Polyreactivity of Natural Antibodies: Exchange by HL-Fragments

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Abstract—The polyreactivity of binding (formation of antibody (AB) complexes not only with specific but also with foreign antigens) is a widespread phenomenon that in some cases can be caused by a conformational lability of the antigen-binding sites of antibodies (which increases upon treatment with various destabilizing agents) and leads to AB binding with very different antigens. Some ABs exist as dimers of the initial ABs and their idiotypes (or anti-idiotypes) capable of producing intramolecular cyclic complexes with features of polyreactants. Another mechanism of binding polyreactivity is an exchange in blood by halves of IgG4 molecules (HL-fragments) against various antigens. Also, for the first time catalytic polyfunctionality of human milk ABs has been detected, which is caused by an exchange by HL-fragments between molecules of λ- and κ-IgG (IgG1-IgG4) and also by λ- and κ-sIgA against different antigens with formation of very different chimeric antibodies. This review considers all possible pathways of formation of polyclonal immunoglobulins and their biological functions described in the literature, as well as mechanisms of binding polyreactivity and catalytic polyfunctionality of natural antibodies.

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For a long time the idea dominated in immunology that the interaction between an antigen (AG) and an AG-binding site could be described by the “lock and key” hypothesis. This mechanism of interaction suggests that the AG-binding site of an antibody (AB) and the antigen epitope should be complementary and have rigid structures [1, 2]. In 1959, David Talmage formulated the concept of receptor polyspecificity, and 10 years later Herman Eisen with colleagues for the first time demonstrated AB polyspecificity in a series of experiments on the interaction of myeloma protein with various antigens [3, 4]. Monoclonal ABs against 2,4-dinitrophenyl were shown to bind both to structurally similar molecules (e.g. menadione) and structurally unrelated molecules (e.g. caffeine) [4]. Such a “degenerate” type of interaction was later confirmed by numerous different studies, and many immunoglobulins (Igs) were shown to be polyreactive and capable of interacting with different chemically unrelated auto- and non-autoantigens [5, 6].

From our viewpoint, “true” polyspecificity of a monomeric molecule of ABs means its interaction with a number of different antigens. However, existing analytical methods often do not allow us to discriminate the “true” and “apparent” polyreactivity. In the majority of cases, polyreactivity of ABs can be revealed by chromatography of polyclonal antibodies on several affinity sorbents that sometimes is associated with analyzing the interaction of resulting Igs with different antigens using enzyme-linked immunosorbent assay (ELISA). This approach for detecting Ig polyreactivity in some cases can lead to wrong conclusions, if under experimental conditions complexes can be produced between ABs to different AGs, or if immobilized antigens contain structural elements corresponding to different types of molecules. Such approaches can lead to detecting “apparent” polyreactivity.

Alongside the “true polyclonal” ABs, there are also broad-specificity antibodies that display a relatively low affinity in the interaction with many structurally similar compounds. In principle, they are also polyspecific, but...
the nature of their polyspecificity can be somewhat different, and up to now the difference between broad-specificity ABs and true polyspecific ABs remains insufficiently clear. Moreover, some molecules with a significantly different structure can contain separate elements with similar structure. This also can lead to the low affinity on AB binding with structurally unrelated antigens.

Polyreactivity of ABs has been analyzed in two reviews [5, 6]. In review [5], polyreactivity caused by conformational lability of AG-binding sites of ABs leading to the binding by these sites of both specific and nonspecific ligands was mainly analyzed. Review [6] considered polyreactive ABs in viral infections, mainly in HIV-infected patients. In the present review, we attempt to analyze molecular mechanisms of “true” and “apparent” polyreactivity of very different ABs, including exchange by halves (HL-fragments) between molecules of ABs against different AGs. Up to now, there is no data about the possible existence of a catalytic polyfunctionality of antibodies-abzymes. In the present review, new data are considered on the possible catalysis by abzymes (resulting due to exchange of HL-fragments between antibody molecules) of some different chemical reactions.

