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Antibody Polyreactivity in Health and Disease: Statu Variabilis

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An Ab molecule or a BCR that is able to bind multiple structurally unrelated Ags is defined as polyreactive. Polyreactive Abs and BCRs constitute an important part of immune repertoires under physiological conditions and may play essential roles in immune defense and in the maintenance of immune homeostasis. In this review, we integrate and discuss different findings that reveal the indispensable role of Ag-binding polyreactivity in the immune system. First, we describe the functional and molecular characteristics of polyreactive Abs. The following part of the review concentrates on the biological roles attributed to polyreactive Abs and to polyreactive BCRs. Finally, we discuss recent studies that link Ig polyreactivity with distinct pathological conditions.

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Antigen-binding receptors on T and B cells, in contrast to germline-encoded innate receptors, possess a great heterogeneity in the molecular organization of their binding sites (1). Hence, they provide broad repertoires of binding specificities. However, the molecular heterogeneity generated by the sole genetic processes of recombination and somatic mutagenesis is finite and still not sufficient to cover the infinite antigenic space (2, 3). The paradox of a finite set of receptor sequences that should be able to recognize at any given moment a potentially infinite set of molecular entities is solved, at least in part, by the ability of some of the receptors to recognize many unrelated molecules. In the literature these receptors have been referred to as “polyreactive,” “polyspecific,” “multispecific,” “degenerated,” “promiscuous,” and other such terms. Thus, polyreactivity of immune receptors magnifies the Ag detection power of the immune system and endows the system with the ability to exert regulation of its own functions.

Polyreactive Abs as well as polyreactive B receptors are normal constituents of the immune system in physiology. They may also arise as a result of different pathological conditions. In this review, we discuss the characteristics of polyreactive Abs as well as their functions in health and disease.

Characteristics of polyreactive Abs

The existence of Igs that are able to recognize many structurally unrelated targets was discovered during the early works on myeloma-derived Abs (4). Later, it was demonstrated that many hybridoma-derived mAbs bind to different tissues and cell types and thus express Ag-binding polyreactivity (5). It was also realized that all healthy individuals contain Abs that are able to specifically bind various autoantigens (6). These Abs arise in absence of deliberate immunization and in most of the cases are polyreactive. They are referred to as natural Abs (7, 8). A typical characteristic of natural polyreactive Abs that distinguishes them from disease-associated Abs is that they recognize their target Ags with relatively lower binding affinity.

Definition of Ab polyreactivity. Despite the long-standing study of Ab polyreactivity, a clear quantitative definition of the phenomenon does not exist. Instead, polyreactivity (and monoreactivity) of Abs are subjectively and differently defined by different laboratories. Thus, an Ab is often designated as polyreactive or monoreactive after screening its reactivity toward a relatively small set of Ags. It has been suggested that screening of the Ab reactivities toward arrays of Ags with a large breadth (10^8 species) would provide better criteria for defining Ab reactivity (9–11). Using such arrays, many Abs defined as monoreactive upon screening their binding against three to four Ags may turn out actually to be polyreactive. The affinity thresholds that distinguish specific from nonspecific interactions are also not clearly defined. When used at very high concentrations, Igs, as many other proteins, may bind to different targets. However, it is questionable whether these interactions bear any physiological meaning.

Therefore, we propose that the definition of Ab polyreactivity should be based on quantitative and functional criteria. Thus, an Ab may be defined as polyreactive if it is able to bind at least two structurally different Ags from a broad Ag repertoire and if the interactions have physiologically relevant affinities (i.e., K_D below micromolar values). Demonstration of the functional consequence of Ab recognition of different Ags would strengthen the definition of polyreactivity.

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Maturation status of polyreactive Abs. It has been demonstrated that all healthy individuals possess significant fractions of B lymphocytes that express polyreactive Ag receptors (12, 13). Initially, it was thought that polyreactive Abs and polyreactive BCRs are mostly expressed by a CD5⁺ subpopulation of B lymphocytes. Ig genes of these cells usually lack somatic mutations (12, 14). However, it has become apparent that other subpopulations of B lymphocytes also express polyreactive receptors (13).

