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Human poly- and cross-reactive anti-viral antibodies and their impact on protection and pathology

Lucile Warter · Ramapraba Appanna · Katja Fink

Katja Fink

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Abstract Anti-viral immune responses have been studied extensively in order to inform rational vaccine design. Following viral infection, the balance of pathologic and protective antibody responses in the host can critically influence clinical outcomes. Comparisons of the different classes of antibodies produced after acute or chronic viral infections have uncovered common features of anti-viral responses, but these analyses have also revealed temporal differences in neutralizing antibody production, variable neutralization potency and differential induction of cross-reactive antibodies. Cross-reactive antibodies are known to play crucial protective roles in host responses to chronic viral infections; recent studies in human immunodeficiency virus long-term controllers have identified a novel class of broadly neutralizing antibodies generated from highly mutated and selected memory B cells. Here, we summarize the various roles played by cross- and poly-reactive antibodies in acute and persistent viral infections, with a focus on the potential contribution of these antibodies to dengue virus (DENV) immunopathology and host protection. Since host antibodies profoundly alter the course of viral infections, effective DENV vaccine design will require a better understanding of the origin, affinity maturation and protective potential of the poly-reactive and cross-reactive antibodies induced by different interventions.

Keywords B cells · Memory · Plasmablasts · Viral infection · Antibodies · Original antigenic sin · Dengue · Influenza · HIV · HCV

Abbreviations

ASC	Antibody secreting cell
DENV	Dengue virus
DF	Dengue fever
DHF	Dengue hemorrhagic fever
PB	Plasmablast
PC	Plasma cell
HIV	Human immunodeficiency virus
HCV	Hepatitis C virus

Introduction

Virus-infected host organisms produce a variety of different classes of antibodies that can influence the efficacy of anti-viral immune responses. When high titers of serotype-specific, highly neutralizing antibodies are produced, the host is protected against later re-infection, and the disease is mild or asymptomatic. In contrast, when cross-reactive, non-neutralizing antibodies prevail, host protection can be limited to the serotype of previous viral infections and allow novel mutant viruses to persist. The efficacy of anti-viral vaccination strategies is similarly modulated by the balance of different antibody classes elicited upon inoculation. The following review summarizes the classes of host antibodies that can alter the course of viral infections and discusses the potential impact of these molecules on viral pathogenesis and vaccine design.

Lucile Warter and Ramapraba Appanna contributed equally to this work.

L. Warter · R. Appanna · K. Fink (✉)
Singapore Immunology Network (SIgN), Agency for Science, Technology and Research (A*STAR), 8A Biomedical Grove, #03 Immunos, Biopolis, Singapore 138648, Singapore
e-mail: Katja_Fink@immunol.a-star.edu.sg

Natural anti-viral antibodies

Natural antibodies are produced by B cells that have not been selected by infection or vaccination, and the antibodies are not affinity matured [1, 2]. Despite the absence of selection in the periphery, natural antibodies are capable of binding to and neutralizing pathogens, albeit with very low efficacy. The biological importance of natural antibodies directed against bacterial and viral infections has been demonstrated in antibody-deficient mice, which are protected against lethal infections after serum transfer from antibody-competent, pathogen-naïve animals [3–5]. The majority of murine natural antibodies are IgM class and are produced by B-1 cells, an innate B cell population that is abundant in the peritoneum [6], but mice can also produce natural IgG, which protects against intranasal infection with *Haemophilus influenzae*, suggesting that natural IgG might play a role in mucosal immunity [7]. In humans, the importance of natural antibodies is most evident in patients with common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA). Both genetic diseases present with very low titers of all Ig isotypes, and patients suffer from common infections of the respiratory and gastrointestinal tracts. Natural antibodies in humans are comprised of IgM, IgG and IgA isotypes [8]. An important direct effect of natural antibodies in human sera is the activation of complement-mediated killing and phagocytosis [9–11]. Natural antibody interactions with complement are essential for clearing oxidatively stressed erythrocytes from the circulation and also help to maintain homeostasis and immunological responsiveness [12]. In addition to the neutralizing effects of natural antibodies and their various complement-mediated functions, indirect effects of natural antibodies have also been reported. For example, human dendritic cell differentiation and maturation are enhanced in the presence of natural antibodies [13].

