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New Insights into the Enigma of Immunoglobulin D

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Summary

Immunoglobulin D (IgD) has remained a mysterious antibody class for almost half a century. IgD was initially thought to be a recently evolved Ig isotype expressed only by some mammalian species, but recent discoveries in fishes and amphibians demonstrate that IgD was present in the ancestor of all jawed vertebrates and has important immunological functions. The structure of IgD has been very dynamic throughout evolution. Mammals can express IgD through alternative splicing and class switch recombination (CSR). Active cell-dependent and T-cell-independent IgM-to-IgD class switching takes place in a unique subset of human B cells from the upper aerodigestive mucosa, which provides a layer of mucosal protection by interacting with many pathogens and their virulence factors. Circulating IgD can bind to myeloid cells such as basophils and induce antimicrobial, inflammatory, and B-cell-stimulating factors upon cross-linking, which contributes to immune surveillance but also inflammation and tissue damage when this pathway is overactivated under pathological conditions. Recent research shows that IgD is an important immunomodulator that orchestrates an ancestral surveillance system at the interface between immunity and inflammation.

Keywords

IgD; class switch recombination; basophil; antimicrobial peptide; autoinflammatory syndromes

Introduction

Immunoglobulin D (IgD) has remained an enigmatic antibody class since its discovery almost 50 years ago. Because of its spotty presence in mammals and absence in birds, IgD was initially thought to be a recently evolved Ig isotype. Recent discoveries of IgD in more ancient vertebrates, such as fishes and amphibians, demonstrate that IgD was present in the ancestor of all jawed vertebrates and arose together with IgM at the time of the emergence of the adaptive immune system, approximately 500 million years ago. While IgM remains stable over evolutionary time, IgD shows greater structural plasticity and can be predominantly expressed as a transmembrane or secreted molecule in a species-specific manner. One possible interpretation is that IgD has been preserved as a structurally flexible locus to complement the functions of IgM.

IgM and IgD are the first antibody isotypes expressed during B-cell ontogeny. After leaving the bone marrow to colonize secondary lymphoid organs, B cells acquire surface IgD of the

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same specificity as surface IgM through alternative splicing of a pre-messenger RNA comprising V(D)J and both heavy chain constant μ (C_μ) and C_δ exons. After encountering antigen in secondary lymphoid organs, mature B cells transcriptionally downregulate surface IgD and undergo somatic hypermutation (SHM) and class switch DNA recombination (CSR) to further diversify their Ig gene repertoire. Some B cells class switch from IgM to IgD, at least in humans, suggesting that IgD confers some functional advantage over IgM. Here we review the literature on the evolution of IgD in jawed vertebrates and focus the discussion on the major problems that have surrounded IgD since its discovery, including the regulation of IgD expression and secretion, the immunological function of secreted IgD, and the putative role of secreted IgD in various diseases. The B-cell-activating and signaling properties of transmembrane IgD will not be discussed in detail, because IgD seems to share most of these functions with IgM.

Discovery and evolution of IgD

Discovery of IgD

It has been almost half a century since IgD was discovered as a novel Ig class, first in humans. In 1964, physicians David Rowe and John Fahey (1–2), while studying the disease multiple myeloma, identified and characterized an unusual myeloma protein with electrophoretic and metabolic properties distinct from the known Ig classes at that time, namely IgM, IgG, and IgA. The myeloma protein displayed no reactivity to the anti-sera against IgM, IgG, or IgA. In addition, an antigenically related form of this protein was detected at low concentrations in the serum of healthy subjects. It did not possess the antigenic determinants characteristic of IgM, IgG, or IgA, and thus did not appear to be a subclass of any of these three Ig classes. The evidence collectively suggested that this myeloma protein represented a member of a novel Ig class rather than an abnormal product of the malignant myeloma cells. They subsequently named this new Ig class IgD. Rowe and Fahey stated in their original paper on the discovery of IgD (2) that the reason why they named the new Ig class IgD was ‘because of the evidence that the distinctive properties lie in the heavy polypeptide chains and the properties are sufficient to clearly differentiate these proteins from IgG, IgA, and IgM classes, or from known subclasses of these groups.’ However, based on some anecdotal communication, the selection of the letter ‘D’ was indeed a decision arrived upon with few other choices (3). IgA, IgM, and IgG had already been designated at that time. When Rowe and Fahey were looking for a name for their newly discovered antibody class, their first choice was IgB or β-globulin, but at that time it was expected that the murine Igs would be called β-globulin even though this never eventuated. The Roman letter ‘C’ has no Greek equivalent. The ‘E’ reactive antibody, later termed IgE, had traditionally been associated with allergy. Thus, Fahey and Rowe were left with little choice but to name the new class of antibody IgD. Interestingly, ‘IgD’ is probably a name that cannot be more appropriate for this Ig class, because it is not only distinctive and to be differentiated from other Ig classes but also displays considerable levels of diversity in both structure and abundance both in a single individual and among different individuals, and is probably the most evolutionarily dynamic Ig class among all vertebrate Igs.

Studies of IgD in other species in the late 1970s and early 1980s identified IgD only in primates, rodents, and selected species of mammals, including dog, mouse, rat, rabbit, and guinea pig, whereas it was undetectable in other mammals, such as swine and birds (4–8). The discordance of the spotty presence of IgD with the animal phylogeny and evolution had led to the general view that IgD was a recently evolved Ig class selected for certain species-specific functions in the respective host. With the increasing availability of animal genome sequences and the rapid developments of gene identification tools, the past 20 years have witnessed a series of discoveries of IgD or its homologs and orthologs in many more

mammalian species, including those where IgD was thought to be absent, such as cattle, sheep, and pig (9–10). More importantly, IgD and its homologs and orthologs have recently been found in a wide spectrum of species that are evolutionarily much more ancient, such as cartilaginous fishes, bony fishes, amphibians, and reptiles, with the exception of birds (9–22). The most primitive form of these species, i.e. the cartilaginous fishes, appeared on earth as many as some 470 million years ago, when jawed vertebrates first evolved and adaptive immune systems first appeared. These findings demonstrated that IgD is indeed an ancient Ig class selected throughout evolution just like IgM and suggested that IgD or its homologs and orthologs are probably present in not only all extant mammals but also all jawed vertebrates (perhaps except birds). This striking evolutionary perpetuation clearly pinpoints to some important functions of IgD associated with survival advantages of the host and has rekindled much research interest in demystifying the functions of this enigmatic Ig class.

Evolution and diversity of IgD

Although as primordial as IgM, IgD in various vertebrate species show much greater plasticity in terms of both the number of C domains and the types of splice variants found, especially in fish. The variability in the numbers of C domains in fish IgW and IgNAR, which are related to mammalian IgD, was frequently caused by various intragenic duplications and alternative splicing. In cartilaginous fish, two of the C domains were derived approximately 250 million years ago by a tandem duplication event (23), and in some bony fish there was a three-domain duplication (11). Within teleost fish, the number of C exons is different in various species (16), and the secreted and transmembrane forms are encoded by different loci in the channel catfish (21). In addition, in teleosts the $C_\mu 1$ domain exon is spliced into the IgD transcript (15,24), a unique way to express IgD in fish. In xenopus, there was a recent two-domain tandem duplication event (12). Xenopus IgD contains eight C_δ domains per chain and represents an intermediate form between fish IgD and mammalian IgD. Splicing of the $C_\mu 1$ exon onto the IgD sequences is not observed in xenopus. Rather, the expression of IgD is similar to that in mammals, where rearranged V(D)J sequences are joined directly to the C_δ sequence. In the reptile leopard gecko (*Eublepharis macularius*), two IgD genes have been discovered (13). The first IgD is made up of 11 C_δ domains without evidence of recent intragenic duplications of exons. The second IgD has seven C domains, with the first four and the seventh generated by a recent partial duplication of the domains of the first IgD gene, and the other two (fifth and sixth) arising from exon shuffling of domains 3 and 4 of an IgA-like molecule. In the green anole lizard (*Anolis carolinensis*), one IgD gene was identified to contain 11 C_δ domains, but only the first four C_δ domains are used in the expression of membrane-bound form of IgD (14). IgD has also been detected at mRNA level in the Chinese soft shell turtle (*Pelodiscus sinensis*) and is predicted to be a non-transmembrane protein with six C_δ domains (25). In mammals, structural diversity of IgD is also widely present. Rodent IgD differs from human IgD by the absence of the $C_\delta 2$ domain. In artiodactyl species including pig, sheep, cow, and horse, in spite of the overall similarity of domain structure to human IgD, the $C_\delta 1$ exon has been deleted and replaced with a duplicated $C_\mu 1$ or $C_\mu 1$-like exon (20,26–27). The hinge region of mammalian IgD is of great diversity in terms of both length and amino acid composition (Fig. 1). Rodent IgD hinge region is encoded by one exon, while in ungulates the IgD hinge regions are encoded by two exons. Ungulate IgD hinge regions, such as those of sheep, cow, pig, and horse, however, are structurally distinct from each other (20). Dog IgD hinge region is related more closely to that of ungulates and is distinct to the hinge regions of primate IgD by the absence of a highly charged C-terminal region. Primate IgD hinge regions are highly conserved, all of which contain an N-terminal sub-region rich in alanine and threonine and a C-terminal sub-region rich in charged amino acids including lysine, glutamate, and arginine.

