MINI-REVIEW
MHC haplotype and B cell autoimmunity: Correlation with pathogenic IgG autoantibody subclasses and Fc glycosylation patterns

Larissa Nogueira Almeida¹, Ann-Katrin Clauder¹, Lingshang Meng², Marc Ehlers³, Sergio Arce⁴ and Rudolf Armin Manz¹

¹ Institute for Systemic Inflammation Research University of Lübeck, Lübeck, Germany
² Center for Systemic Inflammation Research (CSIR), School of Preclinical Medicine, Youjiang Medical University for Nationalities, Baise City (Bose), Guangxi Zhuang, Autonomous Region, China
³ Laboratories of Immunology and Antibody Glycan Analysis, Institute for Nutritional Medicine, University of Lübeck and University Medical Center Schleswig-Holstein, Lübeck, Germany
⁴ Department of Biomedical Sciences, University of South Carolina School of Medicine-Greenville, Greenville, SC, USA

Genome-wide association studies (GWAS) have identified many genes that are associated with the development of certain autoimmune disorders, but the MHC haplotypes still represent the most prevalent genetic risk factor for many autoimmune diseases. The mechanisms by which MHC-associated genetic susceptibility translates into B cell autoimmunity and the development of autoimmune diseases are complex. There is increasing evidence that the MHC haplotype modulates autoreactive B cell responses in multiple ways. Instead of merely inhibiting the production of IgG autoantibodies and mediating complete immunological tolerance, the non-permitting MHC haplotypes seem to facilitate the production of IgG autoantibodies exhibiting Fc glycosylation patterns that are associated with reduced pathogenicity and a protective cytokine profile of T follicular helper (Tfh) cells. Here, we discuss mechanisms linking MHC haplotypes to the production of pathogenic IgG autoantibodies, which could be relevant for the development of improved diagnosis, particularly in the context of individual medicine.

Keywords: autoantibody · autoimmunity · B cells · MHC · T follicular helper

Introduction

Extensive research has been done to screen for genes involved in autoimmune diseases [1]. These investigations have led to the identification of numerous genes. The expression of certain MHC haplotypes, however, still is the most predominant genetic risk factor for the development of common autoimmune diseases, such as rheumatoid arthritis (RA), MS, and type-1 diabetes (T1D) [2].

There are three classes of MHC molecules, all of which are highly polymorphic. The human (HLA-A, -B, -C) and murine (H2-K, -D, -L) MHC class I genes encode proteins that present antigen peptides to CD8⁺ T cells, and the main human (HLA-DR, -DQ, -DP) and murine (H2-A (I-A), -E (I-E)) MHC class II proteins present antigen peptides to CD4⁺ T cells [3]. The proteins encoded by MHC class III genes are not involved in antigen presentation, but include different factors such as components of the
Pemphigoid diseases are a group of autoimmune diseases characterized by an autoantibody-induced immune response against components of the hemidesmosomal anchoring complex at the dermal-epithelial junction of skin and mucous membranes with stratified epithelia, which are required for dermal-epithelial cohesion [13]. Clinically, these diseases present with tense blisters and erosions on skin or mucous membranes.

Although accumulation of autoantibodies at the dermal-epithelial junction is a prerequisite, this alone is not sufficient to induce inflammation and some patients do not develop any skin inflammation despite autoantibody binding and complement activation [14]. There is increasing evidence that in addition to the presence and quantity of autoantibodies, their pathogenic potential is relevant for disease development and progression.

