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Natural Antibodies: from First-Line Defense Against Pathogens to Perpetual Immune Homeostasis

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Abstract
Natural antibodies (nAbs) are most commonly defined as immunoglobulins present in the absence of pathological conditions or deliberate immunizations. Occurrence of nAbs in germ- and antigen-free mice suggest that their production is driven, at least in part, by self-antigens. Accordingly, nAbs are constituted of natural autoantibodies (nAAbs), and can belong to the IgM, IgG, or IgA subclasses. These nAbs provide immediate protection against infection while the adaptive arm of the immune system mounts a specific and long-term response. Beyond immediate protection from infection, nAbs have been shown to play various functional roles in the immune system, which include clearance of apoptotic debris, suppression of autoimmune and inflammatory responses, regulation of B cell responses, selection of the B cell repertoires, and regulation of B cell development. These various functions of nAbs are afforded by their reactivity, which is broad, cross-reactive, and shown to recognize evolutionarily fixed epitopes shared between foreign and self-antigens. Furthermore, nAbs have unique characteristics that also contribute to their functional roles and set them apart from antigen-specific antibodies. In further support for the role of nAbs in the protection against infections and in the maintenance of immune homeostasis, the therapeutic preparation of polyclonal immunoglobulins, intravenous immunoglobulin (IVIG), rich in nAbs is commonly used in the replacement therapy of primary and secondary immunodeficiencies and in the immunotherapy of a large number of autoimmune and inflammatory diseases. Here, we review several topics on nAbs features and functions, and therapeutic applications in human diseases.

Keywords Natural IgM · Natural IgG · Intravenous immunoglobulin · IVIG · Therapy · Immune homeostasis · Autoimmunity

Introduction

The successful treatment of diphtheria using immune serum by Emil Adolf von Behring and Émile Roux in the nineteenth century paved the way for the discovery of antibodies (Abs) in serum as gamma globulin proteins and its basic structure was elucidated in the twentieth century [1, 2]. There was a parallel expansion in the application of serum with anti-infection capabilities against other microbial diseases to confer immunity against dreadful pathogens; hence, the name immunoglobulins (Igs) came into practice. Subsequently, thorough characterization of the antibodies produced following microbial infection or immunization, referred to as immune antibodies, was done [3]. Further studies identified varieties of Igs differing in their structure and function. These are divided into five classes/isotypes, namely IgG, IgM, IgA, IgE, and IgD [4]. Antibody production is the main function of differentiated B cells. Well established as effector molecules of the adaptive compartment, Abs also participate as links or organizing factors for certain functions of the innate immune system by identifying and neutralizing the pathogens in part through the triggering of Fc receptors (FcRs) and activation of the complement system [5].

In the early 1960s, the existence of circulating antibodies in neonates (cord blood) and healthy adults in the absence of exogenous antigen stimulation or deliberate immunization, referred to as natural antibodies (nAbs), was also identified [6]. Although the origin and function of nAbs have been the subject of age-old discussions, one hallmark of nAbs is that they can be found in germ- and antigen-free mice, observations which suggest that their production may be driven, at

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least in part, by self-antigens. However, it is also clear that exposure to microorganisms, either intentionally or environmentally derived, results in long-lasting effects on the clonal diversity of these Abs, their circulating levels, and ultimately their biological functions which include first-line defense as well as immunoregulatory activities. Here, we review several topics on nAbs features and functions, and therapeutic applications in human diseases.

Source and Origin of Natural Antibodies

Emerging Information in Mice Despite the continued interest in nAbs since 1960s, the evidence for their cellular source began to emerge only after 1983, particularly in mice. A subset of B cells, named B-1 cells, was recognized as the source of nAbs. B-1 cells were initially identified by their expression of CD5 and were further characterized by surface expression of IgM^{high}, IgD^{low}, $CD19^{high}$, $B220^{low}$, $CD23^{-}$, and $CD43^{+}$, which contrasts with the surface phenotype of follicular B2 cells: $CD5^{-}$, IgM^{low}, IgD^{high}, $CD19^{+}$, $B220^{+}$, $CD23^{+}$, and $CD43^{-}$ (Table. 1). Subsequently, an additional population of B-1 cells was identified, which shared the characteristics of $CD5^{+}$ B1 but lacked CD5 expression. These two populations of B-1 cells are termed B-1a ($CD5^{+}$) and B-1b ($CD5^{-}$) cells [7, 8]. B-1 cells are found in various tissues of adult mice, including the peritoneal cavity, pleural cavity, spleen, bone marrow, lymph nodes, and blood that contribute to greater than 90% of nAb [7]. Interestingly, B-1 cells located in the peritoneal cavity and pleural cavity serve as an important reservoir for B-1a cells and form a pool of long-lived, self-renewing B cells that produce most of the circulating natural IgM antibodies [9]. However, it has been suggested that within the B-1 cell population, those residing in the bone marrow and the spleen are the true nAb-secreting cells, whereas body cavity B-1 cells constitute a population of responder (memory type) lymphocytes, which after stimulation migrate and differentiate into IgM-secreting cells [8, 10]. In addition, a population of $CD138^{+}$ B-1a cells and marginal zone B cells, subset of B-2 cells, are also found to produce nAbs in mice. Therefore, more than one B cell population is responsible for nAb production and not all subsets of B-1 cells spontaneously secrete nAbs that accumulate in serum, as some of the B-1 cells can differentiate into antigen-induced antibody-secreting cells (Table 1) [7]. It should be noted that, although B cell receptor (BCR)-signaling is critical for B-1 cell development, BCR- and T cell–independent innate immune activation of B-1 cells in body cavities and marginal zone B cells (both referred to as innate-like B cells) can induce nAb production. These stimuli include IL-5, IL-10, toll-like receptor (TLR) agonists, or whole bacteria that can alter the B-1 cell normal trafficking patterns and induce differentiation into cells that secrete large amounts of IgM and/or IgA. Furthermore, similar to phenotypic diversity, B-1 cells are also capable of differentiating into antigen-induced Ab-secreting cells [7]. Thus, the generalized concept of B-1 cells as source/producers of nAbs may not be a complete description. Nevertheless, extensive research points to the possibility that, at least in mice, nAbs can originate from multiple B cell subsets that arise at different times of development from a distinct progenitor cells [11]. Future studies should lead us to an understanding of the role of different source and origin (B cell subsets and their stimuli) of nAbs and their contribution to the nAb pool.

