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Is STAT3 Signaling after Focal Ischemic Stroke Beneficial

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Abstract

Signal Transducer activator of transcription 3 (STAT3) is involved in cell signaling of neuronal stem cell proliferation, angiogenesis, and cell cycle progression. The jury is still out, about the effects of the STAT3 pathway activation after ischemia and if inhibiting or inducing this pathway leads to better functional recovery and neuronal stem cell proliferation to the penumbra. This review will better understand the role of STAT3 after focal ischemic stroke.

Keywords: Ischemia; STAT3; Penumbra

Introduction

Signal Transducer activator of Transcription 3 (STAT3) is a transcription factor and an intracellular signal transducer activated by cytokines, growth factors, and receptor- or nonreceptor-tyrosine kinases [1,2]. STATs are involved in many 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 [1]. Tyrosine phosphorylation of STAT3 at Y705 is required for STAT3 activity. After phosphorylation at Y705, dimerization, and nuclear translocation, STAT3 binds to the promoters of target genes and finally induces gene expression [2].

In this review, we will discuss the importance of STAT3 and its potential neuroprotective strategies and regenerative targets that may expand to it being a molecular therapeutic target after ischemia.

STAT3 after Focal Ischemia

In developed countries, stroke is the leading cause of death and disability and beyond the immediate 4–6 h after an acute ischemic stroke, there is no known therapy that improves outcomes for this health disparity [3]. Numerous pathological events such as necrosis, apoptosis, edema, and altered cellular signaling occur after cerebral ischemia as well as after subdural hematomas [4]. Previous studies have shown that the STAT3 pathway is activated in in vitro and in vivo experimental models of stroke [5,6]. Although most studies show an increase in phosphorylation of STAT3 after stroke, there are conflicting data whether this pathway activation leads to improved neurological recovery.

Several groups have found that treating animals with hypoxic preconditioning, rhEPO, or other novel compounds increased the activation of the STAT3 pathway and improved neurological recovery after experimental stroke [7,8]. Furthermore, it has shown that when STAT3 phosphorylation is blocked with inhibitors AG490 or WP1066 (an analog of AG490) they found that cell death markers or functional performance were worsened [1,7-9]. The latter suggest that treatments that activate the STAT3 pathway after experimental stroke may lead to improved functional performance and decreased cell death [1].

On the contrary, Satriotomo, et al. (2006) found that the JAK2 inhibitor AG490 or a STAT3 siRNA after experimental cerebral ischemia decreased infarction volume, neuronal damage, apoptosis, and GFAP-positive cells [1,10]. These results suggest that activation of the STAT3 pathway leads to decreased cerebral recovery and that blocking this pathway leads to better neurological outcomes. Due to the controversial outcomes of STAT3 activation, further studies are required to determine the functional effects of STAT3 pathway activation following cerebral ischemia. Our group studies the effects of STAT3 on focal ischemia using neuronal STAT3 KO mice to determine if this pathway is indeed beneficial to the outcomes of regenerative repair, angiogenesis, and functional recovery.

STAT3 and Neuroprotection

Previous reports have also shown STAT3 may be involved in neuroprotection against various cerebral ischemia and brain insults [11-15]. After focal ischemia, reactive oxygen species (ROS) are produced in mitochondria. These ROS induce mitochondrial-dependent apoptotic pathways [16-18]. These ROS, are removed by manganese-containing superoxide dismutase (Mn-SOD or SOD2), a primary cellular defense antioxidant enzyme specific to superoxide [16]. STAT3 regulates transcription of the Mn-SOD gene in the mouse cerebral cortex and cortical neurons [14]. Another study used Rice-Vannucci model of severe hypoxia induced insult in postnatal (P7) mice, neuronal deletion of STAT3 reduced forebrain cell death, tissue loss, microglial, and astroglial activation [19]. This data implies that STAT3 plays a critical role and may contribute to neonatal hypoxia induced-brain damage via Tyr705 phosphorylation [19]. Therefore, STAT3 is thought to play a necessary role in neuroprotection after focal ischemia.

Human clinical application to STAT3

Upon infection, inflammatory cytokines trigger cell signaling in local stem cells or differentiated cells [20]. Among other transcription factors, this eventually leads to the activation of STAT3 that mediates regenerative gene-expression programs in human disease. These genes include growth factors, cell-cycle stimulators, cell death inhibitors, and genes promoting dedifferentiation, cell motility and migration as suggested after stroke and after an immune response to infection. STAT3 has regenerative properties that has been extensively studied in hepatocyte cells in the liver [21-23] and has been proven to induce cancer [24].

Adaptation to other Diseases Targeting STAT3 Molecules

STAT3 regulates a wide spectrum of biological programs, including inflammation, tissue regeneration, cell proliferation, cell survival, cellular differentiation, angiogenesis, chemotaxis, and cell adhesion [20-24]. STAT3 plays a role in the latter processes by transcribing the expression of a variety of genes in response to specific external signals sensed by cell-surface receptors [23]. All cell types and tissues do not have the same expression patterns of these STAT3 receptors and their signaling cascade mediators. Nonetheless, STAT3 activation is highly context-dependent, which can often lead to controversial data [20]. The latter is true for the role of STAT3 in inflammation, since it can promote or suppress this process in many diseases [20-24].

Conclusion

Ischemic stroke has been shown to activate the STAT-3 pathway and increase expression of STAT-3 related genes involved in cellular proliferation, differentiation, survival and inhibitory neurotransmission. However, there are conflicting reports on the effects of blocking the STAT3 pathway. Some have reported worsened neurological recovery when blocking this pathway, while others have demonstrated advantageous effects. Further investigation is needed to determine if it is feasible to selectively block only certain genes downstream of the STAT-3 pathway to prevent the deleterious effects associated with activation of this pathway while maintaining the beneficial neuroprotective effects of STAT-3 pathway activation.

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