Polyreactive Abs could be germline or affinity matured. Structural and biophysical analyses reveal that binding of the target Ags by many germline Abs is accompanied by considerable structural alterations in the Ag-binding site (2, 15–17). These Abs are usually characterized by a high level of Ag-binding polyreactivity (2, 3, 16). Enhanced structural adaptability of the Ag-binding site is thought to determine polyreactivity of germline Abs. Generally, the accumulation of mutations during affinity maturation in the genes encoding the variable regions of Igs results in reduction in the molecular flexibility of the Ag-binding site of the Abs (2, 15, 17). The reduction of the molecular flexibility was shown to be associated in some cases with a concomitant decrease in polyreactive Ag binding (2, 3). However, numerous studies demonstrated that Ag-binding polyreactivity is not restricted only to germline Abs but it is also typical for affinity-maturated Abs (18–20).

As result of negative selection during B cell ontogeny, in healthy individuals only ~4% of naive B cells that enter the circulation express polyreactive Abs (21). However, ~23% of IgG⁺ memory B cells express polyreactive Abs (20). Additionally, about a fourth of human intestinal IgA and IgG plasmablasts secrete polyreactive Abs (22). These Abs possess extensively mutated variable regions. Taken together, these observations suggest that polyreactive Abs are positively selected during the affinity maturation of B cells. Positive selection of cells expressing polyreactive Abs may occur also during infections or in the course of autoimmune diseases (18, 19, 23, 24).

The possible explanation of this apparent contradiction of existence of both polyreactive Abs with germline and with mutated variable regions could be that certain Abs retain, or even augment, the structural flexibility of their Ag-binding sites as a result of the affinity maturation. Thus, the polyreactivity may not depend on the maturation status but more on the intrinsic ability of a paratope to assume different conformations.

Correlates of Ab polyreactivity. The molecular mechanism of polyreactive Ag binding by Igs has been extensively studied. The available data suggest that there is no sequence correlate that can predict the polyreactive or monoreactive behavior of an Ab (9, 18, 25, 26). Thus, nucleotide sequence analyses of Ig genes have not revealed any particular gene family encoding H or L chain variable regions that is used exclusively by polyreactive Abs (12, 25, 27). Differences in the overall organization of the Ag-binding sites of monoreactive and polyreactive Abs have also not been observed. By using gene reassortment and site-directed mutagenesis approaches, it was demonstrated that the polyreactivity of Abs is a property defined by the CDR3 region of the H chain (19, 28, 29). This region is also known to play a central role in the recognition of Ags by most of the Abs (30). In some cases, residues from the L chain of Ig play auxiliary roles for determining the polyreactivity of Abs (28). Despite the fact that some studies suggest differences in the sequence and size of CDR H3 as well as in the presence of specific sequence mo-

tifs or amino acid residues in this region, other works failed to find unique sequences or structural characteristics of CDR H3 for polyreactive Abs (9, 18, 19, 25, 28). The effect of Ig regions that are distant from the Ag-binding site on determining Ag-binding polyreactivity should also be considered. Indeed, it has been demonstrated that the subclass of the H chain may influence the binding specificity and affinity as well as the tendency toward polyreactive Ag binding of Abs bearing an identical paratope (31, 32).

It appears that the main factor that determines the polyreactivity of an Ab molecule is the structural dynamics of the Ag-binding site (2, 33, 34). It seems most probable that, rather than the characteristic sequence motif of the CDR H3 region, it is the intrinsic ability of this region to assume various configurations that defines polyreactivity. This property can be conferred by many possible sequences of CDR H3. The other CDR loops as well as the framework regions may also influence the ability of CDR H3 to assume various conformations (15).

Structural mechanisms of Ab polyreactivity. High adaptability of a pliable binding surface can endow Abs with the potential to establish interactions with many structurally unrelated Ags (3, 35). From the accumulated experimental evidence, it becomes apparent that polyreactive Abs may use various molecular mechanisms for interacting with their target Ags (Fig. 1).

