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MEETING REPORT

Meeting report – Desmosome dysfunction and disease: Alpine desmosome disease meeting

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ABSTRACT

Desmosome diseases are caused by dysfunction of desmosomes, which anchor intermediate filaments (IFs) at sites of cell–cell adhesion. For many decades, the focus of attention has been on the role of actin filament-associated adherens junctions in development and disease, especially cancer. However, interference with the function of desmosomes, their molecular constituents or their attachments to IFs has now emerged as a major contributor to a variety of diseases affecting different tissues and organs including skin, heart and the digestive tract. The first Alpine desmosome disease meeting (ADDM) held in Grainau, Germany, in October 2022 brought together international researchers from the basic sciences with clinical experts from diverse fields to share and discuss their ideas and concepts on desmosome function and dysfunction in the different cell types involved in desmosome diseases. Besides the prototypic desmosomal diseases pemphigus and arrhythmogenic cardiomyopathy, the role of desmosome dysfunction in inflammatory bowel diseases and eosinophilic esophagitis was discussed.

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Introduction

Desmosomes in different tissues share an overall similar molecular blueprint, whereby desmosomal cadherins, through different cytoplasmics linker proteins, are coupled to the cytoskeleton and interfaces with components of different signal transduction pathways. However, just as the mechanical and chemical environments for each tissue varies, desmosome composition and structure also exhibit important tissue-specific differences. During the past decade, compelling evidence has accumulated showing that in addition to their functions in adhesion and maintenance of tissue integrity, desmosomes form signaling hubs involved in the regulation of cell behavior. A major challenge for researchers working on the pathophysiology of desmosomal diseases is to unravel the extent to which cell-type-specific or common structural and/or signaling functions of desmosomes contribute to tissue-specific functions during homeostasis, the response to environmental stress and disease.

In line with the differences in molecular composition, diseases associated with desmosome dysfunction are heterogenous with widely varying clinical phenotypes – pemphigus and Darier disease affect the skin, with intraepidermal cleavage occurring through loss of intercellular adhesion, arrhythmogenic cardiomyopathy causes cardiomyocyte death and fibrofatty tissue replacement in the heart, whereas in inflammatory bowel disease (IBD) and eosinophilic esophagitis (EOE), the barrier function of the digestive tract is compromised. It is important to note that no specific treatment options exist for any of these diseases.

The ADDM (www.desmosome-disease-meeting.com), held for the first time on Oct. 12–14, 2022, was organized by Volker Spindler, University of Basel and Jens Waschke, LMU Munich, Germany, to promote interactions between basic research scientists and clinical researchers, and to discuss the diversity of desmosome function and outline mechanistic similarities and differences in the various disease entities. 70 scientists of all career stages participated in the fully-booked conference and gathered for two full days in the beautiful and remote setting at the Eibsee in Grainau, Germany. The meeting comprised the sections ‘basic biology of desmosomes’, ‘pemphigus’, ‘arrhythmogenic cardiomyopathy’ and ‘IBD and other diseases’. Talks of eight invited speakers and a further eight established research group leaders were complemented by short talks that were selected from submitted abstracts. In addition, 42 posters were presented during a lively poster session. The overall conclusion was that the

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desmosome research community would benefit from subsequent events, and accordingly, we are planning to reconvene at the same location in October 2024.

Here, we present an overview on the key messages communicated by the speakers and aim to outline common ground on the view of the function of desmosomes in health and disease.

Composition of desmosomal contacts in the different cell types involved in desmosome-related diseases

Desmosomes are adhesive cell contacts between neighboring cells that provide mechanical strength to intercellular adhesion and thereby are crucial for tissue integrity (Fig. 1A). The adhesion molecules comprise several desmoglein (Dsg) and desmocollin (Dsc) isoforms, which are expressed in a tissue- and layer-specific manner. Within the desmosomal plaque, the cadherins are linked to Armadillo family adaptor proteins, including plakoglobin (Pg) and plakophilin (Pkp, which has three isoforms), and, via desmoplakin (Dp), transfer adhesive forces to intermediate filaments (IFs). Although this backbone of desmosome composition is shared in the different cell types, the molecular composition, as well as the association with other types of junctions, varies (Fig. 1B); presumably, this has profound functional implications, not only under physiological conditions, but also in the pathogenesis of diseases.