One possible interpretation of the presence of this striking diversity of IgD throughout evolution is that IgD has been selected as a structurally flexible locus to back up and complement the functions of IgM. The presence of IgD may ensure the preservation of essential immune functions in case of IgM defects, and the structure flexibility of IgD may provide additional immune functions in a species-specific manner.

Distribution of IgD in human

The distribution of IgD in species other than human and mouse, especially in non-mammals, is poorly characterized. This is at least in part due to the unavailability of antibodies against IgD and the low abundance of IgD in those species. This section therefore focuses on the discussion of the distribution of IgD in human.

Soluble IgD

Secreted IgD has been detected in various human body compartments using different techniques. The first measurement was probably done by Rowe and Fahey (2) when they discovered IgD. Using quantitative gel diffusion, they measured serum IgD concentrations of 72 individuals of different sexes and ages. The median was 30 μg/ml. Some prominent and rather unique features of IgD were observed. Serum IgD concentrations spanned a very wide range, from barely detectable to more than 400 μg/ml. The values were not distributed in a Gaussian manner, in contrast to the log Gaussian distribution of serum IgG, IgM, and IgA concentrations observed by many other studies (28–34). There was also no correlation of serum IgD level with age or sex. In addition, IgD was electrophoretically heterogeneous, indicating differences in molecular weight of IgD molecules found in serum of a given individual and among different individuals (35–38). Other studies carried out later with more sensitive techniques, such as radioimmunoassay, enzyme-linked immunosorbent assay (ELISA), nephelometry, and two-dimensional gel electrophoresis, confirmed the findings of Rowe and Fahey on the heterogeneity of structure and abundance of IgD. The median serum IgD concentrations generally range from 20–50 μg/ml, with considerable variation even among people of the same age and sex. No consistent correlation with sex or age was found. The normal serum range of IgD is wider than that of any other Ig isotype. Individuals can be high or low producers, and low producers can convert to high producers in the setting of certain infections and immune activation. Therefore, the large variability and lack of correlation with demographic parameters of serum IgD might be contributed by the distinct history of immunological exposure in different individuals. In addition to blood, IgD is also present in human nasal, lacrimal, salivary, mammary, bronchial, pancreatic, and cerebrospinal fluids (39–45), and in the amniotic fluid of pregnant women with concentrations progressively increasing during the first half of pregnancy (46). Only trace amounts of IgD are present in intestinal mucosal secretions (39,43,47–49). The distribution of soluble IgD largely correlates with the distribution of IgD-producing B cells. Intestinal mucosa, liver, peripheral lymph nodes, spleen, and bone marrow contain very few IgD-producing B cells, while tonsils, adenoids, salivary, and lachrymal glands, and nasal mucosa harbor abundant IgD-producing B cells (39,43–45,50–53). IgD-producing B cells can account for up to 20% of all Ig-secreting cells in human tonsils (53–55). The reason why they are rarely found in bone marrow and gut associated-lymphoid tissues (GALTs) in healthy individuals is probably because they are not normally generated there and they express a homing profile not in favor of the intestinal mucosa ($\alpha_4\beta_7^{int/low}CCR9^{low}CCR7^{high}CD62L^{high}$) (56). The numbers of IgD-producing B cells in the upper aerodigestive mucosa are drastically increased in patients with IgA deficiency (57–59).

Despite of the fact that IgD-producing B cells express abundant J chain (43,45,47,51), IgD is generally recognized not to associate with J-chain or the secretory component (SC) and not

to cross epithelium, placenta, or blood brain barrier (58). IgD found on the surface of epithelium and in mucosal secretions, in cerebrospinal fluid, as well as in the cord blood of some pregnant women (60–63) is thought to result from paracellular diffusion through cell junctions and production of IgD in the fetus. Nonetheless, evidence supporting the transepithelial and transplacental movements of IgD has been documented (64).

The metabolism of IgD was studied by Rogentine and colleagues (65) soon after its discovery. The half-life of serum IgD was approximately 2.8 days. Serum IgD concentration was largely determined by the rate of synthesis because of the strong correlation between the two parameters. The fractional catabolic rate (fraction of the intravascular pool catabolized per day) of IgD was similar to that of IgA and much higher than those of IgM and IgG, which indicates that IgD might be catabolized in similar ways as IgA but in very different ways from IgM and IgG. IgD is often viewed as a predominantly mucosal Ig isotype because of the preferential localization of IgD-producing B cells in the upper aerodigestive mucosa, such as tonsils, adenoids, and nasal mucosa, but the presence of IgD as well as IgD-producing B cells in circulation in addition to upper aerodigestive mucosa-associated lymphoid tissues (MALTs) indicates that IgD can potentially exert its immunological functions both systemically and in mucosal districts. In fact, intravascular IgD takes up 73% of total IgD in human, despite of its higher susceptibility to proteolysis, in contrast to IgA and IgG, of which only 40–50% is in the vascular compartment and are less susceptible to proteolysis (65). Therefore, this ancient Ig isotype may be equally important in monitoring the presence of systemic antigens as compared to mucosal antigens.

Cell-associated IgD

Cell-associated IgD includes transmembrane IgD, intracellular IgD, and secreted IgD bound to various cell types. Transmembrane IgD is expressed by mature naive B cells prior to antigenic stimulation and class switch recombination (CSR) and by IgD-producing B cells in the upper aerodigestive MALTs and peripheral blood of healthy individuals. B cells, in addition to expressing transmembrane IgD, can also bind secreted IgD (66). The studies of interaction of secreted IgD with T cells postulated a putative IgD receptor on a small fraction of T cells in human peripheral blood and mouse peripheral lymphoid organs, which binds to N-linked carbohydrate moieties of IgD (67–68). Crosslinking of IgD receptor on T cells was shown to protect T cells from apoptosis (69). It has also been shown that this IgD receptor could promote the formation of immune synapse between cognate T cells and naive B cells that express transmembrane IgD and thereby augment antigen presentation and antibody production (70–71). The expression of this receptor was detected on $CD4^+$ T cells in mice within minutes after oligomeric or aggregated but not monomeric IgD injection into mouse and was inhibited by the administration of tyrosine kinase inhibitors (67). However, many data were not readily explainable. IgD receptor-expressing T cells did not immediately show an activated phenotype, such as the expression of CD25. Co-administration of T-cell-specific activating agents with oligomeric IgD did not enhance IgD receptor expression on T cells. The IgD receptor on T cells has not been identified. One reason that may have given rise to the many intriguing data is that this putative IgD receptor may not normally be expressed by T cells but rather be released by other cell types and binds to T cells after oligomeric IgD injection into mice. The release of the IgD receptor and its binding to T cells would be very rapid in response to oligomeric IgD injection, which may explain the rapid appearance of IgD receptor on T cells.

Many myeloid cell types have been shown to be able to bind secreted IgD. In humans, circulating basophils as well as basophils in tonsils, although rare in healthy subjects, displayed abundant surface IgD (53). Circulating malignant mastocytomas also bound IgD on the cell surface (53). This binding pattern of IgD to basophils and mast cells was consistent with the specific binding of IgD to basophilic and mast cell lines *in vitro* (53,72).

