Immunoglobulins with Non-Canonical Functions

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Immunoglobulins are known to combine various effector mechanisms of the adaptive and the innate immune system. Classical immunoglobulin functions are associated with antigen recognition and the initiation of innate immune responses. However, in addition to classical functions, antibodies exhibit a variety of non-canonical functions related to the destruction of various pathogens due to catalytic activity and cofactor effects, the action of antibodies as agonists/antagonists of various receptors, the control of bacterial diversity of the intestine, etc. Canonical and non-canonical functions reflect the extreme human antibody repertoire and the variety of antibody types generated in the organism: antigen-specific, natural, polyreactive, broadly neutralizing, homophilic, bispecific and catalytic. The canonical and non-canonical functions of antibodies greatly enhances the functionality of the human immune system.

Keywords: Immunoglobulines ; antibodies ; non-canonical ; functions ; IgG ; IgA ; sIgA ; IgM ; IgE ; IgD

1. Introduction

Immunoglobulins (Igs) are involved in numerous molecular mechanisms of both innate and adaptive immune systems due to the presence of two functional centers (antigen binding sites (Fab) and fragment crystallizable region (Fc)), as well as a combination of their unique structural and functional properties. Generally, Igs combine the Fab domain-mediated antigen recognition process with the activation of various innate responses mediated by the involvement of various receptors, protective proteins and immune cells by the Fc domain [1]. For a long time, it was believed that the host's immune system generates only highly specific antibodies (Abs) against pathogens [2]. However, the development of experimental methods and animal models made it possible to determine the extreme heterogeneity of the Igs pool, reflecting a wide variety of biological functions of Abs.

Igs have been shown to exhibit their effector functions both in normal and pathological conditions, especially in inflammatory and autoimmune diseases (AIDs). The pathological role of Abs is well documented in the literature (e.g., [3]). At the same time, natural Igs are powerful immunomodulators that both induce and suppress immune responses and inflammatory processes [4]. However, much less attention is paid to the study of Ab effector functions beyond the classical concepts of immunology. Evidence of a significant functional diversity of Abs is the various identified therapeutic effects of intravenous Igs (IVIg) [5]. IVIg preparations are widely used to treat various immunological pathologies. A better understanding of these Ab functions can enrich existing therapeutic strategies.

2. Canonical and Non-Canonical Functions of Immunoglobulins

The human Ab repertoire is created by somatic evolution in B cell populations, which allows the immune system to recognize and eradicate almost any antigen [6]. State-of-the-art immune repertoire next-generation sequencing technologies have allowed a deeper understanding of the diversity of Abs and B cell receptors and thus the immune status of the individuals [7, 8, 9]. The Ab repertoire is flexible and changeable throughout life. Flexibility is achieved due to the presence of an extensive repertoire of native Abs, the diversity of which is increased by somatic hypermutation after exposure to the antigen. Each of the approximately estimated 5×10^9 B cells produces a specific B cell receptor or Ab through somatic recombination of variable (V), diversity (D), joining (J) and constant (C) gene segments (V–(D)–J recombination). The V–(D)–J recombination process results in a light (L) chain, assembled from V, J and C gene segments from one of the light chain loci, and a heavy (H) chain, assembled from V, D, J and C gene segments from the heavy chain locus. Pairs of H and L chains combine to form the following Ab isotypes: monomeric IgG, IgE and IgD; dimeric IgA; and pentameric IgM. Fab contains the variable segments of H and L chains (VH and VL) that bind to a specific surface on the antigen (epitope). Each of the VH and VL segments contains three complementarity-determining regions (CDRs) and four framework regions. The CDRs contain the amino acid residues responsible for antigen binding (paratope). The process of somatic hypermutation after exposure to antigens introduces mutations, primarily in CDRs.

Moreover, Abs have constant domains involved in the formation of Fc, which is responsible for interacting with diverse receptors or complement. Thus, a broad Abs repertoire, a unique structure and processes of affinity maturation determine the variety of functional activities of Abs.

Ab-mediated biological functions should be considered according to functional level [[10]]. The simplest functional level implies the elementary interaction of the Fab domain with the antigen to neutralize the pathogen. The second functional level is the initiation of secondary reactions following antigen recognition. This level is due to both the binding activity of the Fab domain and recognition of the Fc domain by innate immune receptors, complement or immune cells. Examples of well-characterized Ig functions of this functional level are Ab-dependent complement activation, complement-mediated lysis of pathogens or infected cells, Ab-dependent cell-mediated cytotoxicity, phagocytosis, etc. The highest functional level reflects the overall biological role of the Ab in the host's immune defense. All of these functions are ultimately aimed at protecting against pathogens and maintaining immune homeostasis. However, with the development of research technologies, it has become clear that Igs' general biological functions are not limited to antigen recognition processes and the initiation of innate immune responses. In recent years, many Ab functions have been discovered that do not fit into the classical paradigm [10].

