Received: 5 April 2023 | Revised: 5 May 2023 | Accepted: 22 May 2023

DOI: 10.1111/apha.14006

ACTA PHYSIOLOGICA

REVIEW ARTICLE

cAMP: A master regulator of cadherin-mediated binding in endothelium, epithelium and myocardium

Franziska Vielmuth | **Mariya Y. Radeva** | **Sunil Yeruva** | **Anna M. Sigmund** | **Jens Waschke**

Chair of Vegetative Anatomy, Institute of Anatomy, Faculty of Medicine, LMU Munich, Munich, Germany

Correspondence
Jens Waschke, Chair of Vegetative Anatomy, Institute of Anatomy, Faculty of Medicine, LMU Munich, Pettenkoferstraße 11, Munich 80336, Germany.
Email: jens.waschke@med.uni-muenchen.de

Funding information
Deutsche Forschungsgemeinschaft, Grant/Award Number: FOR2497

Abstract

Regulation of cadherin-mediated cell adhesion is crucial not only for maintaining tissue integrity and barrier function in the endothelium and epithelium but also for electromechanical coupling within the myocardium. Therefore, loss of cadherin-mediated adhesion causes various disorders, including vascular inflammation and desmosome-related diseases such as the autoimmune blistering skin dermatosis pemphigus and arrhythmogenic cardiomyopathy. Mechanisms regulating cadherin-mediated binding contribute to the pathogenesis of diseases and may also be used as therapeutic targets. Over the last 30 years, cyclic adenosine 3′,5′-monophosphate (cAMP) has emerged as one of the master regulators of cell adhesion in endothelium and, more recently, also in epithelial cells as well as in cardiomyocytes. A broad spectrum of experimental models from vascular physiology and cell biology applied by different generations of researchers provided evidence that not only cadherins of endothelial adherens junctions (AJ) but also desmosomal contacts in keratinocytes and the cardiomyocyte intercalated discs are central targets in this scenario. The molecular mechanisms involve protein kinase A- and exchange protein directly activated by cAMP-mediated regulation of Rho family GTPases and S665 phosphorylation of the AJ and desmosome adaptor protein plakoglobin. In line with this, phosphodiesterase 4 inhibitors such as apremilast have been proposed as a therapeutic strategy to stabilize cadherin-mediated adhesion in pemphigus and may also be effective to treat other disorders where cadherin-mediated binding is compromised.

KEYWORDS

adherens junction, cadherin, cAMP, desmosome, endothelium, epithelium, myocardium

1 | INTRODUCTION

Maintenance of cell–cell adhesion is crucial for the integrity of internal and external barriers in multicellular organisms allowing to isolate the organism from the surrounding environment and separate different compartments within the body. These barriers include epithelia such as the epidermis as well as the endothelium

outlining the inner wall of blood vessels and the heart. Moreover, the myocardium requires proper cell adhesion to allow the electromechanical coupling of cardiomyocytes during the contractile heart cycle. Although the main barrier-forming cell contacts in endothelium and epithelium are formed by tight junctions (TJ), the general assumption is that adherens junctions (AJ) and desmosomes as adhesive cell contacts are required to provide the mechanical strength for intercellular adhesion.[1-3] Both AJ and desmosomes consist of cadherin-type adhesion molecules which are coupled via adaptor proteins including plakoglobin (Pg) to the cytoskeleton. In endothelial AJ, VE-cadherin is coupled to actin filaments, whereas desmosomal cadherins comprise different desmoglein (Dsg) and desmocollin (Dsc) isoforms and are attached to intermediate filaments.[4,5] In the myocardium, intercalated discs, besides proper desmosomes, also contain areae compositae in which AJ and desmosome components intermingle.[6] This conserved backbone of cadherin-based adhesive contacts serves as the structural basis for shared mechanisms in the regulation of intercellular adhesion in cell types as diverse as endothelial cells, keratinocytes and cardiomyocytes.

Research on the regulation of barrier function in blood vessels goes back to a time when the molecular composition of cell contacts was unknown. Then, vascular physiologists studied the transport of water and fluid across the vessel wall and proposed different forms of pores to allow regulated exchange.[7,8] Meanwhile, it is known that TJ, together with the glycocalyx, are the structures to limit endothelial paracellular permeability.[9,10] The groundbreaking studies of physiologists identified the second messenger, cyclic adenosine 3′,5′-monophosphate (cAMP), as one of the most efficient signaling molecules to reduce permeability against almost all forms of inflammatory stimuli.[11] Later, cAMP in the endothelium was found to regulate the Rho family GTPases and to control VE-cadherin-mediated adhesion, which was identified as a central barrier-supporting adhesion molecule.[12,13] Since Rho family GTPases were identified to regulate cadherin adhesion in desmosomes, the role of cAMP to regulate desmosomal adhesion was explored in keratinocytes and in cardiomyocytes because these cell types are affected by the desmosome-related diseases pemphigus and arrhythmogenic cardiomyopathy, respectively.[14] This review summarizes the current knowledge on the regulation of cadherin-mediated adhesion by cAMP in different tissues and highlights components of the cAMP signaling cascade and its downstream molecules as targets for therapeutic approaches in disease.

2 | cAMP SIGNALING PATHWAY

cAMP was identified as a second messenger by Sutherland and Tall in 1958[15] and plays a critical role in a plethora of cellular functions such as the response to hormones and neurotransmitters, migration, mitochondrial homeostasis, proliferation and cell death.[16] The broad spectrum of cellular functions requires precisely regulated levels of cAMP in the cell and compartmentalization of cAMP signaling to provide a cell- and stimulus-specific response.[17-19] Levels of cAMP are balanced by the activity of adenylyl cyclases (AC) and phosphodiesterases (PDE), of which different isoforms with certain expression pattern and mechanisms of regulation exist.[19,20] The α subunit of G protein drives AC activation. Important members of this G-protein-coupled receptors (GPCR) are the β-adrenoreceptors (Figure 1). Vice versa, AC activity can be inhibited by muscarinic receptors and their α_i subunit of the G_i protein[20] (Figure 1).

cAMP induces activation of protein kinase A (PKA) and exchange protein directly activated by cAMP (Epac).[21,22] PKA consists of two catalytic (C) and two regulatory (R) subunits, the latter of which binds to cAMP.[21] cAMP binding leads to dissociation of the subunits and release of the catalytic subunit affecting a broad range of downstream targets[23] (Figure 1). A-kinase-anchoring proteins (AKAP) attach to the regulatory subunits of PKA to drive compartmentalization of PKA (Figure 1). For instance, AKAPs link PKA to the classical cadherins VE-cadherin and E-cadherin.[24-26] In addition, Epac activates the GTPase Rap1[22] but is also involved in other cellular processes such as cell adhesion,[27,28] differentiation[29] and gene expression.[21]

The cAMP signaling cascade is connected to and regulated by a plethora of other signaling pathways known to be involved in desmosomal and adherens junction adhesion such as Ca^{2+} signaling,[30] Rho family GTPases,[13] PKC,[31] PI3K,[32] PLC and MAPK/ERK signaling.[33]

Pharmacologically, the cAMP signaling cascade can be targeted by several mediators to modulate cadherin-mediated adhesion. A selection of respective compounds and targets are summarized and highlighted in Figure 1.

3 | cAMP REGULATES BARRIER FUNCTION AND CADHERIN-MEDIATED CELL ADHESION OF ENDOTHELIAL CELLS UNDER PHYSIOLOGIC AND INFLAMMATORY CONDITIONS

Endothelium, as a single, semipermeable layer of endothelial cells covering the inner surface of the blood vessels,

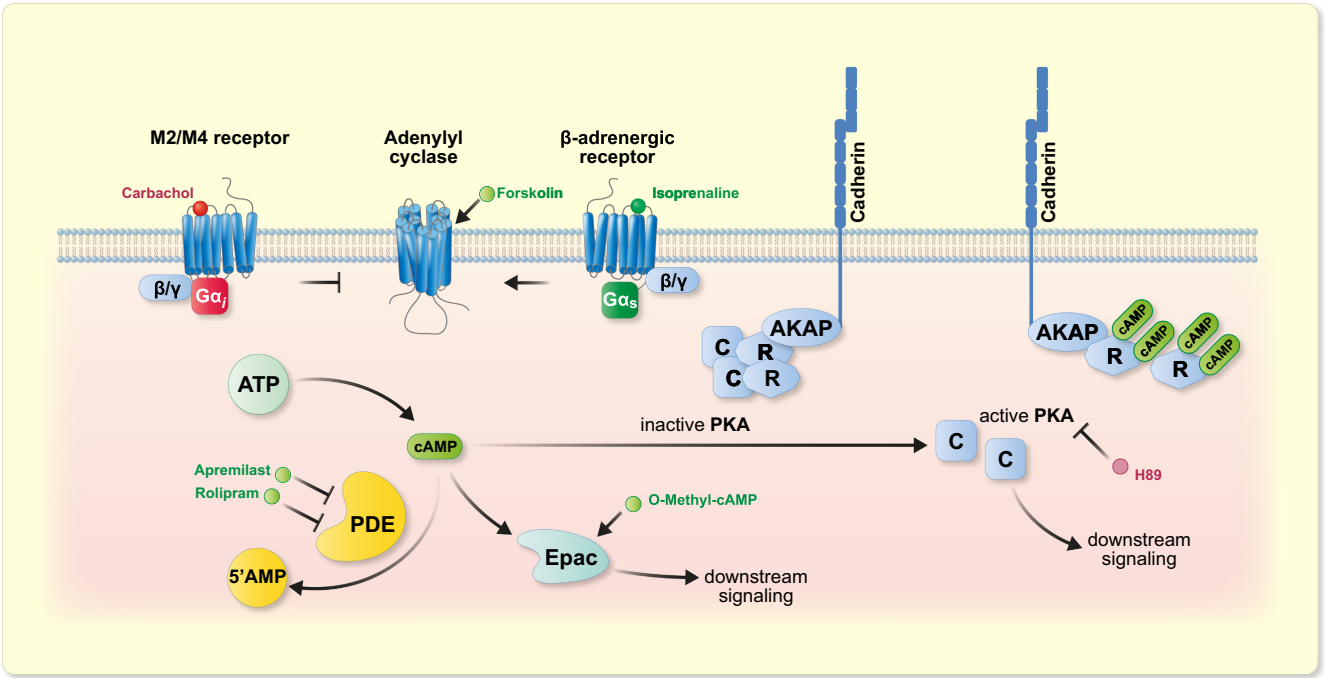

FIGURE 1 cAMP signaling machinery. Intracellular cAMP levels are controlled by phosphodiesterase (PDE) and adenylyl cyclase (AC) activity, the latter of which is regulated by β-adrenoreceptors and M2/M4 muscarinic receptors. cAMP activates PKA and Epac which in turn lead to a plethora of downstream signaling that maintain the respective function of cAMP signaling. Different compounds can be used pharmacologically to regulate cAMP levels: Carbachol: agonist of muscarinic Ach-receptor; Forskolin: activator of adenylyl cyclase; Isoprenaline: agonist of ß-adrenoreceptor; Rolipram: PDE4 inhibitor, Apremilast: PDE4 inhibitor, H89: PKA inhibitor, O-methyl-cAMP: activator of Epac. 5′AMP, 5′adenosine monophosphate; AKAP, A-kinase-anchoring protein; ATP, adenosine triphosphate; C, catalytic units; cAMP, cyclic adenosine 3′,5′- monophosphate; Epac, exchange protein directly activated by cAMP; PKA, protein kinase A; R, regulatory units.

provides a selective barrier between the blood and the surrounding tissue.[4,34] Several processes contribute to the maintenance of endothelial barrier integrity such as actin–myosin contraction, cell–cell and cell–matrix adhesion, actin cytoskeleton remodeling and glycocalyx integrity.[9] Therefore, the balance between adhesion and contraction is crucial for the barrier function and this may be partly controlled by cAMP.[35-37] Endothelial barrier dysfunction, occurring mainly in postcapillary venules,[34,38] is a hallmark of various pathological disorders such as tumor, edema or severe inflammation, which often is accompanied by sepsis and multiorgan failure, remaining a primary cause of mortality in intensive care units.[39-41] Under inflammatory conditions, endothelial barrier breakdown is mostly caused by gap formation at intercellular contacts (paracellular leak), whereas the transcellular leak is less relevant.[4,42,43] Paracellular permeability is controlled by the dynamic opening and closing of intercellular junctions,[40,44] such as AJ and TJ. While the TJ seal the intercellular cleft between neighboring cells and thus directly control paracellular permeability, VE-cadherin-composed AJ provide mechanical strength, initiate cell-to-cell contacts and support their maturation and preservation. It is also believed that AJ assembly is essential for precise TJ organization.[44,45] In addition to the ability to transmit intracellular signals, which can modulate many endothelial functions, both junctional complexes are associated with the actin cytoskeleton, which explains why the regulation of actin dynamic is also crucial for the maintenance of endothelial barrier integrity.[40,45,46,47]

A remarkable number of studies revealed that intracellular cAMP levels drop significantly during onset of inflammation,[48-51] while increased cAMP levels reduce paracellular permeability under basal conditions[52-54] and attenuate the endothelial cells inflammatory response in vitro and in vivo.[50,51,55,56,57,58,59,60,61,62,63,64,65] To do so, cAMP is produced by endothelial cells downstream of β-adrenergic receptors which were found to be necessary for proper barrier function in vivo.[66] Before, cAMP was shown to regulate permeability of brain capillaries[67] However, Fitzroy E. Curry's laboratory was the first to discover the effect of cAMP on baseline endothelial permeability in intact microvessels in vivo. The group reported that treatment with agents enhancing cAMP levels reduce microvascular hydraulic conductivity (Lp) of single intact capillaries and postcapillary venules. Interestingly, the effect was not linked to closure of preexisting gaps but was associated with an increase in the mean number of

