# Whole-genome identification and systematic analysis of lncRNA-mRNA co-expression profiles in patients with cutaneous basal cell carcinoma

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**Abstract.** Cutaneous basal cell carcinoma (BCC) is a common subtype of malignant skin tumor with low invasiveness. Early diagnosis and treatment of BCC and the identification of specific biomarkers are particularly urgent. Long non-coding RNAs (lncRNAs) have been shown to be associated with the development of various tumors, including BCC. The present study conducted a comparative analysis of the differential expression of lncRNAs and mRNAs through whole-genome technology. Microarray analyses were used to identify differentially expressed (DE) lncRNAs and DE mRNAs. Reverse transcription-quantitative (RT-q) PCR confirmed the differential expression of 10 lncRNAs in BCC. Subsequently, a lncRNA-mRNA co-expression network was constructed using the top 10 DE lncRNAs. Finally, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were performed to investigate the possible biological effects of the identified mRNAs and to speculate on the possible biological effects of the lncRNAs. A total of 1,838 DE lncRNAs and 2,010 DE mRNAs were identified and 10 of the DE lncRNAs were confirmed by RT-qPCR. A lncRNA-mRNA co-expression network comprising 166 specific co-expressed lncRNAs and mRNAs was constructed using the top 10 DE lncRNAs. According to the results of the GO and KEGG analyses, lncRNA *XR_428612.1* may serve an important role in mitochondrial dysfunction and the progression of BCC by modulating *TICAM1*, *USMG5*, *COX7A2*, *FBXO10*, *ATP5E* and *TIMM8B*. The present study provided whole-genome identification and a systematic analysis of lncRNA-mRNA co-expression profiles in BCC.

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## Introduction

Cutaneous basal cell carcinoma (BCC) is a common malignant skin tumor originating from the basal layer of the epidermis and its appendages, accounting for 65-70% of all skin tumors (1). Currently, the specific biomarkers useful for identifying BCC are still lacking and most of the studies are focused on analyses at the protein level (2-4). A small number of studies have recently reported that mRNAs may be involved in the process of BCC, but research on lncRNAs remains scarce (5-7).

Long non-coding RNA (lncRNA) is a functional RNA molecule containing >200 nucleotides, which serves an important regulatory role in gene transcription, post-transcriptional translation and epigenetic levels. Studies have suggested that lncRNAs are extensively involved in the biological process of cancer (8-12), but few lncRNA studies have clarified the roles of lncRNA in BCC. Therefore, it is a priority to explore the possible biological effects of the lncRNAs involved in BCC. Since lncRNAs have been considered regulators of mRNAs (13,14), the present study constructed a lncRNA-mRNA co-expression network for BCC with the presumption that the roles of these lncRNAs are affected by the function of related mRNAs. The lncRNA-mRNA co-expression network established bridges between lncRNAs and mRNAs to reveal the potential functional involvement of lncRNAs in BCC pathobiology. The interaction network is based on the hypothesis that once the differential expression levels of two transcripts are linearly related, a bridge can be established to demonstrate that the two are co-expressed. In this case, the two transcripts consisted of one lncRNA and one mRNA.

Overall, determining the important roles of lncRNAs in tumors is essential. Therefore, it is particularly important to conduct a whole-genome analysis of BCC tissues and construct a valid lncRNA-mRNA co-expression network, exploring the

differentially expressed (DE) lncRNAs and making conjectures on their biological functions.

## Materials and methods

*Patients and samples*. The study protocol was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethical Review Board of Peking Union Medical College (approval no. 2016-KY013). The present study recruited thirteen patients (6 male patients and 7 female patients; age range, 50-65 years) and thirteen health volunteers (6 male volunteers and 7 female volunteers; age range, 50-65 years) between February 2017 and November 2017. A total of thirteen basal cell carcinoma samples and thirteen normal tissue samples were collected from patients who underwent biopsy operation at the Institute of Dermatology, Chinese Academy of Medical Sciences. All thirteen BCC samples were pathologically confirmed and all participants provided written informed consent.

*RNA extraction*. Total cellular RNA was isolated from three BCC samples and three normal skin tissue samples using an RNeasy Mini kit (Qiagen GmbH) in accordance with the manufacturer's protocol and then quantified through NanoDrop ND-1000 (Thermo Fisher Scientific, Inc.). Total RNA was assessed by standard denaturing agarose gel electrophoresis.

*Microarray assay*. GeneChip® Human Transcriptome Array 2.0 (HTA2.0, Affymetrix; Thermo Fisher Scientific, Inc.), reportedly covers more than 245,000 coding and 40,000 non-coding RNAs of the human genome from NCBI RefSeq, UCSC, RNAdb, Ensembl, lncRNAs, UCSC, NONCODE and related literature (15). Each transcript was represented by using 1-5 probes.

The microarray hybridization was performed according to the manufacturer's standard protocols (Agilent Technologies, Inc.) including sample labeling, transcribing into double-stranded complementary (c)DNAs, cRNAs and second cycle cDNAs and then hybridizing onto the microarray. Finally, the hybridized slides were washed, fixed and scanned to images by the Affymetrix Scanner 3000 (Affymetrix; Thermo Fisher Scientific, Inc.). The data was collected by Affymetrix GeneChip Command Console (version 4.0; Affymetrix; Thermo Fisher Scientific, Inc.) and normalized by the Robust Multichip Average algorithm through the Expression Console (version 1.3.1, Affymetrix; Thermo Fisher Scientific, Inc.) software. All data were imported into Genespring software (version 12.5; Agilent Technologies, Inc.) for further analysis. The statistical significance of differentially expressed lncRNAs and mRNAs was identified via Volcano plot filtering with the threshold set of fold change ≥2.0 and P-value <0.05. Hierarchical clustering analysis was performed to reveal relationships between transcripts.

*Reverse transcription-quantitative (RT-q) PCR*. A total of ten BCC samples and ten normal tissues were used for RT-qPCR validation. Total RNA was isolated with TRIzol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.) and reverse transcribed into cDNA using the SuperScript III First Strand Synthesis System (Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer's protocol. Subsequently, qPCR was performed using SYBR-Green (Takara Bio, Inc.) quantitative PCR and the ABI 7900HT Fast Real-Time PCR system (Applied Biosystems; Thermo Fisher Scientific, Inc.). The following thermocycling conditions were used for qPCR: 40 cycles at 95˚C for 2 sec, 60˚C for 20 sec and 70˚C for 10 sec. β-actin was used as an internal control. The primers used for qPCR are listed in Table I. For quantitative results, the relative expression level of each lncRNA was calculated using $2^{-\Delta\Delta Cq}$ method (16) and then statistically analyzed.

