Original Article

Whole-genome identification and construction of the lncRNA-mRNA co-expression network in patients with actinic keratosis

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Background: Actinic keratosis (AK) is a common premalignant lesion induced by chronic exposure to ultraviolet radiation and may develop into invasive cutaneous squamous carcinoma (cSCC). The identification of specific biomarkers in AK are still unclear. Long non-coding RNAs (lncRNAs), as transcripts of more than 200 nucleotides, significantly involving in multiple biologic processes, especially in the development of tumors.

Methods: In our study, we obtained data from RNA-sequencing analysis using two AK lesion tissues and three normal cutaneous tissues to comparatively analyze the differentially expressed (DE) lncRNAs and messenger RNAs (mRNAs). Firstly, we used microarray analyses to identify DE lncRNAs and DE mRNAs. Secondly, we performed Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis to analyze the primary function and find out significant pathways of these DE mRNA and lncRNAs. Finally, we used the top ten DE lncRNAs to construct a lncRNA-mRNA co-expression network.

Results: Our results showed that there were a total of 2,097 DE lncRNAs and 2,043 DE mRNAs identified. GO and KEGG analysis and the lncRNA-mRNA co-expression network (using the top 10 DE lncRNAs comprises 130 specific co-expressed mRNAs to construct) indicated that lncRNA *uc011fnr.2* may negatively regulate *SCIMP* and Toll-like receptor 4 (TLR4) and play an important role in Janus kinase-signal transducer and activator of transcription 3 (JAK-STAT3) signaling pathway of AK.

Conclusions: lncRNA *uc011fnr.2* may play an important role in JAK-STAT3 signaling pathway of AK by modulating *SCIMP*, TLR4 and IL-6. Further research is required to validate the value of lncRNA *uc011fnr.2* in the progression of AK.

Keywords: Actinic keratosis (AK); long non-coding RNA (lncRNA); messenger RNA (mRNA); microarray analysis

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Introduction

Actinic keratosis (AK) is a common premalignant lesion induced by chronic exposure to ultraviolet radiation and the lesion usually occurred in the exposed area, and it may develop into invasive cutaneous squamous carcinoma (cSCC). The total clinical AK prevalence in China through 2008–2012 was 0.52% (1). In a study in the United States, the risk of developing non-melanoma skin cancer or melanoma in a patient with AK was six-fold higher than the person without AK (2). In the elderly with multiple AKs,

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the annual progression rate of AK to SCC is 0.6%, and the progression rate after 4 years is 2.57% (3). Therefore, for AK patients, it is recommended to intervene and treat as soon as possible.

Long non-coding RNAs (LncRNAs) are defined as transcripts of more than 200 nucleotides which cannot be translated into proteins (4). They have been proposed to carry out diverse functions including transcriptional regulation in genes, organization of nuclear domains, and regulation of proteins or RNA molecules (5,6). Recently, an increasing number of lncRNAs have been demonstrated to be involved in biological process of cancer (7,8), such as colorectal cancer (9), bladder cancer (10), lung cancer (11) and so on. At present, studies have shown that messenger RNAs (mRNAs) are closely related to the occurrence and development of AK and SCC (12-14), but the research report on the role of lncRNAs in AK remains scarce.

In our study, sequencing and whole-genome analysis was performed to examine the profiles of lncRNA and mRNA expression in AK patients and healthy controls skin tissues. Moreover, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis were used to predict potential functional involvement of these differentially expressed (DE) mRNA and lncRNAs. Last but not least, lncRNAs- mRNAs co-expression analysis was used to clarify the relationship between them. We present the following article in accordance with the MDAR reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-842/rc).

Methods

Patients and samples

We collected two AK patients skin tissue samples and three normal skin tissue samples, all of them underwent biopsy operation at the Institute of Dermatology, Chinese Academy of Medical Sciences. All the samples were pathologically confirmed. The study was approved by the Institutional Review Board of Peking Union Medical College (No. 2016-KY013). The study protocol was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and written informed consent was obtained from all participants.

RNA extraction

RNeasy Mini Kit (Qiagen, Hilden, Germany) was used to isolate total cellular RNA from the AK samples and normal skin tissue samples according to the instructions of manufacturer, and then using the NanoDrop ND-2000 (Thermo Fisher Scientific, Waltham, MA) to quantify RNA. All of the RNA was assessed by standard denaturing agarose gel electrophoresis.

Microarray assay

According to the standard protocols of manufacturer (Agilent Technology, USA) of microarray hybridization, there are some processes to perform, including labeling Sample, transcribing into double-stranded cDNAs, cRNAs, 2nd cycle cDNAs, and hybridizing onto the microarray. And then using the Affymetrix Scanner 3000 (Affymetrix, USA) to wash, fix and scann the hybridized slides to images. Using Affymetrix GeneChip Command Console (version 4.0, Affymetrix) to collect the data and Robust Multichip Average (RMA) algorithm to normalize through the Expression Console (version1.3.1, Affymetrix) software. Finally, all data were imported into Genespring software (version 12.5, Agilent Technologies) for further analysis. A lncRNA or mRNA with a fold change (FC) >2.0 and a P value <0.05 via Volcano plot filtering was considered as the statistical significance of DE lncRNAs or DE mRNAs.

