Supplementary Material

1 Supplementary Figures
**Supplementary Figure 1.** Expression profiling of cAMP signaling pathway components in WT and ΔGnas DCs. (A) Two well-characterized isoforms of GNAS are expressed at substantial levels in WT mice (> 1 TPM on average): GNASL (long) and GNASS (short) variants, also known as GNAS alpha-S2 and alpha-S1, respectively. Expression of both is significantly reduced (FDR<0.05) in ΔGnas DCs. WT n=5, ΔGnas n=4. (B and C) Ratio of GPCRs that are linked to different G protein families in B) WT and C) ΔGnas DCs. (D) Ga mRNA expression profile in WT DCs; n=6. ND = not detected. Data are normalized to the lowest-expressing detectable gene. (E and F) Fold-change of Ga’s in ΔGnas DCs compared to WT DCs via E) independent qPCR; n=6, p<0.0001, and F) RNA-Seq; n=4-5, FDR<0.05. (G) Expression profile of adenylyl cyclase isoforms in WT DCs; n=3. (H) Fold-change in adenylyl cyclase isoforms in ΔGnas DCs compared to WT DCs; n=6. (I) PKA mRNA expression profile in WT DCs; n=5. (J) AKAP expression profile in WT DCs; n=6. (K) Fold-change in mRNA expression of AKAPs in ΔGnas DCs compared to WT DCs; n=6. (L) MRP4 mRNA expression in WT and ΔGnas DCs. dCt values are relative to the housekeeping gene 18S; n=3. (M) Fold-change in MRP4 expression in ΔGnas DCs compared to WT DCs; n=3.
Supplementary Figure 2. PDE4B is the highest expressed PDE isoform in murine and human DCs. (A and B) PDE expression in single cell RNA-Seq data of murine lung DCs from (Bosteels et al. 2020) with A) average expression (Purple) and the number of cells expressing the gene of interest (Blue) plotted and B) visualized in UMAP. (C) PDE expression in human epidermal DC RNA-Seq data from (Bertram et al. 2019); n=4. (D and E) PDE4B transcript variant expression in TPM of D) WT and E) ΔGnas DCs that were detected at mean expression levels >1 TPM in DCs from mice with each genotype. WT n=5; ΔGnas n=4. (F) Percentage of PDE4B transcripts for each variant in WT and ΔGnas DCs. WT n=5; ΔGnas n=4.
Supplementary Figure 3. *PDE4B* expression is decreased by reduced cAMP levels and lack of PKA activity and is increased in murine DC2.4 cells in response to cAMP-elevating drugs. (A) Decreased cAMP accumulation in WT DCs treated with the adenylyl cyclase inhibitor MDL-12,330A (10µM, 2.5 h); n=5, **p<0.01. (B) Basal *PDE4B* expression in murine T cell Kin- S49 cells (which lack PKA activity) compared to WT S49 cells; n=3-5, *p<0.05. (C) *PDE4B* expression of DC2.4 cells incubated with PGE2 (10µM, 24h); n=4-5, p<0.0001. (D) *PDE4B* expression of DC2.4 cells incubated with the cAMP analogs (50µM, 24 hrs) CPT (non-selective cAMP analog), 6MB (PKA-selective cAMP analog), and 8ME (Epac-selective cAMP analog); n=5-11, *p<0.05, **p<0.01.
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2 Supplementary Tables

|          | WT 1 | WT 2 | WT 3 | WT 4 | WT 5 | Avg | Std Dev |
|----------|------|------|------|------|------|-----|---------|
| 0.2 - 1 TPM | 41   | 44   | 34   | 34   | 36   | 38  | 4       |
| 1 - 10 TPM  | 51   | 52   | 52   | 48   | 44   | 49  | 3.1     |
| 10-50 TPM   | 25   | 26   | 25   | 22   | 26   | 25  | 1.5     |
| >50 TPM     | 15   | 15   | 14   | 20   | 14   | 16  | 2.2     |
| Total       | 132  | 137  | 125  | 124  | 120  | 128 | 6.1     |

**Supplementary Table 1.** GPCRs expressed by WT DCs. The number of GPCRs expressed (total and stratified according to level of expression) by 5 biological replicates of WT DCs (WT 1-5).

|          | KO 1 | KO 2 | KO 3 | KO 4 | Avg | Std Dev |
|----------|------|------|------|------|-----|---------|
| 0.2 - 1 TPM | 54   | 39   | 51   | 42   | 47  | 6.2     |
| 1 - 10 TPM  | 44   | 51   | 45   | 51   | 48  | 3.3     |
| 10-50 TPM   | 27   | 31   | 26   | 25   | 27  | 2.3     |
| >50 TPM     | 16   | 11   | 13   | 14   | 14  | 1.8     |
| Total       | 141  | 132  | 135  | 132  | 135 | 3.7     |