Methods that permit the cloning and expression of monoclonal antibodies (mAbs) from individual human B cells have progressed tremendously in the past few years, which has facilitated the study of the 'natural' specificities of large repertoires of B cells and antibodies [14–17]. It is now widely accepted that a hallmark of natural antibodies is their poly-reactivity [17–20]. Natural antibodies often bind to self-antigens and have therefore been the subject of extensive study in patients with autoimmune diseases [21, 22]. Even in healthy individuals, self-reactive B cells are abundant at the early stages of differentiation in the bone marrow, yet most are negatively selected, and relatively few self-reactive B cells are evident in the periphery [23, 24]. Since a positive B-cell receptor (BCR) signal at the pre-B cell stage of differentiation is required for selection [25, 26], it is plausible that B cells that bind to several epitopes may have a survival advantage. In the periphery, poly-reactive B cells that are capable of binding to multiple pathogens provide an efficient immunological defense strategy. Since poly-reactive B cells are present in the organism without prior priming, these B cells can respond immediately after an infection. It remains unclear whether pathogen-specific natural antibodies recognize similar structures to self-reactive antibodies, or whether these molecules represent two genetically and structurally distinct classes of antibodies.

Characteristics of poly-reactive antibodies

A comparison of the structural, biochemical and genetic features of pathogen-specific and self-specific antibodies can provide insight into the origin and relatedness of these two groups of antibodies. A number of comprehensively characterized poly-reactive antibodies are reported in the literature (Table 1).

A common feature of poly-reactive antibodies appears to be their high level of somatic hypermutation (SHM) and a bias toward certain variable gene usage. We recently observed that dengue virus (DENV)-specific antibodies preferentially use VH1 elements (Xu et al., submitted); a feature that is also shared by antibodies specific for HIV, HCV and influenza (Table 1). Given that VH3 dominates in the natural B-cell repertoire [19, 27], it is intriguing that poly- or cross-reactive antibodies with completely unrelated specificities appear predisposed to VH1 usage. VH1*69 elements have been shown to bind to hydrophobic pockets [28, 29]. Highly specific neutralizing antibodies can recognize rapidly mutating, hydrophilic viral epitopes (and possibly also glycosylated epitopes), but antibodies to more conserved hydrophobic residues may also be important for blocking virus entry.

The structural features that define poly-reactivity are not fully understood. Long VH CDR3 regions may be associated with self- or poly-reactivity, but long CDR3 sequences can also be detected in mono-specific antibodies [18, 23]. Structural flexibility of the variable VH region appears to be a particular hallmark of poly-reactive antibodies [30–32]. However, increased flexibility of VH1 and VH4 sequences relative to VH3 sequences has yet to be formally demonstrated. Intriguingly, a fraction of IgG antibodies can acquire or increase poly-specificity upon exposure to denaturing chaotropic agents, low or high pH, high concentrations of salts, ferrous ions and reactive oxygen species [33, 34]. The concept that inflammation induces poly-reactivity was proposed based on the finding that the anti-bacterial binding activity of human IgG transferred into SCID mice was increased after the mice were treated with complete Freund's adjuvant [35]. However, it is unclear whether this poly-reactivity can be attributed to

Table 1 Genotype, phenotype and specificity of poly-reactive antibodies

Target	Origin, clone name	Specificity	Selection (S vs. R mutations)	Mutated	Isotype, VH gene usage	References
Self		Insulin	Yes	VH	IgG1; From insulin-specific germline template	[111]
Self		Polyreactive; IgG, Myoglobin, Thyroglobin, ssDNA	?	No	IgM	[112]
HIV	Phage library from HIV-infected donor	DNA, OVA, transferring, BSA, Tetanus toxoid, EGF, IgG Fc, ganglioside, no binding to HIV	Yes	VH, VL	VH1, VH4	[30]
HIV	Four plasma cell clades	gp41, HepG2 Gut flora lysate	Yes	VH	VH3 dominance in acute phase plasma cells, non-neutralizing	[19]
HIV	410E, 2F5	gp41 membrane proximal region, Cardiolipin, HepG2	?	VH: 12.6%	VH1-69*10 Broadly HIV-neutralizing	[113]
HIV	CAP206-CH12	gp41 membrane proximal region, histones, centromere B autoantigens and ribonucleoprotein	?	VH: 11.9%	VH1-69*04, HIV-neutralizing	[114]
HIV	Memory B cells	gp140, insulin, LPS, ssDNA, dsDNA	?	VH	VH1 dominance	[115]
HIV	Memory B cells	gp140, limited cross-neutralization			VH1 dominance	[116]
HIV	Natural IgM	gp160, p24, p66, beta-galactosidase	No	No	VH3, VH4, Vlambda 1–3, VK4	[117]
Self	Splenic Marginal Zone Lymphoma SMZL	Glandular tissue, gastric glandular, bronchial epithelial cells, PANC1 cell lysate, HEK293T lysate, insulin, ssDNA, lipopolysaccharide (LPS), TG, BSA and HSA	?	VH CDR3	VH1-2,	[118]
Flu	Human IgM+ memory B after vaccination	HA stem helical structure, virus subtype cross-neutralizing, cross-protective against H5N1 and H1N1	?	VH	VH1-69	[28, 119, 120]
Flu	IgG+ ASCs after vaccination	Strain cross-reactive, highest affinity for current vaccine strain	?	VH up to 10%	VH4, ?	[38]
HCV	B-cell lymphoma	E2	Yes	VH	VH1-69	[121]
HCV	B-cell lymphoma	Monoclonal cryoglobulin with RF activity (based on sequence similarity); serum reactivity: RF, HCV	?	VH, VL	Bias to VH1 51p1/VK3 Humkv325,	[122]
HCV	MALT lymphoma	H.pyloris sonicate, IgG, LPS, ssDNA	For some antibodies	VH, long CDR3	VH1-69*1/5 or VH3, long CDR3	[123]