Epidermolysis bullosa acquisita (EBA) is a rare pemphigoid disease, which usually presents in the fourth or fifth decade of life and affects males and females of all races equally. It is driven by anti-type VII collagen (COL7) IgG autoantibodies, whose presence is associated with polymorphisms in HLA-DR genes of patients [15] and supported by the MHC haplotype H2s in mice [16]. In patients and in mice, the disease is mediated by IgG autoantibody binding to COL7 at the skin dermo-epidermal junction, which drives local complement activation and influx of pro-inflammatory effector cells, particularly neutrophils [17]. In a murine EBA model, pathogenic IgG autoantibodies to COL7 and autoimmune blistering skin disease are inducible by a single immunization with a COL7 fragment together with the strong adjuvant Titermax. This model of EBA was used to investigate the immune response to COL7 in congenic mouse strains expressing either the disease-permitting H2s, or the non-permitting H2b MHC haplotype. Interestingly, both, susceptible mice with the MHC H2s allele and non-susceptible mice expressing the MHC H2b allele have developed serum anti-COL7 IgG autoantibodies, but only the susceptible mice have developed skin blisters [12]. Although on average anti-COL7 IgG autoantibody titers were higher in susceptible mice, some susceptible mice have developed disease despite the development of only low anti-COL7 IgG autoantibody titers, while some non-susceptible mice showed increased anti-COL7 IgG autoantibody levels but did not develop any clinical symptoms. Considering that non-susceptible immunized H2b mice have also produced considerable amounts of anti-COL7 IgG autoantibodies, it has become clear that the impact of the MHC haplotype is more complex than merely controlling the absence or presence of anti-COL7 IgG autoantibodies. In accordance, considerable numbers of COL7-specific Th cells have also been found in non-susceptible mice [12]. Hence, the non-susceptible MHC H2b haplotype could neither mediate complete B cell nor complete T cell tolerance to the COL7 autoantigen.

Instead, qualitative differences have been found between the T cell compartment and the anti-COL7 IgG autoantibodies of susceptible mice expressing MHC H2s and non-susceptible mice with the MHC H2b haplotype. Susceptibility to disease has been associated with increased numbers of IFN-γ- and IL-21-producing Th cells, reduced suppressive function of regulatory T cells (Treg), and more pro-inflammatory IgG Fc N-glycosylation patterns of the anti-COL7 IgG autoantibodies [12]. Pro-inflammatory effector functions of IgG antibodies are linked to low levels of IgG Fc galactosylation and sialylation, whereas increased IgG Fc galactosylation and sialylation levels are associated with less inflammatory or even anti-inflammatory effector functions [18].

Accordingly, IFN-γ and IL-21 have been shown to control GC and plasma cell formation, IgG antibody production, and the IgG complement system, TNF-α, and heat shock proteins, among others [4].

Even though many autoimmune diseases show multiple independent MHC associations, diseases with characteristic IgG autoantibodies are often associated with certain MHC class II alleles, while seronegative diseases are more often associated with MHC class I alleles [5]. Notably, the presence of rheumatoid factor (RF) IgG antibodies and anti-citrullinated IgG antibodies (ACPA) are typically associated with more severe disease than seronegative rheumatoid arthritis [6]. Furthermore, studies have shown, for example, that IgG autoantibody formation to transglutaminase 2 in celiac disease is strictly associated with the MHC class II-risk alleles DQ2 and DQ8 [7].

The mechanisms by which certain MHC molecules contribute to the susceptibility of autoimmune diseases is not fully understood, though there is evidence that MHC-linked disease risk is associated with differences in the repertoire of self-peptides that are presented to T cells [8]. There is no evidence that MHC class II molecules have a direct impact on B cell development. However, MHC class II molecules modulate the activation of mature B cells via their interactions with CD4+ T cells, particularly CD4+ T follicular helper (Tfh) and T follicular regulatory (Tfr) cells in the GC reaction. Tfh cells represent a unique subpopulation of CD4+ T cells that specifically localize to the B cell areas of secondary lymphoid tissues, specialized to support B cell activation, GC formation, and memory and plasma cell differentiation [9], while Tfr cells control Tfh cell-driven GC responses [10]. Of note, reciprocal antigen-presentation by B cells’ MHC class II molecules may also have a significant impact on CD4+ T cell responses, particularly those mediated by Tfh cells [11]. MHC class II haplotype-associated changes of the Tfh response may have a major impact on GC B cell responses, but knowledge about the crucial factors involved in the MHC-Tfh-B cell axis that are relevant for B cell autoimmunity have been elusive.

A recent study by our group has identified potential candidate mechanisms involved in this translation and has indicated that MHC class II molecules affect B cell responses in a complex manner, involving quantitative and qualitative changes of Tfh cells eventually modulating autoantibody (sub)class switching and levels as well as IgG Fc N-glycosylation patterns, important for IgG antibody effector mechanisms and pathogenicity [12]. In this review, we will discuss these findings in a broader context.
Fc N-glycosylation pattern [19, 20]. Furthermore, we have shown earlier that in the same model, B cell/plasma cell-derived IL-10 suppresses the production of IFN-γ by COL7-specific T cells but promotes the production of IL-10 by Tregs, which was linked to reduced disease development. [21].