Signaling function of desmosomes

Research from the past decade has provided compelling evidence that, besides their adhesive functions, desmosomes organize signaling hubs regulating cell behavior. Kathy Green highlighted that desmosomes appeared late in evolution, as an innovation in vertebrates. The complexity of desmosomal composition increased, along with the generation of new desmosomal cadherins isoforms, in parallel with the transition from aquatic to terrestrial life, which made it necessary to strengthen body barriers towards the surrounding environment (Green et al., 2020). Thus, desmosomal cadherins of simple and stratified epithelia might regulate epithelial barrier properties in health and disease through cell type-specific or shared functions (Hegazy et al., 2022). Compelling evidence for a signaling function of desmosomal cadherins has been found for Dsg1, which, aside from its critical role for maintenance of epidermal barrier integrity, has been found to have anti-inflammatory functions. Thus, mice deficient for Dsg1 not only develop a severe pemphigus foliaceus-like phenotype of epidermal splitting with complete barrier breakdown, but also show Th17-skewed cytokine profiles similar to those exhibited by patients suffering from psoriasis or severe multiple allergy and metabolic wasting (SAM) syndrome (Godsel et al., 2022; Kugelmann et al., 2019).

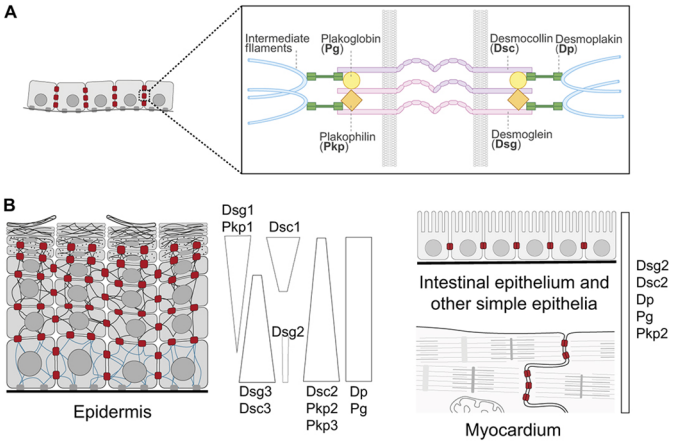

Fig. 1. Schematic overview of desmosome structure and composition. (A) The molecular blueprint of a desmosome. (B) In the epidermis, all desmosomal molecules are expressed to varying extent in a layer-dependent manner. In simple epithelia, such as the intestinal epithelium and in the myocardium, the expression is largely restricted to certain isoforms, as indicated.

Although chronic loss of Dsg1 leads to inflammatory disease, its acute temporary loss in response to environmental stress, such as UV, might in fact be a mechanism to sense and respond to environmental stress, by eliciting changes in secreted factors that stimulate the melanocyte tanning response (Arnette et al., 2020). In this context, Kathy Green discussed whether the immune-modulatory function of Dsg1 might be related to its regulation of cell mechanics during epithelial cell delamination, which is driven by interactions with, and remodeling of, the actin cytoskeleton via actin-binding proteins such as Arp2/3 and cortactin (Nekrasova et al., 2018). In addition to their physiological roles in epithelial differentiation and homeostasis, Jens Waschke reported that the pemphigus antigens Dsg1 and Dsg3, upon autoantibody binding, also function as adhesion-dependent signaling receptors by interacting with overlapping, yet distinct, sets of kinases (Schmitt et al., 2021; Spindler et al., 2013). An interesting question raised by these studies is to what extent the signaling function is shared among the different desmosomal cadherins and whether Dsg and Dsc isoforms of stratified epithelia have acquired new signaling functions during evolution to build more complex physical and immune epithelial barriers.