TJ between cells in vivo.[58,68] The latter observation was in agreement with an in vitro study reporting modulation of TJ complexity by cAMP[54] and supported by the finding that the basal levels of cAMP are crucial for maintaining cell membrane permeability under resting conditions.[69]

As outlined earlier, cAMP is generated by AC in response to various stimuli triggering GPCRs. In contrast, hydrolysis of cAMP via different PDEs leads to its degradation.[70-73] Therefore, it is believed that application of cAMP-enhancing agents such as PDE inhibitors has the potential to overcome the loss of endothelial barrier function. Thus, in this context, PDE inhibitors against the most abundant PDE isoform in endothelium, that is, PDE4, such as rolipram or roflumilast have been intensively tested.[74-76] Several studies were showing that systemic PDE inhibition may attenuate inflammation- or sepsis-derived microvascular leakage in vivo.[77-80] Recently, activation of PDE3A, found to be expressed in the heart and lungs and known to hydrolyze both cAMP and cGMP, was also shown to negatively regulate cAMP levels in LPS-challenged mice in vivo.[81]

It is important to notice that cAMP synthesis within different cell compartments is critical for endothelial barrier function. While the cAMP localized at the plasma membrane strengthens barrier function, the cytosolic pool of cAMP was reported to cause barrier dysfunction.[13,82,83,84,85,86,87] In this line of thoughts, a number of reviews discussed the existence of signalosome complexes where a unique combination of cyclic nucleotide effectors such as PKA or other kinases, phosphatases, ACs and Epac are in interaction with PDE and/or other scaffolding proteins (i.e. AKAPs, β-arrestin, or RACK1) to promote highly compartmentalized cyclic nucleotide signaling platforms.[72,73,88,89,90,91] Interestingly, cAMP extruded into the extracellular space was also identified. This so-called "free" cAMP directly contributes to intercellular communication. Beyond this, cAMP encapsulated within extracellular vesicles was discovered too. The latter acts in a similar fashion to the cAMP localized near the membrane by preserving the intact endothelial barrier.[92,93] However, a recent study revealed that prolong activation of cAMP signaling leads to endothelial barrier dysfunction. In fact, cAMP, as a key regulator of gene expression, repressed the RRAS gene, leading to VE-cadherin clustering and thereby AJ disruption.[94]

Downstream from cAMP, endothelial barrier function is enhanced by the activation of PKA[95-98] and consequent phosphorylation of its substrates such as ERK,[99] ZNF185,[100] MLCK,[61] RhoA,[101] VASP,[102-106] and/or Epac and its effector GTPase Rap1[31] (Figure 2). These otherwise independent pathways may work in parallel to maintain barrier function.[107] Further down, PKA- and Epac-mediated pathways converged on Rac1, the activation of which is Tiam1/Vav2 dependent. Rac1 together with RhoA and Cdc42 belongs to Rho family of small GTPases, which earlier were found to be involved in the regulation of the endothelial barrier.[108-111] Later, the requirement of Rac1 for cAMP-dependent endothelial barrier maintenance in vivo and in vitro was demonstrated and it was shown that Rac1 is crucial for VE-cadherin junctional integrity, strengthening of junction-associated actin cytoskeleton and the VE-cadherin–actin cytoskeleton anchorage.[112,113]

cAMP-mediated Rac1 activation was verified in both micro- and macrovascular endothelium in vitro,[114,115] though the data for the latter are controversial.[116] Meanwhile, it was shown that Epac1 acts as a tonic stabilizer of vascular baseline permeability in vivo.[117] In line with this, in cultured cells, Epac1 was found to be critical for basal and cAMP-mediated endothelial barrier stabilization, which is partly independent of Rac1.[118] Inhibition of Epac also increased the basal permeability in bovine retinal endothelium and the Epac-Rap1 pathway preserved TJ organization of ZO1, claudin-5 and occludin.[119] Independent of cAMP/Epac1 activation, Rap1A can be also triggered by ArhGEF12 to limit disruption of TJ-dependent integrity induced by inflammation.[120] Furthermore, it was shown that FLRT2/LPHN2/cAMP/Rap1 signaling disassemble integrin-based focal adhesions and promotes ZO1-containing TJ. These effects were associated with restriction of YAP/TAZ signaling cascade known to regulate an angiogenic blood vessel formation and function.[121] cAMP/PKA signaling modulates endothelial permeability by phosphorylating the TJ component claudin-5.[122-124] Moreover, it was shown that stimulation of cAMP/PKA/CREB cascade via Gsα leads to an increase of plasmalemma vesicle-associated protein (PLVAP) expression, a membrane protein playing indispensable role in endothelial barrier function.[125] In this context, the role of Gsα was also demonstrated in vivo.

Signaling activation by an EPAC-specific cAMP analog also restored the barrier properties by attenuating VEGF/ERK signaling.[119] Indeed, numerous studies revealed that Rap1, its effectors and their binding partners (Rasip1, Radil, ArhGAP29, Cdc42 and its GEF FGD5, AF6, KRIT1) control RhoA/ROCK signaling, actin dynamics, as well as recruitment and stabilization of junctional complexes.[126-131] In this respect multiple studies reported that cAMP/Epac/Rap signaling promotes augmentation of VE-cadherin-mediated adhesion associated with cortical actin rearrangement.[28,116,132,133,134,135] The impact of VE-cadherin was further demonstrated when strengthening of VE-cadherin transinteraction via a tandem peptide was protective against stimuli compromising the barrier in vivo.[136] In line with this, VE-cadherin extracellular interaction created a positive feedback loop of Rac1-signaling and thereby this VE-cadherin outside-in signaling may

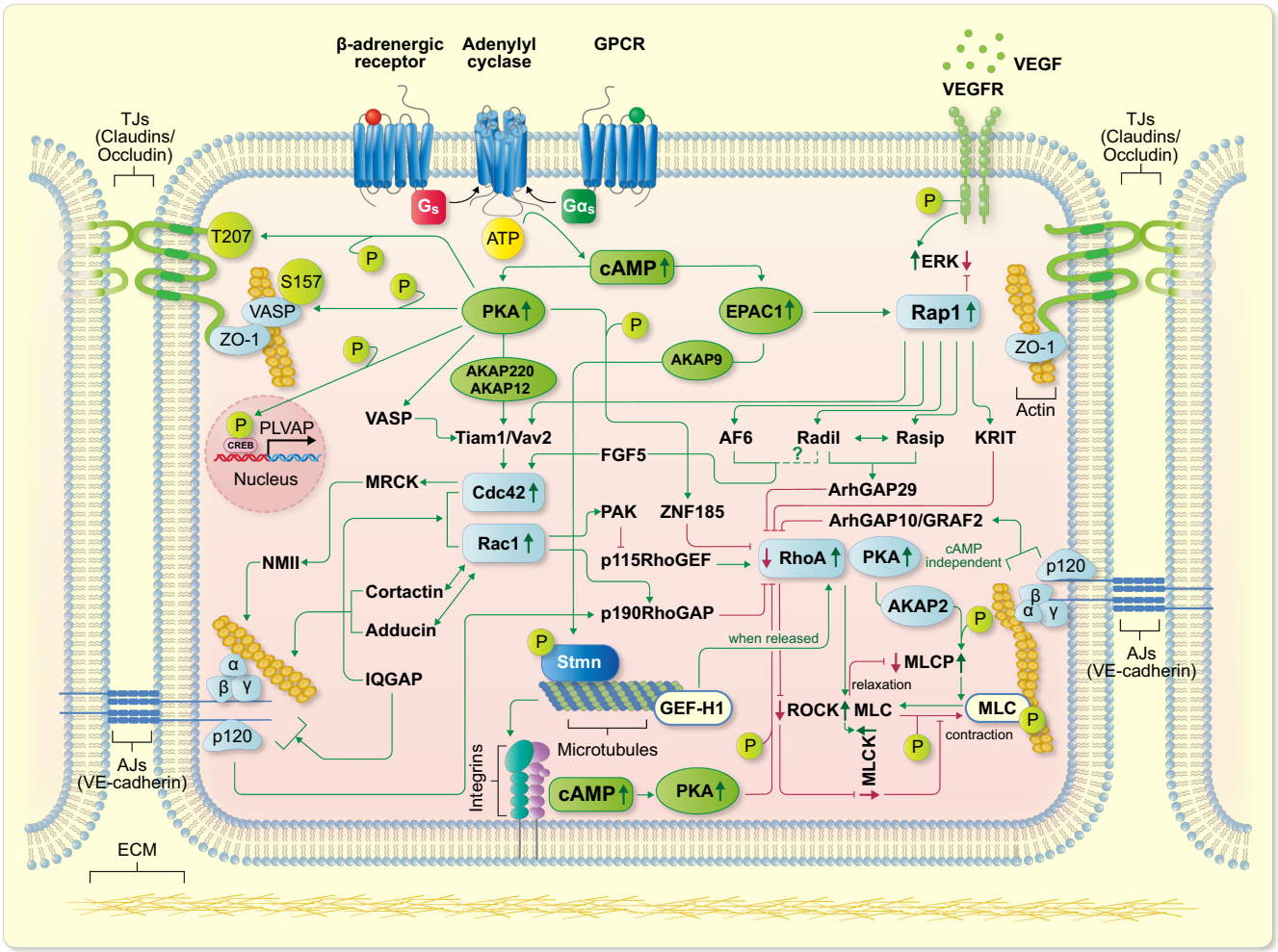

FIGURE 2 Mechanisms involved in cAMP-mediated regulation of cadherin adhesion and barrier function in the endothelium. cAMP produced under control of β-adrenergic signaling activates PKA and Epac1 which control the activity of Rho family GTPases and thereby fine-tune the balance of cytoskeletal anchorage and actin–myosin contraction to regulate endothelial AJ.

control local Rac1 activity.[137] Vice versa, VE-cadherin fragments (sVE-cadherin) released from endothelial cells upon inflammation, which were detected in sepsis patients, interfered with VE-cadherin interaction and therefore promote endothelial barrier breakdown in vitro.[138]

Finally, AKAPs and actin-binding proteins are crucial modulators of cAMP/PKA-dependent Rac1 stimulation (Figure 2). It was shown that AKAPs are required for endothelial barrier integrity in vivo and particularly AKAP220 and AKAP12 control cAMP-mediated Rac1 activation in vitro.[24] AKAP9, downstream from Epac1, was also introduced to promote microtubule growth and thus enhanced endothelial barrier stability.[139] Recently, AKAP2 was identified for cAMP-independent PKA activation, leading to myosin light chain phosphatase (MLCP) stimulation and consequent MLC dephosphorylation resulting in reduced endothelial cell contraction and endothelial barrier preservation.[140] Additionally, actin-binding proteins including vasodilator-stimulated phosphoprotein (VASP),[103,104,106] adducin,[141,142] and cortactin[143] are involved in the modulation of cAMP-mediated Rac1 activity and barrier function. In this context, the role of cortactin was also demonstrated in vivo.

It is important to note that Rac1 activation promoted by both Epac1 and PKA can contribute to the inhibition of RhoA signaling, assuming the existence of a Rac1/RhoA crosstalk mechanism stimulated by cAMP[144,145] (Figure 2). Moreover, cAMP/PKA activation, independently of Rac1, may inhibit the RhoA/ROCK pathway. The latter is reported to reduce MLC phosphorylation via MLCP activation and thereby leading to inactivation of endothelial contractile machinery.[146,147] However, this was shown for macrovascular endothelium in culture in vitro only, which is not the vascular bed relevant for inflammation. Since it was demonstrated that contractile mechanisms are overexaggerated in cultured endothelium,[37] the in vivo relevance of this mechanism is unclear. cAMP-induced PKA activation may also phosphorylate ZNF185, which

together with filamentous actin was reported to localize to the plasma membrane and stabilize cortical actin and thus was found to be important for barrier function in vivo. ZNF185 is also essential for cAMP/PKA-induced RhoA inhibition.[100] Taken together, ample evidence has been provided over the last two decades that cAMP via PKA and Epac1 controls endothelial barrier properties including VE-cadherin adhesion by the regulation of Rap1 and Rho family GTPases. In this process, spatiotemporal regulation is provided by AKAPs and actin-binding proteins which allow actin anchorage of VE-cadherin and actin–myosin contraction along junctions to be fine-tuned.

