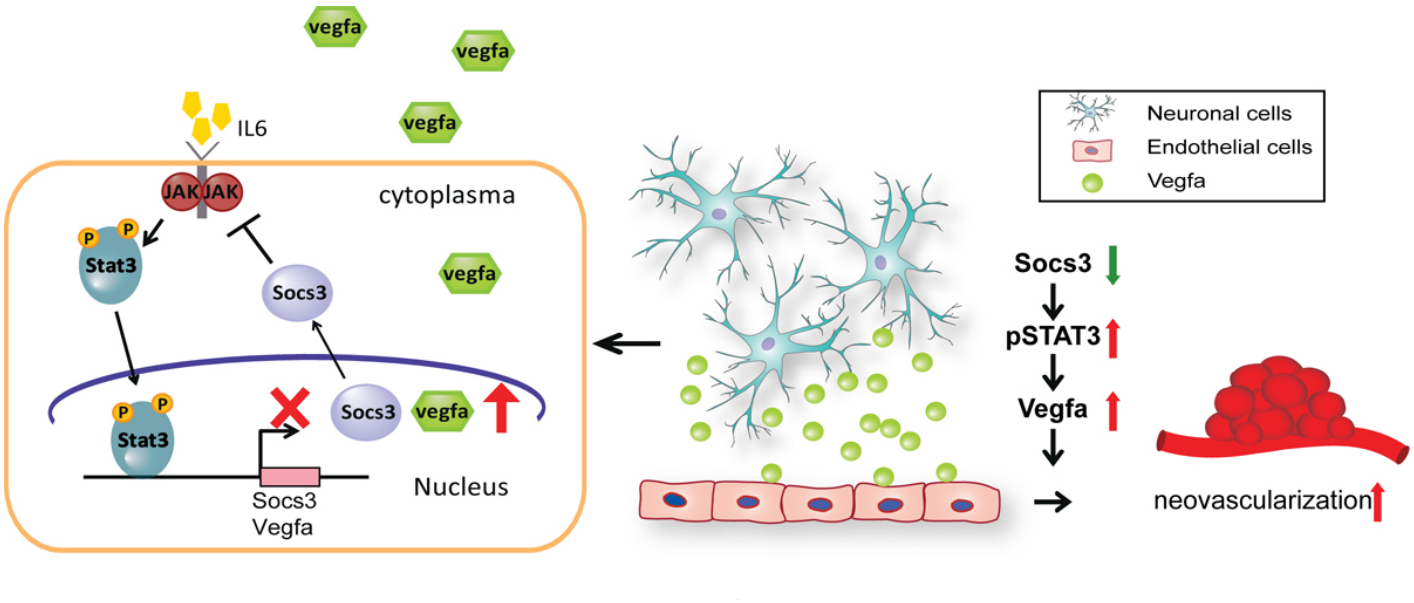
SOCS3 in neurons halts abnormal blood vessel formation in the eye

The leading cause of severe vision loss and blindness in the elderly, as well as in working age adults and in children is abnormal blood vessel growth in the retina. Researchers are still learning about what drives this pathological response and how to stop it. Current treatment blocking vascular endothelial growth factor (VEGF) may acutely block neovessel growth but may also cause loss of the normal vessels and neurons in the retina that are critical for vision.

Blood vessels do not arise *de novo* but have an interactive relationship with the neurons that need them for oxygen and nutrients. Neuro-vascular cross talk is important in many neurological disorders of the central nervous system, such as stroke, Alzheimer's disease, and epilepsy. Retina is part of the central nervous system. Neuro-vascular interactions might promote pathological vessel proliferation in the retina in diabetic patients and preterm infants in a misguided attempt to restore oxygen and nutrients to neurons that ultimately becomes counterproductive. Understanding neuron/blood vessel signaling may allow us to control harmful neovessel growth while maintaining normal vessels.



Schematic representation of neuronal/glial SOCS3 functioning as a modulator of angiogenic activation via VEGF signaling pathway. SOCS3 is one of STAT3 transcriptional target and can feedback inhibit STAT3 transcription activity through JAK kinase inhibition. Loss of SOCS3 decreased the inhibition of JAK kinase activity. This led to up regulation of phosphorylation of STAT3 by activated JAK kinase, then activated phosphor-STAT3 move to nucleus and enhance other downstream target genes, such as VEGF expression. Overexpressed VEGF from neuronal/glial cells may act on other cells, such as endothelial cells and lead to abnormal new vessel growth. Thus SOCS3 may be a new factor in modulating neurovascular crosstalk in

regulating retinopathy and a potential drug target in developing future therapeutics to treat retinopathy.

SOCS3 (suppressor of cytokine signaling 3) is an intracellular protein that suppresses the production of cytokines, growth factors, and inflammation mediators that promote blood vessel proliferation. To learn whether SOCS3 is a key factor for cross talk between blood vessels and their adjacent neurons to control vessel growth, we deleted the SOCS3 gene in neurons in mouse retinas. To mimic pathological vessel growth in preterm infants, we raised the mouse pups in an oxygen chamber. We found that lack of SOCS3 in neurons caused much more abnormal blood vessel proliferation compared with neurons with normal SOCS3 expression. Therefore SOCS3 in neurons dictates growth of abnormal blood vessels, but how does that happen?

VEGF is a protein secreted by cells that at a low level stimulates both normal blood vessel development and at a high level stimulates pathologic blood vessel formation. When preterm infants (or neonatal mice) are treated with oxygen, retinal blood vessels disappear and the retina becomes oxygen starved (hypoxic). VEGF is produced by neurons responding to hypoxia i and is controlled in part by its transcription factor, hypoxia-inducible factor 1. Excess VEGF is produced, beyond the normal level, which can cause pathologic blood vessel growth.

We found that retinal neuronal cells in mice lacking SOCS3 produced much more VEGF than did control mice, which led to more blood vessels. Interestingly, we found that the excess VEGF that caused the abnormal vessel growth was not controlled by hypoxia-inducible factor 1 (HIF1á) but by another transcriptional factor, signal transducer and activator of transcription 3 (STAT3). Lack of SOCS3 in neuronal cells can increase the activity of STAT3 to produce VEGF in neuronal cells. Under those conditions, excess VEGF secreted from neuronal cells during hypoxia diffuses to endothelial cells, to promote formation of pathological blood vessels.

This is a new concept in treating neurological disorders. By targeting neuro-vascular signaling we can stop abnormal blood vessel growth. We may now consider inhibiting only the excess VEGF production by targeting SOCS3 in neuronal cells without influencing normal blood vessel growth. Blocking all VEGF is a blunt instrument, as that may inhibit growth of normal vessels that are critical to healthy tissue function and inhibit neuronal survival. Blocking excess VEGF at the source may allow inhibition of only the pathological blood vessel growth leaving normal vessels and neurons content.

Ye Sun, Lois E. H. Smith

Department of Ophthalmology, Harvard Medical School
Boston Children's Hospital, 300 Longwood Avenue
Boston, MA 02115, USA.

Publication

SOCS3 in retinal neurons and glial cells suppresses VEGF signaling to prevent pathological neovascular growth.
Sun Y, Ju M, Lin Z, Fredrick TW, Evans LP, Tian KT, Saba NJ, Morss PC, Pu WT, Chen J, Stahl A, Joyal JS, Smith LE
Sci Signal. 2015 Sep 22