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J Immunol 2015; 194:13-20; doi: 10.4049/jimmunol.1400844
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Natural Antibodies Bridge Innate and Adaptive Immunity

Saswati Panda¹ and Jeak L. Ding

Natural Abs, belonging to isotypes IgM, IgG3, and IgA, were discovered nearly half a century ago. Despite knowledge about the role of the polyreactive natural IgM in pathogen elimination, B cell survival and homeostasis, inflammatory diseases, and autoimmunity, there is a lack of clarity about the physiological role of natural IgG and natural IgA because they appear incapable of recognizing Ags on their own and are perceived as nonreactive. However, recent research revealed exciting functions of natural IgG in innate immunity. Natural IgG:lectin collaboration swiftly and effectively kills invading pathogens. These advances prompt further examination of natural Abs in immune defense and homeostasis, with the potential for developing novel therapeutics. This review provides new insights into the interaction between natural Abs and lectins, with implications on how interactions between molecules of the innate and adaptive immune systems bridge these two arms of immunity. The Journal of Immunology, 2015, 194: 13–20.

Antibodies belong to the Ig superfamily. Ag-specific Abs are secreted by plasma cells in response to an Ag (1). During the primary innate immune response, APCs, such as dendritic cells (2, 3) and macrophages, recognize the pathogen through an array of pattern recognition receptors (PRRs; e.g., TLRs) (4, 5) and present the processed Ag to B cells. These Ag-stimulated B cells undergo somatic hypermutation (6, 7) and clonal selection to become long-lived plasma cells that produce Ag-specific Abs in the secondary adaptive immune response (8).

Five isotypes of Ig exist (IgM, IgG, IgA, IgE, IgD) that differ based on the H chain C region (9). IgM is the first isotype produced prior to class switching (10); it effectively recognizes and eliminates pathogens in the early stage of immune defense (11). Upon Ag stimulation, the B cells undergo class switching (12, 13) and convert into plasma cells that produce high-affinity IgG, IgA, IgE, and IgD. IgG is the major serum isotype and consists of four subtypes (IgG1, IgG2, IgG3, and IgG4), with further differences in the hinge region of the H chain constant fragment. IgG is the only isotype that can cross the placental barrier to provide immunity to the fetus (14). IgA, present at the mucosal surfaces, such as the gut, respiratory tract, and urogenital tract, plays an essential role in mucosal immunity (15–17). In humans, some B cells are known to generate IgM->IgD+ plasmablasts through both T cell–dependent and T cell–independent (TI) pathways in the secondary lymphoid organs of the upper respiratory mucosa upon Ag exposure. These plasma cells produce IgD that is highly specific to respiratory commensals and pathogens (18). IgD also was shown to be polyreactive and may play a role in energy through tolerogenic pathways. However, there are contradictory reports indicating that IgD may also protect B cells from tolerance (19). Despite these interesting findings, the biological role of IgD is still enigmatic. Further studies are required to provide insights into its role in innate immunity. In general, Ag-specific Abs elicit immune defense through the activation of the classical complement system (20–22), pathogen neutralization (23, 24), phagocytosis of apoptotic cells (25–27), and priming of immune cells (28, 29).

In addition to Ag-specific Abs, there are natural Abs that are produced after birth in neonates and in adults prior to an infection (30, 31). Extensive studies have been performed in mice to shed light on natural Abs. Natural Abs are reportedly produced by B-1 cells (32–34) in both mice (35) and humans (36, 37). Although natural Abs have the ability to recognize certain self-antigens through their V region, they have been perceived to lack specificity for any particular foreign Ag. However, reports indicate that certain natural Abs in mice have the ability to recognize foreign Ags. The T(EPC)-15 or T-15 idiotype natural Ab specifically recognizes phosphocholine on the surface of Gram-negative and Gram-positive bacteria, protozoa, fungi, and even modified low-density lipoprotein (38). The T-15 idiotype Ab was shown to confer protection in atherosclerosis, apoptosis, and immunity against pathogens (39). Natural IgM broadly and nonspecifically recognizes diverse microbial determinants and autoantigens. The significance of natural Abs is becoming increasingly apparent through decades of research on the function of natural IgM, which have shed light on its involvement in multiple biological processes, including infection, B cell homeostasis, inflammation, atherosclerosis, and autoimmunity (40).

