Review > Front Cell Infect Microbiol. 2017 Apr 25;7:138. doi: 10.3389/fcimb.2017.00138. eCollection 2017.

Ectodomain Shedding by ADAM17: Its Role in Neutrophil Recruitment and the Impairment of This Process During Sepsis

Hemant K Mishra [1], Jing Ma [1], Bruce Walcheck [1]

Affiliations + expand

PMID: 28487846 PMCID: PMC5403810 DOI: 10.3389/fcimb.2017.00138

Free PMC article

Abstract

Neutrophils are specialized at killing bacteria and are recruited from the blood in a rapid and robust manner during infection. A cascade of adhesion events direct their attachment to the vascular endothelium and migration into the underlying tissue. A disintegrin and metalloproteinase 17 (ADAM17) functions in the cell membrane of neutrophils and endothelial cells by cleaving its substrates, typically in a *cis* manner, at an extracellular site proximal to the cell membrane. This process is referred to as ectodomain shedding and it results in the downregulation of various adhesion molecules and receptors, and the release of immune regulating factors. ADAM17 sheddase activity is induced upon cell activation and rapidly modulates intravascular adhesion events in response to diverse environmental stimuli. During sepsis, an excessive systemic inflammatory response against infection, neutrophil migration becomes severely impaired. This involves ADAM17 as indicated by increased levels of its cleaved substrates in the blood of septic patients, and that ADAM17 inactivation improves neutrophil recruitment and bacterial clearance in animal models of sepsis. Excessive ADAM17 sheddase activity during sepsis thus appears to undermine in a direct and indirect manner the necessary balance between intravascular adhesion and de-adhesion events that regulate neutrophil migration into sites of infection. This review provides an overview of ADAM17 function and regulation and its potential contribution to neutrophil dysfunction during sepsis.

Keywords: adhesion; bacteria; infection; inflammation; leukocyte.