S silent mutation, *R* replacement mutation, *VH* variable region of the antibody heavy chain

highly mutated clones such as those described in Table 1, or whether the IgG fraction capable of increased binding reactivity was actually comprised of natural antibodies with low binding affinity. Nevertheless, inflammation may impact on antibody poly-reactivity in vivo and could induce secondary rearrangements in memory B cells, resulting in an increased frequency of sequences that incorporate VH1 elements. Several VH1 elements are downstream of VH3, which are the most commonly used elements in human peripheral blood B cells [36]. It is possible therefore that stepwise B cell re-arrangements could occur via successive germinal center reactions.

Selection and maintenance of poly-reactive memory B cells

Germinal centers (GC) are organized structures where B-cell mutation is triggered by soluble and cell-contact dependent signals. B cells that are capable of interacting with antigen presented in GC are stimulated to proliferate. This process creates competition between B cells that express low affinity BCRs and those that express a high-affinity BCR for the available antigen, resulting in the selection and survival of high-affinity memory B cells due to their inherent binding advantage.

GC-independent pathways exist for maintaining specific B cells, but the memory cells generated via these routes differ from classical memory B cells. GC-independent memory B cells incorporate fewer mutations and exhibit either an IgG or an IgA phenotype [37]. The SHM of virus-specific, poly-reactive antibodies (Table 1) is highly suggestive of selection in GC. For persistent viral infections, selection in GC might be a continuous process, but for acute viral infections such as dengue or influenza, new GC are formed during re-infection, and these are likely to be populated with preexisting memory T and B cells. It remains to be determined how poly-reactive B cells as those in Table 1 are maintained in the memory pool without being negatively selected. It is possible that poly-reactive Abs have a competitive advantage because they are selected on self-antigens or structures that are present on commensal bacteria or opportunistic viruses. Moreover, somatically hypermutated B cells with high affinity are preferentially activated during infection [38], and a proportion of these cells might persist in the circulation as memory B cells (Fig. 1).

Of particular relevance in the context of vaccination strategies are the potential negative effects of human cross-reactive antibodies that exhibit high affinity and are efficiently re-activated during re-infection. Severe dengue disease is associated with secondary DENV infections, and there are several lines of evidence indicating that cross-reactive antibodies can enhance disease symptoms. However, this has not been formally proven in humans. To support the development of novel vaccines, it will be crucial to distinguish antibodies that are merely cross-reactive in vitro from those that can successfully mediate cross-protection in vivo. Antibodies with protective capacity against more than one virus serotype are known to exist, but they are not as potent as serotype-specific protective antibodies [39, 40].

