Platelet Activation And Formation Of Neutrophil-Platelet Aggregates In Influenza Pneumonia

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Abstract
Excessive neutrophils recruited during influenza pneumonia contribute to severe lung pathology through induction of neutrophil extracellular traps (NETs) and release of extracellular histones. We have recently shown that activation of platelets during influenza enhances pulmonary microvascular thrombosis leading to vascular injury and hemorrhage. Emerging evidence indicates that activated platelets also interact with neutrophils forming neutrophil-platelet aggregates (NPAs), which contribute to tissue injury. Here, we examined neutrophil-platelet interactions and evaluated formation of NPAs during influenza pneumonia. We also evaluated the efficacy of clopidogrel (CLP), an antagonist of the ADP-P2Y12 platelet receptor, alone or in combination with an antiviral agent, oseltamivir against influenza infection in mice. Our studies demonstrate increased platelet activation and induction of NPAs in influenza-infected lungs and these NPAs lead to NETs release both in vitro and in vivo. Further, neutrophil integrin macrophage-1 antigen (Mac-1) mediated platelet binding was critical in NPAs formation and NETs release. Administration of CLP reduced platelet activation but did not protect mice against lethal-influenza challenge. However, administration of CLP together with oseltamivir improved survival in mice compared to oseltamivir-alone treatment. Combination treatment reduced lung pathology, neutrophil influx, NPAs, NETs release and inflammatory cytokine release in infected-lungs. Taken together, these studies provide first report that NPAs formed during influenza contribute to acute lung injury. Targeting both platelet activation in addition to virus replication could represent an effective therapeutic option for treatment of severe influenza pneumonia.

Selected Relevant Publications for Reference

