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Role of TLR7 in Platelet Activation and Dysfunction in Sepsis

Abstract

Sepsis is a dysregulated host immune response to infection and characterized by organ failure. Sepsis is associated with marked inflammation and hemostatic activation leading to widespread microvascular thrombus formation and global clotting dysfunction, a complication termed sepsis-induced coagulopathy (SIC). Toll-like receptors (TLRs) are innate immune receptors that respond to pathogen (PAMPs) or host-derived danger molecules (DAMPs) and drive profound inflammation. We have established a murine model of SIC which is characterized by timedependent thrombocytopenia, procoagulant activation and consumption, and global clotting dysfunction. We have identified a critical role for TLR7 (a receptor for single-stranded RNAs) in the pathogenesis of SIC including thrombocytopenia, procoagulant (e.g., tissue factor, TF) production, and global clotting dysfunction. Moreover, we have observed a close correlation between the levels of plasma RNAs and sepsis severity and the ability of certain extracellular (ex) microRNAs to activate TLR7 signaling and induce procoagulant production. These data support the hypothesis that miRNA-TLR7 signaling mediates platelet and coagulation activation, and plays an important role in platelet activation and dysfunction in SIC. To test this hypothesis, we propose the following two Specific Aims. In Aim 1, we will test the function and mechanisms of miRNA-TLR7 signaling in platelet activation. In Aim 2, we will determine the role of TLR7 signaling in platelet activation and dysfunction in SIC. Completion of the proposed studies will provide new insight into the role and mechanism of TLR7 signaling in regulating platelet activity and function in SIC, and potentially offer a novel therapeutic target.