4 | cAMP INDUCES POSITIVE ADHESIOTROPY IN CARDIOMYOCYTES

In contrast to endothelial cells, intercellular adhesion of cardiomyocytes depends on both AJ and desmosomes, both of which comprise cadherin-type adhesion molecules to maintain the adhesive function.[6] Impaired cardiomyocyte cohesion can contribute to heart disease. Arrhythmogenic cardiomyopathy in most patients is considered to be an inherited heart disease, the pathogenesis of which is very complex and includes morphological changes such as fibrosis and fatty degeneration, inflammation, arrhythmias and a loss of cell–cell adhesion, all of which affect the myocardium and impair its function leading to an increased risk of sudden cardiac death.[148,149] Fibro-fatty degeneration results from altered signal transduction in Hippo, an interacting partner of Pg, and of Wnt, along with impaired αVβ6-integrin binding and transforming growth factor β (TGF β) release.[2,6,150–155] In addition, inflammation may cause myocardial damage.[156–159] However, early arrhythmias occur without detectable myocardial damage and may be induced by p38MAPK and ERK-mediated loss of gap junction (GJ) component Cx43 and disruption of ryanodine receptor 2 (RyR2).[153,160–162] Excitation propagation is transmitted via GJ using electrotonic and ephaptic coupling with Nav 1.5 channels and depends on Ca^{2+} homeostasis.[163]

It is important that arrhythmogenic cardiomyopathy is considered as a disease of the desmosome[148,149] since more than 60% of patients carry mutations in genes for Dp (*DSP*), Pkp2 (*PKP2*), Pg (*JUP*), Dsg2 (*DSG2*) and Dsc2 (*DSC2*).[148,149] Beta blockers are recommended as the first-line therapy for arrhythmogenic cardiomyopathy patients; however, the prophylactic use of β blockers in healthy gene carriers was not recommended.[164] In contrast, beta-blocker treatment was ineffective in certain arrhythmogenic cardiomyopathy patient's cohorts.[165] Therefore, it is imperative to understand how cAMP, a downstream effector molecule of β-adrenergic receptor, regulates cardiomyocyte cohesion.

In this pursuit, the first evidence for a possible role of cAMP in cardiomyocyte desmosomal adhesion was found when β_1-adrenergic receptor was localized to the intercalated disc of intact mouse myocardium,[166] where the desmosome together with AJ and GJ proteins is localized[6] (Figure 3). Further, in another study, adrenergic signaling phosphorylated Pg at serine 665 by PKA, paralleled by an enhanced desmosomal adhesion via increased Dsg2 interactions at cell borders, eventually leading to enhanced cardiomyocyte cohesion in vitro.[167] Similar to other functions of adrenergic signaling in the heart, this phenomenon was referred to as "positive adhesiotropy." On the ultrastructural level, positive adhesiotropy was characterized by increased area composita length and plaque thickness at intercalated discs in murine slice culture.[168] In line with this, enhanced cardiomyocyte cohesion was abrogated in the Pg-deficient murine arrhythmogenic cardiomyopathy model. Furthermore, Langendorff's experiments with β-adrenergic mediator isoprenaline in Pg-deficient hearts failed to increase pulse pressure and heart rate ex vivo, indicating that the positive adhesiotropic effects of β-adrenergic signaling could be coupled with positive inotropic and chronotropic effects. Indeed, treatment of murine hearts with the inotropic agent digitoxin enhanced desmosomal adhesion, paralleled by increased plaque thickness and enhanced Dp and Dsg2 localization at the intercalated disc.[169] Similar to the abrogation of positive adhesiotropy by adrenergic signaling in Pg-deficient mouse heart,[167] the inotropic agent digitoxin failed to induce positive inotropy and adhesiotropy in the absence of Pg. Overall, these observations strongly support that adhesiotropy and inotropy are interlinked and cAMP via PKA-mediated Pg-S665 phosphorylation can alter both inotropy and adhesiotropy.

The cardiac desmosome is classically thought to function as a cell–cell adhesive structure[170]; however, emerging evidence points to non-canonical roles for the cardiac desmosome in regulating electrical channels and function, independent of its structural roles. Indeed, a functional interplay between desmosomes, GJ protein, and β_1-adrenergic receptors was observed in HL-1 cardiomyocytes.[171] In this study, immunoprecipitation of GJ protein, Cx43, revealed Dsg2 and β_1-adrenergic receptors in complex with Cx43 in vitro. Furthermore, impaired cadherin binding induced by tryptophan or siRNA-mediated depletion of Dsg2 or Pg significantly abrogated cAMP increase and impaired conduction velocity of HL-1 cardiac myocytes in response to β_1-adrenergic receptor activation in vitro. Overall, the findings from this study revealed that desmosomal proteins aid in sufficient GJ and β_1-adrenergic receptor functions,

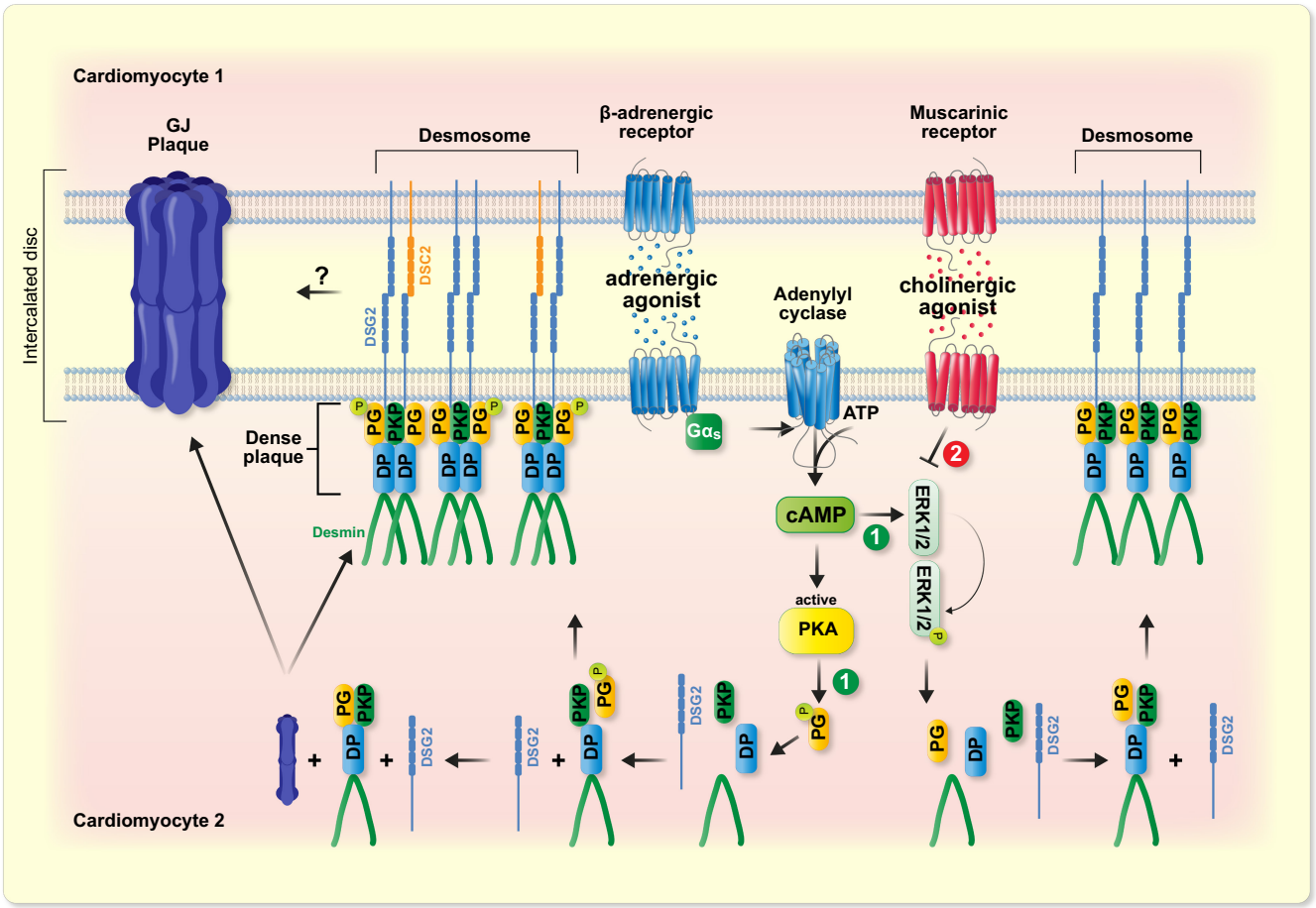

FIGURE 3 cAMP-mediated stabilization of desmosomal adhesion at intercalated discs. Adrenergic and cholinergic signaling have antagonistic effects on desmosomal adhesion which in part are mediated by opposite regulation of signaling molecules such as ERK. In addition, cAMP triggers PKA-mediated Pg phosphorylation at S665, which drives desmosome assembly and enhances GJ function.

and concomitantly, β_1-adrenergic receptor signaling regulates both desmosomal adhesion and GJ function. Although the signaling mechanisms operating between desmogleins and GJ are not clear, a linking peptide enhancing Dsg2 binding rescued GJ function and caused PKC-mediated phosphorylation of Cx43 at Serine 368.[172] Moreover, a loss of interaction between Pkp2, Dp, Cx43, N-cad, and ankyrin G, which necessitate directional transport of Nav 1.5 to the ICDs, disrupted excitatory conduction.[162,166,173–177] Similarly, Dsg2 and Pkp2 probably also influence the functional properties of these channels through their association with Nav1.5.[178–180] In a recent study, Pg deubiquitination enhanced its interaction with the Dp and end-binding protein 1 complex, promoting the microtubule-dependent transport of Cx43.[181]

The downstream mechanisms of cAMP-mediated positive adhesiotropy include PKA-mediated Pg-S665 phosphorylation and ERK1/2[182] (Figure 4), the latter of which was dependent on Pg, Dp, and Dsg2 in vitro. Interestingly, the role of ERK1/2 in desmosomal adhesion contrasts in keratinocytes compared to cardiomyocytes, as ERK1/2 inhibition rather than activation was proven beneficial for desmosomal adhesion in keratinocytes.[183]

It is well established that cardiac stimulation by the sympathetic and parasympathetic autonomic nervous system has antagonistic effects on many aspects of cardiomyocyte physiology. Similarly, recently it was demonstrated that cholinergic signaling in both HL-1 cells and murine ventricular cardiac slices from wild-type and Pg-deficient mice antagonized the positive adhesiotropy of adrenergic signaling[184] (Figure 3). In addition, cholinergic signaling abrogated Dsg2 translocation to cell borders via inhibiting ERK1/2 activation in vitro. This observation was further supported by the finding that cholinergic signaling effectively reduced cardiomyocyte cohesion in PG-deficient murine slices ex vivo, suggesting that alternative pathways independent of Pg exist for cholinergic signaling mediated cardiomyocyte cohesion. Furthermore, cholinergic signaling reduced the translocation of Dsg2 and Dp to cell borders, thereby cardiomyocyte cohesion dependent on the

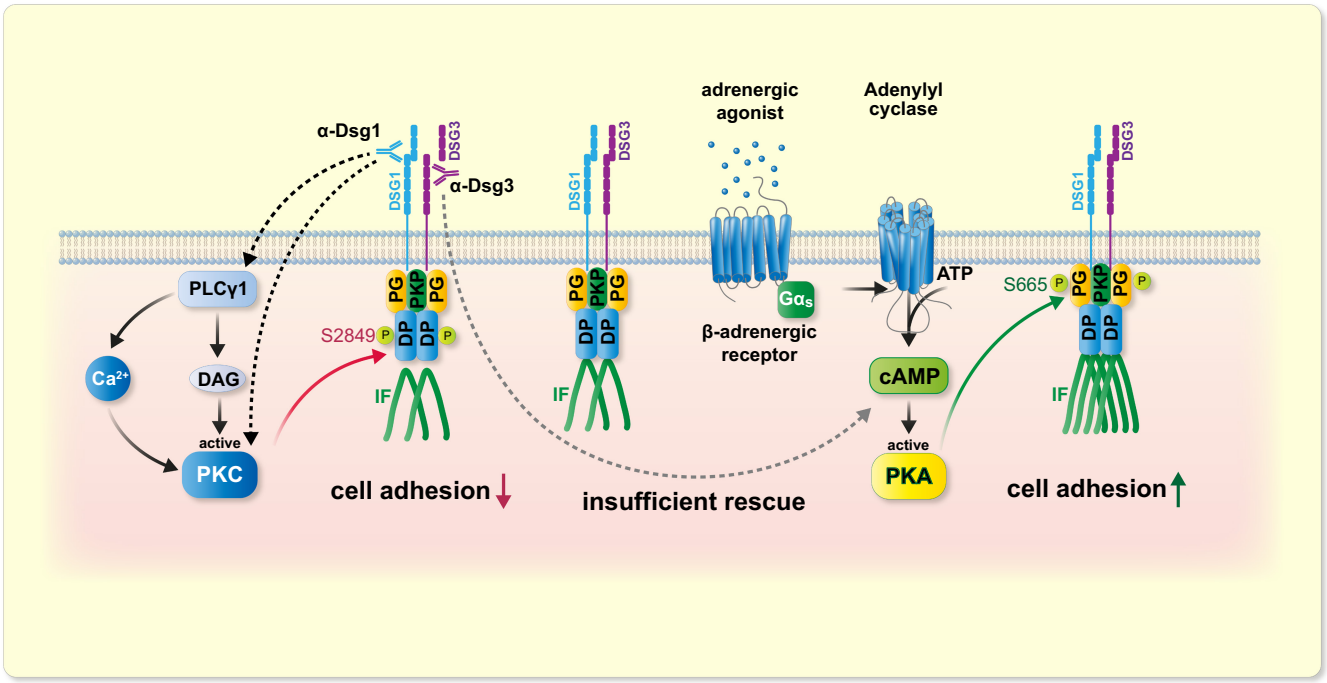

FIGURE 4 Mechanisms by which cAMP and other signaling pathways involved in pemphigus regulate cytoskeletal anchorage of desmosomes. cAMP via PKA-mediated Pg-S665 phosphorylation enhances desmosome anchorage to the intermediate filament cytoskeleton. This outbalances the signaling triggered by pemphigus autoantibodies which bind to Dsg1 and Dsg3. Finally, PKC phosphorylates Dp at S2849 and thereby reduces the cytoskeletal coupling of desmosomes. Therefore, phosphorylation of Pg and Dp serves as molecular switches to balance desmosomal adhesion.

