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REVIEW



The therapeutic implications of activated immune responses via the enigmatic immunoglobulin D

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ABSTRACT

Immunoglobulin D (IgD) is an enigmatic antibody and the least appreciated member of the immunoglobulin (Ig) family. Since its discovery over half a century ago, the essence of its function in the immune system has been somewhat enigmatic and less well-defined than other antibody classes. Membrane-bound IgD (mIgD) is mostly recognized as B-cell receptor (BCR) while secreted IgD (sIgD) has been recently implicated in 'arming' basophils and mast cells in mucosal innate immunity. Activations of immune responses via mIgD-BCR or sIgD by specific antigens or anti-IgD antibody thereby produce a broad and complex mix of cellular, antibody and cytokine responses from both the innate and adaptive immune systems. Such broadly activated immune responses via IgD were initially deemed to potentiate and exacerbate the onset of autoimmune and allergic conditions. Paradoxically, treatments with anti-IgD antibody suppressed and ameliorated autoimmune conditions and allergic inflammations in mouse models without compromising the host's general immune defence, demonstrating a unique and novel therapeutic application for anti-IgD antibody treatment. Herein, this review endeavored to collate and summarize the evidence of the unique characteristics and features of activated immune responses via mIgD-BCR and sIgD that revealed an unappreciated immune-regulatory function of IgD in the immune system via an amplifying loop of anti-inflammatory Th2 and tolerogenic responses, and highlighted a novel therapeutic paradigm in harnessing these immune responses to treat human autoimmune and allergic conditions.

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Introduction

Immunoglobulin D (IgD) is the least recognized member of the immunoglobulin (Ig) antibody family that includes IgA, IgE, IgG and IgM. Since its discovery by Rowe and Fahey over half a century ago [1], the functional significance of IgD in the immune system has been somewhat enigmatic and less clearly defined in comparison to other antibody classes [2]. The expression of IgD emerged in the adaptive immunity at roughly the same time as IgM about 500 million years ago [2–4]. The continued preservation of IgD expression in some (including mouse, primates and human) but not all mammalian species during the evolution of mammals suggests that it may confer a survival advantage and play a significant role in the host's immune [5,6].

The expression of IgD protein (~185 kDa M.W.) can be detected as either membrane-anchored IgD (mIgD) or secreted IgD (sIgD). The full length IgD mRNA is generated via alternative splicing of the

variable region VDJ gene mRNA onto the delta (D) instead of mu (M) heavy chain constant Fc region mRNA by class-switch recombination process that allows IgD to retain the same antigen binding specificity and affinity as germline repertoire IgM [2,3], suggesting IgD may have a similar function as IgM. Indeed, much of the appreciations for IgD came from its role together with IgM as the antigen-recognizing components of B-cell receptor (BCR) complex [7,8], which would suggest a potentially critical role in shaping the development of B cells and antibody responses. However, IgD-knockout and IgM-knockout mouse models showed a relatively intact B-cell development, normal general and antibody responses to foreign antigen immunizations [9–12], demonstrating a non-essential role of mIgD and a compensatory relationship between IgD and IgM in their functions as BCR. Nevertheless, it is clear from experimental data that activated signals by antigens via mIgD-BCR, just as mIgM-BCR, plays an important role in determining both the survival vs. death of maturing B cells

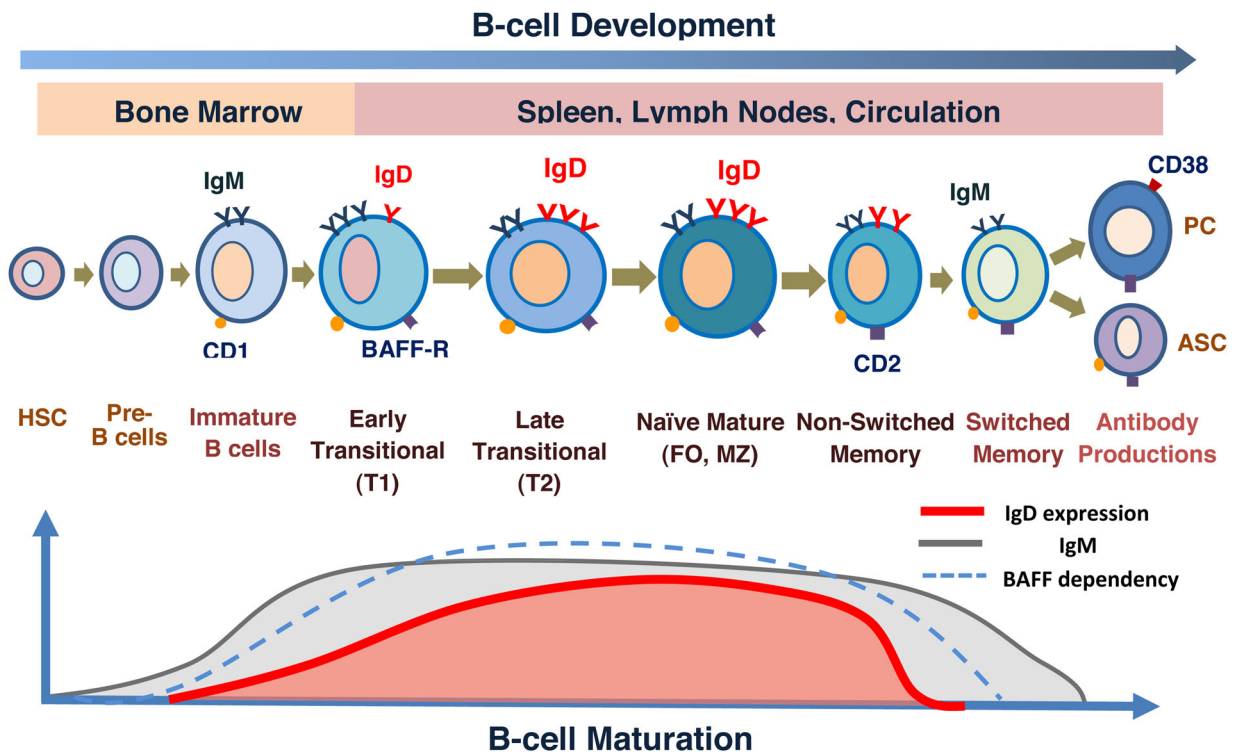


Figure 1. A diagrammatic representation of the expression of IgD and IgM on B cells and their survival dependency on the maturation growth factor BAFF during different stages of development of human and mouse B cells. ASC, Antibody-secreting cells; BAFF, B-cell activating factor; FO, Follicular; HSC, Hematopoietic stem cells; MZ, Marginal zone; PC, Plasma cells; T1/2, Transitional stage 1 or 2.

during clonal selection in an affinity-dependent manner [13,14].

