## Table S2: Microarray data analysis.

**A Pathway analysis:** The clustered differentially expressed genes between EPCR$^+$ versus EPCR$^-$ samples (see Table S1) were used as input to Ingenuity IPA. The tables below show the top 5 scoring Canonical Pathways identified for each of the 10 branches with a cutoff of $p \leq 0.05$ (1.3).

### Branch 1 (upregulated genes in EPCR$^+$ cells): Top 5 Canonical Pathways

| Ingenuity Canonical Pathways | -log(p-value) | Ratio | Molecules |
|---|---|---|---|
| Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes | 2.1 | 0.0588 | MYO5A, TLN2, ARPC1B, FCGR2A, VAV3, PRKD1 |
| Cardiac β-adrenergic Signaling | 1.92 | 0.0455 | PRKACB, GNG11, PPP1R7, GNG2, CACNA1A, MPPE1, PKIG |
| HER-2 Signaling in Breast Cancer | 1.86 | 0.0625 | CCNE1, ERBB3, PIK3R4, ITGB5, PRKD1 |
| Intrinsic Prothrombin Activation Pathway | 1.82 | 0.0938 | F12, PROS1, COL3A1 |
| Huntington's Disease Signaling | 1.68 | 0.0381 | GNG11, POLR2C, HSPA1L, CDK5, GNG2, PIK3R4, GOSR2, SNCA, PRKD1 |

### Branch 2 (upregulated genes in EPCR$^+$ cells): Top 5 Canonical Pathways

| Ingenuity Canonical Pathways | -log(p-value) | Ratio | Molecules |
|---|---|---|---|
| Cdc42 Signaling | 4.94 | 0.0506 | MYLK, MYL9, HLA-DMA, WIPF1, HLA-DMB, HLA-DPB1, HLA-DRB5, HLA-DPA1, ITGA4 |
| Antigen Presentation Pathway | 4.79 | 0.125 | HLA-DMA, HLA-DMB, HLA-DPB1, HLA-DRB5, HLA-DPA1 |
| Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells | 3.18 | 0.0588 | HLA-DMA, HLA-DMB, HLA-DPB1, HLA-DRB5, HLA-DPA1 |
| Allograft Rejection Signaling | 3.13 | 0.0526 | HLA-DMA, HLA-DMB, HLA-DPB1, HLA-DRB5, HLA-DPA1 |
| OX40 Signaling Pathway | 3.06 | 0.0532 | HLA-DMA, HLA-DMB, HLA-DPB1, HLA-DRB5, HLA-DPA1 |

### Branch 3 (upregulated genes in EPCR$^+$ cells): Top 5 Canonical Pathways

| Ingenuity Canonical Pathways | -log(p-value) | Ratio | Molecules |
|---|---|---|---|
| Antigen Presentation Pathway | 3.74 | 0.075 | HLA-DRA, CD74, HLA-F |
| Complement System | 2.36 | 0.0571 | C1R, C3 |
| B Cell Development | 2.31 | 0.0556 | IL7R, HLA-DRA |
| Atherosclerosis Signaling | 2.3 | 0.0233 | COL1A2, VCAM1, MMP3 |
| Graft-versus-Host Disease Signaling | 2.08 | 0.04 | HLA-DRA, HLA-F |

### Branch 4 (upregulated genes in EPCR$^+$ cells): Top 5 Canonical Pathways

| Ingenuity Canonical Pathways | -log(p-value) | Ratio | Molecules |
|---|---|---|---|
| B Cell Development | 3.73 | 0.0833 | HLA-DQA1, HLA-DRB1, HLA-DQB1 |
| Graft-versus-Host Disease Signaling | 3.38 | 0.06 | HLA-DQA1, HLA-DRB1, HLA-DQB1 |
| Autoimmune Thyroid Disease Signaling | 3.35 | 0.0492 | HLA-DQA1, HLA-DRB1, HLA-DQB1 |
| Nur77 Signaling in T Lymphocytes | 3.15 | 0.0476 | HLA-DQA1, HLA-DRB1, HLA-DQB1 |
| Calcium-induced T Lymphocyte Apoptosis | 3 | 0.0429 | HLA-DQA1, HLA-DRB1, HLA-DQB1 |

