Abstract

Anti-neutrophil cytoplasmic antibody-associated (**ANCA-associated**) small vessel necrotizing **vasculitis** is caused by immune-mediated inflammation of the vessel wall and is diagnosed in some cases by the presence of myeloperoxidase-specific antibodies (MPO-**ANCA**). This multicenter study sought to determine whether differences in **ANCA** epitope specificity explain why, in some cases, conventional serologic assays do not correlate with disease activity, why naturally occurring anti-MPO autoantibodies can exist in disease-free individuals, and why **ANCA** are undetected in patients with **ANCA**-negative disease. Autoantibodies from human and murine samples were epitope mapped using a highly sensitive epitope excision/mass spectrometry approach. Data indicated that MPO autoantibodies from healthy individuals had epitope specificities different from those present in **ANCA** disease. Importantly, this methodology led to the discovery of MPO-**ANCA** in **ANCA**-negative disease that reacted against a sole linear sequence. Autoantibodies against this epitope had pathogenic properties, as demonstrated by their capacity to activate neutrophils in vitro and to induce nephritis in mice. The confounder for serological detection of these autoantibodies was the presence of a fragment of ceruloplasmin in serum, which was eliminated in purified IgG, allowing detection. These findings implicate immunodominant epitopes in the pathology of **ANCA-associated vasculitis** and suggest that autoantibody diversity may be common to other autoimmune diseases.