STRUCTURE AND FUNCTIONS OF IMMUNOGLOBULINS

The humoral immune response in vertebrates is determined by synthesis of immunoglobulins (Igs). Ig are expressed as receptors of the plasma membrane of B-lymphocytes and also as soluble molecules secreted by plasma cells, which are present in serum, tissue liquid, and milk. Soluble Igs (antibodies) can bind virtually every natural and artificial molecule (antigens) with high affinity and specificity. The ability of ABs to recognize and bind a broad spectrum of antigens (AGs) is determined by their extreme variety, reaching 10^9-10^10 different variants of AG-binding sites. The adaptive immune system, which is based on Igs, T-lymphocyte receptors, and the major histocompatibility complex proteins appeared in vertebrates about 500 million years ago, and the main features of its functioning have been retained up to the present [7, 8].

Each B- and T-lymphocyte expresses a single receptor type, and the cells carrying receptors interacting with auto-AGs are eliminated, whereas cells with receptors against foreign AGs can receive a signal to proliferate. The contact of a B-lymphocyte receptor with an AG specific for it leads to activation of this lymphocyte and its differentiation into a plasma cell secreting a large amount of Igs, and concurrently some of B-lymphocytes are converted into memory B-cells. The secreted ABs have the same anti-AG specificity as the corresponding receptor of the B-lymphocyte [7].

Human and other mammalian Igs are referred to five classes — IgG, IgA, IgM, IgD, and IgE [1] — which are different in molecular weight, charge, amino acid sequence, and glycosylation. Immunoglobulins of the G class (IgG) are subdivided into four subclasses: IgG1, IgG2, IgG3, IgG4; Igs of the A class — into two subclasses: IgA1 and IgA2. All classes and subclasses of Igs form nine isotypes, which normally are present in all individuals. Each isotype is determined by the amino acid sequence of the heavy chain constant region [7]. Light and heavy polypeptide chains are structural elements of each Ig molecule. The class and subclass of Igs are determined by the heavy chain type: μ (IgM), γ1, γ2, γ3, γ4 (IgG1, IgG2, IgG3, IgG4), α1, α2 (IgA1, IgA2), δ (IgD), ε (IgE) [1].

Sequences of N-terminal domains of every light (L) and heavy (H) chain, V L and V H, are highly variable and form together the AG-binding site of AB. The length of the unique N-terminal sequences in the case of V L and V H is ~110 amino acid residues (a.a.), C-terminal domains of light and heavy chains (C L and C H, respectively) form a constant region responsible for effector functions of Ig, the length of C L also being ~110 a.a. Constant regions of γ-heavy chains contain three domains — C γ1, C γ2, and C γ3 — and they form an Fc-fragment that binds to the Fc-receptor of the effector cells and also activates the complement [9]. The specificity of AG-binding sites of ABs is determined by their complementarity to the three-dimensional conformational structure of the antigen — the antigenic determinant, or epitope.

IgA monomers are joined by plasma cells into dimers immediately before their release from the cell [10], and terminal peptides of the heavy chain of the monomers are concurrently bound by disulfide bonds with a J-chain. The J-chain is a polypeptide with molecular weight of ~15 kDa (137 a.a.) necessary for polymerization and secretion [9]. The IgA dimer binds with a poly-Ig-receptor expressed on the basolateral surface of epithelial cells. The complex is internalized, transported onto the apical surface, and released as a secretary component. The secretory component is a product of decomposition of the poly-Ig-receptor, its molecular weight is 70-80 kDa, and it does not have covalent bonds with the J-chain and the IgA dimer. The secretory component protects sIgA against proteolysis, promotes the retention of Ig in the epithelial membranes, and is responsible for sIgA being the most stable immunoglobulin in the secretions [9, 11].

The light chains (each about 25 kDa) are connected with the heavy chains (each of ~55 kDa) by disulfide bonds and also by noncovalent interactions; the heavy chains are connected to each other similarly. Domains of the heavy and light chains consist of 110 a.a. and form compact structures stabilized by disulfide bonds within a domain. These bonds promote the production of loops consisting of 60-70 a.a., the light chain containing two domains and the heavy chain containing three or four domains [2, 9].

The majority of vertebrates are known to have different forms of Ig light chains — kappa (κ) and lambda (λ) —