Evidence in Humans In line with mice, nAb-secreting cells in humans were first identified as $CD5^{+}$ peripheral B cells [12]. However, $CD5^{-}CD45RA^{lo}$ peripheral B cells were also found to produce natural IgM [8, 13]. Further, expression of surface CD5 on cord blood B cells is not a definitive marker of an auto/polyreactive population, and also, CD5 may be an activation marker on human B cells. Notably, recent efforts based on natural/spontaneous antibody secretion refined the phenotypic characteristics of nAb-producing cells in human adult and cord blood as $CD20^{+}CD27^{+}CD43^{+}CD70^{-}CD38^{mod}$, the majority of which express CD5 and this is in contrast to the phenotype of plasmablasts: $CD20^{-}CD27^{high}CD38^{high}$ (immune Ab-secreting cells) and activated memory B cells: $CD20^{+}CD27^{+}CD43^{+}CD70^{+}$ (Table 1) [14, 15]. Interestingly, similar to mice, not all human B-1 cells spontaneously secrete nAbs, and polyclonal stimulation, like TLR9 ligand, CpG, increased the frequencies of antibody-secreting cells, a feature also seen in memory B cells [15] and transitional B cells [16]. Nevertheless, the phenotype of nAb-secreting cells in humans is still unclear, and further studies are required to clarify the specific types of cells capable of producing nAbs and also their locations other than in blood.

Characteristics and Reactivity of Natural Antibodies

Classes of nAbs and Generation in Mice and Humans Natural antibodies in the circulation of a normal healthy individual can be of IgM, IgG, and IgA classes. However, studies in mice suggest that nAbs are mainly IgM, but also IgA, IgG3, and IgE types, and are proposed to be T cell independent. Although nAbs are mainly germ line–like in mice as evidenced by absence of non-templated nucleotides (N-additions during VDJ recombination) with minimum to no somatic hypermutation in VDJ of B-1a cells [17], nAbs with significantly more N-additions and hypermutations with isotype switching (IgM to IgG) are seen with increasing age [18]. Accordingly, IgG and IgA are also part of the nAb pool in mice, although, unlike serum natural IgM, their levels are dependent on exogenous antigen stimulation as evidenced by decreased amounts in germ-free mice [8]. Interestingly, unlike

Table 1 Cellular source of natural antibodies (nAbs) in mice and humans

Property	Mice				Human	
	B1a	B1b	MZ B2	FO B2	B1-like	B2-like
Cell surface phenotype	IgM^{high}, IgD^{low}, $CD19^{high}$, $B220^{low}$, $CD23^{-}$, $CD43^{+}$, $CD138^{\pm}$, $CD5^{+}$	IgM^{high}, IgD^{low}, $CD19^{high}$, $B220^{low}$, $CD23^{-}$, $CD43^{+}$, $CD138^{\pm}$, $CD5^{-}$	IgM^{high}, IgD^{low}, $CD19^{mid}$, $CD21^{high}$, $CD23^{-}$, $CD43^{-}$, $CD5^{-}$	IgM^{low}, IgD^{high}, $CD19^{high}$, $B220^{+}$, $CD23^{+}$, $CD43^{-}$ and $CD5^{-}$	$CD20^{+}$, $CD27^{+}$, $CD43^{+}$, $CD70^{-}$, $CD38^{mod}$, $CD45RA^{low}$, $CD5^{-/+}$	$CD20^{+}$, $CD27^{+}$, $CD43^{+}$, $CD70^{+}$, $CD38^{mod}$
Development	Positive selection on self-antigen	Unclear pathway	Selection of weak self-reactive	Selection for non-self-reactive usually	Positive selection on self-antigen	Usually selection for non-self-reactive
Tissue distribution	Peritoneal cavity, pleural cavity, spleen, bone marrow, lymph nodes and blood		Spleen	Spleen	Blood, other locations?	Blood, lymph nodes and spleen
Self-renewing B1 cells	Mainly B1 cells from body cavities, but adult bone marrow as precursor		N/A	N/A	Yes	N/A
Spontaneous nAb secretion	Mainly B1 cells from spleen and bone marrow for IgM; and Intestinal mucosa and lung parenchyma for IgA		Nil	N/A	Yes	Nil
Induced nAb secretion	Mainly B1 cells from peritoneal cavity after CpG, LPS for IgM; and Intestinal mucosa and lung parenchyma for IgA			N/A	Yes	stimulus differentiated cells
Stimulus for response	BCR-independent, but need innate receptor or cytokine signals	BCR-dependent expansion	BCR-dependent expansion	BCR-dependent expansion	BCR-independent, and need innate receptor or cytokine signals	BCR-dependent expansion
Contribution to circulating nAbs	Mainly B1 cells from spleen and bone marrow for IgM; and Intestinal mucosa and lung parenchyma for IgA			N/A	Unknown	N/A

N/A not applicable

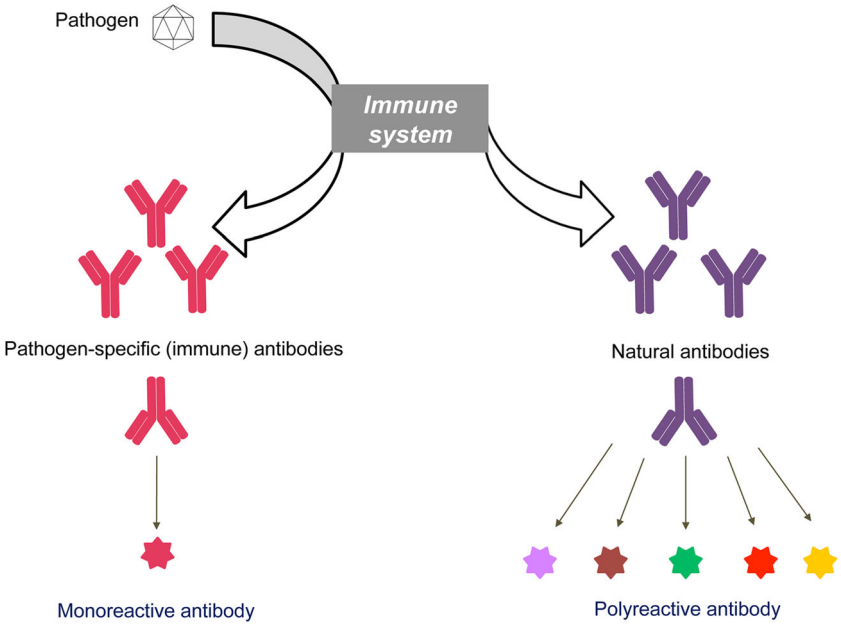

Fig. 1 Natural antibodies and pathogen-specific immune antibodies. In addition to immune antibodies that develop following active exposure to pathogen-derived antigens through infection or immunization, our immune system also produces natural antibodies (nAbs) that are constitutively expressed in the absence of external antigens. Further, unlike the monoreactivity of immune antibodies, nAbs are predominantly polyreactive capable of binding many structurally unrelated antigens with similar affinity

