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Rac1-dependent secretion of platelet-derived CCL5 regulates neutrophil recruitment via activation of alveolar macrophages in septic lung injury

Rundk Ahmed Hwaiz
Clinical Research Centre, Sweden

Accumulating evidence suggest that platelets play an important role in regulating neutrophil recruitment in septic lung injury. Herein, we hypothesized that platelet-derived CCL5 might facilitate sepsis-induced neutrophil accumulation in the lung. Abdominal sepsis was induced by cecal ligation and puncture (CLP) in C57/BL6 mice. CLP increased plasma levels of CCL5. Platelet depletion and treatment with the Rac1 inhibitor NSC23766 markedly reduced CCL5 in the plasma of septic mice. Moreover, Rac1 inhibition completely inhibited proteinase-activated receptor 4-induced secretion of CCL5 in isolated platelets. Immunoneutralization of CCL5 decreased CLP-induced neutrophil infiltration, edema formation and tissue injury in the lung. However, inhibition of CCL5 function had no effect on CLP-induced expression of Mac-1 on neutrophils. Blocking CCL5 decreased plasma and lung levels of CXCL1 and CXCL2 in septic animals. CCL5 had no effect on neutrophil chemotaxis *in vitro*, suggesting an indirect effect of CCL5 on neutrophil recruitment. Intratracheal challenge with CCL5 increased accumulation of neutrophils and formation of CXCL2 in the lung. Administration of the CXCR2 antagonist SB225002 abolished CCL5-induced pulmonary recruitment of neutrophils. Isolated alveolar macrophages expressed significant levels of the CCL5 receptors CCR1 and CCR5. In addition, CCL5 triggered significant secretion of CXCL2 from isolated alveolar macrophages. Notably, intratracheal administration of clodronate not only depleted mice of alveolar macrophages but also abolished CCL5-induced formation of CXCL2 in the lung. Taken together, our findings suggest that Rac1 regulates platelet secretion of CCL5 and that CCL5 is a potent inducer of neutrophil recruitment in septic lung injury via formation of CXCL2 in alveolar macrophages.

Biography

Rundk Ahmed Hwaiz is PhD student at Lund University. She was a Lecturer at Hawler Medical University at Erbil/ Kurdistan, Iraq. She has 10 published papers. She will defend her thesis in April 2015.

rundk.hwaiz@med.lu.se

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