Presentation:
Experimental Models Evaluating DAMP's in Trauma and Sepsis

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Abstract:
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Trauma is the leading cause of mortality and morbidity in the US in individuals under 50 years of age and third leading cause overall. Much of the morbidity results from the systemic inflammatory response that follows injury. Despite the considerable advance in our understanding of the characteristic of the inflammatory response following injury, little is known of the signals that initiate inflammation following trauma and hemorrhagic shock. Based on the similarities between the systemic inflammatory response following trauma and that seen in patients following infection, we pursued the hypothesis that pattern recognition receptors known to be involved in the recognition of microbial products would also be involved in the activation of inflammatory pathways following injury. Our studies in models of hemorrhagic shock, peripheral soft tissue injury, cold and warm ischemia/reperfusion in mice have demonstrated that the local, as well as systemic inflammatory response following these sterile insults requires toll-like receptor 4 (TLR4) signaling. Studies using chimeric mice suggest that TLR4 signaling on both bone-marrow derived cells as well as parenchymal cells participate in these initiating events. The activation of TLR4 signaling is likely to involve endogenous molecules released by either damaged or stressed tissues and not endogenous flora based on studies using CD14 knockout mice and germ free animals. Neutralizing antibodies to the nuclear protein high mobility group box 1 (HMGB1) mimic the TLR4 deficient state in many of these models suggesting that this endogenous protein is at least one damage-associated molecular pattern molecule involved in the initiation of inflammation following sterile injury. Thus, a paradime emerges where pattern recognition receptors are critical to not only the response to infection but also to the systemic response to trauma.