Nature Reviews Nephrology **8**, 64 (2012); published online 10 January 2012; doi:10.1038/nrneph.2011.209

VASCULITIS

Renal involvement in granulomatosis with polyangiitis—role of ANCA isotype and Fc receptor genotype

Granulomatosis with polyangiitis (GPA) is associated with a broad range of clinical manifestations, including renal disease. New findings by James Kelley *et al.* at the University of Alabama at Birmingham, working with the NIH-supported Vasculitis Clinical Research Consortium (VCRC) led by Peter Merkel from Boston University, suggest that antineutrophil cytoplasmic antibody (ANCA) isotype and Fc receptor (FcR) genotype influences disease severity and renal involvement. "These findings provide a whole new way, and mechanism for how ANCAs can contribute to the pathogenesis of GPA", explains Jeffrey Edberg of the study group.

ANCAs are often found in patients with GPA and induce neutrophil activation by engaging FcRs. Previous studies demonstrating that genetic variants of the IgG FcR, *FCGR3B*, influence the ANCA-effector response led the researchers to hypothesize that FcR genotype influences disease severity in GPA. They also thought that IgA ANCAs might have a role in the pathogenesis of GPA. "Because of the extensive involvement of the respiratory system in patients with GPA, we reasoned that IgA ANCAs might also be present. Furthermore, we have previously described a variant in the FcR for IgA, FCAR, that directly modulates the inflammatory potential of this receptor. So, it was a logical next step to probe the IgA–FCAR axis in patients with GPA", says Edberg.

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The researchers assessed the associations between ANCA isotype, FcR genotype and disease severity in 673 patients with GPA. They identified a positive relationship between the homozygotic presence of a proinflammatory allele in *FCGR3B* and severe renal disease. IgA ANCAs were identified in 27% of patients but were less frequent in those with renal disease. The presence of a proinflammatory *FCAR* allele was more common in patients with renal disease than in those without.

In neutrophil activation studies, the researchers found that co-stimulation with both IgA and IgG ANCA resulted in reduced neutrophil activation compared with stimulation with IgG ANCA alone in individuals with the noninflammatory *FCAR* allele.

The researchers hope that by continued collaboration with the VCRC they will better define the roles of ANCA isotypes and their FcRs and reveal new opportunities for the treatment of GPA.

Susan J. Allison

Original article Kelley, J. M. *et al.* IgA and IgG antineutrophil cytoplasmic antibody engagement of Fc receptor genetic variants influences granulomatosis with polyangiitis. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1109227109