IgG4 Subclass of Immunoglobulins; Immunobiology and Roles in Relation to Human Diseases

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ABSTRACT

IgG4, a subclass of antibodies known as immunoglobulins have unique structural features, in particular, their Fc regions, that prevents their interactions with other receptors on effector cells and thus disabling them of activating complements system. IgG4 antibodies can undergo a process called Fab-arm exchange, wherein they exchange half-molecules with other IgG4 antibodies, thus forming bispecific monovalent antibodies. Isotypic switch in mature B cells in germinal centres of secondary lymphoid organs is controlled by Tfh subset of T cells. Functionally IgG4 antibodies exert immunomodulatory and blocking activities, modulating protective inflammation evolved by parasitic invasion and allergic inflammation. From the pathophysiological point of view, IgG4 autoantibodies are prominently observed in autoimmune diseases under the umbrella of IgG4-autoimmune diseases (IgG4-AID). Furthermore, IgG4-related diseases (IgG4-RD) are affecting various organs characterized by lymphoplasmacytic infiltrates and storiform fibrosis in tissues, together with elevated IgG4 levels in the blood. A better understanding of IgG4 immunobiology helps us diagnose and treat patients suffering from these rare forms of diseases.

KEYWORDS

IgG4 subclass; immunobiology; characteristics; IgG4 autoimmune diseases; IgG4 related diseases

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INTRODUCTION

The humoral arm of specific immunity, characterized by the antigen-driven terminal differentiation of mature B cells into plasmablasts and predominantly plasma cells to produce immunoglobulins, is indispensable for protective inflammation. Both inherited and acquired defects in antibody production are a cause of enhanced susceptibility to pathogens invasion, with severe impacts on human health. When homeostatic regulations of B cells differentiation are disrupted, it can result in production of autoantibodies causing damage to various self structures leading to a harmful inflammatory response. There are numerous mutual functional interactions between B cells and T cells. Majority of the antigen-driven B cell activities are regulated by the Th2 subset of polarized T cells mediated by direct cell-to-cell interactions and cytokines. This is true for two processes in B cells, regulating isotypic switching and somatic hypermutation. The isotypic switching is responsible for the production of other classes and subclasses of immunoglobulins instead of IgM class, which is mostly produced in the primary specific humoral response. The somatic hypermutation mediates a gradual increase in antibody affinity during antigen-induced B cell proliferation. The antigen switching is essential to produce IgG4 subclass of IgG antibodies. The immunobiological role of IgG4, the least produced subclass of IgG, is unique in many aspects, and still enigmatic. In addition, enhanced production of IgG4 is associated with the presence of fibroinflammatory lesions in various organs and the presence of IgG4 subclass autoantibodies with IgG4 autoimmune diseases. The aim of this review article is to summarise the unique immunobiological molecular characteristics of the IgG4 subclass, its production, and its roles in health and diseases.

MOLECULAR CHARACTERISTICS OF IgG4 SUBCLASS

It is important to note that approximately threequarters of daily immunoglobulin production is dedicated to IgA2 subclass of IgA immunoglobulins, which forms secretory IgA responsible for protecting mucosal surfaces. However, the IgG class of immunoglobulins is the most abundant in plasma with levels ranging from 5,0–16,0 g/l. The high level of IgG immunoglobulin in plasma and its long 21 days half-life are apparently maintained by production and cellular recycling using FcRn of neonatal IgG1 receptors (1). Based on differences in heavy chain structures, IgG class is further subdivided into four subclasses (2). Each subclass has distinct structural and functional properties leading to different effector functions comprising opsonization, classical pathway complement activation, antibody-dependent cytotoxicity, pathogen neutralization, and immunocomplexes handling (3). IgG4 is the least abundant subclass of IgG in blood and has unique functional features compared to other IgG subclasses. IgG4 has reduced affinity to many effector molecules expressed on immune cells, such as Fc and complement receptors. Furthermore, IgG4 has a significantly limited ability to activate the complement system. This is caused by the presence of several amino acids in the Fc part of molecules together with absent of N-glycans when compared to IgG1 which is highly active in this regard. However, the interactions of IgG4 with the FcγRII inhibitory receptor are not abrogated, contributing to its participation on dampening of inflammatory responses (4). In sharp contrast to other immunoglobulin classes and subclasses, IgG4 does not cross-link antigens. Although initially produced like other subclasses as bivalent, monospecific antibodies by plasma cells, IgG4 immunoglobulins undergo a unique process called "Fab-arm exchange". In this process, half-molecules of IgG4

