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MINIREVIEW

Desmogleins as signaling hubs regulating cell cohesion and tissue/organ function in skin and heart — EFEM lecture 2018

Jens Waschke*

Institute of Anatomy, Faculty of Medicine, LMU Munich, Pettenkoferstr. 11, 80336 Munich, Germany

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ABSTRACT

Cell–cell contacts are crucial for intercellular cohesion and formation of endothelial and epithelial barriers. Desmosomes are the adhesive contacts providing mechanical strength to epithelial intercellular adhesion and therefore are most abundant in tissues subjected to high mechanical stress such as the epidermis and heart muscle. Desmogleins (Dsg) besides intercellular adhesion serve as signalling hubs regulating cell behaviour. In desmosomal diseases such as the autoimmune blistering skin disease pemphigus or arrhythmic cardiomyopathy (AC), which is caused by mutations of desmosomal components of cardiomyocyte intercalated discs, the adhesive and signalling functions of desmosomes are impaired. Therefore, our goal is to elucidate the mechanisms regulating adhesion of desmosomes in order to develop new strategies to treat desmosomal diseases. For pemphigus, we have provided evidence that intracellular signalling is required for loss of keratinocyte cohesion and have characterized a first disease-relevant adhesion receptor consisting of Dsg3 and p38MAPK. We propose that signalling patterns correlate with autoantibody profiles and thereby define the clinical phenotypes of pemphigus. Besides direct modulation of signalling pathways we have demonstrated that peptide-mediated crosslinking of Dsg molecules can abolish skin blistering in vivo. A similar approach may be effective to stabilize adhesion in cardiomyocytes of AC hearts. Since we observed that the adrenergic β1-receptor is localized at intercalated discs we evaluate signalling pathways regulating cardiomyocyte cohesion. With adrenergic signalling we have reported a first mechanism to stabilize desmosomal adhesion in intercalated discs and proposed a new function of the sympathicus in the heart we refer to as positive adhesiotropy.

1. Introduction

Desmosomes besides adherens junctions, are the adhesive contacts providing mechanical coupling of neighboring cells and have been shown to regulate tissue morphogenesis and function (Johnson et al., 2014; Rubsam et al., 2017; Waschke, 2008). The adhesion molecules of desmosomes belong to the cadherin superfamily and are anchored to the intermediate filament cytoskeleton via adaptor proteins such as plakoglobin (Pg), plakophilin and desmoplakin. These adaptor proteins organize desmosomes by forming two electron-dense plaques underneath the cell membrane which render the unique ultrastructural appearance of a desmosome. In simple epithelia and cardiomyocytes Dsg2 and desmocollin (Dsc) 2 are expressed as a single pair of desmosomal cadherins. In contrast, in complex epithelia such as the epidermis four Dsg and three Dsc isoforms are expressed in layer-specific patterns.

There is still matter of debate whether desmosomal cadherins predominantly undergo homophilic or heterophilic binding (Vielmuth et al., 2018a). This can be tested by performing single-molecule atomic force microscopy (AFM) under cell-free conditions when interaction of recombinant Dsg isoforms is blocked by specific inhibitory antibodies. With this approach, in several studies we have observed Ca^{2+}-dependent homophilic adhesion of Dsg1–3 and Dsc3 (Heupel et al., 2009, 2008; Schlegel et al., 2010; Spindler et al., 2009, 2015, 2013; Ungewiss et al., 2018, 2017; Vielmuth et al., 2015a, 2015b, 2018b, 2018c; Walter et al., 2017; Waschke et al., 2005, 2007) whereas heterophilic binding was detectable between Dsg1 and Dsc3 (Spindler et al., 2009) and Dsg2 and Dsg3 (Vielmuth et al., 2018c) only. Besides, the extracellular domain of Dsg2 can also interact directly with epidermal growth factor receptor (EGFR), which maybe relevant to shape the function of EGFR from cell proliferation towards cell adhesion (Ungewiss et al., 2018).

