COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Training The Innate Immune System With Low-dose Endotoxin Provides Broad Defense Against Bacteria-induced Sepsis

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Worldwide, sepsis is responsible for 20% of annual deaths and is a global health priority for research into early biomarkers and treatments. Casualty rate predictions for large-scale combat operations (LSCO) will strain the continuum of care, resulting in prolonged field care and an increased risk of sepsis in battlefield casualties. Additionally, many biological warfare agents trigger septic shock and a common sequela to nerve agent exposure is neuroinflammation. To reduce the died of wounds received in action (DWRIA) rate due to sepsis during prolonged field care, we must develop safe, effective, and broad treatments.

Although targeted medical countermeasures, such as vaccines, are the platinum standard in mitigating infectious disease consequences, a robust biodefense program needs to also provide tools for protection in the absence of a vaccine. The innate immune system, the defense that our bodies developed as part of the ongoing natural arms race with natural pathogens, is therefore a promising target to provide additional protection against bioweapons and emerging disease.

Previous studies show that pre-conditioning with low levels of endotoxins, such as lipopolysaccharides (LPS) and monophosphoryl lipid A (MPLA), reduces mortality in animal sepsis models. Endotoxin pre-conditioning reduces pro-inflammatory cytokine production and increases innate immune cell bactericidal activity.

In our laboratory, we have studied the effect of LPS pre-conditioning on improving survival in multiple sepsis models in mice. We have identified that LPS pre-conditioning improves the phagocytotic activity of Kupffer cells. These specialized cells are localized in the liver and play a key role in responses to infectious agents and toxins. Interestingly, the phagocytotic activity of Kupffer cells responds to LPS pre-conditioning in a dose dependent manner, while that of other phagocytotic cells does not. This result suggests that Kupffer cells are the primary immune cells for the improvement of survival rate in sepsis after pre-conditioning. Additionally, a common injury in battlefield and chemical agent casualties is thermal burns. Burns elicit a unique systemic response characterized by systemic inflammation that can easily transition into either immunological hyper-activation or immunosuppression. We show that LPS pre-conditioning at the minimal dose is sufficient to significantly improve the survival rate of burned mice when challenged with normally lethal doses of Escherichia coli and Staphylococcus aureus.

A key point for this therapy is that we did not start LPS pre-conditioning until 24 hours after thermal injury. This means that we do not need to begin this treatment to mitigate sepsis prior to burn injury.

However, a significant hurdle in translating these findings to the warfighter is the high rate of adverse side effects, such as fever, influenza-like symptoms, and elevated heart rate. We are now exploring commercially available products to use as a platform for safely activating the innate immune system to mitigate sepsis without triggering adverse side effects when using endotoxin directly.