**Supplementary Table 2.** GPCRs expressed by ΔGnas DCs. The number of GPCRs expressed (total and stratified according to level of expression) by 4 ΔGnas biological replicates of ΔGnas DCs (KO 1-4).
| Gene    | Forward Primer                  | Reverse Primer                  |
|---------|--------------------------------|--------------------------------|
| 18s     | GTAACCGTGTGAAACCCATTT           | CCATCACTTGAGTAGTAGG             |
| ADCY1   | TCCACATCAAAAAAGAGACCC          | CATCCTCTTGAGGTGTGTGA           |
| ADCY2   | CGACATCTCAGATGGTCT            | CAGCTATCGCGCTGGTGGAAAAA         |
| ADCY3   | TCAATGACCAAGAAAGATGG           | GGAAGGCTGAGACATGGTGA           |
| ADCY4   | TTCTTCACACTCTGGTCT             | TACGACTTAGGTGAGTAGGTC           |
| ADCY5   | GGGAATTGATTCTAGTCTGGGGT       | TACGCTATCGCGCTGGTGGAAA          |
| ADCY6   | GACCTTCCTAGCCATCTTGGGGG       | TCAGGCTGAGGCGACTATGG           |
| ADCY7   | cGACATCCTCTCCAGCAGTTCT        | TCTTCACAGCAGATCTGAGGG           |
| ADCY8   | GAGAGCCAGTACGAAAGAGAAATG       | CATGACTATGTCAGACATGG           |
| ADCY9   | TCCAGGAAATGCATCCTTGGGGG       | TCAGGCTGAGGCGACTATGG           |
| ADCY10  | ACACTGCTCTCATCTCATTTCC        | TCTTCACAGCAGATCTGAGGG           |
| AKAP1   | TCTTGAGGTGGAGACTGACTG          | CAGCTATCGCGCTGGTGGAAA          |
| AKAP2   | GAAGAGCAATGCCAAGAAATG          | CATGACTATGTCAGACATGG           |
| AKAP3   | TTCTTCACACTCTGGTCT             | TACGACTTAGGTGAGTAGGTC           |
| AKAP4   | GAGAGCAATGCCAAGAAATG          | CATGACTATGTCAGACATGG           |
| EPAC1   | CCTTCCTGTGATCTCTCCTCA         | TCTTCACAGCAGATCTGAGGG           |
| GN1A    | TCTTGCGACAGCTGACTAC           | CATGACTATGTCAGACATGG           |
| GN1B    | CACCTCTCAGCCACCACAATTA         | CGTTCAGACTTTCTTTGTCGCC          |
| MRK4    | GAGAGCAATGCCAAGAAATG          | CATGACTATGTCAGACATGG           |
| PDE1A   | TGCTTGAAGAATCACTCTGGGGG       | TCAGGCTGAGGCGACTATGG           |
| PDE1B   | GACATCGGCAACCCACCTGAA         | CATGACTATGTCAGACATGG           |
| PDE1C   | GAGAGCAATGCCAAGAAATG          | CATGACTATGTCAGACATGG           |
| PDE2A   | GACGAGTAGGAGAATGAGGAGG        | CATGACTATGTCAGACATGG           |
| PDE3A   | TCTTCCTGTGATCTCTCCTCA         | TCTTCCTGTGATCTCTCCTCA          |
| PDE3B   | GAAGAGCAATGCCAAGAAATG          | CATGACTATGTCAGACATGG           |
| PDE4A   | CTCCTCGATCTCTCAACAC           | CATGACTATGTCAGACATGG           |
| PDE4B   | TCTTCCTGCTCAGGAGACTG          | CATGACTATGTCAGACATGG           |
| PDE4C   | CATTGCGACAGATGAGGAGG          | CATGACTATGTCAGACATGG           |
| PDE4D   | CATCTTGGGGGTCAATCACT          | TCTTCAGACTTTCTTTGTCGCC          |
| PDE5A   | CACCACTCTCATCTTGCTGG         | CATGACTATGTCAGACATGG           |
| PDE6A   | GTCCTTCAAGATCACTCTGGGGG       | TCAGGCTGAGGCGACTATGG           |
| PDE6B   | TGAGACTAGTCCATCTTGGGGG        | TCTTCCTCTTTTCTTTGTCGCC          |
| PDE6C   | CCACAGAGCCCGCCTCAACTT         | TCTTCCTGTGATCTCTCCTCA          |
| PDE7A   | ACTTACACTCTACCTACGAGGG        | TCTTCCTCTTTTCTTTGTCGCC          |
| PDE7B   | GAAAGAAATGACTCTAGAAGCCTAACC  | TCTTCCTGTGATCTCTCCTCA          |
| PDE8A   | CATCTCTGCTACCTCAACC           | CATGACTATGTCAGACATGG           |
| PDE8B   | CACCTTCCCTCTCCTCA             | CATGACTATGTCAGACATGG           |
| PDE9A   | TTGACTACAGCAAAGGGAGG          | TCTTCAGACTTTCTCTCCTCA          |
| PDE10A  | TGAGAAAGAGTTGCTGGTCCT         | TCTTCAGACTTTCTCTCCTCA          |
| PDE11A  | ATCAATGGAAGAATGAGGAGG         | TCTTCAGACTTTCTCTCCTCA          |
| PDKA    | CCCGAGATTATCTGAGGCA           | TCTTCCTCTCTCTCTCTCTCTCTCCTCCTCA|
| PDKB    | CACCTTCCCTCTCCTCCTCA          | TCTTCCTCTCTCTCTCTCTCTCCTCCTCCTCA|
| PK2A    | TCTTGGAGGAGGAGGAGGAGG         | TCTTCCTCTCTCTCTCTCTCCTCCTCCTCCTCA|
| PK2B    | CACCTTCCCTCTCCTCCTCA          | TCTTCCTCTCTCTCTCTCCTCCTCCTCCTCA|
| PK2C    | TCTTGGAGGAGGAGGAGGAGG         | TCTTCCTCTCTCTCTCTCCTCCTCCTCCTCA|
| PK2D    | CACCTTCCCTCTCCTCCTCA          | TCTTCCTCTCTCTCTCTCCTCCTCCTCCTCA|

Supplementary Table 3. qPCR primer sequences.