GO and KEGG pathway analyses

GO analysis (http://www.geneontology.org) including three realms, including cellular component, molecular function and biological process, which was used to analyze the primary function of the DE mRNAs. Besides, DE mRNAs were put into the KEGG database (http://www.genome.ad.jp/kegg/) to find out the significant pathways.

Analysis of lncRNA-mRNA co-expression network

The co-expression network was established by calculating the Pearson's correlation coefficient (PCC) between each lncRNA-mRNA pair, and those with $|PCC|>0.99$ and $P<0.01$ were considered significant. The co-expression network was visually constructed using Cytoscape software (available online: https://cytoscape.org).

Statistical analysis

In RNA-sequencing analysis, data were analyzed using SPSS 17.0 software, genes with FC >2 and $P<0.05$ were considered significant. Student's *t*-tests were used to

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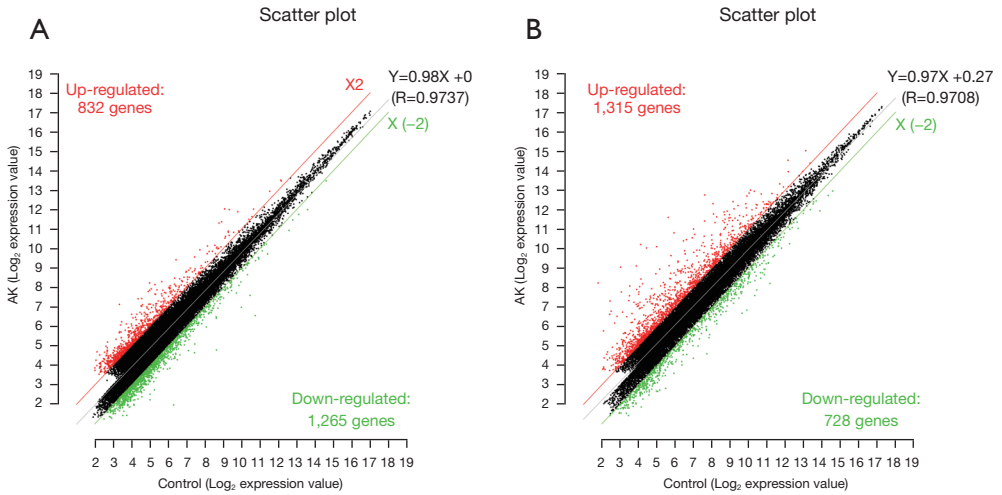

Figure 1 Scatter plots of lncRNAs and mRNAs expression levels. Scatter plots of lncRNAs (A) and mRNAs (B) expression levels between the AK and normal cutaneous tissue specimens (control groups). They show transcripts significantly upregulated in AK (red dots) and downregulated in AK (green dots) (P<0.05; fold change >2.0). The horizontal axis represents expression value in control group (on a $\log_2$ scale) and the vertical axis represents expression value in AK group (on a $\log_2$ scale). lncRNA, long non-coding RNA; mRNA, messenger RNA; AK, actinic keratosis.

generate P values. LncRNAs-mRNAs co-expression networks were calculated by R software (version 3.5.2), using PCC, |PCC|>0.99 and P<0.01 were considered significant, and networks were constructed by Cytoscape software54 (version 3.4.0; The Cytoscape Consortium, San Diego, CA, USA).

Results

Identification of differentially expressed lncRNAs and mRNAs

Based on the results of RNA-sequencing data, the results showed that there were 36612 lncRNAs and 32255 mRNAs in total, all the results are shown in https://cdn.amegroups.cn/static/public/tcr-22-842-1.xlsx. As a result, the expression of 2097 lncRNAs and 2043 mRNAs was found to be significantly changed (P<0.05, FC >2). Of them, 832 lncRNAs (red dots in *Figure 1A*) and 1315 mRNAs (red dots in *Figure 1B*) were significantly upregulated (P<0.05, FC >2) while 1265 lncRNAs (green dots in *Figure 1A*) and 728 mRNAs (green dots in *Figure 1B*) were significantly downregulated (P<0.05, FC >2) in AK. The most upregulated and downregulated DE lncRNAs are *hox-HOXD11-34* and *uc011fnr.2* respectively. And then We created a hierarchical cluster analysis heat map of DE lncRNAs and mRNAs (*Figure 2A*, *Figure 2B*).

