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MINIREVIEW

New Concepts in Antibody-Mediated Immunity

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After stimulating the development of immunology in the early 20th century, the study of the functional aspects of antibody-mediated immunity (AMI) stagnated in the 1960s because the function of antibodies (Abs) was considered understood and available Ab preparations were limited to polyclonal immune sera. Abs in polyclonal sera are heterogeneous, and the uniqueness of each preparation with respect to specificity and isotype posed formidable problems in achieving consistency, reliability, and reproducibility in Ab experimentation. The limitations inherent in studies of AMI with polyclonal sera, combined with the discovery of T cells, an increased interest in cell-mediated immunity, and later a rediscovery of innate immunity, steered immunology research away from studies of AMI. However, by the late 1980s the development of monoclonal antibody (MAb) technology, the discovery of Fc receptors (FcR), and the generation of mice with defined genetic deficiencies made possible studies that rekindled interest in the basic mechanisms of AMI. More than a dozen MAbs are now licensed for clinical use for diverse indications, such as prophylaxis of respiratory syncytial virus disease in neonates, treatment of Crohn's disease, prevention of coronary artery closure after angioplasty, and therapy of refractory rheumatoid arthritis (65). In addition, the fact that the use of passive Abs is currently the only means to provide immediate immunological protection against biological weapons in immunologically naïve populations has stimulated new interest in AMI (9, 13). The availability of new technologies to study AMI and the need for specific, rapidly acting therapies for new and emerging diseases have led to the discovery of new Ab functions that have broadened the classical views of AMI. This review will focus primarily on insights that have emerged from studies with whole Ab molecules, which are the natural products of B cells. However, many contributions to the field of AMI and promising clinical reagents have also come from studies with Ab fragments and antibody-derived peptides, although to date fewer studies have addressed the mechanisms of efficacy for these reagents.

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CLASSICAL VIEWS OF AMI

Antibody molecules consist of two domains, an antigen binding region composed of variable (V) region elements and a constant (C) region. The C region includes an Fc region, which determines the antibody's isotype and functional characteristics, such as its half-life in serum, complement activation, and ability to interact with FcR. The V region binds to antigens by forming hydrophobic, ionic, and van der Waal interactions, while the Fc region binds to cellular receptors and some humoral components of the immune system, such as complement. When AMI is ascribed to such receptor-ligand interactions, Ab function can be viewed as bridging the distance between a microbial antigen and the immune system. The classical functions of specific Abs include direct Ab activities, such as toxin and virus neutralization, and indirect activities that require other immune system components, such as opsonization and complement activation. Each of these functions was initially described at the end of the 19th or in the early 20th century; however, recent studies of Ab-mediated complement activation have revealed that Ab- and complement-mediated opsonophagocytosis can be functionally redundant, at least for some microbes (47). Later, Ab-dependent cellular cytotoxicity was recognized as an important mechanism whereby specific Abs could focus cytotoxic effects of certain host effector cells, such as NK cells, against tumors and microbes.

NEW CONCEPTS OF AMI

(i) Antibodies as positive and negative regulators of inflammation and CMI. Abs have the capacity to amplify or suppress the inflammatory response, depending on their specificity, isotype, and concentration (15). Direct mechanisms by which Ab-antigen (Ag) complexes influence the inflammatory response and cell-mediated immunity (CMI) include the following: complement activation to produce complement-split products, which are proinflammatory; cross-linking of FcR to promote phagocytosis, which can alter the production of cytokines, chemokines, and other inflammatory mediators; and enhancement of Ag presentation and expression of effector cell costimulatory molecules (for a partial view of the extensive literature on the consequences of Fc receptor stimulation, see references 1, 34, 35, 48, 52–55, 60, 62, 79, 80, 84, 89–91, and 94). Abs have been proposed to promote Th1 activation against certain intracellular pathogens by activating FcR (45, 57). An indirect mechanism by which specific Abs can influence the inflammatory response is by promoting the clearance

of proinflammatory and anti-inflammatory microbial antigens. The proinflammatory properties of Abs have been known for some time, as evidenced by such phenomena as serum sickness and the Arthus reaction. However, in recent years Abs have also been shown to have anti-inflammatory effects, a property that has found clinical utility in the use of intravenous immunoglobulin (IVIG) for the treatment of inflammatory conditions (4).

