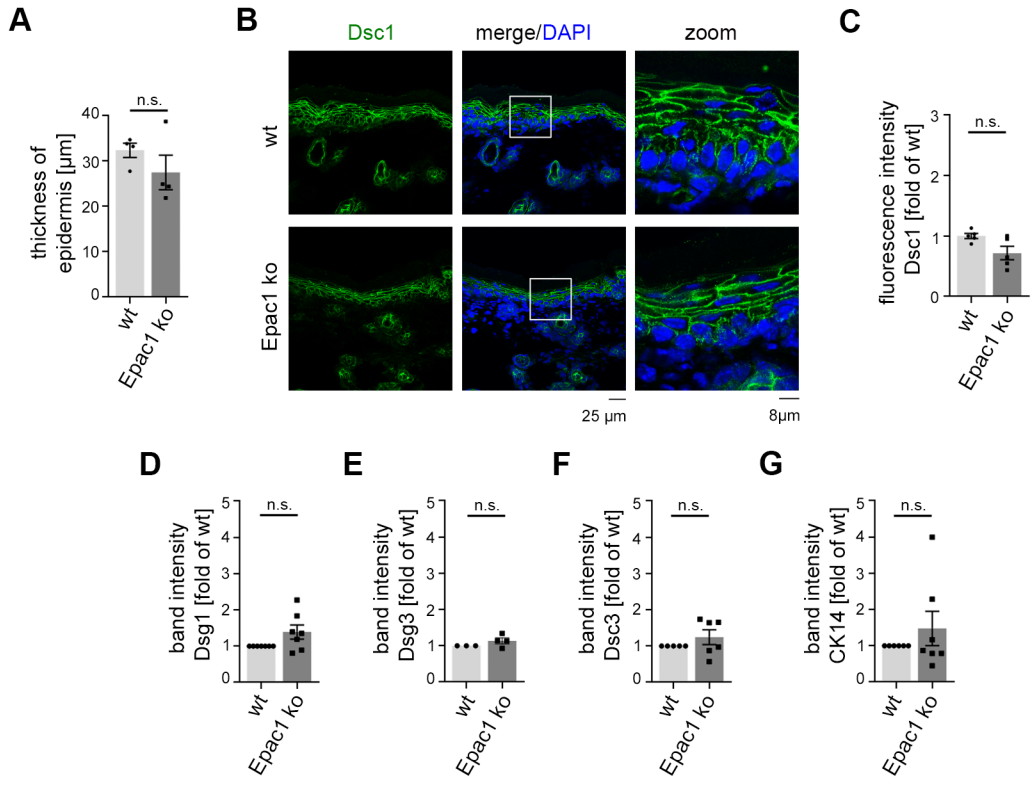


**Fig. S1: Epac1 ko epidermis shows no alterations.**

**A** Quantification of thickness of epidermis depicted in Fig.1 (n=4). Fluorescence staining (**B**) and quantification (**C**) of Dsc1 in murine epidermis showed no difference between wt and Epac1 mice (representative of n>4). (**D-G**) Quantifications of Western blots shown in Fig.2. Bars indicate mean value ±SEM. *P < 0.05. Two-tailed Student's t test.