Neutrophils and/or eosinophils showed no or low IgD binding under physiological conditions (53,73–75) but can bind significant levels of IgD under certain pathological conditions, such as skin allergy and inflammation (76–77). Peripheral blood adherent monocytes have been shown to produce pro-inflammatory cytokines upon IgD treatment (78), but other studies showed that monocytes did not have significant IgD binding (75,79).

The IgD paradox

Soon after the discovery of IgD, a preferential association of many IgD myeloma proteins with λ light chain was observed (80–86). This association was confirmed to be true also for secreted IgD found in healthy individuals (54–55,81,87). Evidence of this preferential association of secreted IgD with λ light chain also came from studies showing that concentrations of both serum IgD and secreted IgD induced in cell culture correlated well with λ light chain concentrations (88–90). While the ratio of κ to λ light chains in other transmembrane or secreted Ig classes are approximately 2:1, the preference for λ light chain in secreted IgD can be as high as 60% to 90%. Transmembrane IgD, in contrast, predominantly contains κ light chain. This biased preference of secreted IgD for λ light chain and of transmembrane IgD for κ light chain observed more than 30 years ago is still not understood and has been termed the ‘IgD paradox’.

It has been hypothesized that the biased λ light chain association with secreted IgD results from receptor editing in the precursors of IgD^+IgM^- B cells in bone marrow or receptor revision in class switched IgD^+IgM^- B cells in the germinal center environment (55). Receptor editing is a process through which B-cell progenitors change the Ig light chain in their BCR in bone marrow in order to limit self-reactivity and is achieved by consecutive rearrangements of V_κ and J_κ gene segments at the κ locus and subsequently rearrangements of V_λ and J_λ gene segments at the λ locus; the latter often occurs after rearrangement of the noncoding combining sequence (RS) element with either a V_κ segment or a recombination signal sequence in the intronic region (IRS) of the Igκ locus, leading to the inactivation of the Igκ locus (RS combination) (91–92). Receptor revision results from secondary Ig gene rearrangement at the Ig light chain loci in the germinal center environment elicited by unfavorable somatic mutations that cause loss of Ig expression or disturb pairing of Ig heavy and light chains. In both cases, the usage of the λ light chain is expected to be increased. However, a recent study (93) found no evidence of receptor revision in class-switched IgD multiple myeloma cells, arguing against receptor revision or receptor editing as the underlying mechanism of the IgD paradox. Interestingly, the development of λ^+ B cells, but not receptor editing, has now been found to be dependent on NF-κB signals (94). Therefore, it is possible that IgD^+IgM^- B cells predominantly develop from a precursor population that relied on NF-κB signals in bone marrow.

Expression of IgD

Vertebrates have evolved two major strategies to express Igs, alternative RNA splicing and CSR. In fish, alternative splicing is used to express multiple forms of IgD, while in other higher vertebrates, the expression of IgD utilizes both strategies.

Expression of IgD by alternative splicing

Bony fishes use alternative splicing as the strategy to produce IgD by splicing the $C_\mu 1$ to numerous duplicated C_δ exons (15,21,95–96). In amphibians, reptiles, and mammals, the C_δ gene is positioned immediately downstream of the C_μ gene in the same transcriptional unit, allowing these two primordial Ig isotypes to be coordinately regulated at the transcriptional level. In early stages of B-cell development prior to the mature B-cell stage, only IgM is expressed. The expression of IgD first starts when the B cell leaves the bone marrow to

populate secondary lymphoid organs. Mature B cells of these species co-express IgM and IgD on the cell surface (Fig. 2A). IgM and IgD are generated by alternative splicing of a long primary mRNA transcript containing the rearranged VDJ exons and the C_μ and C_δ exons. The recombined VDJ exons are spliced to the first C_μ exon to generate IgM, or to the first C_δ exon to generate IgD (Fig. 2B). In addition, alternative splicing also determines if a cell expresses the transmembrane or secreted form of these two isotypes.

The alternative splicing process is tightly regulated during B-cell development. However, the mechanism of regulation is poorly understood. The transcription ratio of μ and δ exons varies in different types of B cells and B-cell lines (97) and does not necessarily reflect the abundance of membrane protein of either isotype. For example, in mature resting follicular mantle B cells, more μ mRNA than δ mRNA is transcribed, but IgD is expressed at higher densities on the surface than IgM. This has been attributed to the higher stability and better translation efficiency of δ mRNA than μ mRNA and the higher turnover rate of transmembrane IgM protein (98–99). When activated by antigen, μ exon transcription is preferentially induced and the half-life of μ mRNA is significantly increased. In contrast, δ exon transcription and IgD expression are significantly repressed. The result is the drastic downregulation of IgD expression by antigen-activated B cells, which explains the low level of IgD found in germinal centers of lymphoid tissues, such as lymph nodes, spleen, and tonsils (Fig. 2C). Studies have shown the existence of a specific region between the μ and δ genes that attenuates the transcription complex 5′ to the δ exons and forces the preferential production of mRNA for membrane IgM. Binding of lineage-specific regulatory proteins to this region may alter the ratio of processing of the primary mRNA transcripts (100–101). In terms of the regulation of alternative splicing between transmembrane and secreted forms, limited information is known for IgM. Peterson and Perry (102) have suggested that there is competition between the tails of $C_\mu 3$ exon and $C_\mu 2$ exon for the cleavage and polyadenylation factors and that the biases in this competition change as the B cell matures. Indeed, these two sites compete for limiting amounts of a factor, CstF-64, that directs the cutting enzymes to the 3′ splice site (103). The site for the transmembrane form of the μ chain is more efficient at binding. Hence, at the low amounts of CstF present in the B cell, only the transmembrane form of IgM is made. However, when the B cell differentiates into a plasma cell, more CstF-64 is produced, and both sites are utilized. The developing plasma cell synthesizes both transmembrane and secreted forms of IgM. Whether such a mechanism is also involved in the regulation of alternative splicing of transmembrane versus secreted forms of IgD is unknown.

Expression of IgD by CSR

In contrast to other Ig isotypes, there is no canonical switch region 5′ to the C_δ gene in mammals. Only rudimentary switch sequences are present in human and mouse. Consequently, CSR from μ to δ is traditionally considered a very rare event. Study of human normal tonsillar and leukemic B cells revealed that a region called σ_δ located in the intron between C_μ and C_δ exons and containing G-rich pentameric repeats is able to serve as an actual switch region to mediate CSR with S_μ and result in the deletion of C_μ (55,104). Study of human and murine myeloma and hybridoma cells also demonstrated recombinations involving two regions that contain homologous sequences, namely I_μ and Σ_μ located 5′ and 3′ to the C_μ gene, respectively, followed by the deletion of C_μ (9,105) (Fig. 2D). Therefore, B cells that switch to IgD and are capable of secreting large amounts of IgD do exist in normal individuals. Indeed, they are quite abundant in the upper aerodigestive MALTs, such as tonsils, adenoids, and nasal mucosa, as discussed earlier, which corresponds to the abundant IgD found in these tissues.

Similar to the regulation of alternative splicing, the regulation of IgD CSR and production are not well understood. Genotypic analysis has obtained evidence of the oligoclonal nature

