DAMPING INJURY AFTER STROKE

Innate immune system's navigation can be hacked for stroke protection

BY SVER AUNE

Stroke patients are faced with danger on two fronts. First, when a clot blocks blood flow, brain tissue is starved of oxygen and begins to die. Second, when blood flow is restored, components of the complement system, part of the innate immune system that protects the body against pathogens and other invaders, rush in to remove the dead tissue. Neighboring brain cells are often attacked and removed as well, producing secondary injury that drives more severe stroke.[1]

Antibody-based complement inhibitors patented by MUSC immunologist **Stephen Tomlinson, Ph.D.**, and his collaborators at the University of Colorado have protected against secondary injury after stroke in preclinical trials by blocking the part of the complement system that attacks endangered, but salvageable, brain tissue.

Tomlinson hopes that one day these complement inhibitors could be given along with tissue plasminogen inhibitor (tPA), the only currently approved therapeutic agent for stroke, to reduce morbidity. Indeed, Tomlinson has shown in a preclinical model that his targeted complement inhibitors can be safely co-administered with tPA and further can prolong the therapeutic window of safe treatment from three to twelve hours after stroke.

After a stroke, immunoglobulins (i.e., antibodies) move in to remove the dead tissue, honing in on danger-associated molecular patterns (DAMPs) expressed on the surface not only of dead cells but also nearby stressed and endangered cells. The immunoglobulins then recruit complement to trigger the digestion of both.

Inhibiting complement offers a promising strategy for protecting the brain after stroke. However, this kind of immunity cannot be blocked systemically without risking infection, and the immune system must be allowed to continue its job of clearing dead tissue.[2]

The complement inhibitors patented by Tomlinson and his colleagues get around these problems by transiently targeting a complement inhibitor specifically to the site of brain injury after stroke.

The precision targeting of the complement inhibitors is made possible by their linkage to the recognition domain of antibodies that Tomlinson has shown are responsible for honing in on DAMPs and initiating secondary injury in a mouse model of stroke. He has also verified that the same DAMPs are present in samples of human brain tissue from stroke patients.

Using a bait-and-switch technology, Tomlinson's inhibitors mimic the ability of immunoglobulins to locate DAMPs on endangered tissue and to recruit complement, but then block complement once it has arrived instead of activating it.

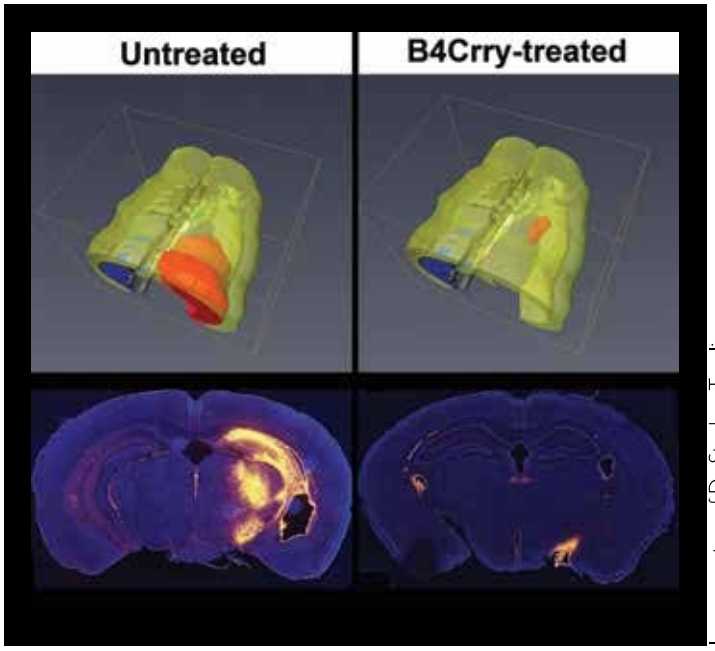

Image courtesy of Dr. Stephen Tomlinson

Targeted complement inhibitor reduces both lesion size (red in upper panel) and activation of immune cells (lower panel) following stroke.

The inhibitors are removed from the circulation very rapidly but remain bound to the injured brain for a prolonged period, thus preventing local inflammation with minimal effects on the immune system as a whole. Importantly, and unlike many other experimental therapies, Tomlinson's inhibitors also provide effective protection into the subacute and chronic phase after stroke.[3]

"Our overall goal in the context of stroke is to provide targeted and transient complement inhibition," said Tomlinson. "The complement inhibitor prevents the early inflammatory reaction. Because the inhibitor is targeted, it stays in the affected tissue and doesn't systemically inhibit complement. Because it's transient, we haven't got a continued block on complement activation, and complement is allowed to perform its physiological role in resolving inflammation in the subacute phase after stroke."

References

[1] Di Napoli M. *Stroke* 2001;32:1443-1448.
[2] Iadecola C, Anrather J. *Nat Med.* 2011;17(7):796-808.
[3] Alawieh A, et al. *J Neuroinflammation* 2015;12:247.