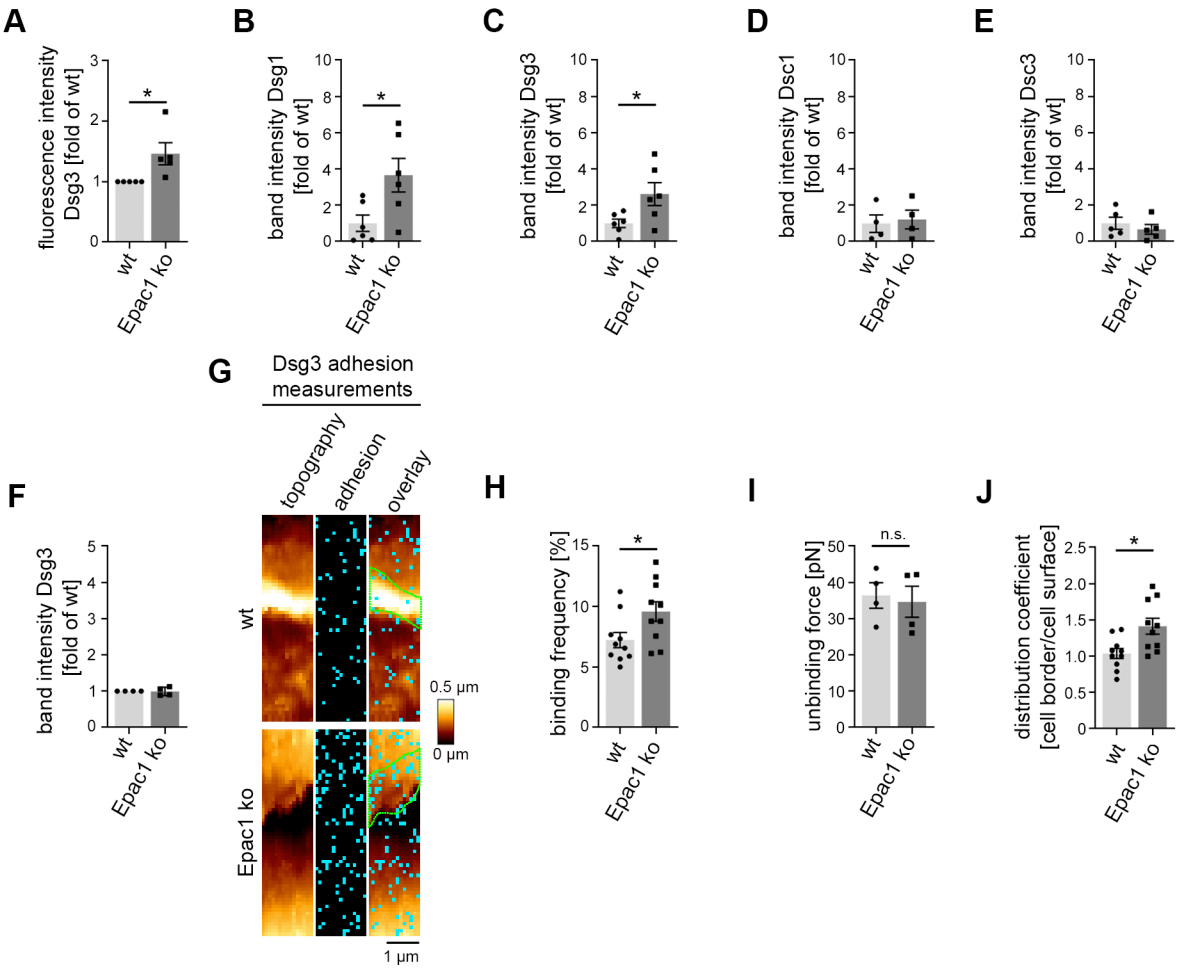


**Fig. S2: Desmosomal proteins are upregulated in Epac1 ko keratinocytes.**
Quantification of fluorescence intensities of Dsg3 immunofluorescence (**A**) and band intensities of Western blots of Triton insoluble fractions of wt and Epac1 ko keratinocytes depicted in Fig.1 (**B-E**). **F** Quantification of band intensity of Dsg3 PCR, normalized to the loading control GAPDH. **G** Topography and adhesion images of atomic force microscopy (AFM) measurements on living keratinocytes using a Dsg3-functionalized tips. Each pixel represents a force-distance-curve. In the adhesion panel each blue pixel represents a Dsg3-specific binding event. **H-J** Quantification of AFM adhesion measurements. Epac1 ko cells displayed higher Dsg3 binding frequencies (**H**) with unaltered unbinding forces (**I**) and enhanced number of binding events at cell borders (**J**) compared to wt cells. Cell borders are marked in green (10 cell borders from 4-5 independent experiments with 900 force-distance curves/ cell border). Bars indicate mean value ±SEM. *P < 0.05. Two-tailed Student's t test.

