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IgG4-mediated autoimmune diseases: a niche of antibody-mediated disorders

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Abstract

Immunoglobulin 4 (IgG4) is one of four human IgG subclasses and has several unique functional characteristics. It exhibits low affinity for complement and for most Fc receptors. It furthermore has generally high affinity for its antigen, with binding occurring in a monovalent fashion, as IgG4 can exchange Fab-arms with other IgG4 molecules. Because of these characteristics, IgG4 is believed to block its targets and prevent inflammation, which, depending on the setting, can have a protective or pathogenic effect. One example of IgG4 pathogenicity is muscle-specific kinase (MuSK) myasthenia gravis (MG), in which patients develop IgG4 MuSK autoantibodies, resulting in muscle weakness. As a consequence of the distinct IgG4 characteristics, the pathomechanism of MuSK MG is very different from IgG1-and IgG3-mediated autoimmune diseases, such as acetylcholine receptor MG. In recent years, new autoantibodies in a spectrum of autoimmune diseases have been discovered. Interestingly, some were found to be predominantly IgG4. These IgG4-mediated autoimmune diseases share many pathomechanistic aspects with MuSK MG, suggesting that IgG4-mediated autoimmunity forms a separate niche among the antibody-mediated disorders. In this review, we summarize the group of IgG4-mediated autoimmune diseases, discuss the role of IgG4 in MuSK MG, and highlight interesting future research questions for IgG4-mediated autoimmunity.

Keywords

IgG4; myasthenia gravis; MuSK; autoimmunity; neuromuscular junction

Introduction to IgG4

Antibody responses are an effective strategy of the immune system to protect against pathogens, but, when they go awry, they can also cause disease. Human antibody responses can consist of immature, low-affinity immunoglobulin (Ig) IgM and IgD responses or more mature IgE and IgG responses. IgG is further subdivided into subclasses on the basis of their

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Competing interests

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morphological and functional characteristics. Structural determinants in the constant, crystallizable fragment (Fc) of the antibody dictate whether an immunoglobulin G (IgG) molecule is able to activate complement, bind and activate or inhibit Fc-receptors and immune cell–mediated cytotoxicity, or interact with other IgGs.[1] On the basis of these characteristics and the type of antigen, human IgG was classified into four subclasses. IgG4 is the least prevalent IgG in healthy adults and makes up approximately 5% of the total IgG pool. Despite approximately 90% amino acid sequence homology with other IgG subclasses, IgG4 is unique, as it is functionally monovalent and causes little to no inflammation.[2] IgGs normally appear as homodimers, but two residues (serine 228 and arginine 409) in IgG4 Fc facilitate continuous exchange of monomers, a process termed *Fab-arm exchange*.[3,4] This results in bispecific antibodies and functionally monovalent binding. In other words, each Fab-arm of an IgG4 molecule will bind a different antigen, which disables its crosslinking capacity and inhibits immune complex formation. The lack of immune complex formation together with reduced binding affinity for complement factor C1q renders IgG4 a poor complement activator.[5] Furthermore, interaction with Fc receptors on immune cells is dependent on the individual receptor and specific residues in the CH2 region of the Fc of an IgG molecule. For IgG4, these Fc determinants result in preferred binding to inhibitory Fc receptors.[6] Lastly, when solid-phase immobilization is used, IgG4 Fc can bind to other Fc from all human IgG subclasses.[7] Together, these distinct functional characteristics led IgG4 to be deemed as an anti-inflammatory antibody. For a comprehensive review on IgG4 morphology and function and the regulation of IgG4 responses, see Lighaam *et al.*[1]

For each of the unique features of IgG4, the (patho-)physiological relevance is largely unclear. Depending on the setting, an IgG4 response can be protective or pathogenic. For example, IgG4 is often considered a protective blocking antibody, as it can inhibit or prevent inflammation by competing for antigen binding with inflammatory IgG subclasses or IgE. Alternatively, IgG4 can cause severe disease in a subset of autoimmune diseases, which is be discussed below.

