Immunoprofiling – The Role of Antibody Isotypes

Introduction

The immune system serves as the body's primary defense mechanism against a wide array of infectious agents, ranging from bacteria and viruses to parasites and fungi. It is an intricate network of specialized cells, tissues, and molecules that work in concert to recognize and eliminate foreign invaders while preserving the integrity of the host organism. Coordination of the activities among the different immune cells is critical. Antibodies, products of B lymphocytes, are a unique soluble component of the immune system that engage with both foreign bodies and host innate immune cells. Antibodies consist of two distinct regions, the Fab region, involved in antigen specificity and binding, and the Fc region involved in effector functions via Fc receptors expressed largely by innate immune cells (Figure 1). Both regions contain valuable information for research and discovery: the Fab region identifies disease-relevant proteins, including autoantigenic, and the Fc region provides information related to specific antibody functionality. While the Fab region possesses enormous diversity for identification of innumerous antigens [4], the Fc region can assume five structurally and functionally different structures, each characteristic of a different isotype: IgM, IgD, IgA, IgG, and IgE (Table 1, Figure 1). Through effector functions from both domains, antibodies help coordinate the activities of the innate and adaptive immune system, directing pathogen removal with different strategies for different pathogens. These strategies include neutralization, agglutination, opsonization and phagocytosis, degranulation, complement activation, and antibody-dependent cellular cytotoxicity. Pathogenesis-specific antibodies are often elicited years before a disease becomes clinically apparent. With high disease specificity, early detection, ease of obtaining, and durability during storage, antibodies make excellent biomarkers. Historically, antibodies were among the first pragmatic biomarkers used by clinicians. They make up a unique subset of the proteome, with over 1 trillion potential combinations [4]. Identifying antibody specificity and isotype class within patients can improve diagnostic accuracy at early stages of disease prior to overt symptoms, has the potential to indicate anatomical/tissue compartment most affected, can provide greater precision for therapeutic intervention and improves our understanding of pathogenic mechanisms. Functional protein antigen microarrays are emerging with the capacity to simultaneously measure antibody specificity and isotypes using miniscule volumes of patient-derived biofluid. This provides a solid platform for disease understanding, antigen discovery, vaccine development, biomarker discovery, development of in vitro diagnostics, and true precision medicine.

Antibody Structure

Antibodies are produced and secreted by B lymphocytes, or B cells. Each B cell (referred to as a B cell clone) produces a unique antibody specificity that recognizes a particular cognate antigen. Most antibodies can be membrane bound or secreted into the lymph and blood. Each symmetric Y-shaped immunoglobulin is composed of two heavy and two light chains, held together by disulfide bonds. Heavy chain C-termini form the Fc region (the stem of the Y), while light chains together with heavy chain N-termini form the Fab region. Antibodies were originally classified into groups, or isotypes, by electrophoresis using Greek letters to designate each fraction [5]. In addition to five distinct isotypes, four subclasses of IgG and two of IgA are also recognized. Some isotypes act as multimers, IgM can form pentamers, and IgA dimers (Figure 2). The most enigmatic isotype, IgD, exists predominantly in membrane bound form.

Antibody	Subclasses	Primary Function	Serum Level (g/L)
IgA	IgA_{1-2}	Pathogen neutralization, anti-inflammatory, mucosal	0.6 - 4
IgG	IgG_{1-4}	Circulating and tissue immunity	7 - 15
IgD	None	Upper aerodigestive immunity, B-cell development, immune regulation	0 - 0.14
IgE	None	Tumor surveillance, anti-venom defense, anti-parasitic defense, type I hypersensitivity	Trace
IgM	None	Immune surveillance, acute response (esp. agglutination, complement activation)	0.6 - 3

Table 1. Antibody Primary Functions and Adult Reference Ranges [2, 6, 7]

At the N-terminus of the Fab region are three hypervariable loops produced through random gene segments recombination and somatic hypermutation. These loops help determine specificity of the paratope, the region of the antibody that makes contact with a cognate epitope on an antigen. In the case of protein antigens, antibodies typically recognize non-continuous epitopes resulting from protein 3D conformational characteristics [8-10]. Random recombination events result in an enormous potential antibody repertoire, up to 1018 combinations [4, 11, 12]. While the Fab region confers antigen specificity, the Fc region interacts will soluble and cellular host components, determining antibody function. The Fc

region constant domains are encoded by different genes that undergo alternative splicing and class switching during B cell development to generate the various isotypes. Class switching is irreversible, involving constant region deletional recombination [1]. This region is involved in anchoring the antibody in the B cell membrane, transducing antigen stimulated signaling, and when secreted, acts as ligand to Fc receptors to bind with and regulate other immune cells.

