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IgM in the Kidney: A Multiple Personality Disorder

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Abstract

IgM in the blood of normal individuals consists mainly of “natural” polyreactive antibodies. Natural IgM are thought to provide an initial defense against infection and promote the healing of wounded cells. Yet, as Panzer and colleagues show, these benefits can be eclipsed when the IgM binds to damaged cells of the glomerulus, activating complement. IgM in glomeruli thus signifies cellular damage and may warn that the pace of that damage exceeds the capacity for repair.

Keywords

innate immunity; immunoglobulin M; complement; kidney disease; autoimmunity; cell membranes

There has always been discussion and sometimes debate about why all immunologically competent individuals have natural antibodies. Natural antibodies (antibodies produced without a known history of exposure to antigen) against blood groups-A and -B, pose a powerful barrier to the transfusion of incompatible erythrocytes and to the transplantation of incompatible organs. Other natural antibodies, particularly natural IgM, have been found to protect against infection (1), suppress autoimmunity (2) and facilitate healing (3). But natural IgM may also incite common types of cellular injury (4). Besides the question of why normal individuals have natural antibodies that can promote disease, there is the question of whether same natural IgM antibodies protect and harm. We think observations reported in a magnificent paper by Panzer et al. (5) provides powerful insights and an intriguing step toward answering those questions.

We usually teach that IgM is the first immunoglobulin produced in response to infection and that the severe bacterial infections experienced by infants with IgM-deficiency affirms its importance for host defense. Because IgM has 10 antigen combining sites, it is confined mainly to the blood vessels. These multiple sites can enable even low affinity IgM to activate complement via the classical pathway. IgM also serves as the antigen receptor (BCR) of naïve B cells. Random recombination of Ig variable region gene segments in developing B cells generates $\sim 10^9$ different BCR in each individual and makes the BCR repertoire of each individual, including identical twins, different. Stimulation of BCR by

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antigen in conjunction T cell-help induces “hypermutation” of germline V region genes and recombination of constant region genes (isotype switching).

Inherited defects in hypermutation and class-switch recombination cause the “hyper-IgM syndrome” which (ironically like IgM deficiency) greatly increases the risk of infection and autoimmune disease. Most B cells with BCR that bind to “self” are deleted during development and this deletion enacts tolerance and averts autoimmunity. Failure of self-censorship allows auto-reactive B cells to undergo hypermutation, selection and isotype switching, which generate pathogenic IgG antibodies (which can leave blood vessels) and cause autoimmune disease.

However, the properties of natural antibodies and the B cells that produce them appear to violate some of these first principles. Unlike antibodies produced in response to infection or vaccination, i.e. elicited antibodies, natural antibodies can recognize many antigens, each antibody being “polyreactive.” Approximately 50–80% of IgM in blood has this property. Some B cells that produce natural antibodies are censored by self-antigens (a person of blood group-A has no B cells capable of secreting anti-A antibodies). But, the B cells that produce polyreactive antibodies are not. Each of these B cells can recognize many self-antigens. The polyreactive antibodies are encoded by germline V region genes, not further diversified by somatic hypermutation. The specificities and even the idiotypes of the natural antibodies are remarkably shared in the population, suggesting the B cells are selected for polyreactivity and auto-reactivity.

Why do healthy individuals have the same auto-reactive natural antibodies, including those that worsen cellular injury? Unexpectedly, Panzer and colleagues may have begun to answer this question (Figure 1). The authors previously studied Adriamycin nephropathy in mice, observing that depletion of B cells prevents deposition of IgM and C3 in glomeruli and lessens the tempo and severity of disease (6), and suggesting the IgM and C3 might be pathogenic and not just markers of non-immune injury. To explore that possibility, Panzer et al. (5) asked whether IgM can add to existing cellular damage, possibly by activating complement via the classical pathway (involving C1q, C4 and C2). The question was addressed using factor H knockout mice. Complement factor H controls, by several mechanisms, the alternative complement pathway, which undergoes continuous activation (unlike the classical pathway which is mainly activated by bound antibodies). Activation of the alternative pathway fixes C3, leaving C1q, C4, IgM and IgG unbound. Consistent with that concept, the glomeruli in young, factor H-deficient mice have deposits containing C3, but no IgG. However, when Panzer and colleagues studied these mice over time, they found that besides deposits of C3, the glomeruli had deposits IgM and C4 (but no IgG). The presence IgM and C4 might reflect “trapping” in a damaged kidney, or auto-immunity caused by factor H deficiency or binding of natural antibodies to damaged cells.

To determine whether IgM and C4 were pathogenic and whether the IgM was autoimmune, the authors examined the kidneys of factor H-deficient mice that had been crossbred with B cell-deficient mice. These mice exhibited only mild mesangial hyper-cellularity. The glomeruli contained no C4 or C1q and the disease did not progress. Thus, progression of kidney disease in factor H-deficient mice depended on binding of IgM to something in the

damaged glomeruli and activation of the classical complement pathway. To confirm this possibility and to provide at least a preliminary glimpse at the nature of the bound antibody, the authors administered IgM isolated from serum of normal mice and a monoclonal “natural” IgM to the cross-bred factor H deficient, B cell-deficient mice. The IgM from normal serum (predominantly natural IgM) and the monoclonal polyreactive IgM bound to glomeruli causing proteinuria. Thus, IgM from normal (not autoimmune) mice and even a monoclonal polyreactive IgM bound to damaged glomeruli, activated complement, and exacerbated underlying injury. Instead of the classical complement pathway recruiting the alternative pathway to amplify injury, as convention holds, in factor H-deficient mice the alternative complement pathway caused IgM to bind recruiting the classical pathway to amplify injury.