Interestingly, mIgD is highly expressed on mature B cells but only miniscule amounts of sIgD can be detected in the serum of healthy individuals. Circulation levels of sIgD make up just under 0.25% of the total serum Ig, in comparison to IgG (75%), IgA (10–15%), IgM (5–10%), but significantly higher than IgE (0.002%) [15,16]. Its shorter half-life of about 3 days also distinguishes it from the other more abundant antibody classes IgA (6 days), IgM (10 days) and IgG (20 days) [2,16]. Despite the miniscule circulation level, sIgD can be detected in the tonsil, nasal mucosa, and lacrimal glands [3,4,16], suggesting a role in mucosal immunity [16]. Unlike other secreted antibody classes, sIgD does not appear to have a specific Fc-region effector and complement fixation function [2,3,16]. Earlier pioneer studies have also suggested that sIgD can bind to T cells [17,18], monocytes [19], and basophils [20,21] via a previously unidentified IgD receptor [17,18]. Indeed, a later study confirmed that sIgD can bind strongly to the cell surface of innate immune cells like basophils, monocytes, and mast cells [22]. These findings demonstrate that sIgD does possess some capacities to directly modulate these innate immune cells via a putative cell surface receptor.

In the past, research studies have utilized monoclonal and polyclonal antibodies (mAb and pAb) specific for IgD (anti-IgD Ab) as methods to activate B cells specifically via mIgD-BCR to study B-cell development and antibody responses. The findings from these studies were sometimes conflicting due to the different characteristics and dosages of the anti-IgD Ab clones used in the experiments [23–31]. However, it was clear from these earlier studies that treatments with anti-IgD mAb or pAb typically activate a complex mix of polyclonal B-cell responses, both T-helper cell type-1 (Th1) and type-2 (Th2) cytokine responses, and polyclonal antibody productions [23–31]. It has also been noted in earlier reports and confirmed in later studies that anti-IgD Ab treatment can also directly modulate innate immune cells like monocytes, basophils and mast cells in vitro and in vivo [19–22]. Due to its broad immune activating properties across the innate and adaptive immune responses in vivo, it was suggested that such immunomodulatory effects of anti-IgD Ab treatment would have the potential to exacerbate the onset of autoantibody-mediated autoimmune diseases, Th1-mediated inflammation, or Th2-mediated allergic reactions [28,30–32]. Contrary to the earlier views, treatments with anti-IgD Ab have shown to suppress and ameliorate inflammations and

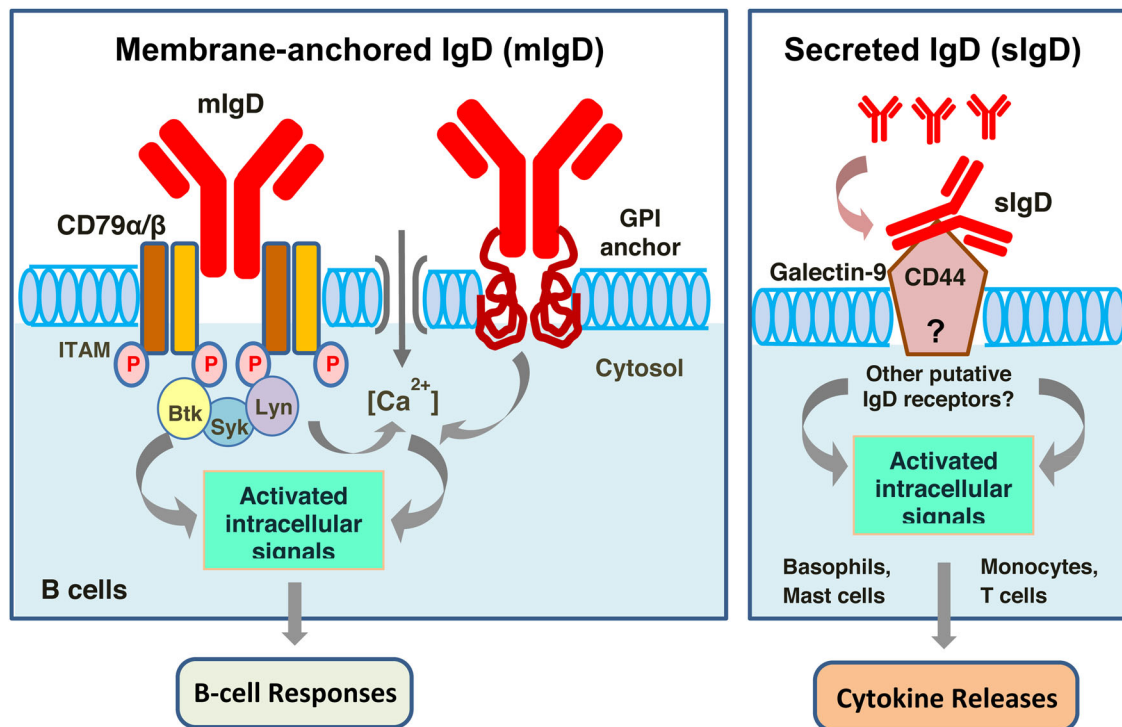


Figure 2. A diagrammatic representation of membrane-bound IgD (mIgD) in B-cell receptor (BCR) complex and soluble secreted IgD (sIgD) bound on cell surface of innate immune cells.

disease severities in a number of mouse models of autoimmune diseases and allergic skin inflammations [33–36]. Collectively, these findings demonstrated an intriguing and novel therapeutic effect of anti-IgD Ab via activation of IgD-mediated immune responses.

This review therefore endeavored to collate and summarize the current published evidence, and discussed the therapeutic implications of immune responses activated via mIgD-BCR on B cells and sIgD bound on the cell surface of innate immune cells. The roles of mIgD-BCR in clonal selection and its intracellular signals are extensively discussed elsewhere [13,14], and thus are not covered by this article. Herein, this review aimed to: (1) summarize the characteristic features of the adaptive and innate immune responses activated via IgD; (2) highlight the therapeutic implications of anti-IgD Ab treatment in autoimmune diseases and allergic conditions; and (3) discuss the underlying advantages of the mechanisms of action of anti-IgD Ab treatment.