mice, IgM is not the only isotype present in the prenatal repertoire of human B cells. It was demonstrated that after 26 weeks of gestation, B cell clones encoding IgG start to appear in a frequency similar to that observed in healthy infants [19]. Therefore, contrary to observations in mice, the nAb pool in humans contains IgM, IgG, and IgA classes and exhibits similar reactivity in cord blood to that of adults. Furthermore, both fetal and adult-derived human B cells express Ig with numerous N-additions in VDJ [8], and somatic hypermutations occur during human fetal B cell development even in a T cell–independent fashion [19]. However, there is no evidence in humans for T cell dependency of nAb production, despite the presence of autoreactive T cells in healthy individuals, although mainly with regulatory roles [20]. Autoreactive $CD4^+$ T cells specific for a number of self-antigens, including myelin basic protein, the acetylcholine receptor, the thyroglobulin-stimulating hormone receptor, and the gpIIbIIIa platelet antigen have been reported in healthy individuals. It has been also hypothesized that natural autoreactive B cells are endowed with some switching ability in the absence of cognate interactions with T cells, based on the finding of small amounts of IgG in the serum of CD40L-deficient patients with the hyper-IgM syndrome [21]. Thus, the mechanisms of generation of natural IgM, IgG, and IgA antibodies are poorly understood and may differ from each other.

Characteristics of nAbs In general, nAbs are characterized by their low affinity, high avidity, and broad/multi reactivity against self-antigens (nAAbs), but some have the ability to recognize evolutionarily conserved epitopes occurring in foreign antigens (Fig. 1). In mice, prenatal B-1 cells express a mainly germ line–encoded repertoire, while postnatally developing B-1 cells can express Ig with a greater degree of variation [7]. Yet, the probability of nAb recognition of foreign structures as a result of cross-reactivity against self-antigens is still a hotly debated topic. However, it is being increasingly appreciated that nAAb production does not represent non-specific, antigen-independent "leakage" of terminal B cell differentiation, but the result of positive selection processes for autoreactive B cells dependent on the variable (V) region, resulting in low-affinity reactivity directed at a set of evolutionarily conserved (auto)antigens, such as circulating antigens, cell surface, and intracellular structures [20, 22]. These epitopes may exist constitutively or represent neoepitopes that result from altered glycosylation of host proteins or oxidation of host constituents. Targeting of these endogenous epitopes, which are usually sequestered from immunosurveillance, provides beneficial housekeeping functions [23]. Therefore, nAAbs are considered to be a manifestation of physiological autoreactivity expressed in healthy individuals and represent normal responses to self-antigens [20]. In line with this, it has been estimated that 5–15% of splenic B cells activated in vivo can secrete nAbs [21] and up to 20% of circulating human B cells are autoreactive [24].

Reactivities of nAbs Notably, the well-characterized epitopes for nAbs to date are shared by pathogens and host, which include phospholipids, oxidized lipids, glycolipids, and glycoproteins, both in mice and humans. The best-characterized B-1 cell–derived nAb binds the phospholipid phosphorylcholine (PC) and utilizes VHS107.1 [25]. PC is

found within the bacterial cell wall of *Streptococcus pneumoniae* and is also exposed on apoptotic cells and oxidized lipids, but hidden in healthy cells [26]. Studies in mice revealed nAb binding to red blood cells treated with bromelain (that exposes phosphatidylcholine, PtC) were B-1 cell-derived and utilized VH11, VH12, and Q52 [8]. Antibodies that recognize glycan epitopes are also highly abundant in both mice and humans. Glycan epitopes are observed on both glycoproteins and glycolipids and can be present in autologous or pathogen-associated exogenous structures. In mice, the specificities of such antibodies include α-1,3-glucan, N-acetyl-d-glucosamine, and α-1,3-galactose epitopes [27]. In humans, the best known anti-glycan antibodies react with blood group antigens A and B, the xenoantigen Gal-alpha-1, 3Gal-beta-1,4GlcNAc, Forssman glycolipid antigen, and gangliosides such as the tumor-associated antigen Neu5GcGM3 [8, 23].

Broad reactivity or polyreactivity of nAbs toward self and/or foreign antigens does not correlate with their connectivity (i.e., their ability to interact with variable regions of other autoantibodies) (reviewed in [28]). Polyreactivity does not suggest lack of specificity, but nAbs are "polyreactive" only in the sense that they bind the identical epitope on a variety of molecular entities and also feature their own distinct set of epitopic specificities. The notion that an antibody must be of high affinity in order to be biologically relevant originates primarily from the analysis of the requirements for an efficient immune response against pathogens. This concept does not necessarily apply to nAbs. Accordingly, earlier literature suggested that nAbs might exhibit a broad range of affinities, with dissociation constants ranging between 10^{-5} and 10^{-8} M. However, advanced technologies to measure protein–protein interactions have shown that overall affinity of natural IgG autoantibodies specific for molecules such as HLA class I, CD4, the RGD (Arg-Gly-Asp tripeptide) motive, and autologous blood group antigens, in the micromolar range [21].

The germ line neonatal B cell repertoire encoding IgM antibodies in the fetus has been evolutionarily selected for its reactivity with self-antigens. Interestingly, the self-reactive repertoire of IgG is established within the first 2–4 years of life and it is highly homogenous among children and similar to that expressed by the IgG of healthy young and older adults, whereas the repertoire of IgG (cross)-reactivities toward foreign and self-antigens is diverse and dependent on the history of each individual's immune system (reviewed in [28]). Therefore, it is now becoming clear that exposure to microorganisms, either intentionally or environmentally derived, results in long-lasting effects on the clonal diversity of these Abs, their circulating levels, and ultimately their biological functions which include first-line defense as well as immunoregulatory activities [23].

Functions of natural antibodies

Several lines of evidence have clarified the evolutionarily conserved (cross-)reactivity of nAbs supporting an important physiological role in the immune system [20], and hence, multiple functions of nAbs have been postulated. Owing to their cross-reactivity to foreign antigens, nAbs neutralize microbes and microbial toxins, strongly suggesting a role for nAbs in natural host defense against infection. A major role for nAbs is in immune regulation, which includes the removal of senescent/altered self-molecules, cells, and tumors, and controlling untoward autoimmune responses, possibly by virtue of their ability to modify the functions of some of their target antigens. Indeed, it has been shown that antibodies from healthy individuals display a promiscuous hydrolytic activity, as opposed to more specific enzymatic activity of antigen-specific autoantibodies in patients with autoimmune diseases (reviewed in [29]).