PI3Kinase-AKT-GSK3-β signaling axis. The counterbalance of enhanced cardiomyocyte cohesion in response to adrenergic signaling by the cholinergic signaling axis was termed as "negative adhesiotropy."

In summary, adrenergic signaling via enhanced cAMP stabilizes desmosomal adhesion by activating PKA-mediated PG-S665 phosphorylation and ERK1/2 activation. Cholinergic signaling interferes with adrenergic signaling and destabilizes desmosomal adhesion via abrogation of ERK1/2 activation and via the PI3Kinase-AKT-GSK3-β signaling axis.

5 | cAMP STABILIZES KERATINOCYTE DESMOSOMAL ADHESION VIA PHOSPHORYLATION OF PLAKOGLOBIN

Similar to cardiomyocytes, AJ and desmosomes provide intercellular adhesion to keratinocytes.[1,185,186] In contrast, desmosomal cadherins, Dsg1-4 and Dsc1-3, which are the adhesion molecules in desmosomes, are expressed in a differentiation dependent manner in human epidermis. Intracellularly, desmosomal cadherins are linked via the desmosomal plaque proteins plakoglobin (Pg), plakophilins (Pkp), and desmoplakin (Dp) to the keratin filament cytoskeleton.[1,187]

With regard to cAMP signaling, keratinocytes comprise the complete adrenergic signaling machinery including several adenylyl cyclases such as AC3, 7, and 9[188,189] and PDE4.[190] Interestingly, β_2-adrenergic receptors are also expressed in keratinocytes of the human epidermis[191] and were initially identified to increase intracellular Ca^{2+} and in turn to activate PKC.[30] Downstream signaling of cAMP involves PKA and Epac1, both of which are expressed in keratinocytes.[192] Furthermore, cAMP signaling was shown to be involved in the regulation of several processes of keratinocyte cell biology including homeostasis and migration. For instance, directional migration was promoted by the decrease of cellular cAMP[193] and β_2-adrenergic stimulation accelerated skin barrier recovery.[194] In addition, TGFβ_1-induced cell scattering and invasiveness were inhibited by cAMP increase.[195] It is important to note that cAMP decrease promotes migration and invasive behavior, both of which are processes that lead to downregulation of adhesion molecules.[196] In the bullous autoimmune disease pemphigus, autoantibodies mainly against the desmosomal cadherins, Dsg1 and Dsg3 (Figure 4), cause blistering of the skin and the mucous membranes.[197] Therefore, pemphigus is an autoimmune desmosome disease. Morphologically, blistering is accompanied by

depletion of Dsg1 and Dsg3 from the cell membrane and alterations of the keratin cytoskeleton, both of which contribute to loss of intercellular adhesion.[198,199] The ultrastructural correlate of these changes is reduced number and size of desmosomes, alterations in the keratin insertion as well as desmosome splitting.[183,200,201] Therapeutic strategies in pemphigus mainly focus on suppression of autoantibody production and thus on the immune system. In contrast, therapies directly targeting keratinocyte cohesion are not established yet but would fulfill an unmet clinical need.[197,202,203]

Mechanisms causing loss of intercellular adhesion in pemphigus comprise direct inhibition of Dsg3 interactions as well as dysregulation of a plethora of signaling pathways.[202,204] Among the signaling pathways, several were identified which were activated upon autoantibody binding and contribute to the loss of adhesion such as p38MAPK,[205–207] Src,[208,209] PLC,[210,211] and Erk[203,212,213] in vivo. Inhibition of these signaling pathways abolished loss of intercellular adhesion and epidermal blistering.[183,214,215]

In contrast, cAMP signaling was also increased in response to pemphigus autoantibodies but seems to represent an insufficient cellular rescue mechanism which can be pharmacologically augmented to abolish loss of keratinocyte cohesion[216] (Figure 4). The AC activator forskolin in combination with the PDE4 inhibitor rolipram (F/R) or the β-receptor agonist isoprenaline protected keratinocytes from loss of intercellular adhesion in vitro and in vivo,[216] but are unsuitable for the use in patient due to expected severe cardiovascular side effects. β_2-adrenergic stimulation of the skin was also associated with PKA-dependent increase of differentiation markers keratin K1 and K10 and involucrin[217] showing cross-regulation of keratin filaments and adrenergic signaling, which explains how desmosomal cadherins regulate epidermal differentiation via cAMP signaling. In this context, it is important to note that β_2 receptors are downregulated in psoriatic skin, where epidermal differentiation is also disturbed.[218]

Meanwhile, further drugs were developed such as the selective PDE4 inhibitor apremilast, which is clinically approved for psoriasis and Behcet's disease, the effects of which primarily were attributed exclusively to the immune system.[219–223] However, recently it was shown that apremilast was protective against pemphigus autoantibody-induced blister formation in vivo in mouse and ex vivo in human skin and abrogated loss of keratinocyte cohesion.[224] Additionally, apremilast was successfully applied and tested for its efficacy in a patient suffering from therapy-resistant pemphigus vulgaris.[225]

cAMP increase by apremilast or F/R restored alterations of the keratin cytoskeleton in cell culture and also in epidermis from a human ex vivo model.[224] Additionally, cAMP drove keratin filament anchorage to desmosomes via recruitment of Dp.[224] Interestingly, high levels of cAMP induced by F/R in addition ameliorated Dsg depletion. Similarly, autoantibody-induced activation of p38MAPK was also abolished by F/R but not by apremilast which is conclusive given a direct connection of p38MAPK signaling and Dsg-dependent signaling as well as Dsg depletion in pemphigus.[213,214,216,226,227] Furthermore, a connection of cAMP and p38MPAK activity was observed in models of other skin diseases such as atopic dermatitis.[228]

Downstream signaling of cAMP in pemphigus is dependent on PKA and importantly, PKA-dependent cAMP signaling accelerated adhesion recovery of keratinocytes exposed to pemphigus autoantibodies.[216] Furthermore, apremilast caused PKA-dependent phosphorylation of Pg at Ser665 along cell borders in vitro (Figure 3). Pg-S665 phosphorylation was crucial for epidermal integrity as revealed by a phospho-deficient Pg-S665A mouse model, where keratin filament organization and intercellular adhesion were severely compromised.[224]

Taken together, adrenergic signaling in keratinocytes regulates both Dsg membrane localization and keratin filament organization. Mechanistically, a PKA-dependent phosphorylation of Pg at S665 is involved. In pemphigus, additional mechanisms may regulate Dsg internalization and p38MAPK signaling. The broad clinical application of PDE4 inhibitors such as apremilast in skin diseases may suggest that adrenergic signaling also is important for modulation of keratinocyte biology in other diseases.[229] For instance, coincidences of psoriasis and pemphigus and elevated risk in psoriasis patients to become affected by pemphigus may argue for similar mechanisms driving pathogenesis.[230–232]

6 | PG AND DP SERVE AS MOLECULAR SWITCHES FOR MODULATION OF DESMOSOME ADHESION

As outlined earlier, in both keratinocytes and cardiomyocytes, cAMP enhances cell cohesion via anchorage of the desmosomal plaque to the intermediate filament cytoskeleton. In both cell types, cAMP induces PKA-dependent Pg phosphorylation on S665,[167,224] which drives binding of intermediate filaments to Dp by a yet unknown mechanism. In contrast, phosphorylation of Dp at S2849 by PKC is known to regulate Dp–keratin interaction negatively and thereby to reduce keratinocyte adhesion, which is important because Ca^{2+} signaling and PLC as regulators of PKC can also be activated by pemphigus autoantibodies.[233,234] In accordance, inhibition of PKC or a phospho-deficient mutant of Dp S2849G protected from pemphigus autoantibody-induced keratin retraction and

loss of cell adhesion in vitro[235] and abrogated skin blistering in vivo.[236] Similarly, the multikinase inhibitor PKC412 ameliorated Dp phosphorylation, keratin aggregation and loss of cell adhesion in cell lines from epidermolysis bullosa simplex patients in vitro.[237] It was proposed that enhanced interaction of dephosphorylated Dp with keratins traps desmosomal proteins within the desmosome and thereby reduces protein exchange with the extradesmosomal pool.[238] Taken together, phosphorylation of the plaque proteins Pg and Dp serves as opposing molecular switches to regulate desmosome cytoskeletal anchorage and thereby allows desmosomes to react to different environmental cues such as wounding and migration.

In contrast, in endothelial cells, cadherin binding is strengthened by cAMP and Rac1 via enhanced anchorage to the cortical actin cytoskeleton, for which the role of Pg and its PKA-dependent phosphorylation is unknown at present. It is possible that some mechanisms outlined above for cAMP-mediated adhesion regulation in endothelial cells may also be relevant for desmosomal adhesion. For instance, recently it was proposed that Dp regulate RhoA-mediated contractile forces at AJs via recruitment of myosin VI and p114Rho GEF[239] indicating that desmosomes and AJ undergo a functional cross-talk, especially since RhoA and Rac1 are also known to regulate Dsg binding and desmosome stability.[240,241]

7 | OUTLOOK: cAMP TO STABILIZE CELL ADHESION IN DISEASE

The cAMP signaling cascade was shown to be a druggable pathway. Studies in endothelial cells provided knowledge on cAMP-dependent regulation of the endothelial barrier by regulation of Rac1 and AKAP-dependent actin dynamics which were later transferred to the in vivo situation. Similarly, in cardiomyocytes and keratinocytes, studies on the cAMP signaling were strengthened by using in vitro, in vivo and ex vivo approaches to identify targets for therapeutic approaches. Most recently, the PDE4 inhibitor apremilast was applied to stabilize cadherin-mediated adhesion in the desmosome disease pemphigus in mice and also to treat a first patient.[224,225] Interestingly, signaling traits regulating cell adhesion are shared in different desmosome-related diseases.[14] Since signaling by p38MAPK and EGFR have been found to be upregulated in models of both pemphigus and arrhythmogenic cardiomyopathy and ADAM17 was found to regulate desmosomal adhesion in keratinocytes in pemphigus and also in cardiomyocytes,[214,242–244] it is possible that cAMP signaling may also serve as a possible target in other desmosome-related diseases. In addition, cAMP signaling may be employed to regulate the behavior of other cells. For instance, E-cadherin expression in Schwann cell development is regulated by cAMP signaling and myelination is Rac1 dependent.[245,246] In addition, N-cadherin expression in ovarian surface epithelium is regulated by gonadotropins in a cAMP-dependent fashion[247] and cAMP is involved in N-cadherin expression regulating trophoblast function.[248,249] Dysregulation of cadherin expression and distinct components of the cAMP signaling cascade were reported in certain tumors such as soluble E-cadherin in salivary gland carcinoma[250] and prostate carcinoma cells, where Epac inhibition was suggested as a potential therapeutic approach.[251] Furthermore, AKAP4 was identified as an oncogene in non-small cell lung cancer and was associated with dysregulation of cadherin expression and cAMP signaling.[252] However, systematic studies are missing and may be subject of further scientific studies to reveal whether modulation of cadherin binding in these cell types can be employed to modulate diseases.

ACKNOWLEDGMENTS

This work is supported by DFG FOR 2497 to FV and JW. We thank the Waschke lab for valuable scientific discussion. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

Franziska Vielmuth received a lecturer fee from Bruker in the past 3 years. Otherwise, the authors have no conflict of interest.

ORCID

Franziska Vielmuth https://orcid.org/0000-0002-8570-7595
Mariya Y. Radeva https://orcid.org/0000-0002-9902-1682
Sunil Yeruva https://orcid.org/0000-0002-1565-2023
Anna M. Sigmund https://orcid.org/0000-0001-8533-9617
Jens Waschke https://orcid.org/0000-0003-1182-5422

REFERENCES

1. Hegazy M, Perl AL, Svoboda SA, Green KJ. Desmosomal cadherins in health and disease. *Annu Rev Pathol*. 2022;17:47-72.
2. Green KJ, Jaiganesh A, Broussard JA. Desmosomes: essential contributors to an integrated intercellular junction network. *F1000Res*. 2019;8:1000 Faculty Rev-2150.
3. Capaldo CT, Farkas AE, Nusrat A. Epithelial adhesive junctions. *F1000Prime Rep*. 2014;6:1.
4. Mehta D, Malik AB. Signaling mechanisms regulating endothelial permeability. *Physiol Rev*. 2006;86(1):279-367.
5. Waschke J. The desmosome and pemphigus. *Histochem Cell Biol*. 2008;130(1):21-54.