Desmosomal diseases are defined by dysfunction of desmosomes and comprise pemphigus and arrhythmic cardiomyopathy

* Corresponding author.
E-mail address: jens.waschke@med.uni-muenchen.de

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as the most-well entities (Waschke, 2008). Some people may wonder whether desmosomes are important since they do not exist in flies. However, as a physician I am convinced that desmosomal diseases are a good indication that we are not flies and demonstrate that desmosomes are of biomedical relevance. Desmosomal diseases are rare but severe. For example, most patients suffering from pemphigus until the sixties of last century, i.e. until systemic glucocorticoids became available, died within two years. Until today, therapy is limited to unspecific immunosuppression, which is accompanied with significant side-effects. Similarly, in arrhythmogenic cardiomyopathy (AC), young adults and primarily athletes die from sudden cardiac death due to malign arrhythmia. Therefore, our goal is to better characterize the adhesive and signalling functions of desmosomes and to elucidate the mechanisms regulating adhesion of desmosomes in order to develop new strategies to enhance desmosome function. In the long run, this may provide the basis for new therapeutic approaches to cure patients suffering from desmosomal diseases.

We also obtained data indicating that the desmosomal protein desmoglein 2 (Dsg2) may contribute to the intestinal epithelial barrier dysfunction in Crohn's disease (Schlegel et al., 2010; Spindler et al., 2015; Ungewiss et al., 2018, 2017), which is supported by very recent in vivo studies from another group (Gross et al., 2018). However, inflammatory bowel diseases are at present not regarded as desmosomal diseases because their pathogenesis is multifactorial. Therefore, this Mini-Review focuses on approaches to stabilize desmosomal adhesion in pemphigus and in AC.

2. In pemphigus, autoantibodies interfere with the adhesive and signaling function of desmosomes

Pemphigus is a model disease to study both mechanisms regulating the turn-over of desmosomes as well as the pathogenesis of desmosomal diseases. This is due the fact that skin blistering in pemphigus, which is mediated by intra-epidermal splitting, is caused primarily by antibodies against Dsg1 and Dsg3 whereas the significance of a plethora of other autoantibodies is unclear yet (Spindler et al., 2018). This is different to most other autoimmune diseases where autoantibodies are produced during the course of the disease but are better regarded as witnesses rather than drivers of pathogenesis. In pemphigus, there are two main forms with different clinical phenotype. In pemphigus vulgaris (PV), which is the more common and more severe form, patients usually begin with a mucosal-dominant phase which is characterized by autoantibodies (PV-IgG) against Dsg3 and rarely also Dsc3 (Kasperkiewicz et al., 2017). Later, when the epidermis is involved also, antibodies against Dsg1 are found also. In pemphigus foliaceus the situation is different since mucous membranes are not affected and antibodies (PF-IgG) target Dsg1 only. Another reason why pemphigus is a model disease to study desmosomes comes from the fact that autoantibodies, which can be purified easily from patients' sera, induce pathogenic effects in very reductive model systems in the absence of immune cells or complement components. For example, autoantibodies induce structural alterations of cultured keratinocytes and reduce loss of cell cohesion, the latter of which can be easily quantified by dissociation assays.

When we started this project, it was mainly believed that antibodies against Dsg1 and Dsg3 interfere with keratinocyte cohesion mainly by directly inhibiting the trans-interaction of molecules from neighboring cells. This was the most likely explanation since Dsg3 was discovered to be the pemphigus antigen (Amagai et al., 1991). However, signaling in response to autoantibody binding was detected early, however, the significance of this mechanism for pemphigus pathogenesis was unknown (Seishima et al., 1995). In order to keep the set-up simple, we used PF-IgG which target Dsg1 only and measured the effect on homophilic Dsg1 binding by cell-free AFM. We were very surprised that in contrast to purchased inhibitory antibodies we were not able to detect direct inhibition of Dsg1 binding by PF patients' IgG although antibodies induced pathogenic effects in cell-culture (Waschke et al., 2005). Later, we found that direct inhibition of Dsg3 binding is detectable in PV and may explain the more severe phenotype compared to PF (Heupel et al., 2008). However, during the last couple of years we observed that direct inhibition of Dsg binding alone is not sufficient to induce complete loss of cell cohesion but rather signaling pathways are required, which in part are regulated by keratin filaments and modulate the binding properties of Dsg1 and 3 (Vielmuth et al., 2018b, 2018c, 2015b).