IgG4-mediated autoimmune diseases

The majority of known antibody-mediated autoimmune diseases are caused by IgG1 and IgG3 autoantibodies. However, in the 1980s, pemphigus, a skin-blistering disease, was recognized as the first autoimmune disease that is hallmarked by IgG4 autoantibody predominance.[8] In recent years, autoimmunity research has focused, for both diagnostic and treatment purposes, on identifying new antigens in a variety of autoimmune diseases. Identification of these new antigens created an opportunity to characterize the predominant antibody subclass and disease mechanisms. To our knowledge, IgG4 plays a prominent role in the pathogenesis of at least 13 autoimmune diseases. For an extensive review on these diseases, see Huijbers *et al.*[9] The idea that IgG4-mediated autoimmune diseases constitute a separate niche among the antibody-mediated autoimmune diseases is based on several observations (Table 1). The differences between IgG1-, IgG3- and IgG4-mediated autoimmune diseases mostly relate to the functional characteristics of the different IgG subclasses. Where IgG1 and IgG3 autoantibodies cause disease by inducing complement-dependent tissue damage, immune cell–mediated cytotoxicity, and crosslinking and internalization of the antigen, those IgG4 autoantibodies for which the disease mechanism is

largely resolved simply block the function of its target antigen. It is furthermore interesting that IgG4-mediated autoimmune diseases are rarely associated with tumors.[10]

Since our first review on the group of IgG4-mediated autoimmune diseases, one disease entity can be added: neurofascin140/186 antibodies in patients with chronic inflammatory demyelinating polyneuropathy (CIDP).[9,11] For several of the other IgG4-mediated autoimmune diseases, more evidence has been presented for a pathophysiological relationship between the IgG4 autoantibodies and disease. An overview of the main characteristics of the IgG4-mediated autoimmune diseases is given in Table 2. For five out of the 13 listed diseases, passive transfer of human total IgG or IgG4 into experimental animals has been shown to induce the symptoms of the respective disease. For the eight remaining diseases, IgG4-mediated autoimmunity is suggested by the observation that serum-derived, antigen-specific autoantibodies are predominantly of the IgG4 subclass and that their titers correlate with disease severity. *In vitro* assays have furthermore elucidated the pathomechanism by which these (IgG4) autoantibodies cause disease in 12 of the 13 listed diseases.

Interestingly, there is a second group of diseases hallmarked by IgG4 autoantibody predominance, but in this group the role of IgG4 in the pathophysiology is unclear. For example, IgG4 autoantibodies dominate the response in bullous pemphigoid patients with BP180 and BP230 autoantibodies, in a subset of patients with Goodpasture disease with collagen IV autoantibodies, and in patients with encephalitis and dipeptidyl-peptidase–like protein 6 autoantibodies (DPPX).[12–15] However, IgG1-related effector functions dictate the pathophysiology in these diseases. This is likely due to the co-occurrence of IgG1 autoantibodies and calls into question the role of IgG4 autoantibodies in the pathomechanism of these diseases. Lastly, anti-cyclic citrullinated protein (ACPA) antibodies are associated with rheumatoid arthritis and are often of the IgG1 and IgG4 subclasses.[16] The role of ACPA antibodies in rheumatoid arthritis pathophysiology remains enigmatic. Since it is not clear whether diseases in this group are truly members of the IgG4-mediated autoimmune diseases niche, they have been summarized separately (Table 3). Passive transfer studies with purified IgG4 from these patients might help to clarify this issue.

The first IgG4-mediated autoimmune diseases to be described were mainly neurological disorders.[9] However, it is clear that IgG4-mediated autoimmunity can also affect other organ systems. In fact, five out of 13 IgG4 diseases do not affect the nervous system. It can be expected that this niche will grow in the coming years as more antigenic targets are discovered.

The identification of a new niche warrants further investigation on the commonalities and differences between these diseases, as it might shed light on the cause and shared potential therapeutic opportunities. A summary of commonalities and differences between the IgG4-mediated autoimmune diseases is given in Table 4. Many of the antigens that are involved in IgG1- and IgG3-mediated autoimmune diseases are multisubunit receptors or ion channels, [10] as exemplified by acetylcholine receptor (AChR) myasthenia gravis (MG). Notably, the IgG4 autoantibodies described thus far do not seem to target multisubunit receptors or ion

channels, but rather bind proteins associated with them.[9] These antigens are often involved in stabilizing the ion channels or receptors or are themselves important for maintaining cell–cell interaction. For example, MuSK is essential in establishing and maintaining the neuromuscular junction and induces AChR clustering, while desmogleins maintain keratinocyte cell–cell interactions. Thus, the antigens function either as bridging proteins themselves or participate in a signalling cascade that facilitates cell–cell interactions. The IgG4 autoantibodies (physically) interfere in the (signalling) function of the antigens and hamper the bridging effects.[9] Lastly, in thrombotic thrombocytopenic purpura with ADAMTS13 IgG4 autoantibodies, the interaction between ADAMTS13 and its substrate von Willebrand factor is obstructed, preventing the degradation of the substrate.[17] In conclusion, the blocking nature of IgG4 can result in pathology through obstruction of three different protein functions (Fig. 1).