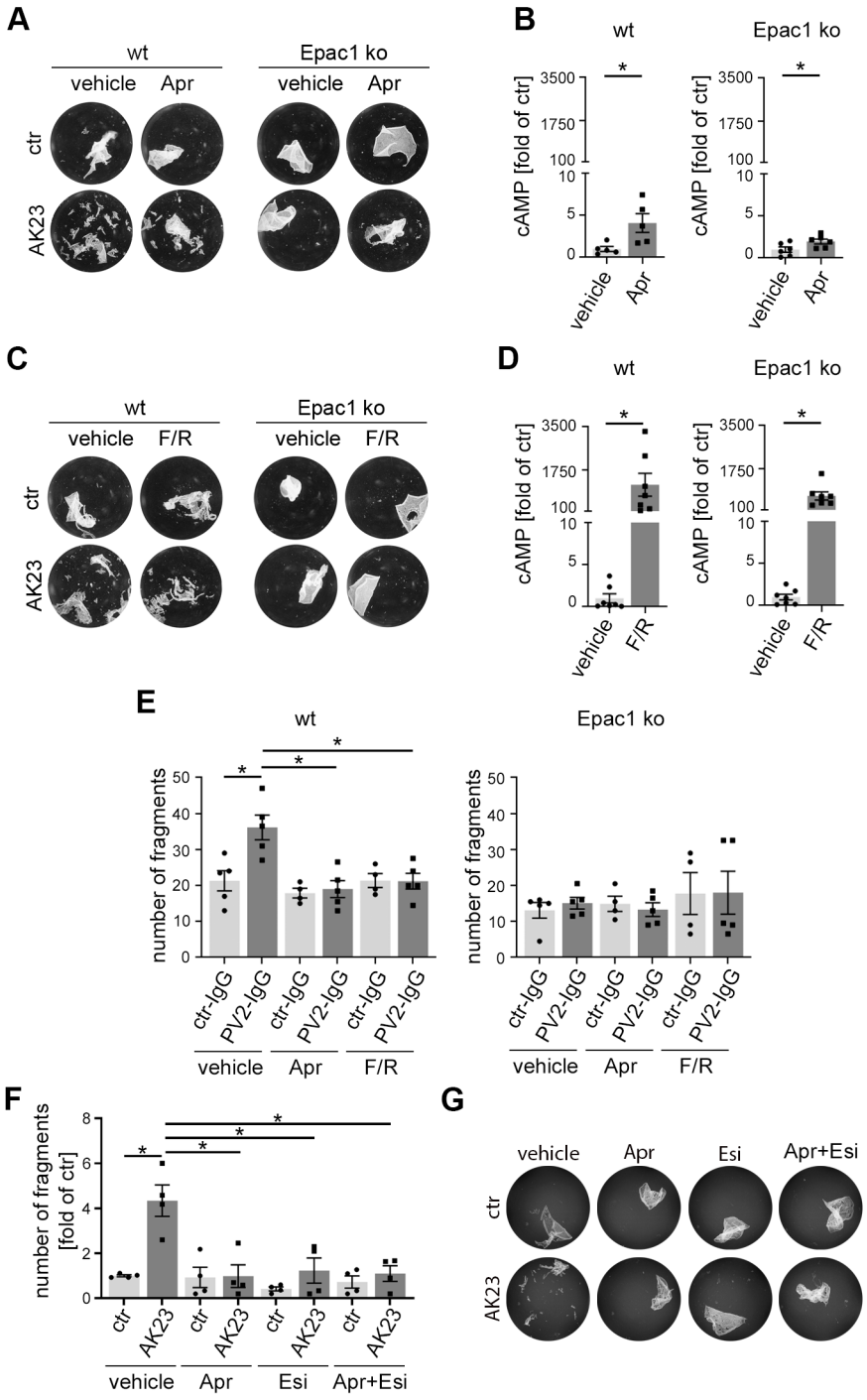


**Fig. S3: Apremilast induces cAMP in Epac1 ko keratinocytes and cells with impaired Epac1 showed increased intercellular adhesion.**

**A, C** Representative pictures of keratinocyte assays presented in Fig. 3A. **B, D** cAMP ELISA of wt and Epac1 ko keratinocytes after incubation with apremilast (Apr) or forskolin/rolipram (F/R), respectively (n>5). **E** Keratinocyte dissociation assays of wt or Epac1 ko keratinocytes revealed no loss of adhesion of Epac1 ko cells after treatment with PV2-IgG. Neither Apr nor F/R affected cell adhesion of Epac1 ko cells (n>4). **F** Inhibition of Epac1 by Esi-09 improved intercellular adhesion upon AK23 treatment, which could not be further enhanced by addition of Apr (n=4). **G** Representative pictures of keratinocyte assays of F. Bars indicate mean value ±SEM. *P < 0.05. Two-tailed Student's t test (B, D). Two-way ANOVA with Bonferroni correction (E, F). Pemphigus vulgaris IgG (PV-IgG), IgG of healthy volunteers (ctr-IgG)