Given the available data, Ig functions can be nominally divided into canonical and non-canonical (summarized in Table 1). The canonical functions of immunoglobulins are well documented (including but not limited to [1, [11], [12], [13], [14], [15], [16], [17], [18], [19]]), thus we will describe them only briefly.

Table 1. The canonical and non-canonical functions of antibodies (Abs).

	Canonical Functions of Abs [1]	
Ig Classes	**Fab-Dependent**	**Fc- and Whole Ab-Dependent**
IgG-mediated	· Agglutination, neutralization, and excretion of specific antigens · Similarly sIgA and sIgM, IgG is involved in controlling the diversity of certain commensal and pathogenic microorganisms	· Ab-mediated complement activation · Ab-dependent cell-mediated cytotoxicity · Ab-dependent cellular phagocytosis through the interaction of IgG with FcγRs, DC-SIGN on macrophages · Participation in antigen processing as a result of FcγRs-mediated internalization of immune complexes · Intracellular Ab-mediated degradation of antigen in the proteasome after interaction with C1q and TRIM21 · Ab-mediated immunomodulation, including the release of pro-inflammatory molecules, activation, differentiation and development of immune cells after interaction of IgG with FcγRs · B cell selection and survival, regulation of plasma cell apoptosis, control of IgG production through the interaction of IgG with FcγRs and CD23 · Provide specific protection for newborns from certain pathogens as a result of transport of mother's IgG through FcRn

IgM-mediated	· Agglutination, neutralization, and excretion of various pathogens · sIgM, together with sIgA regulate bacterial intestinal diversity	· Pronounced Ab-mediated complement activation · Together with complement, provides transport of antigens to secondary lymphoid organs and the initiation of an immune response · Strengthening phagocytosis and promoting the presentation of antigens · Stimulation of macrophage uptake of apoptotic cells and their degradation products · IgM through FcμR is involved in the regulation of B cell development and IgG production, as well as immune tolerance
IgA-mediated	· sIgA promotes the opsonization, agglutination, and excretion of pathogenic microorganisms and their products at mucosal surfaces (immune exclusion) · Low-affinity sIgA retain commensal bacteria in the intestinal lumen (immune inclusion) · sIgA neutralizes intracellular pathogen determinants in the epithelial-cell endosomes	· Serum monomeric IgA promotes anti-inflammatory response after interaction with FcαRI and other receptors · IgA immune complexes contribute to a pro-inflammatory response after interaction with FcαRI and PRR · Serum monomeric IgA, but not sIgA, initiate bacterial phagocytosis due to interaction with FcαRI · Antigens excretion due to the secretion of sIgA through the interaction of the sIgA-antigen complex with pIgR and its release into the lumen of the mucosa · Colostrum and milk IgA provide neonatal intestinal homeostasis

IgE-mediated	· IgE opsonize and mediate the destruction and removal of helminths and other pathogens · IgE contribute to the inactivation of animal poisons and toxins	· IgE initiates mast cell and basophil degranulation, as well as the synthesis of inflammatory mediators and the secretion of cytokines and chemokines after antigen recognition by IgE, associated with FcεRI · Regulate growth, maturation and survival and mast cell homeostasis even in the absence of antigen · Regulate the expression of FcεRI and CD23 · Participate in the transport of allergen from the intestine to the mucous membrane due to the interaction of the allergen-IgE complex with CD23 or FcεRI, thereby facilitating the presentation of the antigen · Stimulate Th2 response and suppression of Treg generation
IgD-mediated	· Secreted IgD is involved in the regulation of commensal and pathogenic bacteria and mucosal allergens	· IgD associated with basophils and other cells, after antigenic stimulation, triggers the release of IL-4, which causes the production of IgG by B cells · IgD receptors expressed on B cells regulate their development and maturation, as well as clonal anergy and self-tolerance

Non-Canonical Functions of Abs [1]