*Analysis of lncRNA-mRNA co-expression network*. To predict the functional roles of lncRNAs, the top 10 were associated with direct regulated expression of target mRNAs using co-expression network. Pearson's correlation Coefficient (PCC) between each lncRNA-mRNA pair was calculated and those with |PCC| >0.99 and P<0.05 were selected. The co-expression network was visually represented using Cytoscape software (version 3.6.1; cytoscape.org), in which each mRNA corresponded to a node and two RNAs linked by an edge indicated a high correlation.

*Gene ontology (GO) and kyoto encyclopedia of genes and genomes (KEGG) pathway analyses*. GO analysis was used to identify the potential functions of significant DE genes, which covered three realms, including biological process, molecular function and cellular component (http://www.geneontology.org). Furthermore, the KEGG database (http://www.genome.ad.jp/kegg/) was conducted to harvest pathway information.

*Statistical analysis*. All statistical analyses were performed using the SPSS version 17.0 software (SPSS, Inc.). Unpaired Student's t-tests were performed to generate P-values. P<0.05 was considered to indicate a statistically significant difference. Data are representative of three independent experiments.

## Results

*Microarray analysis of lncRNAs and mRNAs in BCC*. To obtain the expression profiles of lncRNAs and mRNAs in BCC, three normal skin tissue samples and three BCC tissue samples were examined. The results revealed 32,904 lncRNAs and 32,552 mRNAs in total, with the results are shown in Table SI. Compared with normal samples, 524 lncRNAs (red dots in Fig. 1A) and 1,207 mRNAs (red dots in Fig. 1B) were upregulated (P<0.05; fold change >2) in BCC. In contrast, 1,314 lncRNAs (green dots in Fig. 1A) and 803 mRNAs (green dots in Fig. 1B) were significantly downregulated (P<0.05; fold change >2). The top 200 differentially expressed lncRNAs and mRNAs are presented in the hierarchical cluster analysis heat map (Fig. 2A and B), in which 'Normal' represents three normal skin tissue samples and 'BCC' represents three BCC tissue samples.

*RT-qPCR validation of differentially expressed lncRNAs*. The top 10 DE lncRNAs were selected for RT-qPCR analysis to verify the microarray results in ten BCC tissue samples and ten normal tissue samples. The RT-qPCR results demonstrated that four lncRNAs (*XR_428611.1*, *XR_428612.1*, *ENST00000566225.1* and *ENST00000430816.1*) were downregulated in BCC and six lncRNAs (*NR_002160.1*,

Table I. Primers used for reverse transcription-quantitative PCR.

| lncRNA | Forward primer (5'→3') | Reverse primer (5'→3') |
|---|---|---|
| *XR_428611.1* | GGCTCGCTCTCCACTCCATCC | TTACACACCCCTTCTCCCTTCCAG |
| *XR_428612.1* | TGCTGCTGGCGAGAAGAATGC | ATGTTGAAGACCGGGGCTTTCTG |
| *ENST00000566225.1* | GGAAGGGCACCACTTCTACC | AATTACCTGTGAAGGCCCCG |
| *ENST00000430816.1* | CAGCCAACCACGCAGACCTG | TTCCAGAACAGCACGAAGTCCAC |
| *NR_002160.1* | TGACCGTCAACTTGGGATTGT | TTAAACAAGCCAGCCAAGCG |
| *ENST00000444265.1* | CTGCCAAGAGGAATCCAGCA | TCTGGGTTTTCCATGCGTGT |
| *HIT000067334* | TGCATGTAAGTGGCAAAGATGA | TGCTTCTCCAGAATGGCTTGA |
| *ENST00000598252.1* | GGAGGCAGATTCAGTCAGACG | TGGACAAAAACTCCAGTGTGC |
| *uc003hcu.1* | GTTTTCCCCCTCACCAAGCA | GCGACCAAAGCCACAATAGC |
| *ENST00000548135.1* | TGCCCAGGAAGCTGAGGTGAG | AGCTGCTGGAAGGCGAGGAG |
| *β-actin* | TCCTTCCTGGGCATGGAGT | AGCACTGTGTTGGCGTACAG |

lncRNA, long non-coding RNA.