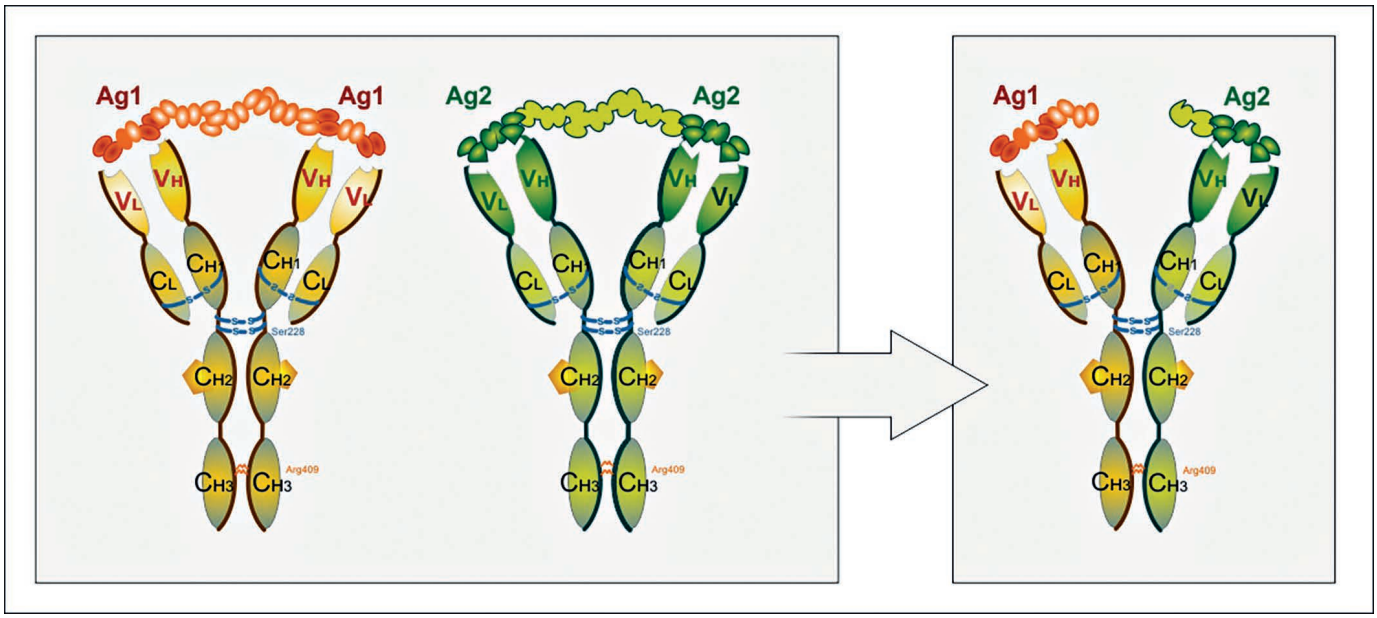

Fig. 1 Fab-arm exange in IgG4 subclass. Legend: IgG4 molecules are characterized by their unique molecular structure. Monomers of heavy (H) and light (L) chains are bound together by two disulfide bounds in hinge region with serin at position 228 and non covalent bond in CH3 domain with arginin at possition 409. Both features are required for Fab arm exchange. A functional consequence is the effective monovalency of IgG4. This eliminates the potential of the antibody to cross-link antigen, further minimizing the immune-activating potential of IgG4.

(made of one heavy and one light chain) are randomly exchanged with half-molecules from other IgG4 antibodies, forming bispecific molecules that target two different antigens (Figure 1). This process is facilitated by two unique amino acids, first one in hinge region and second one in terminal CH3 domain of IgG4. As this reaction does not require any additional proteins, it results in a highly dynamic process during which IgG4 molecule antibodies constantly exchange arms which generate ever-changing repertoire of hetero-bivalent IgG4 antibodies. Owing to the heterogeneity of the IgG4 pool, up to 99% of circulating IgG4 is considered bispecific (5). In summary, IgG4 subclass antibodies are considered immunomodulatory and referred to as "blocking antibodies" that might function to remove antigens to stop their active potential (6).

