Meeting Report of the Pathogenesis of Pemphigus and Pemphigoid Meeting in Munich, September 2016

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Autoimmune blistering diseases are a heterogeneous group of about a dozen complex disorders that are characterized by intraepidermal (pemphigus) and subepidermal blistering (pemphigoid diseases and dermatitis herpetiformis). The Pathogenesis of Pemphigus and Pemphigoid Meeting, organized by the Departments of Dermatology in Lübeck and Marburg and the Institute of Anatomy and Cell Biology, Munich, was held in September 2016 in Munich. The meeting brought together basic scientists and clinicians from all continents dedicating their work to autoimmune blistering diseases. Considerable advances have been made in describing incidences and prevalences of these diseases and linking comorbidities with autoantibody reactivities and clinical variants, for example, dipeptidyl peptidase-IV inhibitor-associated noninflammatory bullous pemphigoid. Although new entities are still being described, diagnosis of most autoimmune blistering diseases can now be achieved using standardized and widely available serological test systems. Various experimental mouse models of pemphigus and pemphigoid disease are increasingly being used to understand mechanisms of central and peripheral tolerance and to evaluate more specific treatment approaches for these disorders, such as molecules that target autoreactive T and B cells and anti-inflammatory mediators, that is, dimethyl fumarate, phosphodiesterase 4, and leukotriene B4 inhibitors in pemphigoid disorders, and chimeric antigen receptor T cells in pemphigus. Very recent experimental data about the immunopathology and the determinants of autoantibody formation and keratinocyte susceptibility in pemphigus were discussed. With regard to cellular mechanisms leading to the loss of cell-cell adhesion, new ideas were shared in the field of signal transduction. Major steps were taken to put the various partly contradictory and controversial findings about the effects of pemphigus autoantibodies and other inflammatory mediators into perspective and broaden our view of the complex pathophysiology of this disease. Finally, two investigator-initiated multicenter trials highlighted doxycycline and dapsone as valuable medications in the treatment of bullous pemphigoid.

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Abbreviations: AIBD, autoimmune blistering disease; BP, bullous pemphigoid; EBA, epidermolysis bullosa acquisita; MMP, mucous membrane pemphigoid; PV, pemphigus vulgaris

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INTRODUCTION

After successful international meetings on autoimmune blistering diseases in Salzburg (1998), Otsu (2008), and Lübeck (2013), we met in Munich September 5–7, 2016 to discuss recent advances in the understanding of these complex prototypic autoantibody-mediated disorders (Figure 1). Plenary lectures were given by the authors flanked by oral presentations selected from the 66 abstracts that were discussed in a poster session. The first day was dedicated to all aspects of the different pemphigoid diseases, and the second day focused on the pathogenesis of pemphigus disorders.

PEMPHIGOID DISORDERS

Epidemiology

Although the incidences of autoimmune blistering disease (AIBD) have been studied in a variety of different populations, data about the prevalence of these disorders are sparse. Franziska Hübner of Lübeck, Germany, collaborated with the largest German health insurance company, the Techniker Krankenkasse. Based on coding from the *International Classification of Disease, 10th revision* (World Health Organization, 1990) she calculated a total number of 40,400 patients (0.05% of a population of 80,925,000) with autoimmune blistering diseases in Germany in 2014 (Hubner et al., 2016). Bullous pemphigoid (BP), pemphigus vulgaris (PV), and mucous membrane pemphigoid (MMP) were identified as the most prevalent disorders with adjusted prevalences of 259.3, 94.8, and 24.56 per million inhabitants, respectively (Hubner et al., 2016).

By far the most frequent AIBD, BP is known to be highly associated with old age, distinct drugs, and several neurologic and psychiatric diseases, collectively affecting 30–50% of BP patients. This last observation is particularly intriguing, because BP180 (type XVII collagen), the main target antigen in BP, is expressed in different parts of the central nervous system such as the hippocampus, thalamus, midbrain, and basal forebrain. In line with this, Laura Huilaja of Oulu, Finland, reported that serum levels of anti-BP180 antibodies correlate with more severe dementia and Alzheimer disease, indicating a potential relation between the autoimmune skin disease and the central nervous pathology (Kokkonen et al., 2017). Drug intake as another potential trigger of BP was addressed by Wataru Nishie. Based on the increasing number of dipeptidyl peptidase-IV inhibitor (gliptin inhibitor for diabetic control)–associated BP, his group observed, using a full-length BP180 ELISA, that dipeptidyl peptidase-IV inhibitor–associated BP tends to show a non-inflammatory phenotype and that autoantibodies are more likely to target epitopes on the BP180 ectodomain outside NC16A (Izumi et al., 2016). These data further support previous observations that not all BP patients generate antibodies against the immunodominant NC16A domain of BP180 and that several clinical BP variants exist in addition to the two classical phenotypes, that is, tense blisters and erosions or urticarial plaques and erythema.