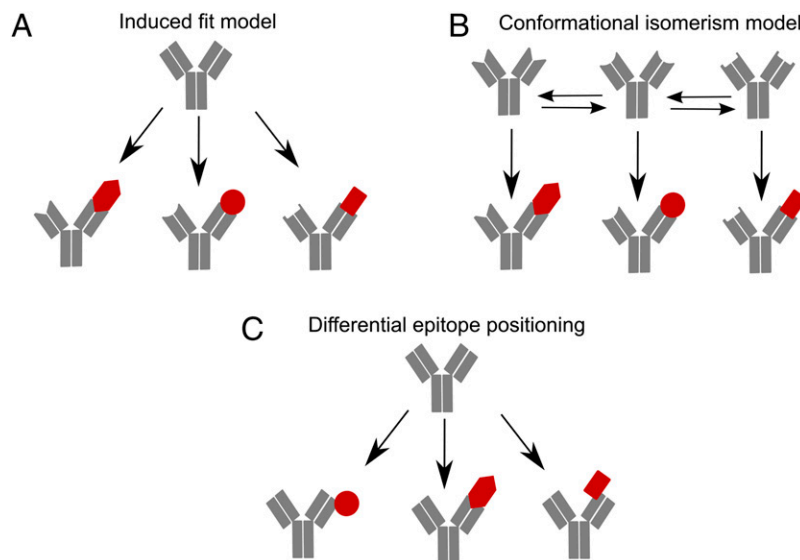
Thus, some polyreactive Abs may adapt to the structural characteristics of the epitope at the time of the interaction (9, 33) (Fig. 1A). Hence, different epitopes will drive the formation of different binding surfaces of a single Ab. This binding mechanism is reminiscent of the model of induced-fit binding or the Koshland–Nemethy–Fimer model initially proposed for binding enzymes to their substrates. Kinetic as well as structural data reveal that some Abs bind multiple Ags with predefined or with nearly predefined configurations of their Ag-binding sites (36, 37). This model, in contrast to the induced-fit binding model, stipulates that an Ab molecule exists as equilibrium between its different structural variants (33, 37) (Fig. 1B). Each variant of the Ag-binding site (i.e., isomer) is adapted to recognize structurally different Ags. The percentage of Abs that exist in such conformational isomers as well as the number of possible “conformers” expressed by one Ab are not known. It has been proposed that germline Abs would have a higher number of conformational isomers (37).

In addition to models that are based on protein flexibility, it was demonstrated that Ab polyreactivity could be also mediated by different positioning of the Ags on a single Ag-binding site (38) (Fig. 1C). In this aspect, a rigid binding surface can accommodate many different targets. Interestingly, structural data have revealed that a human rheumatoid factor binds the Fc portion of IgG by using amino acid residues on the edge of the Ag-binding site (39). The actual binding site of this Ab is not occupied even after binding to Fc fragment and thus could still establish interactions with the target Ag. Fig. 1 depicts schematically the three molecular mechanisms that can result in recognition of multiple Ags by a single Ab molecule.

Induced Ab polyreactivity

In addition to naturally polyreactive Abs, all healthy individuals contain a fraction of circulating Igs that in their native state express low Ag-binding activity but acquire polyreactive characteristics after exposure to certain protein-destabilizing agents (40–43). Thus, the transient contact of polyclonal or

FIGURE 1. Molecular mechanisms of Ab polyreactivity. The induced fit interaction model (**A**) proposes that an Ab molecule (in gray) with pliable Ag-binding site can adapt to different Ags (shapes in red) by structural changes that occur at the time of interaction. In contrast, the conformational isomerism model (**B**) proposes existence of conformational isomers of a single Ab prior to Ag encounter. Each isomer has a different configuration of its Ag-binding site and can bind structurally different Ag. Polyreactive Abs can also simultaneously use both interaction models for binding to various Ags. Some Abs can use different regions from their Ag binding sites for binding to various Ags (**C**).



monoclonal Igs with chaotropic agents, low pH (i.e., <4), or high salt concentrations results in molecular modifications of the Ig and leads to transition toward a multispecific Ag-binding state. Importantly, in many studies of polyreactive Abs, the Igs have been subjected to acidic pH during their purification prior to analysis of their Ag binding. Because this exposure is a strong inducer of polyreactivity in the case of sensitive IgG and IgM Abs (41–43), it may turn out that many Abs considered as polyreactive would not express multispecific Ag binding when purified under different conditions.

It has been suggested that natural polyreactive Abs circulate in plasma as complexes with their cognate Ags or other Igs under physiological conditions (40, 44). Only the dissociation of these complexes during Ab purification reveals their actual autoreactivity. These conclusions, however, can be challenged in the view of the induction of polyreactivity upon exposure of the sensitive Abs to harsh conditions used during conventional Ab purification.