The paradox that Ag-Ab complexes can have both pro- and anti-inflammatory properties is explained by the different effector properties of different Ab isotypes, the existence of stimulatory and inhibitory FcRs, and the fact that the size of the complex formed is a function of both the Ag and Ab concentrations. Immunoglobulin M (IgM) molecules are generally proinflammatory because they are powerful activators of the complement system. This property, combined with the presence of IgM early in the course of infection, contributes to host defense by amplifying the immune response. Naturally occurring IgM has been shown to be critically important for defense against certain experimental bacterial and viral infections (7, 27). However, IgM has also been associated with a reduction in inflammatory responses, as evidenced by data showing that mice that lack IgM develop more severe autoimmune disease and sepsis after gut clamping (7, 8), that type-specific human IgM can downregulate the polymorphonuclear leukocyte proinflammatory mediator release stimulated by pneumococci (11), and that polyclonal IgM can reduce complement and oligodendrocyte activation (77, 92). In patients with sepsis, an increase in endotoxin-specific IgM has been suggested as a surrogate marker for improved survival (92), and polyclonal IgM preparations have shown promise in reducing inflammatory complications of cardiac surgery (33). IgG molecules can also be either pro- or anti-inflammatory depending on their subclass, concentration, and interactions with FcRs. Hence, depending on the Ab type, the cellular target, and the Ag concentration, Fc receptor cross-linking can promote or inhibit inflammation.

Ab administration can reduce the inflammatory response in diverse models of infectious diseases. For example, an Ab protected mice with lymphocytic choriomeningitis virus infection by reducing T-cell-mediated inflammatory damage (96), a specific IgG reduced chemokine levels induced by herpes simplex virus (HSV) infection in vivo (78), FcγRI ligation and an Ab to lipopolysaccharide dampened the inflammatory response to bacterial lipopolysaccharide and elicited interleukin-10 (IL-10) release (34, 80), and a specific Ab altered the cytokine response to *Cryptococcus neoformans* (31, 67, 82). Nonspecific Abs in IVIG can have anti-inflammatory effects, as evidenced by their use as therapy for autoimmune diseases (28). The anti-inflammatory properties of IVIG have been attributed to the ability of certain Igs to activate inhibitory FcRs and to block the activation of stimulatory FcRs (72, 86).

The finding that certain microbes are more virulent and induce more robust inflammatory responses in B-cell-deficient mice provides strong support for the concept that AMI can reduce host damage by modulating inflammation. For example, infections of B-cell-deficient mice with West Nile virus resulted in a disseminated disease, which could be prevented by passive administration of a heat-inactivated immune serum (26); infections with *Chlamydophila abortus* resulted in exacerbated inflammatory reactions, high levels of proinflammatory cytokines, and increased numbers of neutrophils compared to those in healthy mice (10); infections with *Leishmania donovani* resulted in an intense neutrophil response and tissue damage that was reversed with immune serum (76); infections with *Toxoplasma gondii* resulted in gamma interferon (IFN-γ), tumor necrosis factor alpha, and inducible nitric oxide synthase (iNOS) production and in florid inflammation and necrosis that were reversed by Ig administration (46); infections with herpes simplex virus type 1 (HSV-1) resulted in an increased susceptibility to disease and in the activation of Th1- and large reduction in Th2-type $CD4^+$-T-cell cytokine responses (24); and infections with HSV-2 resulted in increased genital inflammation relative to that in healthy mice (42).

Ab-mediated inflammatory effects can also be deleterious. For example, Ag-Ab complexes can trigger cardiovascular collapse due to the Fc receptor-mediated release of platelet-activating factor (48, 74), can promote corneal inflammation in a murine model of *Onchocerca volvulus* blindness (39), and can mediate type III hypersensitivity (Arthus) reactions. IgM and complement mediated inflammation after an experimental reperfusion of ischemic tissue (93), and a specific IgM can initiate hapten-mediated contact sensitivity (85).