How MHC molecules modulate the T cell response is not completely clear. It is possible that the binding of distinct self-peptides to certain MHC haplotypes may deliver distinct signal strength to the T cells. This idea is supported by the observation that T cell receptor signal strength has an impact on the cytokine profile of activated T cells [22]. Nevertheless, this idea remains to be elucidated.

Together, these findings suggest a scenario where susceptible MHC alleles modulate the pathogenicity of the IgG autoantibody response in multiple ways. First, through their impact on the formation and the cytokine profile of Tfh cells and second, during the MHC class II-T cell receptor-mediated crosstalk between activated B cell/plasma cells and autoreactive T cells. IFN-γ, IL-10, and IL-21 seem to be the main players in finally determining the quantity and pathogenicity of the IgG autoantibody response. A scheme of how disease permissive and non-permissive MHC haplotypes may affect pro- and less/anti-inflammatory IgG Fc N-glycosylation is outlined in Fig. 1.

### MHC haplotype and IgG autoantibodies

#### MHC haplotypes and T cell responses

The data from the murine EBA model discussed above indicated that a non-susceptible MHC haplotype does not merely induce T cell tolerance, but an altered less inflammatory phenotype [12]. Though H2s and H2b haplotypes used in the study differ in MHC class I and MHC class II, the effects on the B cell response seem to be mediated primarily via CD4+ T cells and hence through MHC class II. In humans, B cell autoimmunity and IgG autoantibody production are also typically associated with certain MHC class II allotypes, such as HLA-DR2 found in systemic lupus erythematosus (SLE), Sjögren’s Syndrome, and EBA [15,23,24], indicating that B cell-T cell interactions are involved in breaking tolerance. The simplest explanation for this link would be the maintenance of tightly controlled T cell tolerance and the absence of T cell help in non-susceptible individuals. However, autoreactive T cells have been identified in the peripheral blood of many healthy individuals, which is particularly well documented for myelin-reactive CD4+ T cells in humans and mice [25]. Hence, comparable to our mouse model, the mere absence of T cell help could not fully explain undetectable or reduced IgG autoantibody levels in
healthy individuals compared to autoimmune patients. However, the relation between the expression of a susceptible MHC class II haplotype, the presence of autoreactive, non-anergic T cells, and IgG autoantibodies needs to be further elucidated.

Through inhibition of germinal centers, Foxp3+ Tfr cells have a considerable capacity to suppress IgG autoantibody production [26]. Interestingly, we found that B6.s (H2s) mice susceptible to experimental EBA development and non-susceptible C57BL/6J (H2b) mice showed similar populations of Foxp3+ Tregs. However, Treg functions were different between the two mouse lines [12]. Particularly, while present in comparable frequencies and numbers, Tregs from the susceptible mouse line showed a reduced capacity to suppress the proliferation of effector T cells, compared to Tregs from mice expressing non-susceptible MHC haplotype. In addition, Tfh cell cytokine profiles were different between the two mouse lines. Hence, including functional analysis of Foxp3+ Tregs and Tfr cells and the investigation of CD4+ T cell and Tfh cell cytokine profiles could help to improve diagnosis of autoimmune diseases, and whenever possible, in combination with the analysis of autoreactive cells.

**MHC haplotypes influence the pathogenicity of IgG autoantibodies**

The pathogenicity and inflammatory capacities of IgG antibodies do not merely depend on their specificity, which is determined by the antigen-binding sites of their variable regions, but to a great extent also through their subclass and the extent of Fc N-glycosylation [18]. Both properties have a strong impact on their effector functions, such as complement activation and binding to various activating or inhibiting Fc receptors on innate effector cells, such as neutrophils, monocytes/macrophages, or dendritic cells, eventually resulting in the induction or prevention of inflammation [27]. For example, murine IgG2a and IgG2b activate both complement and activating Fcγ receptors (FcγR) [28], while murine IgG1 poorly activates complement but preferentially interacts with the inhibitory FcγRIIB, which results in less inflammatory or even anti-inflammatory antibody responses [29,30].

Following intensive studies in mouse models of various diseases [28,31], the impact of the IgG subclass and the extent of the Fc N-glycosylation were also linked to disease progression or resolution in patients suffering from rheumatoid arthritis [31–33].

Besides IFN-γ, also IL-17-producing Tfh cells have recently been linked to the development of IgG autoantibodies without galactose and sialic acid and disease development [19,20]. Th17 cells have also been linked to the induction of EBA [34]. Thus, it will be interesting to investigate whether susceptible MHC haplotypes also induce Th17 and Tfr17 cells (Fig. 1).

