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MINIREVIEW

Role of Antibodies in Controlling Viral Disease: Lessons from Experiments of Nature and Gene Knockouts

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While the role of antibodies in preventing virus infection and reinfection is unquestionable, their contribution to the resolution of viral disease is much more controversial. When humoral deficiencies, in particular Bruton's X-linked agammaglobulinemia (XLA) (8), were initially described, it was observed that bacterial infections rather than viral infections represented the main cause of morbidity and early mortality. On this basis it was proposed that humoral deficiencies could be seen as experiments of nature, demonstrating that antibodies play little or no role in controlling viral infections while they are crucial in the resolution of bacterial infections (discussed in reference 24). Such a view has acquired dogma status over the years and is commonly found in immunology textbooks and other scientific publications.

Clinical observations made over almost five decades do in fact confirm a preponderance of bacterial infections in XLA patients. There is however a major caveat to these observations. With the exception of patient histories before diagnosis or observations in untreated individuals with mild clinical forms, all patients with antibody deficiency received some kind of immunoglobulin (IgG) replacement therapy which was implemented since the first recognition of XLA (8). Therefore, the fully null phenotype has in fact been little studied. Furthermore, we argue that the progressive change in the clinical picture of antibody deficiencies brought about by the refinement and increased efficacy of IgG replacement therapy is suggestive of a role for antibodies in viral infections. In particular, we find quite persuasive the fact that severe or unusual viral infections, which were not uncommon in individuals with antibody deficiencies in the early years of IgG replacement therapy by the intramuscular (i.m.) route, all but disappeared when high-dose intravenous (i.v.) IgG replacement became standard practice.

As observed by Good and Zak, the value of experiments of nature is in part that they permit observations difficult or impossible to duplicate in the laboratory setting to be made (24). However, current technologies now allow for the modeling of genetic disorders in experimental animals without the confounder of therapy, as in clinical cases. Interestingly, recent experimental observations in B-cell-deficient mice, while validating the crucial role for antibodies in antibacterial responses, also support a significant role for the humoral response in determining the outcome of viral infection. Taken together, this converging evidence is consistent with a view of the immune system in which redundancy and the cooperation of different immune mechanisms coexist with aspects of functional specialization.

Several different antibody deficiencies have been recognized since the original description of XLA in 1952 (8). XLA is due to the loss of function of a tyrosine kinase known as Bruton tyrosine kinase (BTK) which leads to the inhibition of pre-B-cell maturation to B cells in the bone marrow and lack of circulating B cells (79, 81). Mutations leading to both deficient expression and to the expression of nonfunctional BTK alleles have been observed (30). Nonfunctional BTK alleles have been associated with mutations in the kinase domain or in the pleckstrin homology domain, the latter presumably leading to poor membrane recruitment (30). Mild clinical forms of XLA with decreased BTK function also occur (30, 57). In its typical presentation, XLA is diagnosed at an early age following chronic or recurrent bacterial infections of the respiratory tract or bacterial meningitis. An autosomal condition with a similar clinical presentation has recently been ascribed to deficient μ heavy-chain expression (88). Chronic variable hypogammaglobulinemia or common variable immunodeficiency (CVID) represents a cluster of heterogeneous conditions characterized by defective humoral immunity in the presence of normal or reduced, but typically not absent, circulating B cells and variable clinical phenotypes. CVID onset is typically in the second or third decade of life and it can result from a variety of genetic defects (18, 72, 76). As with XLA, recurrent bacterial infections are usually the presenting manifestations. While also somewhat rare, CVID is more prevalent than XLA (18, 72, 76). X-linked hyper-IgM syndrome is an additional form of humoral deficiency (72). It is due to the lack of CD40 ligand, which is necessary for a B-cell response to T-dependent antigens and class switching (18, 72, 76). Last, selective antibody deficiencies characterized by loss of specific antibody classes have been recognized (72).

Replacement therapy, in the form of i.m. IgG, was introduced when antibody deficiencies were first recognized (8). i.m. IgG therapy afforded dosages only as high as 100 mg/kg every 3 to 4 weeks, because patient compliance was limited by pain and adverse reactions (reviewed in references 38 and 56). Such untoward effects are believed to be mainly due to the tendency of IgG prepared by Cohn's alcohol fractionation method to aggregate (2). These IgG preparations cannot be administered i.v. because of severe systemic reactions (3). IgG preparations suitable for i.v. use and allowing for the administration of larger doses were later developed and supplanted i.m. IgG (2, 51). i.v. IgG preparations were approved for clinical use in the United States in the early 1980s, whereas they were introduced in Australia and Europe a decade earlier (10, 63, 75, 78). i.v. replacement regimens originally consisted of up to 200 mg of IgG per kg every 3 to 4 weeks; therapy with

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high-dose i.v. IgG (400 mg/kg for 3 to 4 weeks or more) became possible because of more-tolerated formulations such as low-pH preparations and preparations containing stabilizing additives (10, 75, 78). Levels of IgG in the serum of patients treated in this manner can be maintained in the lower normal range (38, 75). High doses of IgG can also be administered subcutaneously with infusion pumps (22).