Initially, few human leukocyte antigen (HLA) associations were reported for the IgG4-mediated autoimmune diseases, and it was striking that three of them showed an HLA-DQ5 association (MuSK MG, IgLON5 non-REM and REM parasomnia, and pemphigus vulgaris in Jewish patients).[9] However, Tables 2 and 3 show that IgG4 autoimmunity is not restricted to HLA-DQ5. HLA association studies are further limited for some of these diseases owing to the small number of patients described.

Immunosuppression generally forms the first-line treatment for all of these diseases, but not all patients respond well to these therapies. The observation that rituximab seems particularly effective in IgG4-mediated autoimmune diseases is therefore of great clinical value. Rituximab is a CD20 antibody that depletes all CD20-expressing B cells. Whether IgG4-producing B cells are particularly sensitive to this treatment, and why, is not known. The level of CD20 does not seem to differ between IgG4 and IgG1 memory B cells, and rituximab lowers all IgG subclass levels in bullous pemphigoid.[18,19] Moreover, the numbers of total B cells, as well as naive, memory, plasmablast, and transitional B cell subsets, are normal in MuSK MG and pemphigus patients.[20,21] The rapid and sustained reduction in IgG4 autoantibody titers therefore suggests that IgG4 responses might not be dominated by long-lived plasma cells and that IgG4 plasma cells express CD20.[22,23] It will be exciting to learn why rituximab treatment is particularly effective in these diseases.

Several features differ among IgG4-mediated autoimmune diseases (Tables 2–4). These include the antigen that is recognized, the different types of protein domains that form the main immunogenic region (MIR), the need for glycosylation of the antigen for autoantibody binding, the type of HLA association, and the VDJ gene usage of the autoantibodies. Given that many of these disease subsets have only recently been recognized, these details are not yet comprehensively available. For 11 IgG4-mediated autoimmune diseases, the MIR has been mapped, and for five of them the MIR is an Ig-like domain, for three a fibronectin domain, and for two a cadherin-like domain. This suggests that different types of protein domains can be involved in an IgG4 autoimmune response. With more diseases being discovered, it will be interesting to learn whether certain protein domains and structures are more prone to IgG4 responses. Epitope-mapping experiments in all these diseases further suggest that the autoantibody repertoire is oligo- or polyclonal, as epitopes outside the MIR are being recognized as well. Another important determinant of epitope structure is

glycosylation. Therefore, for some antigens, the contribution of glycosylation to autoantibody–antigen binding has been studied. Thus far, contactin 1 in CIDP is the only antigen where glycosylation was proven to be essential for autoantibody binding.[24] For the other IgG4-mediated autoimmune diseases, it may be possible that, while the autoimmune response develops, epitope spreading moves the immune response away from glycosylation-dependent epitopes. Given the involvement of different antigens and MIRs, it is not surprising that VDJ usage and HLA associations differ between these diseases, although it is important to realize that human monoclonal antibodies have only been isolated for three out of the 13 listed diseases. Lastly, for some IgG1- and IgG3-mediated autoimmune diseases, paraneoplastic events are associated with the onset of disease. Such associations have thus far only been only observed in a limited number of patients with IgG4 autoimmunity, which suggests that it is less relevant for IgG4.[10,25,26]