Expression of IgD and in vivo immune responses

Expression of mIgD-BCR

The expression of IgD mRNA is regulated by Pten-mediated signals in B cells [37]. The protein expression of mIgD-BCR on human and mouse B cells is

detected after the appearance of mIgM-BCR expression during B-cell maturation. It first appears on immature B cells and then gradually increases from immature transitional stage 1 (T1) B cells (CD19 + CD27^{neg} IgM^{hi} IgD⁺) to T2 B cells (CD19 + CD27^{neg} IgM^{hi} IgD^{hi}), and peaks from the development of naïve mature B cells through to the differentiation into non-switched memory B cells (CD19 + CD27 + IgM + IgD⁺) (Figure 1). Upon activation by antigens, naïve mature B cells differentiate into class-switched memory B cells (CD19 + CD27 + IgM + IgD^{neg}), which completely lose mIgD expression but retain mIgM-BCR expression and functions that can differentiate further into different classes of antibody-secreting B cells or plasma cells [38]. For this reason, mIgD and mIgM are commonly used as surface markers to identify immature transitional and mature B cells, to distinguish non-switched and class-switched memory B-cell populations [38]. Both mIgD and mIgM are anchored to cell membrane via adaptor transmembrane protein heterodimer CD79α and CD79β [39–41], which mediate all mIgM-BCR and mIgD-BCR intracellular signals (Figure 2). In the absence of CD79α/β expression, mIgD can be anchored to cell membrane by transmembrane glycosyl-phosphatidylinositol (GPI) molecule [42], which can also mediate intracellular signals of activated mIgD-BCR [43].

Table 1. A summary of the immune responses activated via IgD by anti-IgD Ab treatment in pre-clinical and experimental animal models.

Animal models	Antibody clones	Therapeutic effects	Reported immune responses in vivo	Adverse immune effects	Ref.
Normal Mouse	<i>Polyclonal goat anti-mouse IgD IgG fraction</i>	N/A	• Deplete B cells, polyclonal B-cell activations • Induce IgD, IgM, IgG1, IgE • Induce IL10, IL4 productions • Increase FcϵR + basophils	N/R	[20–31,68,69]
Mouse IgD-Knockout in Autoimmune Lupus (MRL/lpr)	<i>IgD-deficiency in lupus-prone mouse</i>	N/A	• Increase IgM, IgG2a/2b, and IgG3 autoantibodies • Reduced mature B cells' death	Exacerbate lupus glomerular nephritis	[61]
Mouse IgD-Knockout in Allergic Lung Inflammation	<i>IgD-deficiency in OVA-induced sensitization</i>	N/A	• Increase inflammatory immune cell infiltrations • Increase basophil and mast cell degranulation, and IgE binding to basophils	Exacerbate lung inflammation	[110]
Rat Autoimmune EAE	<i>MBP-conjugated mouse anti-rat IgD mAb (MARD-3/OX60)</i>	Suppress EAE severity and incidences	• B-T cell antigen presentation? • Induce suppressor T cells? • Th2 cytokine productions?	N/R	[63]
Mouse Autoimmune Lupus (MRL/lpr)	<i>Dextran-conjugated mouse anti-mouse IgD mAb (Hδa/1)</i>	Reduce skin vasculitis, nephritis, proteinuria, Increase survival rates	• Increase C3 deposits • Increase IgM autoantibodies • Reduce IgG2a/b and IgG3 autoantibodies	N/R	[64]
Mouse Autoimmune Arthritis (CIA)	<i>Monoclonal mouse anti-mouse IgD mAb (AMS-9.1)</i>	Suppress bone and joint inflammation and damages	• Deplete T2 and mature B cells • Increase tolerogenic immature T1 B cells, Breg and Treg cells	N/R (Normal responses to vaccines)	[33]
Mouse Skin Allergy (CHS)	<i>Monoclonal mouse anti-mouse IgD mAb (AMS-9.1)</i>	Suppress skin thickening and inflammation	• Reduce IgG2a autoantibody • Deplete mature B cells but increase Breg and Treg cells • Enhance allergen-specific IgG1, total IgE and IgM productions,	N/R	[34]
Mouse Autoimmune Skin Blister (EPA)	<i>Polyclonal goat anti-mouse IgD IgG fraction</i>	Suppress skin blister and inflammation	• Increase IL10 productions • Increase IgM-secreting plasma • Induces Breg and Treg cells	N/R (Normal responses to vaccines)	[35]
Anti-IgD Superantigen Transgenic Mouse	<i>Monoclonal mouse anti-mouse IgD mAb (AMS-9.1)</i>	Negate proliferative effects of excess BAFF cytokine	• Deplete T2 and mature B cells • Increase immature T1 B cells • Suppress IgA but promote IgM and IgE productions • Increase IgM-secreting plasmablasts and B-1 B cells	N/R (Normal response to vaccines and infections)	[65]
Non-human primates (rhesus monkeys)	<i>Polyclonal goat anti-human IgD antiserum and IgG fraction</i>	N/A	• Deplete IgD + B cells • Induce blastogenesis and hypergammaglobulinaemia (only in antiserum group) • Increase IgG productions	Skin rash & fever chills in anti-serum group but not IgG fraction	[118]

Breg/Treg, regulatory B and T cells; CIA, Collagen-Induced Arthritis; EAE, Experimental Allergic Encephalomyelitis; EPA, Epidermolysis Bullosa Acquisita; MBP, Myelin Basic Protein; N/A, Not Available; N/R, None Reported; T1/2, Transitional Stage 1 and 2.

Activated immune responses via mIgD-BCR on B cells

Over the past decades, a number of pioneer studies have utilized the hen-egg-lysozyme (HEL)-specific mIgD-BCR (HEL-IgD) transgenic mouse model or anti-IgD Ab treatments to activate B cells to study the effects of activated mIgD-BCR on the development of B cells in peripheral tolerance, clonal selection, and antibody productions. The findings from these studies suggested that activated mIgD-BCR can induce both negative selection (deletion by apoptosis, developmental arrest, and anergy) and positive selection

(survival, proliferation and accumulation) of B cells [44–47]. This discrepancy may be attributed to the different types of models and binding affinity of the HEL-IgD and anti-IgD Ab clones, with HEL-IgD transgenic mice model demonstrating monoclonal B-cell activation [44–47] whereas anti-IgD Ab treatments demonstrating polyclonal B-cell responses [23–28]. It has also been suggested that tonic signals from mIgD-BCR may contribute to the positive selection and survivals of autoreactive B cells leading to an accumulation of anergic but autoreactive IgD + mature B cells in both human and mouse

studies [48–50], which in turn provide a pool of autoreactive precursor cells for the generation of pathogenic autoreactive antibody-secreting cell (ASC). These mature B cells are also more prone to loss of tolerance and activation by self-antigen compared to the more tolerogenic immature B cells [51–53]. These autoreactive IgD + mature B cells and ASC are then expanded upon their reactivations by autoantigens under autoimmune-promoting conditions such as high levels of BAFF cytokines and chronic inflammation stimuli [46,47,51–59]. These evidences therefore support the notion and a common view that polyclonal activations of B cells via mIgD-BCR may potentiate and exacerbate the onset of autoimmune diseases by reactivations of existing autoreactive IgD + mature B cells [46,51–53,56,60]. However, these views were extrapolative and inconclusive because these studies were not performed or tested in the context of an autoimmune disease model. Indeed, IgD-knockout mice crossed with lupus-prone MRL/lpr mice demonstrated that the loss of IgD expression exacerbated disease severity and enhanced Th1-related autoantibody productions in murine lupus model, suggesting a potential function of IgD expression in dampening pro-inflammatory Th1-related autoantibodies and autoimmune diseases [61]. This was in contrast to IgM-knockout mice which exhibited resistance to the development of arthritic inflammation and have reduced Th1-related autoantibody productions in collagen-induced arthritis (CIA) mouse model [62]. These IgD- and IgM-knockout mouse studies in autoimmune disease animal models therefore demonstrated that mIgM-BCR-mediated signals are required for the development of autoimmune diseases whereas mIgD-BCR-mediated signals may act to dampen and suppress rather than exacerbate autoimmune diseases.