Early reports on XLA were anecdotal in nature and occasionally confounded by the lack of differentiation between different forms of antibody deficiency. Chronic enteroviral encephalitis, typically resulting from echovirus infection and usually associated with peripheral dermatomyositis-like manifestations, was recognized early as a frequent complication in agammaglobulinemic patients (43, 50, 85). Because of their relatively high incidence, such severe enterovirus infections came to be seen as the exception to the rule of antibody deficiencies as exclusively bacterial syndromes in patients with otherwise good antiviral competence.

The first comprehensive multicenter retrospective study of XLA (96 patients, 1,200 patient years) was carried out in the early 1980s in the United States, and it reported experience with the relatively low doses afforded by i.m. IgG replacement (35). This study confirmed the high incidence of bacterial infections in XLA (chronic and recurrent sinus and pulmonary infections, meningitis, etc.) (35). However, the authors of this report also noted a shift in viral etiology in the patient population receiving i.m. IgG treatment. This was exemplified by the observation of a "predominance of viral pathogens [as the cause of meningitis/encephalitis] in patients receiving gammaglobulins [compared to] undiagnosed and untreated patients, in whom greater than 60% of cases were caused by bacteria" (35). Additionally, when all viral infections were considered, infections with agents other than enterovirus (herpes simplex virus [HSV], adenovirus, cytomegalovirus, varicella-zoster virus [VZV], etc.) outnumbered enterovirus infections by more than three to one in this report (35). HSV infections in particular represented 28% of all nonbacterial infections and 37% of all viral infections. Although HSV infections did not have unusually severe courses in the patients in this study, particularly severe HSV manifestations, including extensive cutaneous manifestations and fatal encephalitides, have been observed by others both in XLA patients (39, 60) and in other hypogammaglobulinemias (6, 12, 13, 86). In a study involving eight children with early-onset CVID, unusually severe infections with HSV or VZV were observed in half the patients despite apparently normal T-cell competence (12). While CVID patient observations can be difficult to interpret because accompanying T-cell defects can also be present, these tend to appear late in life (13). Encephalitides caused by other viral agents reported in patients with antibody deficiencies include those due to infections by adenoviruses (33, 35, 38) and measles virus (25, 27).

It should be noted that in patients with antibody deficiencies, serological assays are hindered by the inability to mount humoral immune responses and by the antibody replacement therapy itself. Therefore, etiologic diagnoses, until the relatively recent introduction of PCR-based techniques, could only conclusively be done by culture methods. In the absence of positive culture results, some episodes were either tentatively interpreted as chronic enteroviral encephalitis by default (see for instance reference 60) or their etiology remained unidentified (e.g., see references 35, 40, 46, and 66). The latter were a substantial percentage or even a majority in some reports (35, 40, 46, 64, 66). In a recent report, the etiology of several cases remained unidentified despite the use of PCR to search for enterovirus RNA (64). Other unusual viral infections were anecdotally reported, such as fatal adenovirus type 11 pneumonia and persistent rotavirus enteritis, among others (35, 70, 73).

Consistent with a general role for antibodies in the control of enteroviruses and their neurological spread, several cases of vaccine- and non-vaccine-associated poliomyelitis were reported in XLA patients (1, 28, 67, 87). However, severe complications to smallpox vaccinations, such as progressive and disseminated vaccinia virus infection, were also encountered before smallpox vaccination was deemed contraindicated in XLA patients (5, 35, 59). While poxviruses induce both humoral and cellular responses, both of which have been implicated in protection from reinfection (52), cellular responses are generally believed to be crucial for the resolution of primary infection (19).