### Branch 5 (upregulated genes in EPCR$^{+}$ cells): Top 5 Canonical Pathways

| Ingenuity Canonical Pathways | -log(p-value) | Ratio | Molecules |
|---|---|---|---|
| Huntington's Disease Signaling | 3.68 | 0.072 | CAPN5, PIK3C2B, PIK3CA, POLR2D, GLS, DNM3, CREB3L4, GPAA1, GNG7, EP300, TAF9B, CTSD, GNB3, ARFIP2, PRKCD, PLCB1, STX16 |
| Role of NFAT in Cardiac Hypertrophy | 2.55 | 0.0619 | MAP2K6, PIK3C2B, PIK3CA, ITPR2, MAPK12, MAPK11, GNG7, EP300, RCAN1, GNB3, PRKCD, PLCB1, ADCY7 |
| Role of Tissue Factor in Cancer | 2.34 | 0.0789 | PIK3C2B, PIK3CA, ARRB2, ITGAV, PLCB1, MAPK12, CSF2, MAPK11, PDXP |
| Propanoate Metabolism | 2.25 | 0.0492 | ALDH1B1, ACADVL, PCCA, SUCLG2, ALDH1A3, ACSS1 |
| CCR3 Signaling in Eosinophils | 2.21 | 0.0714 | PIK3C2B, PIK3CA, GNB3, ITPR2, PRKCD, PLCB1, MAPK12, MAPK11, GNG7 |

**Branch 6 (upregulated genes in EPCR$^{+}$ cells):** No results.

### Branch 7 (upregulated genes in EPCR$^{-}$ cells): Top 5 Canonical Pathways

| Ingenuity Canonical Pathways | -log(p-value) | Ratio | Molecules |
|---|---|---|---|
| Hypoxia Signaling in the Cardiovascular System | 2.39 | 0.0462 | UBE2B, CREB1, UBE2D1 |
| Breast Cancer Regulation by Stathmin1 | 1.8 | 0.0192 | TUBA1A, CAMK1, CDKN1B, PPP2R5E |
| ATM Signaling | 1.48 | 0.0339 | SMC3, CREB1 |
| Nucleotide Sugars Metabolism | 1.41 | 0.0154 | GLCE |
| Pathogenesis of Multiple Sclerosis | 1.35 | 0.111 | CXCL11 |

### Branch 8 (upregulated genes in EPCR$^{-}$ cells): Top 5 Canonical Pathways

| Ingenuity Canonical Pathways | -log(p-value) | Ratio | Molecules |
|---|---|---|---|
| Molecular Mechanisms of Cancer | 6.09 | 0.0899 | MAP2K4, RAP2B, RAP2A, BAD, BMP2, NFKBIE, TAB2, HRAS, HIF1A, FZD1, E2F3, CCND1, TGFBR2, PTK2 (includes EG:14083), CASP6, GNA15, RHOD, E2F5, FZD2, LRP5, CDKN2D, PRKAR2A, ARHGEF17, RHOJ, BAK1, BCL2L1, FZD8, FOS, MAPK14, CCND2, IRS1, CDKN1A, PRKAG2, ARHGEF18 |
| O-Glycan Biosynthesis | 5.65 | 0.2 | GALNT5, GALNTL4, GALNT14, ST6GALNAC5, GALNT1, C1GALT1, GALNT6, GALNT10, FUT4 |
| IGF-1 Signaling | 4.47 | 0.132 | RPS6KB1, BAD, SOCS2, SOCS6, PRKAR2A, HRAS, IGFBP7, GRB10, PTK2 (includes EG:14083), FOS, IRS1, PRKAG2, IRS2, CYR61 |
| ILK Signaling | 3.8 | 0.099 | MAP2K4, MYH10, FLNB, PPP2CA, BMP2, PPP2R5D, PPP2R3B, RHOJ, HIF1A, CCND1, PGF, PTEN, PTK2 (includes EG:14083), FOS, RHOD, IRS1, SNAI2, PPP1R12A, IRS2 |
| CDK5 Signaling | 3.77 | 0.128 | PPP1CC, LAMA5, PPP2CA, PPP2R5D, EGR1, ITGA2, PRKAR2A, PRKAG2, PPP1R12A, HRAS, PPP2R3B, NGF |