Evidence for IgG4 involvement in MuSK MG

Witebsky's postulates require confirmation of autoimmunity on several levels.[27] The role of MuSK autoantibodies in MG is supported by the transplacental transfer of disease, by active immunization of mice and rabbits with the MuSK antigen inducing MG, and by passive transfer of both total IgG and purified IgG4 from MuSK MG patients in mice and rabbits.[28–35] The role of IgG4 in MuSK MG was first suggested by the observations that the majority of the MuSK autoantibodies are of the IgG4 subclass and that IgG4 titers correlate with disease severity.[36–38] Direct evidence for the role of IgG4 in MuSK MG comes from passive transfer experiments with affinity-purified polyclonal IgG4 antibodies from MuSK MG patients.[30] A pathogenic potency of monoclonal IgG4 antibodies derived from patients would provide another level of evidence, but such monoclonal antibodies have only recently been isolated and have not been functionally characterized.[39] Low levels of non-IgG4 MuSK antibodies can sometimes also be detected. Whether they play a role in the pathophysiology of the disease is currently unclear, as purified MuSK IgG1–3 antibodies can inhibit AChR clustering in myotube cultures but do not inhibit the LRP4–MuSK interaction (see below).[40,41] Moreover, passively transferred purified IgG1–3 patient antibodies did not bind the NMJ and did not cause MG in mice.[30] In the *in vitro* studies, the dosing of MuSK-specific antibodies was equal for IgG1–3 and IgG4, whereas the *in vivo* experiments did not correct for MuSK-specific antibody dosing.[30,41] This might explain these apparent discrepancies. The IgG1–3 MuSK antibody titers in the majority of patients are low or even undetectable in our experience. Furthermore, it cannot be excluded that epitope specificity might differ between MuSK antibodies of different subclasses, and this may affect their pathogenicity. Lastly, due to Fab-arm exchange, IgG4 is functionally monovalent. For polyclonal patient antibodies, it was shown that these patients carry the genetic variants that enable Fab-arm exchange, and they do so *in vitro* and *in vivo*.[42] Whether the valency of anti-MuSK antibodies is relevant for their pathogenicity is not known. IgG4, likely owing to its monovalency, was shown to block the MuSK–LRP4 interaction, thereby inhibiting the trophic signalling cascade leading to AChR clustering. An important step in this cascade is dimerization and internalization of MuSK, which activates its intracellular kinase domain and transmits the clustering signal.[43] It is conceivable that bivalent IgG1–IgG3 antibodies to MuSK could induce dimerization and internalization of MuSK, which would therefore

strengthen the ongoing neuromuscular junction maintenance pathway and would be unlikely to result in myasthenia. The internalization might also prevent activation of complement or immune cell–mediated cytotoxicity. This hypothesis is consistent with observations that MuSK can be internalized when total IgG from patients is used in myotube cultures and can activate AChR clustering in some cases.[41,44] Alternatively, the IgG1–3 antibodies might also inhibit MuSK function or activate complement. Lastly, the MuSK–ColQ interaction can be blocked by patient IgG.[45] Whether the subclass of the autoantibodies is relevant for this effect is unknown. Patient-derived monoclonal antibodies might be important tools to address these mechanistic questions. In addition, it is important to emphasize that a combination of the aforementioned effects can occur in individual patients, as antibody repertoires likely vary. For MuSK MG, we have not yet encountered patients with high levels of MuSK-specific IgG1. This suggests that either the titers of IgG1–3 autoantibodies do not reach pathogenic levels or that high IgG1–3 autoantibody levels are less pathogenic in MuSK MG.

For the different forms of pemphigus, the role of autoantibody valency has been investigated extensively. In pemphigus vulgaris, active disease is associated with IgG4 autoantibodies, the switch from IgG1 to IgG4 autoantibodies is essential in developing symptoms in an endemic form of pemphigus, and passive transfer of IgG4 from patients induces the disease in mice.[46–48] In contrast, some pemphigus foliaceus patients only have IgG1 autoantibodies, which can cause acantholysis in mice.[49] Epitope specificity and autoantibody pathogenicity differ between autoantibodies of the IgG1 and IgG4 subclasses.[50] These observations suggest that, in pemphigus, antibody isotype is not a major determinant for the pathogenic effects and that epitope specificities and autoantibody titers are more important.[51,52]

Other diseases associated with IgG4

IgG4 plays a key role in a variety of other diseases. These can be distinguished as diseases where the blocking effect of IgG4 is beneficial and diseases in which the IgG4 blocking effect is pathogenic. The pathogenic effect of IgG4 is seen in the previously discussed autoimmune diseases; in melanoma, where IgG4 inhibits endogenous antitumor responses, resulting in worse disease progression and metastasis; in treatment settings with antibiologicals, where IgG4 blocks the function of the biological and renders treatment ineffective; and in a range of IgG4-related diseases where plasma cell infiltrates cause tissue damage.[9,53–56] Like in IgG4-mediated autoimmunity, these IgG4-related diseases form a heterologous group of autoimmune disorders affecting a broad range of organ systems. The symptoms relate to the organ system affected. However, in contrast to IgG4-mediated autoimmunity, increased levels of IgG4 are often found in IgG4-related disease patients, but the exact role of this IgG4 and whether it recognizes a specific antigenic target is unknown. For more specific information on the pathology of IgG4-related disease, the reader is referred to recent reviews.[57,58] In each of the above-mentioned settings except for the IgG4-related diseases, IgG4 antigen-specific titers correlate with disease severity, and a reduction in these titers correlates with improved health.