In this review, we first discuss the findings on natural Abs, focusing on the role of natural IgM. This is followed by an exposition of the recent findings on natural IgG, which...
collaborates with serum lectins, and how this immune complex links innate immunity to adaptive immunity. We discuss how the prevailing microenvironmental changes induced by infection–inflammation conditions might regulate the antimicrobial action elicited by the natural IgG in humans, although these results are restricted to in vitro and ex vivo studies using human serum and are supported by in vivo mouse studies. Last, we provide a current opinion on the impending questions that lie ahead in this field and suggest future work that is needed to explore and exploit the role of natural Abs in health and disease.

**Natural Abs: B cell subsets and their contribution**

In addition to Ag-specific Abs that are produced by B-2 cells during the adaptive immune response (41), a pool of spontaneously occurring Abs is present in human cord blood (33), in normal healthy individuals (30, 31, 42), and in germ-free/Ag-free mice (43–46) that belongs to the IgM, IgG, and IgA isotypes. In mice, natural IgG typically belongs to the IgG3 subclass. Although a study suggested that humans also produce IgG3 subclass-specific natural IgG Abs (47), the subclass specification of human natural IgG has not been confirmed. Mouse B-1 cells produce natural Abs in a TI pathway (48) on exposure to self-antigens, such as dsDNA (49) and nucleosomes (50, 51), and TI Ags (52). B-1 cells are generated predominantly during fetal and neonatal development from precursor cells located in the liver and omentum (32); however, it is unclear whether natural Abs exist before birth. In adults, the B-1 cell population is maintained at a constant size as a result of its self-renewing capacity, thus sustaining the levels of serum natural Abs (53–56).

The B-1 Ig genes tend to have preferential usage of the J_{H1}-proximal V_{H} gene segments during V(D)J recombination, with fewer N-region insertions (32) and a lower rate of somatic mutations (57) compared with the B-2 counterpart, thus giving rise to a restricted natural Ab repertoire. Like their murine counterparts, human peripheral blood B-1 cells produce polyreactive Abs toward a limited range of self-antigens (57). However, it is unclear to what extent human B-1 cells resemble mouse B-1 cells because of the lack of identifiable cell surface markers on human B-1 cells. Interestingly, B-1 cells that produce natural IgM from unmutated or minimally mutated V(D)J genes can enter the follicular pathway to undergo somatic hypermutation and class switching to produce higher-affinity natural IgG or IgA autoantibodies (42), particularly under autoimmune conditions, such as systemic lupus erythematosus (SLE) (58) and rheumatoid arthritis (59). In addition to B-1 cells, natural Abs are produced by a subset of B-2 cells, which may include marginal zone (MZ) B cells (60), transitional B cells (61), and/or an unidentified population of B cells (62). However, there is a lack of information on the origin and type of signals that stimulate natural Ab production by these B-2 cell subsets. B-1 cells respond to certain altered-self components or danger-associated molecular patterns (DAMPs), such as asialylated glycoproteins with exposed terminal galactose residues. The human anti-galα1-3 gal Ab is one such abundant natural IgG that is a xenoreactive natural Ab (63). Other examples include natural IgG Abs with specificities toward gal α1-2 gal, gal α1-4 gal, and gal α1-6 glc (melibiose), which are not xenoreactive (64). Isohemagglutinins, such as anti-A and anti-B blood group Abs, are well-known examples of natural IgM Abs. These Abs play a critical role in blood transfusion, transplantation, and graft rejection through complement activation (65).

Although earlier studies suggested that peritoneal B-1 cells are the main source of natural Abs (66), B-1 cells in the bone marrow (67) and splenic MZ B cells (52, 68–70) also were shown to produce natural Abs. The bone marrow B cell precursors, which are generally considered to be the progenitors of conventional (B-2) B cells, also produce B-1 cells both in the fetus (71, 72) and adult (56). Extensive research efforts have shed light on the developmental origin of B-1 cells. It is now increasingly evident that B-1 cells arise at different times of development from a distinct population of progenitor cells according to the layered immune system model (reviewed in Ref. 73). Further studies in this area should provide more insight into understanding B cell immunity and related pathological issues.