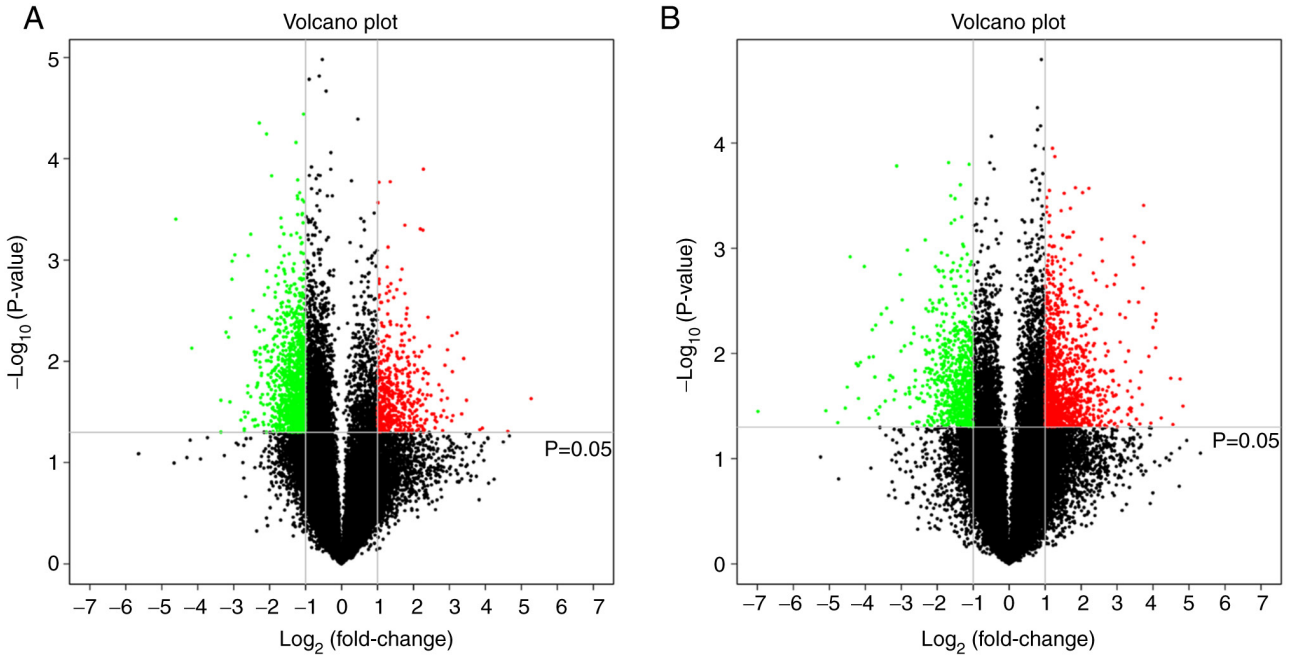


Figure 1. DE lncRNAs and DE mRNAs. The expression of lncRNAs and mRNAs were compared between BCC and normal cutaneous tissue specimens. Volcano plot of lncRNAs (A) and mRNAs (B) illustrate the difference in the expression levels of each transcript. The red dots represent transcripts significantly upregulated in BCC and the green dots represent transcripts significantly downregulated in BCC, based on the statistical criteria (fold change >2; P<0.05). The horizontal axis represents fold of change in expression (on a $\log_2$ scale) and the vertical axis represents P-value (on a negative $\log_{10}$ scale). In the plot, the vertical line on the left stands for a two-fold downregulation while the right one stands for a two-fold upregulation and the horizontal line represents P=0.05. DE, differentially expressed; lncRNA, long non-coding RNA; BCC, cutaneous basal cell carcinoma.

*ENST00000444265.1*, *HIT000067334*, *ENST00000598252.1* and *uc003hcu.1*, *ENST00000548135.1*) were upregulated in BCC. As shown in Fig. 3, the relative values of the expression levels detected by RT-qPCR were found to be consistent with the microarray data. This result suggests that the transcript identification and abundance estimates were highly reliable.

*Construction of a lncRNA-mRNA co-expression network*. To construct the lncRNA-mRNA co-expression network in BCC, the correlation of the expression levels of the top 10 lncRNAs and individual mRNAs in the samples were investigated by Pearson correlation coefficient (PCC) and tested the reliability of PCC by P-value. A strict positive correlation and a negative correlation is indicated by a PCC equal to 1 or -1 (17). The present study limited the PCC value to >0.99 or <-0.99 and set the P-value to <0.05, which is a strict standard used to establish a correlation (18).

The lncRNA-mRNA network we constructed consisted of 10 lncRNA nodes (green rectangles in Fig. 4), 150 mRNA nodes (purple dots in Fig. 4) and 166 edges. Different edge types represent different interrelationships. As shown in the figure, *ENST00000598252.1* is co-expressed with 54 of the 150 mRNAs

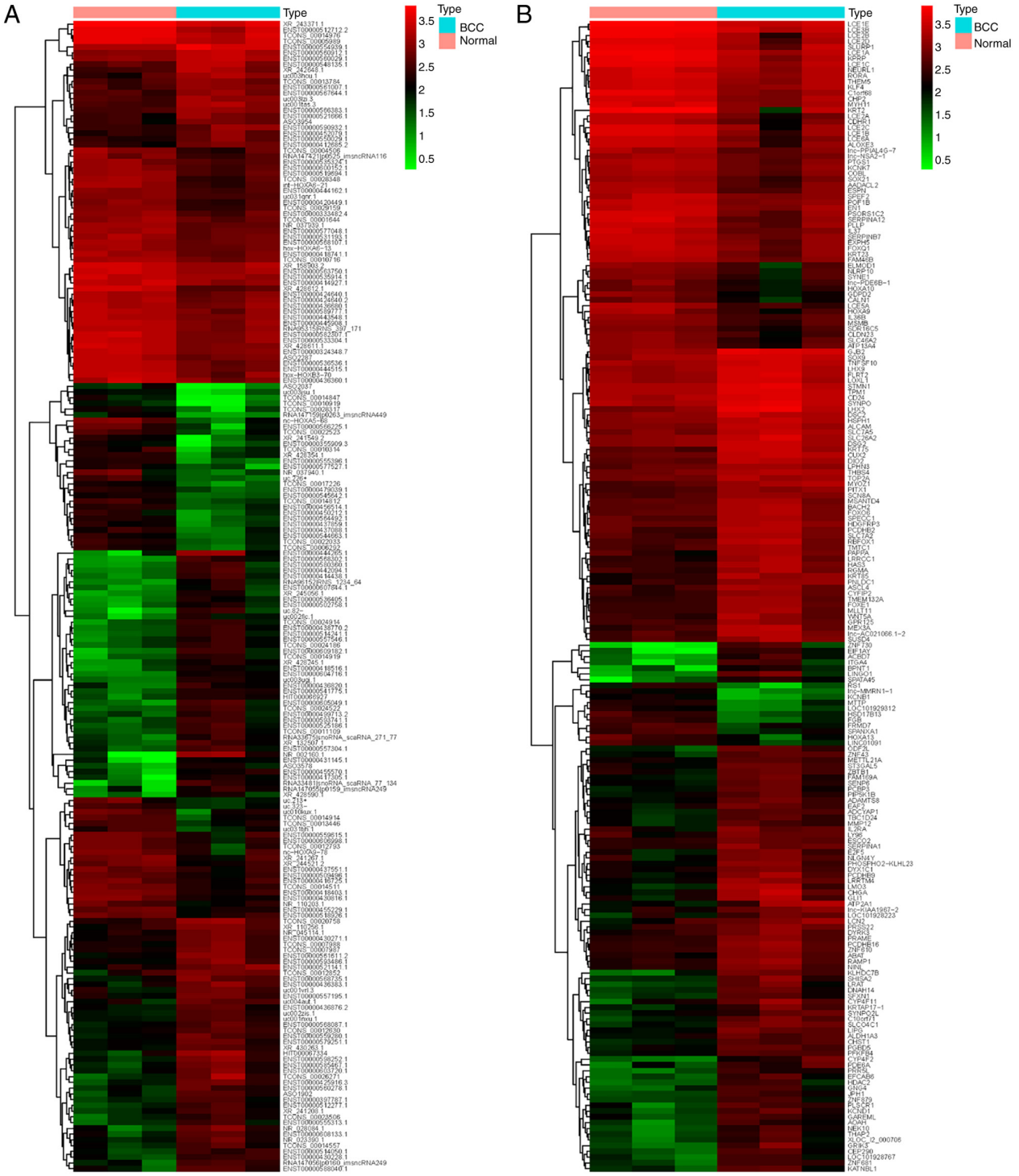


Figure 2. Hierarchical Clustering analysis of DE lncRNAs and DE mRNAs. Hierarchical Clustering analysis of (A) lncRNAs and (B) mRNAs depict the top 200 difference in the expression levels of each transcript within two groups (normal cutaneous tissue samples and BCC samples). Red, high relative expression. Green, low relative expression. DE, differentially expressed; lncRNA, long non-coding RNA; BCC, cutaneous basal cell carcinoma tissue.

identified, the most of all identified DE lncRNAs. The next most abundant, *NR_002160.1*, was co-expressed with as many as 38 mRNAs. Moreover, TICAM1 mRNA was co-expressed with the maximum number (three) among the 10 DE lncRNAs.