IGG4 IMMUNOGLOBULINS FORMATION

After antigen-independent B cells differentiation in primary lymphoid organs, mature naive B cells accumulate in B-cell-rich areas of secondary lymphoid organs, such as lymph nodes, spleen, and mucosa associated lymphoid tissues. These are sites of encounters for antigenic stimuli. When an antigen is specifically recognized via BcR receptors and a sufficient level of costimulatory signals provided by membrane-to-membrane contacts and soluble mediators is reached, the B cell undergoes clonal expansion and terminally differentiate to the antibody-producing plasma cells. The response to antigenic stimulation of B cells is inseparably linked to affinity maturation and isotypic switching (7). The initial response to antigen is predominantly driven by the extrafollicular pathway. It involves a subset of T follicular helper cells (Tfh) driving the differentiation of antigen-stimulated B cells into short-lived plasmablasts, which will maintain a primary antibody production for up to a week after the trigger (8). To create an immune response based on IgG4, B cells must undergo class switch recombination and somatic hypermutation. These processes are hallmarks of follicular response, which take part in germinal centres of lymph nodes and spleen. In the follicular pathway, B cells develop high affinity and specificity and become memory B cells or long-lived antibody-producing plasma cells predominantly residing in the bone marrow. The germinal centres are divided into dark and light zones, with functional differences. The dark zone promotes the proliferation of B cells, as well as somatic hypermutation and isotypic switch. (9) Given its mechanisms, switching into Ig class follows a segmental pattern from Cμ/Cδ constant genes adjacent to already rearranged VDJ genes segment, marking specificity to γ3, γ1, and α1, thus forming IgG3, IgG1 and IgA1 subclasses instead of IgM (7). A secondary switch gives rise to more distal classes of IgG2, IgG4, IgE and IgA2, respectively. The isotypic switch is under the control of a functionally polarized subset of Th2 T cells which provide stimuli to antigen-driven differentiated B cells in both humoral and membrane associated molecules, such as IL-4, IL-13, CD40 – CD40L, and ICOS-ICOSL (10). After this cooperation in between Th2 subsets and B cell clones, high affinity and specificity B-cell clones migrate to the light zone of lymph nodes where they undergo a selection according to interactions with follicular dendritic cells and highly specialized set of follicular T helper cells (Tfh). Once the highly specific clones of B cells are selected, they leave germinal centres and become long-lived plasma cells or memory B cells (3).

A specialized subset of helper T cells, Tfh cells, deserve special attention as they have a profound influence over specific humoral immune responses by guiding antigen-driven B cell differentiation, maturation, isotypic switching, and their terminal differentiation into IgG4 subclass producing plasma cells. Tfh cells are localized in germinal centres of secondary lymphoid organs but also dynamically recirculate across injured tissues, lymph nodes, and peripheral blood. The Subset of Tfh cells has emerged as pivotal orchestrators in the balance between immune tolerance and inflammation. They play a role in driving the production of IgG4 and IgE immunoglobulins which are crucial in both physiological and pathophysiological processes (11).

Tfh cells migrate aptly to CXCL13-rich B cells follicles using CXCR5 chemokine receptors to enhance formerly described fundamental B cells functions. Moreover, Tfh cells enhance overall B cell survival and differentiation by expressing CD40L (CD154). An indispensable role in programming early Tfh cell development is given to membrane expression of ICOS (CD278) costimulatory molecules. This process is checked by checkpoint inhibitory molecules such as PD-1 (CD279) interacting with PD-1L (CD274), expressed on B cells to modulate excessive activation within germinal centres (12). The master regulator of Tfh seems to be the Bcl-6 molecule with lower expression in peripheral blood circulating Thf. The crucial expression of Bcl-6 is regulated by the action of Aiolos transcription factor (13). The population of Thf could be subdivided into several functionally polarized subsets, such as Thf1, Thf2, Tfh13, Tfh17, and Tfhreg, respectively, thus partially reflecting functional polarization of the subpopulation of T helper T cells as a whole. Isotyping switching to IgG4 secretion and terminal differentiation into long-lived plasma cells require IL-4 produced by Tfh2 and IL-10 produced by Tfhreg T cells (14).