Crosstalk of desmosomes with cell junctions, other organelles and the cytoskeleton

Evidence is emerging that desmosomes are functionally, spatially and temporally linked with other types of cell junctions and the different cytoskeletal components. Carien Niessen presented work showing that E-cadherin- and P-cadherin-based adhesion and α-catenin are required for the assembly of nascent desmosomal junctions (Michels et al., 2009; Shafraz et al., 2018). Moreover, she emphasized that cortical tension exerted by the actin cytoskeleton is a driver of desmosome formation. An E-cadherin–Dsg1 complex coordinates a tension gradient within the epidermis through regulation of receptor tyrosine kinase signaling, which is essential to position the tight junctional barrier in the upper granular layer (Broussard et al., 2021; Rubsam et al., 2017). Supporting a role for cortical tension in desmosome function, Rudolf Leube discussed work showing that actomyosin contractility regulates desmosomal protein turnover, size and composition (Moch et al., 2022). He further highlighted that newly forming desmosomes, as well as hemidesmosomes serve as nucleation sites for keratin filaments, which is required for localized *de novo* keratin network formation (Moch and Leube, 2021; Moch et al., 2020).

Importantly, desmosomes might not only be physically and functionally coupled to the cytoskeleton and other cell junctions, but also to cell organelles. Andrew Kowalczyk demonstrated a close spatial proximity of the desmosomal plaque, keratin filaments and the endoplasmic reticulum (ER) using volume electron microscopy (EM) approaches (Bharathan et al., 2022 preprint). Genetic perturbations and live-cell optical imaging experiments suggest that desmosomes are required for the dynamics and positioning of the ER complex, and likewise, the ER appears to contribute to keratin organization and desmosome assembly at nascent sites of cell contact formation. Although the precise functional

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consequences are not fully resolved yet, these results might have implications for Darier disease, in which loss-of-function mutations in the ER Ca^{2+}-ATPase SERCA2 leads to impaired desmosome function.

It is becoming clear that integrating desmosome function with that of other organelles and with cell and tissue mechanics will be a major future topic in the field, and is expected to support the identification of novel mechanisms of how desmosomes shape cellular behavior.

Desmosomes in pemphigus

Pemphigus is the best-characterized desmosome disease. Enno Schmidt gave a detailed overview about the different clinical forms and diagnosis of pemphigus (Schmidt et al., 2019). With the ground-breaking discovery of Masayuki Amagai and John Stanley (Amagai et al., 1991) that the pemphigus autoantigen Dsg3 is a desmosomal cadherin family adhesion molecule, studies on the underlying mechanisms of autoantibody formation and loss of desmosomal adhesion in keratinocytes have been guided into a new direction. Even before this, disease models including *ex vivo* human skin organ culture, *in vivo* active and passive transfer mouse models and *in vitro* immunostaining techniques had been developed to study how autoantibody binding causes acantholysis in skin and mucous membranes. The large set of model systems has enabled the understanding that autoantibody-mediated loss of desmosomal adhesion in keratinocytes is the central step in patient lesion formation (Kasperkiewicz et al., 2017). The resulting data have shaped our current understanding of the underlying mechanisms. Aimee Payne and Enno Schmidt summarized the consensus model for pemphigus pathogenesis. After autoantibody binding, which causes direct inhibition of Dsg interaction via steric hindrance and activation of a complex signaling response, desmosome turnover is severely impaired through depletion of Dsg molecules, phosphorylation of desmosomal components and reorganization of the IF and actin cytoskeleton (Spindler et al., 2018). Antibodies against Dsg1 and Dsg3 have been shown to be sufficient for acantholysis in pemphigus and to induce autoantibody-specific signaling pathways, all of which induce alterations of the desmosome ultrastructure (Egu et al., 2022). In this context, Franziska Vielmuth outlined how single-molecule atomic force microscopy (AFM) helped to determine that the pemphigus autoantigens Dsg1 and Dsg3 undergo both homophilic and heterophilic interactions and to elucidate how pemphigus autoantibodies modulate Dsg-binding properties and induce binding of Dsg3 to Dsg2 (Fuchs et al., 2022; Sigmund et al., 2020; Vielmuth et al., 2018).