*GO enrichment and pathway analysis*. To further explore potential targets of the DE lncRNAs in BCC progression, GO enrichment and KEGG pathway analyses were performed on the DE mRNAs (Fig. 5).

Numerous GO terms were targeted by these coding mRNAs, including 3,625 biological processes, 635 molecular functions and 446 cellular components. The target genes and detailed information are represented in Table SII. GO analysis is widely used to identify a set of gene products in three categories: Biological processes, cellular components and molecular functions (19). For the DE mRNAs in BCC identified by microarray, the most significant emerging themes as determined by P-value were 'keratinization' (biological process; Fig. 5A blue),

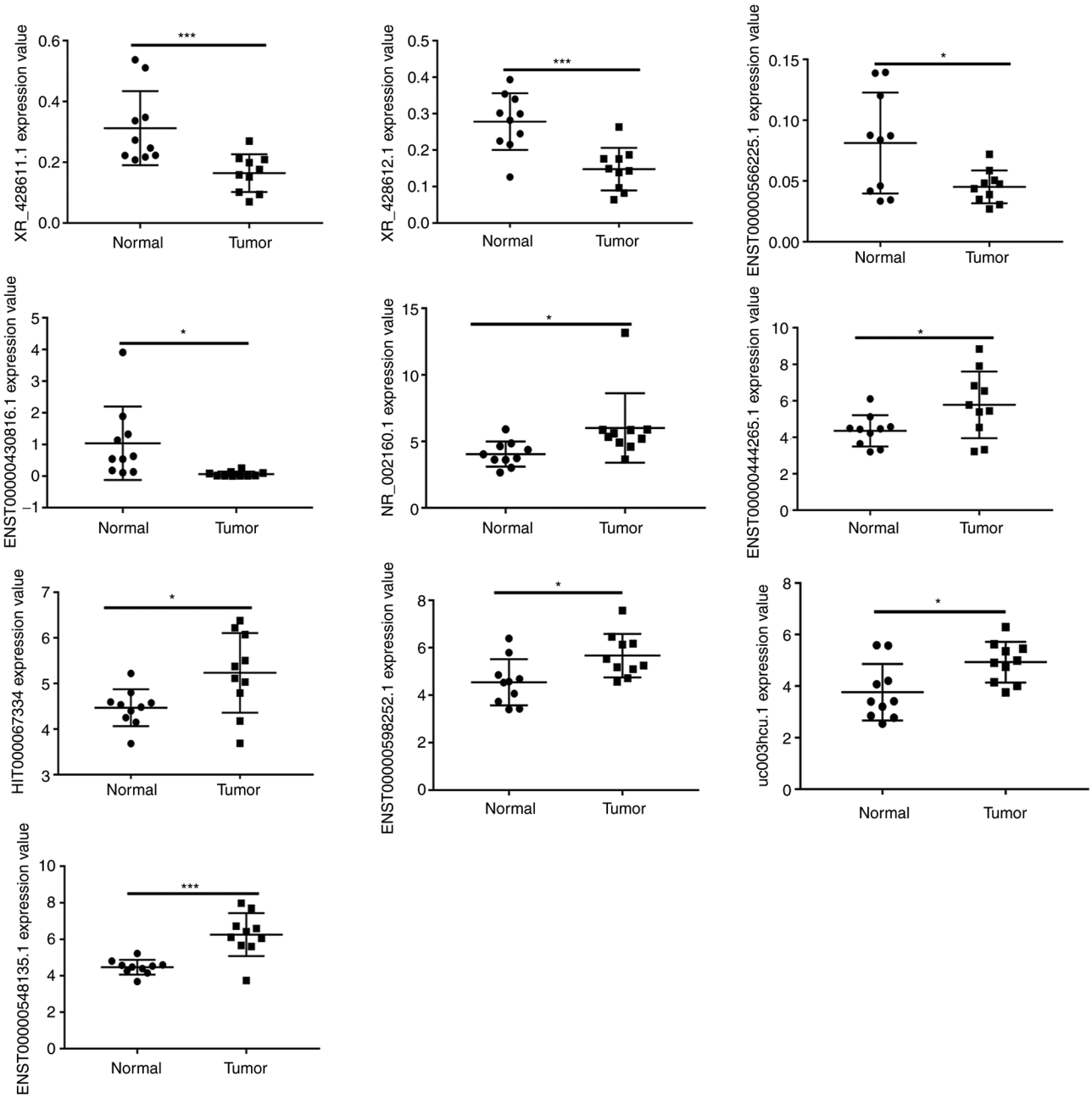


Figure 3. Validation for the DE lncRNAs by RT-qPCR. The expression levels of ten lncRNAs were compared between cutaneous basal cell carcinoma and normal skin tissues. The vertical axis represents the expression value computed from the qPCR data, which are consistent with the data from microarray. *P<0.05 and ***P<0.001. DE, differentially expressed; lncRNA, long non-coding RNA; RT-qPCR, reverse transcription-quantitative PCR.

'cornified envelope' (cellular component; Fig. 5A yellow) and 'unfolded protein binding' (molecular function; Fig. 5A red).

In addition, 152 KEGG pathways enriched with the DE mRNAs were detected. For KEGG pathway analysis, the top 20 of the 152 identified KEGG pathways were selected and analyzed. The majority of the KEGG pathways most enriched included the p53 signaling pathway, fructose and mannose metabolism, protein processing in the endoplasmic reticulum, microRNAs in cancer and apoptosis (Fig. 5B).