Several groups, including ours, demonstrated that redox-active substances and cofactors, such as reactive oxygen species, iron ions, and heme, are able to uncover the cryptic polyreactivity of the sensitive fraction of Abs present in all healthy individuals (45–47). This may have in vivo relevance because large amounts of pro-oxidative molecules are released under certain pathological situations and upon recruitment and activation of neutrophils. Indeed, the exposure of IgG to sites of acute inflammation results in an increase in the total immunoreactivity of exogenously administered polyclonal IgG preparations, probably due to uncovering of the cryptic polyreactivity of the sensitive Abs present in the Ig pool (48). Interestingly, the Abs with induced polyreactivity demonstrate powerful anti-inflammatory activity, as their administration in vivo resulted in a protective effect in models of septic shock and autoimmune diabetes (46, 49).

Physiological roles of polyreactive Abs

The high prevalence of polyreactive Abs and polyreactive BCRs in healthy individuals cannot be explained merely as a “haphazard” byproduct of immune responses. Various roles for these Abs have been proposed (Fig. 2), but further experimental

evidence is needed for their better understanding. All of these functions may be assured by the capacity of polyreactive Abs to diversify immune repertoires.

Polyreactivity increases diversity of immune repertoires. One of the most important physiological roles of Ig polyreactivity could be its contribution to the evolution of new Ab specificities (Fig. 2). The work of Tawfik et al. (33, 50) at the Weizmann Institute delineates the role of protein dynamics and of catalytic or binding promiscuity as factors of evolution of new protein functions. Thus, the promiscuous binding behavior of certain Ig receptors may provide the immune system with primordial specificities for further evolution of highly specific Abs. The initial low-affinity binding of a polyreactive receptor to a given Ag can be stabilized and refined after microevolution processes of mutations and rounds of selection in the germinal centers. Hence, the polyreactivity of immune receptors may help in magnifying the Ag detection power of the immune system and, at the same time, provide the required dynamics for evolution of highly specific receptors (3). In this respect, the role of Abs or BCRs with cryptic polyreactivity is intriguing. The expression of polyreactivity of these molecules occurs only in cases of severe inflammation and tissue damage (48). Rapid posttranslational diversification of Ag-binding repertoires may serve as an additional source of specificities that may be required for coping with infection and/or inflammation.

Hence, the normal immune repertoire consists of a complex pool of B cells that represents a physiological baseline—expressed repertoire from which the immune system can select clones to cope with “immunological events.” The normal repertoire may be composed of three sets of B cells: monoreactive B cells that are activated only when they encounter their cognate Ags; polyreactive B cells that are activated less specifically but can evolve through somatic mutations leading to the generation of more specific and proficient Abs; and a cryptic set of polyreactive B cells that is uncovered only in extreme immunological situations accompanied by inflammation and oxidative stress. Because the latter type of Abs is not genetically encoded, it may be seen as an epigenetic diversification of the B cell repertoire. Unanswered questions remain about the functions and properties of the BCR and Ig secreted by this

