Correspondence

Alternative Complement Pathway Induction by ANCA

To the Editor-in-Chief:

Last year J.C. Jennette and collaborators¹ published an excellent paper in *The American Journal of Pathology*, demonstrating that anti-neutrophil cytoplasmic antibodies (ANCA) induce disease via complement amplification in a mouse model for ANCA-induced glomerulonephritis and vasculitis. The data imply that these autoantibodies do not generate a regular immune complex that would have induced classical pathway complement activation. Instead, by binding to neutrophils, these autoantibodies induce the release of factors capable of stimulating complement amplification. The authors could not address the nature of these factors but list a few components that might be involved, such as the release of properdin, which could bind apoptotic cells, attract C3b, and generate an amplifying C3 convertase, as shown recently.² However, as indicated, neutrophils also release proteases, among which elastase,² cathepsin G,³ and PR3⁴ are known to generate F(ab')₂-like fragments from IgG molecules. F(ab')₂-containing immune complexes have been known for many years to stimulate complement amplification together with a serum factor.⁵ My group has recently identified this factor as anti-hinge natural antibodies, which together with F(ab')₂-containing immune complexes generate rigidified, secondary immune complexes that capture dimeric C3b, a potent precursor of the amplifying C3 convertase in human plasma.⁶ It is, however, unlikely that this very same mechanism may operate in mice, since mice lack IgG anti-hinge natural antibodies.⁷ On the other hand, it is possible that certain anti-idiotypic antibodies exert a similar effect in mice as ANCA-induced glomerular damage is significantly higher when splenocytes rather than the IgG fraction from MPO-immunized Mpo^{-/-} mice are injected.^{1,8} I encourage researchers in this field to elucidate the actual mecha-

nism of how ANCA antibodies mediate complement amplification in mice, so that we may gain better insight into how the mouse model differs from the events presumably operating in humans.

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