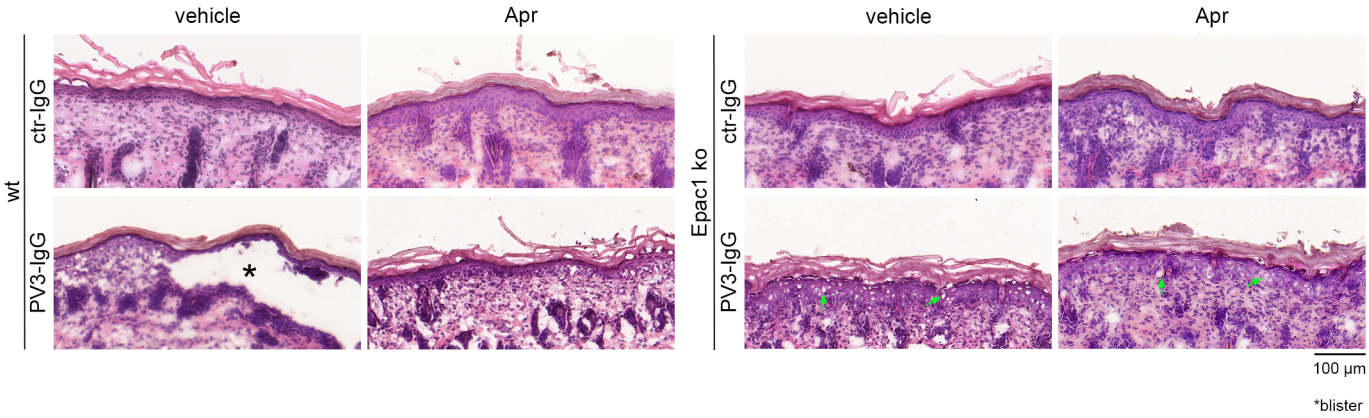


**Fig. S4: Apremilast does not further enhance improved cell cohesion of Epac1 ko mice in the pemphigus mouse model.**

H.&E.-staining of epidermis of the pemphigus mouse model after injection of vehicle or apremilast (Apr) prior to injection of PV3-IgG or ctr-IgG. PV-IgG induced suprabasal blistering of wt epidermis, which was rescued by apremilast. Micro-blisters in Epac1 ko epidermis (marked with green arrows) were not improved by apremilast (representative of n>3). Pemphigus vulgaris IgG (PV-IgG), IgG of healthy volunteers (ctr-IgG)

**Supplemental Table 1: Antibodies**

| Antibody | Species | Company | Dilution |
|---|---|---|---|
| **anti-Dsg1** | mouse | Santa cruz, Dallas, USA | 1:1000 (WB)<br>1:100 (IF) |
| **anti-Dsg2** | rabbit | Abbexa, Cambridge, UK | 1:1000 (WB |
| **anti-Dsg3** | rabbit | Biozol, Eching, Germany | 1:1000 (WB)<br>1:100 (IF) |
| **anti-Dsg3 (AK18)** | mouse | MBL, Schaumburg, USA | 1:1000 (WB)<br>1:100 (IF) |
| **anti-Dsc1** | rabbit | Abcam, Cambridge, UK | 1:1000 (WB)<br>1:100 (IF) |
| **anti-Dsc3** | rabbit | Progen, Heidelberg, Germany | 1:1000 (WB)<br>1:100 (IF) |
| **anti-Dp** | rabbit | Abclonal, Woburn, USA | 1:1000 (WB)<br>1:100 (IF) |
| **anti-α-Tubulin** | mouse | Abcam, Cambridge, UK | 1:1000 (WB) |
| **anti-GAPDH** | mouse | AviaSysBio, San Diego, USA | 1:1000 (WB) |
| **anti-Epac1** | rabbit | Abbexa, Cambridge, UK | 1:1000 (WB) |
| **anti-P-Dp (S2849)** | rabbit | Gift of K. J. Green, Chicago, USA | 1:1000 (WB) |
| **anti-P-Dp (S165)** | rabbit | Cell signaling, Leiden, Netherlands | 1:1000 (WB) |
| **anti-p-Pg** | mouse | Yeruva, Kempf et al. 2020 | 1:10 (WB) |
| **anti-Pg** | mouse | Progen, Heidelberg, Germany | 1:1000 (WB) |
| **anti-CK14** | mouse | Abcam, Cambridge, UK | 1:1000 (WB)<br>1:100 (IF) |

Yeruva, S., E. Kempf, D. T. Egu, H. Flaswinkel, D. Kugelmann and J. Waschke (2020). "Adrenergic Signaling-Induced Ultrastructural Strengthening of Intercalated Discs via Plakoglobin Is Crucial for Positive Adhesiotropy in Murine Cardiomyocytes." Front Physiol **11**: 430.

**Supplemental Table 2: Primers used for PCR analysis**

| Target analyzed | 5'-> 3' | Amplicon size (bp) |
|---|---|---|
| **Mouse Dsg1** | FW: ACTGTGTTAAATGTCATCGAGGG<br>REV: TGCCTGTTCTTGAGTCAACAAC | 198 |
| **Mouse Dsg3** | FW: CAGCCATAGTTGATCGTGAGG<br>REV: ATCTGCATCCGTGGCATTTAG | 221 |
| **Mouse Epac1** | FW: CAGGTCAGCGTACGGATGAAGAAC<br>REV: GCTTCCACATCCTTGATGATGCG | 378 |
| **Mouse Epac2** | FW: ATCTACGACGAGCTCCTTCATATTAAA<br>REV: GACTACATTCACGGATCCTTTCAGA | 176 |
| **Mouse GAPDH** | FW: GTCATCATCTCCGCCCCTTCTGC<br>REV: GATGCCTGCTTCACCACCTTCTTG | 443 |
| **Mouse Dsg3** | FW: GCTGCCTCCTCTGTCAGATATG<br>REV: GGAGGTCTTACCAGTGTTTTCGTC | 177 |
| **Mouse Dsg3** | FW: CAGCCATAGTTGATCGTGAGG<br>REV: ATCTGCATCCGTGGCATTTAG | 221 |