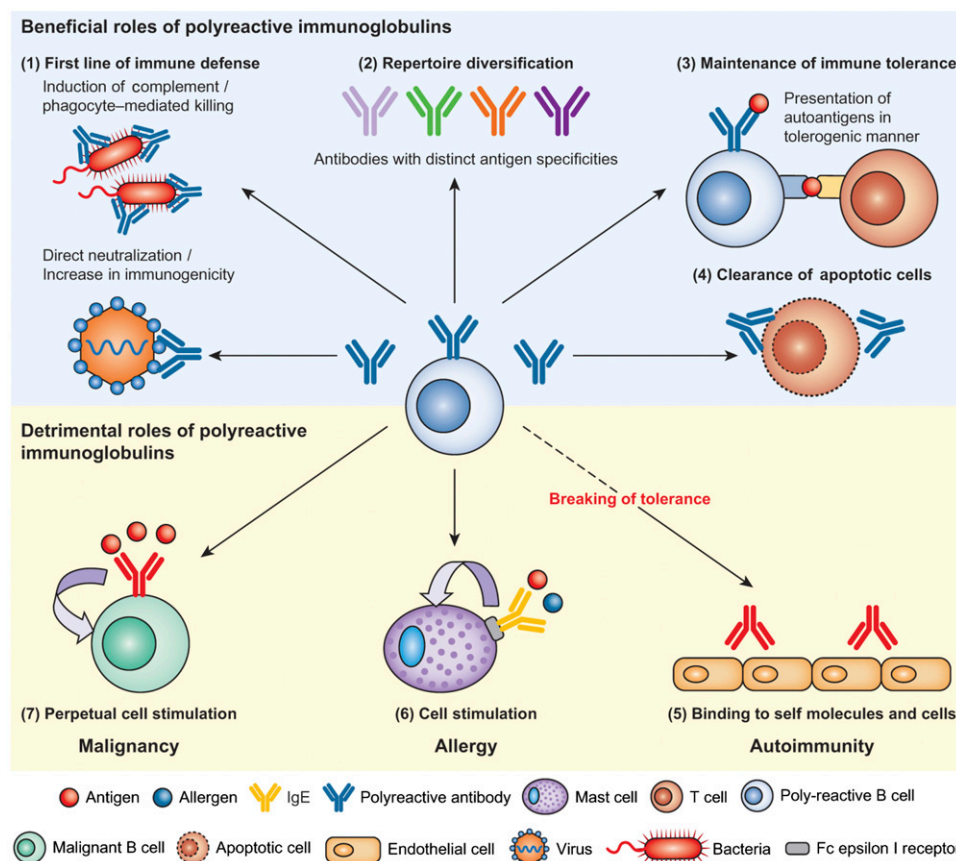


FIGURE 2. Beneficial and detrimental effects of polyreactive Abs. The beneficial functions of polyreactive Abs or polyreactive BCRs are depicted on the *upper half* of the figure; detrimental consequences are shown on the *lower half* (1). The immune defense function of polyreactive Abs can be exerted by direct neutralization of viruses or trapping to the secondary lymphoid organs and increase in their immunogenicity. Opsonization of bacteria with polyreactive Abs can induce secondary reactions, that is, activation of complement system or phagocytosis, resulting in a bactericidal effect (2). Polyreactive BCRs contribute to the diversification of immune repertoires by providing primordial Ag specificities for evolution of high-affinity Ag-specific Abs (3). Polyreactive B cells may participate in maintenance of peripheral immune tolerance by binding and presenting endogenous Ags to T cells in a tolerogenic manner (4). Soluble polyreactive Abs may help in clearance of apoptotic cells and modified proteins, thus exerting anti-inflammatory function (5). In some autoimmune diseases, polyreactive autoantibodies may play a critical role in pathology by forming immune complexes with autoantigens or initiating cellular damage (6). Polyreactive IgE molecule bound to the surface of mast cells could stimulate degranulation following binding to various autoantigens or allergens (7). Malignant B cells expressing polyreactive BCR could receive continuously survival signals through binding to various endogenous or bacterial Ags.

third pool of B cells, in particular with respect to the pool of intrinsically polyreactive B cells and to a putative advantage of this additional layer of diversification of Ag-binding specificities.

Polyreactive Abs and immune surveillance. Polyreactive Abs and BCRs have also been suggested to maintain immune homeostasis by exerting different immunoregulatory and immune surveillance activities (6, 7, 26, 51, 52). Their promiscuous binding to many endogenous molecules would endow the immune system with an analytical capacity for the ceaseless sampling of the state of immune, metabolic, and tissue homeostasis (51–54).

An explanation for a putative role of polyreactive BCR-expressing B cells proposes a function in transport and tolerogenic presentation of Ags to T cells (26, 55) (Fig. 2). Such B cells would participate in the induction of tolerance to Ags that are not expressed in the thymus for the negative selection of autoreactive clones.

Polyreactivity of natural IgM Abs and their ability to recognize various neoepitopes on self-Ags contribute to their role in clearance of apoptotic cells and of modified macromolecules, thus reducing the inflammation (8, 56–58) (Fig. 2). It is still

unclear why natural polyreactive Abs, arising in all healthy individuals without prior immunization, bind to pathogens and altered self-structures and do not induce damaging effects on healthy cells. It could be speculated that the low binding affinity of polyreactive Abs and the presence of defense molecules (e.g., complement regulators, such as CD46, CD55, CD59) (59) that are highly expressed on healthy cells allow the normal cells to remain unaffected. Thus, binding of polyreactive Abs to healthy cells would purge the expressed repertoire of Abs with specificities for self-Ags and would spare the polyreactive Abs carrying specificities toward cryptic self-Ags and bacterial targets. Hence, the latter Abs would be readily available to act on altered self and on pathogens.