Antibody Effector Functions

The immune response is somewhat tailored by the inciting stimulus. The environment, type of stimulus (pathogen, trauma, toxin, etc.), and the encounter location within the body influence the humoral system response resulting in class switching to antibody isotypes matched to handle the insult [2]. The isotypes bind with cognate Fc receptors expressed on other cell types to modulate the appropriate immune response (Table 2). Fc receptor nomenclature incorporates the isotype-corresponding lowercase Greek letter. For example, FcγRI refers to the first IgE receptor discovered, expressed by mast cells, basophils, and eosinophils. Often there are multiple Fc receptor subtypes for an individual isotype with differing affinities and differential expression across different immune cells. Altogether, the antibody, antigen and innate immune effector cell form a complex that results in a specific defense strategy determined by the Fc receptor binding, the binding affinity, and the cell types involved[3]. As an example, IgG1 opsonizes virus and via FcγRI receptor signaling, stimulates macrophage phagocytosis of virus. Similarly, IgM influences macrophages, but IgM activates complement that then activates macrophages. IgD can bind directly to basophils, promoting an inflammatory response via IL-4 release [13]. The antibody isotype and subclass, including glycosylation status, play a crucial role in shaping the immune response, impacting various aspects of immune defense that when known can provide clues to researchers regarding the antigens encountered, tissues involved, immune systems engaged, potential for inflammation, and disease status.

B Cell Development, Activation and Antibody Production

Initially, IgM is the first isotype expressed by B cells. During B cell development, immature bone marrow B cells express membrane-bound IgM, forming part of the B-cell receptor (BCR) complex, with the Fc region inserted into the cell membrane and the Fab region exposed extracellularly to interact with antigen (Figure 3). A signal transduction region (CD79A, CD79B) couples with the IgM to complete the complex. Early during development, BCRs with strong affinity for self-antigens will usually undergo clonal deletion via apoptosis, decreasing the likelihood of autoreactive antibodies. Surviving B cells undergo further maturation in the spleen or lymph nodes where they express transmembrane bound IgD or IgM antibodies. When B cells encounter an unrecognized antigen for the first time, the initial antibody response comprises IgM released into the serum predominantly as a pentamer. Although short lived, IgM is the first circulating antibody, marking disease early in infection. Among other functions, IgM can neutralize and agglutinate extracellular organisms, for example preventing bacteria from accessing the gut lumen, or activate complement in response to viruses. As the initial wave of IgM mounts and peaks, class switching and somatic hypermutation occur to tailor the immune response to the inciting event at a slight delay. Specificity remains intact, but the isotype switches to strategically match the inciting context, influenced by the specific biological compartment. B cells then form germinal centers expressing high levels of secreted antibody cognate to the stimulating antigen. [12, 14-16].

Protects From	Effector Function	Isotypes	FC Receptors	Effector Cells Examples
Intracellular Organisms	Opsonization	IgA1	αRI	Macrophages
		IgG3	γRI, γRIIa, γRIIIa	
Helminths	Degranulation	IgG4	γRIIa	Neutrophils, Mast Cells, Basophils, Eosinophils
		IgE	εRI	Mast Cells, Basophils, Eosinophils
Extracellular Organisms	Opsonization, Degranulation	IgG2	γRIIa	Macrophages, Neutrophils
	Opsonization, Degranulation	IgA2	αRI	Macrophages, Neutrophils
	Neutralization, Degranulation	IgD	Galectin-9/CD44	Mast Cells, Basophils
	Neutralization, Agglutination	IgA, IgM	pIgR	Epithelial Cells of Mucosal Membranes
		IgE	εRII	Intestinal Epithelial Cells, Antigen Presenting Cells
Viruses	Opsonization, Phagocytosis	IgG1	γRI, γRIIa, γRIIIa	Macrophages, Monocytes, Natural Killer Cells
		IgA1	αRI	Macrophage, Neutrophil, Natural Killer Cells
	Complement Activation	IgM	C1q	Macrophages
Tumor Growth	Antibody-Dependent Cell-mediated Cytotoxicity	IgG1, IgG3	γRIIIa	Natural Killer Cells