Natural Antibodies as a First-Line of Defense Against Pathogens

The most relevant roles for infectious disease control are the ability of nAbs to provide protection against pathogens, and in the clearance of endotoxin. The first indication of the crucial role of nAbs in controlling infections came from the evidence that primary Ig-deficient patients display high susceptibility for recurrent infections from bacteria, virus, fungi, and parasites. In particular, nAbs have been shown to provide protection against *Streptococcus pneumoniae*, *Borrelia hermsii*, *influenza virus*, *Listeria monocytogenes*, *vesicular stomatitis virus*, *lymphocytic choriomeningitis virus*, *Cryptococcus neoformans*, *Pneumocystis murina*, *and Francisella tularensis* (reviewed in [8]). Such protection is afforded by virtue of nAbs' cross-reactivity toward ubiquitous bacterial antigens/epitope recognition. For example, in mice, nAbs to phosphocholine can protect against intravenous infection with type 3 *Streptococcus pneumoniae* [30].

Studies using mice and human sera antibodies suggest that anti-microbial nAbs are mainly of IgM isotype (Fig. 2), and act by virtue of the ability of polyclonal nIgM to directly recognize a wide range of pathogen-associated molecular patterns (PAMPs) that leads to inhibition of the growth of microbial pathogens through their direct neutralization, by activation of the classical complement pathway to inhibit bacterial growth by lysis, generation of anaphylatoxin C5a, enhancement of phagocytosis, neutralization of the functional activity of endotoxin, and amplification of humoral immune responses, leading to the enhanced phagocytosis of these opsonized pathogens [31–33]. Mice deficient in natural IgM might be less resistant to viral infection or also succumb to infections as a result of a lack of pathogen clearance, decreased

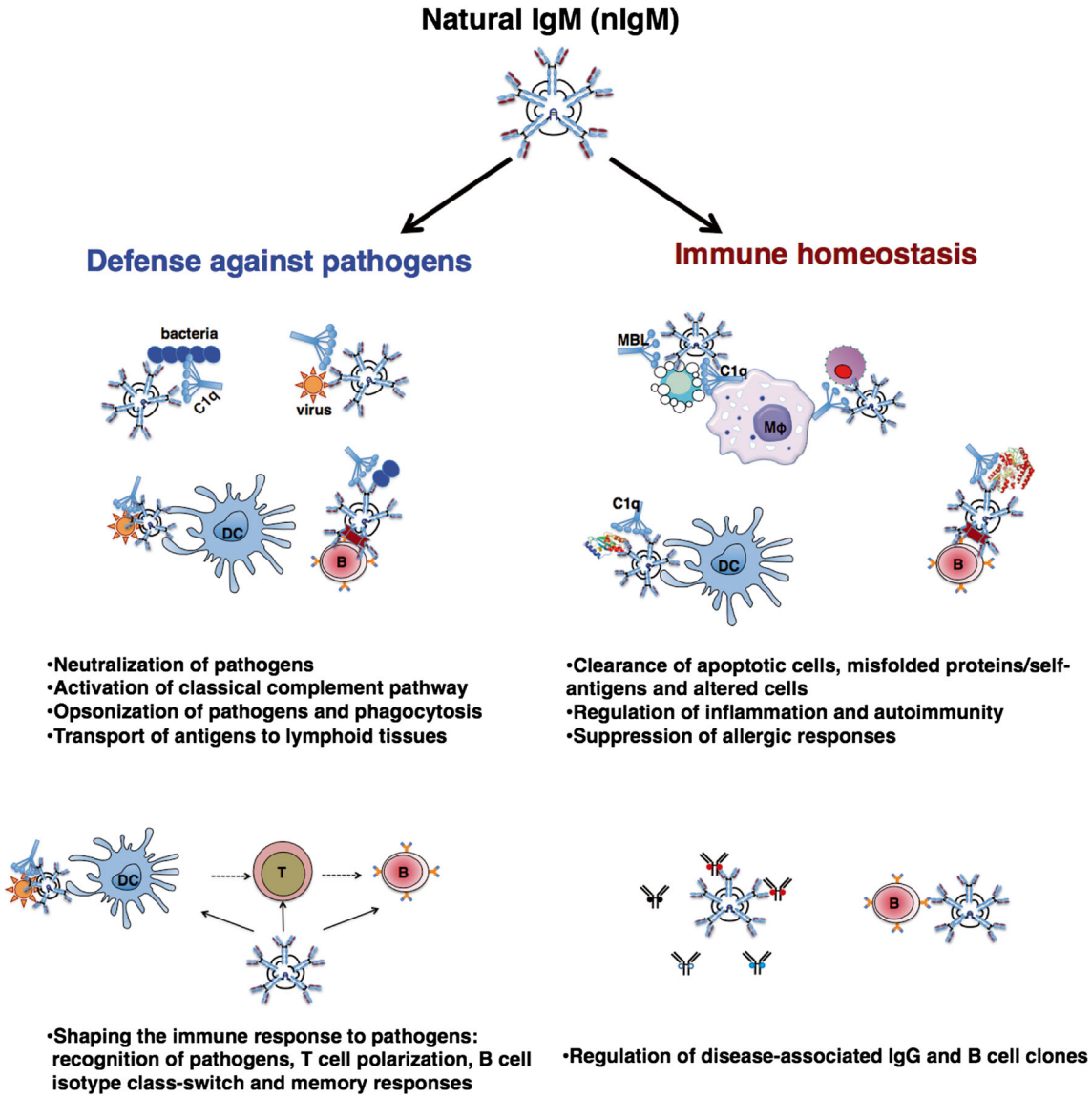

Fig. 2 Natural IgM in immune tolerance and homeostasis. nIgM can sustain immune equilibrium by acting as a first line of defense against invading pathogens, shaping the anti-microbial response, and by regulating the immune tolerance and homeostasis. nIgM confer protection against pathogens through direct neutralization, activation of the classical complement pathway, opsonization of pathogens and their phagocytosis by innate cells like dendritic cells (DC) and macrophages (MΦ), and transportation of antigens to secondary lymphoid organs for initiating the immune responses. In addition, nIgM can also shape the immune response to pathogens by regulating the T cell polarization and B cell class-switch. The role of nIgM in immune homeostasis involves recognition and clearance of apoptotic cells, altered cells, and misfolded proteins, and regulation of disease-associated B cell clones and IgG antibodies. B, B cell; C1q, complement C1q (classical complement pathway); T, T cell. The figure is reproduced with modifications by permission from The Journal of Immunology, The American Association of Immunologists, Inc. [53]

neutrophil recruitment, and elevated proinflammatory serum cytokines [32, 34].