6. Yeruva S, Waschke J. Structure and regulation of desmosomes in intercalated discs: lessons from epithelia. *J Anat*. 2023;242(1):81-90.
7. Renkin EM. Cellular aspects of transvascular exchange: a 40-year perspective. *Microcirculation*. 1994;1(3):157-167.
8. Pappenheimer JR, Renkin EM, Borrero LM. Filtration, diffusion and molecular sieving through peripheral capillary membranes; a contribution to the pore theory of capillary permeability. *Am J Physiol*. 1951;167(1):13-46.
9. Radeva MY, Waschke J. Mind the gap: mechanisms regulating the endothelial barrier. *Acta Physiol (Oxf)*. 2018;222(1):e12860.
10. Curry FE, Adamson RH. Endothelial glycocalyx: permeability barrier and mechanosensor. *Ann Biomed Eng*. 2012;40(4):828-839.
11. Michel CC, Curry FE. Microvascular permeability. *Physiol Rev*. 1999;79(3):703-761.
12. Spindler V, Schlegel N, Waschke J. Role of GTPases in control of microvascular permeability. *Cardiovasc Res*. 2010;87(2):243-253.
13. Schlegel N, Waschke J. cAMP with other signaling cues converges on Rac1 to stabilize the endothelial barrier- a signaling pathway compromised in inflammation. *Cell Tissue Res*. 2014;355(3):587-596.
14. Spindler V, Gerull B, Green KJ, et al. Meeting report—Desmosome dysfunction and disease: alpine desmosome disease meeting. *J Cell Sci*. 2023;136(1):jcs260832.
15. Sutherland EW, Rall TW. Fractionation and characterization of a cyclic adenine ribonucleotide formed by tissue particles. *J Biol Chem*. 1958;232(2):1077-1091.
16. Lefkimmiatis K, Zaccolo M. cAMP signaling in subcellular compartments. *Pharmacol Ther*. 2014;143(3):295-304.
17. Fischmeister R. Is cAMP good or bad? Depends on where it's made. *Circ Res*. 2006;98(5):582-584.
18. Vandecasteele G, Rochais F, Abi-Gerges A, Fischmeister R. Functional localization of cAMP signalling in cardiac myocytes. *Biochem Soc Trans*. 2006;34(Pt 4):484-488.
19. Sassone-Corsi P. The cyclic AMP pathway. *Cold Spring Harb Perspect Biol*. 2012;4(12):a011148.
20. Cooper DM. Regulation and organization of adenylyl cyclases and cAMP. *Biochem J*. 2003;375(Pt 3):517-529.
21. Cheng X, Ji Z, Tsalkova T, Mei F. Epac and PKA: a tale of two intracellular cAMP receptors. *Acta Biochim Biophys Sin (Shanghai)*. 2008;40(7):651-662.
22. de Rooij J, Zwartkruis FJT, Verheijen MHG, et al. Epac is a Rap1 guanine-nucleotide-exchange factor directly activated by cyclic AMP. *Nature*. 1998;396(6710):474-477.
23. Taylor SS, Buechler JA, Yonemoto W. cAMP-dependent protein kinase: framework for a diverse family of regulatory enzymes. *Annu Rev Biochem*. 1990;59:971-1005.
24. Radeva MY, Kugelmann D, Spindler V, Waschke J. PKA compartmentalization via AKAP220 and AKAP12 contributes to endothelial barrier regulation. *PloS ONE*. 2014;9(9):e106733.
25. Oldenburger A, Poppinga WJ, Kos F, et al. A-kinase anchoring proteins contribute to loss of E-cadherin and bronchial epithelial barrier by cigarette smoke. *Am J Physiol Cell Physiol*. 2014;306(6):C585-C597.
26. Gorski JA, Gomez LL, Scott JD, Dell'Acqua ML. Association of an A-kinase-anchoring protein signaling scaffold with cadherin adhesion molecules in neurons and epithelial cells. *Mol Biol Cell*. 2005;16(8):3574-3590.
27. Rangarajan S, Enserink JM, Kuiperij HB, et al. Cyclic AMP induces integrin-mediated cell adhesion through Epac and Rap1 upon stimulation of the beta 2-adrenergic receptor. *J Cell Biol*. 2003;160(4):487-493.
28. Cullere X, Shaw SK, Andersson L, Hirahashi J, Luscinskas FW, Mayadas TN. Regulation of vascular endothelial barrier function by Epac, a cAMP-activated exchange factor for rap GTPase. *Blood*. 2005;105(5):1950-1955.
29. Kiermayer S, Biondi RM, Imig J, et al. Epac activation converts cAMP from a proliferative into a differentiation signal in PC12 cells. *Mol Biol Cell*. 2005;16(12):5639-5648.
30. Grando SA, Pittelkow MR, Schallreuter KU. Adrenergic and cholinergic control in the biology of epidermis: physiological and clinical significance. *J Invest Dermatol*. 2006;126(9):1948-1965.
31. Birukova AA, Burdette D, Moldobaeva N, Xing J, Fu P, Birukov KG. Rac GTPase is a hub for protein kinase A and Epac signaling in endothelial barrier protection by cAMP. *Microvasc Res*. 2010;79(2):128-138.
32. Gunduz D, Troidl C, Tanislav C, Rohrbach S, Hamm C, Aslam M. Role of PI3K/Akt and MEK/ERK Signalling in cAMP/Epac-mediated endothelial barrier stabilisation. *Front Physiol*. 2019;10:1387.
33. Bruce JI, Straub SV, Yule DI. Crosstalk between cAMP and Ca^{2+} signaling in non-excitable cells. *Cell Calcium*. 2003;34(6):431-444.
34. Michel CC, Curry FE. Microvascular permeability. *Physiol Rev*. 1999;79(3):703-761.
35. van Hinsbergh VW, van Nieuw Amerongen GP. Intracellular signalling involved in modulating human endothelial barrier function. *J Anat*. 2002;200(6):549-560.
36. Curry FR, Adamson RH. Tonic regulation of vascular permeability. *Acta Physiol*. 2013;207(4):628-649.
37. Waschke J, Drenckhahn D, Adamson RH, Curry FE. Role of adhesion and contraction in Rac 1-regulated endothelial barrier function in vivo and in vitro. *Am J Physiol Heart Circ Physiol*. 2004;287(2):H704-H711.
38. Majno G, Palade GE. Studies on inflammation. 1. The effect of histamine and serotonin on vascular permeability: an electron microscopic study. *J Biophys Biochem Cytol*. 1961;11(3):571-605.
39. Opal SM. The host response to endotoxin, antilipopolysaccharide strategies, and the management of severe sepsis. *Int J Med Microbiol*. 2007;297(5):365-377.
40. Dejana E, Tournier-Lasserve E, Weinstein BM. The control of vascular integrity by endothelial cell junctions: molecular basis and pathological implications. *Dev Cell*. 2009;16(2):209-221.
41. Opal SM, van der Poll T. Endothelial barrier dysfunction in septic shock. *J Intern Med*. 2015;277(3):277-293.
42. Komarova Y, Malik AB. Regulation of endothelial permeability via paracellular and transcellular transport pathways. *Annu Rev Physiol*. 2010;72:463-493.
43. Goldenberg NM, Steinberg BE, Slutsky AS, Lee WL. Broken barriers: a new take on sepsis pathogenesis. *Sci Transl Med*. 2011;3(88):88ps25.
44. Dejana E, Orsenigo F, Lampugnani MG. The role of adherens junctions and VE-cadherin in the control of vascular permeability. *J Cell Sci*. 2008;121(Pt 13):2115-2122.
45. Bazzoni G, Dejana E. Endothelial cell-to-cell junctions: molecular organization and role in vascular homeostasis. *Physiol Rev*. 2004;84(3):869-901.
46. Gonzalez-Mariscal L, Tapia R, Chamorro D. Crosstalk of tight junction components with signaling pathways. *Biochim Biophys Acta*. 2008;1778(3):729-756.

47. Waschke J, Curry FE, Adamson RH, Drenckhahn D. Regulation of actin dynamics is critical for endothelial barrier functions. *Am J Physiol Heart Circ Physiol*. 2005;288(3):H1296-H1305.
48. Koga S, Morris S, Ogawa S, et al. TNF modulates endothelial properties by decreasing cAMP. *Am J Physiol*. 1995;268(5 Pt 1):C1104-C1113.
49. Seybold J, Thomas D, Witzenrath M, et al. Tumor necrosis factor-alpha-dependent expression of phosphodiesterase 2: role in endothelial hyperpermeability. *Blood*. 2005;105(9):3569-3576.
50. Schlegel N, Baumer Y, Drenckhahn D, Waschke J. Lipopolysaccharide-induced endothelial barrier breakdown is cyclic adenosine monophosphate dependent in vivo and in vitro. *Crit Care Med*. 2009;37(5):1735-1743.
51. Schlegel N, Waschke J. Impaired cAMP and Rac 1 signaling contribute to TNF-alpha-induced endothelial barrier breakdown in microvascular endothelium. *Microcirculation*. 2009;16(6):521-533.
52. Langeler EG, van Hinsbergh VW. Norepinephrine and iloprost improve barrier function of human endothelial cell monolayers: role of cAMP. *Am J Physiol*. 1991;260(5 Pt 1):C1052-C1059.
53. Rubin LL, Hall DE, Porter S, et al. A cell culture model of the blood-brain barrier. *J Cell Biol*. 1991;115(6):1725-1735.
54. Wolburg H, Neuhaus J, Kniesel U, et al. Modulation of tight junction structure in blood-brain barrier endothelial cells. Effects of tissue culture, second messengers and cocultured astrocytes. *J Cell Sci*. 1994;107(Pt 5):1347-1357.
55. Grega GJ, Maciejko JJ, Raymond RM, Sak DP. The interrelationship among histamine, various vasoactive substances, and macromolecular permeability in the canine forelimb. *Circ Res*. 1980;46(2):264-275.
56. Suttorp N, Weber U, Welsch T, Schudt C. Role of phosphodiesterases in the regulation of endothelial permeability in vitro. *J Clin Invest*. 1993;91(4):1421-1428.
57. Sheldon R, Moy A, Lindsley K, Shasby S, Shasby DM. Role of myosin light-chain phosphorylation in endothelial cell retraction. *Am J Physiol*. 1993;265(6 Pt 1):L606-L612.
58. He P, Curry FE. Differential actions of cAMP on endothelial $[Ca^{2+}]i$ and permeability in microvessels exposed to ATP. *Am J Physiol*. 1993;265(3 Pt 2):H1019-H1023.
59. Baluk P, McDonald DM. The beta 2-adrenergic receptor agonist formoterol reduces microvascular leakage by inhibiting endothelial gap formation. *Am J Physiol*. 1994;266(4 Pt 1):L461-L468.
60. Barnard JW, Seibert AF, Prasad VR, et al. Reversal of pulmonary capillary ischemia-reperfusion injury by rolipram, a cAMP phosphodiesterase inhibitor. *J Appl Physiol*. 1994;77(2):774-781.
61. Garcia JG, Davis HW, Patterson CE. Regulation of endothelial cell gap formation and barrier dysfunction: role of myosin light chain phosphorylation. *J Cell Physiol*. 1995;163(3):510-522.
62. Seeger W, Hansen T, Rössig R, et al. Hydrogen peroxide-induced increase in lung endothelial and epithelial permeability—effect of adenylate cyclase stimulation and phosphodiesterase inhibition. *Microvasc Res*. 1995;50(1):1-17.
63. Carson MR, Shasby SS, Shasby DM. Histamine and inositol phosphate accumulation in endothelium: cAMP and a G protein. *Am J Physiol*. 1989;257(4 Pt 1):L259-L264.
64. Adamson RH, Zeng M, Adamson GN, Lenz JF, Curry FE. PAF- and bradykinin-induced hyperpermeability of rat venules is independent of actin-myosin contraction. *Am J Physiol Heart Circ Physiol*. 2003;285(1):H406-H417.
65. Casnocha SA, Eskin SG, Hall ER, McIntire LV. Permeability of human endothelial monolayers: effect of vasoactive agonists and cAMP. *J Appl Physiol*. 1989;67(5):1997-2005.
66. Spindler V, Waschke J. Beta-adrenergic stimulation contributes to maintenance of endothelial barrier functions under baseline conditions. *Microcirculation*. 2011;18(2):118-127.
67. Joo F, Rakonczay Z, Wollemann M. cAMP-mediated regulation of the permeability in the brain capillaries. *Experientia*. 1975;31(5):582-584.
68. Adamson RH, Liu B, Fry GN, Rubin LL, Curry FE. Microvascular permeability and number of tight junctions are modulated by cAMP. *Am J Physiol*. 1998;274(6):H1885-H1894.
69. He P, Zeng M, Curry FE. Dominant role of cAMP in regulation of microvessel permeability. *Am J Physiol Heart Circ Physiol*. 2000;278(4):H1124-H1133.
70. Rall TW, Sutherland EW. Formation of a cyclic adenine ribonucleotide by tissue particles. *J Biol Chem*. 1958;232(2):1065-1076.
71. Chen J, Levin LR, Buck J. Role of soluble adenylyl cyclase in the heart. *Am J Physiol Heart Circ Physiol*. 2012;302(3):H538-H543.
72. Maurice DH, Ke H, Ahmad F, Wang Y, Chung J, Manganiello VC. Advances in targeting cyclic nucleotide phosphodiesterases. *Nat Rev Drug Discov*. 2014;13(4):290-314.
73. Fertig BA, Baillie GS. PDE4-mediated cAMP signalling. *J Cardiovasc Dev Dis*. 2018;5(1):8.
74. Netherton SJ, Maurice DH. Vascular endothelial cell cyclic nucleotide phosphodiesterases and regulated cell migration: implications in angiogenesis. *Mol Pharmacol*. 2005;67(1):263-272.
75. Lugnier C. Cyclic nucleotide phosphodiesterase (PDE) superfamily: a new target for the development of specific therapeutic agents. *Pharmacol Ther*. 2006;109(3):366-398.
76. Mokra D, Mokry J. Phosphodiesterase inhibitors in acute lung injury: what are the perspectives? *Int J Mol Sci*. 2021;22(4):1929.
77. Sanz MJ, Cortijo J, Taha MA, et al. Roflumilast inhibits leukocyte-endothelial cell interactions, expression of adhesion molecules and microvascular permeability. *Br J Pharmacol*. 2007;152(4):481-492.
78. Schick MA, Wunder C, Wollborn J, et al. Phosphodiesterase-4 inhibition as a therapeutic approach to treat capillary leakage in systemic inflammation. *J Physiol*. 2012;590:2693-2708.
79. Flemming S, Schlegel N, Wunder C, et al. Phosphodiesterase 4 inhibition dose dependently stabilizes microvascular barrier functions and microcirculation in a rodent model of polymicrobial sepsis. *Shock*. 2014;41(6):537-545.
80. Schick MA, Schlegel N. Clinical implication of phosphodiesterase-4-inhibition. *Int J Mol Sci*. 2022;23(3):1209.
81. Zemskov EA, Wu X, Aggarwal S, et al. Nitration of protein kinase G-Ialpha modulates cyclic nucleotide crosstalk via phosphodiesterase 3A: implications for acute lung injury. *J Biol Chem*. 2021;297(2):100946.
82. Sayner SL, Frank DW, King J, Chen H, VandeWaa J, Stevens T. Paradoxical cAMP-induced lung endothelial hyperpermeability revealed by *Pseudomonas aeruginosa* ExoY. *Circ Res*. 2004;95(2):196-203.
83. Sayner SL, Alexeyev M, Dessauer CW, Stevens T. Soluble adenylyl cyclase reveals the significance of cAMP compartmentation on pulmonary microvascular endothelial cell barrier. *Circ Res*. 2006;98(5):675-681.
84. Fischmeister R. Is cAMP good or bad? Depends on where it's made. *Circ Res*. 2006;98(5):582-584.