Interestingly, IgG4 can also have protective effects. This is seen in infections with filarial parasites and helminths, where IgG4 dampens ongoing inflammation, and in situations

where prolonged inflammation or allergic responses cause serious disease.[1,59] Seminal work by Aalberse and colleagues revealed that tolerance is induced in beekeepers that, after prolonged immunization, have undergone a class switch to IgG4. The IgG4 competes for binding with IgE and IgG1 to the allergen. In addition, the increase in IgG4 titer is an order of magnitude higher than IgE and IgG1, which further contributes to its competitive ability. Owing to its inability to activate neutrophils and complement, IgG4 inhibits ongoing inflammation, resulting in tolerance and reduced allergic symptoms. In these settings, the increase of antigen-specific IgG4 correlates with improved health. Figure 2 gives an overview of the effect of IgG4 in different IgG4-associated diseases.

Thus, depending on the setting, IgG4 can have beneficial or detrimental effects. It is tempting to speculate that specific modulation of IgG4 production could be a promising therapeutic strategy for all of the above-mentioned IgG4-associated diseases. It is possible that these treatments would be better than general immunosuppression, as they might not affect other useful immune responses. Furthermore, low levels of IgG4 are generally well tolerated and are therefore expected to result in fewer side effects. Given the clinical relevance, a range of studies have investigated the regulation of IgG4 responses. Although many aspects of the induction, maintenance, and inhibition of IgG4 responses are still unknown, several factors have been described to contribute to IgG4 production: (1) prolonged exposure to an allergen;[60] (2) T_H2-related cytokines interleukin (IL)-4 and IL-13 inducing a class switch to IgG4 and IL-21 and IL-4 stimulating IgG4 production by plasma cells;[61–63] (3) IL-10 derived from regulatory T and B cells;[64–66] and (4) growth hormone and growth factor.[67]

How (and if) these factors contribute specifically to the onset and progression of IgG4-mediated autoimmune diseases is thus far not known. A small number of studies has investigated whether these factors are dysregulated in MuSK MG. These studies are all hampered by the limited number of patients included and the heterogeneous treatment regimens they received. Plasma levels of T_H1−, T_H2−, and T_H17-related cytokines do not differ between MuSK MG patients and healthy individuals.[68] *In vitro* production of IL-4, IL-6, IL-13, and TNF-α was normal in $CD40^+$ and nonspecific B cell receptor–stimulated MuSK MG immune cells.[68,69] Transcriptomic analysis and MuSK-specific stimulation did not show altered cytokine expression compared with controls. Interestingly, interferon-γ, IL-10, IL-17A, and IL-21 production was increased in these cultures.[68] Other studies have also suggested that B cell–activating factor, a factor that is secreted by dendritic cells and myeloid cells to promote B cell survival, is increased in MuSK MG patients.[20,70] Furthermore, regulatory B10 cells are reduced in MuSK MG. Each of these observations could contribute to the breakdown of tolerance in MuSK MG and suggest a role for T_H1 and T_H17 immune regulation. The latter is particularly striking, as IgG4 production usually is related to a T_H2 response. The increased production of IL-10 in immune cell cultures matches its described role as a potent IgG4 stimulator. Higher-powered studies, which also separate on the basis of treatment regimen, could shed more light on the immune status of MuSK MG patients during the disease.

Conclusions

IgG4 is an enigmatic antibody with unique characteristics that is associated with a range of (autoimmune) diseases. Depending on the setting, IgG4 can have protective or pathogenic effects. There is strong evidence that IgG4 is pathogenic in MuSK MG and other IgG4-mediated autoimmune diseases. The blocking effect of IgG4 is a pathomechanistic feature thus far shared by these diseases, but mostly different from other IgG1- and IgG3-mediated autoimmune diseases. Therefore, IgG4-mediated autoimmune diseases constitute a newly recognized and exciting niche among the antibody-mediated autoimmune diseases. Many aspects of the role and development of the IgG4 immune response in MuSK MG and other newly identified IgG4-mediated autoimmune diseases are still unknown and form interesting lines of research for the future (Table 5).