Since direct inhibition was not detectable in PF, we focused on signaling pathways and started with Rho GTPases because we came from the endothelial field where we found that small GTPases are the main regulators of the endothelial barrier and are important in sepsis (Radeva and Waschke, 2018; Schlegel et al., 2009; Spindler et al., 2010a; Waschke et al., 2004). We established a human ex-vivo model in our lab and showed that specific activation of RhoA is sufficient to prevent autoantibody-induced blistering (Spindler et al., 2007; Waschke et al., 2006). Moreover, autoantibodies reduced the activity of RhoA which was suggesting that Dsg1 and Dsg3 act as signaling molecules. This event was dependent on p38MAPK, which had been reported to be an important signaling molecule for pemphigus pathogenesis (Berkowitz et al., 2005, 2006). The underlying mechanism how RhoA regulates desmosome assembly at least in part appears to involve Rho kinase-mediated phosphorylation of the actin-binding protein adducin (Rotzer et al., 2014).

However, still the question was how the signal upon antibody-binding is transferred into the cell? To address this, we used peptides to specifically interact with Dsg binding (Heupel et al., 2009). Using a so-called tandem-peptide, which was designed to cross-link Dsg molecules, we showed that this approach is effective to abolish skin blistering in a passive immune-transfer mouse model in vivo (Spindler et al., 2013). Noteworthy, the peptide can be applied topically as an ointment on the skin and penetrate the epidermis. With this peptide, we identified a first disease-relevant adhesion receptor consisting of Dsg3, Dsc3, plakoglobin and p38MAPK, in which interaction of active p38MAPK increased upon autoantibody-binding but was reduced by peptide-mediated crosslinking of Dsg3 (Rotzer et al., 2016; Spindler et al., 2014, 2013). However, since in pemphigus there are several signaling pathways involved, we proposed that signaling pattern exist which correlate with autoantibody profile and define the different clinical phenotypes in pemphigus (Walter et al., 2017). We observed that antibodies from mucosal-dominant PV directed against Dsg3 activate p38MAPK and Src whereas autoantibodies from cutaneous pemphigus including autoantibodies against Dsg1 besides p38MAPK activate Erk1 and induce rapid influx of Ca^{2+}. We now started to evaluate all these signaling pathways in human skin ex vivo and meanwhile showed that inhibition of p38MAPK is effective to abrogate blistering in human skin (Egu et al., 2017). Apparently, human skin more closely reflected the pemphigus phenotype of patients compared to mouse skin where selective inactivation of Dsg3 by an autoantibody or by genetic knock-out can cause blistering (Egu et al., 2017; Rotzer et al., 2016; Spindler et al., 2013). Another advantage of the human skin model besides the fact that it reduces the need of animal experiments is that it allows to study the ultrastructural alterations of desmosomes which have been characterized in detail in lesions of pemphigus patients (Sokol et al., 2015) and to relate them to a specific signaling pathway involved in pemphigus pathogenesis. By this approach, we demonstrated that p38MAPK regulates desmosome size, number and keratin filament insertion and sug-