Ig Classes	**Fab-Dependent**	**Fc- and Whole Ab-Dependent**

IgG-mediated	· Antigen cleavage due to the catalytic activity of IgG · Direct inactivation of pathogens in the absence of effector cells and molecules · Cofactor effects of IgG in neutralizing pathogens · Triggering of cell signaling through receptor agonist activity of Igs · Compensation of innate immune defects due to anti-cytokine activity or other mechanisms · Carriage, bioavailability regulation and protection of hormones from proteolytic degradation · ROS detoxification due to redox activity of IgG	· Modulation of intracellular insulin signaling due to the interaction of the hyposialylated IgG Fc domain with FcγRIIb · Ab-dependent enhancement of infection or disease
IgA-mediated	· Antigen cleavage due to the catalytic activity of IgA · Intestinal sIgA regulates the penetration of microbial metabolites into the systemic circulation involved in regulating the metabolism and immunity of the host · High avidity pathogen-specific sIgA contribute to the formation of bacterial clusters, “enchained growth” and enhanced clearance	· Transepithelial transfer of bacteria from the small intestine to Peyer's patches and induction of T cell-dependent Ab responses · The Fc domain of sIgA, interacting with bacterial glycans, modulates the expression of polysaccharide utilization loci, including MAFF
IgM-mediated	· Antigen cleavage due to the catalytic activity of IgM · Direct inactivation of pathogens in the absence of effector cells and molecules	· Modulation of lymphocyte intracellular signaling due to the interaction of the Fc domain of IgM with FcμR

1 The table was compiled based on the works [1, 10-19, [20], [21], [22], [23], [24], [25], [26], [27], [28]]. Abbreviations: C1q—complement component 1q, CD—a cluster of differentiation, DC-SIGN—dendritic cell-specific intercellular adhesion molecule 3 grabbing non-integrin, Ig—immunoglobin, IL—interleukin, FcRn—neonatal Fc receptor, FcαRI—Fc receptor for IgA, FcγRs—Fc receptors for IgG, FcεRI—Fc receptor for IgE, FcμR—Fc receptor for IgM, MAFF—mucus-associated functional factor, pIgR—polymeric immunoglobulin receptor, PRR—pattern recognition receptor, ROS—reactive oxygen species, sIgA—secretory immunoglobulin A, TRIM21—tripartite motif-containing protein 21, Th2—type 2 helper T cells, Treg—regulatory T cells.

A quick look at Table 1 allows us to make the corollary that Abs exhibit more numerous canonical functions at the second and highest functional levels. However, the functions of Igs should be considered depending on their classes and subclasses, since their functions differ significantly. For example, pathogen recognition by IgG triggers complement activation, Ab-dependent cell-mediated cytotoxicity, or directs immune complexes to degradation into proteasomes through endocytosis after interaction with C1q and TRIM21 [10]. In general, IgG3 has the highest functional activity, followed by IgG1, whereas IgG2 and IgG4 have the least functional activity in subclasses. IgG also provides specific protection for newborns from certain pathogens as a result of the transport of the mother's IgG through the neonatal Fc

receptor (FcRn) [14]. IgM can markedly activate complement [[29]]. Together with complement, IgM provides transport of antigens to secondary lymphoid organs and the initiation of an immune response [10,13,14]. Secretory IgA (sIgA) is classically known to promote both immune exclusion and immune inclusion of various microorganisms on the mucous membranes [13,14]. Moreover, sIgA neutralizes intracellular pathogen determinants in the epithelial cell endosomes. Furthermore, sIgA provides antigen release into the lumen of the mucous membrane through its secretion after the interaction of the sIgA-antigen complex with the polymeric immunoglobulin receptor (pIgR) [13,14]. Thus, IgA actively regulates the diversity of commensal bacteria in the intestine [13,14]. However, it is important to note that microbiota metabolites affect the production of IgA, as well as systemic IgG responses [22]. IgE, in its turn, initiates mast cell and basophil degranulation after antigen recognition by IgE, associated with the Fc receptor for IgE (FcεRI). IgE also mediates destruction and removal of helminths and other pathogens, as well as inactivation of animal poisons and toxins [17,18]. Secreted IgD is involved in the regulation of commensal and pathogenic bacteria and mucosal allergens [18]. Furthermore, each of the classes of Igs is involved in the regulation of proliferation, development and homeostasis of the immune system cells, depending on the receptors expressed. Indeed, IgG participates in B cell selection and survival, as well as regulation of plasma cell apoptosis [11,12]. According to recent data, IgM through Fc receptor for IgM (FcμR) is involved in the regulation of B cell development and IgG production, thereby providing immune tolerance [12,14]. Serum monomeric IgA, on the one hand, promotes anti-inflammatory response after interaction with the Fc receptor for IgA (FcαRI) and other receptors [13]. On the other hand, IgA immune complexes contribute to a pro-inflammatory response after interaction with FcαRI and pattern recognition receptors (PRRs) [14]. Thus, the realized effect depends on the joint involvement of other receptors. Furthermore, IgE regulate growth, maturation, survival and homeostasis of mast cells [17]. IgD receptors expressed on B cells regulate their development and maturation, as well as clonal anergy and self-tolerance [19,[30]]. IgD associated with basophils and other cells, after antigenic stimulation, triggers the release of IL-4, which causes the production of IgG by B cells [19].