## Discussion

The role of lncRNAs in cancer has been recognized and a number of studies have been conducted with lung cancer, breast cancer, liver cancer, gastrointestinal tumors and skin cancer (20-22). LncRNAs can be upregulated or downregulated in a variety of cancer processes, including cutaneous tumors, affecting upstream and downstream target genes, signaling pathways and metabolic pathways and ultimately promoting tumor proliferation and invasion (23). As a common cutaneous tumor, BCC has also been studied to determine its possible pathogenesis. It is currently hypothesized that abnormal activation of the Hedgehog pathway induced by the *PTCH1* gene serves a major role in BCC (24). In addition, abnormal upregulation of the *SMO* gene, loss of tumor suppressor p53 and activation of the Hippo-Yes-associated protein pathway are considered to be involved in the progression of BCC. Some oncogenes, such as *ARID1A*, *CASP8*, *CSMD1*, *GRIN2A*,

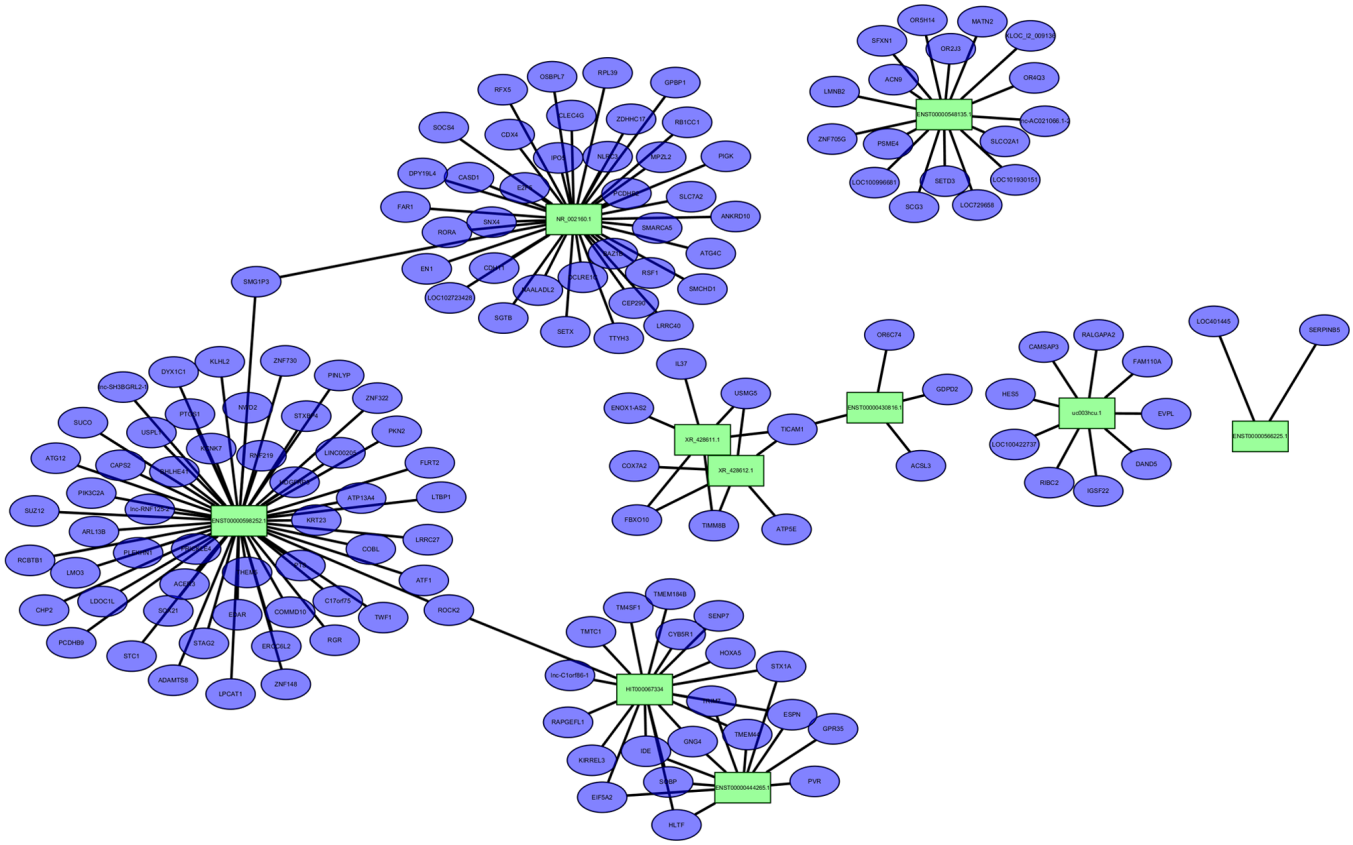


Figure 4. lncRNA and mRNA co-expression networks in cutaneous basal cell carcinoma tissues. The co-expression network consists of the top 10 DE lncRNAs (green rectangles), correlated 150 mRNAs (purple dots) and 166 edges. Each edge represents correlation r value >0.99 or <-0.99 with P<0.05. lncRNA, long non-coding RNA; DE, differentially expressed.

*KRAS*, *NOTCH1*, *NOTCH2*, *NRAS*, *PIK3CA*, *PREX2* and *RAC1*, are also mutated in BCC (25,26). In summary, lncRNAs are currently important for cancer study, but their role in BCC is seldom mentioned and remains unclear.

To explore the potential role of lncRNAs in the processes of BCC, the present study performed whole-genome identification of lncRNAs using an array to detect the expression profiles of lncRNAs and mRNAs in three normal tissue samples and three BCC tissue samples. A total of 32,904 lncRNA probes and 32,552 mRNA probes were detected and a number of RNAs were found to be differentially expressed, including 1,838 lncRNAs and 2,010 mRNAs. The selection criteria, fold change >2 and P<0.05, ensured the significance of the differential expression data. The top 10 DE lncRNAs, including four downregulated lncRNAs and six upregulated lncRNAs, were verified through RT-qPCR. The RT-qPCR results showed a trend in expression levels consistent with those of the lncRNA array analysis.

Some of the DE lncRNAs identified in the present study have been reported to be involved in carcinogenesis; for example, the p27963 probe detected lncRNA *nc-HOXA5-68*, one of the top 10 downregulated DE lncRNAs (27). As suggested by its name it has a regulatory effect on the proto-oncogene *HOXA5*. *HOXA5* can affect various systemic systems and can serve a pivotal role in the cancer process (28). The first studied lncRNA *HOTAIR* can also be regulated to induce cancer progression, such as liver cancer, cervical cancer and cutaneous melanoma (29,30).