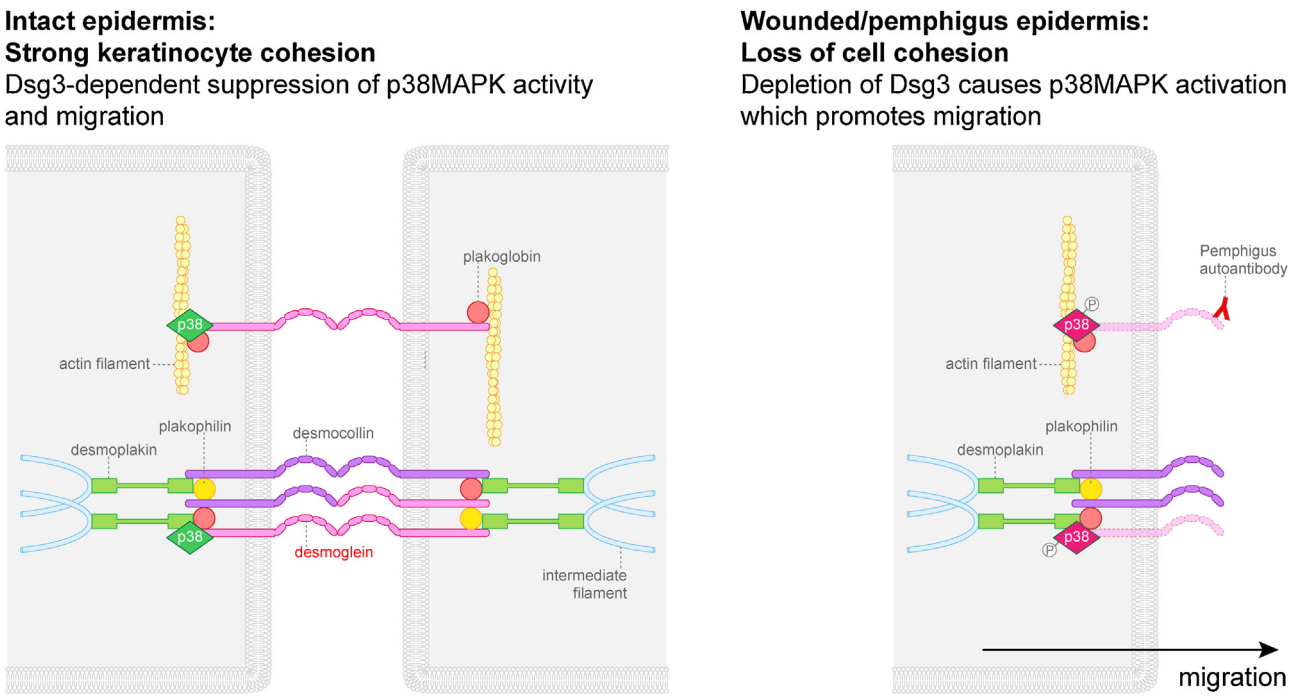

Fig. 1. In keratinocytes the Dsg3/p38MAPK coordinates desmosomal adhesion with migration.
We propose that in keratinocytes p38MAPK activity is controlled by Dsg3. When intercellular cohesion is intact such as in healthy skin, p38MAPK is kept inactive which allows stable adhesion of desmosomes. When Dsg3 binding is compromised as in pemphigus or after wounding, desmosomes are destabilized and migration of keratinocytes is facilitated, both of which is required for would healing and closure of pemphigus skin lesions.

gested that the parameter most closely correlating with blister formation is the number of desmosomes. We conclude that the pathogenesis of pemphigus is complex and that autoantibodies interfere with desmosome turn-over on the level of desmosome formation as well as by un-coupling of desmosomes from the intermediate filament cytoskeleton, events which involve a set of signaling pathways (Spindler et al., 2018; Spindler and Waschke, 2018).

Based on these studies we proposed that desmosomal contacts orchestrate signaling hubs which regulate assembly and disassembly of desmosomes and thereby control cell cohesion and other cell type-specific functions (Spindler and Waschke, 2014; Waschke and Spindler, 2014), which is a key message of this article. These signaling hubs for instance regulate p38MAPK, Src and PKC. With this respect, we found that p38MAPK is bound to Dsg3 both within desmosomes as well as outside of desmosome, i.e. extradesmosomal (Hartlieb et al., 2014; Spindler et al., 2013). In contrast, PKC was shown to be recruited to desmosomes specifically via keratin-mediated sequestration (Kroger et al., 2013) whereas Src was bound to extradesmosomal Dsg3 only (Rotzer et al., 2015). In contrast to p38MAPK, which impairs desmosome turn-over by depletion of Dsg3 and keratin filament retraction (Berkowitz et al., 2005; Jolly et al., 2010; Spindler et al., 2013), Src appears to be important for desmosome formation and to form a kind of intermediate complex between AJ and desmosomes which besides Dsg3 also contains E-cadherin (Rotzer et al., 2015). The latter may also explain why upon cell contact AJ form first and are required for desmosome assembly.