of tonsillar IgD-secreting B cells and their generation in superantigen-driven immune responses (106). Germinal center $IgD^+IgM^-CD38^+$ B cells in tonsils could differentiate into IgD-secreting cells in the presence of the combined stimulation of CD40 ligand (CD40L) (or CD154), IL-2, and IL-10. However, these germinal center-derived precursor cells were probably already switched to IgD before stimulation, because they lacked the expression of IgM. It was also clear that stimulation through CD40 is dispensable in the induction of IgD secretion (9). IL-2 and IL-10 thus contribute to the differentiation of IgD class-switched B cells and their secretion of IgD *in vitro*. IgD can be spontaneously secreted by cultured peripheral blood and tonsil mononuclear cells, and the secretion was markedly increased by anti-CD40 stimulation in the presence of T-helper 2 (Th2) cytokines such as IL-4 and IL-10. However, the spontaneous and Th2 cytokine-induced IgD secretion was only observed in certain healthy donors. Furthermore, as no assessment of CSR was performed and mixed populations of unswitched and IgD class-switched B cells were present in the culture, it was not possible to delineate whether anti-CD40 and Th2 cytokines induced B cells to undergo IgD CSR and differentiation into IgD-secreting cells or simply increased IgD secretion by unswitched or IgD class-switched B cells. The signals for IgD CSR and secretion *in vivo* are further obscured by the frequently increased IgD levels in patients with HIGMs. These patients have elevated serum IgM but reduced IgG, IgA, and IgE due to defects in various components of the CSR machinery. The increase in IgD may be a result of the compensatory response from IgM^+IgD^+ B cells due to the absence of other switched isotypes rather than an indication of the inhibitory effect of the CSR machinery on IgD CSR and secretion *in vivo*. Therefore, the delineation of the signals that drive C_μ-to-C_δ CSR and the secretion of IgD requires an experimental strategy that directly assesses C_μ-to-C_δ CSR and differentiation of IgD-producing cells and simultaneously correlates those with the secretion of IgD. Using unswitched IgD^+IgM^+ B cells purified from human peripheral blood, we found that B-cell activation factor of the tumor necrosis factor family (BAFF), also known as B lymphocyte stimulator (BLyS), in combination with IL-15 and IL-21or IL-2 and IL-21 could simultaneously induce CSR to IgD, development of IgD^+IgM^- B cells, as well as IgD secretion *in vitro*. A proliferation-inducing ligand (APRIL) in combination with IL-15 and IL-21 or IL-2 and IL-21 was also able to do so (53). The number of circulating IgD class-switched B cells is reduced in patients with defects in the CD40L–CD40 and BAFF/APRIL-transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) signaling pathways, suggesting the involvement of both T-cell-dependent and T-cell-independent pathways for IgD CSR *in vivo*. The localization of IgD class-switched B cells both inside germinal centers and outside follicles also seems to support the notion that multiple pathways participate in IgD CSR *in vivo*. Activation-induced cytidine deaminase (AID), a DNA-editing enzyme essential for CSR to other Ig isotypes, was required for CSR to IgD both *in vivo* and *in vitro*.

Biochemical properties of IgD and functional implications

IgD is a monomer made up two identical heavy and light chains organized into variable and constant domains, similar to IgG. Human IgD has three C_δ domains. The structure of $C_\delta 1$ and $C_\delta 2$ domains is similar to that of C domains of other Ig isotypes. $C_\delta 3$, in contrast, is unique by the absence of several proline residues (which usually introduce turns in polypeptide backbones) and by the presence of two N-linked glycosylations. The overall conformation of $C_\delta 3$ domain is thus different from that of the C domains of other isotypes. Several studies suggest that these structural features and the resulting configuration of the molecule participate in specific biological properties of IgD (37,107–109). An additional N-linked glycosylation in the $C_\delta 2$ domain close to the inter-H chain disulfide bond was found to be essential for the folding and secretion of the intact IgD molecule (110). This glycan is usually in the high-mannose form and is buried within the folded IgD molecule.

Mammalian IgD has a hinge made up of 64 amino acids, longer than the hinge of any other Ig isotype. It includes two sub-regions encoded by two exons respectively (Fig. 1). The first sub-region is alanine- and threonine-rich and is densely decorated with multiple (up to seven) O-linked glycosylations that contain N-acetylgalactosamine moieties in the attached glycans, a unique structure only found in IgA1 and IgD (9,37,108,110–114). Together with the N-linked glycans, they can contribute up to 15% of the molecular weight of an IgD molecule. This high carbohydrate content and the differential degrees of glycosylation in different IgD preparations had in fact led to discrepancies in the findings of several studies in the 1970s and caused confusion as to whether the δ chain had three or four constant domains (115). The second sub-region has a highly charged and hydrophilic stretch of amino acids, a feature unique to IgD (Fig. 3A). Such a high degree of hydrophilicity in the IgD hinge results from the presence of abundant charged amino acid residues, especially lysine (K), glutamate (E), serine (S), and threonine (T). The sequence of this sub-region might explain the very high sensitivity of IgD to proteolytic enzymes, as studies of IgD myeloma proteins showed the presence of sites of ‘spontaneous’ proteolysis in this glutamate- and lysine-rich sub-region (116–117). However, it was possible that the IgD preparations in those studies were contaminated with plasmin, as IgD purified from serum by a two-step procedure of ammonium sulfate precipitation and gel filtration was stable for extended periods (118). Sites susceptible to proteolysis have also been found in the $C_{\delta}1$ domain and in the lysine- and arginine-rich C-terminal portion of the $C_{\delta}3$ domain. Noteworthy, IgD is known to display significant heterogeneity in both size and charge not only in healthy individuals but also in myeloma patients that have mostly monoclonal IgD (35,37–38), highlighting the susceptibility of IgD to multiple post-translational modifications and the complexity of the regulation of its metabolism and function.

The average structure of a myeloma IgD protein in solution has been predicted using constrained X-ray scattering (119), which revealed some unique features of IgD. The hinge of IgD adopts a semi-extended α-helical conformation in solution. The entire IgD molecule adopts an overall flexible T shape rather than Y shape as predicted for other Ig isotypes. The two Fab fragments are located primarily on the two sides of the Fc fragments and can swivel about the Fc fragments owing to the flexibility of the semi-extended hinge. The Fc fragments are thus shielded by the Fab fragments (Fig. 3B). There are two major conclusions based on this structure model: (i) the antigen-binding part of the IgD molecule is very flexible, and (ii) the Fc part of the IgD molecule is usually concealed by the motion of the Fab part in solution. These two conclusions have several important functional implications. (i) The co-expression of IgM and IgD as B-cell antigen receptors may optimize the recognition of antigens at different antigen concentrations (120). IgM facilitates antigen binding at high concentrations, while IgD facilitates antigen binding at lower concentrations owing to its reach and flexibility. (ii) The Fab part of IgD may mask large regions of the surface of the Fc part in solution, which might provide a mechanism to regulate the binding of IgD to its potential receptor(s). The interaction of IgD with its receptor(s) might only be possible when the motion of the Fab part is somewhat constrained by binding to antigen or certain auxiliary molecules, or by proteolytic cleavage of the Fab part. Heavy O-glycosylation in the first sub-region of the hinge may increase the rigidity of the hinge and limit the movement of the Fab parts, thus facilitating the exposure of the Fc part and its interaction with potential receptor(s); it may also restrict the access of proteolytic enzymes to the second sub-region of the hinge. All these factors potentially contribute to the complexity of the regulation of IgD’s function.

Immunological functions of IgD

Transmembrane and GPI-anchored IgD as B-cell antigen receptors

IgD is found as an antigen receptor on the surface of the majority of human (121–123) and murine B cells prior to antigenic stimulation and CSR (124–125). The advantage of having both IgD and IgM with the same antigen specificity on the same cell is still not clear. Initially, it was proposed that the two receptor classes deliver different signals to the B cell (126–128). However, contradictory results were obtained. Engagement of IgM on immature B cells *in vivo* and in IgM-transfected cells *in vitro* results in apoptosis, whereas engagement of IgD failed to do so (129–130). Reverse results were obtained in another study, which showed that a minimal stimulation with anti-IgD antibodies but not with anti-IgM antibodies induced apoptosis of mature resting B cells (131). Reasons for the discrepancies in the results might be that BCR signaling depends on the developmental stage of the B cell, the type of B cell line used, as well as the receptor density on the cell surface (132–133). Experiments involving transgenic mice showed that IgD could fully substitute the function of IgM in early B-cell development (134), and BCR of one class could largely compensate for the loss of the other because mice deficient for either the IgM or IgD heavy chain showed only mild phenotypes (135–137). Mice deficient in IgD did not show apparent abnormality in B-cell development and function, although the antibody response was slightly delayed as compared to wildtype mice (136–137). IgD-deficient mice had 30–50% reduction in the number of peripheral mature B cells, pointing to a role of IgD in B-cell homeostasis (136–137).