Similarly, the use of anti-IgD Ab as a method to activate polyclonal B cells also demonstrate activation of mIgD-BCR plays a diverse role in the survival and proliferation of B cells, and serum Ig productions in vivo [23–31]. Earlier works in normal mouse models have demonstrated that cross-linking of mIgD-BCR led to polyclonal activations of B cells and increases in serum Ig productions of mainly of IgM, IgG1 and IgE classes [23–31]. Anti-IgD Ab treatment was therefore thought to have the potentials to activate polyclonal responses of autoreactive IgD + mature B cells and their autoantibody productions, and thereby exacerbate the onset of autoimmune diseases and allergic reactions.

On contrary to this expectation, a number of studies have instead demonstrated activation of mIgD-

BCR with anti-IgD Ab treatment led to the suppression of autoimmune diseases (Table 1). The early evidence of a suppressive effect of targeting mIgD-BCR by anti-IgD Ab were demonstrated in the experimental allergic encephalitis (EAE) [63] and systemic lupus erythematosus (SLE) MRL-lpr mouse models [64], using peptide-conjugated and dextran-conjugated anti-IgD Ab as treatments respectively. However, in both studies, the authors attributed the suppressive effects to the presence of the conjugates and autoantigen presentation to T cells rather than the activating property of anti-IgD Ab [63,64]. In contrary to this notion, treatments with an unconjugated mouse anti-mouse IgD mAb that has been known to activate B cells in vivo [26,33] led to the suppression and amelioration of autoimmune inflammations in CIA mouse model [33] and allergic skin inflammations in chronic contact hypersensitivity (CHS) mouse model [34]. This unexpected and novel therapeutic effect of anti-IgD Ab treatments were later confirmed by two independent studies in two different mouse models of autoimmune diseases [35,36]. One of these studies utilized a polyclonal IgG fraction of goat anti-mouse IgD pAb, which strongly activates polyclonal B-cell responses in vivo [24–28], in mouse model of autoantibody-mediated epidermolysis bullosa acquisita (EBA) skin autoimmune conditions [35], and the other used a mouse anti-IgD mAb in a Th1-mediated CIA mouse model [36]. Interestingly, treatments with anti-IgD Ab in these studies were consistently effective only when administered soon after the onset of disease inflammation [33–36], demonstrating a therapeutic effect rather than a preventive or an exacerbating effect on autoimmune diseases. Consistent with this notion is the evidence that the transgenic mice model constitutively expressing anti-IgD mAb, using the exact same anti-IgD mAb clone as reported in the therapeutic treatments in CIA [33] and CHS [34] models, as a superantigen specific for mIgD-BCR activation shows no signs of autoimmune lupus or immunopathology despite the continuous activation of IgD + B cells due to anti-IgD superantigen expression or even in the presence of constitutively high levels of autoimmune-promoting B-cell activating factor (BAFF) cytokine in cross-breeding with BAFF transgenic mice [65]. Similarly, short course of repeated treatments with anti-IgD mAb can also override the proliferative effects of excess BAFF cytokine on mature B cells in vivo [66], demonstrating activating mIgD-BCR can negate the stimulatory effect of BAFF by suppressing the upregulation of BAFF receptor expression on activated B cells [33,65–67]. In

all these studies, and as shown in previous studies, activation of B cells by anti-IgD Ab resulted in a selective depletion of IgD^{hi} IgM⁺ T2 and mature naive B cells while the more tolerogenic immature IgD^{neg/low} IgM^{hi} T1 B cells were spared [23,33–35,65,66]. Activation of mIgD-BCR by anti-IgD Ab treatments also consistently led to the induction of IL10-producing B cells and plasmablasts, and regulatory T cells [30,33–35,66,68,69], which all have potent tolerogenic and suppressive effects on both Th1-mediated autoimmune diseases and Th2-mediated allergic inflammations [70]. In addition, activated mIgD-BCR resulted in a decrease of Th1-related antibody responses (IgG2a, IgG2b) while promoted a skew toward a Th2-related cytokine (IL4, IL10) and polyclonal antibody responses (IgG1, IgE) [27–30,33–35,61,65–69], that can also have suppressive effects on Th1-mediated inflammations. Collectively, the compelling evidence from the studies of IgD-knockout in MRL/lpr mouse model [61], IgD superantigen transgenic mice [65], and treatments with an activating anti-IgD Ab in mouse models of autoimmune diseases [33–36] demonstrate that activated immune responses via mIgD-BCR can exert a suppressive effect instead of an exacerbating effect on Th1-mediated autoimmune diseases.

Production of sIgD

Circulating sIgD exists as a monomer glycoprotein antibody at minute concentrations in the serum of healthy individuals, making up just under 0.25% of the total serum Ig [71]. Just like other secreted antibody classes, sIgD monomer glycoprotein also contains glycosylated motifs within its Fc, Fd and hinge regions that play a critical role in the correct folding assembly and secretion of sIgD [71,72]. Despite the minute serum concentration, sIgD can be detected in mucosal tissues of upper respiratory tracks such as the tonsils, lacrimal and salivary glands, and in nasal mucosal secretions [2–4,16]. The detection of sIgD in mucosal tissues is coincided with the presence of IgD⁺-only B cells and plasmablasts, suggesting local responses and productions rather than diffusions of circulating sIgD [73,74]. This presence of sIgD and sIgD-secreting B cells in the nasal airway mucosa thus suggests a potential role of sIgD in mucosal immunity against pathogens encountered in respiratory track [16]. Indeed, respiratory pathogen *Moraxella catarrhalis* can bind strongly to mIgD and vigorously activate polyclonal B-cell proliferation and productions of IgM, IgG and IgA by human tonsil B cells in the presence of Th2 cytokines (IL4, IL10) [75,76].

Furthermore, nasal secretions and serum levels of sIgD are often elevated in patients with chronic obstructive pulmonary diseases [77].

