

SUPPLEMENTARY TABLES

Table S1. MiRNA expression in cSCC. *Abbreviations:* RDEB, Recessive dystrophic epidermolysis bullosa.

| MiRNA | Study population | Results | Author | Year |
|----------|---|--|----------------------------|------|
| MiR-21 | 19 specimens consisting of invasive cSCC ($n=13$) and cSCC in situ ($n=6$) | Upregulated in invasive cSCC compared to cSCC in situ ($P<0.05$) | Stojadinovic et al [32] | 2017 |
| MiR-205 | | Upregulated in invasive cSCC compared to cSCC in situ ($P<0.05$) | | |
| MiR-31 | cSCC cell line (A-431) and normal skin cell line (HaCaT) | miR-31 expression is upregulated in cSCC vs normal skin cell lines ($P<0.01$). Overexpression of miR-31 significantly increased cell viability and inhibition of miR-31 reduced viability of A-431 cells, $P<0.01$ | Lin et al [33] | 2017 |
| MiR-181a | HaCaT, SCC13 and HEK293T cell lines | miR-181a showed low abundance among cSCC compared to normal skin ($P=0.0088$). miR-181a overexpressing cells grew slower and reach termination criteria at later time points ($P=0.0001$) | Neu et al [37] | 2017 |
| MiR-186 | Human cSCC cell line A-431 and the 293-T cell line, 15 paired cSCC and adjacent normal tissues | Invasion and migration were enhanced in A-431 cells transfected with miR-186 mimics and attenuated in A-431 cells transfected with the miR-186 inhibitor compared with the negative control-treated cells ($P<0.01$) | Tian et al [34] | 2018 |
| MiR-221 | 64 pairs of cSCC tissues and adjacent non-tumor tissues. CSCC cell lines (SCC13, A431, HSC-5 and SCL-1) and HaCaT | miRNA-221 expression was significantly higher in cSCC tissues and cell lines than in normal tissues and cells ($P<0.05$). Upregulation of miR-221 significantly promoted cell proliferation, while down-regulated expression of miR-221 significantly inhibited cell proliferation | Gong et al [35] | 2019 |
| MiR-10b | Cell lines from several donors including RDEB, otherwise healthy, non-RDEB patients, as well as RDEB- and healthy control keratinocytes | Overexpression of miR-10b conferred the stem cell-characteristic of 3D-spheroid formation capacity to keratinocytes. The actin- and tubulin cytoskeleton-associated protein DIAPH2 was identified as a novel putative target of miR-10b | Wimmer et al [31] | 2020 |
| MiR-130a | UT-SCC-7 human cSCC cell line, human cSCC tissue samples | MiR-130a expression was almost undetectable in cSCC samples. Overexpression of miR-130a led to a significant reduction in tumor volume by week 4 ($P<0.05$) and week 5 ($P<0.01$) | W Lohcharoenkal et al [36] | 2021 |

Table S2. CircRNAs identified with altered expression in cSCC. *Abbreviations:* FC, fold change.