In terms of signaling, transmembrane IgM and transmembrane IgD are associated with different signaling molecules in human B cells (9). The cytoplasmic parts of IgM and IgD are identical, consisting of only three amino acids. The association of different signaling molecules may lead to different functional outcomes when the B cell is stimulated through IgM as compared to through IgD or through both IgM and IgD. Geisberger and colleagues (138) proposed that transmembrane IgD modulates the function of transmembrane IgM by increasing the threshold of IgM signaling required for inducing cell activation, anergy, or cell death; therefore, IgD delivers a negative or tolerogenic signal. This model is supported by several studies using human and mouse B cells (139–142). Loset and colleagues(120), however, have proposed another model that IgD and IgM are optimal for antigen capturing at different concentrations of the antigen. This model is supported by the solved crystal structure of IgD showing that IgD is a T-shaped molecule with flexible $F(ab')_2$ domains owing to the long hinge region (119). IgD can also be post-translationally processed and linked to the membrane lipids via a GPI anchor (143), initiating different signaling cascades from the transmembrane IgD molecule. The GPI-anchored IgD selectively activates cyclic adenosine monophosphate (cAMP)-dependent signaling pathways (144), which synergizes with transmembrane IgM and transmembrane IgD in initiating Ca^{2+}-dependent signaling.

Secreted IgD as an immunomodulator in immunity and inflammation

The function of secreted IgD is yet another mystery of IgD and has been a longstanding puzzle in immunology. IgD secreted by IgD class-switched B cells was shown to be frequently autoreactive (145). Secreted IgD can bind to many pathogenic microorganisms and their products, many of which are virulence factors used in pathogenesis, such as rubella virus, measles virus, diphtheria toxin, *Escherichia coli*, streptococci streptolysin O, *Moraxella catarrhalis* and *Haemophilus influenzae* adhesin MID (also called Hag) (53,64,146–152). The fact that many of the above-mentioned microorganisms are pathogens found in the same anatomic location where IgD is abundant, i.e. the upper aerodigestive MALTs, strongly supports the notion that IgD has protective functions against these pathogens perhaps by contributing to immune exclusion or neutralization. Further evidence

supporting this notion are the markedly increased numbers of IgD-producing B cells in these locations in IgA deficiency (59) and frequently increased serum IgD levels during various infections (153). Studies of immunosenescence also lend credence to this notion, as there is an age-dependent drop of serum IgD concentration, which correlates with a gradual decline of immunity in older people (154).

A careful scrutiny of the old literature reveals many intriguing connections of secreted IgD with myeloid cells. Early studies showed that granulocytes, such as neutrophils and eosinophils, could bind significant levels of IgD under certain pathological conditions, such as skin allergy and inflammation (76–77), although they bound little IgD under physiological conditions (73–75). IgD was the predominant Ig class present on neutrophils, probably together with complement, in patients with allergic contact dermatitis (76). IgD on the surface of neutrophils seemed to inhibit the release of oxygen free radicals, in contrast to IgG and IgA, which stimulated the release of oxygen free radicals (155). More recently, peripheral blood adherent monocytes were shown to produce pro-inflammatory cytokines including tumor necrosis factor (TNF), IL-1β, and IL-1 receptor antagonist (IL-1RA) upon incubation with IgD purified from serum, and this effect was not due to endotoxin contamination present in the IgD preparation (78). Confounding findings do exist in the literature regarding the binding of IgD to monocytes, neutrophils, and eosinophils. Several studies employing different methodologies showed no binding of IgD to monocytes, neutrophils, and eosinophils (73–75). Remarkably, Sjoberg isolated lymphocytes from peripheral blood using Ficoll-Isopaque gradient (density 1.076 – 1.078 g/mL) (156–157) and showed the presence of IgD receptor on T lymphocytes as well as many more non-T lymphocytes that were not monocytes (79). Based on what we now know about the composition of peripheral blood leukocytes isolated by Ficoll-Isopaque gradient, which include T cells, B cells, NK cells, monocytes, and basophils, the cells seen by Sjoberg to express IgD receptor could be basophils. Many studies have showed the presence of IgD on the surface of basophils and basophillic cell lines (53,72,158–159). Crosslinking of surface IgD on basophils using an anti-IgD antibody or incubation of the basophilic cell line KU812 with polymerized IgD prepared by glutaldehyde crosslinking could induce the release of cytokines and chemokines without inducing degranulation and the release of histamine (53,72). Studies on the ability of IgD to function as a chemotactic agent (the so-called cytotaxigen or cytotaxinogen) found that IgD could induce the infiltration of myeloid cells, mainly composed of neutrophils and low numbers of eosinophils but not lymphoid cells, into skin at an early stage of inflammation in patients with contact dermatitis but not skin ulcers (77). Increased infiltration of basophils was also observed in this study, but due to low basophil number and large variations, statistical significance could not be determined. This observation is in line with our finding showing massive infiltration of basophils and/or mast cells in the tonsil of a patient with periodic fever, aphthous-stomatitis, pharyngitis, adenitis (PFAPA) syndrome (53). In addition, crosslinking of surface IgD on basophils from healthy donors *in vitro* induced the release of antimicrobial and B-cell-stimulating factors, such as LL-37 and BAFF, that augmented microbial killing and B-cell antibody responses. The ability to induce BAFF production, a B-cell homeostatic cytokine, by basophils may explain the observation of peripheral B-cell deficiency observed in $IgD^{-/-}$ mice (136–137). Basophils found in the tonsil of the patient with PFAPA syndrome also contained LL-37 and BAFF. Findings suggesting the connection of IgD and basophils were also obtained in mouse studies long time ago. Injection of a goat polyclonal antibody against mouse IgD results in increased numbers of basophils that produced IL-4 in the bone marrow and spleen (160–163). These studies collectively support the notion that IgD is an important immunomodulatory molecule and that IgD promotes immune defense by inducing the activation and infiltration of IgD-interacting cells into tissues and their production of immune-activating factors, and overactivation of this pathway can cause inflammation and tissue damage (Fig. 4).

IgD in diseases

The wide range and high degree of variability of serum IgD concentration among different individuals have rendered the exact role of IgD in various diseases poorly defined. Serum IgD has been considered to be a valuable indicator only for IgD multiple myeloma (164). A good review of the perturbation of serum IgD concentration was provided by Vladutiu (153), and this article will therefore focus on the discussion of IgD's role in diseases in the context of B-cell and myeloid cell biology. Nonetheless, a careful examination of this body of literature not only sheds light on the immunomodulatory functions of IgD but also reinforces the idea that IgD's functions may contribute to disease pathogenesis or may be exploited to achieve disease amelioration.

Immunodeficiencies

Individuals with primary immunodeficiencies were found to have either increased or decreased IgD production (165). These patients frequently have accompanying infections; hence, it is unclear whether the perturbation of IgD production in these patients is a result of immunodeficiency *per se* or a result of infections. Within the entire group of immunodeficiencies, a positive correlation of IgD with IgA and IgE was noted. In human immunodeficiency virus (HIV)-infected people, significantly increased IgD levels were found in asymptomatic or mildly symptomatic individuals (166–169). This hyper-production of IgD became progressively more pronounced in patients with increasingly severe infection and reached its most marked level in patients with AIDS-related complex (ARC) (166), suggesting a possible protective role of IgD in the body's attempt to cope with severe infection. Remarkably, the production of IgD in HIV-infected people is independent of T-cell defects (167), highlighting the importance of T-cell independent pathways of IgD production. Further indirect evidences of the possible protective role of IgD in immunodeficiency and infection come from selective IgA deficiency, where there were significantly increased numbers of IgD-producing B cells in the upper aerodigestive MALTs (43,59). Secreted IgD may provide a layer of mucosal protection during IgA deficiency. However, it is important to note that serum IgD concentration was found to be in the normal range of children with selective IgA deficiency (50).

Infections

Many chronic infections can lead to the increase of serum IgD concentration (153,170), which might suggest some protect roles of IgD in infection. Serum IgD was increased in patients with leprosy (171), tuberculosis (172–173), salmonellosis, infectious hepatitis (174), and malaria (175). IgD reactive to pathogens has been detected in patients with rubella (64) and sub-acute sclerosing panencephalitis (146). It has also been found that IgD can react to various virulence factors of pathogens, including diphtheria toxin, streptococci streptolysin O, *M. catarrhalis* and *H. influenzae* adhesin MID (also called Hag), as well as whole bacteria such as *M. catarrhalis*, *H. influenzae*, *Escherichia coli*, and streptococcus group A (53,147–152,176). Many patients with elevated IgD had recurrent staphylococcal infections (177), and increased values of serum IgD were found in some patients with viral infections (64,178). The clinical significance of these specific IgD antibodies is to be determined.