GO enrichment and KEGG pathway analysis

GO enrichment analysis is widely used to reveal that DE mRNAs were significantly enriched in three categories, including biological processes, cellular components, and molecular functions. KEGG is a database for systematic analysis of gene function, and KEGG pathway database is mainly about intermolecular interaction and intermolecular interaction network. Here we performed GO enrichment and KEGG pathway analysis on the DE mRNAs to further explore potential targets in AK progression (*Figure 3*).

GO analysis showed that 7,773 GO terms in biological processes, 735 in molecular functions, and 1,541 in cellular components in total were differentially expressed in AK. *Figure 3A* presented in the top 20 significantly enriched GO terms, and the most significant expressed themes determined by P value were 'skin development' (biological process, *Figure 3A* blue), 'keratin filament' (cellular component, *Figure 3A* yellow) and 'structural constituent of muscle' (molecular function, *Figure 3A* red).

The KEGG pathway analysis showed that 282 KEGG pathways significantly enriched with the DE mRNAs. The top 20 significantly enriched KEGG pathways are presented in *Figure 3B*, the top 5 most enriched KEGG pathways included the peroxisome proliferator-activated receptors (PPARs) signaling pathway, staphylococcus aureus infection, cardiac muscle contraction, retinol metabolism

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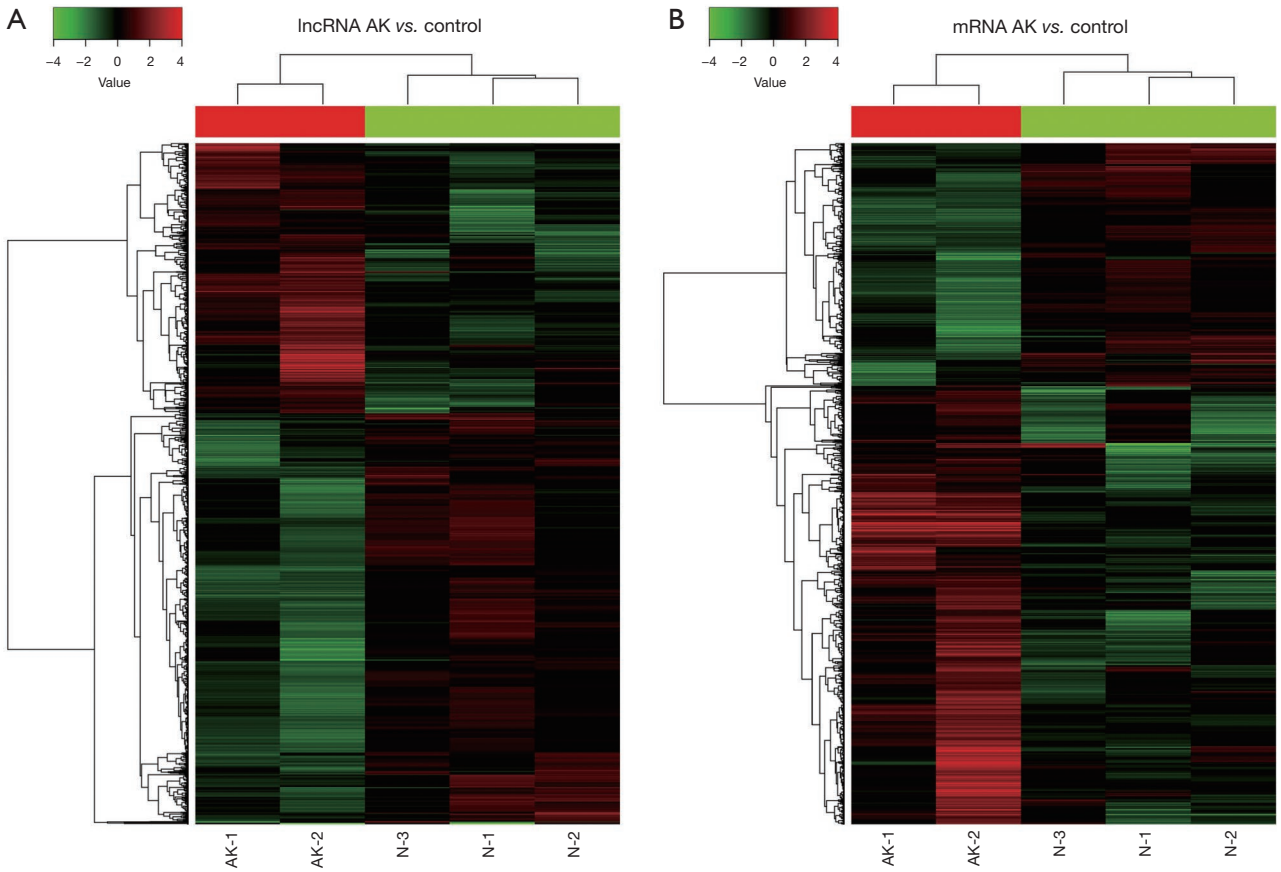

Figure 2 Heat map of DE lncRNAs and mRNAs. Hierarchical clustering analysis heat map of DE lncRNAs (A) and DE mRNAs (B) in the expression levels of AK patients and normal controls, 'N' for normal cutaneous tissue samples and 'AK' for AK tissue samples. Red represents high relative expression. Green represents low relative expression. DE, differentially expressed; lncRNAs, long non-coding RNAs; mRNAs, messenger RNAs; AK, actinic keratosis.

and biosynthesis of unsaturated fatty acids.