Serotype cross-reactive antibodies in acute and chronic viral infections

Acute infections: dengue and influenza viruses—original antigenic sin

Influenza virus

'Original antigenic sin' is a phenomenon whereby newly formed antibodies react more strongly with a primary historical antigen than with the current antigen eliciting the

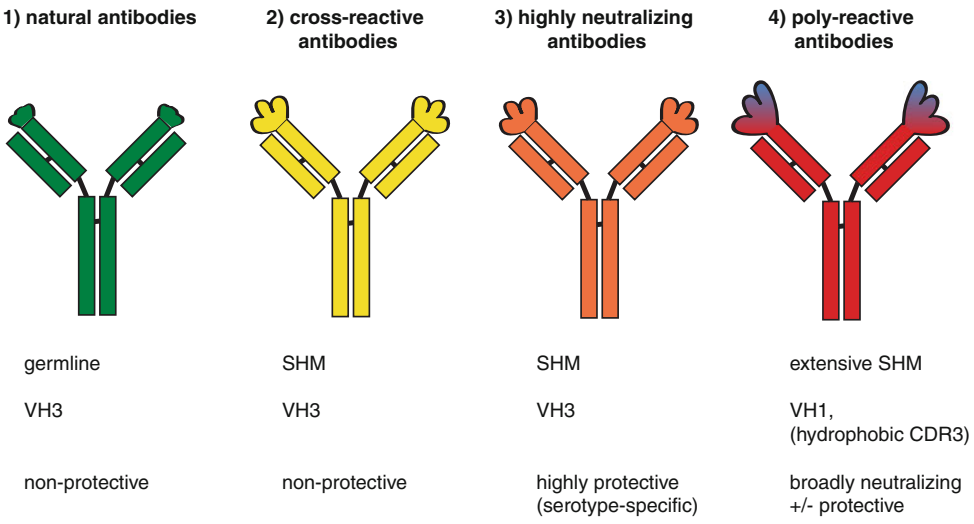

Fig. 1 Types of antibodies generated after viral infections

antibody response. This phenomenon was initially described by Davenport and colleagues, who observed that humans raised only limited antibody responses to infection with new strains of influenza, but simultaneously mounted strong antibody responses to influenza strains that they had previously been infected with [41]. Since this initial observation more than 50 years ago, 'original antigenic sin' has been extensively studied in human influenza infection and in numerous animal models of disease. Recently, the existence of original antigenic sin has been called into question by two studies showing that most of the antibodies generated after virus-specific influenza vaccination in humans do in fact bind to the current vaccine strain with higher affinity than to the previous vaccine strains [38, 42]. However, this discrepancy can most likely be attributed to the use of inactivated influenza vaccine strains in a murine model, which cannot replicate original antigenic sin [43].

Dengue virus (DENV)

The original antigenic sin phenomenon is a notable feature of sequential human infections with dengue virus (DENV). While DENV infection leads to potentially life-long protection against the infecting serotype, it does not protect against subsequent infections with heterologous serotypes. It is therefore possible for an individual to be infected four separate times by each different strain of DENV. During sequential DENV infections, titers of antibodies specific for the primary serotype remain higher than those specific for the serotype causing ongoing infection. DENV is therefore thought to induce an 'original antigenic sin' effect comparable to that described for influenza [44, 45]. Interestingly, it has been shown that secondary infection with new DENV serotypes also elicits the proliferation of cross-reactive, high-affinity T-cell clones that compete with low-avidity naïve T cells for the current DENV serotype [46]. These data suggest that a phenomenon analogous to antibody-associated original antigenic sin may also characterize T-cell responses after secondary and sequential DENV infections [46, 47]. While the phenomenon of original antigenic sin has now been well documented, the mechanisms that underpin this effect have not been fully elucidated. Viral induction of original antigenic sin may represent a potential immune escape mechanism [43], and it will be important to determine the factors that drive this effect in order to design more effective novel vaccines.

Until very recently, antibody responses to DENV were investigated primarily in murine models. However, during the last few years, human antibody responses to primary and sequential DENV infections have become increasingly well characterized through the analysis of sera and monoclonal antibodies derived from DENV-infected patients. Human antibody responses to DENV primarily target the envelope protein (E), the precursor membrane (prM) and the nonstructural protein 1 (NS1), although antibody responses targeting alternative nonstructural proteins, including NS3 and NS5, have also been described [45, 48–53].

To date, DENV-specific antibody responses in humans have been investigated largely in recovered patients. Surprisingly, most human antibodies elicited after primary DENV infection appear to be serotype cross-reactive and non-neutralizing, with only a minority of antibodies exhibiting both serotype specificity and neutralizing potency [45, 48–53] (Table 2). Specific antibodies against prM, E domain I, E domain II and NS1 are mostly cross-reactive and display poor neutralizing capacity. A major component of the cross-reactive B-cell response during primary DENV infections are prM-specific antibodies. In contrast, E domain III–specific antibodies are highly neutralizing and serotype specific [49, 51], with only a minority exhibiting cross-reactivity. During secondary DENV infections, all cross-reactive antibody responses are drastically amplified, including the cross-reactive and neutralizing E domain III–specific antibodies [45].