Skin microbiota have recently been highlighted as related to disease expression in a variety of inflammatory disorders. Meriem Belheouane presented unpublished work on the role of skin microbiota in modulating BP susceptibility. Using both a human cohort and experimental BP in adult mice, she found that the composition of skin microbiota is associated with disease severity, which supports a role of the skin microbiota in the onset and development of BP.

Diagnosis

Diagnosis of AIBDs is based on three columns: clinical presentation, direct immunofluorescence microscopy, and detection of serum autoantibodies. Although direct immunofluorescence microscopy can still be regarded as the diagnostic criterion standard, in many patients diagnosis can be made by serological analyses and the clinical picture alone. In pemphigoid diseases, immunoglobulin deposition at the dermal-epidermal junction is not entirely linear but slightly undulated. Two patterns can be observed by direct immunofluorescence microscopy: the u-serrated pattern, with arches closed at the bottom unique to autoimmunity against type VII collagen (epidermolysis bullosa acquisita [EBA] and bullous systemic lupus erythematosus), and the n-serrated pattern, with arches closed at the top. The n-serrated pattern is seen in all other pemphigoid disorders. Pattern analysis is particularly valuable in EBA patients because in this group, serum autoantibodies can be detected in only about half of patients. Although the concept of a pattern diagnostic was developed about a decade ago, it still needs to spread widely in the routine diagnostic workup of AIBDs.

Serological diagnosis of AIBDs has been a rapidly expanding field over the last years. Gabi Ommen of Lübeck, Germany, introduced a previously undescribed multivariant ELISA that compiled six recombinant target antigens, that is, desmoglein 1, desmoglein 3, envoplakin, BP180, BP230, and type VII collagen. In two prospective studies, this ELISA allowed the one-step serological diagnosis of 95% of pemphigus and 71% of pemphigoid diseases and will further facilitate the diagnosis of AIBDs (Van Beek et al., 2017). Another diagnostic approach was chosen by Jane Setterfield analyzing saliva in patients with MMP. With a BP180 NC16A ELISA, reactivity was seen in 45% of MMP patients' saliva compared with 52% in serum. In 64 MMP patients, additional use of saliva increased detection of IgG and/or IgA to BP180 NC16A to 67%, representing a 30% increase (Ali et al., 2016).

Treatment

On behalf of the UK Dermatology Clinical Trials Network in collaboration with seven German centers, Karen Harman presented the results of the BLISTER trial. This prospective controlled multicenter trial showed that initiation of treatment with doxycycline at 200 mg/day was noninferior in terms of blister control at 6 weeks and superior in terms of number of severe treatment-related events by 52 weeks compared with tapering doses of prednisolone at 0.5 mg/kg body weight/day. This pragmatic trial suggests that for BP patients in whom topical treatment is not possible, a policy of starting treatment with oral doxycycline produces acceptable blister control in the short term and better long-term safety than conventional treatment with oral prednisolone (Williams et al., 2017). Another investigator-initiated multicenter prospective controlled trial in BP investigated the efficacy and safety of

Figure 1. Participants of the Pemphigus and Pemphigoid Pathogenesis Meeting, Munich, September 2016.

dapsone and azathioprine, both in combination with tapering doses of prednisolone 0.5 mg/kg/day. Dapsone appeared to be associated with a lower cumulative prednisolone dose, suggesting dapsone as a corticosteroid-sparing agent in BP. Although a gluten-free diet initially in combination with dapsone is standard in the treatment of dermatitis herpetiformis, Marzia Caproni described that even cutaneous manifestations of nonceliac gluten sensitivity including itching, eczematoid and psoriasiform lesions, and C3 deposits at the dermal-epidermal junction may rapidly resolve with a gluten-free diet (Bonciolini et al., 2015).

Pathophysiology

IL-17 and IL-17–related cytokines are currently the focus of research projects in several inflammatory diseases, also because of the potential application of anti–IL-17 therapy. Frank Antonicelli and colleagues identified neutrophils as a major source of IL-17 and related cytokines such as IL-22 and IL-23, being released in the serum and blister fluids of BP patients. This inflammatory network enhances MMP-9 secretion and CXCL10 expression from several leukocyte cell types and may lead to a feedback loop and the perpetuation of the autoinflammatory process (Riani et al., 2016). In line with this, sustained or enhanced serum levels of IL-17, IL-23, and CXCL10 were associated with relapses in BP (Plee et al., 2015). Another important aspect of BP pathophysiology, complement activation, was addressed by Hideyuki Ujiie. He showed that both monoclonal human IgG4 to BP180, which lacks complement activation ability, and IgGs from patients with BP can induce skin fragility in wild-type and complement-deficient mice, respectively. These data indicate that complement-independent pathways play an important role in blister formation of BP.

