



# Editorial: Autoantibodies

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## Editorial on the Research Topic

### Autoantibodies

## AUTOANTIBODIES

Autoantibodies have become a popular research topic with a constantly growing number of research reports. The increasing interest from the scientific community is also reflected by the high number of articles within this Research Topic, which are illustrated by an interaction map that has been drawn by using the keywords of all articles from this collection (**Figure 1**). These articles, selected from the theme of this topic, cluster around “Autoantibodies” and “Autoimmunity.” Clustering was also observed for specific diseases, namely, pemphigus and pemphigoid, lupus, arthritis, and neuroimmunology. Cytokines, B cells, cell signaling, and the complement cascade are the focus of many manuscripts within this Research Topic. This clustering was the basis for the selection of the manuscripts discussed in this editorial.

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## PEMPHIGUS AND PEMPHIGOID

We received a number of submissions on the topics of pemphigus and pemphigoid, which are characterized and caused by autoantibodies to structural proteins of the skin [(1, 2); Liu et al.]. After binding to their target antigens, these autoantibodies directly (in the case of pemphigus) or indirectly (in the case of pemphigoid) cause skin blistering, which is the common clinical denominator of these diseases. Diagnosis is based on the clinical presentation, the detection of autoantibodies and/or complement deposits in the skin (detected by direct immunofluorescent (IF) microscopy), as well as the serological detection of the autoantibodies (3). For both pemphigus and pemphigoid systemic immunosuppression corticosteroids are still the main treatment. However, the lack of efficacy and/or the adverse events contribute to the medical burden of these diseases, which have an overall high unmet medical need (4). Within this Research Topic “Autoantibodies,” insights into the pathogenesis, as well as novel biomarkers and treatments, are presented with the prospect that they might improve the diagnosis and treatment of pemphigus and pemphigoid.

## SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a complex and multifactorial systemic autoimmune disease that primarily affects young women. The chronic inflammatory processes triggered during this disease can affect a variety of organ systems, including the skin, blood vessels, kidneys, and joints. Loss of humoral tolerance toward nuclear antigens such as RNA, DNA, and histones is one hallmark of the disease, although the direct contribution of autoantibodies to the disease pathology in humans is still controversial.



proteins (ACPA), have been described. The successful treatment with antibodies targeting B cells, reviewed by Hoffmann et al., have been key to the revival of the belief of the major role of B cells in RA and in several other autoimmune diseases. As in most autoimmune diseases, these autoantibodies appear years before the clinical onset of the disease. Sieghart et al. analyzed the isotype distribution of the different RA autoantibodies in early and established RA and showed that both the ACPA and RF of the IgG isotypes are specific for diagnosis but that the analysis of the IgM isotype increased the sensitivity of the test. RA has a high level of different antibodies, and the report emphasizes the value of analyzing different specificities for the diagnosis. Bitoun et al. immunized Macaque monkeys with citrullinated peptides and showed that the T cell response, but not the B cell response, was mainly directed to citrulline; this is similar to what has been observed in humans. However, in contrast to humans, monkeys with the MHC class II alleles (known to be associated with RA in humans) did not have predisposed T cell or B cell responses to citrullinated peptides. This indicates that we still lack an animal model that accurately reflects the autoimmune process leading to an ACPA response, which is known to occur in RA. Tong et al. highlights another autoantibody in RA, that are likely to also be pathogenic. The target antigen is type II collagen and in the report Tong defines and epitope targeted by such antibodies that is shared between type II and type XI collagen and they also show that both the native and the citrullinated form of the epitope is targeted by antibodies in RA.

## AUTOIMMUNE NEUROLOGICAL DISEASES

Several articles also focused on autoimmune neurological diseases, mostly on improved diagnostics. Autoantibodies have been shown to be the cause of several neurological diseases, such as anti-NMDA receptor encephalitis (13) or myasthenia gravis. Within this article collection, the role of autoantibodies in “classical” neurodegenerative diseases, such as Parkinson’s Disease, is discussed (Jiang et al.). This finding contributes to the current observations that autoantibodies to specific neuronal surface antigens are detected in a number of neuropsychiatric disorders (14). Functional validation of these autoantibodies would change the landscape of treatment for a number of neuropsychiatric diseases.

## INSIGHTS INTO PATHOGENESIS

Animal model systems, even with their limitations (15), can significantly contribute to the understanding of disease pathogenesis. Within this Research Topic, two new animal models are described: Zheng et al. describe an immunization-based mouse model for primary Sjögren’s Syndrome (Yin et al.). Tong et al. describe the shared epitopes among type XI and type II collagens in mice and humans with arthritis. Furthermore, an immunization-based arthritis model in the macaque (Bitoun et al.) and a model of feline limbic encephalitis (Tröscher et al.) are described within this Research Topic.