Few data are available that describe antibody responses at the single human B-cell level during acute primary or secondary infection with DENV [54]. Mathew and collaborators demonstrated that DENV E protein–specific antibody responses are predominantly serotype specific

Table 2 Onset of cross-reactive antibodies in acute versus chronic human viral infections

Infection	Virus	Cross-reactive antibodies: time of onset	References
Acute	Dengue virus	After primary infections: 5–10 days	[51, 124]
		After repeated infection; 3–5 days	
	Influenza virus	After primary infections: ~9 days	[125]
		After repeated infection: <7 days	[126]
Chronic	HCV	In chronic phase after primary infection	[62]
		In acute phase after secondary or sequential infection	[63]
	HIV	2.5 years (rare cases; 1 year)	[55]

during primary infections, while they are highly serotype cross-reactive during and after secondary infections [54]. These data suggest that cross-reactive B cells may have a survival advantage.

Chronic infections: human immunodeficiency virus (HIV) and hepatitis C virus (HCV)

Human immunodeficiency virus (HIV)

Up to 30% of patients with chronic HIV-1 infection develop cross-neutralizing antibodies within an average time of 2.5 years postinfection. In rare cases, these cross-neutralizing antibodies can be detected as early as 1 year postinfection [55] (Table 2). The fact that cross-reactive neutralizing antibodies may arise several years after initial infection suggests that maturation of the antibody response is necessary to efficiently target conserved viral epitopes [56]. In line with this notion are several studies reporting that the breadth of cross-reactive neutralizing antibody responses correlates with plasma viral load, suggesting that persistent HIV replication is necessary to elicit potent cross-reactive antibodies [57, 58]. While the level of cross-neutralizing antibodies does not affect the disease course and resultant immunodeficiency [59, 60], the induction of broadly cross-reactive neutralizing antibody responses might yet prove key to the development of an effective HIV vaccine [56, 61].

Hepatitis C virus (HCV)

Human HCV infections are associated with the induction of cross-reactive antibodies that bind to multiple virus variants. Levels of HCV cross-reactive antibodies are higher in patients with chronic HCV infection compared with acute HCV infection, suggesting that cross-reactive antibodies might be induced by amino acid evolution of the virus over the course of disease, due to the virus lacking a proofreading polymerase [62]. In a recent study that compared primary and secondary HCV infections, spontaneous clearance of the virus was achieved in more than 80% of re-infected patients compared with only 25% of primary infections. During the acute phase, cross-reactive antibodies were detected in the majority of re-infected patients who subsequently cleared the virus, but not in patients who progressed to chronic infection [63] (Table 2). The detection of HCV cross-reactive antibodies in patients with chronic infections [62], together with the lack of cross-reactivity in *re*-infected chronic patients [63], suggests that antibody responses to the virus are markedly different between primary and secondary exposures, and imply a role for cross-reactive antibodies in HCV clearance upon re-infection.

Pathology related to cross-reactive antibodies

Cross-reactive antibodies in dengue and other viral infection

The most severe form of dengue disease, dengue hemorrhagic fever (DHF), is associated with preexisting immunity to the virus. A study carried out among infants and children in Thailand confirmed that up to 99% of DHF cases exhibited cross-reactive antibodies against the DENV serotype of infection that caused the DHF [64, 65]. After secondary infection with a heterotypic serotype, the pre-existing cross-reactive antibodies form virus–antibody complexes. These complexes bind to Fc receptor–bearing cells, which can lead to virus uptake and replication [50, 66–68]. Further evidence for 'antibody-dependent enhancement' (ADE) of the infection is provided by infants born to mothers with established dengue immunity. The maternally derived DENV-neutralizing IgG elicits protection for several months, but as titers of IgG decline below a protective threshold, infants enter a period of increased DHF risk [69–71]. Another study in Thai children indicated that viral titers in plasma from patients with DHF are higher than those in patients with dengue fever (DF), which is a milder form of the disease [66]. Guzman et al. [72] reported that the majority of DHF cases recorded during the DENV 2 epidemic in Cuba in 1981 occurred in patients with dengue antibodies acquired during the previous DENV 1 epidemics in 1977. Several studies have succeeded in demonstrating ADE in vitro, reporting that virus titers are significantly increased following Fc receptor (FcR)–mediated uptake of virus–antibody complexes by monocytic cells [73–75]. In a monkey model of infection, prior injection of a humanized mAb increased DENV infection, and this effect was abrogated when the Fc part of the antibody was mutated to prevent binding to Fcγ receptors (FcγR) [67].