The serum levels of sIgD are also increased in patients of periodic fever or hyperimmunoglobulinemia D syndrome (HIDS) [78–80], and in some allergic conditions [73,74,81–85] and chronic infections [77,86–89]. The elevated levels of sIgD in these conditions are indications of early B-cell activations [88,89]. The synthesis and secretions of both human and murine sIgD can also be induced by B-cell activations with allergen-specific immunotherapy (AIT) [85] or anti-IgD Ab treatments [90–92]. Similar to the production of Th2-related IgG1 and IgE, the synthesis and secretion of sIgD also requires the presence of Th2 cytokines (IL4, IL10) but is suppressed by Th1 cytokines (IFN γ) [90–92]. This dichotomy of Th1/Th2 dependency suggests that sIgD responses belong to the group of Th2-mediated antibody responses (IgG1, IgE) which have a cross-inhibitory effect on the Th1-driven responses that favor IgG2a and IgG2b productions [93]. This notion is further supported by the evidence of a positive correlation between total IgD and IgE productions in some patients with Th2-related allergic conditions [82–84]. As mentioned above, sIgD retains the same antigen specificity as natural IgM repertoire [3,49,50], which are often autoreactive and polyreactive to both endogenous self-antigens and infectious pathogens [94,95]. Thus, it is not surprised that sIgD are also reactive to some of these pathogens [96–99] as well as autoreactive to self-antigens of autoimmune conditions [100–103]. Collectively, these evidence showed the fundamental features of sIgD responses, in an analogy to the other more abundant and well-defined antibody classes, may be characterized as early local mucosal antibody responses (like IgA) in the upper respiratory track that is positively regulated by Th2 cytokines (like IgE and IgG1) and have the same or similar antigen specificities and affinities as polyreactive natural IgM antibodies.

Activated immune responses via surface-bound sIgD on T cells and innate immune cells

It was thought early on that IgD is only present on B cells as BCR expression but not present on other immune cells due to the minute serum concentrations and a lack of sensitive detection techniques and studies of sIgD on these cells. However, the early pioneer works by Thorbecke GJ and colleagues have consistently demonstrated the presence of IgD on human and murine CD4⁺ and CD8⁺ T cells [17,18]. Since T

cells do not express IgD mRNA the detection of IgD on T cells raised the possibility of a putative and not yet defined receptor for sIgD. Further evidence showed that the additions of purified sIgD to human monocyte cultures could enhance LPS-induced secretions of pro-inflammatory cytokines TNF α and IL1 β [19], and sIgD could induce T cell's cytokine productions in culture [104], further demonstrating sIgD could directly interact with these cells via the putative sIgD receptor and modulate their immune responses. Later investigations went on to demonstrate that, as a glycoprotein like IgA1 and IgE, sIgD could indeed bind to human and murine T cells via the glycosylated motifs on its hinge, Fc and Fd regions, which allow sIgD to interact with glycan-binding lectin expressed on these cells [105–109]. Indeed, such interaction has been confirmed in recent studies showing sIgD can bind brightly and strongly to basophils and mast cells via Galectin-9 and proteoglycan CD44 [22,74,110], and possibly in a much lesser extent to monocytes [22,33] and neutrophils [22]. These new evidence in human and murine studies thus provide a new insight into a previously unrecognized capacity of sIgD to bind to T cells and innate immune cells to directly modulate their activities in vivo.

The binding of sIgD to basophils and mast cells suggests that, just like mIgD-BCR on B cells, these innate immune cells can be activated by both specific antigens (self or foreign) via antigen-binding variable regions of sIgD or by treatment with anti-IgD Ab that binds specifically to the heavy chain of sIgD (Figure 2). Indeed, ligations of surface-bound sIgD by soluble antigens or anti-IgD Ab treatment activates basophil and mast cells to secrete anti-microbial molecules (β defensin-3, cathelicidin, SPAG11, CRP), chemokines (IL8, CXCL10), both pro-inflammatory Th1 cytokines (IL1 β , TNF α) and Th2 cytokines (IL4, IL10, IL13), and B-cell stimulatory cytokine BAFF [22,74,110], suggesting a role of sIgD in arming and activating the mucosal innate immune responses [22]. Co-cultures of sIgD-activated basophils or mast cells with B cells significantly enhanced the productions of Th2-related antibody IgG1 and IgE [74,110], demonstrating the ability of sIgD to amplify Th2-mediated antibody responses via basophils and mast cells, and strengthening the notion of a Th2-favoured immune response by anti-IgD Ab treatment in previous studies mentioned above.

Collectively, the evidence of an amplified Th2 cytokine and Th2-related antibody responses by 'sIgD-armed' basophil and mast cells, which are highly implicated in Th2-mediated allergic responses, suggest activations of these innate immune cells with anti-IgD Ab treatment could thereby potentially exacerbate

allergic inflammation in vivo. Again contrary to this conventional paradigm, anti-IgD mAb treatment suppressed severe allergic skin inflammation and thickening in murine models of chronic CHS despite the presence of an apparently enhanced allergen-specific IgG1 and polyclonal total IgE production as well as an increased infiltration of mast cells at the site of inflammation, suggesting an anti-inflammatory Th2 immune response rather than a pro-inflammatory Th2 immune response [34]. On this basis and other evidence, it was proposed that the fundamental characteristics of in vivo immune responses activated by anti-IgD Ab may have contributed to this anti-inflammatory Th2 response [34,111]. Such mechanisms may be attributed to: (1) a polyclonal IgE response that may compete out the synthesis and binding of pathogenic allergen-specific IgE; (2) a polyclonal and specific IgG1 responses that can bind and activate inhibitory Fc γ IIB receptor pathway [112–114]; (3) an induction of regulatory B cells and regulatory T cells [33–35,68,69] or even IL10-producing mast cells [74,115,116]. It was also suggested that anti-IgD Ab may also have a direct effect via sIgD bound on surface of basophils and mast cells [34]. Consistent with this notion is the evidence of ligation of sIgD on human basophils and mast cells by sIgD-specific allergens or anti-IgD mAb treatment can inhibit sIgE-activated degranulation and the release of histamine from basophils and mast cells [22,110], suggesting activated immune responses via sIgD on basophils and mast cells can suppress a key process in Th2-mediated allergic immune reactions. Such notion is also supported by the evidence of IgD-knockout mice in ovalbumin (OVA)-induced allergic lung inflammation model which has showed the absence of IgD expression resulted in a significant increase of degranulated product Mcpt8, inflammatory markers and bronchoalveolar lavage infiltrations of pro-inflammatory immune cells, demonstrating a suppressive function of sIgD on allergic inflammations in an animal model [110]. This notion of a suppressive effect on allergic response is further strengthened by reports of an increase in allergen-specific sIgD productions in house dust mite-sensitized asthmatic and egg/milk allergic patients who successfully desensitized and developed tolerance to allergens but not in those failed to respond to immune tolerance induction in AIT treatments, suggesting an association between allergen-specific sIgD productions and immune tolerance to allergens [85,110].