| CircRNA | Study population | Results | Author | Year |
|-----------------------|--|--|----------------------|------|
| Circ_EPSTI | 9 cSCC and 7 healthy skin samples | Most upregulated in cSCC with a 33-fold increase in expression ($P < 0.03$) compared to healthy skin | Mahapatra et al [39] | 2020 |
| Circ_IFFO2 (novel) | 9 cSCC and 7 healthy skin samples | Most significantly downregulated circRNA compared to healthy skin (5.3-fold, $P < 0.0001$) | | |
| Circ_KRT1 (novel) | 9 cSCC and 7 healthy skin samples | Differentially expressed in cSCC ($P = 0.00276$, FC 0.03RPM) | | |
| Circ_POF1B (novel) | 9 cSCC and 7 healthy skin samples | Differentially expressed in cSCC ($P = 0.009963$, fold change 0.06 RPM) | | |
| circ_TNFRSF21 (novel) | 9 cSCC and 7 healthy skin samples | 4.6-fold upregulated in cSCC compared to healthy skin ($P < 0.0001$) | | |
| hsa_circ_0068631 | 3 cSCC and 3 non-lesional skin tissues | Upregulated in cSCC vs normal skin ($\log_{2}FC = 2.984716944$, $P = 0.008509$) | Wei et al [40] | 2021 |
| hsa_circ_0070933 | 3 cSCC and 3 non-lesional skin tissues | Upregulated in cSCC vs normal skin ($\log_{2}FC = 2.933784833$, $P = 0.000342$) | | |
| hsa_circ_0067772 | 3 cSCC and 3 non-lesional skin tissues | Upregulated in cSCC vs normal skin ($\log_{2}FC = 2.601642222$, $P = 0.00443$) | | |
| hsa_circ_0003528 | 3 cSCC and 3 non-lesional skin tissues | Upregulated in cSCC vs normal skin ($\log_{2}FC = 2.59531925$, $P = 0.004158$) | | |
| hsa_circ_0070934 | 3 cSCC and 3 non-lesional skin tissues | Upregulated in cSCC vs normal skin ($\log_{2}FC = 2.589680778$, $P = 0.00126$) | | |
| hsa_circ_0001955 | 3 cSCC and 3 non-lesional skin tissues | Upregulated in cSCC vs normal skin ($\log_{2}FC = 2.564198778$, $P = 0.001089$) | | |
| hsa_circ_0022392 | 3 cSCC and 3 non-lesional skin tissues | Downregulated in cSCC vs normal skin ($\log_{2}FC = -5.562538167$, $P = 7.57E-08$) | | |
| hsa_circ_0022383 | 3 cSCC and 3 non-lesional skin tissues | Downregulated in cSCC vs normal skin ($\log_{2}FC = -5.410590778$, $P = 3.68E-07$) | | |
| hsa_circ_0005085 | 3 cSCC and 3 non-lesional skin tissues | Downregulated in cSCC vs normal skin ($\log_{2}FC = -4.348301556$, $P = 2.05E-05$) | | |
| hsa_circ_0046449 | 3 cSCC and 3 non-lesional skin tissues | Downregulated in cSCC vs normal skin ($\log_{2}FC = -3.714428278$, $P = 0.00126$) | | |
| hsa_circ_0072279 | 3 cSCC and 3 non-lesional skin tissues | Downregulated in cSCC vs normal skin ($\log_{2}FC = -3.601349444$, $P = 0.000606$) | | |
| hsa_circ_0000375 | 3 cSCC and 3 non-lesional skin tissues | Downregulated in cSCC vs normal skin ($\log_{2}FC = -3.501067111$, $P = 0.000994$) | | |

Table S3. Transcription factors with altered expression in cSCC. *Abbreviations:* C.C, correlation coefficient; KA, keratoacanthoma; PO4-, phosphorylated.

| TF | Study population | Results | Author | Year |
|----------|---|---|----------------------|------|
| SMAD 2/3 | cSCC ($n=238$), cSCC in situ ($n=2$) and KA ($n=9$) were analysed in comparison with tissues from normal human scalp ($n=10$) | Reduction in active nuclear PO4-SMAD2 and PO4-SMAD3 staining was detected in invasive tumours vs matched perilesional tissue ($P<0.001$). High-risk tumour depths ($\geq 4\text{mm}$) demonstrated a highly significant negative dependence on both PO4-SMAD2 (C.C -0.214; $P=0.001$) and PO4-SMAD3 (C.C -0.200; $P=0.002$) | Rose et al [41] | 2018 |
| E2F1 | 9 cSCC and 7 healthy skin samples | Overrepresented binding sites among differentially expressed coding genes in cSCC (Z-score 38.02, P-value 0) | Mahapatra et al [39] | 2020 |
| ETS1 | | Overrepresented binding sites among differentially expressed coding genes in cSCC (Z-score 47.28, P-value 0) | | |
| FOXP3 | | Overrepresented binding sites among differentially expressed coding genes in cSCC (Z-score 47.55, P-value 0) | | |
| Oct-3/4 | | Overrepresented binding sites among differentially expressed coding genes in cSCC (Z-score 39.09, P-value 0) | | |
| SOX2 | | Overrepresented binding sites among differentially expressed coding genes in cSCC (Z-score 36.77, P-value 0) | | |