LncRNA-mRNA co-expression network

We constructed lncRNA-mRNA co-expression network analysis which consists of the top 10 DE lncRNAs, the individual mRNAs expression levels in the samples was tested by PCC and the reliability of PCC was tested by P value (PCC >0.99 or <–0.99, P value to <0.01). PCC equal to 1 or –1 indicates strict positive correlation and negative correlation individually.

We found that 130 mRNAs (blue dots in *Figure 4*) had significant correlation with the expression levels of the top 10 DE lncRNAs (red squares in *Figure 4*), and then we built as 156 edges of co-expression lncRNA-mRNA. As shown in the figure, lncRNA *ENST00000445908.1* which is co-expressed with 28 of the 130 mRNAs identified was the one that obtained the highest number of interactions in the co-expression network. *boxHOXD1134* co-expressed with as many as 23 mRNAs was the next most abundant.

Discussion

Current studies have shown that some lncRNAs may become potential therapeutic targets or biomarkers in AK and cSCC (15). And there is a study identified that *PRECSIT*, which as a new p53-regulated lncRNA, is up-regulated in invasive cSCC, cSCC *in situ* and AK *in vivo*, and can promotes progression of cSCC via activator of transcription 3 (STAT3) signaling (16). Although a growing number of evidence has showed that lncRNAs played important roles in AK or SCC, the detailed functions and potential mechanisms remain still unclear.

In the present study, we carried out whole-genome

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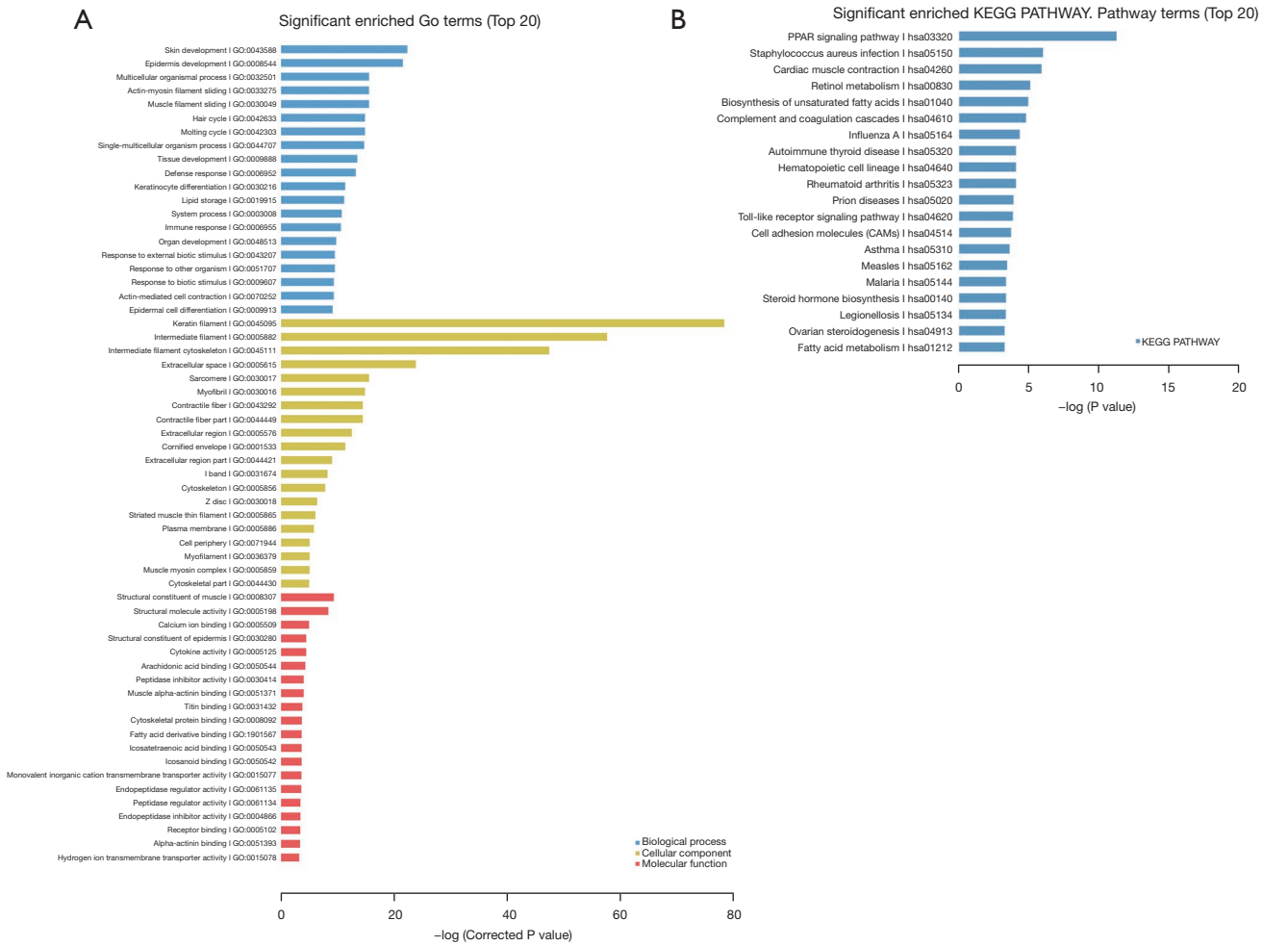