**Functions of natural IgM in mice: hints on linkage between innate and adaptive immunity**

The contribution of natural Abs to immunity has been brought into focus by studies on natural IgM. Pentameric natural IgM, with 10 potential Ag-binding sites (74), recognizes multiple phylogenetically conserved structures like nucleic acids, phospholipids, and carbohydrates (40). Natural IgM also may exist in the monomeric form in patients suffering from autoimmunity (75) and chronic liver disease (76). A protective role for natural IgM was found in numerous viral, bacterial, fungal, and parasitic infections (77). For example, vesicular stomatitis virus, lymphocytic choriomeningitis virus, influenza virus, Streptococcus pneumoniae, and Cryptococcus neoformans (78, 79) are bound, neutralized, and cleared by natural IgM (80–83). Natural IgM also alerts and primes the adaptive immune system against subsequent pathogen attack by directing Ags to the secondary lymphoid organs. Mice deficient in natural IgM succumb to infections as a result of a lack of pathogen clearance, decreased neutrophil recruitment, and elevated proinflammatory serum cytokines (84). The level of natural IgM is unaffected by foreign Ags (45), ascertaining the innate immune character of natural IgM.

Under the innate immunity arm, natural IgM limits the spread of infection by using strategies like neutralization (80, 81, 83), complement-mediated immune complex formation and pathogen elimination by complement activation (83, 85), and recruitment of Ags into secondary lymphoid organs, thus priming the subsequent adaptive immune response (81, 86) and linking the innate and adaptive immune systems. Natural IgM also plays a role in clearing apoptotic cells (87), maintaining B cell homeostasis (88), inflammation (89, 90), ath- ersclerosis (91), and autoimmunity (92, 93). Natural IgM was proposed to bind strongly to complement factor C1q and to activate the complement cascade (85, 94). Natural IgM also binds mannose-binding lectin (MBL), which is bound to apoptotic cells (95, 96), and directs the clearance of immune complexes by binding to the putative Fce/μR receptor on phagocytes. Conversely, natural IgM bound to apoptotic cells may recruit MBL, and the immune complex may be cleared by the phagocytic calreticulin receptor (89). Fig. 1 summarizes the diverse roles of natural IgM identified through studies in mice.
Natural IgG is not quiescent: it collaborates with serum lectins in frontline immune defense

Despite vast knowledge about natural IgM, the existence and physiological function of natural IgG and IgA, which are predominant serum and mucosal natural Abs (32), are unclear and, hence, have been a subject of interest since their discovery almost 50 y ago (97). Because of their low affinity, nonspecificity, and low valency, natural IgG and natural IgA appeared to be unreactive and were deemed incapable of recognizing and eliminating pathogens.

Recent studies exploring the untapped potential of these natural Ab isotypes demonstrated that both mice and human natural IgG is not nonreactive, rather it plays a proactive fundamental role in the systemic innate immune response (98). In vitro studies revealed that natural IgG purified from uninfected/healthy human serum recognized a range of Gram-negative and Gram-positive bacteria with the aid of serum lectin PRRs (e.g., ficolin and MBL), which are known bind to sugar residues (e.g., N-acetylglucosamine) on the microbes. The partnership between natural IgG and lectins (prebound on the microbe) efficiently drove phagocytosis of the bacteria via the FcyR1 receptor on human monocytes. The importance of natural IgG during infection was demonstrated further in vivo in AID<sup>2-/-</sup> mice (these mice lack class switching and produce IgM but not other subclasses of Abs). The susceptibility of AID<sup>2-/-</sup> mice to infection was overcome by i.v. administration of purified natural IgG, which was shown to collaborate with the serum lectins to elicit effective antimicrobial activity (98). Future studies using ficolin and MBL double knockout mice and FcyR1<sup>-/-</sup> mice might provide insight into the collaboration between natural IgG and lectins at the crossroad of the innate–adaptive immune defense. Fig. 2 summarizes the natural IgG–mediated bacterial recognition and clearance in collaboration with serum lectins and highlights the gray areas that warrant further exploration. These efforts will pave the way for developing natural IgG–mediated therapies.