The interesting question is why humans need a desmosome disassembly complex including p38MAPK if not only to make us prone to get pemphigus? This reminded us of a puzzling observation in Dsg3-k.o. mice which has not been reported before: Dsg3-depleted mice have pemphigus-like lesions in skin and conjunctiva in which p38MAPK is activated (Koch et al., 1997; Vielmuth et al., 2016) and which heal spontaneously with several days (Rotzer et al., 2016). We found that loss of Dsg3 adhesion facilitates keratinocyte migration and wound healing and propose that in intact skin, Dsg3 inactivates p38MAPK to stabilize cell cohesion and to suppress migration. In contrast, after wounding or in pemphigus, loss of Dsg3 adhesion facilitates p38MAPK activation, which destabilizes existing desmosomes and induces migration, both of which is required for wound closure (Fig. 1). This may also explain why in PV and PF the site of cleavage within the epidermis is different. Unfortunately, this finding also limits the use of an approach to treat pemphigus patients with already existing blisters by inhibition of p38MAPK since it may have negative effects on healing of lesions.

3. Adrenergic signaling stabilizes cardiomyocyte cohesion which we refer to as positive adhesiotropy

AC is a rare heart disease manifesting mostly when young adults and primarily athletes die from sudden cardiac death resulting from arrhythmia. It is well-established that AC is caused primarily by mutations in genes coding the desmosomal components of the intercalated disc (Corrado et al., 2017). As outlined above, our goal is to characterize AC pathogenesis in order to establish new strategies for therapy. Therefore, we transfer the insights gained from regulation of desmosomal adhesion in keratinocytes to evaluate whether compromised cell adhesion as under condition of AC can be compensated by signaling mechanisms stabilizing cardiomyocyte cohesion. Interestingly, although several signaling pathways have been shown to be involved in AC pathogenesis (Corrado et al., 2017), regulation of cardiomyocyte cell–cell adhesion has not been studied in detail.

Based on the observations that adrenergic signaling can stabilize desmosomal adhesion in keratinocytes and protect epidermis against pemphigus IgG in mouse skin in vivo (Spindler et al., 2010b) and the finding that the β_1-adrenergic receptor in cardiomyocytes is localized in intercalated discs (Schlipp et al., 2014), we worked on the question whether adrenergic signaling would modulate