The expression of an MHC haplotype that is not associated with the development of the autoimmune disease may not necessarily prevent the production of IgG autoantibodies, but the expression of a disease-prone MHC haplotype seems to be associated with the induction of pro-inflammatory IgG Fc N-glycosylation and highly pathogenic IgG autoantibodies [12]. In this context, it is interesting that various IgG autoantibodies are found in the peripheral blood of a considerable number of healthy individuals [35–37]. In some cases, these individuals may develop autoimmune diseases later [38]. In other cases, however, the IgG autoantibodies may exhibit a lower or even anti-inflammatory capacity.

**MHC haplotypes influence the specificity of autoantibodies**

Autoantibody reactivity to specific epitopes on the IA-2 autoantigen in type 1 diabetes is associated with different HLA-DR and DQ genotypes [39]. Likewise, the expression of the disease permissive H2s haplotype in experimental EBA is associated with the production of autoantibodies binding to specific regions of the COL7 autoantigen [16]. These findings indicate that MCH haplotypes may have an impact on the fine specificity of autoantibodies. However, the mechanisms underlying these associations remain to be elucidated. As of today, there is no evidence that MHC molecules are involved in B cell development and selection. Despite this, the B cell repertoire is already altered in naive B cells from RA patients [40]. But whether this is due to different MHC haplotype preferences or is a consequence of chronic inflammation and therapeutic treatment, is unclear.

Due to technical limitations, it is also difficult to determine if the autoantibodies from patients expressing different MHC haplotypes bind to completely different epitopes, or if they have developed different affinities. Since antibody binding to linear epitopes is generally poor, only high-affinity antibodies might be identified while low-affinity antibodies might be counted as non-binders. Therefore, it is possible that autoantibodies from patients having different MHC haplotypes bind to the same epitopes, however with different affinities. Since affinity maturation in germinal centers is strictly dependent on T cell help, MHC haplotypes could control autoantibody affinities via altered Tfh responses.

**Clinical perspective**

Already years before disease onset, autoantibodies can be present in patients that later develop RA or SLE. Similar studies are lacking for most other diseases. Quantification of autoantibodies is widely used as diagnostic criteria and helps to narrow the diagnostic possibilities (Table 1). For example, the presence of anti-Sm and anti-dsDNA autoantibodies are both highly specific for SLE and help to differentiate SLE from other collagen vascular diseases or predict the development of an undifferentiated collagen vascular disease/overlap syndrome into SLE. However, the mere presence of autoantibodies is often not sufficient to predict the clinical course of the disease. In part, that might be because not all autoantibodies are pathogenic, but instead, some autoantibodies seem to be non-pathogenic or even protective [41, 42]. Moreover, what we sometimes call a “disease” is more of a “clinical syndrome,” or a disease comprising slightly different
Table 1. Challenges of current diagnostics based on autoantibodies

| Clinical implication | Disease | Autoantibody | Reference |
|----------------------|---------|--------------|-----------|
| Pathogenic autoantibodies | SLE, Lupus nephritis, GPA | anti-dsDNA, PR3-ANCA | [41, 42] |
| Contribution of autoantibodies to the pathogenesis/diagnosis of various disease subgroups | Systemic sclerosis, Myasthenia gravis | Anti-centromere, Anti-topoisomerase, Anti-LRP4ACPA, Anti-CarP, Rheumatoid factor Anti-BP180, -BP230, anti-laminin 332, laminin γ1 | [43, 44, 45, 46] |
| Distinct pathogenicity depending on glycosylation/sialylation of the Fc glycan | ANCA-associated vasculitis, GPA | MPO-ANCA, PR3-ANCAPR3-ANCA | [50, 51] |
| T-cell dependent autoantibody responses | SLE | anti-Smith, anti-RNA | [53, 54] |

phenotypes that may even have different causes. Hence, autoantibodies may contribute in a distinct manner to the pathogenesis of various disease subgroups. For example, the presence of anticientromere autoantibodies in systemic sclerosis helps define a clinical subgroup with limited skin disease, better prognosis overall, but with an increased risk of developing pulmonary hypertension. Likewise, anti-topoisomerase autoantibodies define a disease subgroup with more systemic involvement, increased likelihood of developing pulmonary fibrosis, and overall worse clinical outcomes [43]. Disease subgroups are found in many diseases where autoantibodies contribute, such as Myasthenia gravis [44], RA [45], and pemphigoid diseases [46], among many others.