Thus, most of the biological activity of various classes of Abs is mediated through interactions between the Fc domain and Fc receptors, while additionally involving other receptors [28,[31]]. Five Fc receptors for IgG (FcγR), two Fc receptors for IgE (FcεR), one for IgA (FcαR) and for IgM (FcμR), as well as for IgA and IgM (FcRα/μR), were identified in humans [12,16,28]. The diversity of Fc domains further extends Ig functions due to the presence of sequence polymorphisms and variations in the glycosylation patterns [[32],[33]]. Activation of Fc receptors by Igs or immune complexes leads to several subsequent effects, depending on the Fc receptor-expressing cell, type of Ig or immune complex, cytokine environment and complement presence. Consequently, depending on the immunological context, the responses initiated are different. The diversity of canonical biological outcomes caused by different classes and subclasses of Abs allows for fine-tuning of the immune response, depending on the pathological conditions.

Non-canonical functions of Igs impart even more possibilities for immune responses. These functions include either atypical strategies for pathogen neutralization or actions distinctive of other proteins (extensively reviewed in [10]). Such non-canonical functions of Abs are often due only to theAb's Fab domain (see Table 1). These functions arise in consequence of the extreme diversity of sequences and structural conformations of the antigen-binding site, which are formed both by genetic processes of recombination and mutation, and by post-translational mechanisms [[34]]. The catalytic activity of Igs is typical, and is one of the most common examples of the non-canonical function of different classes of Igs. The results of structural and sequence analyses of the antigen-binding sites of some Abs demonstrate the similarity of sequences and topographic characteristics with the active sites of canonical enzymes [20]. These features give Igs the ability to catalyze specific chemical reactions [20]. Abs with catalytic activity can promote immune defense by hydrolysis of functional molecules important for pathogens. In addition, they can minimize the autoimmune response by reducing the amount of antigen available for immune recognition, or by hydrolyzing pro-inflammatory molecules. Abs with natural catalytic activity are found in the immune repertoire in both physiological and pathological conditions. Immune pathologies are often accompanied by both the expanded diversity and increased level of catalytic activity of Igs.

In addition to catalytic activity, non-canonical functions include direct inactivation of pathogens in the absence of effector cells or molecules. For example, two monoclonal Abs, IgM and IgG, induced changes in the expression genes and metabolism of the *Cryptococcus neoformans* fungal pathogen after binding to the cell surface [10]. Furthermore, it was shown that the Fc domain of sIgA, interacting with bacterial glycans, can modulate the expression of polysaccharide utilization loci, including an uncharacterized family called the mucus-associated functional factor (MAFF) family [[35]]. Another example is a monoclonal Ab specific to the *Escherichia coli* β-barrel assembly machine (BamA), which interferes with the folding and assembly of membrane proteins [[36]]. Thus, some Abs are able to change the basic biological processes of pathogens, leading to their inactivation. Furthermore, several Abs can cause conformational changes in the target molecules of the pathogen [10].

Abs with agonistic activity play an important role in the expansion of the functions of Igs. Many examples are known in which Igs modulate intracellular signaling, including acting as agonists or antagonists of receptors [37]. In some cases, signaling modulation occurs through the Fc domain. For example, IgGs can modulate intracellular insulin signaling due to the interaction of the hyposialylated IgG Fc domain with FcγRIIb [38].

A no less important non-canonical function of Igs is the compensation of innate immune defects due to anti-cytokine activity or other mechanisms [10]. For example, Abs against staphylococcal lipoteichoic acid can protect against staphylococcal infections in individuals with congenital insufficiency of the toll-interleukin 1 receptor (TIR) domain-containing adapter protein (TIRAP) [27]. It is also interesting that some IgGs are involved in the carriage, bioavailability regulation and protection of hormones from proteolytic degradation [10]. However, Ab-dependent enhancement of infection or disease may be a negative function of IgG [31].