B-cell malignancies

A well-known type of B-cell malignancy related to IgD is IgD multiple myeloma (MM). MM is a cancer of plasma cells characterized by the neoplastic proliferation of a single clone of plasma cells that usually produce a monoclonal Ig that can be found in blood and/or urine, although there has been a longstanding controversy of whether the precursors of myeloma cells are hematopoietic stem cells (179), pre-B cells (180), germinal center (GC) B cells (181), circulating memory cells (182–183), or plasmablasts (184). IgD MM, as the name

implies, is the MM of the IgD-producing plasma cells. It is a rare (< 2%) (83,185) but aggressive form of MM. IgD in the serum of IgD MM patients is always increased and often found to contain a monoclonal IgD protein (86). Sixty to 90% of IgD MM cases are of the λ type (83,86), a manifestation of the IgD paradox discussed earlier. Although IgD MM cells are suggested to have a GC origin and are frequently observed to have undergone SHM and CSR to IgD (55,104–105,186), the exact precursor of the malignant IgD MM cells is not known. The signals involved in the IgD CSR and sustained survival of IgD MM are also poorly understood. Some cases of hairy cell leukemia, a type of mature B-cell neoplastic disease, were also found to express only IgD on the cell surface, suggesting that these cells had undergone CSR (187–189).

Allergic diseases

Elevation of serum IgD has been reported in patients with many allergic diseases, such as atopic diseases, allergic asthma, rhinitis, allergic bronchopulmonary aspergillosis, and antibiotic allergy (158–159,173,190–196). Notably, among asthmatic children, such increases were mostly observed during first diagnosis and during disease attack (190,194). There was evidence suggesting that allergen-specific IgD and allergen-specific IgE were similarly regulated during allergic responses (191). These findings have led to the postulation that the increase of IgD might represent an attempt of the host to block asthma and that IgD might be a protective regulatory factor (190,194). Indeed, the ability to block IgE-mediated responses has been documented for IgD (197).

Autoimmunity

Serum IgD is often increased in patients with autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (174,198–201), consistent with the observation that many mature B cells class switched to IgD are autoreactive in healthy individuals (145). Anti-nuclear IgD antibodies were found in SLE patients (145,193,202–206), and a slight increase of serum IgD was found in patients with Sjögren's syndrome and in a patient with autoimmune thyroiditis (207). In addition, elevated concentrations of autoantibodies against IgD, mainly of the IgA and IgG classes, were detected in many patients with rheumatoid diseases such as RA, SLE, and mixed connective tissue disease (MCTD) syndrome (208). In mice, naturally occurring IgD that recognizes heat shock proteins (HSPs), such as Hsp70 and gp96, has been found in the serum in an individual-specific and strain-specific manner but does not seem to be related to autoimmunity, as no HSP-reactive IgD was detected in the autoimmune *lpr* mouse model (209).

Hyper-IgD syndrome and other autoinflammatory syndromes

There is a group of hereditary syndromes called autoinflammatory syndromes or periodic fever syndromes, which include hyper-IgD syndrome (HIDS), familial Mediterranean fever (MFM), TNF receptor-associated periodic syndrome (TRAPS), Muckle-Wells syndrome (MWS) or cryoprin-associated periodic syndrome, familial cold autoinflammatory syndrome (FCAS), neonatal onset multisystem inflammatory disease (NOMID), and PFAPA syndrome (210). These diseases involve recurrent attacks of fever and inflammation in the absence of infection. Many patients also have elevated levels of serum IgD during attacks. Due to the complex etiology of this group of syndromes, this section will limit the review to HIDS, which more specifically and almost always involves the elevation of serum IgD.

Patients with HIDS have recurrent attacks of fever that usually start in infancy (211). During the fever episodes, all patients have elevated serum IgD and frequently also have elevated serum IgA, while between attacks serum IgD level can be normal (211–212). The attacks generally recur every four to six weeks (213–214). HIDS is caused by a deficiency of mevalonate kinase (MvK), a key enzyme in the cholesterol biosynthetic pathway (213,215).

Multiple mutations in the MvK gene have been found in HIDS patients whose MvK activity is reduced to 5% to 15% of the normal level. MvK is located predominantly in peroxisomes (216). It is intriguing why the deficiency of a metabolic enzyme leads to the hyper-production of an Ig and inflammation. There are hypotheses proposing that MvK deficiency leads to the defects in the production of certain downstream metabolites, such as isoprenoids, that are involved in the regulation of immunity and inflammation (217). There have been reports showing exaggerated macrophage activation and dysregulated innate immune responses in HIDS patients (218–219). There are often increased levels of many pro-inflammatory cytokines and acute phage proteins during attacks, such as TNF, IL-6, C-reactive protein (CRP), IL-1β, IL-8, monocyte chemoattractant protein-1 (MCP-1), and IFN-γ during fever attacks. We have observed increased number of IgD class-switched B cells not only in the upper aerodigestive mucosa but also systemic lymphoid organs, such as the spleen, of HIDS patients (Chen and Cerutti, unpublished data). It is important to note the distinction of HIDS and selective IgA deficiency, both of which have increased numbers of IgD-producing B cells in upper aerodigestive mucosal districts. In HIDS, inflammation and fever may be further contributed to by an increase of IgD-producing B cells in the systemic immune system, which is not seen in selective IgA deficiency, a condition with very different clinical presentation (50). These clinical data are consistent with the observation of IgD's inflammation-inducing capacities, which include its ability to bind to cells of the myeloid lineage in the systemic circulation, such as basophils, and its ability to activate these cells to produce pro-inflammatory cytokines upon cross-linking (53). A mouse model of HIDS was created recently with the deletion of one allele of the MvK gene (220). Multiple matings failed to produce an $MvK^{-/-}$ mouse, probably due to embryonic lethality. $MvK^{+/-}$ mice had significantly elevated levels of serum IgD. Serum TNF levels were also increased, though not statistically significant, and cholesterol levels in tissues and blood and isoprenoids in tissues were normal. This model should prove invaluable in understanding the pathogenesis of HIDS.

Concluding remarks

Having both seen the limelight and been left in oblivion since its discovery almost 50 years ago, IgD still remains an enigmatic player in the immune system. Its perpetuation through hundreds of millions of years of evolution from fish to human clearly evinces its important functions, which remain to be addressed by future research. Clearer pictures of the function of IgD in health and disease will depend on further breakthroughs such as understanding more detailed signals that promote IgD CSR and production *in vivo*, the B-cell precursors that preferentially switch to IgD under physiological and pathological conditions, as well as the isolation of the IgD receptor and delineation of its signaling pathways in myeloid cells. To that end, we should be able to harness the functions of IgD in order to better combat infection and regulate immunity.

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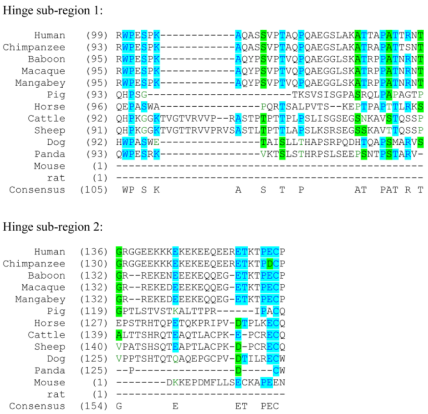

Fig. 1. Protein sequence alignment of mammalian IgD heavy chain hinge region

Sequences, with accession numbers in brackets, were downloaded from NCBI GenBank: human (P01880.2), chimpanzee (AAB89456.1), baboon (ABB89458.1), macaque (ABB89463.1), mangabey (ABB89466.1), pig (AAN03672.1), horse (AAU09794.1), cattle (AAN03673.1), sheep (AAN03671.1), dog (ABB89467.1), giant panda (AAX73311.1), mouse (P01881.2), and rat (P01883.1). Sequences were aligned using VectorNTI (Invitrogen Corporation). Hinge regions are divided into two sub-regions, with the second sub-region containing the conserved stretch of charged amino acids in primates. Hinge region boundary is based on the peptides encoded by the two hinge exons of human IgD.

