; IGFR, insulin-like growth factors receptor; IL, interleukin; IPC, ischemia preconditioning; IPTC, ischemic postconditioning; I/R, ischemic/reperfusion; JAKs, Janus kinases; JH1, JAK Homology 1; JH2, JAK Homology 2; KIR, kinase inhibitory region; KOR, kappa-opioid receptor; LDH, lactic dehydrogenase; LIF, leukemia inhibitory factor; MAP2, microtubule-associated protein 2; MAPK, mitogen-activated protein kinase; MCAO, middle cerebral artery occlusion; Mn-SOD, manganese superoxide dismutase; MT, metallothionein; MTT, mean transit time; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Nfl, neurofilament light chain; NPN, neuropoitin; NRIPoC, non-invasive remote limb IPTC; NRU, nitrogen rejection unit; NSPC, neural stem and progenitor cells; OGD, oxygen-glucose deprivation; OGD+R, oxygen glucose deprivation and reperfusion; OPRK1, opioid receptor kappa 1; OSM, oncostatin M; OVX, variectomized; PC, preconditioning; PDGFR, platelet-derived growth factor receptor; PKC, protein kinase C; PGZ, pioglitazone; PIAS, protein inhibitor of activated STAT; PI3K, phosphatidylinositol 3-kinase; P-JAK2, phosphorylated JAK2; PPARγ, peroxisome proliferator-activated receptor gamma; PPARs, peroxisome proliferator-activated receptors; P-STAT3, phosphorylated STAT3; PTPs, protein tyrosine phosphatases; PTPRT, protein tyrosine phosphatase receptor T; RBA-2, brain astrocyte-2; ROS, reactive oxygen species; RTKs, receptor tyrosine kinases; SAH, subarachnoid hemorrhage; sgp130, soluble gp130; SH2, Src homology 2; SHP-1, Src homology domain protein tyrosine phosphatase-1; SHP-2, Src homology domain protein tyrosine phosphatase-2; sIL-6R, soluble IL-6 receptor; SOCS, suppressor of cytokine signaling; SOD2, superoxide dismutase 2; STATs, signal transducers and activators of transcription; STAT3, signal transducer and activator of transcription 3; tFCI, transient focal cerebral ischemia; TIMP-1, tissue inhibitor of matrix metalloproteinases-1; TNF-α, tumor necrosis factor α; TSPO, translocator protein; UPR, unfolded protein response; varepsilonPKC, PKC epsilon; VEGF, vascular epidermal growth factor.

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pharmacological and physical therapies. Finally, we highlight research progress on STAT3 in stroke. This review presents the important roles of STAT3 in the nervous system and may contribute to the promotion of STAT3 as a new therapeutic target.



**Contents**



## 1. Introduction

Stroke, which is also known as cerebrovascular accident (CVA) or cerebrovascular insult (CVI), refers to the loss of brain function due to a disturbance in the blood supply to the brain (Zuhaid et al., 2014). This disturbance is due to either ischemia or hemorrhage. Accordingly, stroke can be classified into two categories: ischemic and hemorrhagic stroke. Following stroke, the affected area of the brain cannot function normally, which may result in the inability to move one or more limbs on one side of the body, a failure to understand or formulate speech, or visual impairment of one side of the visual field (Extramiana and Maison-Blanche, 2015). A 2011 WHO report indicated that stroke was the second most frequent cause of death worldwide, accounting for 11% of the total number of deaths (Farkouh et al., 2012). However, the clinical management of stroke is challenging and often ineffective because strokes can cause permanent neurological damage; moreover, the restoration of blood flow and neurosurgery are insufficient to restore neurological function. To develop effective treatments for cerebral ischemia, several studies have focused on the evaluation of neuroprotective drugs, and these studies have proven important for current and future studies (Moonis et al., 2014). Currently, several promising alternative candidate neuroprotective strategies have been investigated, such as physical therapy treatments, including electroacupuncture pretreatment, hypothermic suppression, ischemic preconditioning (IPC), and non-invasive remote limb ischemic postconditioning (IPTC) (NRIPoC), and pharmacological therapies, including puerarin, fludarabine, diosmin, SMND-309 (a novel derivative of salvianolic acid B), and other small-molecule drugs (Cheng et al., 2014; Crowley and Kash, 2015; Kojima et al., 2013; Petrone et al., 2014; van Rijt et al., 2014; Xu et al., 2015). These strategies exert their neuroprotective effects