(ii) Antibodies as direct antimicrobial molecules. The classical view of AMI attributed the antimicrobial activities of Abs to indirect functions, such as their opsonic and complement-activating properties. However, there are now many examples of Abs with direct antimicrobial activities. An early example of direct Ab-mediated antimicrobial effects was the report that an Ab to *Escherichia coli* lipopolysaccharide was bacteriostatic because it interfered with the release of an iron chelator, enterochelin, thereby preventing iron acquisition by the bacterium (32). Similarly, IgM MAbs to membrane proteins of *Acinetobacter baumannii* have been reported to be bactericidal by inhibiting iron uptake (37). Other examples of direct Ab effects include the observations that IgM and IgG Abs to *Borrelia burgdorferi* surface proteins damage the surface protein coat of the organism, leading to a bactericidal effect in the absence of complement (21, 22), and that Ab binding to certain gut extraluminal parasites causes expulsion (12), which may be caused by parasite immobilization (20). For the fungi, Abs to *C. neoformans* glucosylceramide (69) and cell-wall-associated melanin (70) inhibit cell growth in the absence of complement, and Fab fragments to cell wall mannoprotein can block the yeast-to-hypha transition of *Candida albicans* (16). In fact, a MAb to *C. albicans* was recently described that mediated direct antifungal activity through the following three mechanisms: interference with adherence, inhibition of germination, and direct candidacidal activity (58). Similarly, a human Ab binding to the *Candida* sp. heat shock protein 90 was shown to mediate direct antifungal effects and to have a synergistic antifungal activity with amphotericin B (56). A remarkable example of the potential of AMI to mediate direct antimicrobial effects is provided by the broad-spectrum antimicrobial activities of anti-idiotypic Abs to a neutralizing MAb to *Pichia anomala* killer toxin (17, 64, 73). These Abs mediate antimicrobial activity by mimicking the internal image of the toxin in the Ag binding site and reproducing the antimicrobial effects of killer toxin.

(iii) Antibodies as singular and interactive effector molecules. Passive Ab protection experiments in healthy and im-

munodeficient mice revealed that Ab efficacy is sometimes dependent on CMI (15). For *C. neoformans*, the efficacy of passive Abs requires intact CMI, since no protection was observed when a protective IgG1 was administered to mice deficient in $CD4^+$ T cells (97), IFN-γ (97), iNOS (67), or several Th1- and Th2-associated cytokines (5). In contrast, IgG1 was protective in mice deficient in $CD8^+$ T cells (97) and complement component 3 (75). A specific Ab to *C. neoformans* induces the production of Th2 cytokines in the setting of a Th1-dominated response, which can be associated with a reduction in organ damage (31, 67). In light of these observations, the dependence of Ab-mediated protection against *C. neoformans* on CMI can be explained by the fact that Abs promote a more effective inflammatory response, thereby reducing host damage. Other microbes for which passive Ab efficacy requires an intact immune system include *Pseudomonas aeruginosa* (51), *Francisella tularensis* (23), and HSV (59). However, for HSV-2, an IgG2a MAb was protective in T-cell-depleted mice (30), suggesting that the efficacy of some Ab isotypes against HSV is not always T cell dependent. Similarly, although T cells were required for complete Ab-mediated clearance, an immune serum provided partial protection against the obligate intracellular pathogen *Ehrlichia chaffeensis* in SCID mice (95). Ab efficacy against arenavirus and Friend murine leukemia virus requires $CD8^+$ T cells (3, 43). The dependency of Abs on CMI is likely a general mechanism of Ab action that is not limited to infectious agents, as exemplified by data showing that the efficacy of an Ab to a solid lymphoma was completely dependent on the presence of $CD8^+$ T cells and an intact FcγR (88).

Abs are effective against some microbes in the absence of intact CMI. For example, an immune serum to a polyomavirus cleared the infection in SCID mice (81), a human immunoglobulin reduced *Plasmodium falciparum* parasitemia in SCID mice reconstituted with human monocytes (2), and IgM and IgG MAbs to *Pneumocystis carinii* surface antigens were protective against the development of pneumonia in SCID mice through interference with attachment (36). Similarly, the administration of an IgG1 MAb to a lipophosphoglycan antigen of *Entamoeba histolytica* prevented amoebic liver abscesses in SCID mice (50) by blocking adherence to target cells, and an Ab reduced abscess formation through enhanced bacterial opsonization in RAG-2 and SCID mice infected with anaerobic bacteria (44).

Yet another interactive role for Abs involves the ability of Abs in Ag-Ab complexes to regulate the Ab response. This phenomenon has been known for decades, but it is often not taken into account when considering the effect of an Ab on the outcome of infection. The mechanism for this effect is not well understood, and various explanations have been proposed based on Fc receptor uptake, epitope masking, altered antigen processing, and the expression of cryptic epitopes. The ability of a passively administered exogenous Ab to modify the antibody response is illustrated by recent experiments in which mucosal immunization with *Streptococcus mutans* coated with a MAb was shown to alter the amount, specificity, and isotype distribution of the antibody response to a bacterial antigen relative to that observed when mice were immunized with bacteria only (66, 87). In another study, the postinfection administration of a polyclonal immune serum with a high neutralizing titer of antibodies to simian immunodeficiency virus enhanced the neutralizing antibody response of infected macaques (38). The use of Ab-hepatitis B virus surface Ag (HBSAg) complexes has been proposed as a therapeutic vaccine for hepatitis B, based on the ability of such complexes to reduce HBSAg levels and to stimulate Abs to HBSAg (98). These studies raise the possibility that a developing Ab response can modulate itself by forming complexes with antigens and by altering the subsequent Ab response, thereby focusing the response on Abs that minimize the host inflammatory response. Further support for Ab-mediated regulation of the inflammatory response is found in studies that demonstrate an adjuvant effect for naturally occurring Abs in inducing T-cell stimulation and maintaining serological and T-cell memory (6, 19).