85. Prasain N, Alexeyev M, Balczon R, Stevens T. Soluble adenylyl cyclase-dependent microtubule disassembly reveals a novel mechanism of endothelial cell retraction. *Am J Physiol Lung Cell Mol Physiol*. 2009;297(1):L73-L83.
86. Sayner SL. Emerging themes of cAMP regulation of the pulmonary endothelial barrier. *Am J Physiol Lung Cell Mol Physiol*. 2011;300(5):L667-L678.
87. Mewes M, Lenders M, Stappers F, et al. Soluble adenylyl cyclase (sAC) regulates calcium signaling in the vascular endothelium. *FASEB J*. 2019;33(12):13762-13774.
88. Dodge-Kafka KL, Soughayer J, Pare GC, et al. The protein kinase A anchoring protein mAKAP coordinates two integrated cAMP effector pathways. *Nature*. 2005;437(7058):574-578.
89. Houslay MD, Baillie GS, Maurice DH. cAMP-specific phosphodiesterase-4 enzymes in the cardiovascular system: a molecular toolbox for generating compartmentalized cAMP signaling. *Circ Res*. 2007;100(7):950-966.
90. Kritzer MD, Li J, Dodge-Kafka K, Kapiloff MS. AKAPs: the architectural underpinnings of local cAMP signaling. *J Mol Cell Cardiol*. 2012;52(2):351-358.
91. Viña D, Seoane N, Vasquez EC, Campos-Toimil M. cAMP compartmentalization in cerebrovascular endothelial cells: new therapeutic opportunities in Alzheimer's disease. *Cell*. 2021;10(8):1951.
92. Sayner SL, Choi CS, Maulucci ME, et al. Extracellular vesicles: another compartment for the second messenger, cyclic adenosine monophosphate. *Am J Physiol Lung Cell Mol Physiol*. 2019;316(4):L691-L700.
93. Hofer AM, Lefkimmiatis K. Extracellular calcium and cAMP: second messengers as "third messengers"? *Physiology (Bethesda)*. 2007;22:320-327.
94. Perrot CY, Sawada J, Komatsu M. Prolonged activation of cAMP signaling leads to endothelial barrier disruption via transcriptional repression of RRAS. *FASEB J*. 2018;32:5793-5812.
95. Stelzner TJ, Weil JV, O'Brien RF. Role of cyclic adenosine monophosphate in the induction of endothelial barrier properties. *J Cell Physiol*. 1989;139(1):157-166.
96. Lum H, Jaffe HA, Schulz IT, Masood A, RayChaudhury A, Green RD. Expression of PKA inhibitor (PKI) gene abolishes cAMP-mediated protection to endothelial barrier dysfunction. *Am J Physiol*. 1999;277(3):C580-C588.
97. Patterson CE, Lum H, Schaphorst KL, Verin AD, Garcia JN. Regulation of endothelial barrier function by the cAMP-dependent protein kinase. *Endothelium*. 2000;7(4):287-308.
98. Yuan SY. Protein kinase signaling in the modulation of microvascular permeability. *Vascul Pharmacol*. 2002;39(4–5):213-223.
99. Liu F, Verin AD, Borbiev T, Garcia JGN. Role of cAMP-dependent protein kinase A activity in endothelial cell cytoskeleton rearrangement. *Am J Physiol Lung Cell Mol Physiol*. 2001;280(6):L1309-L1317.
100. Suzuki S, Ando F, Kitagawa S, et al. ZNF185 prevents stress fiber formation through the inhibition of RhoA in endothelial cells. *Commun Biol*. 2023;6(1):29.
101. Qiao J, Huang F, Lum H. PKA inhibits RhoA activation: a protection mechanism against endothelial barrier dysfunction. *Am J Physiol Lung Cell Mol Physiol*. 2003;284(6):L972-L980.
102. Comerford KM, Lawrence DW, Synnestvedt K, Levi BP, Colgan SP. Role of vasodilator-stimulated phosphoprotein in PKA-induced changes in endothelial junctional permeability. *FASEB J*. 2002;16(6):583-585.
103. Schlegel N, Burger S, Golenhofen N, Walter U, Drenckhahn D, Waschke J. The role of VASP in regulation of cAMP- and Rac 1-mediated endothelial barrier stabilization. *Am J Physiol Cell Physiol*. 2008;294(1):C178-C188.
104. Schlegel N, Waschke J. VASP is involved in cAMP-mediated Rac 1 activation in microvascular endothelial cells. *Am J Physiol Cell Physiol*. 2009;296(3):C453-C462.
105. Schlegel N, Waschke J. Impaired integrin-mediated adhesion contributes to reduced barrier properties in VASP-deficient microvascular endothelium. *J Cell Physiol*. 2009;220(2):357-366.
106. Schlegel N, Waschke J. Vasodilator-stimulated phosphoprotein: crucial for activation of Rac1 in endothelial barrier maintenance. *Cardiovasc Res*. 2010;87(1):1-3.
107. Lorenowicz MJ, Fernandez-Borja M, Kooistra MRH, Bos JL, Hordijk PL. PKA and Epac1 regulate endothelial integrity and migration through parallel and independent pathways. *Eur J Cell Biol*. 2008;87(10):779-792.
108. Hippenstiel S, Tannert-Otto S, Vollrath N, et al. Glucosylation of small GTP-binding rho proteins disrupts endothelial barrier function. *Am J Physiol*. 1997;272(1 Pt 1):L38-L43.
109. Wojciak-Stothard B, Potempa S, Eichholtz T, Ridley AJ. Rho and Rac but not Cdc42 regulate endothelial cell permeability. *J Cell Sci*. 2001;114(Pt 7):1343-1355.
110. Wojciak-Stothard B, Ridley AJ. Rho GTPases and the regulation of endothelial permeability. *Vascul Pharmacol*. 2002;39(4–5):187-199.
111. Adamson RH, Curry FE, Adamson G, et al. Rho and rho kinase modulation of barrier properties: cultured endothelial cells and intact microvessels of rats and mice. *J Physiol*. 2002;539(Pt 1):295-308.
112. Waschke J, Baumgartner W, Adamson RH, et al. Requirement of Rac activity for maintenance of capillary endothelial barrier properties. *Am J Physiol Heart Circ Physiol*. 2004;286(1):H394-H401.
113. Waschke J, Drenckhahn D, Adamson RH, Barth H, Curry FE. cAMP protects endothelial barrier functions by preventing Rac-1 inhibition. *Am J Physiol Heart Circ Physiol*. 2004;287(6):H2427-H2433.
114. Baumer Y, Spindler V, Werthmann RC, Bünemann M, Waschke J. Role of Rac 1 and cAMP in endothelial barrier stabilization and thrombin-induced barrier breakdown. *J Cell Physiol*. 2009;220(3):716-726.
115. Birukova AA, Zagranichnaya T, Fu P, et al. Prostaglandins PGE(2) and PGI(2) promote endothelial barrier enhancement via PKA- and Epac1/Rap1-dependent Rac activation. *Exp Cell Res*. 2007;313(11):2504-2520.
116. Spindler V, Peter D, Harms GS, Asan E, Waschke J. Ultrastructural analysis reveals cAMP-dependent enhancement of microvascular endothelial barrier functions via Rac1-mediated reorganization of intercellular junctions. *Am J Pathol*. 2011;178(5):2424-2436.
117. Kopperud RK, Rygh CB, Karlsen TV, et al. Increased microvascular permeability in mice lacking Epac1 (RapGef3). *Acta Physiol (Oxf)*. 2016;219:441-452.
118. García-Ponce A, Schuster K, Døskeland SO, et al. Epac1 is crucial for maintenance of endothelial barrier function through a mechanism partly independent of Rac1. *Cell*. 2020;9(10):2170.
119. Ramos CJ, Lin C, Liu X, Antonetti DA. The EPAC-Rap1 pathway prevents and reverses cytokine-induced retinal vascular permeability. *J Biol Chem*. 2018;293(2):717-730.