Large-scale genetic analyses, such as genome-wide association studies, have provided detailed insights into the underlying genetic association of autoimmune diseases, with the HLA locus as a major risk allele (16–19). Work summarized within this Research Topic demonstrates a co-occurrence of autoimmune diseases, namely, pemphigus and thyroid autoimmunity. Interestingly, the increased prevalence of anti-TPO autoantibodies was associated with the absence of certain HLA alleles and with the presence of non-desmoglein antibodies (Seiffert-Sinha et al.). Overlap at the mRNA expression level is also prevalent in different autoimmune diseases, specifically between pemphigus and systemic lupus erythematosus (SLE) (Sezin et al.). These comparative approaches may be useful to identify novel therapeutic targets that are either specific to one particular autoimmune disease or that may even be effective in the treatment of a specific cluster of autoimmune diseases. Examples of newly identified and validated risk alleles for SLE are described within this Research Topic: Gene expression in the B cells of quiescent SLE patients demonstrated an increased expression of *TRIB1*. To resolve the functional relevance of this gene for SLE pathogenesis, transgenic mice with the B cell-specific overexpression of *Trib1* were generated in the C57BL/6 genetic background. *Trib1* overexpression in B cells led to lower IgG1 concentrations under normal conditions. The immunization of mice with a T cell-dependent antigen also led to lower antigen-specific IgG titers, and the basal or forced anti-dsDNA IgM titers were lower in mice overexpressing *Trib1*. Collectively, these data point toward the *Trib1* regulatory role in autoantibody production in health and in disease (Simoni et al.). Based on the recent discovery of the rare null alleles of deoxyribonuclease 1-like 3 (*DNASE1L3*) and Fc gamma receptor IIB (*FCGR2B*) in SLE patients and genetic mouse models, Weisenburger et al. investigated the functional impact on these 2 genes in mice. For this purpose, mice deficient in both *Dnase1l3*- and *Fcgr2b* were generated in the C57BL/6 genetic background. In these mice, high levels of anti-DNA IgG were observed as early as 10 weeks of age. Autoantibody titers in these mice exceeded those observed in 9-month-old NZB/W mice. In conclusion, both genes synergize to promote the IgG anti-DNA autoantibody production by B cells (Weisenburger et al.). For the organ-specific autoimmune disease pemphigus, novel associations with complement genes (Bumiller-Bini et al.) and within the neonatal Fc receptor are described within the Research Topic (Recke et al.).

However, genetics only partially explains disease susceptibility, and (at least in mice) the genetically determined disease susceptibility can be overcome by changing daily habits (20). Indeed, autoantibody production is modulated by environmental factors, such as the diet and the microbiota (Edwards et al.; Petta et al.). Furthermore, gender may have a greater impact on autoantibody production than previously appreciated (Edwards et al.). Within this Research Topic, several manuscripts addressed the contribution of environmental factors on the generation of autoantibodies and/or autoimmune diseases: In their study, Issac et al. showed that the mice who are unable to clear a *Salmonella* infection spontaneously develop anti-dsDNA autoantibodies. This was associated with an

increased CD25 expression for both CD4+ and CD8+ T cells. This effect was specific to *Salmonella* infections, as infections caused by other bacteria did not induce autoantibody production (Issac et al.). Two articles demonstrate that pemphigoid can be induced by treatment with gliptins or by physical triggers, such as burns (Gaudin et al.; Mai et al.).

Once autoantibodies are bound to their target antigen, they may induce disease through a variety of mechanisms (21). These are either direct (Fab-mediated effects), such as the induction of aberrant signaling, or alternatively, Fc-mediated events, such as the activation of complement and the engagement of activating Fc-receptors, that drive tissue damage.