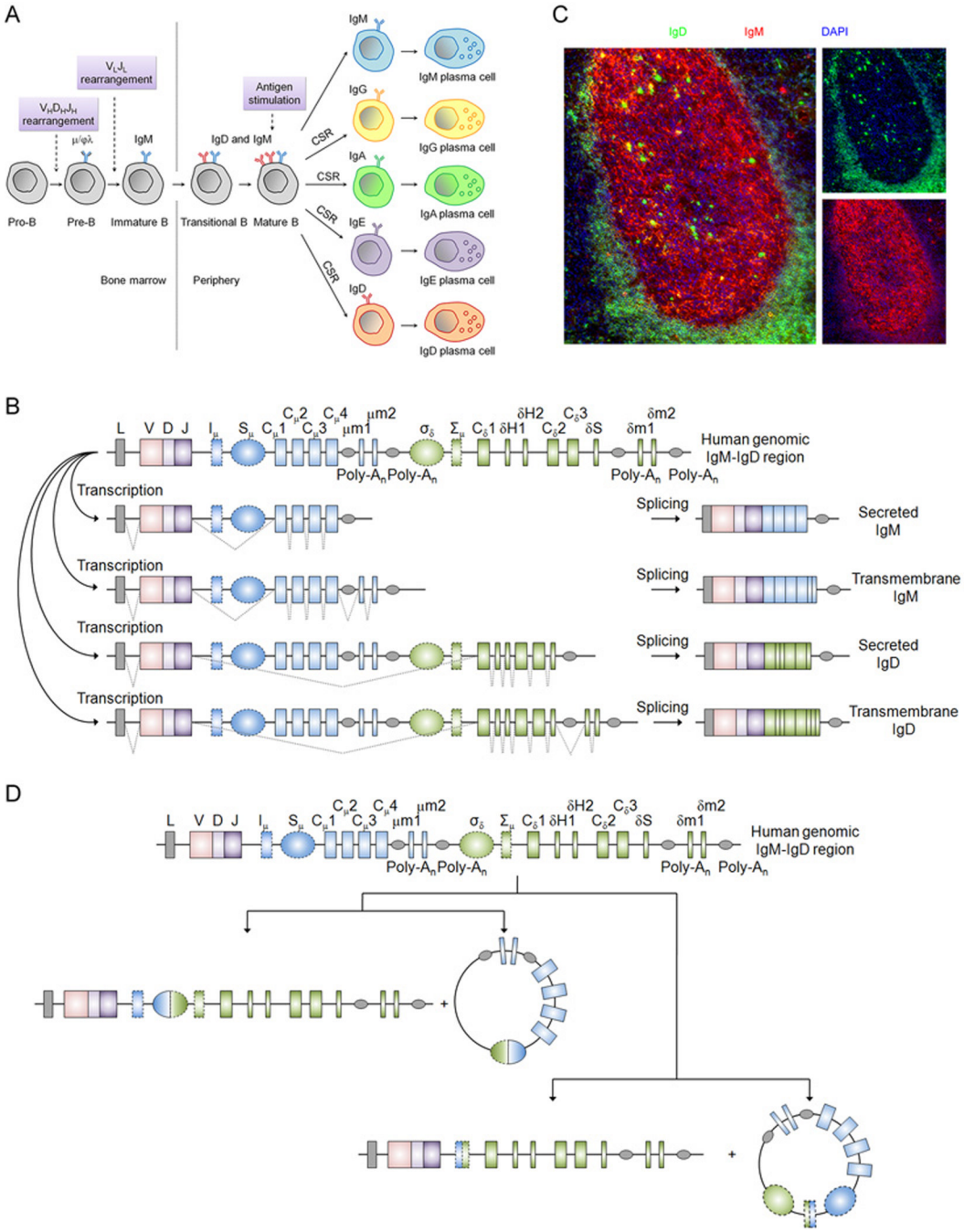

Fig. 2. Expression of human IgD by alternative splicing and CSR

(A) Ig isotype expression during human B-cell development. Pre-B cells and immature B cells developing in the bone marrow express μ heavy chain associated with either surrogate light chains VpreB and $V_{\lambda}5$ before light chain rearrangement or rearranged L chain after L chain rearrangement. Upon exiting the bone marrow, transitional and mature B cells co-express IgM and IgD through alternative splicing. IgD is expressed at a higher level on the cell surface than IgM. After antigenic stimulation, most mature B cells rapidly downregulate IgD expression and undergo class switch recombination (CSR) to express either IgG, IgA, or IgE in response to the antigenic signals encountered. Some human B cells also undergo CSR to IgD. Class-switched B cells can further differentiate into plasmablasts or plasma cells

(PCs) that secrete the respective Ig isotype. Some mature B cells can downregulate IgD and develop into IgM-secreting PCs perhaps either without undergoing CSR or by undergoing 'silent CSR' involving intra-S_μ region DNA recombination (Chen and Cerutti, unpublished data). (B) Expression of IgD and IgM by alternative splicing in mature B cell. Exons encoding the rearranged VDJ region and the various domains (including the membrane and secreted portions) of IgM and IgD are shown in boxes. Dotted gray lines show the various splicing configurations of primary transcripts to yield secreted and transmembrane forms of IgM and IgD. (C) IgD and IgM expression in follicular mantle and germinal center B cells. A lymphoid follicle in human tonsil is shown. Mature B cells located in the follicular mantle zone prior to antigen encounter express more IgD (green) than IgM (red) on the surface due to the higher stability and translation efficiency of δ mRNA than μ mRNA. After antigenic stimulation, they enter the germinal center, where IgD is rapidly downregulated at transcriptional level and IgM is transcriptionally upregulated and the half-life of μ mRNA is significantly prolonged, as evidenced by the drastic reduction of IgD and increase in IgM in the germinal center. Cells that stain strongly with IgD in the germinal center are class switched IgD-secreting cells. Some IgM staining in the germinal center is contributed by follicular dendritic cells that capture IgM-containing immune complexes. DAPI (blue) stains cell nuclei. Original magnification, ×40. (D) Expression of IgD by CSR. Schematic representation of C_μ-to-C_δ CSR in human, which has been found to occur between S_μ and σ_δ regions (left) and between I_μ and Σ_μ regions (right) in normal and malignant B cells. The intervening DNA is looped out after CSR and forms a switch circle.