120. Khan A, Ni W, Baltazar T, Lopez-Giraldez F, Pober JS, Pierce RW. ArhGEF12 activates Rap1A and not RhoA in human dermal microvascular endothelial cells to reduce tumor necrosis factor-induced leak. *FASEB J*. 2022;36(4):e22254.
121. Camillo C, Facchinello N, Villari G, et al. LPHN2 inhibits vascular permeability by differential control of endothelial cell adhesion. *J Cell Biol*. 2021;220(11):e202006033.
122. Ishizaki T, Chiba H, Kojima T, et al. Cyclic AMP induces phosphorylation of claudin-5 immunoprecipitates and expression of claudin-5 gene in blood-brain-barrier endothelial cells via protein kinase A-dependent and -independent pathways. *Exp Cell Res*. 2003;290(2):275-288.
123. Scalise AA, Kakogiannos N, Zanardi F, Iannelli F, Giannotta M. The blood-brain and gut-vascular barriers: from the perspective of claudins. *Tissue Barriers*. 2021;9(3):1926190.
124. Soma T, Chiba H, Kato-Mori Y, et al. Thr(207) of claudin-5 is involved in size-selective loosening of the endothelial barrier by cyclic AMP. *Exp Cell Res*. 2004;300(1):202-212.
125. He L, Lu H, Ji X, et al. Stimulatory G-protein alpha subunit modulates endothelial cell permeability through regulation of plasmalemma vesicle-associated protein. *Front Pharmacol*. 2022;13:941064.
126. Wilson CW, Ye W. Regulation of vascular endothelial junction stability and remodeling through Rap1-Rasip1 signaling. *Cell Adh Migr*. 2014;8(2):76-83.
127. Post A, Pannekoek WJ, Ross SH, Verlaan I, Brouwer PM, Bos JL. Rasip1 mediates Rap1 regulation of rho in endothelial barrier function through ArhGAP29. *Proc Natl Acad Sci U S A*. 2013;110(28):11427-11432.
128. de Kreuk BJ, Gingras AR, Knight JDR, Liu JJ, Gingras AC, Ginsberg MH. Heart of glass anchors Rasip1 at endothelial cell-cell junctions to support vascular integrity. *eLife*. 2016;5:e11394.
129. Wilson CW, Parker LH, Hall CJ, et al. Rasip1 regulates vertebrate vascular endothelial junction stability through Epac1-Rap1 signaling. *Blood*. 2013;122(22):3678-3690.
130. Ramos CJ, Antonetti DA. The role of small GTPases and EPAC-rap signaling in the regulation of the blood-brain and blood-retinal barriers. *Tissue Barriers*. 2017;5(3):e1339768.
131. Pannekoek WJ, Vliem MJ, Bos JL. Multiple Rap1 effectors control Epac1-mediated tightening of endothelial junctions. *Small GTPases*. 2020;11(5):346-353.
132. Fukuhara S, Sakurai A, Sano H, et al. Cyclic AMP potentiates vascular endothelial cadherin-mediated cell-cell contact to enhance endothelial barrier function through an Epac-Rap1 signaling pathway. *Mol Cell Biol*. 2005;25(1):136-146.
133. Kooistra MR, Corada M, Dejana E, Bos JL. Epac1 regulates integrity of endothelial cell junctions through VE-cadherin. *FEBS Lett*. 2005;579(22):4966-4972.
134. Wittchen ES, Worthylake RA, Kelly P, Casey PJ, Quilliam LA, Burridge K. Rap1 GTPase inhibits leukocyte transmigration by promoting endothelial barrier function. *J Biol Chem*. 2005;280(12):11675-11682.
135. Noda K, Zhang J, Fukuhara S, Kunimoto S, Yoshimura M, Mochizuki N. Vascular endothelial-cadherin stabilizes at cell-cell junctions by anchoring to circumferential actin bundles through alpha- and beta-catenins in cyclic AMP-Epac-Rap1 signal-activated endothelial cells. *Mol Biol Cell*. 2010;21(4):584-596.
136. Heupel WM, Efthymiadis A, Schlegel N, et al. Endothelial barrier stabilization by a cyclic tandem peptide targeting VE-cadherin transinteraction in vitro and in vivo. *J Cell Sci*. 2009;122(Pt 10):1616-1625.
137. Birukova AA, Tian Y, Dubrovskyi O, et al. VE-cadherin trans-interactions modulate Rac activation and enhancement of lung endothelial barrier by iloprost. *J Cell Physiol*. 2012;227(10):3405-3416.
138. Flemming S, Burkard N, Renschler M, et al. Soluble VE-cadherin is involved in endothelial barrier breakdown in systemic inflammation and sepsis. *Cardiovasc Res*. 2015;107(1):32-44.
139. Sehrawat S, Ernandez T, Cullere X, et al. AKAP9 regulation of microtubule dynamics promotes Epac1-induced endothelial barrier properties. *Blood*. 2011;117(2):708-718.
140. Bátori R, Kumar S, Bordán Z, et al. Differential mechanisms of adenosine- and ATPgammaS-induced microvascular endothelial barrier strengthening. *J Cell Physiol*. 2019;234(5):5863-5879.
141. Moztarzadeh S, Radeva MY, Sepic S, et al. Lack of adducin impairs the stability of endothelial adherens and tight junctions and may be required for cAMP-Rac1-mediated endothelial barrier stabilization. *Sci Rep*. 2022;12(1):14940.
142. Kugelmann D, Waschke J, Radeva MY. Adducin is involved in endothelial barrier stabilization. *PLoS ONE*. 2015;10(5):e0126213.
143. Schnoor M, Lai FPL, Zarbock A, et al. Cortactin deficiency is associated with reduced neutrophil recruitment but increased vascular permeability in vivo. *J Exp Med*. 2011;208(8):1721-1735.
144. Birukova AA, Zagranichnaya T, Alekseeva E, Bokoch GM, Birukov KG. Epac/rap and PKA are novel mechanisms of ANP-induced Rac-mediated pulmonary endothelial barrier protection. *J Cell Physiol*. 2008;215(3):715-724.
145. Birukova AA, Burdette D, Moldobaeva N, Xing J, Fu P, Birukov KG. Rac GTPase is a hub for protein kinase A and Epac signaling in endothelial barrier protection by cAMP. *Microvasc Res*. 2010;79(2):128-138.
146. Aslam M, Härtel FV, Arshad M, et al. cAMP/PKA antagonizes thrombin-induced inactivation of endothelial myosin light chain phosphatase: role of CPI-17. *Cardiovasc Res*. 2010;87(2):375-384.
147. Goeckeler ZM, Wysolmerski RB. Myosin phosphatase and cofilin mediate cAMP/cAMP-dependent protein kinase-induced decline in endothelial cell isometric tension and myosin II regulatory light chain phosphorylation. *J Biol Chem*. 2005;280(38):33083-33095.
148. Austin KM, Trembley MA, Chandler SF, et al. Molecular mechanisms of arrhythmogenic cardiomyopathy. *Nat Rev Cardiol*. 2019;16(9):519-537.
149. Corrado D, Basso C, Judge DP. Arrhythmogenic cardiomyopathy. *Circ Res*. 2017;121(7):784-802.
150. Schinner C, Xu L, Franz H, et al. Defective desmosomal adhesion causes arrhythmogenic cardiomyopathy by involving an integrin-alphaVbeta6/TGF-beta signaling cascade. *Circulation*. 2022;146(21):1610-1626.
151. Maione AS, Pilato CA, Casella M, et al. Fibrosis in arrhythmogenic cardiomyopathy: the phantom thread in the fibro-adipose tissue. *Front Physiol*. 2020;11:279.
152. Lorenzon A, Calore M, Poloni G, de Windt LJ, Braghetta P, Rampazzo A. Wnt/beta-catenin pathway in arrhythmogenic cardiomyopathy. *Oncotarget*. 2017;8(36):60640-60655.
153. Dubash AD, Kam CY, Aguado BA, et al. Plakophilin-2 loss promotes TGF-beta1/p38 MAPK-dependent fibrotic gene expression in cardiomyocytes. *J Cell Biol*. 2016;212(4):425-438.

154. Chen SN, Gurha P, Lombardi R, Ruggiero A, Willerson JT, Marian AJ. The hippo pathway is activated and is a causal mechanism for adipogenesis in arrhythmogenic cardiomyopathy. *Circ Res*. 2014;114(3):454-468.
155. Rouhi L, Fan S, Cheedipudi SM, et al. The EP300/TP53 pathway, a suppressor of the Hippo and canonical WNT pathways, is activated in human hearts with arrhythmogenic cardiomyopathy in the absence of overt heart failure. *Cardiovasc Res*. 2022;118(6):1466-1478.
156. Chelko SP, Asimaki A, Andersen P, et al. Central role for GSK3beta in the pathogenesis of arrhythmogenic cardiomyopathy. *JCI Insight*. 2016;1(5):e85923.
157. Chelko SP, Asimaki A, Lowenthal J, et al. Therapeutic modulation of the immune response in arrhythmogenic cardiomyopathy. *Circulation*. 2019;140(18):1491-1505.
158. Smith ED, Lakdawala NK, Papoutsidakis N, et al. Desmoplakin cardiomyopathy, a fibrotic and inflammatory form of cardiomyopathy distinct from typical dilated or arrhythmogenic right ventricular cardiomyopathy. *Circulation*. 2020;141(23):1872-1884.
159. Asimaki A, Tandri H, Duffy ER, et al. Altered desmosomal proteins in granulomatous myocarditis and potential pathogenic links to arrhythmogenic right ventricular cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2011;4(5):743-752.
160. Kam CY, Dubash AD, Magistrati E, et al. Desmoplakin maintains gap junctions by inhibiting Ras/MAPK and lysosomal degradation of connexin-43. *J Cell Biol*. 2018;217(9):3219-3235.
161. Lyons KS, Dixon LJ, Johnston N, et al. Late gadolinium enhancement is common in patients with hypertrophic cardiomyopathy and no clinical risk factors for sudden cardiac death: a single center experience. *Cardiol J*. 2014;21(1):29-32.
162. Wang Y, Li C, Shi L, et al. Integrin beta1D deficiency-mediated RyR2 dysfunction contributes to catecholamine-sensitive ventricular tachycardia in Arrhythmogenic right ventricular cardiomyopathy. *Circulation*. 2020;141(18):1477-1493.
163. Veeraraghavan R, Hoeker GS, Alvarez-Laviada A, et al. The adhesion function of the sodium channel beta subunit (beta1) contributes to cardiac action potential propagation. *eLife*. 2018;7:e37610.
164. Corrado D, Wichter T, Link MS, et al. Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement. *Circulation*. 2015;132(5):441-453.
165. Marcus GM, Glidden DV, Polonsky B, et al. Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: a report from the north American ARVC registry. *J Am Coll Cardiol*. 2009;54(7):609-615.
166. Schlipp A, Schinner C, Spindler V, et al. Desmoglein-2 interaction is crucial for cardiomyocyte cohesion and function. *Cardiovasc Res*. 2014;104(2):245-257.
167. Schinner C, Vielmuth F, Rötzer V, et al. Adrenergic signaling strengthens cardiac myocyte cohesion. *Circ Res*. 2017;120(8):1305-1317.
168. Yeruva S, Kempf E, Egu DT, Flaswinkel H, Kugelmann D, Waschke J. Adrenergic signaling-induced ultrastructural strengthening of intercalated discs via plakoglobin is crucial for positive adhesiotropy in murine cardiomyocytes. *Front Physiol*. 2020;11:430.
169. Schinner C, Olivares-Florez S, Schlipp A, et al. The inotropic agent digitoxin strengthens desmosomal adhesion in cardiac myocytes in an ERK1/2-dependent manner. *Basic Res Cardiol*. 2020;115(4):46.
170. Broussard JA, Getsios S, Green KJ. Desmosome regulation and signaling in disease. *Cell Tissue Res*. 2015;360(3):501-512.
171. Schinner C, Erber BM, Yeruva S, Waschke J. Regulation of cardiac myocyte cohesion and gap junctions via desmosomal adhesion. *Acta Physiol (Oxf)*. 2019;226(2):e13242.
172. Schinner C, Erber BM, Yeruva S, et al. Stabilization of desmoglein-2 binding rescues arrhythmia in arrhythmogenic cardiomyopathy. *JCI Insight*. 2020;5(9):e130141.
173. Agullo-Pascual E, Reid DA, Keegan S, et al. Super-resolution fluorescence microscopy of the cardiac connexome reveals plakophilin-2 inside the connexin43 plaque. *Cardiovasc Res*. 2013;100(2):231-240.
174. Kim JC, Pérez-Hernández M, Alvarado FJ, et al. Disruption of Ca(2+)(i) homeostasis and connexin 43 hemichannel function in the right ventricle precedes overt arrhythmogenic cardiomyopathy in plakophilin-2-deficient mice. *Circulation*. 2019;140(12):1015-1030.
175. Leo-Macias A, Agullo-Pascual E, Sanchez-Alonso JL, et al. Nanoscale visualization of functional adhesion/excitability nodes at the intercalated disc. *Nat Commun*. 2016;7:10342.
176. Patel DM, Dubash AD, Kreitzer G, Green KJ. Disease mutations in desmoplakin inhibit Cx43 membrane targeting mediated by desmoplakin-EB1 interactions. *J Cell Biol*. 2014;206(6):779-797.
177. Sato PY, Coombs W, Lin X, et al. Interactions between ankyrin-G, plakophilin-2, and connexin 43 at the cardiac intercalated disc. *Circ Res*. 2011;109(2):193-201.
178. Cerrone M, Lin X, Zhang M, et al. Missense mutations in plakophilin-2 cause sodium current deficit and associate with a Brugada syndrome phenotype. *Circulation*. 2014;129(10):1092-1103.
179. Rizzo S, Lodder EM, Verkerk AO, et al. Intercalated disc abnormalities, reduced Na(+) current density, and conduction slowing in desmoglein-2 mutant mice prior to cardiomyopathic changes. *Cardiovasc Res*. 2012;95(4):409-418.
180. Sato PY, Musa H, Coombs W, et al. Loss of plakophilin-2 expression leads to decreased sodium current and slower conduction velocity in cultured cardiac myocytes. *Circ Res*. 2009;105(6):523-526.
181. Xie W, Gao S, Yang Y, et al. CYLD deubiquitinates plakoglobin to promote Cx43 membrane targeting and gap junction assembly in the heart. *Cell Rep*. 2022;41(13):111864.
182. Shoykhet M, Trenz S, Kempf E, et al. Cardiomyocyte adhesion and hyperadhesion differentially require ERK1/2 and plakoglobin. *JCI Insight*. 2020;5(18):e140066.
183. Egu DT, Schmitt T, Waschke J. Mechanisms causing acantholysis in pemphigus-lessons from human skin. *Front Immunol*. 2022;13:884067.
184. Yeruva S, Körber L, Hiermaier M, Egu DT, Kempf E, Waschke J. Cholinergic signaling impairs cardiomyocyte cohesion. *Acta Physiol (Oxf)*. 2022;236(3):e13881.
185. Samuelov L, Sprecher E, Paus R. The role of P-cadherin in skin biology and skin pathology: lessons from the hair follicle. *Cell Tissue Res*. 2015;360(3):761-771.
186. Rübsam M, Broussard JA, Wickström SA, Nekrasova O, Green KJ, Niessen CM. Adherens junctions and desmosomes coordinate mechanics and signaling to orchestrate tissue morphogenesis and function: an evolutionary perspective. *Cold Spring Harb Perspect Biol*. 2018;10(11):a029207.