Although lncRNAs do not encode proteins directly, they can be involved in various biological processes including the progression of cancer by interacting with other biomolecules such as transcription factors, miRNAs, mRNAs and RNA-binding proteins to form gene regulatory networks (31). Several studies have been conducted to obtain lncRNA biomarkers associated with tumor development and prognosis by constructing lncRNA-mRNA networks, such as thyroid cancer, hepatocellular carcinoma and ovarian cancer (32-34). To further explore the potential role and mechanism of lncRNAs in BCC, the present study constructed a lncRNA-mRNA co-expression network focusing on the top 10 specific DE lncRNAs. The most striking example involved the largest downregulation of lncRNA, *XR_428612.1*, in BCC. This lncRNA has not been studied, but the co-expression network demonstrated that it has a co-expression relationship with six mRNAs, *TICAM1*, *USMG5*, *COX7A2*, *FBXO10*, *ATP5E* and *TIMM8B*. Notably, all these mRNAs are reported to be associated with mitochondrial dysfunction and glucose metabolism (35-41). In the co-expression network of the present study, lncRNA *XR_428612.1* was positively correlated with TIR domain-containing adaptor molecule-1 (*TICAM1*). It has been reported that *TICAM1* downregulation is an essential step in Toll-like receptor 3 (TLR3) activation and stops TLR3-mediated IFN production (35). Activated TLR3 induces the upregulation of transactivating p63 isoform α (TAp63α), a p53-related protein that downregulates the expression of Bcl-2, an anti-apoptosis molecule and induces cell apoptosis in a caspase-dependent manner through death receptors and mitochondria (36). The

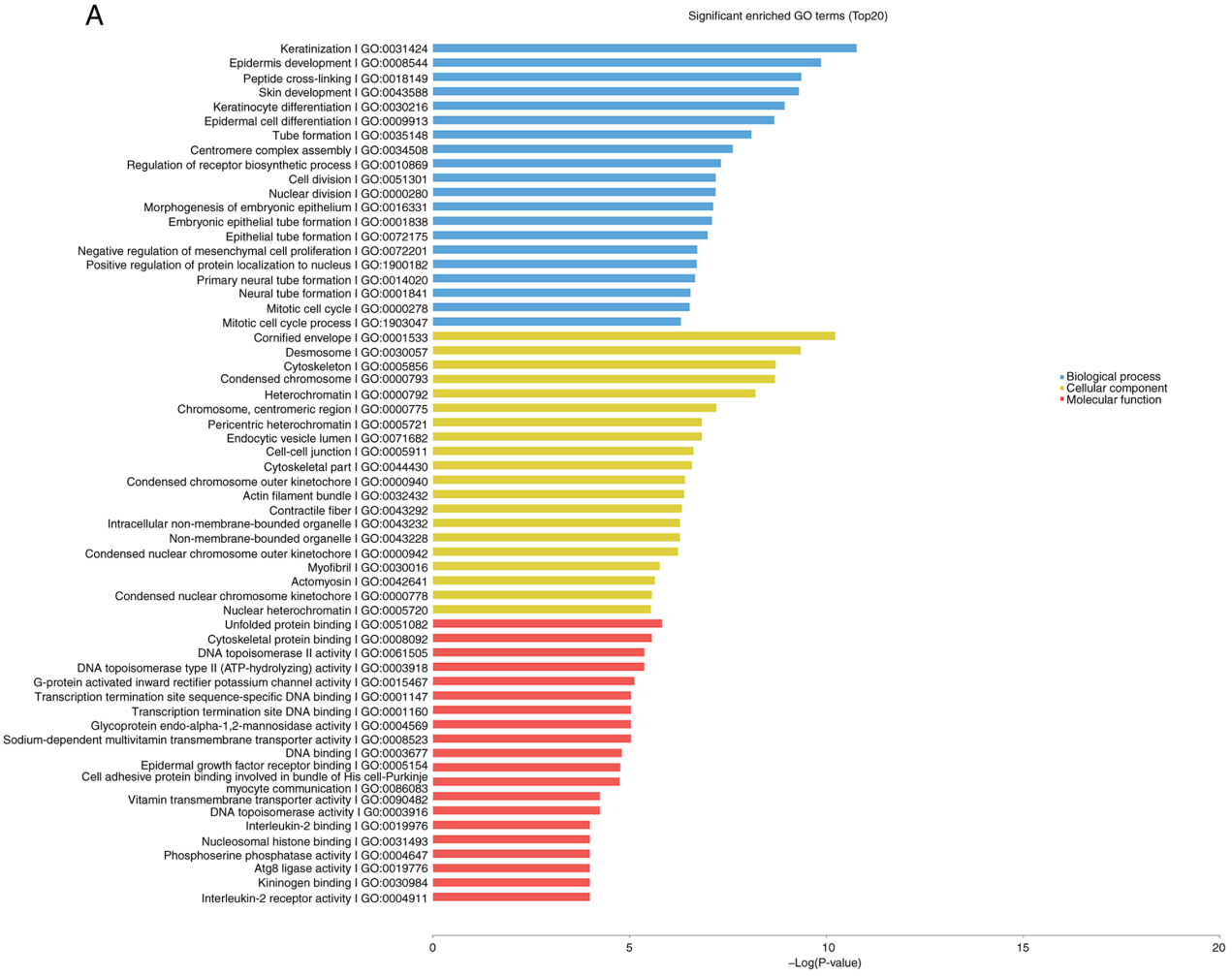


Figure 5. GO and KEGG pathway analysis of DE mRNAs in BCC. (A) The 20 most enriched GO terms (vertical axis) for DE mRNAs in BCC selected based on P-value (horizontal axis). The enriched GO terms at the vertical axis are grouped into 'Biological Process' (blue), 'Cellular Component' (yellow) and 'Molecular Function' (red). (B) The 20 most enriched KEGG pathways (vertical axis) for DE mRNAs in BCC are selected based on P-value (horizontal axis). The most enriched KEGG pathway is at the top of the vertical axis. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; DE, differentially expressed BCC, cutaneous basal cell carcinoma tissue.

present study noted that *TICAM1* was co-expressed with the maximum number (three) of lncRNAs, which indicated that it may serve an important role in the pathogenesis of BCC. In addition, *FBXO10* is also thought to control the degradation of Bcl-2 and to regulate cell apoptosis (37). TIMM8B, a mitochondrial ribosomal protein (MRP), has been reported to be upregulated in colon mucosa carcinogenesis mediated by diabetes (28). MRPs may be affected by glucose metabolism and participate in proliferation, metastasis, or cellular migration in malignancies (38). In addition, diabetes-associated protein in insulin-sensitive tissues (DAPIT) encoded by *USMG5* (39), ATP synthase epsilon subunit (ATP5E) and cytochrome c oxidase subunit 7A2 (COX7A2) are partial components of ATP synthase and participate in the interconversion of mitochondrial oxidative phosphorylation (OXPHOS) and glycolysis, both of which are sources of ATP (40,41). The upregulation of these transcripts clearly contribute to modulating tumor anabolism, redox and calcium homeostasis, apoptosis and metastasis by governing mitochondrial function.