IGG4 ROLES IN PHYSIOLOGICAL IMMUNE REACTIVITY

Owning to Fab-arm exchange, and the effective monovalency of majority of the IgG4 molecules *in vivo* preventing the cross-linking of antigens together, with the overall reduced ability of IgG4 to activate Fcγ receptors and complement system, the IgG4 is often regarded as a natural type of "blocking" antibody dampening the inflammatory responses (4).

The best examples of this IgG4 response are parasitic infections. The host develops a strong innate and specific T and B cell response during the acute phase of infection. Specific response is dominated by Th1 T cells activity and the recruitment of eosinophils. If the pathogen fails to evade the host response this leads to parasite clearance. If the host effort fails, the chronic phase of infection is an-

ticipated. This phenomenon is associated with the switch from a potentially damaging Th1-driven response to a Th2 response which is sparing tissue integrity. In addition, Treg T cell activities are upregulated by parasites to escape from the Th1 immune response (15). The net result is that up to 90% of parasite-specific antibodies are IgG4 subclass in asymptomatic patients. Interestingly, it has been suggested in so-called "hygiene hypothesis" that IgG4-mediated attenuation of host immunity by the parasites may be a form of protection of the host from allergies and autoimmune diseases (9).

Allergic diseases comprise heterogeneous set of illnesses affecting almost any organ. They can develop in predisposed atopic individuals after exposure to specific allergens. The clinical presentation reflects the complexity of allergic inflammation. However, the role of allergen-specific IgE antibodies is very relevant in the immediate phase of allergic response. This is caused by the rapid release of numerous biologically active compounds stored in granules of mast cells and basophils induced by allergen crosslink of IgE molecules tightly bound to high-affinity receptors FcεRI. Tolerance to allergens can be achieved by long-term natural chronic exposure to allergens or by specific allergen immunotherapy. For almost all individuals with a history of allergic symptoms, the IgG4 can constitute more than 75% of allergen-specific IgG after continuous exposure to allergens (16). The protection against the symptoms of allergy mediated by IgG4 is thought to be the result of at least several actions. These are blocking activities of allergen-specific membrane-bound IgE by competing for allergen binding sites thus blocking mast cell degranulation, preventing the immune complex formation, and inhibiting antigen presentation to T cells by B cells and dendritic cells. There is a raise in IL-10 production by Treg which is to provide tolerogenic stimuli to T cells and also enhance isotypic switch in B cells to produce allergen-specific IgG4 antibodies (17).

THE ROLES OF IGG4 IN PATHOLOGICAL PROCESSES

A selective lack or extremely reduced plasma concentrations of IgG4 are rare and are often associated with recurrent respiratory and/or gastrointestinal tract infections, impaired immunity against fungal invasion, and increased risk of IgE-mediated pathologies (18).

There are clinically more challenging diseases in which autoantibodies against defined targets are formed in the IgG4 subclasses. This emerging subgroup of autoimmune diseases is called the IgG4 autoimmune diseases (IgG4--AID) (19).

On the other hand, immunopathological disorders characterized by elevated plasma level of IgG4 are in the majority patients concomitantly present with lymphoplasmacytic infiltration of the affected organs and storiform fibrosis of tissues (20).

Autoantibodies produced by autoreactive B cells under the regulation of functionally polarized Th2 T cells are key pathogenic players in many immunopathological disorders, with rheumatoid arthritis and connective tissue diseases being the most prevalent. They cause the immunopathological processes by a range of different effector mechanisms such as antibody-enhanced endocytosis and activation of complement cytotoxicity that are dependent on the engagement of the Fc part of antibodies. These effector functions are not available to the IgG4 subclass. The pathogenicity of IgG4 subclass autoantibodies in IgG4-AIDs is largely mediated by blocking spatially protein-protein cell-cell interactions thus competing with the physiological roles of targeted proteins (21).