187. Delva E, Tucker DK, Kowalczyk AP. The desmosome. *Cold Spring Harb Perspect Biol*. 2009;1(2):a002543.
188. Simard M, Morin S, Rioux G, Séguin R, Loing E, Pouliot R. A tissue-engineered human psoriatic skin model to investigate the implication of cAMP in psoriasis: differential impacts of cholera toxin and isoproterenol on cAMP levels of the epidermis. *Int J Mol Sci*. 2020;21(15):5215.
189. Takahashi H, Kinouchi M, Tamura T, Ishida-Yamamoto A, Iizuka H. Adenylate cyclases in keratinocytes: FRSK cells express types I, II, III, IV, VI and VIII, and 1,25(OH)2D3, retinoic acid and TPA augment forskolin-induced cyclic AMP accumulation in the absence of altered isozyme expression. *Arch Dermatol Res*. 1998;290(8):407-412.
190. Tenor H, Hatzelmann A, Wendel A, Schudt C. Identification of phosphodiesterase IV activity and its cyclic adenosine monophosphate-dependent up-regulation in a human keratinocyte cell line (HaCaT). *J Invest Dermatol*. 1995;105(1):70-74.
191. Steinkraus V, Mak JCW, Pichlmeier U, Mensing H, Ring J, Barnes PJ. Autoradiographic mapping of beta-adrenoceptors in human skin. *Arch Dermatol Res*. 1996;288(9):549-553.
192. Mitev V, Miteva L. Signal transduction in keratinocytes. *Exp Dermatol*. 1999;8(2):96-108.
193. Pullar CE, Isseroff RR. Cyclic AMP mediates keratinocyte directional migration in an electric field. *J Cell Sci*. 2005;118(Pt 9):2023-2034.
194. Denda M, Fuziwara S, Inoue K. Beta2-adrenergic receptor antagonist accelerates skin barrier recovery and reduces epidermal hyperplasia induced by barrier disruption. *J Invest Dermatol*. 2003;121(1):142-148.
195. Santibanez JF, Olivares D, Guerrero J, Martínez J. Cyclic AMP inhibits TGFbeta1-induced cell-scattering and invasiveness in murine-transformed keratinocytes. *Int J Cancer*. 2003;107(5):715-720.
196. Jeanes A, Gottardi CJ, Yap AS. Cadherins and cancer: how does cadherin dysfunction promote tumor progression? *Oncogene*. 2008;27(55):6920-6929.
197. Schmidt E, Kasperkiewicz M, Joly P. Pemphigus. *Lancet*. 2019;394(10201):882-894.
198. Spindler V, Waschke J. Pemphigus-a disease of desmosome dysfunction caused by multiple mechanisms. *Front Immunol*. 2018;9:136.
199. Schlögl E, Radeva MY, Vielmuth F, Schinner C, Waschke J, Spindler V. Keratin retraction and desmoglein3 internalization independently contribute to autoantibody-induced cell dissociation in pemphigus vulgaris. *Front Immunol*. 2018;9:858.
200. Sokol E, Kramer D, Diercks GFH, et al. Large-scale electron microscopy maps of patient skin and mucosa provide insight into pathogenesis of blistering diseases. *J Invest Dermatol*. 2015;135(7):1763-1770.
201. Diercks GF, Pas HH, Jonkman MF. The ultrastructure of acantholysis in pemphigus vulgaris. *Br J Dermatol*. 2009;160(2):460-461.
202. Kasperkiewicz M, Ellebrecht CT, Takahashi H, et al. Pemphigus. *Nat Rev Dis Primers*. 2017;3:17026.
203. Burmester IAK, Flaswinkel S, Thies CS, et al. Identification of novel therapeutic targets for blocking acantholysis in pemphigus. *Br J Pharmacol*. 2020;177(22):5114-5130.
204. Spindler V, Eming R, Schmidt E, et al. Mechanisms causing loss of keratinocyte cohesion in pemphigus. *J Invest Dermatol*. 2018;138(1):32-37.
205. Berkowitz P, Hu P, Liu Z, et al. Desmosome signaling. Inhibition of p38MAPK prevents pemphigus vulgaris IgG-induced cytoskeleton reorganization. *J Biol Chem*. 2005;280(25):23778-23784.
206. Berkowitz P, Diaz LA, Hall RP, Rubenstein DS. Induction of p38MAPK and HSP27 phosphorylation in pemphigus patient skin. *J Invest Dermatol*. 2008;128(3):738-740.
207. Egu DT, Walter E, Spindler V, Waschke J. Inhibition of p38MAPK signalling prevents epidermal blistering and alterations of desmosome structure induced by pemphigus autoantibodies in human epidermis. *Br J Dermatol*. 2017;177(6):1612-1618.
208. Chernyavsky AI, Arredondo J, Kitajima Y, Sato-Nagai M, Grando SA. Desmoglein versus non-desmoglein signaling in pemphigus acantholysis: characterization of novel signaling pathways downstream of pemphigus vulgaris antigens. *J Biol Chem*. 2007;282(18):13804-13812.
209. Kugelmann D, Rötzer V, Walter E, et al. Role of Src and cortactin in pemphigus skin blistering. *Front Immunol*. 2019;10:626.
210. Seishima M, Esaki C, Osada K, Mori S, Hashimoto T, Kitajima Y. Pemphigus IgG, but not bullous pemphigoid IgG, causes a transient increase in intracellular calcium and inositol 1,4,5-triphosphate in DJM-1 cells, a squamous cell carcinoma line. *J Invest Dermatol*. 1995;104(1):33-37.
211. Schmitt T, Egu DT, Walter E, et al. Ca(2+) signalling is critical for autoantibody-induced blistering of human epidermis in pemphigus. *Br J Dermatol*. 2021;185:595-604.
212. Frušić-Zlotkin M, Raichenberg D, Wang X, et al. Apoptotic mechanism in pemphigus autoimmunoglobulins-induced acantholysis—possible involvement of the EGF receptor. *Autoimmunity*. 2006;39(7):563-575.
213. Walter E, Vielmuth F, Rotkopf L, et al. Different signaling patterns contribute to loss of keratinocyte cohesion dependent on autoantibody profile in pemphigus. *Sci Rep*. 2017;7(1):3579.
214. Schmitt T, Waschke J. Autoantibody-specific signalling in pemphigus. *Front Med (Lausanne)*. 2021;8:701809.
215. Sajda T, Sinha AA. Autoantibody signaling in pemphigus vulgaris: development of an integrated model. *Front Immunol*. 2018;9:692.
216. Spindler V, Vielmuth F, Schmidt E, Rubenstein DS, Waschke J. Protective endogenous cyclic adenosine 5′-monophosphate signaling triggered by pemphigus autoantibodies. *J Immunol*. 2010;185(11):6831-6838.
217. Mammone T, Marenus K, Maes D, Lockshin RA. The induction of terminal differentiation markers by the cAMP pathway in human HaCaT keratinocytes. *Skin Pharmacol Appl Skin Physiol*. 1998;11(3):152-160.
218. Takahashi H, Kinouchi M, Tamura T, Iizuka H. Decreased beta 2-adrenergic receptor-mRNA and loricrin-mRNA, and increased involucrin-mRNA transcripts in psoriatic epidermis: analysis by reverse transcription-polymerase chain reaction. *Br J Dermatol*. 1996;134(6):1065-1069.
219. Hatemi G, Mahr A, Ishigatsubo Y, et al. Trial of apremilast for oral ulcers in Behcet's syndrome. *N Engl J Med*. 2019;381(20):1918-1928.
220. Rodríguez-Carrio J, Nucera V, Masala IF, Atzeni F. Behcet disease: from pathogenesis to novel therapeutic options. *Pharmacol Res*. 2021;167:105593.
221. Chimenti MS, Gramiccia T, Saraceno R, et al. Apremilast for the treatment of psoriasis. *Expert Opin Pharmacother*. 2015;16(13):2083-2094.

222. Keating GM. Apremilast: a review in psoriasis and psoriatic arthritis. *Drugs*. 2017;77(4):459-472.
223. Pincelli C, Schafer PH, French LE, Augustin M, Krueger JG. Mechanisms underlying the clinical effects of apremilast for psoriasis. *J Drugs Dermatol*. 2018;17(8):835-840.
224. Sigmund AM, Winkler M, Engelmayer S, et al. Apremilast prevents blistering in human epidermis and stabilizes keratinocyte adhesion in pemphigus. *Nat Commun*. 2023;14(1):116.
225. Meier K, Holstein J, Solimani F, Waschke J, Ghoreschi K. Case report: apremilast for therapy-resistant pemphigus vulgaris. *Front Immunol*. 2020;11:588315.
226. Sigmund AM, Winkler M, Engelmayer S, et al. Author correction: apremilast prevents blistering in human epidermis and stabilizes keratinocyte adhesion in pemphigus. *Nat Commun*. 2023;14(1):665.
227. Jolly PS, Berkowitz P, Bektas M, et al. p38MAPK signaling and desmoglein-3 internalization are linked events in pemphigus acantholysis. *J Biol Chem*. 2010;285(12):8936-8941.
228. Qi XF, Kim DH, Yoon YS, et al. The adenylyl cyclase-cAMP system suppresses TARC/CCL17 and MDC/CCL22 production through p38 MAPK and NF-kappaB in HaCaT keratinocytes. *Mol Immunol*. 2009;46(10):1925-1934.
229. Mehta H, Sharma A, Dogra S. Evolving utility of apremilast in dermatological disorders for off-label indications. *Clin Exp Dermatol*. 2022;47(12):2136-2149.
230. Zhang X, Mao X, Theresia C, et al. Pemphigus associated with psoriasis vulgaris: a retrospective study of seven patients and a review of the literature. *Acta Dermatovenerol Croat*. 2018;26(3):226-232.
231. Balighi K, Daneshpazhooh M, Mahmoudi H, Tavakolpour S. Switching from pemphigus vulgaris to psoriasis: a rare report of three cases. *Int J Dermatol*. 2020;59:e144-e146.
232. Kridin K, Ludwig RJ, Damiani G, Cohen AD. Increased risk of pemphigus among patients with psoriasis: a large-scale cohort study. *Acta Derm Venereol*. 2020;100(17):adv00293.
233. Albrecht LV, Zhang L, Shabanowitz J, et al. GSK3- and PRMT-1-dependent modifications of desmoplakin control desmoplakin-cytoskeleton dynamics. *J Cell Biol*. 2015;208(5):597-612.
234. Hobbs RP, Green KJ. Desmoplakin regulates desmosome hyperadhesion. *J Invest Dermatol*. 2012;132(2):482-485.
235. Dehner C, Rötzer V, Waschke J, Spindler V. A desmoplakin point mutation with enhanced keratin association ameliorates pemphigus vulgaris autoantibody-mediated loss of cell cohesion. *Am J Pathol*. 2014;184(9):2528-2536.
236. Spindler V, Endlich A, Hartlieb E, Vielmuth F, Schmidt E, Waschke J. The extent of desmoglein 3 depletion in pemphigus vulgaris is dependent on Ca(2+)-induced differentiation: a role in suprabasal epidermal skin splitting? *Am J Pathol*. 2011;179(4):1905-1916.
237. Rietscher K, Jahnke HG, Rübsam M, et al. Kinase inhibition by PKC412 prevents epithelial sheet damage in autosomal dominant epidermolysis bullosa simplex through keratin and cell contact stabilization. *J Invest Dermatol*. 2022;142(12):3282-3293.
238. Bartle EI, Rao TC, Beggs RR, et al. Protein exchange is reduced in calcium-independent epithelial junctions. *J Cell Biol*. 2020;219(6):e201906153.
239. Nanavati BN, Noordstra I, Verma S, Duszyc K, Green KJ, Yap AS. Desmosome-anchored intermediate filaments facilitate tension-sensitive RhoA signaling for epithelial homeostasis. *bioRxiv*. 2023.
240. Waschke J, Spindler V, Bruggeman P, Zillikens D, Schmidt G, Drenckhahn D. Inhibition of rho a activity causes pemphigus skin blistering. *J Cell Biol*. 2006;175(5):721-727.
241. Spindler V, Drenckhahn D, Zillikens D, Waschke J. Pemphigus IgG causes skin splitting in the presence of both desmoglein 1 and desmoglein 3. *Am J Pathol*. 2007;171(3):906-916.
242. Kugelmann D, Anders M, Sigmund AM, et al. Role of ADAM10 and ADAM17 in the regulation of keratinocyte adhesion in pemphigus vulgaris. *Front Immunol*. 2022;13:884248.
243. Shoykhet M, Dervishi O, Menauer P, et al. EGFR inhibition leads to enhanced desmosome assembly and cardiomyocyte cohesion via ROCK activation. *JCI Insight*. 2023;8(6):e163763.
244. Shoykhet M, Waschke J, Yeruva S. Cardiomyocyte cohesion is increased after ADAM17 inhibition. *Front Cell Dev Biol*. 2023;11:1021595.
245. Crawford AT, Desai D, Gokina P, Basak S, Kim HA. E-cadherin expression in postnatal Schwann cells is regulated by the cAMP-dependent protein kinase A pathway. *Glia*. 2008;56(15):1637-1647.
246. Guo L, Moon C, Niehaus K, Zheng Y, Ratner N. Rac1 controls Schwann cell myelination through cAMP and NF2/merlin. *J Neurosci*. 2012;32(48):17251-17261.
247. Pon YL, Auersperg N, Wong AS. Gonadotropins regulate N-cadherin-mediated human ovarian surface epithelial cell survival at both post-translational and transcriptional levels through a cyclic AMP/protein kinase A pathway. *J Biol Chem*. 2005;280(15):15438-15448.
248. Liu M, Chen X, Chang QX, et al. Decidual small extracellular vesicles induce trophoblast invasion by upregulating N-cadherin. *Reproduction*. 2020;159(2):171-180.
249. Ng YH, Zhu H, Leung PC. Twist regulates cadherin-mediated differentiation and fusion of human trophoblastic cells. *J Clin Endocrinol Metab*. 2011;96(12):3881-3890.
250. Chen W, Ye S, Wang X, Qian J, Xia L, Tian Z. Soluble E-cadherin promotes invasiveness of neoplastic cells in salivary gland carcinoma ex pleomorphic adenoma. *J Oral Pathol Med*. 2023;52(1):63-71.
251. Grandoch M, Rose A, ter Braak M, et al. Epac inhibits migration and proliferation of human prostate carcinoma cells. *Br J Cancer*. 2009;101(12):2038-2042.
252. Zhang B, Hu Q, Zhang J, et al. Silencing of A-kinase anchor protein 4 inhibits the metastasis and growth of non-small cell lung cancer. *Bioengineered*. 2022;13(3):6895-6907.

How to cite this article: Vielmuth F, Radeva MY, Yeruva S, Sigmund AM, Waschke J. cAMP: A master regulator of cadherin-mediated binding in endothelium, epithelium and myocardium. *Acta Physiol*. 2023;238:e14006. doi:10.1111/apha.14006