Furthermore, beside the correlation between antibody specificity and certain diseases, the quality of the identified autoantibodies might characterize their disease state.

Accordingly, disease subgroups may differ in the age of onset, the presence of a combination of certain autoantibodies, symptoms, severity, disease progression, clinical outcomes, treatment, and comorbidities, such as susceptibility to infections, cardiovascular disease, and cancer [47, 48].

Optimized protocols for antibody diagnostics that include a more detailed analysis of the subclass, Fc N-glycosylation patterns, and antibody pathogenicity may help define disease staging and predict treatment success or failure.

As outlined above, the pro-/or even anti-inflammatory potential of IgG depends on their IgG subclass and also on the extent of glycosylation/sialylation of the Fc glycan, which determines the affinity of IgG-binding to different Fc-receptors on innate effector cells [49]. As a proof of principle that Fc N-glycosylation patterns correlate with disease in a subgroup-specific manner was recently demonstrated in anti-neutrophil cytoplasmic autoantibodies (ANCA)-associated vasculitis, which split up into patients producing ANCA against myeloperoxidase (MPO) or proteinase 3 (PR3). ANCA patients with an active disease showed reduced Fc glycosylation of total IgG. Interestingly, normalization of this parameter was associated with clinical remission in PR3-ANCA patients, however the same was not true for MPO-ANCA patients [50]. Hence, MPO and PR3-ANCA differ with respect to the changes of IgG Fc glycosylation during active disease and remission. Moreover, in patients with Granulomatosis with Polyangiitis (GPA), which is a subgroup of ANCA-associated vasculitis, low IgG Fc glycosylation was shown to predict disease reactivation, while the quantity of PR3-ANCA was not of diagnostic value for disease reactivation [51]. Hence, analysis of IgG Fc N-glycosylation patterns may serve as an additional biomarker relevant for diagnosis and treatment. In addition, IgG Fc N-glycosylation and distribution of autoantibody subclasses could be relevant for grouping patients in clinical trials, as including these parameters could surely increase group homogeneity.

Optimal study protocols may also include the analysis of autoantigen-specific T cell subsets by flow cytometry. Cytokines provided by autoantigen-specific Tfh cells and Tfr cells control the formation of autoantibodies in the context of follicular B cell responses initiated within germinal centers [52]. Recently, in addition, a Th cell subset distinct from Tfh cells was identified in SLE patients. These CXCR3+CXCR5+ Th cells support the ongoing activation of naïve B cells, extrafollicular plasma cell formation independent of germinal centers, even in presence of B cell memory and long-lived plasma cells exhibiting similar autoreactivity [53]. This autoreactive extrafollicular plasma cell response is supported by CD4 Th cells distinct from Tfh cells, these cells provide B cell help mainly through IL-10, but not via IL-21 [53, 54]. Both, these newly discovered extrafollicular T helper cells and Tfh cells are found in the peripheral blood. Cytokine profiles and subpopulation distribution of autoreactive T cells can provide interesting insights into the pathogenesis of autoimmune disease and may also provide interesting information when included in a diagnostic setting.

In addition to staining with MHC-tetramers, autoantigen-specific T cells can be detected following rapid antigen-induced up-regulation of CD154 by flow cytometry [55]. With reasonable effort, these methods can be adopted to identify lymphocytes
specific to a broad range of different (auto)antigens, in mouse models as well as in patient samples [12, 55]. Therefore, identification and analysis of specific (auto)reactive T cell populations is not only possible, but likely to become essential in certain clinical settings. Analysis of autoreactive T cell populations and IgG Fc N-glycosylation patterns may provide helpful tool to guide therapy to come closer to “personalized medicine.”

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**Abbreviations:** ACPA · anti-citrullinated IgG antibodies · ANCA · anti-neutrophil cytoplasmic autoantibodies · EBA · Epidermolysis bullosa acquisita · GPA · granulomatosis with polyangiitis · GWAS · genome-wide association studies · MPO · myeloperoxidase · PR3 · proteinase 3 · RA · rheumatoid arthritis · RF · rheumatoid factor · SLE · systemic lupus erythematosus · T1D · type-1 diabetes · Tfh · T follicular helper · Treg · regulatory T cell

**Full correspondence:** Rudolf Armin Manz, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany.

E-mail: rudolf.manz@uksh.de

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