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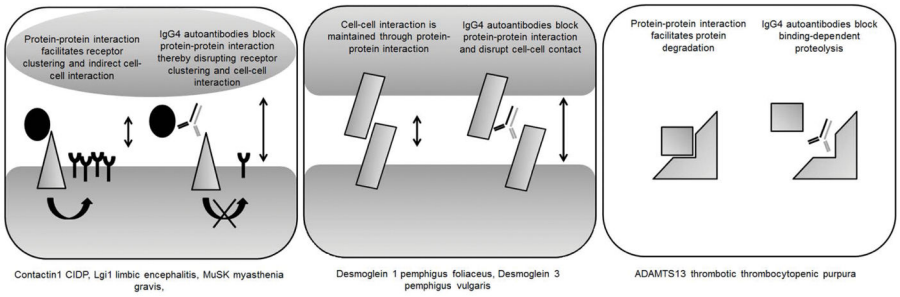

Figure 1.

A graphic representation of the three main pathological blocking effects of IgG4 autoantibodies. The diseases, for which the pathomechanism is well characterized, are grouped below the associated IgG4 effects.

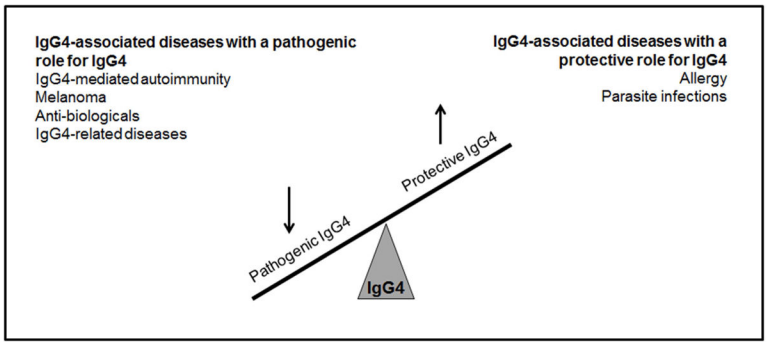

Figure 2.

An overview of the effect of IgG4 in different IgG4-associated diseases and potential therapeutic strategies.

Table 1

The differences between IgG1−, IgG3−, and IgG4-mediated autoimmune disease.

IgG1 and IgG3	**IgG4**
Antigens are receptors, ion channels, or multisubunit proteins	Antigens are typically not receptors, ion channels, or multisubunit proteins
Pathomechanism requires complement and immune cell–mediated cytotoxicity and inflammation	Pathomechanism is blocking of essential protein–protein interactions
Structural damage to target tissue	No structural damage to target tissue
Crosslinking and internalization of the antigen	Monovalent antigen binding, no crosslinking
Sometimes associated with paraneoplastic events	No clear tumor association
Result from T_H1-related cytokine expression	Result from T_H2-related cytokine expression

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Table 2

Overview of the characteristics and experimental evidence for the IgG4-mediated autoimmune diseases.