Table 2. Examples of Isotype Context-Specificity [1-3]

The Value of Isotype Screening in Understanding Disease

Antibodies are excellent biomarkers for diseases not only infectious diseases, but all diseases. They are highly specific to antigens, are easy to obtain from serum, and are highly stable frozen for years. However, most analyses have focused on IgG and IgM antibodies [6]. Isotype identification has been underutilized, but the isotype carries quite valuable information. The different isotypes are expressed at different times during disease, are privy to different tissue compartments, and interact with different immune mechanisms, resulting in unique spatial and temporal expression patterns that can delineate disease. For example, while IgM and IgG are the most abundant isotypes in nearly all autoimmune diseases, IgA autoantibodies are prominent in antiphospholipid syndrome of the vascular system and IgE is prevalent in SLE [17]. Taken together, the advantages of antibody and isotype screening for medicine include improved early disease detection, disease monitoring, outcome prediction, patient stratification, and greater understanding of immune mechanisms.

There are two basic approaches to antibody screening, targeted and untargeted. In a targeted approach, often used to refine diagnostics, specific antigens are assessed for antigenicity related to disease. In a meta-analysis of Rheumatoid Arthritis (RA) patients, Motta et. al. evaluated the diagnostic potential of different antibody isotypes to rheumatoid factor (RF). While IgM and IgG to RF are known to dominate serum, IgA emerged with the highest specificity to RA of 91%, but the sensitivity was only 49% [18]. Many of the studies in the analysis did not measure multiple isotypes simultaneously, which could have raised both specificity and sensitivity. A multiple monitoring approach was used by Sieghart et. al. By combining quantification of antibody isotypes IgG, IgM, and IgA with antigen specificities to rheumatoid arthritis related antigens (RF, ACPA and RA33) they found a 30% improvement in diagnoses [19].

Targeted antibody screening is often used in infectious diseases where the antigen is known. Assessing the ratios of isotypes expressed in these cases has merit beyond diagnosis. It may help predict predisposition to future disease. In a study of human papillomavirus (HPV), anti-HPV IgA and IgG1 were the most abundant isotypes found in patient serum, but with different pathologies. IgA was present early in disease while IgG1 persisted long-term, suggesting lifetime cumulative exposure to virus in some patients. Further, IgG1 expression and titer correlated with future risk of cervical cancer while the early presence of IgA correlated with reduced risk [20]. These data indicate that the isotype expressed may help assess patient risk. By looking for antibody specificities and isotypes, researchers can also identify patient liabilities and stratify patients into appropriate treatment routines. In another example, HIV patients infected with SARS-CoV-2 lacked anti-Spike Protein IgA, but not IgG1 [21]. IgA is one of the first lines of defense against respiratory infections. In this case, infection with HIV may affect susceptibility and severity of future novel respiratory infections. With this information, clinicians can better direct care for HIV patients.

A better understanding of disease pathology can be achieved when examining multiple isotypes. In dengue virus (DENV), secondary infections are much more severe than initial infections. In the past, DENV research focused mainly on IgM and IgG antibody responses to DENV. More recently, Waickman et. al. found that following primary DENV infection, IgM, IgG, and IgA are expressed in near equal proportions. Further IgG1 and IgA dominated secondary infections. The researchers suggested that IgA may be competing with IgG1 for binding with DENV, preventing the IgG mediated immune responses and enabling the virus to persist in secondary infections [22]. In this case, the virus appears to take advantage of the IgA response.

IgA is the most abundant isotype in the body (Table 1) found mostly in mucosal membranes. This isotype is one of the first to combat respiratory infections. Interestingly, IgA has access to the gut microbiome and it is believed that through regulating the gut flora, IgA may have strong influence on diseases such as cancer and neurodegenerative [23-26]. IgA is emerging as a particularly specific isotype for disease detection across a variety of diseases, but it is not often studied.