In the second part of their talks, Aimee Payne and Enno Schmidt summarized present and future paradigms in therapy. The B cell-depleting anti-CD20 antibody rituximab has been implemented as first-line therapy for moderate to severe pemphigus vulgaris/foliaceus. Aimee Payne spoke about the several trials that are underway to test new treatment paradigms, including use of Dsg3-CAART cells, which her group have been successfully applied in experimental models of pemphigus vulgaris (Ellebrecht et al., 2016; Lee et al., 2020) (NCT04422912), as well as downregulation of autoreactive T cells via Dsg3-coated nanoparticles (EudraCT-Nr. 2019-001727-12), or targeting of FcRn function (Goebeler et al., 2022). Ritva Tikkanen presented data showing that targeting FcRn by efgartigimod rescued the loss of keratinocyte adhesion caused by recombinant monoclonal anti-Dsg3 antibodies derived from pemphigus mouse models or patients, and suggested that FcRn, besides controlling autoantibody turnover, might also have direct effects on desmosomes (Zakrzewicz et al., 2022). This is in line with recent data presented in the short talk by Anna Sigmund (LMU Munich, Germany) demonstrating that the phosphodiesterase 4 inhibitor apremilast, which is used in the clinic for the treatment of psoriasis and was thought to mainly affect immune cells, stabilizes keratin anchorage of desmosomes and is protective against PV-IgG-induced skin blistering (Sigmund et al., 2022 preprint).

Eliane Müller shared unpublished data showing that experimental monospecific pemphigus autoantibodies can be used to unravel new functions of Dsg3 in the regulation of stem cell quiescence in the hair follicle, implicating known and hair follicle-specific signaling responses leading to the loss of desmosomal adhesion as well as blister repair.

However, although new treatment approaches have been developed and substantial progress has been made in the understanding of how autoantibodies cause loss of cell adhesion in pemphigus, the precise mechanisms by which autoantibody binding controls signaling responses and whether novel treatment strategies to stabilize keratinocyte desmosomal adhesion can be clinically applied remains unsolved at present.

Role of desmosome protein mutations in arrhythmogenic cardiomyopathy

Several talks addressed arrhythmogenic cardiomyopathy (ACM) and discussed its genetic basis and clinical manifestations. ACM caused by mutations in the gene encoding desmoplakin (Dp; also known as *DSP*) was considered somewhat a distinct entity, as it typically involves both ventricles, resembling dilated cardiomyopathy (DCM), and exhibits myocardial inflammation and fibrosis. Given that the majority of the known genes for ACM encode desmosome proteins, impaired cardiomyocyte coupling might be the crucial initial step in disease development.

In this context, Volker Spindler reported that mice with a constitutive substitution of alanine for tryptophan in the extracellular domain 1 of the Dsg2 protein showed a loss of intercellular adhesion and develop major features of the human disease. The findings also presented a mechanism by which the loss of Dsg2 binding drives myocardial fibrosis (Schinner et al., 2022). However, the pathogenesis of ACM appears to be more complex. Indeed, Brenda Gerull reported their findings showing that overexpression of Dsc2 induces an ACM-like phenotype, whereas deletion of the *Dsc2* gene did not cause a discernible phenotype (Brodehl et al., 2017).

Likewise, in his talk, Ali Marian reported that epicardium-restricted loss of desmoplakin contributes to myocardial fibrosis through the release of paracrine factors and increased differentiation of the epicardium-derived cells into fibroblasts (Yuan et al., 2021). Overall, the findings imply the complexity of the pathways involved in the pathogenesis of ACM, as the loss of myocyte-to-myocyte attachment might be sufficient to cause the disease under certain conditions, whereas additional pathogenic stimuli might be necessary to induce the phenotype under different conditions. An important candidate in this regard might be an inflammatory reaction in the heart. Brenda Gerull also summarized data on the occurrence of immune infiltrates in different mouse models of ACM (Gerull and Brodehl, 2020) and reported that experimental viral infection could unmask the ACM phenotype in conditional *PKP2* mutant mice. This suggests that, besides the genetic variant, additional environmental factors can contribute to reaching the threshold required for disease manifestation. Along these lines, Ali Marian presented data describing how the loss of Dp after activating the TNFR pathway causes cardiomyocyte apoptosis, necroptosis

