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Targeting ADAM17 in Leukocytes Increases Neutrophil Recruitment and Reduces Bacterial Spread During Polymicrobial Sepsis

Hemant K Mishra [1], Timothy J Johnson [1], Davis M Seelig [2], Bruce Walcheck [3]

Affiliations + expand

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Abstract

A rapid and robust recruitment of circulating neutrophils at sites of infection is critical for preventing bacterial spread. The efficiency of this process, however, is greatly diminished during sepsis, a severe systemic inflammatory response to infection. The proteolytic activity of a disintegrin and metalloprotease-17 is induced in the cell membrane of leukocytes upon their activation, resulting in the conversion of membrane to soluble TNF-α and the release of assorted receptors from the surface of neutrophils important for their effector functions. We show that conditional knockout mice lacking a disintegrin and metalloprotease-17 in all leukocytes had a survival advantage when subjected to polymicrobial sepsis. Bacteremia and the levels of circulating proinflammatory cytokines, key determinants of sepsis severity, were significantly reduced in conditional a disintegrin and metalloprotease-17 knockout mice during sepsis. Although cecal bacterial microbiota and load were similar in unmanipulated conditional a disintegrin and metalloprotease-17 knockout and control mice, peritoneal spread of bacteria was significantly reduced in conditional a disintegrin and metalloprotease-17 knockout mice following sepsis induction, which was associated with an amplified recruitment of neutrophils. Taken together, our findings suggest that extensive a disintegrin and metalloprotease-17 induction during sepsis may tip the balance between efficient and impaired neutrophil recruitment.

Keywords: TACE; inflammation; microbiota.