These targeted approaches are straightforward, simple, and target known antigens. ELISA and protein microarrays are most suitable for this methodology. However, no new antigens or antigenic pathways are discovered. In an untargeted approach, the researcher compares antigen presence or absence between patients and control subjects against a massive library of potential antigens, numbering in the thousands. The approach is exploratory and often utilizes a second validation study with a new group of patients to verify the results. This approach can uncover novel antigens related to disease. New disease related protein pathways can also be discovered with the potential for uncovering novel druggable targets. Functional protein microarrays are among the best technologies for this approach.

Large scale, untargeted antibody screening has been used to detect complex diseases such as cancer and neurodegenerative diseases, both of which produce aberrant protein expression patterns that humoral immune system recognizes as foreign [27, 28]. These complex diseases can affect multiple organs resulting in production of several disease related antibodies with unique specificities and different tissue specific isotypes. In a recent, comprehensive study by

Patel et. al., 60 different IgG antibodies of interest were uncovered from a screen of more than 1600 antigens across a cohort of 157 patients with non-small cell lung cancer (NSCLC). Eighteen of the 60 antibodies correlated with post-resection survival rates. Evaluating various permutations of these 18 antibodies revealed that 13 strongly correlated with 5-year patient survival in both the study and validation cohorts [29]. The repertoire of antibodies induced by these complex diseases can not only accurately detect disease early, ahead of many other diagnostics, but also indicate potential druggable protein pathways [30]. In this case, Cancer Testis Antigens (CTA) featured prominently. CTAs are typically expressed in male germ cells and during embryogenesis. Thus, their ectopic expression in NSCLC patients (male and female) may provide an excellent well aimed therapeutic target.

For diseases such as cancer and Parkinson's, researchers have yet to examine multiple isotypes. These diseases remain difficult to diagnose. Future research evaluating different antibody isotypes and their antigen specificities is likely to provide greater understanding of these diseases and better diagnostics.

The Role of Antibody Isotypes in Drug Development

Detecting the isotypes present in patient sera can provide valuable insights regarding inflammatory status that can lead to undesired drug reactions. Some isotypes can react with complement, promoting inflammation. IgG1, IgG3 and IgM are examples, and can induce macrophage activation leading to inflammatory cytokine release [1]. Others, such IgG2 and IgG4 are anti-inflammatory. Examining patient serum for various isotypes and antigen specificities can help researchers identify autoantigens that induce inflammation. Further, this can help clinicians monitor patients and may provide valuable insight into adverse events from treatments [31]. For example, distinct autoantibody signatures predict adverse events in patients receiving immune checkpoint inhibitor monoclonal antibody therapy [32, 33]. In neurodegenerative research, a promising finding regarding the effector function of IgG antibodies on microglial cells has promoted research into monoclonal antibody therapy for Alzheimer's and Parkinson's. Microglial cells increase uptake and degradation of tau and α-synuclein particles in vitro in response to FcγR activation, an important finding that could lead to new treatments for neurodegenerative diseases involving protein aggregates (Parkinson's, Alzheimer's, Huntington's). However, FcγR activation results in inflammation [34]. Further, most monoclonal antibody therapies utilize IgG1 antibodies that can react with Fcγ R. For future monoclonal antibody therapies, researchers have started examining IgG4, an isotype with low affinity for FcγR and that does not react with complement [1, 35]. Patient immunoprofiling may help determine the likelihood of inflammatory adverse events based off the repertoire of antibodies and isotypes present in serum. Further, selecting antibody isotypes will become an important decision to ensure the safety and efficacy of future monoclonal antibody therapies.