In pemphigus, autoantibodies to the desmosomal proteins desmoglein (Dsg) 3 and (often) Dsg 1 cause intraepidermal blistering in the skin and mucous membranes (22). In addition to Dsg 1/3, a wide range of autoantibodies has been identified in pemphigus patients (Amber et al.). The pathogenic relevance of these autoantibodies is not as firmly established as it is for anti-Dsg1/3. However, the injection of IgG from a patient with Dsg 3-reactivity, but not Dsg 1-reactivity, into Dsg 3-deficient mice led to the induction of intraepidermal blistering (23). Recently, a model has been proposed to explain how Dsg- and non-Dsg autoantibodies can lead to intraepidermal blistering. In brief, this model proposes that, depending on the pathogenic activity of all autoantibodies toward the structures on keratinocytes, they are either capable of inducing disease alone or in combination with other autoantibodies (24). The precise mechanisms by which autoantibodies in pemphigus lead to desmosome dysfunction remain to be fully elucidated (Spindler and Waschke): Steric hindrance, i.e., the blockade of homophilic Dsg interactions within the desmosome through autoantibody binding, is believed to be one cause of blistering in pemphigus. Furthermore, Dsg3 is internalized after binding to anti-Dg3 autoantibodies (Schlögl et al.), a process that requires p38 MAPK activation (Cipolla et al.; Vielmuth et al.). In addition to Dsg3 internalization, keratin retraction, induced by pemphigus autoantibodies, has recently been demonstrated to be important in mediating autoantibody-induced cell dissociation (Schlögl et al.).

## NOVEL DIAGNOSTICS / BIOMARKERS

Precise molecular diagnostics, paired with predictive biomarkers, form the basis of diagnosis as well as the selection of the appropriate treatment for each individual patient. Hence, almost 20% of the articles within the Research Topic “Autoantibodies” have focused on this topic.

The serological detection of autoantibodies is the basis of the diagnosis of many autoimmune diseases (21). Anti-nuclear antibodies (ANAs) are among the most-known autoantibodies. ANAs are associated with several rheumatic diseases, such as systemic lupus erythematosus and systemic sclerosis. However, low titers of ANAs are also present in healthy individuals (25). The gold standard for their detection is by indirect immunofluorescence and

incubating the patient serum with Hep-2 cells (26). However, conventional ANA testing requires time, is laborious, and requires microscopy expertise. To overcome these limitations and to standardize and automate ANA indirect IF testing, a fully automated system, which includes staining pattern recognition, was recently developed (27). The workflow and performance characteristics of the fully automated ANA IIF system were compared to manual ANA testing by Ricchiuti et al. The use of fully automated ANA determination has significant labor savings and good concordance with manual ANA readings.

As mentioned above, ANAs are also found in quite a proportion of healthy individuals, ranging from 5 to 30% depending on the population and method used (25, 28–30). This by far exceeds the prevalence of ANA-associated rheumatic diseases. If the target antigen is identified, autoantibodies against DFS70 are often found. Interestingly, isolated anti-DFS70 reactivity, which was observed in over 500 serum samples, was not associated with rheumatic disease. Hence, if the dense, fine speckled nuclear pattern, which corresponds to anti-DFS70 reactivity, is observed in Hep cells in ANA testing and anti-DFS70 reactivity is confirmed, then the presence of rheumatic disease is very unlikely (Carter et al.). In contrast, the detection of anti-cN-1A autoantibodies, which are found in 12% of patients with primary Sjögren’s syndrome and in 10% of SLE patients, is associated with the presence of other autoimmune diseases (Rietveld et al.).

If an autoimmune disease is suspected but no autoantibodies can be detected by routine methods, these may be identified by applying novel techniques such as the determination of the specific isotypes of the autoantibodies in a suspected case of rheumatoid arthritis (Sieghart et al.) or by the use of a keratinocyte binding assay in a suspected case of pemphigus (Giurdanella et al.). In addition, autoantibodies are also found in certain diseases that are just beginning to be understood to be mediated by autoantibodies. These include neurological conditions (Scharf et al.), chronic obstructive pulmonary disease (Wen et al.), and cardiovascular diseases (Basavalingappa et al.; Ernst et al.; Meier and Binstadt). However, with few exceptions, such as anti-NMDA receptor autoantibodies (31), the pathogenic relevance of these autoantibodies needs to be determined.

Bullous pemphigoid (BP) is the most frequent type of pemphigoid disease (32). BP responds well to systemic (whole body) topical steroid treatment (33). After stopping steroid treatment, relapse occurs in 30–40% of patients (34). Hence, biomarkers that allow for the prediction of relapse would allow for patient selection for whom steroid treatment can be stopped or for determining which patients require prolonged steroid and/or adjuvant treatment. In a retrospective analysis of BP patients, Dr. Koga and colleagues demonstrated that high BP180 autoantibody levels were associated with future relapse. In contrast, age, BP230 antibodies or total IgE levels had no predictive value (35). Researchers from France described elevated anti-type VII collagen autoantibodies, which are the cause

of epidermolysis bullosa acquisita (36), in almost half of the BP patients at the time of relapse (Giusti et al.). This is also a retrospective chart analysis with a limited number of patients. However, both studies imply the possibility that predictive biomarkers for BP relapse can be identified. The steps toward this are a joint analysis of retrospective patient cohorts from several departments as well as a prospective diagnostic study.