Table S4. LncRNA expression in cSCC. *Abbreviations:* FC, fold change; FDR, false discovery rate; Lce, late cornified envelope.

| LncRNA | Study population | Results | Author | Year |
|-----------------------|--|--|----------------------|------|
| AK144841 | Mouse skin | AK144841 expression was 40-fold higher in cSCC than in healthy skin. AK144841 downregulated the expression of genes of the Lce1 family | Ponzio et al [44] | 2017 |
| LINC00319 | 60 paired cSCC and matched normal skin samples. HaCaT, 4 cSCC cell lines (A431, HSC-5, SCC13, and SCL-1) | LINC00319 overexpression accelerated SCL-1 cell proliferation compared with empty control group, whereas LINC00319 knockdown slowed A431 cell proliferation (P<0.01) | Li et al [46] | 2018 |
| TINCR | cSCC cell line A431 | TINCR overexpression promoted apoptosis induced by ALA-PDT and silencing TINCR inhibited apoptosis (P<0.05) | Zhou et al [51] | 2018 |
| LINC00520 | Human cSCC cell line A431 | Downregulated in cSCC | Mei et al [50] | 2019 |
| LINC01048 | 80 pairs of human CSCC samples and adjacent non-tumorous tissues. Human cSCC cell lines (SCC13 and SCL-1), HaCaT | LINC01048 was upregulated in cSCC compared with adjacent noncancerous tissues (P<0.01). Mechanistically, LINC01048 was transcriptionally activated by <i>USF1</i> | Chen et al [45] | 2019 |
| HOTAIR | HaCaT and 4 cSCC cell lines: A431, HSC-5, SCC13, and SCL-1 | Level of HOTAIR in cSCC was increased remarkably vs HaCaT (P<0.05). Downregulation of HOTAIR decreased the tumor volume and tumor weight (P<0.05) | Yu et al [49] | 2019 |
| MALAT1 | cSCC lines (A431, HSC-1, and HSC-5), HaCaT | MALAT1 knockdown drastically inhibited A431 and HSC-1 cell invasiveness (P<0.001) | Y. Zhang et al [43] | 2019 |
| KB-1410C5.3/lnc-GRHL2 | 9 cSCC and 7 healthy skin samples | Most downregulated lncRNA (0.005-fold compared to healthy skin, FDR 8.95E-29) | Mahapatra et al [39] | 2020 |
| RP11-493L12.5 | | Most upregulated lncRNA in cSCC (46.77-fold compared to healthy skin, FDR 4.05E-16) | | |
| EZR-AS1 | 66 cSCC tissues and healthy adjacent non-cancerous tissues. CSCC cell lines (SCL-1, SCC13, A431 and HSC-5) and HaCaT | EZR-AS1 mRNA expression levels were significantly upregulated in cSCC compared with adjacent healthy tissues and HaCaT cells (P<0.01) EZR-AS1 knockdown inhibited cSCC cell migration and invasion, and promoted cell apoptosis | Lu et al [47] | 2020 |
| HCP5 | cSCC and healthy skin tissue controls from 60 patients CSCC cell lines (A431, COLO-16, SCC13, SCL-1, HSC-1, and HSC-5) and HaCaT | HCP5 had the greatest upregulation in cSCC (logFC=1.8) and the highest relative expression levels in cSCC vs normal adjacent tissue (P<0.001). Silencing of HCP5 expression resulted in significant decreases in A431 cell viability, invasion (P<0.001) and migration (P<0.01) vs normal tissue | Zou et al [48] | 2021 |
| AL353997.3 | Paired human cSCC and normal skin samples | Differentially expressed in cSCC (threshold of FC ≥ 2.0 and P ≤ 0.05). Upregulated in cSCC vs normal skin | Hu et al [42] | 2022 |
| BX004987.5 | | Differentially expressed in cSCC (threshold of FC ≥ 2.0 and P ≤ 0.05). Downregulated in cSCC vs normal skin | | |
| CTD-2521M24.9 | | Differentially expressed in cSCC (threshold of FC ≥ 2.0 and P ≤ 0.05). Upregulated in cSCC vs normal skin | | |
| CTD-2619J13.13 | | Differentially expressed in cSCC (threshold of FC ≥ 2.0 and P ≤ 0.05). Downregulated in cSCC vs normal skin | | |
| LINC00478 | | Differentially expressed in cSCC (threshold of FC ≥ 2.0 and P ≤ 0.05). Downregulated in cSCC vs normal skin | | |
| MIR4720 | | Differentially expressed in cSCC (threshold of FC ≥ 2.0 and P ≤ 0.05). Downregulated in cSCC vs normal skin | | |
| PVT1 | | Differentially expressed in cSCC (threshold of FC ≥ 2.0 and P ≤ 0.05). Upregulated in cSCC vs normal skin | | |
| LINC01003 | Matched tumor and blood DNA from 25 patients with regional metastases of cSCCHN | Significant functional alterations were observed in the tumor suppressing lncRNA LINC01003 (68% of specimens, Q-value: 0.0158) | Thind et al [16] | 2022 |