Non-canonical functions of IgA, in addition to catalytic activity, include regulation of penetration into the systemic circulation by microbial metabolites, which are involved in the regulation of the metabolism and immunity of the host [14]. Moreover, high-avidity pathogen-specific sIgA contributes to the formation of bacterial clusters, “enchained growth” and enhanced clearance [14]. IgA is also involved in the transepithelial transfer of bacteria from the small intestine to Peyer’s patches and induction of T cell-dependent Ab responses [10].

Non-canonical functions of IgM can be attributed to catalytic activity, direct inactivation of pathogens in the absence of effector cells and molecules, as well as modulation of lymphocyte intracellular signaling due to the interaction of the Fc domain of IgM with FcμR [12,28].

Thus, Igs due to canonical and non-canonical functions significantly expand the functionality of the immune system. The variety of canonical and non-canonical functions of Igs is also reflected in the extreme diversity of Abs generated in an organism.

3. Diversity of Abs Types: Antigen-Specific, Natural, Polyreactive, Broadly Neutralizing, Homophilic, Bispecific, Catalytic Abs

The plethora of Ig functions in the immune system may partly be explained by the wide variety of synthesized Ab types. For a long time, the central paradigm of immunology has been that the immune system generates highly specific Abs against environmental components. At the same time, it learns not to recognize the components of its tissues during ontogenesis (the clonal selection theory) [2]. According to this theory, it was also argued that the failure of immunological tolerance leads to the generation of autoantibodies (autoAbs) and the development of AIDs. The results of investigations of the presence, in healthy individuals, of autoAbs that recognize their autoantigens with low avidity were mainly ignored [2]. However, with the development of research technologies and complex animal model systems, more studies have appeared that prove that autoreactive B cells, as well as natural auto- and polyreactive Abs, are abundantly present and are actively involved in maintaining immunological homeostasis.

The immune system constantly generates many types of Abs (summarized in a somewhat simplified form in Table 2). In general, antigen-specific or adaptive Abs are generated by plasma cells in response to the antigen. During the primary immune response, antigen-presenting cells recognize the pathogen through numerous PRRs and present the processed antigen to B cells [39]. After antigen stimulation, somatic hypermutation and clonal selection, B cells become long-lived plasma cells that produce antigen-specific adaptive Abs in the secondary immune response [39]. Such Abs are characterized by high affinity and specificity. Their main role is the specific binding of the antigen and the initiation of innate responses (see Table 2). The functions of antigen-specific Abs in inflammatory and AIDs are well described [3], so we will not review them here.

Table 2. Comparison of the origin and features of various Ab types in humans.

Abs Type	Origin	Affinity	Specificity	Biological Roles

Antigen-specific adaptive Abs	**B2 cells**	**High**	**High**	• The binding of a specific pathogen • Ab-mediated complement activation • Ab-dependent cell-mediated cytotoxicity • Ab-dependent phagocytosis • Regulation of immune cells homeostasis
Natural Abs	**B1 cells and marginal zone B cells**	**Low**	**Low**	• Direct pathogen neutralization • Classical complement activation • Antigen transport to secondary lymphoid organs and presentation • Ab-dependent cell-mediated cytotoxicity • Phagocytosis of apoptotic cells • Clearance of DAMPs and prevention of autoimmunity • Regulation of immune cells homeostasis
Polyreactive Abs	**B1 cells**	**Low**	**Moderate**	**The same functions as natural Abs**
Broadly neutralizing Abs	**B1 cells**	**Low**	**Moderate**	**The same functions as natural Abs**
Homophilic Abs	**B2 cells**	**High**	**High**	**The same functions as antigen-specific Abs**
Bispecific Abs	**B2 cells**	**High**	**High**	**The same functions as antigen-specific Abs**
Catalytic Abs	**Unknown, presumably B1 cells**	**Low**	**Moderate**	• Hydrolysis of antigen • ROS detoxification due to redox activity • Promoting of autoimmune reactions • Minimization of inflammatory reactions