Furthermore, ADE also seems to be a mechanism whereby immature or partially mature virions, which cannot attach to host receptors, can still be brought into cells via FcγR-mediated uptake and produce infectious progeny. Cleavage of the prM structural protein and virion maturation occur once the immature virus–antibody complex is internalized, allowing the virus to fuse with the host cell membrane and release viral RNA into the cell [76]. Intriguingly, the uncleaved prM protein and fusion loop, which are exposed on immature virus particles seem to be highly immunogenic structures that trigger an abundant antibody response [50]. Besides antibodies to immature virus particles, neutralizing E protein–specific antibodies can also enhance infectivity at low antibody concentrations and weak avidity [71, 77]. However, the lack of relevant animal models of dengue disease has so far prevented a direct proof of the relevance of ADE in humans.

The phenomenon of ADE of viral infection has been documented in several viruses besides DENV, including respiratory syncytial virus (RSV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), Ebola virus and Hantavirus [78–82].

ADE of RSV infection was first observed in two monocyte-like cell lines (U937 and THP-1) in the presence of RSV-specific monoclonal antibodies [83]. By blocking the binding of these RSV-specific antibodies, infection of macrophages was significantly diminished. Antibody-mediated enhancement of virus uptake into macrophages may contribute to the pathogenesis of RSV bronchiolitis [78].

HCV often induces persistent infection despite the presence of high levels of anti-viral antibodies. Limited neutralizing activity of mAb against HCV pseudotypes has been observed in animals immunized with recombinant HCV envelope proteins or in sera from chronic HCV patients. Sera from vaccinees that contain antibodies that bind to the HCV envelope glycoprotein are unable to efficiently neutralize the infection [81, 84–87]. Further experiments revealed an increase in HCV pseudotype plaque formation when neutralizing sera were diluted below effective levels. This enhancement of HCV pseudotype titers was shown to be mediated by Fcγ receptor I (FcγRI) or FcγRII [81].

During HIV infection, the cross-linking of virus-activated complement components and virus/antibody conjugates with Fc receptors or complement receptors has been shown to enhance the infection of susceptible cells. During acute infection, non-neutralizing antibodies which bind to the HIV-1 envelope have been proposed to play a role in HIV-1 dissemination and disease pathogenesis [82]. HIV-1 activates complement, which facilitates viral interactions with host cells that express complement receptors such as CR2, CR3 and CR4 [88]. Interestingly, the CD4 receptor seems to be involved in complement-mediated enhancement of infection. The deposition of complement on the virus brings the gp120 protein close to CD4 molecules on the surface of the cells, eventually leading to viral entry [82, 89].

During Ebola Zaire virus infection in humans, antibodies have been shown to play an important role in enhancing viral infectivity [80]. Most strains of Ebola virus trigger a rapidly fatal hemorrhagic disease in humans. Sera derived from recovered patients enhance the infection of primate kidney cells, and this enhancement is mediated by antibodies against viral glycoprotein and involves complement component C1q [80]. In vitro data from macrophage-like cell lines J774.1, P388D1 and U937 have further demonstrated ADE in hantavirus infection. Monoclonal antibodies to envelope glycoproteins of hantavirus can support ADE activity, whereas antibodies against nucleocapsid protein cannot [79].

Infection-induced autoantibodies and their pathogenic role in dengue and viral diseases

Clinical signs such as fever, thrombocytopenia, hemorrhagic tendency and plasma leakage are key characteristics of severe DENV disease [90, 91]. In DENV infection, high levels of viral NS1 protein in the circulation alongside pre-existing cross-reactive, non-neutralizing antibodies have been shown to activate the complement system, which contributes to vascular leakage. In addition, DENV-specific antibodies that cross-react with host proteins were detected in sera from infected patients [92, 93], including anti-platelet IgM antibodies derived from a DHF/DSS patient. In vitro, autoantibodies derived from DHF patient sera exhibit higher binding activity against platelets than antibodies derived from DF patients. These antibodies can also induce platelet lysis through complement activation and inhibition of platelet aggregation [92]. Moreover, the generation of cross-reactive autoantibodies against endothelial cells in DHF patients has been proposed to induce endothelial dysfunction [93], and autoantibodies can indeed induce endothelial cell apoptosis in patients infected with different DENV serotypes [94]. Liu J et al. generated a panel of murine monoclonal antibodies against DENV and showed that an anti-NS1 mAb DB16-1 could cross-react with HUVEC cells and human blood vessels. These data suggested that DB16-1 might act as an autoantibody against the amino acid sequence of LYRIC (Lysine-rich CEACAM1 co-isolated protein) expressed on endothelial cells and drives the transient vascular leakage that occurs in DHF/DSS [95]. The anti-NS1 autoantibodies were shown to specifically cross-react with noninfected endothelial cells and trigger intracellular signaling pathways that lead to the production of nitric oxide (NO) [94], which is typically produced by macrophage-lineage cells in order to inhibit DENV replication [96].