IgG4-AIDs is heterogeneous group of immunopathological disorders that can affect many organs, depending on the major site of action of targeted autoantigens, including central and peripheral nervous systems, kidney, skin, and hematopoietic system. A recent comprehensive review on the IgG4-AID and autoantigens involved in this disorder is available (22). IgG4-AIDs is evidenced in animal models by passive transfer of autoantibodies comprising subtype of myasthenia gravis characterized by the presence of IgG4 autoantibodies targeting muscle-specific tyrosine kinase (MuSK) critical for the proper clustering and functionality of acetylcholine receptor at the muscle endplate of the neuromuscular junction (23). The presence of IgG4 autoantibodies specifically identifying epitopes on desmoglein 1 and desmoglein 3 is characteristic of pemphigus foliaceous and pemphigus vulgaris, respectively. Desmogleins are Ca2+-dependent transmembrane proteins localized in keratinocyte desmosomes and play a critical role in maintaining the integrity and cohesion of keratinocytes within the epidermis. Desmoglein 1 is primarily located in superficial layers, while desmoglein 3 is found in basal layers of the skin. The interaction with IgG4 autoantibodies results in the obstruction of keratinocyte-keratinocyte adhesion leading to formation of skin blisters (3). The last example of IgG4 AID is thrombotic thrombocytopenic purpura. In this immunopathology, ADAMTS13 metalloproteinase activity is blocked by IgG4 autoantibodies. ADAMTS13 is a proteinase found in blood circulation. It is responsible for the proteolytic cleavage of multimeric form of von Willebrand factor (vWF) and ensuring normal haemostasis. ADAMTS13 proteolytic activity is disturbed by the binding of IgG4 autoantibodies. This result is the accumulation of vWF multimers which cause platelet aggregation and the formation of microthrombi leading to the characteristic phenotype of microangiopathic haemolytic anaemia. It has to be emphasized that the autoimmune nature of IgG4-AID is based on significant HLA association, particularly HLA-II class molecules (7).

IgG4-related disease (IgG4-RD) is a systemic immunopathological reaction characterized by fibroinflammatory lesions in various organs. These lesions can mimic inflammatory disorders, infections, or malignancies. IgG4-RD is often accompanied by elevated IgG4 plasma levels, although not always (24). IgG4-RD is characterized by three major histopathological findings; dense lymphoplasmacytic infiltrates, fibrosis predominantly in storiform pattern, and obliterative phlebitis with an increased number of IgG4+ plasma cells in affected tissues. The comprehensive criteria to diagnose the IgG4-RD were established (25).

Five clinical phenotypes of IgG4-RD were identified based on patterns of affected organs. Group 1 with pancreatic-biliary lesions, is common in older patients and

Tab. 1 Clinical phenotypes of IgG4 – related disease.

	Group 1	Group 2	Group 3	Group 4	Group 5
Pattern	Pancreato-hepato biliary disease	Retroperitoneum and aorta	Head-and neck-limited	Mikulicz and systemic disease	Hematologic diseases
Presentation	Autoimmune pancreatitis sclerosing cholangitis	Retroperitoneal fibrosis aortitis large vessel disease	Salivary and/ or lacrimal gland enlargement adnexal orbital involvement	Symetric salivary gland enlargement with involvement in chest and/or abdomen	Lymphadenopathy Eosinophilia
Phenotype	Proliferative	Fibrotic	Proliferative	Proliferative	Proliferative/Fibrotic
Serum IgG4 level	Elevated	Normal or mildly elevated	Elevated	Very highly elevated	Mildly Elevated

may develop pancreatic and bile duct cancer due to chronic inflammation caused by autoimmune pancreatitis and IgG4-related sclerosing cholangitis. Group 2 with retroperitoneal fibrosis is predominantly found in older males associated with elevated plasma CRP levels and lower IgG4 levels compared to other groups of IgG4-RD. Group 3 with head and neck lesions predominantly in salivary and/or lacrimal glands and, group 4 with Mikulicz disease characterized also by lesions in salivary and lacrimal glands associated with systemic lesions, more prevalent in middle-aged females often accompanied by allergies with higher plasma levels of IgG4 compared to other groups (20, 26, 28).