The quest for more specific anti-inflammatory regimens was driving the work by Ralf Ludwig, who made use of in vitro and in vivo model systems that reflected major pathophysiological aspects of EBA. Dimethyl fumarate was identified to be effective in experimental EBA by inhibiting neutrophil functions (Muller et al., 2016). Licensed for the treatment of psoriasis and multiple sclerosis, dimethyl fumarate will soon be evaluated in an investigator-initiated prospective controlled trial in patients with BP. Hiroshi Koga used a similar approach and showed that phosphodiesterase 4 inhibition significantly reduces the pathogenic effect of anti-type VII collagen IgG (Koga et al., 2016). Studies by Christian Sadik provided evidence that eicosanoids play a critical role in neutrophil homing into the skin and skin inflammation in response to binding of anti-type VII collagen antibodies at the dermal-epidermal junction (Sezin et al., 2017). Markus Niebuhr of Lübeck, Germany, using the immunization-induced EBA mouse model, performed T-cell repertoire analyses and proposed that CD4-positive T cells are not only instrumental in providing B-cell help for Ig class switching but also in expressing the proinflammatory cytokine IFN-γ in the skin in an autoantigen-driven manner. For a detailed study of autoantibody binding and neutrophil extravasation, Jennifer Klöpper of Lübeck, Germany used fluorescent-labeled anti-type VII collagen IgG and enhanced green fluorescent protein transgenic mice under the lysozyme M promotor in experimental murine EBA by multiphoton microscopy.

A thus far unreported mouse model of anti-laminin 332 MMP that reflected major clinical, histopathological, and immunopathological characteristics of the human disease was introduced by Eva Heppe of Lübeck, Germany. In this model, ocular, oral, and pharyngeal lesions predominate, and lesions formation was completely dependent on Fcγ receptors and, in part, on complement activation.

PEMPHIGUS

Immunopathogenesis

There is general agreement that T helper cells are critically involved in regulating the formation of autoantibodies in the pathogenesis of pemphigus. Masayuki Amagai presented his view of peripheral tolerance mechanisms down-regulating Dsg3-specific CD4 T cells in an active disease mouse model for PV. The model was generated by adoptive transfer of peripheral lymphocytes from desmoglein (Dsg) 3-deficient ($^{-/-}$) mice to Rag2$^{-/-}$ immunodeficient mice, because Dsg3-reactive T and B lymphocytes are not present in wild-type mice that express Dsg3. Dsg3-specific

T cell clones were isolated, and Dsg3-specific TCR transgenic mice were generated. A yet unpublished model to analyze peripheral tolerance of Dsg3-specific T cells was introduced by bone marrow transfer of Dsg3-specific TCR transgenic mice to recipient mice with thymus transplantation from $Dsg3^{-/-}$ and wild-type mice. In this context, the importance of the peripheral tolerance model for the development of a future antigen-specific therapeutic strategy was discussed.

The current concept of T-cell involvement in PV from the human angle was presented by Rüdiger Eming, with a translational approach using a previously established preclinical HLA class II transgenic PV mouse model. Activation of autoreactive T cells responsive to the PV autoantigens, Dsg 1 and 3, in the context of HLA-DRB1*04:02, led, via B-cell help, to the induction of IgG autoantibodies and, eventually, loss of epidermal adhesion. Using this model, he further showed that T regulatory cells down-regulate autoreactive T cells and may thus be exploited therapeutically (Schmidt et al., 2016). This preclinical model is currently used to develop a Dsg3 peptide-based, T-cell–targeted immunotherapy of PV. Robert Pollmann of Marburg, Germany, presented evidence that IL-21–producing T helper type 17 cells and T follicular helper cells are augmented in PV (Hennerici et al., 2016).