The follicular or B2 B cells are known to be the main producers of antigen-specific Abs and the most common B cells in humans [39]. However, B1 cells exist in mice, as well as most likely in humans [[40]]. B1 lymphocytes are a special subtype of B cells producing polyreactive and low-affinity natural Abs against viral and bacterial antigens [[41]]. B1 lymphocytes respond effectively to non-specific inflammatory and pathogen-associated stimuli by migrating to secondary lymphoid tissues, where they undergo rapid differentiation into plasma cells secreting natural Abs [40]. B1 cells are selected for autoreactivity and form a pool of long-lived, self-renewing B cells that produce the majority of circulating, naturally occurring, low-affinity IgM and IgG, that cross-react with both autoantigens and conservative microbial antigens. According to recent data, Toll-like receptors (TLR)-mediated activation of B1 cells through CpG oligonucleotides, or lipopolysaccharides, leads to a rapid increase in the production of protective natural Abs (IgM, IgG) [[42], [43]]. Interestingly, B2 lymphocytes can differentiate directly into B1 lymphocytes, and this process is controlled by a self-reactive B cell receptor [[44]]. Depending on the presence or absence of a surface CD5 marker, B1 cells can be subdivided into subpopulations of B1a ($CD5^+$) and B1b ($CD5^-$) [40]. It was found that B1a cells producing natural Abs counteract a wide range of viral and bacterial antigens, whereas B1b cells secrete more specific induced Abs against certain bacteria [[45]]. In summary, B2 cells produce highly specific Abs, whereas B1 cells synthesize non-specific, polyreactive, low-affinity Abs against various antigens.

The biological role of natural Abs (mainly IgM and IgG) produced by B1 cells is direct neutralization of specific pathogens, classical complement activation, antigen transport to secondary lymphoid organs and presentation, Ab-dependent cell-mediated cytotoxicity, phagocytosis of apoptotic cells, regulation of immune cells homeostasis, etc. (see Table 2) [[46]]. Ultimately, natural Abs help reduce inflammation and autoimmune reactions by removing damage-associated molecular patterns (DAMPs), such as extracellular DNA [45,46].

Among natural Abs, polyreactive Abs are also nominally distinguished (see Table 2) [4,[47]]. During the development of B cells, highly polyreactive Abs are known to be removed from the repertoire using physiological mechanisms, including deletion and editing of receptors. However, a low number of polyreactive Abs remains. Such Abs have pronounced protective functions against autoantigens, as well as viral pathogens [[48]]. Furthermore, polyreactive Abs are involved in the regulation of microbiota [[49]]. Among polyreactive Abs that neutralize viral pathogens (especially human immunodeficiency virus (HIV)), broadly neutralizing Abs are especially distinguished [[50]]. A feature of these Abs is that they are able to neutralize multiple HIV-1 clades [50]. There are high hopes associated with the development of HIV vaccines based on broadly neutralizing Abs [[51]].

Some Igs are capable of self-association through interactions between their antigen-binding sites [[52]]. Such Igs are called homophilic Abs. Homophilic interactions allow for more efficient binding to the target antigen, especially antigens with a repetitive nature. For example, highly protective Abs against specific antigens of *Plasmodium falciparum* have recently been shown to use homophilic interactions to bind more efficiently to the antigen [[53]]. Homophilic Ab interactions promote clustering of many Ig molecules, increased affinity for repeating antigens and subsequently more efficient recruitment of the complement system and activation of B cells [52,53]. Interestingly, some therapeutic Abs (e.g., rituximab) use homophilic binding to recognize antigens and promote cytotoxicity [52].

Bispecific Abs containing two different antigen-binding sites are most often generated by genetically engineered pathways [[54]]. However, such Abs can be detected in low concentrations in humans. In our work, we showed that natural bispecific Abs are found in the blood of healthy humans [[55]]. Nearly 9% of IgG molecules of healthy donors contained two different chains of both the kappa and lambda light chains simultaneously. Furthermore, bispecific Abs were observed in human placenta (IgG1-IgG4) [[56]]. It was shown that up to 15.0% IgG from placenta contained two different (kappa and lambda) light chains simultaneously. Moreover, human milk also contains chimeric kappa and lambda Abs (IgG and sIgA) in even higher concentrations than in the serum of healthy donors and the placenta [[57], [58]].

In addition to these types of Abs, the immune system also generates catalytic Abs (see Table 2). Their formation is most often associated with autoimmune reactions (for more details see the full article).

This largely simplified and possibly incomplete scheme (see Table 2) reflects the diversity of Ab types. Different types of Abs provide different functions of the adaptive immune system. We cannot exclude the possibility that other specific types of Abs possessing new canonical and non-canonical functions will be discovered.

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