AIMS

Traumatic spinal cord injury (SCI) initiates a cascade of pathophysiological events that cause secondary injury and determine the extent of functional recovery. Although the processes that occur following SCI are complex, inflammation is considered to play a key role in the progressive degenerative events that take place, especially within the lesion penumbra. The complement system plays a key role in the pathogenesis of many inflammatory and ischemic conditions, and recent evidence indicates it also plays an important role in secondary SCI. Various systemic complement inhibitors are currently under therapeutic investigation as anti-inflammatory agents, but there remain concerns regarding their efficacy and safety. Complement activation products are important for host defense and immune homeostasis mechanisms, and systemic complement inhibition can compromise the protective and immunomodulatory roles of complement. In this context, CNS injury has been shown to be immunosuppressive, and further immune suppression by systemic complement inhibition may not be optimal in patients at risk of infection (urinary tract infection is a frequent complication during initial and ongoing medical rehabilitation after SCI).

The current aim is to provide pilot data in support of a long term goal to develop a neuroprotective strategy based on attenuating complement-dependent secondary damage after SCI. We have developed strategies to target complement inhibitors to sites of complement activation and injury, and have shown that targeted complement inhibitors are 10-20 fold more effective both in vitro and in experimental models of disease compared to conventional systemic approaches to inhibit complement. We hypothesize that our strategy to target complement inhibitors to the site of SCI will improve bioavailability, obviate the need to systemically inhibit complement, and provide a safe and highly efficacious therapy. We propose to investigate our hypothesis in a mouse model of SCI. Targeted complement inhibition will be achieved by the use of an antibody fragment (scFv) specific for mouse P selectin that blocks P-selectin function. We have already prepared anti-mouse P selectin scFv and shown that it targets to ischemic cerebral vaculature. There are other potentiall benefits of using a P-selectin targeted approach. Others have shown that P-selectin is expressed in the spinal cord following SCI and that P-selectin deficiency is protective in rodent models (1, 2). Thus, a P-selectin targeted complement inhibitor may have a dual and potent function by inhibiting two effector mechanisms (leukocyte adhesion and infiltration, and complement activation) that appear play a pathophysiological role in SCI.

The specific aims are to prepare soluble recombinant chimeric molecules consisting of an anti-mouse P selectin scFv fragment (targeting moiety) linked to a complement inhibitor. Complement inhibitors will be rodent Crry (inhibits early in the complement pathway) or CD59 (inhibits late in pathway). In addition to therapeutic endpoints, we will utilize targeted complement inhibitors that function at different points in the complement cascade to investigate disease mechanisms in a clinical setting. We will determine in vivo relationships between the generation of different complement activation products, adhesion molecule expression and leukocyte infiltration and activation. If these studies are successful, they will identify an efficacious treatment for post traumatic injury, result in a better understanding of the mechanisms of secondary tissue injury after SCI, will identify a specific point in the complement cascade as an optimum target for therapy and provide data for a competitive application for NIH funding.