Antigen	Disease	Symptoms	Prevalence	HLA association	Target organ	Main immunogenic region	Passive transfer confirmation in experimental animals	Disease mechanism	VDJ gene usage	Reference
ADAMTS13	Thrombotic thrombocytopenic purpura	Thrombocytopenia, microangiopathic hemolytic anemia resulting in organ failure	13 per million	HLA-DRB1*11	Vasculature	Cysteine-rich spacer domain	N/A	Inhibition of ADAMTS13-dependent von Willebrand factor cleavage	*VH1-3, VH1-69, VH3-30, VH4,28*	74, 79, 84
CASPR1	Chronic inflammatory polyneuropathy	Progressive weakness, sensory disturbances, neuropathic pain	3 cases	N/A	Paranode of Ranvier on motor neurons	N/A	N/A	Blocking of CNTN1–Caspr1–NF155 complex	N/A	76, 82
CASPR2	Limbic encephalitis, neuromyotonia and Morvan syndrome	Impaired cognition, seizures, fasciculations and cramps, sometimes autonomic dysfunction and insomnia	~ 200 patients have been described thus far	N/A	Juxtaparanode of Ranvier on motor neurons and inhibitory neurons in the CNS	Discoidin domain, but with many epitopes all over the extracellular domain; glycosylation independent	N/A	Inhibition of Caspr2–TAG1 interaction altering gephyrin clustering	N/A	72, 89
Contactin1	Chronic inflammatory polyneuroathy	Severe symmetric sensory and motor polyradiculoneuropathy, poor IV Ig response	3–7% of CIDP patients	N/A	Paranode of Ranvier on motor neurons	Ig-like domain dependent on N-glycans	Yes, IgG4 and IgG1	Inhibition of CNTN1–CASPR1 interaction disrupting node of Ranvier	N/A	83
Desmoglein1	Pemphigus foliaceus	Acantholysis (skin blistering)	2–10 per million in central Europe, with higher incidence among specific ethnic groups	HLA-DRB1*4, DRB1*14 Different HLAs associated with specific ethnic groups and geography	Skin keratinocyte desmosomes	N-terminal cadherin-like domain 1 and 2; glycosylation independent	Yes	Inhibition of trans-adhesion	*VH1, VH3*	75
Desmoglein3	Pemphigus vulgaris	Acantholysis (skin blistering) and blisters on mucosal membranes	2–10 per million in central Europe, with higher incidence among specific ethnic groups	HLA-DRB1*4, HLA-DRB1*08, HLA-DRB1*14 HLA-DQB1*5 Different HLAs associated with specific ethnic groups and geography	Skin keratinocyte desmosomes and mucous membranes	N-terminal cadherin-like domain 1 and 2; glycosylation independent	Yes	Inhibition of trans-adhesion between desmoglein3 receptors, signaling inhibition and desmosome shrinkage	*VH1-46* *VH1, VH3, VH4*	75
IgLON5	Non-REM and REM parasomnia with sleep breathing dysfunction and a tauopathy	Disordered sleep and ventilation, sometimes with brain stem, gait, cognitive, or movement disorders	At least 30 patients have been identified	HLA-DQB1*0501 HAL-DRB1*1001	Brain neuropil	Ig-like 2 domain; glycosylation independent	N/A	IgG1 caused IgLON5 cluster internalization; IgG4 has unknown effects	N/A	77
LGI1	Limbic encephalitis	Memory, behavioural, and orientation deficits; faciabrachial dystonic seizures, often with hyponatremia	~ 300 patients have been described	HLA-DR7 HLA-DRB4	CNS predominantly in hippocampus and temporal cortex	EPTP repeat and leucine-rich repeat domain	Yes	Inhibition of Lgi1-ADAM interaction and AMPAR clustering	N/A	12, 86
MuSK	Myasthenia gravis	Fatigable muscle weakness	2–9 per million	HLA-DR14-DQ5	Muscle/neuromuscular junction	N-terminal Ig-like domain; glycosylation independent	Yes, IgG_{total} and IgG4	Inhibition of MuSK–LRP4 interaction and AChR clustering	N/A	81
Neurofascin140/186	Chronic inflammatory polyneuroathy	Severe symmetric sensory and motor polyradiculoneuropathy.	4 patients described thus far	N/A	Motor neurons, (para)node of Ranvier	Ig-like domains; fibronectin V domain	N/A	N/A	N/A	11
Neurofascin155	Chronic inflammatory polyneuroathy	Aggressive, distal, sensorimotor neuropathy, poor response to IV Ig	~ 3–7 % of CIDP patients	N/A	Motor neurons, (para)node of Ranvier	N-terminal Ig-like domain; fibronectin III,IV domain	N/A	Inhibition of cell adhesion at paranodal junction	N/A	83
PLA2R1	Membranous nephropathy	Proteinuria, nephritis	70% of membranous nephropathy patients	HLA-DQA1 HLA-DRB1	Kidney, podocytes	N-terminal Cys-R domain; fibronectin II domain and CTLD1 domain	No, as antigen is not expressed on podocytes in rodents	Perhaps inhibition of PLA2R binding to collagen	N/A	73, 85, 87
THSDA7A	Membranous nephropathy	Proteinuria, nephritis	5% of membranous nephropathy patients	N/A	Kidney, podocytes	N/A	Yes	Binding to THSDA7A alters cytoskeletal organization through unknown mechanism	N/A	87

Table 3

Overview of autoimmune diseases hallmarked by high levels of IgG4 autoantibodies, but with poorly defined roles for IgG4 in the disease.