With the introduction of i.v. IgG replacement therapy, the prevalence and severity of most bacterial manifestations in agammaglobulinemic patients were greatly reduced. For instance, changing from i.m. to i.v. therapy greatly reduced the incidence of bacterial meningitis in patients treated with both high- and low-dose i.v. IgG (38). In the same study however, severe pulmonary infections, such as pneumonia, were only markedly reduced by high-dose i.v. IgG therapy, possibly reflecting the limited ability of parenterally administered antibodies to partition into secretory fluids and because of predisposing conditions such as bronchiectasias (38). However, patients treated with i.v. IgG from an early age are almost devoid of pulmonary manifestations and pneumonia-predisposing sequelae such as bronchiectasias (75). Following the introduction of i.v. IgG treatment, unusual presentations of viral infections and viral infections in general, including those by agents other than enterovirus, were also virtually eliminated (38, 75). A long-term retrospective study of Australian children treated with i.v. IgG (18 patients, 162 treatment years, including 10 XLA and 8 CVID patients) showed infection rates similar to those of nonimmunodeficient children, and no central nervous system (CNS) infections—viral or bacterial—were encountered in these patients (75).

The sporadic cases of severe or unusual viral infections in the years of i.m. IgG replacement and in the early years of transition to i.v. therapy may appear to be of little general importance. However, if the number of individuals affected by XLA (0.5 to 1 per million [4, 29, 41, 65]) and CVID (about 0.5 to 1 per 100,000 [4, 29, 41, 65]) is taken into account, it is safe to state that the incidence of severe viral manifestations, such as encephalitis, was considerably higher in these patients than in the general population, even when enterovirus infections are excluded. For instance, in the years of i.m. replacement therapy, adenovirus was isolated from the CNS of XLA patients with encephalitides three times (33, 35, 38), while worldwide an average of only six adenovirus isolates from the CNS per year were reported to the World Health Organization in the decade from 1967 to 1976 (71). Similarly, since HSV encephalitis has an estimated incidence of one to four cases per million (77, 83, 84), a much higher susceptibility is suggested by the few cases reported in antibody-deficient patients (6, 12, 13, 39, 86). It is difficult to separate the role of antibodies in infection prophylaxis and control of viral disease in patients receiving IgG replacement therapy. However, the higher incidence of severe viral complications, such as encephalitis, in antibody-deficient patients is suggestive of a role for antibodies in the control of viral infections and in determining the severity of manifestations.

Many animal studies support the notion that antibody responses could be especially important against neurotropic viruses. In some cases, antibodies have been shown to limit or

prevent virus spread to the CNS. In others, antibodies have been shown to restrict virus expression. Tyler and colleagues, for instance, showed that specific monoclonal antibodies could protect the CNS not only from reoviruses that spread through the bloodstream but also from reoviruses that spread transneuronally (80). The natural resistance of certain mouse strains to street rabies virus, which also spreads transneuronally, has also been ascribed to the antibody response on the basis of depletion experiments (61). Passive transfer of specific monoclonal antibodies to nude mice infected intracerebrally with Theiler's murine encephalomyelitis virus results in reduced infectious virus in the brain, increased survival, and various degrees of recovery from the demyelinating lesions, suggesting that antibody modulation of virus replication plays a protective role (9). Similarly, passive transfer of specific monoclonal antibodies protects newborn Lewis rats from measles virus encephalitis by restricting virus expression (37). In addition, the expression of Sindbis virus in the CNS of SCID mice can be virtually abolished by passive immunization with specific antibodies, through mechanism(s) which are clearly independent of cellular immunity or complement and in the absence of any detectable cell damage (36).

Studies with B-cell-deficient mice as well as B-cell-depletion studies also support a role for antibodies in the control of some viral infections. B-cell-deficient mice have higher susceptibility to HSV encephalomyelitis than normal mice (7, 14). Mice depleted of B cells with an antibody to μ heavy chains are less efficient in containing primary HSV infection of the peripheral and central nervous system and have a higher incidence of latent infection (32, 74). Consistently, administration of IgG can reduce the number of acutely infected ganglionic neurons following viral challenge (42, 47). Mester and Rouse suggested that antibodies can act in vivo both by decreasing virus expression in infected sensory neurons and by limiting HSV spread to the sensory ganglia (47). Consistent with this view, a human recombinant antibody prevented neuronal spread to epithelial cells in an in vitro model (48) and when administered to HSV-infected animals, the same antibody was found to strongly localize on HSV-infected nerve fibers and sensory neurons (69). Evidence that antibodies can decrease virus expression in in vitro paradigms has also been reported both for HSV (55) and for other neurotropic and nonneurotropic viruses (21, 23, 36, 53, 54). However, although topically applied antibody protected mice from vaginal transmission of HSV type 2 (89), the course of vaginal HSV shedding following primary infection of B-cell-deficient mice did not differ from that of normal control mice (17). Taken together with the aforementioned reports demonstrating a higher rate of HSV spread to the nervous system in B-cell-deficient mice, this observation could indicate that natural antibody responses are more important in the control of HSV in certain anatomical sites and routes of infection than others.