In the present study, GO and KEGG pathway analyses showed significant changes among the DE mRNAs. KEGG analysis found that the 'p53 signaling pathway', 'fructose and mannose metabolism', 'protein processing in the endoplasmic reticulum', 'microRNAs in cancer' and 'apoptosis' were the top five significantly changed pathways. P53 has been reported to be overexpressed in BCC (42). It interferes with Bcl-2 in mitochondria, which results in the release of cytochrome c and promotes apoptosis by activating the mitochondrial pathway (42,43). In fact, three of the five top significant KEGG pathways, including the 'p53 signaling pathway', 'fructose and mannose metabolism' and 'apoptosis', were aligned with the carcinogenic mechanisms of the mRNAs co-expressed with lncRNA *XR_428612.1*, as aforementioned. Since the construction of lncRNA-mRNA co-expression network and KEGG analysis relationships are independent, this outcome greatly increases the reliability of the present study. Therefore, it was hypothesized that mitochondrial dysfunction involving OXPHOS and glycolysis modulated by lncRNA *XR_428612.1* may serve a considerable role in the progression of BCC and deserves to be the focused of a follow-up study.

In conclusion, the present study provided a comprehensive analysis of lncRNA-mRNA co-expression profiles of patients with cutaneous basal cell carcinoma. GO and KEGG analyses further revealed the function of mRNAs and suggested the possible biological effects of lncRNAs. The results indicated that lncRNA *XR_428612.1* may serve an important role in mitochondrial dysfunction and the progression of BCC by modulating *TICAM1*, *USMG5*, *COX7A2*, *FBXO10*, *ATP5E* and *TIMM8B*. These data argue for further intensive research to provide a more comprehensive understanding of the molecular mechanisms underlying the metabolism of BCC.

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**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Authors' contributions**

JZ, XZ, DH, MJ, CL and KC conceived and designed the study. DH, YH, RL and SJ collected the samples and acquired the data. JZ, XZ and CZ interpretated or analyzed data. XZ, CZ, YH, RL and SJ prepared the manuscript, which was revised for important intellectual content by JZ, CL and KC. All authors reviewed and approved the final manuscript. CL and KC confirm the authenticity of all the raw data.

**Ethics approval and consent to participate**

The study protocol was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethical Review Board of Peking Union Medical College (approval no. 2016-KY013). All participants provided written informed consent.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**References**

1. Puig S and Berrocal A: Management of high-risk and advanced basal cell carcinoma. Clin Transl Oncol 17: 497-503, 2015.
2. Pellegrini C, Maturo MG, Di Nardo L, Ciciarelli V, Gutierrez Garcia-Rodrigo C and Fargnoli MC: Understanding the molecular genetics of basal cell carcinoma. Int J Mol Sci 18: 2485, 2017.
3. Ciążyńska M, Bednarski IA, Wódz K, Kolano P, Narbutt J, Sobjanek M, Woźniacka A and Lesiak A: Proteins involved in cutaneous basal cell carcinoma development. Oncol Lett 16: 4064-4072, 2018.
4. Sălan AI, Mărăşescu PC, Camen A, Ciucă EM, Matei M, Florescu AM, Pădureanu V and Mărgăritescu C: The prognostic value of CXCR4, α-SMA and WASL in upper lip basal cell carcinomas. Rom J Morphol Embryol 59: 839-849, 2018.
5. Sun H and Jiang P: MicroRNA-451a acts as tumor suppressor in cutaneous basal cell carcinoma. Mol Genet Genomic Med 6: 1001-1009, 2018.
6. Vand-Rajabpour F, Sadeghipour N, Saee-Rad S, Fathi H, Noormohammadpour P, Yaseri M, Hesari KK, Bagherpour Z and Tabrizi M: Differential BMI1, TWIST1, SNAI2 mRNA expression pattern correlation with malignancy type in a spectrum of common cutaneous malignancies: Basal cell carcinoma, squamous cell carcinoma, and melanoma. Clin Transl Oncol 19: 489-497, 2017.
7. Sand M, Hessam S, Amur S, Skrygan M, Bromba M, Stockfleth E, Gambichler T and Bechara FG: Expression of oncogenic miR-17-92 and tumor suppressive miR-143-145 clusters in basal cell carcinoma and cutaneous squamous cell carcinoma. J Dermatol Sci 86: 142-148, 2017.