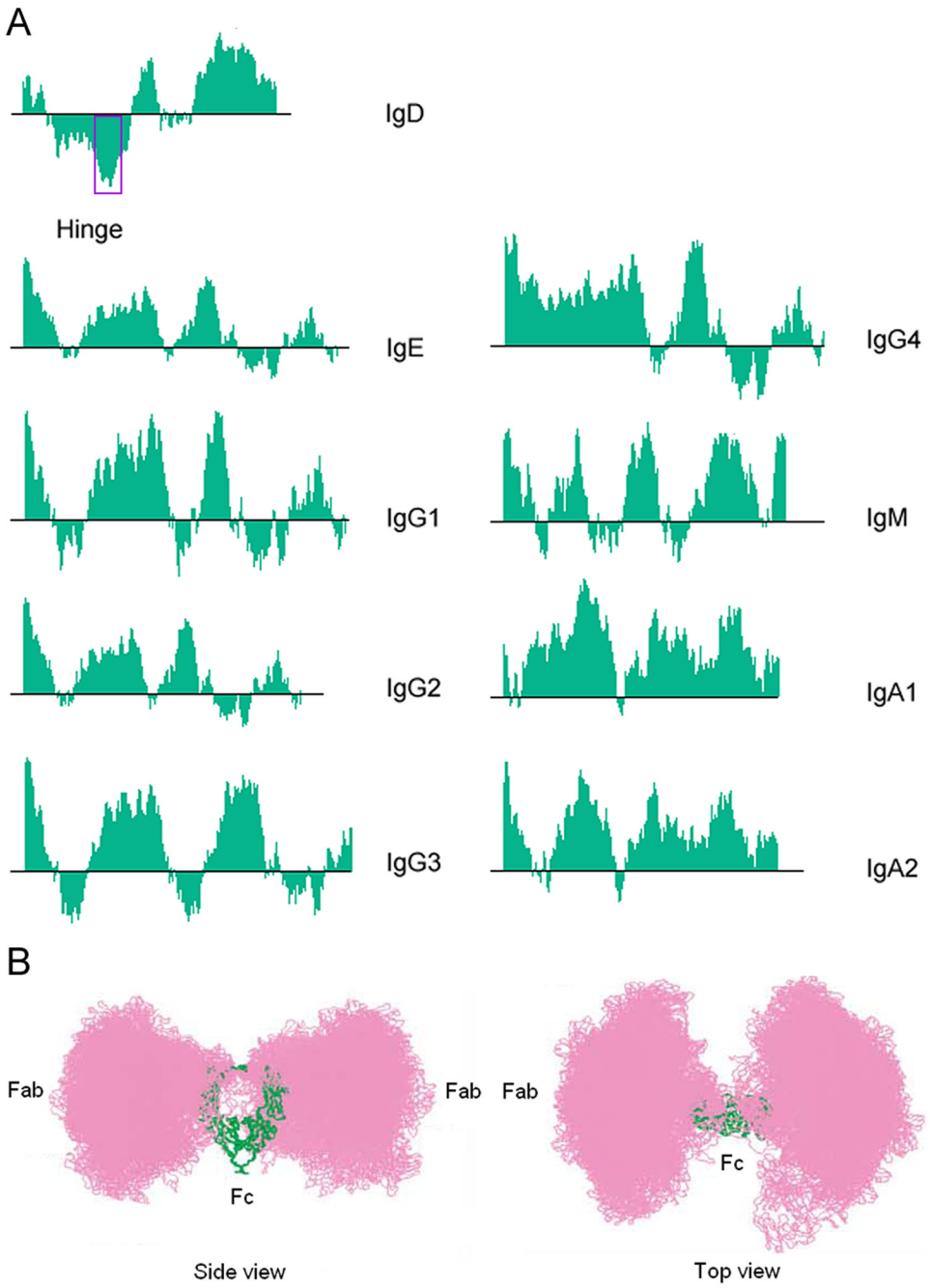

Fig. 3. Human IgD hinge region contains a sequence resembling that of consensus ligand of heparin

(A) Hydrophobicity indices of human Ig isotypes at pH 3.4 determined *in silico* using the VectorNTI software. The region of high hydrophilicity in IgD is demarcated by a rectangle. Sequences of these proteins were downloaded from NCBI GenBank, with GenBank ID in brackets: IgD (P01880.2), IgE (P01854.1), IgG1 (AAH73782), IgG2 (AAH62335), IgG3 (AAH33178), IgG4 (AAh25985), IgM, (AAH89412), IgA1 (AAH87841), IgA2 (AAH73765). (B) Three-dimensional motions of the IgD Fab parts around the Fc part. The Fab parts are colored in pink and the Fc part is colored in green. The length and the semi-extended flexible conformation of the IgD hinge allow the Fab parts to swivel around the Fc

part in three dimensions in solution. This motion gives the Fab parts extraordinary flexibility in capturing antigens, as well as renders the Fc part shielded by the Fab parts in solution. The Protein Data Bank (PDB) ID of the best-fit IgD structure predicted in this study is 1ZVO. Modified from (119) with permission. [Permission from Elsevier to use the figure shown in Fig. 3B, modified from (119), can be found at https://s100.copyright.com/CustomerAdmin/PLF.jsp?lID=2010031_1268678952456.]

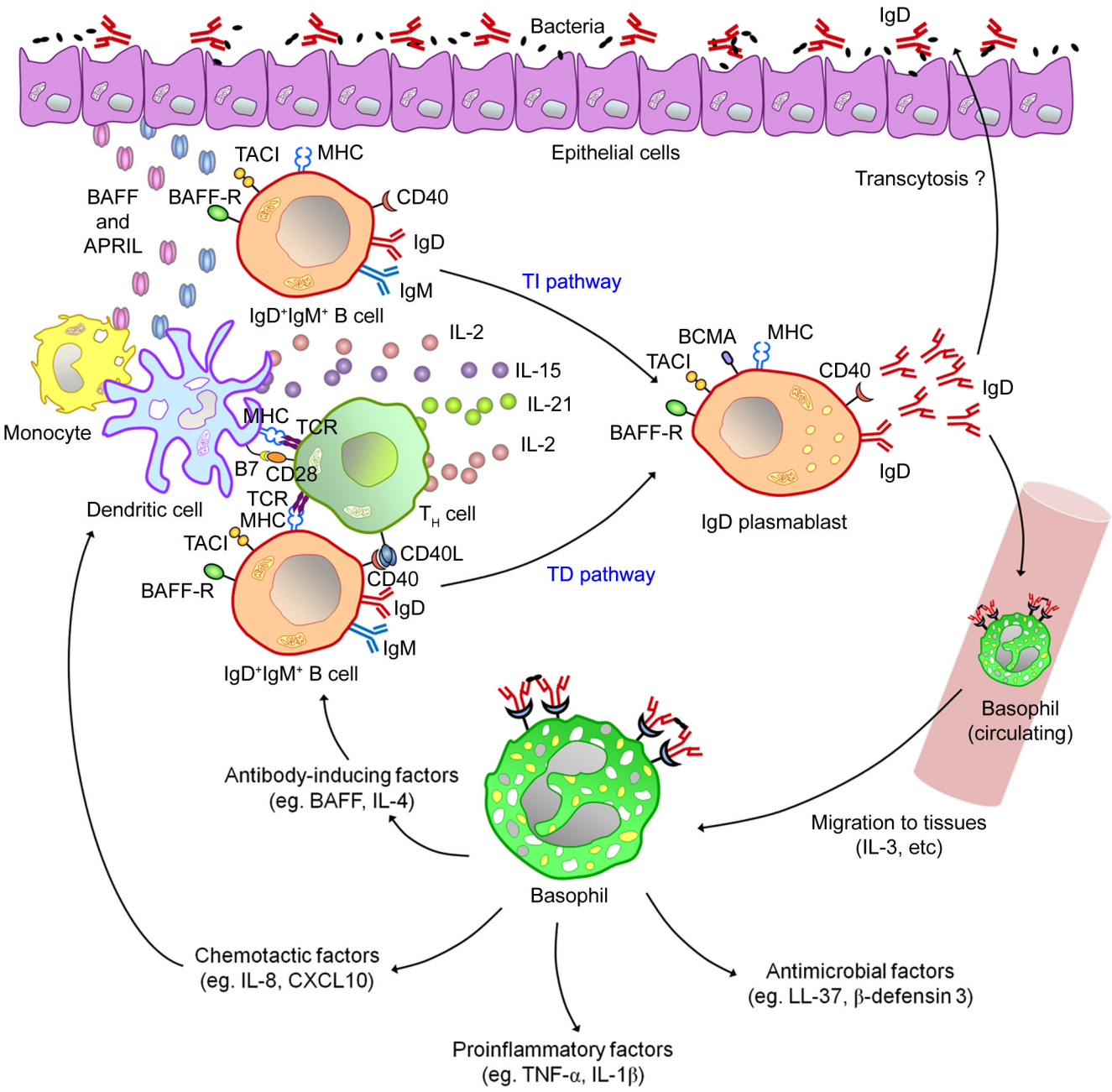

Fig. 4. Model of human IgD regulation and function

B cells from the upper aerodigestive mucosa undergo CSR from C_μ to C_δ through local T-dependent (TD) and T-indepdent (TI) pathways involving CD40L, BAFF, or APRIL together with a unique cocktail of cytokines, including IL-2 and IL-21 or IL-15 and IL-21. CSR requires AID and generates mucosal and circulating IgD plasmablasts that secrete IgD reactive against respiratory bacteria. Mucosal IgD might enhance local immunity after translocating across epithelial cells, whereas circulating IgD binds to basophils. In addition to delivering rapid innate immune signals and alerting the immune system as to the presence of invading bacteria, basophils exposed to IgD-reactive antigens migrate to systemic and mucosal lymphoid organs, perhaps in response to chemotactic factors released by IgD-

stimulated mast cells. Tissue-based basophils enhance immune protection by releasing antimicrobial, opsonizing, B-cell-stimulating, chemotactic and pro-inflammatory mediators such as cathelicidin, IL-1β, IL-4, IL-8, IL-13, CD40L, BAFF, APRIL, TNF, and CXCL10, but not histamine. Finally, IgD-armed basophils may regulate B-cell homeostasis through tonic release of the obligatory B cell survival factor BAFF in response to IgD-reactive foreign or autologous antigens.