In addition, nAbs also alert and prime the adaptive immune system against subsequent pathogen attack and are essential in the induction of an immune response that protects against bacterial and viral pathogens. The IgG response to T cell–dependent antigens was impaired in IgM-deficient mice, which can be rescued by administration of normal IgM prior to immunization [35]. For example, lack of natural anti-influenza IgM leads to delayed T cell–dependent IgG2a response and increased mortality in mice [36]. Several mechanisms may be involved in this function of nAbs. The formation of immune complexes by nAbs can direct Ags to the secondary lymphoid organs, where presentation to T and B cells is efficient. nAbs may guide the ensuing functional polarization of T cell responses, as well the isotype class-switch recombination of the induced B cell response and the induction of long-term immune memory. IgM immune complexes with pathogens bind complement that in turn binds to complement receptors on dendritic cells (DCs) and B cells [34,

37]. It is known that cross-linking the complement receptor 2 (CR2) reduces the triggering threshold of B cells. By allowing simultaneous engagement of BCR and the CD21/CD19, nAbs may therefore lower the threshold of B cell activation. Furthermore, virus/nAb complexes with increasing particle size enhance phagocytosis by macrophages in a CR3- and CR4-dependent fashion, which can now present virus-derived peptides to T cells. Finally, polymeric IgM nAbs can cross-link the BCR on B cells that have already captured antigen (Fig. 2) (Reviewed in [28]).

Interestingly, in contrast to the direct recognition of microbes by nIgM, recent in vitro studies have revealed that natural IgG purified from uninfected/healthy human serum recognize a range of gram-negative (e.g., *Pseudomonas aeruginosa*) and gram-positive (e.g., *Staphylococcus aureus*) bacteria with the aid of serum lectin innate receptors (e.g., ficolin and Mannan-binding lectin, MBL), which are known to bind to sugar residues (e.g., N-acetylglucosamine) on the microbes. The partnership between natural IgG and lectins (prebound on the microbe) efficiently drive phagocytosis of the bacteria via the FcγRI receptor on human monocytes [38]. Furthermore, the interaction between natural IgG (CH2-CH3 domain on Fc) with ficolin (P-subdomain of FBG domain) can be triggered under infection–inflammation conditions to augment the immune response [39].

As previously discussed, exposure to microorganisms that have antigenic epitopes similar to that of self-antigens influences the clonal diversity of nAbs. It is proposed that neonatal exposure to conserved epitopes (host and bacterial cells and other common environmental allergens) reprograms the nAb repertoire directed toward these antigens by clonal expansion, alterations in clonal dominance, and increased serum antibody levels. For example, the production of nAbs to N-acetyl-D-glucosamine (GlcNAc) shared with bacterial polysaccharide (PS) substantially increases in humans with neonatal infection of pneumococcus or group A streptococcus (GAS) levels. This has been demonstrated to provide protection against diverse pathogenic organisms that may be relevant to the development of allergic diseases. The proposed mechanisms of neonatal microbial exposure-induced protection against allergic airway inflammation is by engaging epitopes common to multiple allergens, including GlcNac (chitin), PC, and glucans, and this leads to interruption of microorganism–innate receptor interactions, which can result in an attenuated allergic airway response to fungi-, house dust mite-, and cockroach-associated allergens as seen in mouse models. Here, nAbs may abrogate the recognition of these moieties with innate receptors, which recognize the allergens and promote immune activation that results in sensitization [23]. However, significant protection against airway sensitization is dependent on the timing of induction and the antigenic targets of these Abs. The similarities between the murine and human natural antibody repertoires suggest that reduced microbial exposure in children may have the opposite effect, providing a potential mechanistic explanation for the hygiene hypothesis. In line with this, it is suggested that understanding the effects of childhood infections on the natural antibody repertoire and the mechanisms of antibody-mediated immune regulation observed in allergy models will lead to the development of prevention/interventional strategies for the treatment of allergic asthma [23].

In further support for the role of nAbs in protection against infections, the therapeutic preparation of polyclonal immunoglobulins, intravenous immunoglobulin (IVIG), rich in nAbs is commonly used for antibody replacement therapy in primary and secondary immunodeficiency patients [40]. Routinely, IVIG (400 mg/kg) is used in patients with X-linked agammaglobulinemia (XLA), common variable immunodeficiency (CVID), X-linked hyper-IgM, severe combined immunodeficiency, Wiskott-Aldrich syndrome, and selective IgG class deficiencies (Table 2) [40]. Variations in the processing of IVIG products and the geographical location of plasma donors might influence the efficacy of IVIG in immunodeficiency [41]. Interestingly, several lines of experimental and clinical evidence gathered in recent years reveal that therapeutic benefits of IVIG therapy extend beyond the mere anti-infective mechanisms via passive transfer of antibodies into the active role of immune homeostasis even in immunodeficiency [29, 40, 42–45].

Natural Antibodies in Tissue Homeostasis and Immune Tolerance

nAbs may have first arisen to reinforce an important goal of maintaining homeostasis. In line with this, as noted previously, the repertoire of nAbs is dominated by self-reactive ones (nAAbs) and contributes/mediates the immune regulatory functions of nAbs in physiology, and also the disease ameliorative effects of therapeutic immunoglobulin (IVIG) in autoimmune and inflammatory disorders. Interestingly, antibody immunodeficiencies are also associated with autoimmunity and inflammatory conditions, suggestive of a dysregulated immune status, thus supporting the role of nAbs in immune tolerance and maintaining tissue homeostasis [46].

Natural IgM: Role of nAbs in Apoptosis and Immune Regulation Apoptosis is an obligatory outcome of development, proliferation, and cell differentiation that continues throughout life. Every day, $>10^{11}$ cells in our body die by apoptosis, and therefore, apoptotic cell (AC) clearance is essential for tissue homeostasis. In health, ACs do not pose an immediate threat to the host, as there are redundant means mediated by soluble innate immune molecules, such as complement C1q mannose-binding lectin (MBL) and nAbs to ensure rapid and efficient cell corpse clearance by macrophages and DCs [47]. If the efficiency of AC clearance is limited,

Table 2 Therapeutic utility of IVIG in immunodeficiency, and autoimmune and inflammatory pathologies