Taken together, these evidence demonstrate that activated immune responses via sIgD bound on the surface of basophil and mast cells, while eliciting an

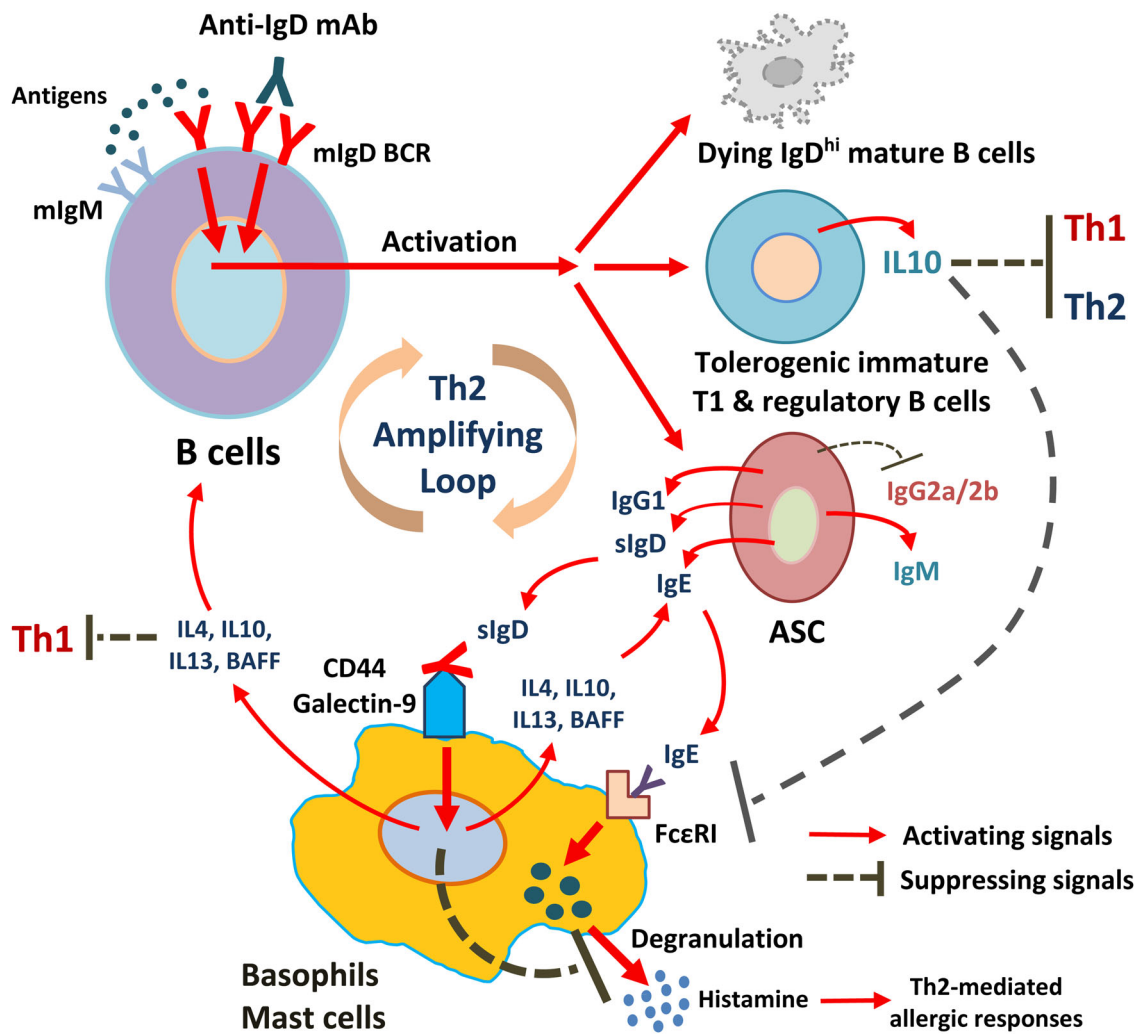


Figure 3. A diagrammatic representation of the putative amplifying loop of anti-inflammatory Th2 and tolerogenic negative feedback responses via mIgD BCR and sIgD activated by anti-IgD antibody (Ab) or IgD-specific antigen. ASC, Antibody-secreting cells; BCR, B-cell receptor; FcεRI, Fc epsilon receptor-1; mAb, monoclonal antibody; mIgD and sIgD, membrane-bound IgD and secreted IgD; T1, Transitional stage 1; Th1/Th2, T helper cell type-1 and type-2 responses.

early release of pro-inflammatory cytokines, chemokines and anti-microbial mediators in a mucosal innate immune responses, they also produce an enhanced Th2 cytokine response that in turn has an amplifying positive effect on Th2-dependent IgG1 and IgE productions (Figure 3). These activated immune responses also simultaneously exert a negative feedback and anti-inflammatory effects on Th2-mediated allergic inflammations by IgE-activated basophils and mast cells. Such notion implies that sIgD may have important immune-regulatory functions in both allergic immune responses as well as immune surveillance in mucosal immunity.

The therapeutic effects of anti-IgD Ab in preclinical models

The collective evidence above demonstrated and corroborated that activation of immune responses via

both mIgD and sIgD can exert a regulatory and suppressive effect on autoimmune diseases and allergic immune responses in animal models (Table 1). Thus, harnessing these regulatory functions of activated IgD-mediated immune responses by treatment with anti-IgD Ab represents an exciting and novel therapeutic paradigm for human autoimmune diseases and allergic conditions [70].

The evidence of a therapeutic effect of anti-IgD Ab treatment on autoimmune diseases was first reported in the CIA mouse model [33], a well-characterized animal model of autoimmune arthritis which is primarily driven by a Th1 cell-mediated inflammation and autoantibodies following immunization with self-antigen. This therapeutic effect was independently confirmed later in other studies of mouse models of the autoantibody-mediated skin autoimmune model of EPA [35], chronic CHS mouse model of skin allergic

inflammation [34], and again in CIA mouse models [36]. The most important feature and common finding in all of these studies was that anti-IgD Ab treatments consistently ameliorate inflammation and clinical diseases when administered as a therapeutic treatment given soon after the onset of observable inflammation and swelling but not as a preventive treatment that is given prior to disease induction by antigen challenges [33–36]. This important finding demonstrated a therapeutic effect rather than a preventive effect that suggest a more clinically relevant and practical application as a treatment for patients with early onsets of disease in clinical settings. Another consistent finding in these studies and previous studies are the characteristic hallmarks of the activated immune responses in vivo by anti-IgD Ab treatments that underlie the mechanisms of action of its therapeutic effect on autoimmune diseases and allergic inflammations (Table 1). On the whole, the mechanisms of action of anti-IgD Ab treatment are characteristically defined by: (1) a highly specific depletion of IgD⁺T2 and mature B cells; (2) the sparing of the tolerogenic immature T1 B-cell subsets; (3) the augmentation of regulatory B cells and regulatory T cells; and (4) a shift toward an anti-inflammatory Th2-skewed cytokine and antibody responses.