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and pyroptosis, thus linking the desmosomes to the expression of proinflammatory genes and myocardial fibrosis and remodeling. Hendrik Milting reported a lack of clear genotype–phenotype correlations in ACM, as the pathogenetic impact of >75% of ClinVar-listed variants in the cardiac desmosomal cadherin genes *DSG2* and *DSC2* are of unknown significance. Moreover, pathogenic variants might lead to different clinical outcomes. He outlined that especially nonsense variants that lack the transmembrane domains in both cadherin genes might be deleterious when homozygously inherited, whereas heterozygous individuals exhibit either no or only mild forms of cardiac disease (Brodehl et al., 2021; Gerull et al., 2013). Therefore, a rigorous analysis of the mechanistic effects of specific variants, taking into account their clinical significance, in a well-defined patient population would be necessary to perform risk stratification for genetic counseling of patients.

From these talks, it is clear that the molecular mechanisms involved in the pathogenesis of ACM remain poorly understood. Deciphering the specific pathogenic pathways activated by different mutations will be crucial to identifying the modifier genetic and environmental factors, and to delineate their interactions to better understand the disease heterogeneity and develop targeted treatment options.

Desmosomes and digestive tract inflammation

In contrast to pemphigus and ACM, desmosomes have only recently been recognized as being involved in digestive tract inflammation, including inflammatory bowel disease (IBD) and eosinophilic esophagitis (EOE), as was presented by Nicolas Schlegel and Pavel Strnad. The major difference is that, at least in most patients, desmosome dysfunction is secondary to the inflammatory response and contributes to barrier dysfunction as part of a multifactorial pathogenesis (Schlegel et al., 2021). Alterations in desmosome ultrastructure and keratin filament organization in patients suffering from IBD, which parallel the well-known tight junction (TJ) defects, are reminiscent of epidermal lesions in pemphigus (Meir et al., 2019). Changes of desmosomes and some TJ proteins are preserved in organoids from IBD patients, suggesting a defect in the intestinal stem cell niche (Meir et al., 2020). In animal models, a genetic loss of desmosomal components, including Dsg2, Dsc2, Dp and Pkp2, impairs intestinal barrier properties and wound healing, and enhances the susceptibility to inflammation (Flemming et al., 2020; Gross et al., 2018, 2022; Nagler et al., 2022). In line with this, rare Dp and periplakin variants were found in familial EOE, whereas an acquired loss of both proteins was seen in non-familial cases. The consecutive changes in barrier integrity and Rho GTPase activity are thought to contribute to disease pathogenesis (Shoda et al., 2021). In contrast, evidence for a genetic cause of IBD is missing so far, although unpublished data presented by Elisabeth Butz (LMU Munich, Germany) suggest that, in some patients, Dsg2 mutations might serve as a risk factor for the disease. With regard to acquired changes, Nicolas Schlegel and Pavel Strnad outlined that cytokines such as IL-13 and TNFα downregulate Dsg1 or Dsg2, as observed in both EOE and IBD, respectively (Sherrill et al., 2014; Spindler et al., 2015). Downregulation of Dsg isoforms might have direct implications for epithelial barrier dysfunction – Dsg1 was found to be crucial for epithelial barrier function in the epidermis, and Dsg2 was shown to regulate claudin 2 expression and TJ function by sequestration of phosphoinositide 3-kinase (PI3K) (Burkard et al., 2021; Kugelmann et al., 2019). The major task in this area of research is to unravel the contribution of desmosome dysfunction to the pathogenesis of diseases caused by digestive tract inflammation and to investigate whether stabilization of epithelial cell adhesion can serve as a future therapeutic paradigm.