Table S5. Proteins downregulated in cSCC. *Abbreviations:* TP/PP, cancer tissues (TPs) and noncancerous tissues (PPs) ratio.

| Protein | Study population | Results | Author | Year |
|------------------|---|---|--------------------|------|
| β -catenin | 85 human epidermal resection specimens: normal ($n=42$), pre-cancerous ($n=34$) and cSCC ($n=51$) | Membrane β -catenin expression significantly reduced from normal to SCC (93% to 69%, $P<0.001$) | Sun et al [52] | 2019 |
| CK10 | | Inversely correlated with cancer development ($r_s=-0.626$, $P<0.001$) | | |
| COL1A1 | 20 pairs of primary human cSCC and matched noncancerous tissue samples | Decreased in cSCC, mapped to protein digestion and absorption and platelet activation pathways (TP/PP=0.24). Also connected to focal adhesion pathway | W. Chen et al [53] | 2021 |
| COL28A1 | | Decreased in cSCC, mapped to protein digestion and absorption pathway (TP/PP=0.06) | | |
| COL6A6 | | Decreased in cSCC, mapped to protein digestion and absorption pathway (TP/PP=0.08). Also connected to focal adhesion pathway | | |
| TLN2 | | Decreased in cSCC, mapped to platelet activation pathway (TP/PP=0.51). Also connected to focal adhesion pathway | | |

Table S6. Proteins upregulated in cSCC. *Abbreviations:* AK, actinic keratosis; BD, Bowen disease; FC, fold change; WT, wild-type.