Simultaneous Measurement of Antibody Isotypes

Isotype screening has traditionally been done with immunochemistry using ELISA technology and isotype specific secondary antibodies. However, ELISA lacks the throughput and sensitivity of more modern protein microarrays. For biomarker discovery, functional protein microarrays are an excellent, cost effective, reliable, high throughput means of quickly profiling the myriad of antibodies present in an individual's serum, and uncovering those related to disease. In these arrays, thousands of proteins are printed onto a slide surface. Antibodies from patient serum bind cognate proteins that are illuminated with indirect immunofluorescence. Secondary antibodies directed to IgG, IgA, IgM, etc. can be applied singly or in pairs to recognize both specificity and isotype from a single sample. Done properly, protein microarrays can accurately determine disease related antibodies and isotypes from small serum samples while also retaining function, allowing examination of post translational modifications, such as glycosylation and citrullination. Specificity, isotype and post translational activity can be studied from a single sample. However, specificity is tightly linked to antigen shape, not protein sequence [8, 10]. Sengenics is one of the few companies that offers a validated, high-quality dual color detection analysis that considers antigen shape. Using the patented KREX technology, only correctly folded proteins with discontinuous epitopes intact are present on the array. This results in highly specific, highly reproducible antibody-antigen binding, a necessity for dual isotype profiling where non-specific binding could seriously confound the results (Figure 4). With this technology, distinct IgA and IgG profiles were observed among individuals with autoimmune disease, thus providing greater detail regarding the disease and possibly more accurate diagnosis (Figure 5).

Conclusions

Circulating antibodies are among the first manifestations of disease, furnishing clinicians with unheralded details about patient status, often before symptoms. Identifying isotype and antigen specificity provides highly specific metrics for detecting and understanding disease pathology that allows clinicians to develop tailored strategies for different patients, monitor progress, and watch for adverse events. Study

of different antibody isotypes in disease, especially complex diseases like cancer and neurodegenerative diseases, is in the early stages. Newer technologies such as next generation sequencing, modern protein microarrays, and machine learning have begun to enable researchers to capture this information.

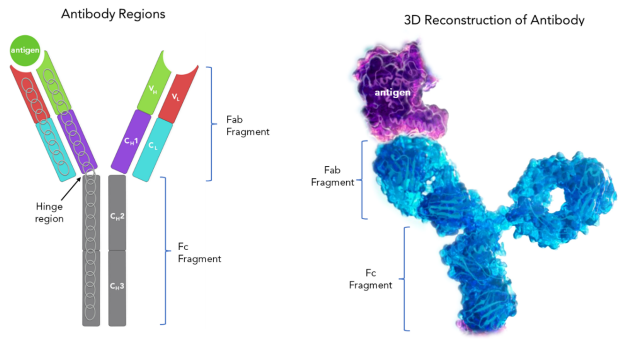

Figure 1 The Basic Structure of an Antibody. Left, General overview of antibody structure highlighting location of Fab and Fc regions. Right, 3D reconstruction illustrating antibody shape.

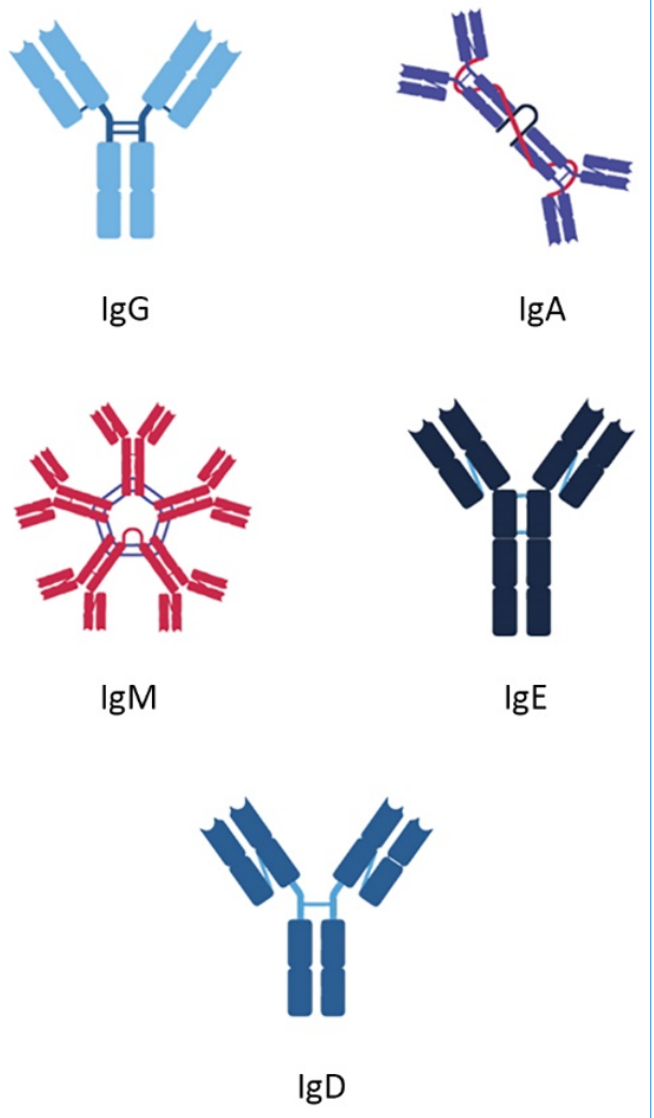

Figure 2. The five basic antibody isotypes.