Licensed FDA/EMA*	Off-label
• Primary immunodeficiencies (e.g., X-linked agammaglobulinemia (XLA), common variable immunodeficiency (CVID))	• Myasthenia Gravis[a]
• Secondary immunodeficiencies (e.g., B cell chronic lymphocytic leukemia (CLL), pediatric HIV infection)	• Autoimmune hemolytic anemia
• Idiopathic thrombocytopenic purpura[a]	• Acquired immune thrombocytopenias
• Kawasaki Disease [a]	• Juvenile idiopathic arthritis
• Chronic inflammatory demyelinating polyneuropathy [a]	• Anti-phospholipid antibody syndrome
• Guillain–Barré syndrome[a] [#]	• Lambert–Eaton syndrome
• Multifocal motor neuropathy[a]	• Dermatomyositis[a]
• Bone marrow transplantation	• Parvovirus B19-associated red cell aplasia
	• Anti-factor VIII autoimmune disease
	• Acquired von Willebrand disease
	• Autoimmune neutropenia
	• Steroid-dependent severe atopic dermatitis
	• Stiff person syndrome
	• Toxic epidermal necrolysis
	• Polymyositis
	• Multiple sclerosis
	• Rheumatoid arthritis and Felty's syndrome
	• Systemic lupus erythematosus
	• Autoimmune skin blistering diseases [a]
	• Antibody-mediated rejection of the graft
	• Graft versus host disease[a]
	• Autoimmune uveitis and birdshot chorioretinopathy
	• Streptococcal or staphylococcal sepsis and toxic shock syndrome
	• ANCA-positive systemic vasculitis
	• Graves ophthalmopathy

[a] Indicates pathologies for which evidence for the clinical benefits of IVG has been obtained through controlled clinical trials

[*] Licensed for use by US FDA and EMA, [#] Approved by European Medical agency (EMA) only

there can be progression to secondary necrosis and the ensuing release of nuclear Ags and other components of dying cells (danger-associated molecular patterns, DAMPS), which are believed to activate pattern-recognition receptors (PRRs) of innate immune cells that include TLR, leading to inflammatory responses. Necrotic cells can also release autoantigens that can select pathogenic B and T cell clones, which together can lead to the development of autoimmune disease in predisposed individuals [47, 48].

Newborn humans and naïve mice have considerable levels of nIgM that recognize AC membranes (ACMs), whereas even higher levels can be induced by intravenous infusions of large numbers of ACs [49, 50]. Furthermore, experimental models have shown that suppression of inflammatory arthritis mediated by ACs may require nIgM that can directly inhibit macrophage and DC activation [49] and may also promote IL-10–secreting B and T cells [51]. It is observed that these effects are facilitated mainly by nAbs to the oxidation-associated phosphorylcholine (PC) and malondialdehyde (MDA) neodeterminants on ACMs, which can distinguish healthy versus apoptotic cells [50]. Therefore, nIgM directed against PC and MDA can have two major regulatory functions, enhanced clearance of ACs by phagocytes (termed efferocytosis), and direct suppression of proinflammatory responses induced by agonists for TLR3, TLR4, TLR7, and TLR9 and likely many other innate pathways [49, 50]. In consensus with murine studies, observations in patients with systemic lupus erythematosus highlighted the association of nIgM levels in protection against autoimmunity. For example, decreased levels of anti-PC IgM Abs are characteristic features of active lupus compared with the disease in remission [52]. Therefore, nIgM, through clearance of apoptotic cells,

may serve as regulators of the innate immune system to help maintain homeostasis and, in certain cases, suppress the development of inflammatory and autoimmune diseases (reviewed in [53]).

Furthermore, nIgM is also implicated in suppression of disease-associated IgG autoantibody production, since insufficiency of serum IgM may predispose humans for the development of IgG autoantibodies [54]. It has also been argued that the protective effect of IgM may at times involve anti-idiotypic (i.e., targeting of the Ag receptors of some clonally related lymphocytes) downregulation of some autoimmune responses or result from the induction by some IgM anti-idiotypic Abs of apoptotic death of pathogenic B cell clones or the selection of other protective B cell subsets. Another important role of nIgM in tissue homeostasis implicates clearance of altered or malignant cells via complement-dependent cell lysis and induction of apoptosis [55]. The maintenance of tissue homeostasis by nIgM may also involve the enhanced clearance of misfolded proteins, which could have clinical implications for conditions like Alzheimer's disease in which pathogenesis results from the deposition of misfolded proteins such as β-amyloid plaques in the brain (Fig. 2) (reviewed in [53]).

Normal human plasma contains a substantial amount of nIgM. An IgM-enriched Ig preparation, Pentaglobin®, that contains 12% IgM has been successfully used for treating infections associated with sepsis in patients, as well as transplant rejection, and for certain inflammatory conditions in experimental models [53, 56]. Such preparations may also provide benefits to combat infections that arise in patients with autoimmune disease [57]. Interestingly, a natural human mAb, IgM22, that binds to oligodendrocytes and promotes their remyelination was recently tested in human clinical trial and has demonstrated safe profiles [53].

Natural IgG: Role of nAbs in Immune Tolerance/Homeostasis

As mentioned previously, in addition to nIgM, IgG also constitutes a major portion of nAbs (as nAAbs). There is little information on direct demonstration of the functions of nAbs in immune homeostasis. However, most of the functions that have been attributed to IgG nAbs are deduced from the wide range of observed effects of IVIG when administered to patients with autoimmune and inflammatory situations [29, 58]. IVIG symbolizes a complete repertoire of normal circulating IgG. The distribution of IgG subclasses and IgG glycosylation patterns in IVIG generally overlaps with normal human plasma/serum. Although a single donor might lack certain individual IgG specificities, it is likely to be compensated in IVIG because of pooling of plasma. As IVIG is nothing but pooled IgG from normal donors, the effect of IVIG likely represents a primordial function of circulating nIgG in regulating immune homeostasis [59]. Natural antibodies and natural autoantibodies with low to medium affinity are likely to be the major active components of IVIG, but these specificities are not in high frequencies. Thus, given the altered physiology in autoimmune patients, it is conceivable that these natural autoantibodies are needed at higher amounts than those present in the normal circulation of a donor.

IVIG is prepared from pools of plasma obtained from several thousand healthy blood donors, and hence, IVIG represents a privileged source of nAbs (nAAbs) [60]. Although initially conceived for the IgG replacement therapy of primary and secondary immunodeficiencies, following successful use of IVIG in immune thrombocytopenic purpura (ITP) by Paul Imbach [61], high-dose IVIG (1–2 g/kg) is now used for the immunotherapy of many autoimmune and inflammatory diseases including Guillain–Barré syndrome, Kawasaki disease, myositis, immune thrombocytopenic purpura, chronic inflammatory demyelinating polyradiculoneuropathy, and many others [42, 62, 63]. Newer indications are continuously being explored, and IVIG is currently used in more than 100 different diseases in an off-label manner (Table 2) [42, 58, 64]. As discussed below, numerous mutually non-exclusive mechanisms may play a role in the beneficial effect of IVIG therapy in these diseases. The success of IVIG in these wide-range pathologies provides strong arguments for the therapeutic value of nIgG.

