

# Effects of JAK2-STAT3 signaling after cerebral insults

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**Keywords:** JAK2-STAT3, traumatic brain injury, stroke, status epilepticus, preclinical injuries

The JAK2-STAT3 signaling pathway has been shown to regulate the expression of genes involved in cell survival, cell proliferation, cell-cycle progression, and angiogenesis in development and after cerebral insults. Until recently, little has been known about the effects of this pathway activation after cerebral insults and if blocking this pathway leads to better recovery. This review examines the role of this pathway after 3 cerebral insults (traumatic brain injury, stroke, and status epilepticus).

## Introduction

Cerebral insults such as a traumatic brain injury (TBI), stroke, or status epilepticus (SE) can lead to detrimental outcomes for patients who suffer from one of these events. All of these insults have been shown to cause acute cell death, disruption of the blood brain barrier, reduced neurological functional performance and altered cellular signaling within the injured tissue. One signaling pathway that has been shown to be activated after all of these cerebral insults is the Janus kinase 2 and signal transducer and activator of transcription 3 (JAK2-STAT3) signaling pathway. This pathway activates numerous genes responsible for many cellular functions that may play a critical role in both neural injury and repair; however, the precise contribution of JAK2-STAT3 activation after TBI, stroke, and SE remains incompletely understood.

When the JAK2-STAT3 pathway is activated after cerebral insults, it leads to the increased expression of genes associated with cell proliferation, differentiation and survival.<sup>1-6</sup> Activation of this pathway occurs when a hormone, growth factor or cytokine binds to a receptor which then phosphorylates JAK2. JAK2 in turn phosphorylates STAT3, which then dimerizes and translocates to the nucleus where it binds to the promoter region of genes containing gamma-activated sequences. In the adult nervous system, this pathway is mostly dormant unless the central nervous system suffers a stressor or insult. The insult, whether a TBI, stroke, or SE, leads to release of hormones, growth factors and cytokines

which result in activation of this pathway. This review will examine the effects of JAK2-STAT3 activation in each of these injury models and how altering this pathway after these cerebral insults affects neurological recovery in preclinical models.

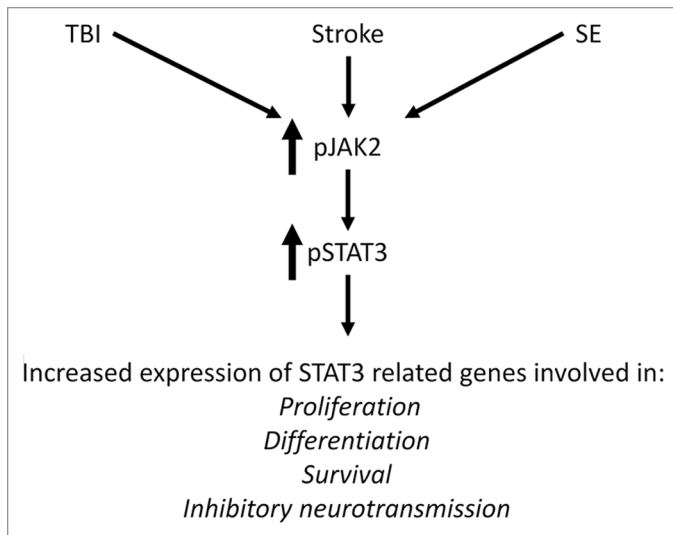
## JAK2-STAT3 Activation after TBI

Traumatic brain injury (TBI) is a major public health problem and is the leading cause of morbidity and mortality in individuals under the age of 45.<sup>7</sup> TBI causes a host of health issues including cognitive and motor defects as well as posttraumatic epilepsy.<sup>8-11</sup> These adverse outcomes significantly decrease the quality of life for individuals who suffer TBI and new therapies are needed. One approach is to identify and disrupt the cellular and molecular changes that contribute to these adverse outcomes. The JAK2-STAT3 pathway has been shown to become activated after TBI in several different experimental models. Although there are several differences in the method of experimental TBI, the current findings all show that there is an increase in the phosphorylation of JAK2 and/or STAT3 within the injured tissue as early as 3 h after injury.<sup>3,4,12-14</sup> Several groups have also shown that many known STAT3 genes have increased expression after experimental TBI,<sup>3-6,12</sup> however, the effect of JAK2-STAT3 pathway modulation on outcome is variable.

Zhao et al. 2011 has been able to partially block JAK2 and STAT3 phosphorylation 3 h after a TBI with administration of the JAK2 inhibitor AG490. They also determined that neurological recovery was worsened with the administration of AG490 after a TBI. This same group also found that giving human recombinant erythropoietin (rhEPO) after a TBI increased JAK2 and STAT3 phosphorylation and decreased apoptosis of cortical cells in peri-injured cortex cells of rats after an experimental TBI. When they added both rhEPO and the JAK2 inhibitor AG490 they found that pJAK2 and pSTAT3 levels were reduced and that the mRNA levels of several apoptosis related genes were increased while they did not see a difference in TUNEL staining. Their findings suggest that activation of the JAK2-STAT3 pathway after a TBI is advantageous for neuronal recovery.