Figure 3 GO Enrichment analysis and KEGG pathway analysis. (A) GO enrichment analysis: it shows that compared with normal skin controls, the top 20 most enriched GO terms of DE mRNAs in AK skin tissues. The enriched GO terms consist of three categories: biological process (blue), cellular component (yellow) and molecular function (red); (B) KEGG pathway analysis: it shows that compared with normal skin controls, the 20 most enriched KEGG pathways of DE mRNAs in AK. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; DE, differentially expressed; mRNAs, messenger RNAs.

identification of lncRNAs and mRNAs in the normal skin tissue and AK tissue samples. Our results showed that 36,612 lncRNA probes and 32,255 mRNA probes were detected in total, and 2,097 lncRNAs and 2,043 mRNAs were found to be significantly DE (FC >2 and P value <0.05). Four downregulated lncRNAs and six upregulated lncRNAs in the top 10 DE lncRNAs.

Some of the DE lncRNAs we identified have been reported to have roles in oncogenesis or development, such as the p33920 probe detected lncRNA *box-HOXD11-34*, the most upregulated DE lncRNAs, and the p27963 probe detected lncRNA *nc-HOXA5-68*, the 11th downregulated DE lncRNAs. They are both belonged to Hox genes family. Hox genes which are highly conserved subgroup of the homeobox superfamily, and they have crucial roles in apoptosis, receptor signaling, differentiation, motility, angiogenesis and oncogenesis (17). There are studies (18,19) showed that *HOXD11* gene plays critical roles in skeletal homeostasis. But *HOXA5* gene is mainly reported to be involved in tumor progression and metastasis, such as colorectal cancer (20), cervical cancer (21), breast cancer (22), liver cancer (23) and so on.

In addition, GO and KEGG pathway analysis showed that the DE mRNAs changed significantly. From the