The effective immunotherapy of autoimmune and inflammatory diseases using IVIG also led to the investigation of cellular and molecular mechanisms of action [65]. Autoimmune and inflammatory diseases are characterized by abnormal activation of the cells of innate and adaptive immune compartments and release of inflammatory mediators. The emerging evidence suggests that IVIG targets various arms of the immune system, culminating in inhibition of inflammatory cells and soluble mediators while reciprocally enhancing immune regulatory cells and their functions. Several mechanisms of action for IVIG have been proposed since its first successful therapeutic use in ITP [3]. It was thought initially that IVIG exerts a beneficial effect in autoimmune disease patients via saturation/blockade of Fc receptors on phagocytes such as monocytes and macrophages and reduces the immune complex-mediated activation of these innate cells [59, 66]. In addition, saturation of FcRn (neonatal Fc receptor), a protective receptor that prevents the catabolism of IgG, by IVIG is implicated in accelerated clearance of pathogenic antibodies and has a role at least in the initial phase of ameliorative effects of IVIG [65, 67]. IVIG has also been shown to neutralize pathogenic autoantibodies by anti-idiotypic Abs against idiotypes expressed by disease-associated autoantibodies (to factor VIII, acetylcholine receptor, thyroglobulin, DNA, and others) and by inhibiting autoantibody production by binding to autoreactive B lymphocytes [59, 65, 68]. Further, binding of IVIG to C3b and C4b fragments of complement, thereby inhibiting their tissue deposition as well as generation of the C5 convertase, and

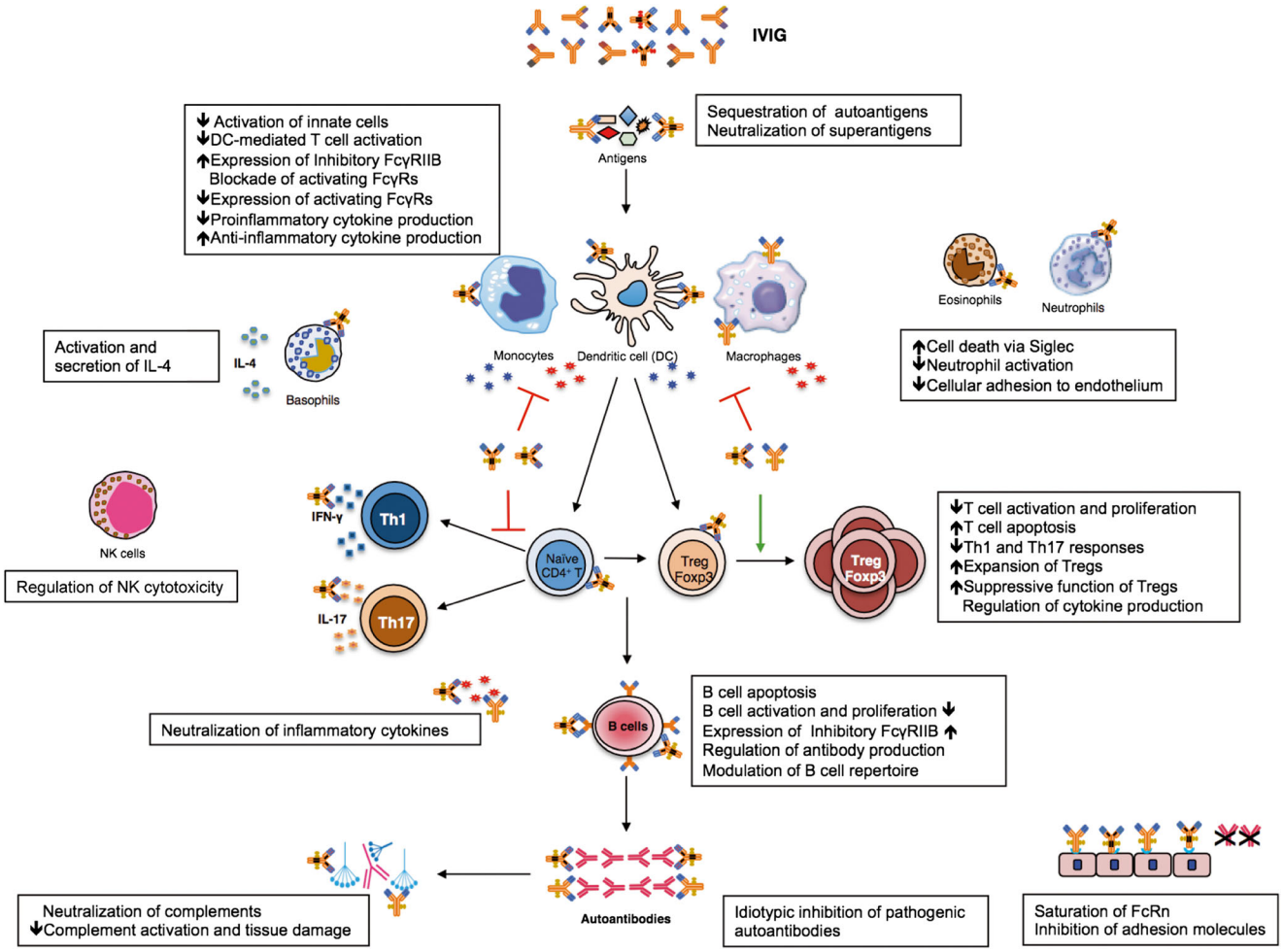

Fig. 3 The mechanisms of action of IVIG on various arms of autoimmune and inflammatory responses. The autoantigens endocytosed by the innate immune cells such as dendritic cells and macrophages are presented to the self-reactive T and B cells leading to the proliferation of autoreactive cells and production of inflammatory cytokines and autoreactive antibodies. IVIG targets different soluble and cellular compartments of the immune system to exert its therapeutic effects on diverse autoimmune diseases. IVIG neutralizes autoantigens and superantigens, and inhibits the activation of diverse innate immune cells such as dendritic cells, macrophages, monocytes, granulocytes, and NK cells. Concerning the effector phase of autoimmune response, IVIG inhibits the activation and proliferation of effector T (Th1, Th17) and B cells while enhancing the expansion and function of regulatory T cells (Tregs). IVIG also induces expression of inhibitory FcγRIIB in a subset of macrophages and B cells. Further, IVIG saturates the neonatal Fc receptors (FcRn), modulates the cytokine network, induces apoptosis of immune cells, neutralizes pathogenic autoantibodies by anti-idiotypic interaction, inhibits the activation of complements, and regulates the B cell repertoire. ADCC, antibody-dependent cell-mediated cytotoxicity; FcγR, Fcγ receptors; NK, natural killer cell

hampering the subsequent formation of C5-C9 membrane attack complex, as a consequence, prevents complement-mediated cell death and tissue damage. Additionally, IVIG neutralizes C3a and C5a anaphylatoxins via a $F(ab')_2$-mediated mechanism [62, 69]. IVIG also contains an array of anti-cytokine antibodies against various inflammatory cytokines, including granulocyte-macrophage colony-stimulating factor (GM-CSF) and B cell activating factor (BAFF), that can dampen inflammatory process [59, 70, 71].