Depletion of mature B cells

A common feature of anti-IgD Ab treatments in mouse models is the selective depletion of IgD^{hi}IgM⁺T2 and mature naïve B cells while the more tolerogenic immature IgD^{neg/low}IgM^{hi} T1 B cells were spared from depletions [23,25,33–35,65]. Depletions of IgD⁺B cells by anti-IgD Ab treatment have also been reported in other animal models, including rats and rhesus monkeys [117,118]. In anti-IgD superantigen transgenic mice, which represent a model of life-long chronic exposure to anti-IgD mAb treatment, B-cell development was arrested at the late T1 stage [65]. In contrast to the depletion of the conventional mature B-2 B cells, anti-IgD Ab treatments increased numbers of CD19⁺IgD^{neg/low}IgM^{hi} B cells in the peritoneal cavity [33,65], which are characterized as innate-like B-1 B cells [94], and IgM-only secreting plasmablasts in spleen and lymph nodes [65]. These B-1 B cells are both major producers of natural IgM antibody responses [94,95], suggesting a shift favoring toward natural IgM responses that also have potential beneficial effects against autoimmunity [95] and respiratory infections [94]. Thus, highly expressing mIgD B cells (like T2 and mature naïve B cells) are more prone to depletion by anti-IgD Ab

treatments while B cells lacking mIgD expression (like immature T1, innate B-1 and switched memory B cells, and plasmablasts) are more likely to be spared. Interestingly, anti-IgD Ab can also deplete mature B cells even in the presence of high levels of BAFF or constitutive expression of proliferative oncogene BCL-2 in vivo [65,66]; and the pattern of mature B-cell depletion and development are similar to that of BAFF-deficient mice [65]. On this comparison, anti-IgD Ab treatment may have similar effects on B cells as anti-BAFF antibody (BelimumabTM) treatment, a clinically approved treatment for human lupus, by negating the proliferative effects of BAFF and BCL-2 oncogene in vivo. Therefore, the therapeutic effects of anti-IgD Ab treatment may involve its ability, possibly by reactivating peripheral immune tolerance check-point signals via mIgD, to deplete the populations of mature B cells which are a major source of autoreactive ASC precursors under autoimmune conditions.

Induction of regulatory B cells and regulatory T cells

Another common feature of anti-IgD Ab treatments is the induction of regulatory IL10-producing B cells and regulatory T cells in vivo [33–35,66,68,69]. Both of these regulatory adaptive immune cells have potent tolerogenic and suppressive effects on both Th1-mediated autoimmune diseases and Th2-mediated allergic inflammations, which may explain the underlying therapeutic effects of anti-IgD Ab treatment in both Th1-mediated CIA and Th2-mediated CHS mouse models [33,34,70]. Interestingly, these IL10-producing and regulatory B cell populations are extensively depleted by anti-CD20 Ab treatment [34,119–121] but are not depleted and instead augmented by anti-IgD Ab treatments [33–35,66,68], demonstrating a highly selective pattern of B-cell depletion by anti-IgD Ab compared to anti-CD20 Ab. In addition, the IgD^{neg/low}IgM⁺ immature T1 B cells that are spared from depletion by anti-IgD Ab treatment also have an immune-tolerogenic phenotype, which are thought to contribute to the overall therapeutic effects of the clinically approved anti-CD20 B cell depletion therapy (RituximabTM) as the immature T1 B cells reemerging after the depletion [70,119,120]. Furthermore, a subset of the mature B cells but with IgD^{neg/low}IgM^{hi} expression that are extensively depleted by anti-CD20 Ab, but are spared by anti-IgD Ab, have also recently demonstrated to promote immune tolerance and regulatory T cell homeostasis by IL10-independent mechanisms [121]. As mentioned above, anti-IgD Ab treatments can augment the populations of innate-like

B-1 B cells and IgM + plasmablasts that also have important immune regulation via their productions natural IgM and IL10 in vivo [35,65,122,123]. Collectively, these evidence suggest a highly diverse population of regulatory B cells which are either selectively spared or augmented by anti-IgD Ab treatment that may contribute to its immune tolerance and therapeutic effects, and demonstrate a potential advantageous feature of anti-IgD mAb treatment over the current B-cell depletion therapies.

Anti-inflammatory Th2-skewed cytokine and antibody responses

It is clear from the studies highlighted above that, while anti-IgD Ab treatments can induce the productions of both the classic Th1 (IL2, IFN γ) and Th2 (IL4, IL10) cytokines by T cells [30,33], the consistent characteristic feature of activated immune responses by anti-IgD Ab treatments is defined by a shift toward a Th2-skewed phenotypic immune response. This Th2-skewed immune response is characterized by enhanced productions of Th2-related cytokines (IL4, IL10, IL13) by T cells [33,35,69], basophils and mast cells [22,74,110], and an increase in Th2 cytokine-dependent IgG1 and IgE polyclonal productions [27,28,34,65], and with a suppression of Th1-related IgG2a/2b classes [33,61,65,110]. A unique feature of anti-IgD mAb treatment is that it can suppress both Th1-mediated autoimmune diseases and Th2-mediated allergic inflammations, despite the presence of an apparent Th2-skewed response. This feature implies an anti-inflammatory Th2-biased response rather than a pro-inflammatory Th2 response. Given the fact that Th1 and Th2 immune responses can exert a cross-inhibitory effect on one and another [93,124], the Th2-skewed response may account in parts for the suppressive effects of anti-IgD mAb treatments against Th1-mediated inflammations. However, it was unexpected that this Th2-skewed response did not exacerbate Th2-mediated allergic responses but instead suppressed it. This paradox is somewhat similar to the suppression of both Th1-mediated autoimmune diseases and Th2-mediated allergic conditions by chronic helminthic infections [70], which could be explained by their similarities in immunomodulation of a Th2-skewed response [28,125–127] and their abilities to induce regulatory B cells and regulatory T cells [70,128,129].