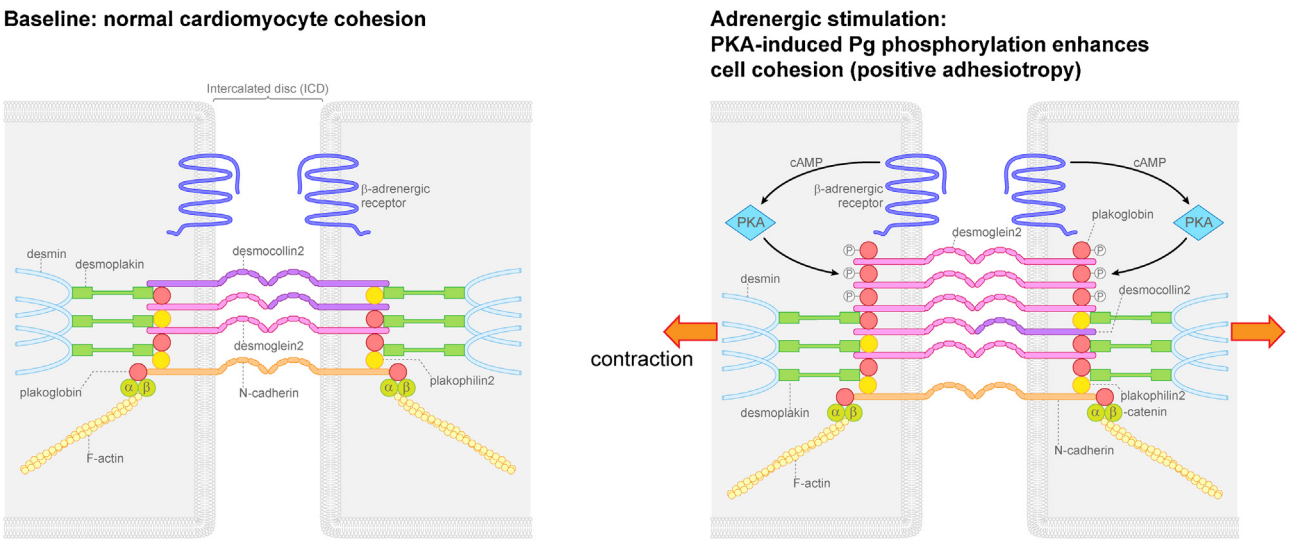

Fig. 2. Positive adhesiotropy stabilizes cardiomyocyte cohesion during adrenergic stimulation.
Adrenergic signaling via PKA-mediated phosphorylation of plakoglobin stabilizes cardiomyocyte cohesion. We believe that this is important to withstand the increased mechanical load during enhanced cardiac contraction.

cardiomyocyte cohesion. We generated a cardiomyocyte-specific Pg-deficient AC mouse model in our lab (Schinner et al., 2017), in which hearts are structurally normal at two weeks but become dramatically enlarged and fibrotic within 12 weeks. Interestingly, intercalated discs still formed with the only other component besides Pg missing was Dsg2 suggesting that Pg may be especially important to regulate Dsg2 turnover. We tested adult hearts by Langendorff perfusion where mutants in contrast to wild-type hearts upon adrenergic signaling failed to display a positive inotropic and chronotropic response. Rather, intercalated discs were ruptured after the adrenergic challenge suggesting that enhanced or at least intact cardiomyocyte cohesion was required to withstand the mechanical load induced by cardiomyocyte contraction. Indeed, adrenergic signaling enhanced cardiomyocyte cohesion and recruited Dsg2-specific binding events as to cell borders as revealed by AFM. We refer to this new function of the sympathicus in the heart as positive adhesiotropy (Schinner et al., 2017) and found that the response is dependent on Pg. As part of this mechanism, PKA directly phosphorylates Pg at S665 which appears to be required to increase adhesion (Fig. 2).

In summary, for establishment of new therapeutic strategies to treat desmosomal diseases it is required to delineate the cell-type specific functions of the desmosomal contacts related to both adhesion and signaling regulation in order to restore or at least enhance desmosome function. Based on our results it seems to be at least possible that these strategies may involve peptide-mediated Dsg crosslinking or signaling pathways which strengthen adhesion of desmosomes. However, this still is a long road to go and many additional studies would be required to test feasibility and efficacy before any recommendations can be made to treat patients.

Acknowledgements

At the XXVI International Symposium of Morphological Sciences (ISMS) 2018, held in Prague from July 5–7, 2018, it was my huge honor and great pleasure to deliver the 11th lecture of the European Federation for Experimental Morphology (EFEM). The theme of the symposium was “From molecule to organ in the heart of Europe”. In this article, I outlined the main thoughts of the lecture. In all our projects we study the interplay between cell cohesion and signaling and have a strong medical focus on the pathogenesis of diseases during which cadherin-mediated adhesion is impaired. However, in this lecture I focused on two projects related to desmosomal diseases.

Herewith, I would like to thank all present and former members of my group and all collaboration partners, who contributed most of the data reported and discussed here. First of all, I thank Volker Spindler, who has significantly contributed to our projects for many years and now is a professor for anatomy in Basel, Switzerland, and also Franziska Vielmuth, who meanwhile is a long-standing co-worker of mine. Other data discussed in this article were from the doctoral theses and post-doctoral research of Paola Bruggeman, Moritz Heupel, Eva Arnold (née Hartlieb), Vera Rötzer, Camilla Schinner, Elias Walter, Desalegn Tadesse Egu, and Hanna Ungewiss. Moreover, I would like to acknowledge Mariya Radeva and Daniela Kugelmann, who supported these projects with their expertise. The projects were funded via several projects by the DFG including the SPP 1782 and FOR 2497.

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