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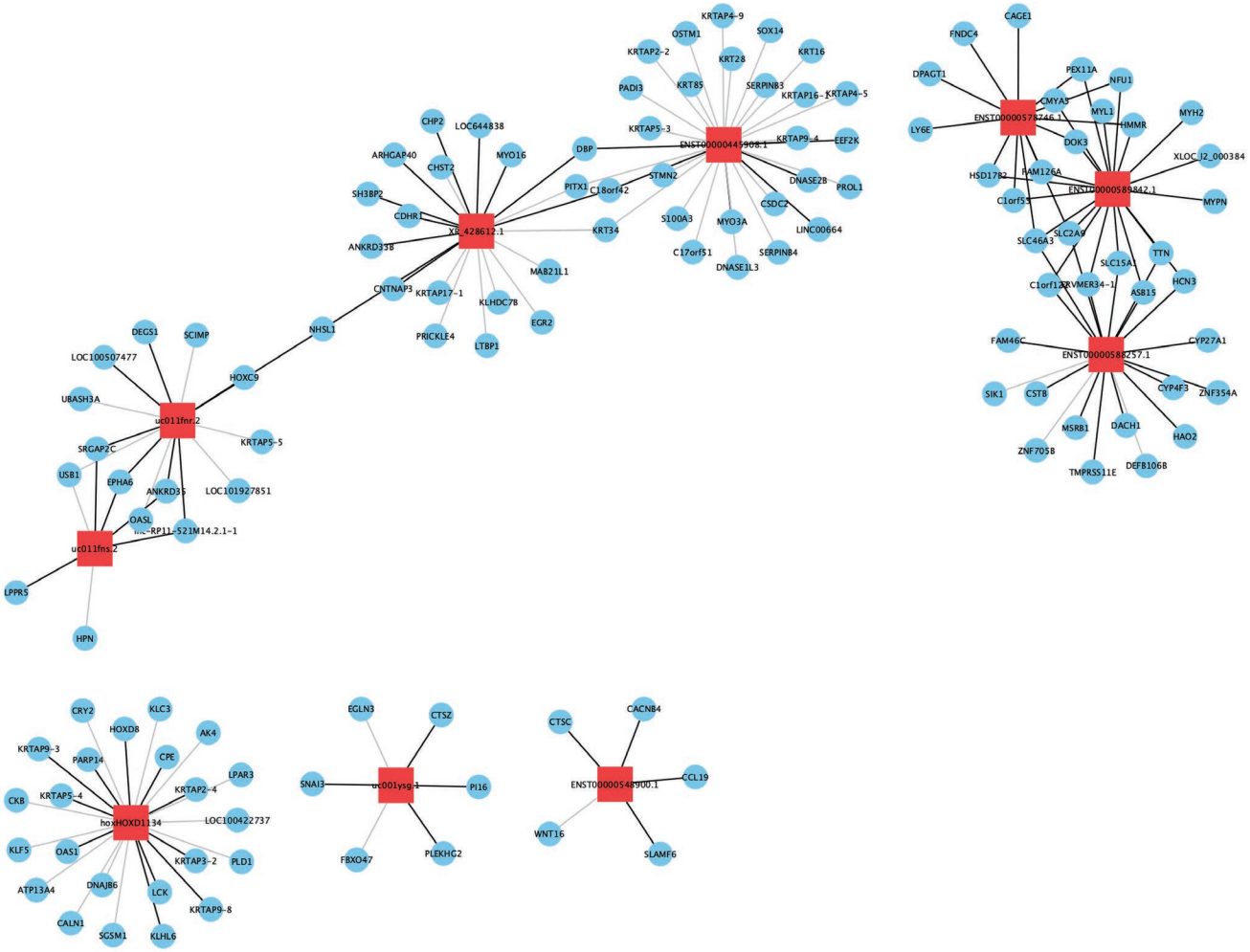

Figure 4 LncRNA and mRNA co-expression network. The lncRNA-mRNA co-expression network includes the top 10 DE lncRNAs (red squares), and 150 mRNAs (blue dots) and 156 edges which were correlated with the lncRNAs. Each edge represents correlation R value greater than 0.99 or smaller than –0.99 with P value <0.01. DE, differentially expressed; lncRNA, long non-coding RNA; mRNA, messenger RNA.

KEGG analysis, we found the top significantly changed pathway was the PPARs signaling pathway which are the number of nuclear receptor super-family. PPARs are transcription factors and play an important role in glucose and lipid metabolism (24). Toll-like receptors (TLRs) signaling pathway was the twelfth significantly changed pathway. TLRs are a pattern recognition receptors family which has important roles in host defense from infection, Yusuf's study showed that mice with a loss-of-function mutation in TLR4 developed more tumors than wild-type mice, and the reason may be the decrease activation of interferon (IFN)-γ-dependent anti-tumor T-cell responses (25,26), which indicates TLR signaling pathway may play an important role in the process of AK development. Janda found a significant increase in expression of TLR4 occurs in keratinocytes during the progression from normal skin to AK, and their data showed that pharmacological TLR4 antagonism (resatorvid) can suppress UV-induced cutaneous signaling (27).

To further explore the detailed functions and underlying mechanisms of lncRNAs in AK, we used the top ten specific DE lncRNAs to construct a lncRNA-mRNA co-expression network. The most downregulated lncRNA, *uc011fnr.2*, in AK had not been studied, and we found that it has a co-

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expression relationship with fourteen mRNAs through our co-expression network, including *USB1*, *OASL*, *UBASH3A*, *SCIMP* and etc. All of the four RNAs mentioned above were related to inflammation. *USB1* is associated with the recessive disorder poikiloderma with neutropenia (28). *OASL* has been reported that it can inhibit IFN induction *in vivo* and *in vitro* during DNA virus infections, while promoting IFN antiviral activity against RNA virus infection (29). *UBASH3A* was thought to mediate risk for type 1 diabetes through inhibiting T-cell receptor-induced NF-κB signaling, and the disruption of *UBASH3A* increased the degree of salivary gland inflammation in female mice which dependent on type II IFN signaling (30,31). SLP adaptor and C-terminal Src kinase-interacting membrane protein (*SCIMP*) which was negatively correlated with *uc011fnr.2* in our co-expression network is an immune-restricted, transmembrane adaptor protein, as a non-Toll/Interleukin-1 receptor (TIR)-containing adaptor, it can bind directly to the TLR4-TIR domain and promote selective proinflammatory cytokine responses by direct modulation of TLR4. In macrophages, *SCIMP* can facilitate TLR-inducible production of the proinflammatory cytokines IL-6 and IL-12p40 (32). IL-6 is a major mediator of inflammation which can be expressed at high levels in the tumor microenvironment, it can activate Janus kinase (JAK)-signal transducer and STAT3 signaling in both tumor cells and tumor-infiltrating immune cells, promoting tumor-cell proliferation, survival, invasiveness, and metastasis (33). JAK-STAT3 are very important for cancer development in tumor cells and tumor microenvironment and have become the most promising new targets for cancer therapy (34). In inflammation related colon cancer, increased TLR4 expression in intestinal epithelial cells will induce STAT3 activation, thus promoting the growth of colon tumors *in vivo*, in addition, TLR4-STAT3 signal transduction is related to the clinical stage of human colon adenocarcinoma (35). At the same time, TLR4 also promotes the formation of lymphoma by up regulating IL-6 and miR-21 (36). In addition, *SCIMP*, as a TLR adapter protein, was identified that it can mediate a process that apolipoprotein C3 can activate the nod-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome in human monocytes by inducing an alternative NLRP3 inflammasome via caspase-8 and dimerization of TLRs 2 and 4 (37).