In addition, other potential mechanisms underlying the observed anti-inflammatory Th2 responses may also involve: (1) a benign polyclonal IgE response that can compete out the synthesis and binding of pathogenic allergen-specific IgE [130] and (2) a polyclonal

or antigen-specific IgG1 response that bind and activate inhibitory Fc γ IIB receptor pathway [112–114]. These polyclonal IgG1 and IgE responses may also produce highly sialylated antibodies that have anti-inflammatory mechanisms similar to that of intravenous immunoglobulin (IVIg) infusion [131,132]. This notion is supported by the evidence demonstrates both type-1 and type-2 T cell-independent (TI-1 and TI-2) activations of B cells by TI antigens such as lipopolysaccharides or LPS (TI-1), and BCR activating agent Ficoll (TI-2), but not T cell-dependent (TD) antigens OVA or bovine serum albumin (BSA), resulted in productions of polyclonal and antigen-specific sialylated IgG antibodies that have potent anti-inflammatory effects against delayed type-hypersensitivity (DTH) and protect mice from nephrotoxic nephritis-induced death [133]. The fact that anti-IgD Ab treatments are often used as a potent BCR activating TI-2 agent to study TI activation of B cells [27–29,64] suggest anti-IgD Ab may have similar effects on antibody sialylation as other TI-antigens like LPS and Ficoll. Such potential effects of anti-IgD Ab on antibody glycosylation and sialylation will need further proof and warrant further investigations.

Potential adverse effects of activated immune responses by anti-IgD Ab treatments

The frequent uses of anti-IgD Ab as a BCR-activating agent in numerous animal studies (including mouse [23–31], rat [117], and rhesus monkeys [118]) presented above demonstrated that repeated activations via mIgD BCR and sIgD do not cause any significant signs of adverse immune events such as cytokine release syndromes, severe immunosuppression or anaphylactic reactions that are commonly observed in other methods of immune activation via the classic receptors such as the toll-like receptor-4 (TLR-4) of the innate system, or the T-cell receptors CD3 and CD28, or repeated allergen exposures in AIT [70]. Indeed, short and long courses of repeated intravenous or intraperitoneal injections with high doses of anti-IgD mAb and pAb [30,33–35,63,64] or life-long chronic exposures to anti-IgD mAb stimulation in anti-IgD superantigen transgenic mice [65] did not show any apparent undesirable or severe adverse immune effects in animals (Table 1). Treated animals also have relatively competent T-cell responses [104,107] and humoral antibody responses to immunizations with both foreign TI and TD antigens [29,33,65], demonstrating an intact and competent general immune defence against potential pathogens. Indeed, this notion is supported by evidence that anti-

IgD Ab treatment in mice infected with *Influenza A* [65], *Histoplasma capsulatum* [69], and *Listeria monocytogene* [134] showed a short delay in clearing the infections, possibly due to the Th2-skewed response (but not polarized) cross-inhibitory dampening effects on Th1-mediated anti-pathogen immune responses [69,134], but these anti-IgD Ab-treated mice nonetheless eventually and competently eliminated the pathogens without any signs of immunopathology. Thus, the uses of anti-IgD Ab in numerous preclinical experimental studies demonstrated a good safety profile of anti-IgD Ab treatments in animal models that potentially afford it suitable as a chronic treatment. Nevertheless, it is reasonable to expect that, as a potent immunomodulatory drug, the safety profile and therapeutic efficacy of anti-IgD Ab will critically depend on its antibody designs and characteristic features, dosing and timing of treatment. It therefore remains essential and very important that the safety profile and the therapeutic efficacy of a fully humanized anti-IgD mAb must be carefully developed and evaluated during its clinical development phase as a new therapeutic treatment for human conditions.

Future perspectives and concluding remark

The evidence presented in this review demonstrated and corroborated that activated immune responses via both mIgD-BCR on B cells and sIgD bound on cell surface of basophils and mast cells can exert tolerogenic and suppressive effects on autoimmune diseases and allergic inflammations that are characterized by: (1) a highly specific depletion of IgD⁺ T2 and mature B cells; (2) the sparing of the tolerogenic immature T1 B-cell subsets; (3) the augmentation of regulatory B cells and regulatory T cells; and (4) a shift toward an anti-inflammatory Th2-related cytokine and antibody responses. In addition, the production and secretion of sIgD upon the activations of B cells [90–92] may provide a mechanism of arming of basophils and mast cells with sIgD. Together, these mechanisms of actions collaborate to form a potential amplifying loop of anti-inflammatory Th2 and tolerogenic responses that may underlie the therapeutic effects of anti-IgD Ab treatment (Figure 3). It also suggests a new understanding for a novel regulatory role of IgD in the immune system that function as an inbuilt and intrinsic negative feedback mechanism by activated immune responses via IgD that act to maintain the immune homeostasis in accordance to the universal paradigm of Newton's Third Law of Fundamental Physics [70].

This new understanding of activated immune responses via IgD revealed and implies an important

and unappreciated immune-regulatory function and property of the enigmatic IgD in our immune system that has not been previously recognized. It also provides us with an exciting opportunity to optimize ways to harness these tolerogenic and suppressive immune responses to treat human autoimmune diseases and allergic inflammations that, more importantly and uniquely, do not produce any apparent signs of undesirable or serious adverse effects such as cytokine storm syndromes, or anaphylactic reaction, or impairments of immune defence against foreign pathogens. Harnessing these unique and useful features of immunomodulation via IgD by using either sIgD-specific antigen complex or anti-IgD mAb represents a novel therapeutic application as either an allergen-specific tolerance induction in AIT or a therapeutic antibody drug treatment for a range of human autoimmune diseases and allergic conditions [70]. The molecular designs and the essential characteristics of such therapeutic anti-IgD mAb or antigen-sIgD complex to achieve these beneficial immune responses will critically determine their safety profiles and clinical efficacies. This will require insightful knowledge and understandings that need further investigations, which are actively in progress and warranted. More insights into the role of these immune responses and sIgD productions in respiratory infections and conditions will also help us in our fights against invading respiratory pathogens. In addition, it is of great therapeutic interests to examine the potential anti-inflammatory phenotypes of glycosylation of Th2-mediated polyclonal sIgD, IgG1 and IgE antibodies via T1 B-cell activations by anti-IgD Ab treatment that further elucidate the mechanism of action underlying its anti-inflammatory Th2-related antibody responses. Thus, there is a need for more researches focusing on these areas that will allow us to harness its therapeutic potentials as well as expand our understandings of the functional roles and mechanisms of IgD in the regulation of mucosal immunity, autoimmune disease and allergic inflammatory responses, and shed further lights into the function of this enigmatic member of the Ig family that has been overlooked in immunological research so far.

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Disclosures

Dr TG Nguyen is the founder of IgD Mab Technology (IMT) group and has been named as the leading inventor on granted patents related to the therapeutic applications of Methods of anti-IgD antibody (WO2007124529A1).

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