Group 5 of IgG4-RDs are manifested in hematologic diseases, i.e. lymphadenopathy, eosinophilia, and polyclonal hypergammaglobulinemia. The disease can be easily mistaken, as patients may present with clinical problems that mimic disorders such as multicentric Castleman disease, lymphoma, plasma cell neoplasms, and hypereosinophilic syndromes. When IgG4-RD is suspected, a firm histological diagnosis is essential to confirm the diagnosis and to rule out mimickers. The central histopathological features are a dense, polyclonal, lymphoplasmacytic infiltrate enriched with IgG4-positive plasma cells (with an IgG4/IgG ratio >40 %), storiform fibrosis, and obliterative phlebitis. It is of high importance to haematologists, that the latter two features are seen in all tissues except bone marrow and lymph nodes, making these two sites suboptimal for histological confirmation. Many patients follow an indolent course and respond well to treatment, but a significant proportion may have highly morbid or fatal complications such as periarteritis, severe retroperitoneal fibrosis, or pachymeningitis. Corticosteroids are effective, and the initial response rates to rituximab are high but durable remissions are rare (29).

ACR (American College of Rheumatology) / EULAR (European League Against Rheumatism) classification of clinical criteria for IgG4-RDs was developed and validated in 2019. These criteria should contribute substantially to future clinical, epidemiologic, and basic science investigations. A 3-step classification process was developed. Firstly, it must be demonstrated that a potential case with is involved in one of 11 possible organs in a manner consistent with IgG4-RD classification. Secondly, exclusion criteria which consists of clinical, serologic, radiologic, and pathologic items must be applied, and the presence of any of these criteria eliminates the patient from IgG4-RD classification. Thirdly, 8 weighted inclusion criteria domains, addressing clinical findings, serologic results, radiology assessments, and pathology interpretations, are applied. These criteria were shown to have robust test characteristics over a wide range of thresholds (25).

Current studies using the most advanced molecular biological methods yield evidence that support the pathogenesis of IgG4-RD is an antigen-driven process mediated by B and T cell interactions. Many studies suggest the role of autoantigens, such as carbonic anhydrase II, lactoferrin, annexin A11, galectin 3 (7).

One of the key histopathological features commonly observed in affected organs and tissues in IgG4-RD is the formation of tertiary lymphoid tissues, a process believed to induce the mass formation and swelling of these organs parallel with an increased number of IgG4 plasma cells. Tertiary lymphoid organs are characterized by the accumulation of B cells interacting with Tfh cells expressing CXCR5 chemokine receptor, PD1, and TIGIT regulatory membrane molecules which are stimulated by follicular dendritic cells. Somatic hypermutations and isotypic switching to IgG4 production drives the cellular and cytokine microenvironment (27). Extrafollicularly, there is the presence of macrophages polarized to the M2 subset producing TGFβ to stimulate fibroblasts to produce extracellular matrix molecules, leading to storiform fibrosis. There is also an accumulation of cytotoxic CD8+ T cells together with a unique subset of cytotoxic T helper T cells. Cytotoxic CD4+ T cells are mainly found within effector, effector/memory, antigen-experienced highly differentiated T cells that downregulate costimulatory receptors such as CD27 and CD28. Using specific transcription factors, they store cytotoxic compounds such as various granzymes and perforins in cytotoxic vesicles in parallel with surface molecules expressed on innate lymphoid cells (30).

CONCLUSION

Both IgG4-autoimmune diseases and IgG4-related diseases have low prevalence fulfilling the criteria of orphan diseases. However, the individual burden of these diseases could be very high. Being entirely different in their clinical presentation, IgG4-autoimmune diseases have a lot in common. They share the substantial contribution of the

IgG4 subclass of IgG immunoglobulins with its unique immunobiological characteristics in immunopathogenesis. The correct diagnosis of such diseases is an important basis for their effective treatment. Regardless of the role of IgG4 in immunopathology, numerous positive roles of IgG4 antibodies in normal physiological immune responses have not to be omitted.

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ABBREVIATIONS

CD	Cluster of Differentiation
Fab	Antigen binding fragment of immunoglobulins
Fc	Constant fragment of immunoglobulins
FcRn	Neonatal receptor for IgG1
HLA	Human Leucocyte Antigen
IgG4	IgG4 subclass of IgG immunoglobulins
IgG4-AID	IgG4-AutoImmune Diseases
IgG4-RD	IgG4-Related Diseases
Tfh	T follicular helper T cell

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