Therefore, combined with previous research findings and our existing research results, we speculate that *uc011fnr.2* can inhibit JAK-STAT3 signaling pathway by negatively regulating *SCIMP*, TLR4 and IL-6 molecules, protecting the development of AK, *uc011fnr.2* may become one of the biomarkers of AK in the future.

Conclusions

In conclusion, we identified 2,097 DE lncRNAs and 2,043 DE mRNAs from the microarray of AK patients' tissues and healthy skin tissues. And then, we analyzed GO enrichment and KEGG pathway to find out the potential function of mRNAs and lncRNAs. Finally, we performed a comprehensive analysis of lncRNA-mRNA co-expression network to provides a better understanding of potential functions of DE genes in AK. The results indicated that lncRNA *uc011fnr.2* may play an important role in JAK-STAT3 signaling pathway of AK by modulating *SCIMP*, TLR4 and IL-6. Further research is required to validate the value of lncRNA *uc011fnr.2* in the progression of AK.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-842/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-842/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-842/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Institutional Review Board of Peking

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Union Medical College (No. 2016-KY013). The study protocol was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and written informed consent was obtained from all participants.

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References

1. Zhao Y, Li CY, Wen CM, et al. The prevalence of actinic keratosis in patients visiting dermatologists in two hospitals in China. Br J Dermatol 2016;174:1005-10.
2. Chen GJ, Feldman SR, Williford PM, et al. Clinical diagnosis of actinic keratosis identifies an elderly population at high risk of developing skin cancer. Dermatol Surg 2005;31:43-7.
3. Criscione VD, Weinstock MA, Naylor MF, et al. Actinic keratoses: Natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. Cancer 2009;115:2523-30.
4. Derrien T, Johnson R, Bussotti G, et al. The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. Genome Res 2012;22:1775-89.
5. Ulitsky I, Bartel DP. lincRNAs: genomics, evolution, and mechanisms. Cell 2013;154:26-46.
6. Kopp F, Mendell JT. Functional Classification and Experimental Dissection of Long Noncoding RNAs. Cell 2018;172:393-407.
7. Gupta RA, Shah N, Wang KC, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature 2010;464:1071-6.
8. Kawasaki Y, Komiya M, Matsumura K, et al. MYU, a Target lncRNA for Wnt/c-Myc Signaling, Mediates Induction of CDK6 to Promote Cell Cycle Progression. Cell Rep 2016;16:2554-64.
9. Wang L, Cho KB, Li Y, et al. Long Noncoding RNA (lncRNA)-Mediated Competing Endogenous RNA Networks Provide Novel Potential Biomarkers and Therapeutic Targets for Colorectal Cancer. Int J Mol Sci 2019;20:5758.
10. Cao HL, Liu ZJ, Huang PL, et al. lncRNA-RMRP promotes proliferation, migration and invasion of bladder cancer via miR-206. Eur Rev Med Pharmacol Sci 2019;23:1012-21.
11. Zhen Q, Gao LN, Wang RF, et al. LncRNA DANCR Promotes Lung Cancer by Sequestering miR-216a. Cancer Control 2018;25:1073274818769849.
12. Lohcharoenkal W, Li C, Mahapatra KD, et al. MicroRNA-130a acts as a tumor suppressive miRNA in cutaneous squamous cell carcinoma and regulates the activity of the BMP/SMAD1 pathway by suppressing ACVR1. J Investig Dermatol 2021;141:1922-31.
13. Meyer JM, Lee E, Celli A, et al. CERKL is upregulated in cutaneous squamous cell carcinoma and maintains cellular sphingolipids and resistance to oxidative stress. Br J Dermatol 2021;185:147-52.
14. Riihilä P, Viiklepp K, Nissinen L, et al. Tumour-cell-derived complement components C1r and C1s promote growth of cutaneous squamous cell carcinoma. Br J Dermatol 2020;182:658-70.
15. Das Mahapatra K, Pasquali L, Søndergaard JN, et al. A comprehensive analysis of coding and non-coding transcriptomic changes in cutaneous squamous cell carcinoma. Sci Rep 2020;10:3637.
16. Piipponen M, Nissinen L, Riihilä P, et al. p53-Regulated Long Noncoding RNA PRECSIT Promotes Progression of Cutaneous Squamous Cell Carcinoma via STAT3 Signaling. Am J Pathol 2020;190:503-17.
17. Shah N, Sukumar S. The Hox genes and their roles in oncogenesis. Nat Rev Cancer 2010;10:361-71.
18. Sheth R, Marcon L, Bastida MF, et al. Hox genes regulate digit patterning by controlling the wavelength of a Turing-type mechanism. Science 2012;338:1476-80.
19. Song JY, Pineault KM, Dones JM, et al. Hox genes maintain critical roles in the adult skeleton. Proc Natl Acad Sci U S A 2020;117:7296-304.
20. Ordóñez-Morán P, Dafflon C, Imajo M, et al. HOXA5 Counteracts Stem Cell Traits by Inhibiting Wnt Signaling in Colorectal Cancer. Cancer Cell 2015;28:815-29.
21. Ma HM, Cui N, Zheng PS. HOXA5 inhibits the proliferation and neoplasia of cervical cancer cells via downregulating the activity of the Wnt/β-catenin pathway and transactivating TP53. Cell Death Dis 2020;11:420.
22. Wang H, Wei H, Wang J, et al. MicroRNA-181d-5p-Containing Exosomes Derived from CAFs Promote EMT by Regulating CDX2/HOXA5 in Breast Cancer. Mol Ther Nucleic Acids 2020;19:654-67.

