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· Inflammatory Signaling Response to Thermal Injury

· Head Injury in Anticoagulated Patients

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Inflammatory Signaling Response to Thermal Injury

Severe thermal insult induces a major disturbance in the homeostatic mechanisms with significant disturbances in hemodynamic, respiratory, and metabolic pathways. Potential post-injury complications include severe sepsis, multisystem organ failure, and death. Since an aberrant systemic inflammatory response appears to be the underlying mechanism for ultimate organ failure, most studies have focused on systemic therapy to control this over-exuberant immune response. However, systemic administration of several anti-inflammatory or immunomodulatory agents, such as platelet activating factor receptor antagonists, anti-TNF antibodies, and IL-1 receptor antagonists, have failed to demonstrate improvement in survival or organ failure. In addition, the systemic administration of immunomodulators is associated with multiple disadvantages. These agents are not tissue specific and act on multiple organs. In a complex interacting system of cell-specific pathways, systemic inhibition of one pathway may have unpredictable deleterious results.

We therefore propose a new approach which calls for "inflammatory source control." The hypothesis is that burn injury induces dermal inflammation and production of pro-inflammatory mediators, which act as a lasting trigger stimulating the systemic inflammatory response syndrome. Therefore, controlling local inflammatory signaling may attenuate the subsequent complications such as acute lung injury. In this approach, we use topical agents to inhibit post-injury burn wound inflammatory signaling. The agent that we use is a potent inhibitor of p38MAPK, which is a pro-inflammatory signaling pathway that plays a prominent role in the regulation of inflammatory cell responses. The p38MAPK inhibitors are applied to the burn wound using a simple acetone-olive oil vehicle.

Topical p38MAPK inhibition attenuates the burn wound inflammatory response. There is a significantly less pulmonary inflammatory response via reduction of pulmonary neutrophil sequestration, pulmonary cytokine expression, microvascular injury and edema formation. Topical inhibition of p38 MAPK decreased pulmonary collagen deposition and improved pulmonary function with significantly reduced inspiratory and expiratory time. In a burn-pneumonia model, application of p38 MAPK inhibitor to the wound reduced the mortality rate back to sham level (Figure 1). While dermal gene upregulator ATF-2, a downstream p38 MAPK target, was significantly reduced, there was no reduction in pulmonary ATF-2 expression, arguing against significant systemic absorption of the topical inhibitor. These experiments also confirm the strong interaction and dependence on dermal inflammation to drive the systemic inflammatory response.

In summary, topical p38 MAPK inhibition in burn wounds to prevent inflammatory cell activation appears to be an effective strategy to reduce the systemic inflammatory response and end-organ failure. This novel therapy is practical and fits the current clinical practice of daily application of topical antimicrobial agents to the burn wound. Moreover, it is tissue restricted and avoids potential side effects from systemic administration. I have worked on intracellular inflammatory pathways for the last 10 years, elucidating the mechanism of action of p38MAPK in response to injury. My goal is to continue this investigation and develop an effective practical therapy in severe burns.

While chronic anticoagulation may be beneficial in management of some chronic medical conditions, it is a significant liability in trauma.

Head Injury in Anticoagulated Patients

As the U.S. population ages, chronic oral anticoagulation with warfarin is employed with increasing frequency. The number of people using warfarin has progressively increased, with over one million Americans being prescribed warfarin, most of whom are older than 65 years of age. Recent studies have demonstrated that 11-20% of trauma patients 65 or older were being treated with warfarin at the time of injury. While chronic anticoagulation may be beneficial in management of some chronic medical conditions, it is a significant liability in trauma. Due to increased bleeding propensity, intracranial hemorrhage (ICH) such as subdural and subarachnoid hematomas may rapidly increase in size and are associated with a several-fold increase in disability and mortality. However, studies have demonstrated that because of diagnostic and therapeutic difficulties, anticoagulated patients with traumatic ICH are not initiated on reversal agents in a timely fashion. A previous study of a hospital-based protocol demonstrated that rapid confirmation of ICH by expedited head CT scan combined with prompt reversal of warfarin anticoagulation with plasma decreases ICH progression and reduces mortality in patients with traumatic brain injury (TBI). However, no one has implemented and evaluated such protocols in a large regional health care system. In cooperation with the Washington State Department of Health, the Central Region Trauma Council, which governs the development and operational activities of trauma hospitals in King County (the most populated county in Washington State), will implement a regional protocol, "Head Injury in Anticoagulated Patients" (HIAP). The goal of the HIAP protocol is to reduce the time from presentation to reversal of anticoagulation in patients with ICH who are on chronic warfarin therapy, and thereby reduce morbidity and mortality due to trauma. Since one of the major obstacles in treatment has been rapid availability of plasma, in part due to the time consuming process of thawing fresh frozen plasma (FFP), and a large transfusion volume, this protocol will also use prothrombin complex concentrate (PCC) for the initial reversal of anticoagulation.

In the next few years, we will investigate the population-based prevalence of pre-injury use of warfarin in Washington State trauma patients, time from presentation to diagnosis, and the initial treatment of patients with TBI who are on chronic warfarin therapy. Recently, the Washington State Department of Health has modified the state trauma registry to collect state-wide data on trauma patients on chronic anticoagulation. These additional data will include a requirement to document warfarin use; moreover, in patients who are on warfarin, time to head CT scan and administration of therapy to

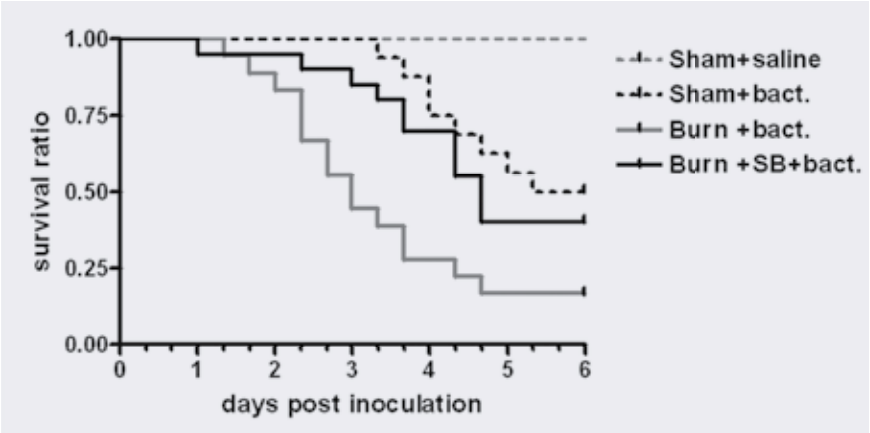

Figure 1: Dermal inflammatory source control improves survival in a burn-pneumonia two hit model.

reverse anticoagulation will be documented. Analyses of the Washington State trauma registry over the course of this project will provide state-wide data on pre-injury warfarin use and treatment of trauma patients for the first time.

In the second phase of the study, we will investigate the effectiveness of a regional protocol to rapidly identify ICH in anticoagulated patients and to reverse anticoagulation. We hypothesize that patients in areas where the protocol is in effect will have a shorter time from presentation to both diagnosis of ICH and reversal of anticoagulation.

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