One of the proposed mechanisms of DENV-induced autoimmunity is molecular mimicry [97]. A proteomic study and sequence analysis identified homology between the C-terminal region of DENV NS1 with host target proteins. Further sequence homology between coagulation molecules and different regions of the core, prM, E and NS1 virus proteins was also observed. In addition, titers of plasminogen cross-reactive antibodies correlated with the occurrence of hemorrhage in dengue patients, with amino acid sequence 101–106 of E protein displaying similarity to factors XI, X, IX, VII, II (thrombin), plasminogen and tissue plasminogen activator [97–100]. Plasminogen is known as the primary mediator of fibrinolysis [98]. However, with the exception of isolated case reports, patients with DHF usually recover rapidly without any sign of autoimmune disease. The role played by autoantibodies in the pathogenesis of DHF in humans thus remains ambiguous and will require further investigation (Fig. 2).

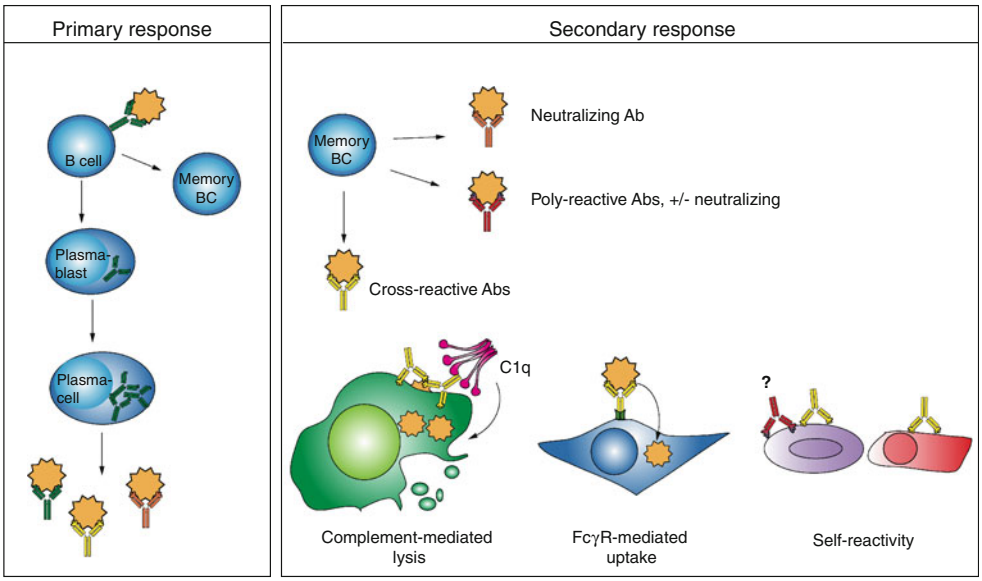

Fig. 2 Protective and pathologic mechanisms of antibodies produced after primary and secondary dengue infection