While several groups have investigated inhibitory neurotransmitter receptor regulation, specifically GABA(A) receptor regulation, after a TBI, Raible et al. has found a correlation between pSTAT3 levels and GABA<sub>A</sub>  $\alpha$ 1 after an experimental TBI, suggesting that activation of this pathway may lead to altered

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Submitted: 05/06/2014; Accepted: 06/06/2014; Published Online: 06/12/2014  
Citation: Raible DJ, Frey LC, Brooks-Kayal AR. Effects of JAK2-STAT3 signaling after cerebral insults. JAK-STAT 2014; 3:e29510; <http://dx.doi.org/10.4161/jkst.29510>



**Figure 1.** Overview of JAK2-STAT3 signaling pathway after cerebral insults. Traumatic brain injury (TBI), stroke, and status epilepticus (SE) injury models have shown that the JAK2-STAT3 pathway becomes activated which is indicated either by the increased phosphorylation of JAK2 and/or STAT3.<sup>1,3,4,10-12,15-23,34-36</sup> When JAK2-STAT3 becomes phosphorylated it results in the increased expression of STAT3 related genes involved in cell proliferation,<sup>1,4-6</sup> cellular differentiation,<sup>1,4-6</sup> cell survival,<sup>1,3-6,15,20</sup> and inhibitory neurotransmission.<sup>1,10,34</sup>

inhibitory signaling.<sup>12</sup> Since one of the sequelae of a TBI is the subsequent development of epilepsy, preventing this alteration of inhibitory signaling after injury could inhibit the development of post traumatic epilepsy.

### JAK2-STAT3 Activation after Stroke

Within 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 illness.<sup>15</sup> Numerous pathological events such as necrosis, apoptosis, edema, and altered cellular signaling occur after cerebral ischemia as well as after subdural hematomas.<sup>16</sup> As with TBI, several groups have shown that the JAK2-STAT3 pathway is activated in *in vitro* and *in vivo* experimental models of stroke.<sup>17-25</sup> While all of the research to this point has shown that there is an increase in phosphorylation of JAK2 and/or 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 JAK2-STAT3 pathway and improved neurological recovery after experimental stroke.<sup>18,22</sup> Furthermore, some investigators have blocked JAK2-STAT3 phosphorylation with AG490 or WP1066 (an analog of AG490) and found that cell death markers or functional performance were worsened.<sup>18,19,22</sup> These findings suggest that treatments that activate the JAK2-STAT3 pathway after experimental stroke may lead to improved functional performance and/or decreased cell death.

On the contrary, Satriotomo et al. found that administration of the JAK2 inhibitor AG490 or a STAT3 siRNA after experimental cerebral ischemia decreased infarction volume, neuronal damage, apoptosis, and GFAP-positive cells.<sup>14</sup> These results suggest that activation of the JAK2-STAT3 pathway leads to decreased cerebral recovery and that blocking this pathway leads to better neurological outcomes. The jury thus remains out and further studies are required to determine the functional effects of JAK2-STAT3 pathway activation following cerebral ischemia.

### JAK2-STAT3 Activation after SE

Status epilepticus (SE) is clinically defined as the occurrence of a single unremitting seizure with a duration longer than 15–30 min or frequent clinical seizures without interictal return to baseline lasting at least 15–30 min. SE is a common life-threatening neurological disorder that is seen most commonly in the pediatric population.<sup>26-30</sup> Individuals who have had SE may experience morbidities including cognitive impairment, epilepsy, and recurrent SE.<sup>27,31</sup> Pilocarpine or kainic acid induced SE in rodents is a common model used by researchers to study the mechanisms underlying epilepsy development or epileptogenesis. These SE models mimic human SE and result in rodents that have similar morbidities as humans.<sup>32-35</sup>

As with both TBI and stroke, several studies have found that the JAK2-STAT3 pathway is activated in the hippocampus as early as 1 h after experimental SE and that several known STAT3 regulated genes are activated.<sup>1,36-38</sup> Two reports have shown JAK2-STAT3 activation can be blocked pharmacologically (by WP1066 or Pyridone 6) and prevent some STAT3-related genes from being activated.<sup>1,20</sup> These STAT3 regulated genes are involved in GABA<sub>A</sub>R subunit regulation, cell survival, cell proliferation, and cell cycling. Grabenstatter et al. found that when STAT3 phosphorylation was blocked during SE, the severity of the subsequent epilepsy was reduced in the rat pilocarpine model.<sup>1</sup> This may suggest that JAK2-STAT3 activation after SE at least partially contributes to the subsequent development of epilepsy. This same study also found that after administration of WP1066, there was no difference in FJB staining; suggesting that cell death was not altered by blocking JAK2-STAT3 activation after insult.<sup>1</sup>

### Conclusion

Multiple types of cerebral insults, including TBI, stroke and SE, have been shown to activate the JAK2-STAT3 pathway and increase expression of STAT3 related genes involved in cellular proliferation, differentiation, survival and inhibitory neurotransmission (Fig. 1). However, there are conflicting reports on the effects of blocking this 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 JAK2-STAT3 pathway to

prevent the deleterious effects associated with activation of this pathway while maintaining the beneficial neuroprotective effects of JAK2-STAT3 pathway activation.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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