In conclusion, the different physiological functions of polyreactive Igs or BCRs imply that a complete and healthy immune repertoire should consist of receptors with both stringent and promiscuous specificities. The former will provide fidelity of the immune reactions and will be of utmost importance for building the memory of the system. The latter will endow the immune system with adaptability and evolvability, with the potential to cover a much broader antigenic space and with the ability to exert self-regulation.

Polyreactive Abs in disease

The presence of polyreactive Abs has been associated with different autoimmune, inflammatory, and infectious diseases (Fig. 2). However, at present, it is not well understood whether polyreactive Abs or receptors play a direct role in these pathologies or whether their appearance results from a mere dysregulation of the immune system, or even an attempt of the immune system to exert immunoregulatory effects.

Polyreactive Abs in infectious diseases. Polyreactive Abs have been suggested to provide a first line of defense against pathogens (6, 9) (Fig. 2). Low-affinity multispecific binding to pathogen-associated molecules may delay the propagation of pathogens or increase their immunogenicity by Ab-mediated trapping in secondary lymphoid organs (60). It was demonstrated that certain polyreactive Abs can bind to a variety of bacteria and evoke secondary effector functions, such as complement activation and phagocytosis, resulting in bactericidal activity (61).

A recent study revealed that infection of mice with the intracellular bacteria *Ehrlichia muris* results in the generation of pathogen-specific IgM Abs that exhibit high levels of Ag-binding polyreactivity and bind to various autoantigens (44). Such Abs were also detected in humans infected by the same pathogen. Interestingly, most of the polyreactive *Ehrlichia*-specific Abs demonstrated specificity to the bacterial protein OMP-19, implying that this protein is the main driver of the polyreactive response. The authors proposed that the bacteria-induced polyreactive Abs contribute to the direct neutralization of the pathogen. Alternatively, by virtue of polyreactive binding to self-Ags, these Abs may dampen the infection-induced inflammation by participating in clearance of apoptotic cells and cellular debris (44).

Infections by certain viruses, including dengue virus, HIV, influenza virus, and hepatitis C virus, are characterized by the generation of virus-specific polyreactive and cross-reactive Abs (for a comprehensive review, see Ref. 62). Polyreactive Abs induced by viral infections can play both beneficial and detrimental roles. It has been observed that HIV-infected patients possess considerably higher levels of polyreactive Abs than do healthy individuals (19, 23, 63, 64). These Abs are highly mutated, implying that the B cells producing them have been positively selected (19, 23, 65). Moreover, HIV-binding polyreactive Abs showed bias in the usage of the gene families that encode their H chain variable regions (19, 23, 65). These Abs are mostly encoded by VH1 and VH4 gene families, and less frequently by the most prevalent family in human Ab repertoire, VH3.

It still needs to be confirmed whether polyreactive Abs play a direct role in virus neutralization or are the product of immune responses that are severely dysregulated following infection by HIV. It has been suggested that HIV infection-associated polyreactive IgG Abs contribute to virus neutralization by an increased avidity due to the simultaneous binding to HIV spike protein by one of the Ag-binding sites and binding to another (yet unidentified) molecule on the virus envelope by the other Ag-binding site (23, 64), a type of interaction defined as heterologation. Indeed, some well-characterized monoclonal broadly neutralizing HIV-specific human Abs have polyreactive Ag-binding activity (66–68). The polyreactive binding of HIV-specific Abs has been demonstrated to play a direct role in virus neutralization (69, 70). Thus, the gp41-specific Abs 4E10 and

2F5 possess also high reactivity to phospholipids. It was suggested that these Abs initially interact with the phospholipid membrane of the HIV envelope by using the long and hydrophobic CDR3 region of their H chains (69). This interaction provides appropriate orientation of the Ag-binding site for accommodation to the membrane-proximal external region of the gp41 protein. Recently, we proposed that HIV-specific polyreactive Abs may also have an advantage over Abs with stringent specificity by virtue of their higher tolerance to mutations in the target epitopes (71).

Despite the beneficial neutralization effects, in certain viral infectious diseases such as dengue, the binding of polyreactive Abs to the virion may promote infection by facilitating entry into the target cells (62). Moreover, one study demonstrated that polyreactive Abs that arise as result of HIV infection have the ability to initiate cytotoxic reactions against T lymphocytes (72). The depletion of T cells by these Abs in different compartments of the immune system was demonstrated in vivo. Thus, HIV-induced polyreactive Abs may synergize with the virus and contribute to AIDS.

