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· Inflammatory Signaling Response to Thermal Injury Beta-Blocker Therapy in the Injured Patient

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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

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

Controlling local inflammatory signaling may attenuate the subsequent complications such as acute lung injury.

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 immuno-modulators 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

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.

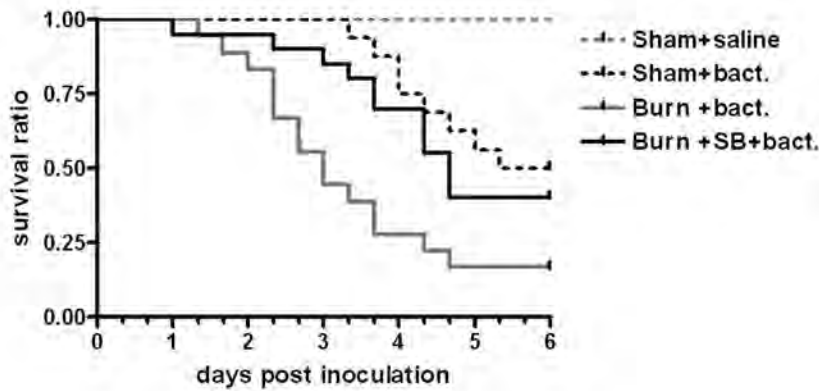


FIGURE 1: Dermal inflammatory source control improves survival in a burn-pneumonia two hit model.

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.

Beta-Blocker Therapy in the Injured Patient

Major injury induces a significant sustained release of catecholamines for several days or weeks after trauma. This catecholamine surge is especially increased when there is a significant head injury. The highest concentration of beta-adrenoreceptors is in the cerebral cortex. Activation of these receptors by catecholamines increases cerebral metabolism, glucose and oxygen consumption, which may be beneficial by increasing alertness at times of stress. However, increased cerebral oxygen consumption in the presence of elevated intracranial pressure post-trauma may worsen cerebral ischemia and secondary brain injury (Figure 2). Beta-blockers can break this Trauma-Catecholamine-Head Injury cycle by decreasing the cerebral oxygen requirement, which may attenuate cerebral ischemia and secondary brain injury. Overall, beta-blockers can be beneficial by decreasing hypermetabolism, alleviating cardiac workload and ischemia, and by decreasing cerebral oxygen requirement in head injury.

Following our original study in burn patients, we reviewed outcomes for 4,711 trauma patients from 2001 to 2004 and found that 7% received beta-blockers. In the beta-cohort, 45% of patients were on beta-blockers pre-injury. The most common reason to initiate beta-blocker therapy was blood pressure (60%) and heart rate (20%) control. The overall mortality rate was 5.6%, and head injury was considered to be the major cause of death. After adjusting for age, ISS, blood pressure, GCS, respiratory status, and mechanism of injury, the odds ratio for fatal outcome was 0.3 (p<0.001) for beta-blocker cohort as compared to control. Decreased risk of fatal outcome was more pronounced in patients with a significant head injury. We concluded that beta-blocker therapy is safe and may be beneficial in selected trauma patients with or without head injury. We are planning further studies looking at beta-blocker therapy in trauma patients and their effect on cerebral metabolism.

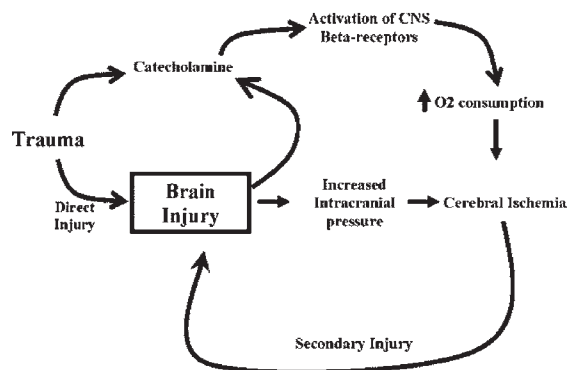


FIGURE 2: Trauma-Catecholamine-Head Injury Cycle

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