| Protein | Study population | Results | Author | Year |
|------------|--|---|---------------------|------|
| ALB | Human normal epidermis (n=4, pooled), AK (n=10), BD (n=10) and cSCC (n=10) | Differentially abundant in cSCC compared to AK (Fold change 19.9, adjusted P<0.05; n ≥8) | A. Azimi et al [54] | 2018 |
| APOA1 | | Differentially abundant in cSCC compared to AK (FC=5.3, adjusted P<0.05; n ≥8) | | |
| FLNA | | Differentially abundant in cSCC compared to normal skin – unique to cSCC vs AK and BD (FC=6.8, adjusted P<0.05; n ≥8) | | |
| FSCN1 | | Differentially abundant in cSCC compared to normal skin – unique to cSCC vs AK and BD (FC=4.2, adjusted P<0.05; n ≥8) | | |
| HLA-B | | Differentially abundant in cSCC compared to AK (FC=5.2, adjusted P<0.05; n ≥8) | | |
| HP | | Differentially abundant in cSCC compared to AK (FC=4.8, adjusted P<0.05; n ≥8) | | |
| IGHA1 | | Differentially abundant in cSCC compared to normal skin – unique to cSCC vs AK and BD (FC=5.4, adjusted P<0.05; n ≥8) | | |
| LGALS1 | | Differentially abundant in cSCC compared to normal skin – unique to cSCC vs AK and BD (FC=4.3, adjusted P<0.05; n ≥8) | | |
| MAP4 | | Differentially abundant in cSCC compared to normal skin – unique to cSCC vs AK and BD (FC=4.9, adjusted P<0.05; n ≥8) | | |
| SERPINA1 | | Differentially abundant in cSCC compared to AK (FC=6.9, adjusted P<0.05; n ≥8) | | |
| TXNDC5 | | Differentially abundant in cSCC compared to AK (FC=4.4, adjusted P<0.05; n ≥8) | | |
| IGF2BP | Human cSCC tissues from 9 patients, surrounding normal skin samples. A431 human cSCC cell line | IGF2BP1 knockout significantly inhibited A431 cell survival and proliferation (P<0.05) | Z. Liu et al [58] | 2018 |
| CD44 | 85 human epidermal resection specimens: normal (n=42), pre-cancerous (n=34) and cSCC (n=51) | Positively stained in 17% of normal tissues vs 61% in SCC, P<0.001. Positive correlation with cancer development, rs=0.383 (P<0.001) | Sun et al [52] | 2019 |
| CK17 | | Positively correlated with cancer development (rs=0.67, P<0.001). Positively stained in 9% of normal tissues vs 82% in SCC | | |
| E-cadherin | | Positively stained in 98% of normal tissues vs 92% in SCC, P<0.001 | | |
| EXOSC10 | | Expression increased from normal to cSCC (14% to 65%, P<0.001). EXOSC10 staining was positively correlated with disease development (rs=0.392, P<0.001) | | |
| EZR | | Positively stained in 21% of normal tissues vs 96% in SCC, P<0.001. Positive correlation with cancer development, rs=0.717 (P<0.001) | | |
| Hsp75 | | Expression increased from 7% in normal skin to 73% in cSCC (P<0.001) | | |
| Hsp90-α | | Expression increased from 29% in normal skin to 100% in SCC (P<0.001) | | |
| SOD2 | | Positively stained in 2% of normal tissues vs 63% in SCC (P<0.001) | | |
| CMG2 | HPV38E6E7 SCC cell line | CMG2 was significantly overexpressed in tumor tissue, with detectable expression in the UV-control | Crawford et al [56] | 2019 |
| TEM8 | | TEM8 was significantly overexpressed in tumor tissue compared to UV-control | | |
| Cox-2 | Hair follicle stem cell-originating cSCC wild-type Cox-2 (n=15), Cox-2 knockout (n=11) | WT Cox-2 tumors frequently demonstrated mesenchymal-like spindle cell carcinomas with minimal keratinization (11 of 15). Cox-2 KO tumors were often well-differentiated with significant hyperkeratosis or papillomatous growths (6 of 11). | H Moon et al [55] | 2020 |
| LPCAT1 | 43 human cSCC samples | LPCAT1 is upregulated in cSCC samples and cell lines vs primary human epidermal keratinocytes (P<0.001). LPCAT1 depletion increased both the early and late apoptosis rates, with the total rate approaching 12-19% vs 3-4% in controls | Y Huang et al [57] | 2021 |
| PIK3CB | 20 pairs of primary human cSCC and matched noncancerous tissue samples | Elevated in cSCC, mapped to platelet activation pathway (TP/PP=4.11) | W. Chen et al [53] | 2021 |

Table S7. Proteins with roles in cSCC metastasis and differentiation. *Abbreviations:* FC, fold change; MET, patients with lymph node metastases, but with no available primary tumor; NHEK, normal human epidermal keratinocyte; NS, normal healthy skin; RDEB, Recessive dystrophic epidermolysis bullosa; SES, sun-exposed skin; Padj, adjusted P-value; PRI-, locally confined tumors; PRI+, primary tumors that had metastasized; TAp63^{-/-}, homozygous deletion of TAp63; WT, wild-type.