### Branch 9 (upregulated genes in EPCR$^{-}$ cells): Top Canonical Pathways

| Ingenuity Canonical Pathways | -log(p-value) | Ratio | Molecules |
|---|---|---|---|
| FXR/RXR Activation | 2.2 | 0.0297 | IL18 (includes EG:16173), FBP1, SLCO1B3 |

| Ingenuity Canonical Pathways | -log(p-value) | Ratio | Molecules |
|---|---|---|---|
| Hypoxia Signaling in the Cardiovascular System | 1.5 | 0.0308 | EDN1, UBE2E2 |
| PXR/RXR Activation | 1.45 | 0.0227 | IGFBP1 (includes EG:16006), SLCO1B3 |
| Leukocyte Extravasation Signaling | 1.3 | 0.0151 | CXCR4, CYBA, NCF2 |

**Branch 10 (upregulated genes in EPCR$^-$ cells)**: **Top 5 Canonical Pathways**

| Ingenuity Canonical Pathways | -log(p-value) | Ratio | Molecules |
|---|---|---|---|
| Role of Tissue Factor in Cancer | 3.76 | 0.0702 | FYN, CTGF, CXCL1, HBEGF, MAPK13, F3, EGFR, FGF5 |
| Hepatic Fibrosis / Hepatic Stellate Cell Activation | 3.03 | 0.0544 | IGFBP4, IL1A, CTGF, FGFR1, IGFBP3, IL6, PDGFC, EGFR |
| Coagulation System | 2.82 | 0.105 | THBD, SERPINE1, F3, PLAT |
| Nitrogen Metabolism | 2.77 | 0.0333 | MARC2, LOXL1, CA12, CTH |
| HMGB1 Signaling | 2.63 | 0.06 | IL1A, MAPK13, SERPINE1, RHOF, FNBP1, PLAT |

**B Ingenuity analysis of gene signatures defining subpopulations of skin cancer stem cells regulated by TGF-β and integrin signaling:** Gene lists from Schober M, *et al*. (2011) *PNAS* 108:10544-10549 with more than average 1.5-fold changes between CD34$^+$ vs. CD34$^-$ skin carcinoma populations deficient in TGF-β receptor II (TGFBR2) or focal adhesion kinase (FAK) were included in the analysis. Gene lists with up- and down-regulation were considered separately (cutoff of $p \leq 0.05$ (1.3)).

| Branch 1 | -log(p-value) | Ratio | Molecules |
|---|---|---|---|
| TGFBR2-KO upregulated | 2.05 | 0.0413 | TRIP13, ID2, TGFBI, SLC14A1, FAM129A, ADA, BLM, CENPH, ESCO2 |

| Branch 2 | -log(p-value) | Ratio | Molecules |
|---|---|---|---|
| TGFBR2-KO downregulated | 3.03 | 0.0346 | COL16A1, FAM176B, WIPF1, FN1, ZBTB20, BAMBI, CSGALNACT1, GBP2 (includes EG:14469), SMARCD3 |

| Branch 3 | -log(p-value) | Ratio | Molecules |
|---|---|---|---|
| TGFBR2-KO downregulated | 4.24 | 0.0231 | VCAM1, SPP1 (includes EG:20750), C3, KCNJ15, NUPR1, ARHGEF25 |
| FAK-KO upregulated | 3.1 | 0.027 | COL5A2, VCAM1, SPP1 (includes EG:20750), C3 |

| Branch 4 | -log(p-value) | Ratio | Molecules |
|---|---|---|---|
| FAK-KO upregulated | 5.29 | 0.0405 | CCL2, HLA-DQA1, MGP, POSTN, HLA-DRB1, GPNMB |
| TGFBR2-KO upregulated | 1.66 | 0.0138 | ACP5, S100A3, HLA-DQA1 |
| TGFBR2-KO downregulated | 1.44 | 0.0115 | MGP, HLA-DRB1, GPNMB |

| **Branch 5** | **-log(p-value)** | **Ratio** | **Molecules** |
|---|---|---|---|
| TGFBR2-KO upregulated | 2.45 | 0.0642 | MAP2K6, CENPM, SRD5A1, SPC25 (includes EG:100144563), TTK, NCAPD2, DONSON, NEK2, DSCC1, SHMT1, RAD51C, EXO1 (includes EG:26909), E2F8, TK1 |

| **Branch 8** | **-log(p-value)** | **Ratio** | **Molecules** |
|---|---|---|---|
| TGFBR2-KO downregulated | 3.04 | 0.0769 | SOX4, FHL1 (includes EG:14199), MMP14, FAM43A, ANGPTL2, SLC35F3, FZD1, NFKBIZ, AXL, PLXND1, RNASE4, SEPP1, TGM2, TGFBR2, LIFR, LGMN, RGS10, SLC9A3R2, HEBP2, KLF2 |
| FAK-KO upregulated | 1.6 | 0.0743 | SEPP1, TGM2, CH25H, CCND2, NFKBIE, FAM43A, CHKA, CD14, RHOJ, NFKBIZ, CCDC80 |

