IMMUNOLOGY

IgG1 protects against renal disease induced by pathogenic antibody isotypes

Immunoglobulin isotypes that poorly activate effector mechanisms that protect the host against pathogens can induce anti-inflammatory effects and protect against immune-complex-dependent renal disease, according to new research. “Our findings indicate that less pathogenic antibody isotypes, such as mouse IgG1 and probably human IgG4, can protect against disease that is induced by the more pathogenic isotypes,” explains researcher Fred Finkelman.

The mechanism by which most immunoglobulins protect against disease involves activation of complement and stimulatory immunoglobulin crystallizable fragment receptors (FcRs), leading to aggregation of microbial pathogens. Some immunoglobulin isotypes, however, such as murine IgG1 and human IgG4, cannot activate complement by the classical pathway and have limited ability to bind and activate FcRs. “We had always wondered why mice and humans make antibody isotypes, such as mouse IgG1 and human IgG4, that are relatively deficient in their effector mechanisms, such as aggregating pathogens, activating complement and activating phagocytic cells through their FcRs,” says Finkelman. “We hypothesized that these ‘wimpy’ antibody isotypes might protect against inflammatory disease, but could not think of an easy way to test that hypothesis.”

The researchers say that an approach to test their hypothesis arose accidentally, when they injected IgG1-deficient mice with a goat antibody to mouse IgD (GaMD) to see whether the IgE produced would be more likely to stimulate anaphylaxis in the absence of IgG1. “GaMD stimulates a very large, rapid anti-goat IgG antibody response, with formation of high levels of circulating immune complexes,” notes Finkelman. “These immune complexes did not cause detectable disease in normal mice, which produce predominantly IgG1 antibodies

to goat IgG, but killed the IgG1-deficient mice. We realized that this deleterious effect might have arisen because IgG1 antibodies normally protect against immune complex disease, leading to the mechanistic experiments that resulted, about 10 years later, in this paper.”

Assessment of the cause of mortality in GaMD-immunized IgG1-deficient mice revealed a severe renal phenotype, characterized by increased urinary protein and blood urea nitrogen (BUN), decreased serum albumin, precipitation of immune complexes in glomerular capillaries and subsequent development of renal fibrosis. Analysis of the immune complexes identified IgG3 as the dominant isotype present in these immune complexes. To investigate whether the renal disease was caused by complement and FcR-dependent pathways, the researchers used genetic models deficient in either complement component C3 or FcR γ -chain (FcR γ). Renal disease still developed in GaMD-immunized IgG1-deficient mice that lacked both C3 or FcR γ , demonstrating that the pathogenic mechanism was independent of both complement and FcR γ .

Finkelman and colleagues then used a passive immunization model, in which mice were injected with different isotypes of IgG anti-trinitrophenyl (TNP) antibody plus a TNP-protein conjugate, to evaluate whether the development of renal disease in GaMD-immunized IgG1-deficient mice is caused by IgG3-antigen immune complex precipitation in glomerular capillaries. Wild-type, C3-deficient and FcR γ -deficient mice injected with IgG3 anti-TNP antibody and a TNP-protein conjugate developed increased BUN, urinary protein and glomerular capillary deposits. By contrast, mice injected with the TNP-protein conjugate plus IgG1 failed to develop renal disease. Of note, IgG1, IgG2a, and IgG2b anti-TNP antibodies protected against renal disease

IgG1-deficient mice immunized with a potent antigen develop glomerulopathy characterized by periodic acid–Schiff (PAS)-positive deposits and fibrosis, whereas similarly immunized wild-type mice do not develop renal disease. Permission obtained from Nature Publishing Group © Strait, R. T. et al. Nature doi:10.1038/nature13868.

in mice injected with TNP-protein conjugate plus IgG3 anti-TNP, with IgG1 being the most protective. “Our studies show that some antibody isotypes, such as IgG3, can cause severe renal disease even in the absence of complement and FcR activation, by precipitating as large immune complexes within glomerular capillaries,” says Finkelman. “Furthermore, we show that less pathogenic antibody isotypes, such as mouse IgG1 and probably human IgG4, can protect against disease that is induced by the more pathogenic isotypes.”

The researchers now plan to use chimeric mouse-human antibodies to determine whether their observations in mice are applicable to humans. They are also planning further studies to determine whether mouse IgG1 and/or human IgG4 antibodies that bind to a specific molecule or epitope can suppress established disease caused by more inflammatory isotypes.

Susan J. Allison

Original article Strait, R. T. et al. IgG1 protects against renal disease in a mouse model of cryoglobulinaemia. Nature doi:10.1038/nature13868