| Protein | Study population | Results | Author | Year |
|---------------|---|---|------------------------|------|
| ΔNp63 | Genetically engineered mouse models: Lgr5CreER and K14CreER mice | p63 was only expressed in tumor epithelial cells (TECs) and not in tumor mesenchymal-like cells (TMCs). Proportion of well-differentiated SCCs was strongly increased in tumors that expressed ΔNp63 (P=0.0009) | Latil et al [26] | 2017 |
| LGALS3BP | Human cSCC: low-risk (n=10), metastasizing (n=10), RDEB cSCC (n=10) | Significantly increased abundance of LGALS3BP in high-risk cSCC vs low-risk cSCC (P<0.05) | Föll et al [60] | 2018 |
| MARCKS | | MARCKS was present in both groups of high-risk cSCC and virtually absent in low-risk cSCC (P<0.01) | | |
| PABPC1 | | Staining for PABPC1 revealed strong presence in cancer keratinocytes of both high-risk cSCC compared to low-risk cSCC (P<0.05) | | |
| RAC1 | | In metastasizing cSCC, RAC1 showed clear membrane-associated staining of individual cSCC keratinocytes within tumor islands. Staining was significantly less intense in low-risk cSCC (P<0.05) | | |
| SND1 | | SND1 was significantly increased in both groups of high-risk cSCC and compared to low-risk cSCC (P<0.05) | | |
| iASPP | 116 human cSCC samples, 10 human cSCC cell lines | Poorly differentiated cSCC displayed significantly higher cytoplasmic and lower nuclear iASPP expression (high nuclear iASPP expression found in 48% of well-differentiated cSCC vs 4.2% in poorly differentiated cSCC) | DJ Robinson et al [62] | 2019 |
| TAp63 | 5 human cSCC cell lines (COLO16, SRB12, SRB1, IC1, and RDEB2), NHEK, mouse models | Higher frequency of cSCC in TAp63 ^{-/-} cohort vs WT (46.67% vs 20%). No metastases were found in WT mice, whereas multiple lung metastases were observed in TAp63 ^{-/-} mice with cSCC | Davis et al [63] | 2020 |
| APCS | Primary (n=20) and metastatic cSCC (n=25) samples | Decreased in metastatic cSCC compared to the primary lesions (Padj=6.50E-04, FC=-7.1) | A. Azimi et al [59] | 2020 |
| APOA1 | | Increased in metastatic cSCC compared to the primary lesions (Padj=4.79E-02, FC=2.5) | | |
| CST6 | | Decreased in metastatic cSCC compared to the primary lesions (Padj=2.57E-02, FC=-3.9) | | |
| DMKN | | Decreased in metastatic cSCC compared to the primary lesions (Padj=6.50E-04, FC=-9.4) | | |
| ISG15 | | Increased in metastatic cSCC compared to the primary lesions (Padj=3.33E-02, FC=2.7) | | |
| MARCKS | | Increased in metastatic cSCC compared to the primary lesions (Padj=3.91E-02, FC=1.9) | | |
| ENTPD1 (CD39) | | Human cSCC, unmatched NS | | |
| uPAR | cSCCHN from 50 patients. 21 PRI-, 14 PRI+, 15 MET, matched SES | Significantly increased uPAR staining in MET tissues compared to PRI- (P<0.0001) | Minaei et al [7] | 2022 |

Table S8. Metabolites mapped to regulatory pathways in cSCC.

| Metabolite | Study population | Results | Author | Year |
|-------------------|--|---|--------------------|-------------|
| L-Glutamate | 20 pairs of primary human cSCC and matched noncancerous tissue samples | Elevated in cSCC, mapped to protein digestion and absorption pathway (TP/PP=3.70) | W. Chen et al [53] | 2021 |
| L-Arginine | 20 pairs of primary human cSCC and matched noncancerous tissue samples | Elevated in cSCC, mapped to protein digestion and absorption pathway (TP/PP=2.43) | | |
| L-Aspartate | 20 pairs of primary human cSCC and matched noncancerous tissue samples | Elevated in cSCC, mapped to protein digestion and absorption pathway (TP/PP=3.40) | | |
| L-Glutamine | 20 pairs of primary human cSCC and matched noncancerous tissue samples | Elevated in cSCC, mapped to protein digestion and absorption pathway (TP/PP=2.40) | | |
| L-Phenylalanine | 20 pairs of primary human cSCC and matched noncancerous tissue samples | Elevated in cSCC, mapped to protein digestion and absorption pathway (TP/PP=2.01) | | |
| Arachidonate | 20 pairs of primary human cSCC and matched noncancerous tissue samples | Decreased in cSCC, mapped to platelet activation pathway (TP/PP=0.24) | | |