Interestingly, $F(ab')_2$ and Fc portions of IVIG can inhibit lymphocyte (B and T cells) proliferative responses and modulate inflammatory cytokines [63, 72, 73]. In addition, IVIG can also induce apoptosis of mononuclear cells implicating death receptor Fas [74], polymorphonuclear cells via Siglec [75], and also conversely block of Fas in toxic epidermal necrolysis to inhibit apoptosis [76]. IVIG also normalizes the functions of DCs and other innate immune cells [43, 77, 78]. Further, IVIG induces expansion of regulatory T cells (Tregs) and reciprocally inhibits Th17 cells [79–89]. Interestingly, recent studies in mouse models suggest that α(2,6)- sialylated Fc of IVIG signals through type II lectin receptors to enhance inhibitory FcγRIIB on effector macrophages via basophil-secreted IL-4 and induce Tregs by dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN)-induced IL-33 secretion [90, 91]. However, translation of these findings to humans failed to recapitulate the mechanisms although requirement for sialylation has been confirmed in other experimental

Table 3 Comparison of natural antibodies, immune antibodies and pathogenic autoantibodies

Feature	Pathogen-specific immune antibodies	Natural Antibodies (nAbs)		Pathogenic autoantibodies
		Pathogen cross-reactive	Self-reactive	
Develops following	Infection or immunization	Constitutive/Homeostasis	Constitutive/Homeostasis	Uncontrolled autoimmunity
Influence of external antigen on clonal diversity	Yes	Yes	No	Yes?
Source/Cells				
Mouse	B2*, also B1*	B1 mainly	B1 mainly	B2 mainly
Human	$CD20^{-}CD27^{high}CD38^{high}$	$CD20^{+}CD27^{+}CD43^{+}CD70^{-}CD38^{mod}$	$CD20^{+}CD27^{+}CD43^{+}CD70^{-}CD38^{mod}$	$CD20^{-}CD27^{high}CD38^{high}$
Somatic hypermutation	Present	Nil to minimum	Nil to minimum	Present
Isotypes	IgG mainly, also IgA, IgM, IgE	IgM mainly, also IgG and IgA	IgM and IgG, also IgA	IgG mainly, also IgM and IgA
T cell dependence for induction	Yes	Nil to minimum	Nil to minimum	Yes
Affinity	Usually High	Low	Low	High
Avidity	High	High	High	High
Reactivity	Pathogen epitope specific	Self, cross-reactive to conserved epitopes	Polyreactive to self-antigens	Specific self-antigen
Examples of antigens	Influenza Hemagglutinin	Phosphorylcholine (PC)	HLA class I, CD4	Citrullinated protein antigens
Functional outcome	Prevention and control of pathogen-induced disease	Prevention of pathogen infection	Beneficial housekeeping tissue homeostasis functions	Inflammation and tissue destruction leading to disease

*B1: IgM^{high}, IgD^{low}, $CD19^{high}$, $B220^{low}$, $CD23^{-}$, and $CD43^{+}$; $CD5^{+}$ (B1a) or $CD5^{-}$ (B1b)

*B2: IgM^{low}, IgD^{high}, $CD19^{high}$, $B220^{+}$, $CD23^{+}$, and $CD43^{-}$

models [78, 79, 82, 83, 88, 89, 92]. Studies in humans have revealed that IVIG can directly interact with basophils to induce IL-4 secretion and can act either directly on Tregs or on DCs to expand Tregs [46, 65, 93–96].

In summary, IVIG can interfere at all steps of immune response from the early initiation phase to the later effector phase that leads to clinical disease (Fig. 3). Accordingly, binding of nAAbs to antigens contributes to their internalization by antigen-presenting cells and thus modulates the processing of antigens and their subsequent presentation to T cells. Of particular interest for the dissection of the effects of IVIG in autoimmune diseases, it is the role of nAAbs in the inhibition of soluble mediators of inflammation (including complements and cytokines), maintenance of cellular homeostasis, in preventing the expansion of specific autoreactive clones of T and B cells, and in the ability of nAAbs to regulate self-reactivity (pathogenic autoantibodies). Thus, the mechanisms of action of IVIG are complex and unlike other specific antibody-based therapies that are either in clinic or in development [97–102], a single mechanism might not account for its therapeutic benefit in autoimmune diseases [42, 65, 103].

In line with the immune modulatory effects of IgG and IgM nAbs, other subclasses of normal Igs, particularly IgA, have been explored. Preclinical evaluation of pooled IgA (analogous to IVIG) provided evidence that normal IgA also ameliorates inflammation and hence demands further clinical evaluation [104, 105].

Conclusions

Natural antibodies are distinct from pathogen-specific immune antibodies and pathogenic autoantibodies (Table 3). Notably, nAbs can exert immune modulatory functions as evidenced by activating as well as inhibitory effects based on the host immune status (immunodeficiency versus inflammatory). This phenomenon is similar to the diverse effects of B cells (source of Abs/nAbs) on different immune cells, e.g., DCs, depending on the activation stimuli [106–110]. More than half of the nascent B cells in humans initially express autoreactive antibodies. However, most of these autoantibodies are removed from the repertoire at two checkpoints before maturation into naive B cells. A third checkpoint excludes remaining autoantibodies from the antigen-experienced IgM^+ and IgG^+ memory B cell pool [111, 112]. Nevertheless, low-affinity self-reactive antibodies of all classes IgM, IgG, and IgA are frequently found in the serum of normal individuals. However, little attention has been paid to their role in immune responses or how their production can be manipulated to the host's advantage [113, 114]. The inordinate focus on the dogma that high-affinity IgG response is the goal of immunization and that so-called sticky, low-affinity Abs should be avoided is the primary reason for this dearth of information. Recent investigations in the field should lead to more focus on the functions of this first-line component of the adaptive immune response.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval and Informed Consent Not applicable.

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