Based on phylogeny or pathogen class, there is no obvious group of microbes with common pathogenetic characteristics for which Ab-mediated protection depends on CMI. In fact, the apparent interdependence versus independence of CMI and AMI against a given microbe may reflect whether or not Ab protection is a singular property of the immunoglobulin molecule, i.e., whether the Ab can exert a direct antimicrobial effect, or whether the Ab efficacy is mediated through interactions with components of the immune system that are dependent on CMI. In those instances in which Ab molecules can be directly microbicidal, can activate complement-mediated lysis, and/or can promote phagocytosis that leads to microbial killing, Ab efficacy may not depend on CMI. However, when the resolution of microbial infection requires changes in the inflammatory response or the activation of effector cells to kill and ingest the microbe, Ab efficacy may be dependent on intact CMI.

(iv) The efficacy of AMI is the sum of the efficacies of individual Ab molecules in a particular host. The application of hybridoma technology to problems in infectious diseases has greatly enhanced our understanding of AMI by revealing the functional complexity of individual Abs and the dependence of Ab efficacy on the host immune function. In contrast to immune sera, which are polyclonal preparations in which specific Abs are only a small fraction of the total immunoglobulin present, all of the protein in MAb preparations is an immunoglobulin of a single specificity and isotype. Hence, experiments with MAb preparations enable the study of single components of the Ab response. This has permitted a more mechanistic understanding of Ab function, since the influence of individual Ab characteristics on Ab efficacy can be rigorously controlled. An early example of the unique insights that can come from studies with defined MAbs was the demonstration that the passive administration of a murine IgG1 MAb reliably protected mice against *C. neoformans*, despite the fact that consistent protection could not be demonstrated with immune sera (29). Passive protection experiments have revealed the existence of protective and nonprotective MAbs against a variety of pathogens, for which Ab efficacy is a function of the Ab isotype, specificity, or both, including *C. neoformans* (49, 61, 63), *C. albicans* (40), *Streptococcus pneumoniae* (18, 71), and *Mycobacterium tuberculosis* (83). For *C. neoformans*, MAbs have been described that are protective in some hosts and that enhance disease in others (97). Since a MAb with a defined specificity and isotype is only one Ab that has arisen in an Ab

response, the efficacy of Abs in serum represents an aggregate of the efficacies of individual molecules. The different amounts, specificities, and other characteristics of the individual Abs that constitute a polyclonal serum compound its complexity and can diminish the efficacy of its individual Ab components, making it difficult to predict its efficacy. Since the simultaneous administration of protective and nonprotective MAbs reduces the efficacy of the protective MAbs (63), the efficacy of polyclonal immune sera reflects the net effect, or sum, of the biological activities of many different Abs. This concept predicts that qualitative as well as quantitative differences in the Ab responses to certain microbes may determine their relative efficacies and provides a potential explanation for why it has been so difficult to demonstrate Ab efficacy against certain microbes, such as fungi and mycobacteria, which can elicit protective and nonprotective Abs (14). The existence of protective and nonprotective Abs implies that it may be possible to design vaccines that elicit protective responses that mediate protection through AMI, even against microbes for which the primary host defense mechanism is CMI. This principle was demonstrated by the synthesis of conjugate vaccines against both *C. neoformans* (25) and *C. albicans* (41).

SUMMARY AND CONCLUSIONS

The field of AMI is experiencing a renaissance. The engines driving the field are the application of hybridoma technology to understanding the mechanisms of AMI, the revolution in antibody engineering, and the availability of mice with defined genetic defects, which provide model systems to study Ab efficacy in the setting of immune deficiency. Since the presence of Abs remains the only reliable correlate of immunity to many infectious diseases (68), a better understanding of the parameters that influence AMI is likely to enhance our understanding of vaccine efficacy and host susceptibility to infection. Hence, the beginning of the 21st century resembles the beginning of the 20th century, when AMI promised, and delivered, great benefits to humankind in the form of serum therapy and new vaccines.

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