Aimee Payne gave insights into the lineage relationships of the IgG1-, IgG4-, IgA1-, and IgA2-specific B-cell repertoires in pemphigus using deep sequencing approaches paired with antibody phage display to identify Dsg-reactive lineages. Whereas IgA1 and IgA2 B-cell repertoires showed significant clonal overlap and shared mutations suggestive of sequential class switch from anti-Dsg IgA1 to IgA2, IgG4 B cells showed infrequent clonal overlap with other isotypes, with only one example of anti-Dsg IgG1 to IgG4 sequential class switch. These data indicate that anti-Dsg IgG1, IgG4, and IgA B-cell repertoires largely evolve independently from one another or arise from common precursors but through divergent pathways of somatic mutation. Christoph Ellebrecht of Philadelphia, Pennsylvania, USA, presented an exciting approach to treating autoimmunity in pemphigus using chimeric immunoreceptors adapted from those that have been used to successfully treat B-cell leukemias. Using the autoantigen Dsg3 as the extracellular domain of a "chimeric autoantibody receptor", he showed that Dsg3 chimeric autoantibody receptor T cells specifically kill anti-Dsg3 B cells in a PV mouse model, even in the presence of soluble anti-Dsg3 antibodies, thus providing a potent and feasible strategy for targeted B-cell depletion in pemphigus, which could potentially be extended to any autoantibody-mediated disease (Ellebrecht et al., 2016).

Role of anti-desmoglein versus non–anti-desmoglein antibodies and other factors

In the session on different antibodies and nonantibody factors in skin blistering, Jens Waschke revisited data showing that immunoadsorption of antibodies targeting Dsg1 and Dsg3 abrogated pathogenic effects of patients' IgG. Because, on the other hand, Dsg3-specific autoantibodies such as AK23 induce loss of keratinocyte cohesion and Dsg3-deficient mice show pemphigus-like lesions in epidermis and conjunctiva, these data support the notion that anti-Dsg antibodies are pathogenic. In line with this, Stephanie Goletz of Lübeck, Germany, presented unpublished data on Dsg1- and Dsg3-specific immunoadsorption in the neonatal pemphigus mouse model. Because targeting Dsg3 was paralleled by activation of p38 mitogen-activated protein kinase, the inhibition of which reduced loss of cohesion, Jens Waschke proposed that desmogleins form signaling hubs regulating keratinocyte adhesion and migration (Rotzer et al., 2015) and that signaling patterns may correlate with clinical phenotypes. A role for p38 mitogen-activated protein kinase in the pathogenesis of pemphigus foliaceus was also shown in unpublished data from Kenji Yoshida of Tokyo, Japan, indicating that Dsg1 clustering is mediated by polyclonal IgG.

The role of autoantibodies directed against other antigens was reviewed by Sergei Grando. He suggested that antibodies targeting other cell-membrane and intracellular antigens, such as mitochondrial proteins, synergize with anti-desmoglein antibodies to cause pemphigus. In line with this, Animesh Sinha reported recent data indicating IgG reactivity against muscarinic acetylcholine receptors and thyroid peroxidase, the expression of which was driven by HLA (Sajda et al., 2016). Finally, Carlo Pincelli of Modena, Italy presented that PV-IgG–induced Dsg3 cleavage is inhibited by anti-FasL antibodies, indicating a role for FasL in pemphigus.

Mechanisms causing blister formation in pemphigus

Marcel Jonkman reported that desmosomes become reduced in size and number in PV and PF patients' skin biopsy specimens. Depletion of desmogleins begins in the lower epidermis, whereas the IgG-dependent clustering of Dsg molecules is not required for acantholysis. Ena Sokol from the same group presented unpublished work on morphological changes in keratinocytes as a result of autoantibody exposure, which may be required for desmoglein internalization. Andrew Kowalczyk showed unpublished data on the mechanisms of lipid raft-mediated turnover of desmosomal molecules. The close relationship of lipid rafts and desmosomes was further underscored in a talk by Antje Banning of Giessen, Germany, who showed that reduced levels of the lipid raft markers flotillin-1 and -2 result in altered Dsg3 distribution and loss of cell cohesion (Vollner et al., 2016). Volker Spindler showed that modulation of signaling can overcome the effects of inhibitory autoantibodies (Vielmuth et al., 2015) and suggested a scenario in which altered keratin filament distribution in response to signaling may compromise desmosome function. In line with this, modulation of signaling pathways mediated by extra-desmosomal Dsg3 receptors was suggested as a therapeutic approach by Eliane Müller in her talk summarizing the role of different published and unpublished signaling molecules in pemphigus (Luyet et al., 2015). Eli Sprecher outlined that PV patients can carry a variant of the *ST18* gene, which enhances susceptibility of keratinocytes to the deleterious effects of autoantibodies, indicating that autoantibody pathogenicity may be genetically modulated (Vodo et al., 2016).

The meeting was closed by a consensus session moderated by Carien Niessen of Cologne, Germany, in which the main controversies in the pathogenesis of pemphigus were addressed and discussed to reach a conceptual framework that the scientific community largely agrees on. The results of this session are planned to be presented as a review on pemphigus pathogenesis in the near future.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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