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New ‘Guidance’ for the treatment of hepatic ischemia reperfusion injury through semaphorins and plexins

Tobias Eckle, M.D., Ph.D.

Associate Professor of Anesthesiology, Cardiology and Cell Biology, Department of Anesthesiology, University of Colorado Denver, 12700 E 19th Avenue, Mailstop B112, RC 2, Room 7121, Aurora, CO 80045

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Semaphorins constitute a family of genes encoding secreted and membrane bound proteins which share a common domain called the *sema* domain. The name semaphorin is composed of the Greek words *sema*, meaning ‘signal’ and *phore*, which means to carry. In the mammalian system there are eight major classes of semaphorins based on structure and phylogenetic tree analyses (1). The main receptors for semaphorins are the so-called plexins. There are four subfamilies of vertebrate plexins (1), which are transmembrane receptors that regulate the motility and positional maintenance of cells. As such, semaphorins assist growing axons in finding appropriate targets to form synapses and are therefore called *neuronal guidance molecules*. Over the last decade numerous studies provided ample evidence that *neuronal guidance proteins* and their receptors do not only control neuronal development but provide an alternative guidance for the immune response, particularly with regard to the activation and migration of leukocytes (2–5).

In this issue of *Critical Care Medicine*, König and colleagues present compelling data that inhibiting one specific semaphorin-plexin system, the Semaphorin7A (Sema7A) - Plexin C1 signaling pathway, protects from liver ischemia through modulation of neutrophil properties (6). Sema7A acts through binding to its receptor Plexin C1 which is expressed by dendritic cells, monocytes, and neutrophils (1). As such, Sema7A holds the ability to induce the production of cytokines in neutrophils, macrophages and monocytes, all which play a significant role during the effector phase of the inflammatory immune response (1).

Before the current work by König et al., other investigators presented evidence for the Sema7A signaling pathway as potent pro-inflammatory pathway during hypoxia (7), acute lung injury (8), peritonitis (9), contact hypersensitivity and experimental autoimmune encephalomyelitis (10). For example, Morote-Garcia et al found that less neutrophils crossed

Correspondence should be addressed to: Tobias Eckle, M.D., Ph.D., Office: +1-303-724 -2932 or - 2947, Fax: +1-303-724-2852, tobias.eckle@ucdenver.edu.

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the endothelial barrier during hypoxia in studies using Sema7a-deficient mice (7). Similar, in a study on Plexin C1, the Sema7A receptor, Granja et al found that Plexin C1 deficient mice had decreased alveolar inflammation and improved survival in a murine model for acute lung injury (8). In another study, Suzuki and colleagues evaluated the role of Sema7A in contact hypersensitivity and experimental autoimmune encephalomyelitis using Sema7A deficient mice (10). During both disease conditions Sema7A deficient mice were resistant to disease development and showed almost no immune cell activation.

Although the importance of the semaphoring-plexins has been widely recognized in a variety of disease, König and colleagues at the University of Tübingen, Germany, where the first to investigate their role during hepatic ischemia and reperfusion (IR) injury. These findings are extremely important as hepatic IR injury has been reported to cause up to 10% of early organ dysfunction after liver transplant surgery (11). In their studies, König et al provided clear evidence that pharmacologic inhibition of the Plexin C1 receptor significantly dampens experimental IR injury of the liver. This is evidenced by measurements of liver enzymes and pro-inflammatory makers which were dramatically reduced after pre-treatment with a Plexin C1 antibody. König et al further supported their findings by studies in gene targeted mice. Here the authors found Plexin C1 deficient mice to be protected during hepatic IR injury. These observations open up the possibility that Plexin C1 is a worthwhile drug target for scientists and pharmaceutical companies, who are seeking to develop novel approaches for the treatment of hepatic IR injury.

A critical aspect of targeted pharmacological treatment is the understanding what tissues are affected by the semaphorin-plexin pathway. To dissect such mechanisms, König et al used so called 'chimeric mice'. 'Chimeric mice' are generated by transplanting bone marrow from a donor mouse into a bone marrow depleted mouse. In this particular case, the authors transplanted bone marrow from wildtype mice into bone marrow depleted Plexin C1 deficient mice and vice versa. The chimeric mice were then exposed to hepatic IR injury. König and colleagues found that while the Plexin C1 deficient mice with wildtype bone marrow had a wildtype phenotype, the wildtype mice with Plexin C1 deficient bone marrow had the same phenotype as the whole body Plexin C1 deficient mice. These studies suggest that Plexin C1 receptors on bone marrow derived, inflammatory cells such as neutrophils are the major cause for the observed liver damage in Plexin C1 minus mice. This is an important finding as it has implications for future drug development: If the Plexin C1 receptor on circulating cells such as neutrophils causes liver damage during IR injury, systemic Plexin C1 antagonists need to be designed that do not have major systemic side effects.

In another effort to target the Sema7A-Plexin C1 pathway, recent studies by Granja et al used a Sema7A peptide sequence which was reported to be the conserved semaphorin moiety to lock to Plexin C1 receptor (7). Using this peptide, Granje et al were able to show improved survival with dampened neutrophil extravasation in experimental lung injury (7). König et al also injected this peptide prior to hepatic ischemia and found decreased levels of the liver enzymes in association with reduced infiltration of neutrophils into the injured liver tissue.

While there are also limitations to these studies such as pre-administration of Plexin C1 antagonists or a short follow up period after liver ischemia, the accumulated evidence for the Sema7A-Plexin C1 pathway as a strong pro-inflammatory pathway in numerous disease states gives guidance for the development of a novel and very specific anti-inflammatory drug therapy to prevent or treat liver IR injury. In fact, not without reason the semaphorin-plexin system was recently highlighted in *Drug Discovery*, an edition by *Nature Reviews*, that highlights novel and promising therapeutic targets (1). Given that the semaphorin-plexin system has critical functions in various disease processes that depend on specific protein-protein interactions, these proteins are promising drug targets. However, based on the extreme novelty of this system and the lack of human studies, it might be too early for clinical trials and its potential will need to be critically explored in the coming years.

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