These findings certainly advance understanding about how glomerular disease progresses; how widely this understanding can be applied will be seen with time. Yet, the implications of the work extend beyond the subject of kidney disease to the questions posed at the outset – why normal individuals have natural IgM auto-antibodies and whether the same natural antibodies that defend against microbial infections and heal damaged cells also cause disease?

The most immediate danger infection and tissue injury impose are dissemination of microorganisms and uncontrolled necrosis (releasing C3b, thrombin and cytokines). Both can trigger the systemic inflammatory response syndrome and multi-organ failure. The cellular elements of innate immunity circumscribe infection and necrosis by recognizing the products of damaged cells, particularly endothelial cells and provoking endothelial cell activation, hemostasis, coagulation, vasoconstriction, etc. The humoral elements of innate immunity, natural antibodies and complement probably do likewise. And there is a physiological reason for recognition of damaged cells. Neither inflammatory receptors nor natural antibodies can recognize all of the organisms, toxins, etc. that pose threats but, as Panzer and colleagues show, natural antibodies can recognize damaged cells and their products, and such self recognition may circumscribe damaged tissue, providing the time needed for an elicited immune response to ensue. Natural antibodies might also facilitate healing of damaged cells. The repair of cell membranes wounded by physical injury and pore-forming proteins can require binding of annexins to acidic moieties in the inner membrane and clustering in a way that surface tension decreases and the wounded membrane is removed (7). Recognition of acidic moieties on damaged cell surfaces by polymeric natural IgM should have the same impact. However, other natural antibodies recognize basic proteins such as annexins and the binding of these natural antibodies to ischemic tissues worsens injury (8). Why then do we have these antibodies that promote and inhibit repair? If these antibodies inhibit the anti-coagulant function of annexins, they might help sequester microorganisms and the contents of cells damaged beyond repair, at the expense of local tissue injury. But, can natural antibodies with the same specificity incite injury and protection and repair? Panzer and colleagues provide an exciting hint.

Panzer et al. clearly show that natural antibodies in factor H-deficient mice cause glomerular damage that progresses over six months, the proof drawn from comparing this course with the milder non-progressive course of glomerular disease in factor H-deficient mice lacking

B cells. However, if the course of kidney disease in factor-H deficient mice is more severe in mice that produce natural antibodies, it is strikingly mild when compared with the immediate and devastating course of kidney disease in recipients of ABO-incompatible allografts and xenografts. These differences are yet more striking if one considers that complement regulation is normal in ABO-incompatible transplantation (it is abnormal in xenotransplantation). Various explanations for these differences come to mind, but one we find appealing is that in factor H deficient mice, antibodies and complement induce “accommodation” (9), that is acquired resistance of the kidneys and other organs to complement-mediated injury. Accommodation is seen archetypically when natural antibodies are depleted before an incompatible transplant is performed and then allowed slowly to return. If the kidneys of factor-H deficient mouse are accommodated, as we suspect, the extent of damage inflicted by IgM and complement exceeds the capacity for repair. But in the absence of accommodation things could be far worse.

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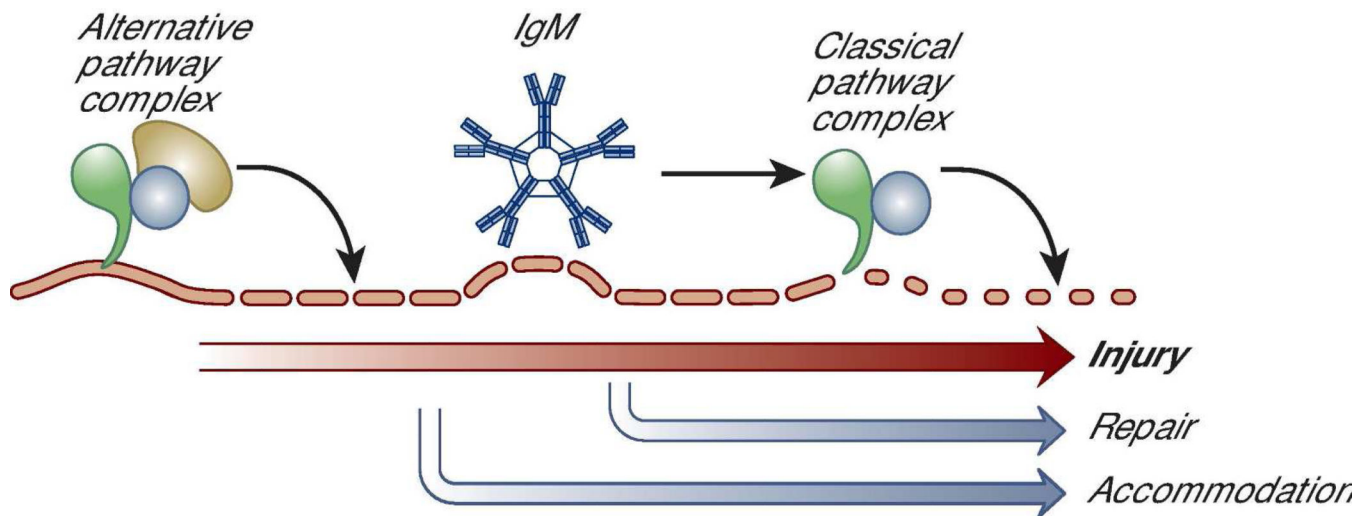


Figure 1. Natural IgM and complement in the injury and potentially in the repair of cell surfaces in factor H deficient mice

In mice lacking complement factor H, the complement system is constitutively activated and that damages cells in the glomerulus and elsewhere. In some systems binding of natural antibodies and activation of complement at a low-level induced repair and protection against further injury, a condition called accommodation. However, when IgM binds to damaged cells of the glomerulus, complement is further activated via the classical pathway and the rate and/or extent of damage exceeds the capacity for repair or accommodation.