Antigen	Disease	Symptoms	Prevalence	HLA association	Target organ	Main immunogenic region	Passive transfer confirmation in experimental animals	Disease mechanism	VDJ gene usage	Reference
ACPA	Rheumatoid arthritis	Stiff hands and feet joints due to chronic inflammation	~ 60% of all rheumatoid arthristis patients	DRB1*01:01,01:02 DBR1*04:01,*04:04,*04:05,*04:08 DRB1*09:01 DRB1*10:01	Joints	Different citrullinated proteins carry the epitope: fibrin, fibrinogen, enolase, collagen, vimentin, and EBNA	Yes, partially. Passive transfer can exacerbate disease	Mixed effects of both IgG1 and IgG4 autoantibodies. Inflammation plays a key role.	Varying dependent on antigen	71, 88
BP180 (type XVII collagen)	Bullous pemphigoid	Acantholysis (skin blistering)	10 per million	HLA-DQB1*0301 HLA-DRB1*04, HLA-DRB1*1101, HLA-DQB1*0302	Skin hemidesmosomes	Non-collagenous 16A domain	Yes	Mixed effects of both IgG1 and IgG4 autoantibodies. Complement is likely involved.	*VH4*	12, 80
BP230 (dystonin-e)	Bullous pemphigoid	Acantholysis (skin blistering)	10 per million	HLA-DQB1*0301	Skin hemidesmosomes	Broad response, epitopes throughout the antigen, but most against collagen B and C subdomains	N/A	Mixed effects of both IgG1 and IgG4 autoantibodies. Complement is likely involved	N/A	12, 86
Collagen IV	Goodpasture disease	Alveolar hemorrhage and glomerulonephritis	1 per million	HLA-DRB1*1501	Kidney	α3(IV)NCI-domain	Yes	Unclear if involved in pathogenesis, mostly IgG1–3	*V1-8* *V3-48* *V3-21* *V-3-23* *V1-69* Derived from humanized model	78
DPPX	Encephalitis	Memory and cognitive dysfunction, seizures, hyperekplexia, tremor, diarrhea	39 patients described	N/A	CNS, hippocampus	N/A	N/A	Decreased expression of DPPX and Kv4.2. Increased excitability and action potential frequency	N/A	13

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Table 4

An overview of the commonalities and differences between the several specific IgG4-mediated autoimmune diseases.

Commonalities
• Predominating IgG4 autoantibodies
• The antigens (so far) do not include essential ion channels or multisubunit receptors
• The antigens are part of important protein–protein interactions that maintain cell–cell contact, stabilize ion channels, or mediate proteolysis.
• The antigens are highly N-glycosylated
• The pathogenic mechanism is blocking of protein–protein interaction and function
• Strong HLA class II associations
• Good response to rituximab treatment
Differences
• The antigens recognized
• Main immunogenic regions reside in different types of protein domains
• Some require proper antigen glycosylation for autoantibody–antigen binding
• Type of HLA class II genes associated
• Type of VDJ gene usage

Table 5

An overview of the accepted knowledge and unresolved questions about MuSK MG pathophysiology and the involvement of IgG4.

Accepted knowledge
• Polyclonal patient IgG4 induces MG-like features *in vitro* and *in vivo*
• Polyclonal patient IgG1–3 sometimes induce MG-like features *in vitro*
• MuSK antibodies cause MG by inhibiting LRP4–MuSK signalling, resulting in AChR declustering
• MuSK antibodies in some cases induce MuSK internalization and MuSK–ColQ interaction inhibition
• Polyclonal IgG4 MuSK patient antibodies exchange Fab-arms
• The N-terminal Ig-like domain 1 is the main immunogenic region, and epitopes outside this domain exist
Unresolved questions
• Do IgG4 and IgG1 MuSK autoantibodies recognize similar epitopes?
• Can IgG1–3 MuSK autoantibodies cause MG *in vivo*?
• Is the valency of the autoantibodies relevant to their pathogenicity?
• Do MuSK MG patients have dysgammaglobulinemia?
• Do non-pathogenic MuSK antibodies exist?
• Are antibodies binding different epitopes on MuSK equally pathogenic?
• Do MuSK-specific IgE, IgA and IgM exist? What is their role?
• What causes the (IgG4) MuSK autoimmune response?
• Do IgG4-mediated autoimmune disease share a similar aetiology?
• Why is rituximab such an effective therapy in MuSK MG? Why do some patients remain in stable remission while other relapse?