Antineutrophil cytoplasmic autoantibodies against the murine homolog of proteinase 3 (Wegener autoantigen) are pathogenic in vivo.

Abstract:
Antineutrophil cytoplasmic autoantibodies (ANCAs) recognizing human proteinase 3 of neutrophil granules are a diagnostic hallmark of Wegener granulomatosis, an autoimmune systemic vasculitis with predilection for the respiratory tract and kidneys. In vitro experiments have implicated several mechanisms by which ANCAs may lead to tissue injury. However, little is known about the pathogenic significance of proteinase 3-specific antibodies in vivo. In vivo models for ANCA-mediated proinflammatory effects have not been forthcoming, primarily because ANCA epitopes on human proteinase 3 are not shared by the murine homolog. In this study we generated ANCAs against recombinant murine proteinase 3 in proteinase 3/neutrophil elastase-deficient mice that recognized the murine antigen on the surface of neutrophils. Local inflammation induced by intradermal injection of tumor necrosis factor alpha triggered a stronger subcutaneous panniculitis in the presence of passively transferred systemic proteinase 3-ANCAs than in the presence of mock immune serum. When we transferred mouse proteinase 3-ANCA serum to systemically lipopolysaccharide-primed wild-type mice, mice treated with proteinase 3-ANCAs did not develop significantly stronger signs of inflammation of the
lungs or kidneys than the respective mock immune serum-treated animals. In conclusion, our in vivo study provides the first evidence for a pathogenic effect of proteinase 3-specific ANCAs at local sites of inflammation.