Shared signaling traits regulating cell adhesion in desmosome diseases

Although there is ample data, included that presented during this meeting, showing that the mechanisms involved in desmosome dysfunction in the different diseases are to a substantial extent cell type specific, possibly caused by a different composition of desmosomes or different mechanical cues the cells are exposed to. Nevertheless, because in several diseases the same components of desmosomes are affected, although by diverse mechanisms, including genetic alteration, autoantibody formation or cytokine exposure, the question arises as to whether some mechanisms also may be shared. Jens Waschke summarized our current knowledge on the signaling traits involved in the regulation of desmosome adhesion, which are shared between different cell types affected by desmosome-related diseases, such as keratinocytes, enterocytes and cardiomyocytes. There is convincing evidence for a role of signaling in loss of keratinocyte adhesion in pemphigus. Specifically, p38 MAPK signaling and EGFR activation in response to autoantibodies against Dsg1 and Dsg3 have been shown to be autoantibody specific and to contribute to loss of cell adhesion and alterations of desmosome ultrastructure in different *in vivo* and *ex vivo* models (Egu et al., 2022; Schmitt and Waschke, 2021). Similarly, in biopsies from IBD patients, p38 MAPK proteins were activated, and Dsg2 was found to regulate both EGFR and p38MAPK signaling (Schlegel et al., 2021), and both kinases are also required for barrier restoration.

For the regulation of cell adhesion in cardiomyocytes, the precise role in electromechanical coupling of the myocardium is less clear than for epithelial cell behavior, where barrier regulation or tissue homeostasis are affected. The notion that the autonomous nervous system, via adrenergic and cholinergic signaling, exerts opposing effects on cardiomyocyte desmosomal adhesion (referred to as positive and negative adhesiotropy) suggests that a physiological and possibly pathophysiological role for regulation of cardiomyocyte adhesion exists (Schinner et al., 2017; Yeruva et al., 2022). For patients suffering from ACM, how signaling mechanisms regulating desmosome adhesion contribute to disease is unclear at present. However, as presented by Sunil Yeruva and Konstanze Stangner (LMU Munich, Germany), unpublished data suggest that signaling is altered in both genetic ACM mouse models and in cardiomyocytes challenged with autoantibodies from ACM patients. This might be relevant because some signaling pathways that regulate cardiomyocyte adhesion also exist in keratinocytes, suggesting that, similar to pemphigus, cardiomyocyte adhesion in ACM might be altered via signaling pathways (Shoykhet et al., 2020). Moreover, Jens Waschke reported that the mechanisms underlying the regulation of desmosomal adhesion are also comparable to some extent between cardiomyocytes and keratinocytes, as has been demonstrated for protein kinase A (PKA)-mediated Pg phosphorylation, which stabilizes cell adhesion downstream of adrenergic signaling (Schinner et al., 2017; Sigmund et al., 2022 preprint). Whether this also holds true for other regulatory mechanisms, such as PKC-mediated Dp phosphorylation, which negatively regulates desmosome maturation in keratinocytes (Bartle et al., 2020), remains unclear at present.

Concluding remarks – the major challenges for desmosome research

At present, it remains largely unclear which of the mechanisms involved in disease pathogenesis are cell type specific and whether

they are caused by differences in desmosome composition. Even the role of cell adhesion might be different in the pathogenesis of different desmosomal diseases. In pemphigus, autoantibody-induced loss of desmosome adhesion certainly has a crucial role. Similarly, in digestive tract inflammation, where desmosomes are affected as a secondary effect to inflammation, loss of cell adhesion contributes to barrier dysfunction. In contrast, the contribution of altered desmosomal adhesion to the clinical phenotype might be different in ACM, depending on the desmosome component affected by genetic mutations. In this context, it must be considered that even if the same molecule is affected during disease pathogenesis in different tissues, its functional role might be completely different, and it is complicated to discriminate between a pathogenic mutation and a variant of unknown significance. Finally, the mechanical properties of tissue varies widely and ranges from cardiomyocytes that are subjected to high contractile forces to enterocytes embedded in the expanded surface area of the mucosa, where presumably they are exposed to less mechanical load. This might explain why functional alterations of a desmosomal component, for example, in response to a genetic mutation in ACM, might affect the heart, but do not cause intestinal barrier breakdown. Addressing these hypotheses and open questions by combining the expertise of the different biomedical disciplines holds great promise to deepen our insights into the molecular mechanisms underlying desmosome-related diseases. The ADDM 2022 served as first step to achieve this goal by connecting experts of all relevant fields.

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Competing interests
The authors declare no competing or financial interests.

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