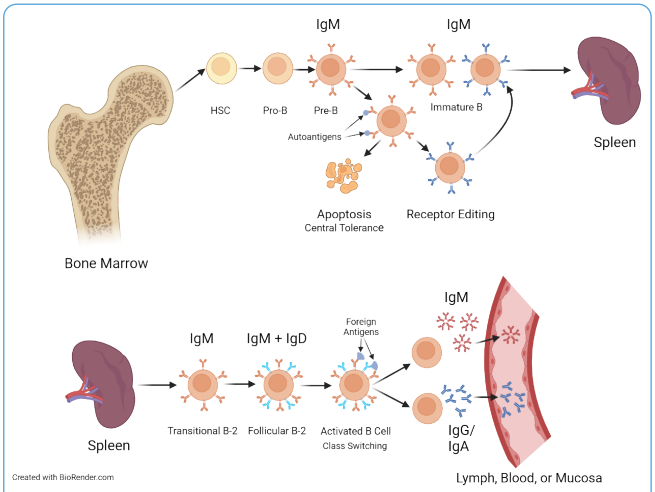

Figure 3. Maturation of B Cells and production of secreted antibodies.

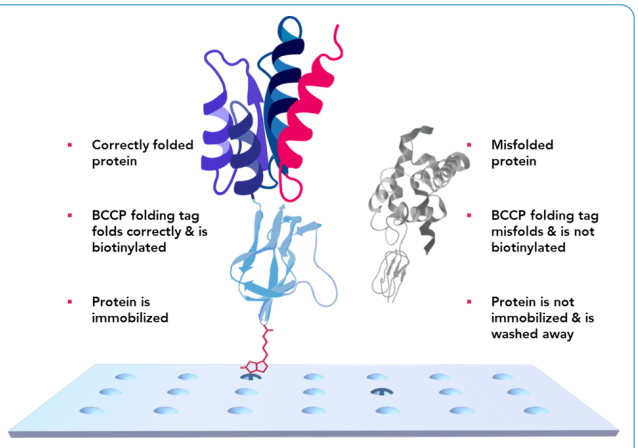

Figure 4. KREX technology ensures only full-length correctly folded proteins are on the array chip. A biotin carboxyl carrier protein (BCCP) is coded in frame with each protein serving as a link between the streptavidin surface and the recombinantly engineered biotinylated protein. A misfolded or fragmented protein results in BCCP misfolding and an inability to bind with the slide. Incorrectly folded proteins are simply washed away.

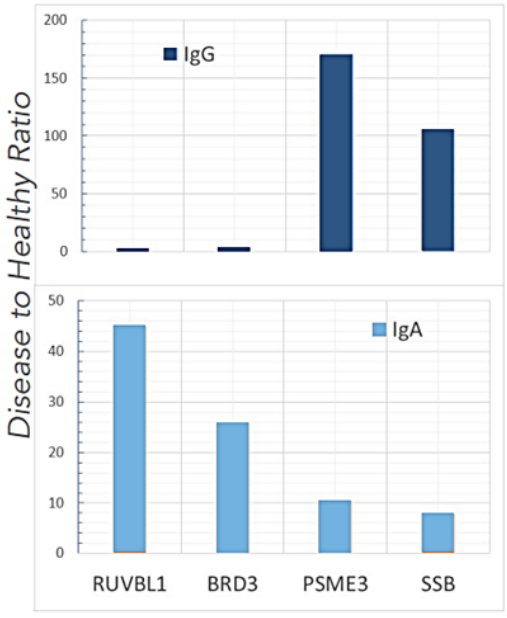

Figure 5. Pooled sera from autoimmune disease patients and healthy controls compared using the Sengenics IgG/IgA Dual Color Assay shows unique biomarkers of each isotype. The IgG and IgA isotypes identify different antigens, improving the level of detection.

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