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Blocking ADAM17 Function with a Monoclonal Antibody Improves Sepsis Survival in a Murine Model of Polymicrobial Sepsis

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Abstract Sepsis is the culmination of hyperinflammation and immune suppression in response to severe infection. Neutrophils are critical early responders to bacterial infection but can become highly dysfunctional during sepsis and other inflammatory disorders. The transmembrane protease ADAM17 (a disintegrin and metalloproteinase 17) is expressed by leukocytes and most other cells and has many substrates that regulate inflammation. We have reported that conditional knockout mice lacking ADAM17 in all leukocytes had a survival advantage during sepsis, which was associated with improved neutrophil effector functions. These and other findings indicate aberrant ADAM17 activity during sepsis. For this study, we evaluated for the first time the effects of an ADAM17 function blocking monoclonal antibody (mAb) on the pathogenesis of polymicrobial sepsis. Mice treated with the ADAM17 mAb MEDI3622 prior to sepsis induction exhibited significantly decreased mortality. When the ADAM17 mAb was combined with antibiotic administration, sepsis survival was markedly enhanced compared to either intervention alone, which was associated with a significant reduction in plasma levels of various inflammation-related factors. MEDI3622 and antibiotic administration after sepsis induction also significantly improved survival. Our results indicate that the combination of blocking ADAM17 as an immune modulator and appropriate antibiotics may provide a new therapeutic avenue for sepsis treatment. **Full article**

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