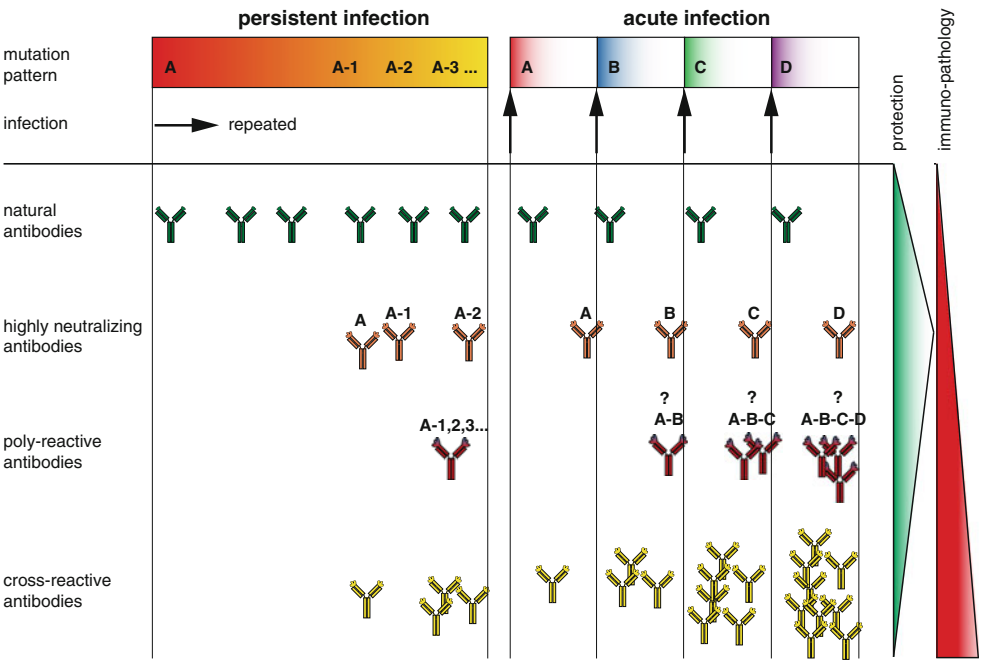

Fig. 3 Protective capacity of different types of antibodies in acute and chronic infections. During chronic infection, the virus mutates (from A to A-1 to A-2, etc.) and escapes the immune response repeatedly, thus enabling new rounds of infection. During acute infections, the virus is controlled before it can accumulate enough mutations to escape the immune response, and neutralizing antibodies are specific for the infecting strain (virus A, B, C or D)

The possible role of molecular mimicry in DENV pathogenesis can also be extended to numerous other viral infections. For example, in AIDS-free HIV patients, molecular mimicry between HIV-gp20 and platelet gpIIIa was suggested to play a role in thrombocytopenia [101]. Similarly, HCV core envelope 1 protein seems to induce thrombocytopenia due to a mimicry with platelet gpIIIa [102]. In 5% of patients with chronic HCV infection, anti-liver–kidney microsome type 1 (LKM1) autoantibodies are directed against cytochrome P450 2D6 (CYP2D6) [103]. Moreover, mixed cryoglobulinemia in HCV-infected patients can cause vascular damage in the liver, kidneys and the skin [104–106].

Conclusions

An important difference between the viruses described in this review is the extent of amino acid variation among the virus variants, genotypes and serotypes. While HCV has no serotypes, there are six distinct HCV genotypes, and dozens of subtypes and quasi-species are observed in patients

[107]. Influenza evolves rapidly and undergoes continuous mutation known as 'genetic drift', thus antibodies to closely related variants are still cross-protective. However, no cross-protection occurs if a new subtype of influenza emerges due to re-assortment of two distinct strains (genetic shift) [108]. Given these differences in mutation rates, it can be expected that cross-reactive antibodies will have differing clinical significance in different viral infections (Fig. 3). The enhanced disease severity observed during repeated dengue infections might be related to the genetic similarity of each dengue serotype. The pathogenesis of DENV may therefore result from maintaining a mutation rate high enough to allow immune escape, but simultaneously low enough for efficient binding of cross-reactive antibodies to enhance viral uptake by host cells and/or to activate complement.

In chronic viral infections in man, cross-reactive antibodies arise much later than during acute viral infections, suggesting that cross-reactive antibodies might play a positive role in clearance of acute viral infections. While cross-reactive antibodies have long been thought to be of minor importance for the control of HIV, the idea that rare variant cross-neutralizing antibodies might be the key to combating this virus is gaining increasing support [109, 110]. Cross-reactive antibodies associated with HCV clearance during secondary and sequential infection have also recently been identified [63], further highlighting a possible role for these antibodies in viral control.

'Pathologic antibodies' are non-neutralizing, possibly auto-reactive and/or poly-reactive, and might precipitate and form complexes that cause vascular damage such as that observed in HCV. Immune complex deposition is not well described in dengue disease, but may contribute to the induction of cytokines and the characteristic muscle and joint pain that presents in this disease.

Several dengue candidate vaccines are currently being evaluated. Clinical trials provide an opportunity to study antibody specificity and affinity in longitudinal human samples over several years. This type of research is rarely possible for natural infection, especially since the serotypes and time-points of past infections cannot be reliably determined.

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