Infection–inflammation condition triggers the interaction between natural IgG:ficolin and enhances the immune response

Infection or injury causes an influx of inflammatory cells to the site, leading to inflammation (99, 100). Inflammation is characterized by a drop in the pH (101–103) and calcium (104–106) levels in the microenvironment of infection/injury. In vitro and ex vivo studies with human samples, using a simulated uninfected normal condition (typically, pH 7.4 and 2.5 mM calcium) and an infection-inflammation condition (pH 6.5 and 2 mM calcium) (98, 107) explored various PRR:PRR interactions under infection-induced changes in the microenvironment. The infection–inflammation condition increases PRR:PRR interaction affinity and boosts the immune responses. Examples include the C-reactive protein (CRP):ficolin interaction, which synergistically enhances the classical and lectin complement pathways (107), and the natural IgG:ficolin interaction, which facilitates bacterial phagocytosis (98, 108). These studies demonstrate how perturbations in the serum that result in mild local acidosis and hypoccalcaemia change the conformation of PRRs, exposing novel interaction motifs between them and leading to more effective pathogen binding and clearance. The identification of the amino acids involved in the molecular interplay between natural IgG:ficolin (109) showed that infection–inflammation–induced lower pH regulates the intermolecular electrostatic interaction. By hydrogen-deuterium exchange mass spectrometry, Panda et al. (109) delineated the binding interfaces of the CH2–CH3 region of natural IgG Fc and the P-subdomain of the ficolin FBG domain. Notably, histidine is critical for the molecular interaction. Mild acidosis at the site of infection–inflammation probably resulted in protonation of histidine side chains that increased the interaction affinity overall (109). These studies also imply that the immune system exploits the prevailing physicochemical changes at the infection site for effective immune defense.

The immunomodulatory activities resulting from the pH change ensure a specific immune response rather than a random PRR:PRR interaction, which could lead to immune overactivation that manifests as autoimmune diseases. Interestingly, formation of the natural IgG:ficolin immune complex is similar in humans and mice. During infection, the human and mouse ficolins bind to the pathogen and recruit natural IgG to form an immune complex. Conservation of this phenomenon suggests the fundamental significance of natural IgG:ficolin-mediated innate immune defense.

Natural IgG specifically collaborates with pathogen-associated lectins to elicit an effective antimicrobial action against opportunistic Pseudomonas aeruginosa and Staphylococcus aureus (98). The immune evasiveness of such pathogens is a significant barrier to their clearance and resolution of the infection and inflammation; hence, a continuing effort to devise new and more effective therapies is needed to combat such infections. Because natural IgG (specifically IgG3 isotype) interacts with pathogen-associated ficolins through its conserved CH2–CH3 region in the constant Fc region, it is plausible that IgG3 derived from plasma cells in bone marrow interacts with ficolins in a similar manner once the ficolins have bound to the pathogen. Further studies are required to investigate this hypothesis. Nevertheless, new insights into the mechanism of interaction between the innate and adaptive immune proteins should advance our understanding of how the host might counter the immune evasiveness of these pathogens.

Natural IgG bridges innate and adaptive immunity and boosts immune response

The mechanisms underlying the ligand specificity, signaling pathways, and cellular trafficking of PRR immune complexes have been characterized extensively. Interestingly, multiple pathogen-associated molecular patterns that simultaneously activate numerous PRRs (4, 110) were shown to induce PRR:PRR interactions as a prerequisite for effective immune responses. For example, CRP and ficolins, which are initiators of the classical and lectin complement pathways, respectively, interact with each other to boost the immune response against pathogens (107). Second, TLRs in collaboration with other PRRs orchestrate both pathogen- and cell type–specific host responses to fight infections (111–113). Third, interactions between C1q and CRP were observed during the immune response (114). Last, several studies showed the Ab-like behavior of pentraxins, which bind to FcγRs on macrophages and other immune cells to elicit immune responses. For example, serum amyloid P, an acute-phase pentraxin, was shown to bind to FcγRIIA (115).
FIGURE 1. Diverse roles of natural IgM (nIgM) in immunity. nIgM, produced by B-1 cells in the peritoneum, bone marrow, and splenic MZ B cells, plays a crucial role in many immune processes: (1) direct pathogen neutralization; (2) classical complement activation in collaboration with C1q; (3) Ag recruitment to secondary lymphoid organs and priming of subsequent TI adaptive immunity; (4) Ab-dependent cell-mediated cytotoxicity: nIgM clears target cells through NK cell–mediated release of perforin and granzymes; (5) apoptotic cell phagocytosis in collaboration with C1q and MBL through C1qR and FcγRIIa, which reduces inflammation and restores homeostasis [figure adapted with permission from Ehrenstein and Notley (40)]; (6) prevention of autoimmunity by clearance of DAMPs, such as dsDNA; and (7) immune regulation and B cell homeostasis.
Another pentraxin, PTX3, binds to FcγRIII (116), suggesting its potential role in neutrophil and NK cell activation. These PRR:PRR interaction–mediated mechanisms induce stronger and rapid immune responses that prime and shape adaptive immunity.