| **Branch 9** | **-log(p-value)** | **Ratio** | **Molecules** |
|---|---|---|---|
| TGFBR2-KO downregulated | 5.19 | 0.0308 | EDN1, CXCR4, RGCC, ZEB1, EFEMP1, CXCL2, INHBB, MECOM |
| FAK-KO upregulated | 3.45 | 0.0338 | CXCR4, CYBA, RGCC, EFEMP1, CXCL2 |

| **Branch 10** | **-log(p-value)** | **Ratio** | **Molecules** |
|---|---|---|---|
| TGFBR2-KO downregulated | 5.22 | 0.0577 | FCGRT, FYN, RGS2 (includes EG:19735), LAPTM5, IFI27, CXCL1, SLIT2, ARHGDIB, RRAGD, COL5A1, FSTL1, TTC28, CYP4V2, SERPINE1, PLAC8 |
| FAK-KO upregulated | 3.02 | 0.0541 | COL5A1, ITGB2, FSTL1, RGS2 (includes EG:19735), LAPTM5, LOXL1, CXCL1, PLAC8 |
| FAK-KO downregulated | 1.76 | 0.133 | FHIT, GNAI1 |

**C Test for enrichment of stem cell and EMT signatures:** The individual branches were analyzed through the use of IPA (Ingenuity® Systems, www.ingenuity.com) for enrichment of the 40- and 380-gene embryonic stem cell-like signatures, and 654-gene PRC2 signature described by Ben-Porath *et al*. (2008) *Nature Genetics* 40:499-507. Results with a p value of 0.05 (1.3) are shown. We found a significant representation of targets for the Polycomb Repressive Complex 2 (PRC2) that are silenced in embryonic stem cells in Branch 3 of genes upregulated in EPCR$^{+}$ cells, whereas the transcripts of the signature of human embryonic stem cells (hESC 380) were represented in cluster 7 and 8 of genes upregulated in EPCR$^{-}$ cells. The recently identified mammary stem cell marker and developmental driver, Sox9 (Guo W *et al.* (2012) *Cell* 148: 1015-1028) was differentially expressed at the mRNA, but not the protein level and appeared to be rather regulated by post-translational mechanisms (see Supplementary Fig. 2D). A 64 gene EMT signature (Anastassiou D, et al. (2011) "Human cancer cells express Slug-based epithelialmesenchymal transition gene expression signature obtained in vivo." *BMC Cancer* 11:529) was also represented in both EPCR$^+$ and EPCR$^-$ subpopulations (cut-off, $p \leq 0.05$).

| **Branch 3** | **-log(p-value)** | **Ratio** | **Molecules** |
|---|---|---|---|
| Anastassiou: EMT signature | 1.85 | 0.0317 | COL1A2, COL5A2 |
| Ben-Porath: PRC2 654 | 1.61 | 0.00776 | OLIG2, HOXB6, DNAJC22, IRX5, HOXC4 |

| **Branch 4** | **-log(p-value)** | **Ratio** | **Molecules** |
|---|---|---|---|
| Anastassiou: EMT signature | 3.02 | 0.0476 | POSTN, SPARC, FAP (includes EG:14089) |

| **Branch 7** | **-log(p-value)** | **Ratio** | **Molecules** |
|---|---|---|---|
| Ben-Porath: hESC 380 | 2.74 | 0.0185 | HELLS, BMPR1A, GINS4, MAT2A, WDHD1, FRAT2, DSG2 |

| **Branch 8** | **-log(p-value)** | **Ratio** | **Molecules** |
|---|---|---|---|
| Ben-Porath: hESC 380 | 1.41 | 0.058 | PLA2G16, DEK, DLGAP5, PODXL, SORL1, CHST7, POLE2, HMGA1, SLC38A1, KLHL7, SPRY4, MRS2 (includes EG:380836), USP44, GMNN, JARID2, DNAJB6, TMPO, HOMER1, NFYB, UNG, BUB3 (includes EG:12237), HMGB3 |

| **Branch 10** | **-log(p-value)** | **Ratio** | **Molecules** |
|---|---|---|---|
| Anastassiou: EMT signature | 1.94 | 0.0635 | COL5A1, LOX (includes EG:16948), COL6A3, CDH11 |