Taken together, these studies indicate that the immune system responds to pathogens by producing both monoreactive and polyreactive Igs. The role of monoreactive pathogen-specific Abs is rather well elucidated and logically acceptable. In contrast, the role of polyreactive Igs in infection is still not well understood. Polyreactive Abs may directly participate in pathogen neutralization, as in case of some HIV-neutralizing Abs, or their functions could be beyond a direct neutralization of the pathogen, but instead exert regulatory effects on pathogen-specific immune responses at a systemic level.

Polyreactive Abs in B cell malignancies. Conditions where the polyreactivity of Ig receptors may play a direct role in the pathogenesis are B cell malignancies such as chronic lymphocytic leukemia, MALT lymphoma, and splenic marginal zone lymphoma (Fig. 2). In these disorders, the Ig receptor of the neoplastic B cells can express high level of polyreactivity (73–76). Polyreactive BCRs can be in germline configuration (as in chronic lymphocytic leukemia) (73, 74) or highly mutated (chronic lymphocytic leukemia and certain lymphomas) (74–76). The polyreactive BCR may play an important pathogenic role by providing continuous stimulation and transmission of survival signals to the transformed B cell clones upon binding to various self or foreign Ags (74). Indeed, it was observed that chronic lymphocytic leukemia progresses more aggressively in patients who possess transformed B cells expressing polyreactive BCR as compared with patients who possess B cell clones expressing monoreactive BCR (74).

Polyreactive Abs in autoimmune diseases. Polyreactive IgG Abs have also been associated with autoimmune diseases (Fig. 2). A high prevalence of naive B cells expressing polyreactive BCRs was observed in patients with systemic lupus erythematosus and rheumatoid arthritis (77, 78). These observations were explained by a disruption of B cell tolerance mechanisms. The polyreactive Abs may contribute to the immunopathology of the autoimmune disease by binding to various self-Ags and eliciting inflammatory reactions. Indeed, it was demonstrated that human polyreactive Abs isolated from lupus patients bind to mouse glomeruli (79). Moreover, the administration of these polyreactive Abs to the brain of mice resulted in neurologic damages, thus revealing their potential in inducing neuro-

psychiatric lupus (79). The difference between pathogenic polyreactive Abs found in autoimmune disease and the natural polyreactive Abs found in healthy individuals remains to be understood. The possible differences could be in the spectrum of antigenic specificities and in the binding affinities for disease-associated Ags.

Polyreactive Abs in allergy. In addition to autoimmune diseases, polyreactive Abs may play an important role in allergic conditions (Fig. 2). Thus, a recent study demonstrated a link between the polyreactivity of monoclonal IgE Abs and their cytokinergic potential, that is, their ability to promote survival, cytokine secretion, and degranulation of mast cells (80). The monoclonal IgE Abs that were able to recognize multiple autoantigens stimulated the mast cells much more efficiently than did the monoreactive IgE Abs. Based on the results from patients with atopic dermatitis, the authors proposed that polyreactive/autoreactive IgE Abs may contribute to the pathogenesis by providing continuous stimulation of the mast cells upon interaction with endogenous auto-allergens (80). Interestingly, the Ab used for demonstrating the structural basis of multispecificity based on conformational isomerism model belongs to the IgE class (37); it also demonstrated high cyto-kinergic potential (80).

Conclusions

The immune system constantly produces polyreactive Igs that are able to recognize multiple structurally unrelated Ags. These Igs may play important roles in the functioning of the immune system in health and disease. Many questions related to their origin, mechanism of action, and physiological relevance remain unanswered. It is now clear that polyreactive Abs are “friends,” participating as a first line of defense against pathogens, facilitating the silent clearance of altered or dying cells, contributing to the maintenance of immune homeostasis, and providing raw material for evolution of high-affinity Abs. Nevertheless, polyreactive Abs could also be foes, because alterations of the repertoire of polyreactive Abs and polyreactive B cell receptors are associated with autoimmunity, allergic diseases, and malignancies. Furthermore, certain pathogens hijack the immune system by using multispecific Abs as a vehicle. We think that a better understanding of the mechanisms of action and physiological roles of polyreactive Abs could contribute to the development of novel therapeutics that can combat rapidly evolving pathogens and cancer cells or control overwhelming inflammation and autoimmune manifestation where the currently employed conventional monoreactive (therapeutic) Abs prove inefficient.

Disclosures

The authors have no financial conflicts of interest.

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