Natural IgG was recently shown to interact with pathogen-associated lectins, such as ficolin and MBL, and to form immune complexes to clear the pathogens (98, 108). Axiomatically, Ag-specific IgG that binds directly to pathogens, SLE; (ii) ameliorating inflammation with applications for rheumatoid arthritis and atherosclerosis, (iii) immune regulation and homeostasis, and (iv) development of safer and more effective immunomodulators and antimicrobial therapies in conjunction with partner proteins (right).

Implications of natural Abs in autoimmunity and inflammatory diseases

Natural IgG was reported to control autoimmunity and inflammatory diseases. Mouse models of SLE have reduced levels of natural IgM (118) with an increase in the B-1 cell subset and an increase in IgG autoantibodies (92, 93). Decreased natural IgM apparently makes these mice susceptible to numerous infections. Natural IgM with C1q is known to recognize, bind, and clear autoantigens (e.g., oxidized low-density lipoprotein in atherosclerotic plaques (119, 120) and phospholipids and dsDNA expressed on apoptotic cells (87)). Hence, a reduction in natural IgM levels is associated with ineffective clearance of apoptotic cells, resulting in autoimmune diseases. Conversely, stronger and persistent recognition of apoptotic cells by natural Abs may lead to overactivation of the immune system and chronic inflammation. Further studies on the extent of apoptotic cell uptake, immunomodulation by infection-induced microenvironmental changes, and cytokine responses by natural Abs in autoimmune patients will provide clarity about the overall contribution of natural Abs in autoimmunity.

FIGURE 2. Current and future perspectives on the roles of natural IgG (nIgG) in immune defense. nIgG is an understudied, but important, molecule of the natural Ab repertoire. Recent studies on the role of nIgG in pathogen recognition and clearance (left) showed that it collaborates with ficolin and MBL to indirectly recognize the pathogen and clear it via FcγR1-mediated phagocytosis, thus controlling inflammation by regulating the production of cytokines (reducing proinflammatory TNF, IL-6, and IL-8 and increasing anti-inflammatory IL-10). Future research on nIgG would elucidate its unexplored role in health and disease: (i) controlling or exacerbating autoimmune disease, SLE; (ii) ameliorating inflammation with applications for rheumatoid arthritis and atherosclerosis, (iii) immune regulation and homeostasis, and (iv) development of safer and more effective immunomodulators and antimicrobial therapies in conjunction with partner proteins (right).

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How do natural Abs control inflammatory diseases? On one hand, natural IgM reduces the inflammatory response by removing the apoptotic cells and preventing inflammatory arthritis (121) and atherosclerosis (91). On the other hand, natural IgM enhances inflammation through increasing the precipitation of urate crystals, which recruits neutrophils and worsens inflammation (122). Natural IgM is also involved in ischemia–reperfusion injury, including myocardial infarction and intestinal ischemia–reperfusion injury, wherein it targets autoantigen-expressing endothelial cells (123, 124). It is likely that these two opposing and parallel processes of the natural IgM–mediated immune response maintain homeostasis. The potential role of natural IgG in controlling inflammation was recently uncovered based on the existence of the natural IgG: hemoglobin complex that is formed under hemolytic conditions: natural IgG facilitated uptake of the redox active hemoglobin by immune cells (125), leading to resolution of inflammation and restoration of homeostasis. Recently, Hess et al. (126) also reported that Abs produced in a TI manner, similar to natural Abs, elicit anti-inflammatory properties. This is suggested to be attributable to differences in their glycosylation patterns compared with conventional Abs, which lead to a proinflammatory response. Natural Abs exhibit a sialylated pattern, which confers an anti-inflammatory nature. In contrast, Ag-specific Abs are either agalactosylated or asialylated and exhibit proinflammatory properties. This finding has important implications in the immunoregulatory nature of Abs during a TI response to self-antigens in autoimmunity or inflammatory diseases initiated by TI Ags. In addition, this information could aid in vaccine design for developing specific Abs with unique glycosylation patterns to protect against infections without provoking excessive proinflammatory responses.