Passive immunization can confer full protection in the immune-competent mouse even after HSV has already reached the peripheral nervous system (16, 47). However, if administered postexposure to athymic or SCID mice, while it can greatly prolong survival, antibody alone does not prevent disease (49, 68). Thus, while converging lines of evidence support a role for antibodies in the acute phase of primary HSV infections, the cooperative interaction between humoral and cellular responses appears to be necessary for its optimal resolution.

In murine models of rotavirus infection, humoral and cellular responses also appear to cooperate in the resolution of primary infection, despite some strain-specific differences (20, 44, 45). In one study, μMT B-cell-deficient mice infected with murine rotavirus did not fully resolve primary infection, while J_HD B-cell-deficient mice were capable of resolving primary infection but, unlike immunocompetent mice, were susceptible to reinfection (44). In a second study, it was observed that, while the majority of rotavirus-inoculated J_HD B-cell-deficient mice were capable of resolving primary infection, a small percentage of them became chronically infected (20). Also in this study, J_HD B-cell-deficient mice did not develop immunity against reinfection (20).

B-cell-deficient mice also display a much higher susceptibility to acute type A influenza virus infection than normal mice as well as to rechallenge following exposure to an attenuated strain (26). There is, however, conflicting evidence on whether antibodies alone can resolve experimental influenza virus infection. In fact, some authors found that passive immunization of nude mice with specific antibodies after infection with influenza A virus induced only a transient recovery (34). This is consistent with the notion that, while antibody-mediated control of virus expression may contribute to recovery of acute infection, in the absence of T-cell antibody alone antibody is insufficient in clearing the virus (34). In contrast, Mozdzanowska and associates observed a permanent cure of SCID mice following therapeutic passive immunization with neutralizing anti-heamagglutinin antibodies but not with nonneutralizing antibodies to either of the other transmembrane proteins, neuraminidase and matrix 2. These latter antibodies, however, could reduce virus titers (53).

Interestingly, there are also indications from studies with B-cell-deficient mice that antibodies can be crucial in the control of persistent infections. Weck and associates observed that gammaherpesvirus latency was regulated by B cells and that the majority of persistently infected B-cell-deficient mice succumbed between 100 and 200 days postinfection, whereas normal control mice were capable of maintaining the virus in a latent state (82). Similar observations were made by R. M. Zinkernagel and associates in mice persistently infected with lymphocytic choriomeningitis virus (personal communication). Additionally, virus production in B-cell-deficient mice during recurrences of primary murine cytomegalovirus infection was higher than that in normal mice (31). However, in the case of other viruses, such as human immunodeficiency virus, antibodies appear to have little effect on virus replication in established infection and on the course of the disease itself, at least in the SCID mouse model, and can be considered one of possibly many exceptions to the general thesis of the present review (62).

Last, it has been proposed that natural antibodies may contribute to innate responses to both bacteria and viruses. These antibodies are typically IgM, but can also be IgG, and are usually characterized by moderate affinity for antigen and polyreactive behavior (11, 15). Ochsenbein et al. showed that natural IgM antibodies with avidity for infectious agents decrease viral or bacterial titers in peripheral organs and increase their immunogenicity through antigen trapping in secondary lymphoid organs (58). Interestingly, in that study, CNS dissemination of vesicular stomatitis virus, a virus related to rabies virus and neurotropic in some species, was impaired by natural antibodies (58).

In summary, the high incidence of bacterial infections in XLA patients suggested that antibodies were the crucial line of defense against bacterial infections but quite dispensable in antiviral protection. However, the clinical records of viral manifestations in XLA patients—sometimes unusual or severe—during the years of i.m. IgG therapy argue against an intact antiviral immunity in these patients. The introduction of i.v. IgG regimens not only drastically reduced the incidence and severity of bacterial infections in patients with antibody defi-

ciencies but also all but eliminated the occurrence of unusual viral manifestations. Experimental evidence, including that from B-cell-deficient mice, also supports a role for antibodies in determining the outcome and severity of viral infections. In particular, antibodies have been shown to contribute to the resolution of the acute phases of some viral diseases, to the control of several neurotropic viruses, and to the long-term control of some persistent viral infections. Thus, while each of the arms of the immune system may be sufficient in certain situations, these observations suggest that humoral responses act in concert with cellular immunity in the control of viral disease.

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