## NOVEL TREATMENTS

Based on the understanding of disease pathogenesis, novel treatment targets or therapeutic approaches for autoantibody-mediated diseases have emerged. Within the Research Topic “Autoantibodies,” several articles have focused on new treatments.

The anti-CD20 antibody rituximab has dramatically improved the treatment of several autoantibody-mediated diseases, which was most recently demonstrated in a phase III clinical trial in pemphigus patients (37). Notably, the response to rituximab is not uniform across all autoantibody-mediated diseases, as was demonstrated by the lower efficacy of anti-CD20 treatment in pemphigoid patients when compared to that in pemphigus patients (Lamberts et al.). Rituximab and other emerging treatments to modulate B and plasma cells were the topic of three reviews within the Research Topic (Hofmann et al.; Malkiel et al.; Musette and, Bouaziz). In this Research Topic, Roders et al. also identified SYK as a regulator of B cell activation. Thus, targeting SYK not only affects the effector functions (see below) but also possibly affects the generation of autoantibodies. A different approach to modulate autoantibody concentrations may be to enhance their turnover by inhibiting the neonatal Fc receptor (38) or by selective immunoadsorption using recombinant antigens to specifically elute autoantibodies (Hofrichter et al.).

A blockade of autoantibody functions, either by targeting the Fab or Fc fragments, is another highly interesting treatment approach for autoantibody-mediated diseases. High doses of intravenous immunoglobulins (IVIg) are an effective second- or third-line treatment for a number of autoimmune diseases (39–41). How IVIg mediates the therapeutic effects is controversial (42): One hypothesis claims that all of the therapeutic effects of IVIg are mediated through the inhibition of the neonatal Fc receptor (FcRn) (43). By administering excess IgG, the FcRn becomes saturated, and thus, all IgG molecules (including the autoantibodies) are more rapidly cleared. Others provide compelling evidence that the anti-inflammatory effect of IVIg is mediated by regulating the activation threshold in myeloid effector cells by changing the ratio of activating versus inhibitory FcγR expression (44). This effect required both terminal sialic acid residues at the Fc portion of IgG, as well as the expression of the inhibitory molecule FcγRIIB (45). Finally, the presence of anti-idiotypic antibodies has been reported, specifically, the presence of anti-anti-Dsg 3 autoantibodies in IVIg preparations (46, 47). In this Research Topic, Kamaguchi et al. isolated anti-idiotypic antibodies against type XVII

collagen, the major autoantigen in bullous pemphigoid (Liu et al.), and demonstrated a significant inhibitory activity of these antibodies against the pathogenic effects of BP patients' autoantibodies (Kamaguchi et al.).

In addition to the modulation of the Fab function of autoantibodies, their function can also be manipulated by changing the conserved N-linked Fc-glycan attached to the asparagine at position 297 in the constant region of the Fc heavy chain domains (Dekkers et al.). Indeed, the treatment of mice with endo-β-N-acetylglucosaminidase (EndoS), which hydrolyses the β-1,4-di-N-acetylchitobiose core of the N-linked complex type glycan on asparagine 297 (48), suppressed the induction of experimental arthritis (Nandakumar et al.), which was associated with the inhibition of the formation of large immune complexes and was independent of changes in the complement cascade or in antigen binding. The modulation of the conserved IgG's N-glycosylation site may have implications beyond the mere effector functions as was reported by Bartsch et al.: In their work, they demonstrate that antigen-specific sialylated autoantibodies but not non-specific sialylated IgG antibodies, attenuate disease manifestation in experimental lupus and arthritis. The antigen-specific sialylated autoantibodies modulated the B and T cell functions rather than modulating the effector functions of the autoantibodies.

In several autoimmune diseases, such as arthritis and pemphigoid disease, the activation of complement, the binding of immune cells to their immune complexes, and the subsequent intracellular signaling events are important for pathogenesis (21). The generalized inhibition of complement inhibition, which is achieved by the anti-C5 antibody eculizumab (49), is, however, associated with the risk of potentially life-threatening infections (50). These adverse effects could be reduced by restricting the complement inhibition at the site of complement activation or, even more ideally, at the site of pathologic tissue damage. By coupling a cyclic-RGD peptide to a function blocking C5 antibody, the construct is directed to the sites of the damaged endothelial cells. Thus, C5 inhibition preferentially occurs where endothelial damage is present (Durigutto et al.). In addition to the targeted delivery of C5-inhibitory compounds, selectivity may also be achieved by certain complement pathways, which are upregulated in specific diseases. The dissection of the individual contributions of the complement activation cascades in the pemphigoid disease epidermolysis bullosa acquisita [(51); Mihai et al.] demonstrated the predominant role of alternative complement activation and no contribution from the membrane attack complex. Thus, the selective targeting of C1q had therapeutic effects in an animal model of epidermolysis bullosa acquisita (Mihai et al.).