8. Wang KC and Chang HY: Molecular mechanisms of long noncoding RNAs. Mol Cell 43: 904-914, 2011.
9. Mohammad F, Pandey GK, Mondal T, Enroth S, Redrup L, Gyllensten U and Kanduri C: Long noncoding RNA-mediated maintenance of DNA methylation and transcriptional gene silencing. Development 139: 2792-2803, 2012.
10. Yu X, Zheng H, Tse G, Chan MT and Wu WK: Long non-coding RNAs in melanoma. Cell Prolif 51: e12457, 2018.
11. McCarthy N: Epigenetics. Going places with BANCR. Nat Rev Cancer 12: 451, 2012.
12. Li R, Zhang L, Jia L, Duan Y, Li Y, Bao L and Sha N: Long non-coding RNA BANCR promotes proliferation in malignant melanoma by regulating MAPK pathway activation. PLoS One 9: e100893, 2014.
13. Wang KC, Yang YW, Liu B, Sanyal A, Corces-Zimmerman R, Chen Y, Lajoie BR, Protacio A, Flynn RA, Gupta RA, *et al*: A long noncoding RNA maintains active chromatin to coordinate homeotic gene expression. Nature 472: 120-124, 2011.
14. Panda AC, Abdelmohsen K and Gorospe M: SASP regulation by noncoding RNA. Mech Ageing Dev 168: 37-43, 2017.
15. Koczan D, Fitzner B, Zettl UK and Hecker M: Microarray data of transcriptome shifts in blood cell subsets during S1P receptor modulator therapy. Sci Data 5: 180145, 2018.
16. Schmittgen TD and Livak KJ: Analyzing real-time PCR data by the comparative C(T) method. Nat Protoc 3: 1101-1108, 2008.
17. Cao L, Zhang P, Li J and Wu M: LAST, a c-Myc-inducible long noncoding RNA, cooperates with CNBP to promote CCND1 mRNA stability in human cells. Elife 6: e30433, 2017.
18. Vila-Casadesús M, Gironella M and Lozano JJ: MiRComb: An R package to analyse miRNA-mRNA interactions. Examples across five digestive cancers. PLoS One 11: e0151127, 2016.
19. Lan X, Zhang H, Wang Z, Dong W, Sun W, Shao L, Zhang T and Zhang D: Genome-wide analysis of long noncoding RNA expression profile in papillary thyroid carcinoma. Gene 569: 109-117, 2015.
20. Prensner JR and Chinnaiyan AM: The emergence of lncRNAs in cancer biology. Cancer Discov 1: 391-407, 2011.
21. Esteller M: Non-coding RNAs in human disease. Nat Rev Genet 12: 861-874, 2011.
22. Hulstaert E, Brochez L, Volders PJ, Vandesompele J and Mestdagh P: Long non-coding RNAs in cutaneous melanoma: Clinical perspectives. Oncotarget 8: 43470-43480, 2017.
23. Botchkareva NV: The molecular revolution in cutaneous biology: Noncoding RNAs: New molecular players in dermatology and cutaneous biology. J Invest Dermatol 137: e105-e111, 2017.
24. Biehs B, Dijkgraaf GJ, Piskol R, Alicke B, Boumahdi S, Peale F, Gould SE and de Sauvage FJ: A cell identity switch allows residual BCC to survive Hedgehog pathway inhibition. Nature 562: 429-433, 2018.
25. Lobl M, Hass B, Clarey D, Higgins S, Sutton A and Wysong A: Basal cell carcinoma gene mutations differ between Asian, hispanic, and caucasian patients: A pilot study. J Drugs Dermatol 20: 504-510, 2021.
26. Stacey SN, Helgason H, Gudjonsson SA, Thorleifsson G, Zink F, Sigurdsson A, Kehr B, Gudmundsson J, Sulem P, Sigurgeirsson B, *et al*: New basal cell carcinoma susceptibility loci. Nat Commun 6: 6825, 2015.
27. Saijo S, Kuwano Y, Tange S, Rokutan K and Nishida K: A novel long non-coding RNA from the HOXA6-HOXA5 locus facilitates colon cancer cell growth. BMC Cancer 19: 532, 2019.
28. Jeannotte L, Gotti F and Landry-Truchon K: Hoxa5: A key player in development and disease. J Dev Biol 4: 13, 2016.
29. Aalijahan H and Ghorbian S: Long non-coding RNAs and cervical cancer. Exp Mol Pathol 106: 7-16, 2019.
30. Abbastabar M, Sarfi M, Golestani A and Khalili E: lncRNA involvement in hepatocellular carcinoma metastasis and prognosis. EXCLI J 17: 900-913, 2018.
31. Zhang J, Le TD, Liu L and Li J: Inferring and analyzing module-specific lncRNA-mRNA causal regulatory networks in human cancer. Brief Bioinform 20: 1403-1419, 2019.
32. Du Y, Xia W, Zhang J, Wan D, Yang Z and Li X: Comprehensive analysis of long noncoding RNA-mRNA co-expression patterns in thyroid cancer. Mol Biosyst 13: 2107-2115, 2017.
33. Lim LJ, Jin Y, Yang H, Chung AYF, Goh BKP, Chow PKH, Chan CY, Blanks WK, Cheow PC, Lee SY, *et al*: Network of clinically-relevant lncRNAs-mRNAs associated with prognosis of hepatocellular carcinoma patients. Sci Rep 10: 11124, 2020.
34. Guo Q, Cheng Y, Liang T, He Y, Ren C, Sun L and Zhang G: Comprehensive analysis of lncRNA-mRNA co-expression patterns identifies immune-associated lncRNA biomarkers in ovarian cancer malignant progression. Sci Rep 5: 17683, 2015.
35. Tao S, Zhu L, Lee P, Lee WM, Knox K, Chen J, Di YP and Chen Y: Negative control of TLR3 signaling by TICAM1 down-regulation. Am J Respir Cell Mol Biol 46: 660-667, 2012.
36. Sun R, Zhang Y, Lv Q, Liu B, Jin M, Zhang W, He Q, Deng M, Liu X, Li G, *et al*: Toll-like receptor 3 (TLR3) induces apoptosis via death receptors and mitochondria by up-regulating the transactivating p63 isoform alpha (TAP63alpha). J Biol Chem 286: 15918-15928, 2011.
37. Chiorazzi M, Rui L, Yang Y, Ceribelli M, Tishbi N, Maurer CW, Ranuncolo SM, Zhao H, Xu W, Chan WC, *et al*: Related F-box proteins control cell death in Caenorhabditis elegans and human lymphoma. Proc Natl Acad Sci USA 110: 3943-3948, 2013.
38. Del Puerto-Nevado L, Santiago-Hernandez A, Solanes-Casado S, Gonzalez N, Ricote M, Corton M, Prieto I, Mas S, Sanz AB, Aguilera O, *et al*: Diabetes-mediated promotion of colon mucosa carcinogenesis is associated with mitochondrial dysfunction. Mol Oncol 13: 1887-1897, 2019.
39. Kontro H, Cannino G, Rustin P, Dufour E and Kainulainen H: DAPIT over-expression modulates glucose metabolism and cell behaviour in HEK293T cells. PLoS One 10: e0131990, 2015.
40. Huang YJ, Jan YH, Chang YC, Tsai HF, Wu AT, Chen CL and Hsiao M: ATP synthase subunit epsilon overexpression promotes metastasis by modulating AMPK signaling to induce epithelial-to-mesenchymal transition and is a poor prognostic marker in colorectal cancer patients. J Clin Med 8: 1070, 2019.
41. Deng S, Li Y, Yi G, Lei B, Guo M, Xiang W, Chen Z, Liu Y and Qi S: Overexpression of COX7A2 is associated with a good prognosis in patients with glioma. J Neurooncol 136: 41-50, 2018.
42. Adamkov M, Halasova E, Rajcani J, Bencat M, Vybohova D, Rybarova S and Galbavy S: Relation between expression pattern of p53 and survivin in cutaneous basal cell carcinomas. Med Sci Monit 17: BR74-BR80, 2011.
43. Chipuk JE, Kuwana T, Bouchier-Hayes L, Droin NM, Newmeyer DD, Schuler M and Green DR: Direct activation of Bax by p53 mediates mitochondrial membrane permeabilization and apoptosis. Science 303: 1010-1014, 2004.