Uncontrolled/chronic infection may also result in overactivation of the immune system, leading to autoimmunity (82). Hence, a timely and well-regulated immune response is necessary to resolve infection and restore normalcy. Further work is required to fully understand the mechanisms of action of natural Abs in autoimmunity and chronic infection/inflammation. Moreover, knowledge of the role of natural IgG and IgA in immunoregulation and homeostasis is still in its infancy, and much remains to be explored.

Conclusions

Extensive research has highlighted the role of natural IgM in health, infection, inflammation, and autoimmune diseases. Recent studies revealed the early protective role of natural IgG in infection, demonstrating that natural IgGlectin interaction led to enhanced pathogen clearance (98). This collaboration between molecules of the innate and adaptive immune systems blurs the boundaries between the seemingly discrete arms of immunity and opens up a vast area to explore fundamental immunology: what lies at and ahead of the crossroad of these immune pathways?

Elucidation of the precise contact points between natural IgG and ficolins (109) offers the potential for development of effective immunomodulatory drugs to intercept the immune complexes of natural IgG and lectins, to ameliorate immune overreaction, and to pre-empt chronic inflammatory diseases, such as rheumatoid arthritis, atherosclerosis, and SLE. Such therapies could also be tunable to the prevailing pH and calcium conditions in the infection–inflammation microenvironment to modulate the downstream immune response. To this end, various questions need to be addressed. What is the spectrum of apoptotic cell DAMPs and autoantigens recognized by the natural Abs:PRR immune complexes? What mechanism does natural IgG use to ameliorate inflammation? Is it through the removal of pathogens, apoptotic cell debris, and/or harmful DAMPs? Which immune cell type(s) does natural IgG regulate? What are the dynamics of the cytokine profile during such a response? How can i.v. Ig, involving natural IgG and/or lectins, aid in controlling inflammation? How do natural IgG Abs regulate ongoing immune processes and specifically control autoimmunity-related inflammation? Is there a potential feedback/autoregulation of the production of natural IgG? Some of these questions may be answered with in vivo studies on IgG-deficient or conditional knockout mice to provide mechanistic insights.

Ig infusions, consisting primarily of IgG, have been used to treat inflammatory and autoimmune diseases, with limited success. Additionally, the finding that differential glycosylation patterns in the Fc region of Abs determines the immune response (sialylated leading to anti-inflammatory response and agalactosylated or asialylated leading to proinflammatory response) (126) could aid in efficient vaccine design and i.v. Ig therapy to treat these inflammatory diseases. There are no reports on the use of natural IgG Abs in i.v. Ig therapy for recurrent infections in patients with primary immune deficiencies. However, recent findings on the association between natural IgG and ficolins (lectins that bind to microbial sugar residues) regulated by perturbations in pH and calcium conditions in the microenvironment (98) suggest the potential use of i.v. Ig treatment for patients affected by primary Ab deficiencies. With a view to using the protective outcome of natural IgG:ficolin interaction in i.v. Ig therapy, it will be particularly interesting to study the levels of natural IgG and ficolins and the prevailing microenvironmental conditions during recurrent infections in these patients. It will also be crucial to take into account the role of other serum factors that may contribute through new and yet-to-be-explored compensatory mechanisms under such conditions. Thus, the existing and exciting new findings in the field of natural Abs provide a better understanding of their role (in collaboration with partner proteins) and extend the possibilities for developing effective drugs to effectively counteract these diseases.

Disclosures

The authors have no financial conflicts of interest.

References


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