In addition to complement anaphylatoxins, cytokines recruit leukocytes to the sites of autoantibody-induced pathology. Thus, their inhibition has become a well-established therapeutic principle for several chronic inflammatory diseases (52). So far, however, each of the licensed biologics targets a single cytokine. To enhance the anti-inflammatory activity, Abraham et al. used phage display to identify promiscuous chemokine-binding peptides. These bind to a number of pro-inflammatory chemokines, such as CCL2, CCL5, and CXCL9-11. The use

of their selected lead compounds in models of autoimmune diseases ameliorated clinical disease manifestation (Abraham et al.). This approach may be applicable in endemic pemphigus foliaceus, where alterations in cytokine and chemokine serum concentrations have previously been noted (Timóteo et al.).

Once bound to the immune complexes, a complex signaling cascade is triggered in the leukocytes, which ultimately leads to their activation and subsequent inflammation and tissue damage (53). By contrasting the mRNA expression between inflamed and healthy skin in experimental pemphigoid disease, several hub-genes that potentially contribute to tissue damage in pemphigoid were identified. The spleen tyrosine kinase was among the identified hub-genes. Both LysM-specific SYK knockout mice and mice treated with an inhibitor of the small molecule SYK were completely protected from the induction of experimental pemphigoid disease by autoantibody transfer [Samavedam et al.; (54)]. Corresponding findings were made in a mouse model of arthritis (Németh et al.). Taken together, these findings suggest that targeting SYK is a potential therapeutic approach for a number of autoantibody-mediated diseases. Furthermore, in the pemphigoid mouse model, the inhibition of PI3K $\delta$  also prevented disease onset. Furthermore, pharmacological PI3K $\delta$  inhibition improved clinical disease manifestation when applied in therapeutic, experimental settings (Koga et al.). In addition to these signaling pathways, others also contribute to the pathogenesis of pemphigoid disease, which has recently been reviewed elsewhere (53).

In pemphigus, in addition to the above-described alterations in cell signaling, several lines of evidence suggest that apoptosis contributes to the loss of keratinocyte adhesion and consequently intraepidermal blistering (55). Initially, the contribution of apoptosis was suggested by an increased expression of molecules involved in this process, i.e., different caspases, Fas, as well as FasL (56). Following this concept, the inhibition of the Fas-FasL interaction by a function blocking anti-FasL antibody can inhibit pemphigus IgG-induced pathology *in vitro*. Furthermore, mice lacking the expression of the secreted, soluble FasL do not develop intraepidermal blistering when injected with IgG antibodies from pemphigus patients (Lotti et al.).

All of the abovementioned treatments focused on targeting IgG-mediated autoimmunity. In addition to IgG-mediated autoimmunity, IgA autoantibodies have also long been recognized as pathogenic. However, only recently has attention

been attributed to IgE-mediated autoimmunity (Maurer et al.). Despite their presence at high frequencies in many autoimmune diseases, the pathogenic relevance of IgE autoantibodies has thus far not been the focus of studies. In atopic dermatitis, a common, chronic inflammatory skin disease (57), the removal of immunoglobulins by immunoabsorption (and even the selective removal of IgE) has therapeutic effects [(58); Kasperkiewicz et al.; Kasperkiewicz et al.], which are comparable to that of biological atopic dermatitis treatment (59). However, immunoabsorption is a very specialized procedure. In addition, especially in the *S. aureus*-colonized skin of atopic dermatitis patients, central intravenous lines may lead to severe infectious complications.

## CONCLUDING REMARKS

“Autoantibodies” are a hot research topic, as was reflected by the articles of this Research Topic. Based on an enhanced understanding of disease pathogenesis, as well as the advancement of technology, we are at the verge of developing specific treatments for autoantibody-mediated diseases that may even be able to lead to a cure. This development is, for example, reflected by the use of chimeric autoantigen receptor T cells in the treatment of experimental pemphigus (60). In addition, novel developments in diagnostics now allow for the better diagnosis of patients as well as for the better understanding of the autoimmune nature of diseases, which had not been thought to be caused by an underlying autoimmune mechanism (Scharf et al.). Therefore, even if causal treatment is not possible, we may still be able to carefully select treatments that are tailored to each patient’s needs based on the detected biomarkers.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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