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23. Liao Y, Wang C, Yang Z, et al. Dysregulated Sp1/miR-130b-3p/HOXA5 axis contributes to tumor angiogenesis and progression of hepatocellular carcinoma. Theranostics 2020;10:5209-24.
24. Mirza AZ, Althagafi II, Shamshad H. Role of PPAR receptor in different diseases and their ligands: Physiological importance and clinical implications. Eur J Med Chem 2019;166:502-13.
25. Rakoff-Nahoum S, Medzhitov R. Toll-like receptors and cancer. Nat Rev Cancer 2009;9:57-63.
26. Yusuf N, Nasti TH, Long JA, et al. Protective role of Toll-like receptor 4 during the initiation stage of cutaneous chemical carcinogenesis. Cancer Res 2008;68:615-22.
27. Janda J, Burkett NB, Blohm-Mangone K, et al. Resatorvid-based Pharmacological Antagonism of Cutaneous TLR4 Blocks UV-induced NF-κB and AP-1 Signaling in Keratinocytes and Mouse Skin. Photochem Photobiol 2016;92:816-25.
28. Hilcenko C, Simpson PJ, Finch AJ, et al. Aberrant 3' oligoadenylation of spliceosomal U6 small nuclear RNA in poikiloderma with neutropenia. Blood 2013;121:1028-38.
29. Ghosh A, Shao L, Sampath P, et al. Oligoadenylate-Synthetase-Family Protein OASL Inhibits Activity of the DNA Sensor cGAS during DNA Virus Infection to Limit Interferon Production. Immunity 2019;50:51-63.e5.
30. Ge Y, Paisie TK, Newman JRB, et al. UBASH3A Mediates Risk for Type 1 Diabetes Through Inhibition of T-Cell Receptor-Induced NF-κB Signaling. Diabetes 2017;66:2033-43.
31. Chen YG, Ciecko AE, Khaja S, et al. UBASH3A deficiency accelerates type 1 diabetes development and enhances salivary gland inflammation in NOD mice. Sci Rep 2020;10:12019.
32. Luo L, Bokil NJ, Wall AA, et al. SCIMP is a transmembrane non-TIR TLR adaptor that promotes proinflammatory cytokine production from macrophages. Nat Commun 2017;8:14133.
33. Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nat Rev Clin Oncol 2018;15:234-48.
34. Yu H, Lee H, Herrmann A, et al. Revisiting STAT3 signalling in cancer: new and unexpected biological functions. Nat Rev Cancer 2014;14:736-46.
35. Eyking A, Ey B, Rünzi M, et al. Toll-like receptor 4 variant D299G induces features of neoplastic progression in Caco-2 intestinal cells and is associated with advanced human colon cancer. Gastroenterology 2011;141:2154-65.
36. Ochi A, Graffeo CS, Zambirinis CP, et al. Toll-like receptor 7 regulates pancreatic carcinogenesis in mice and humans. J Clin Invest 2012;122:4118-29.
37. Zewinger S, Reiser J, Jankowski V, et al. Apolipoprotein C3 induces inflammation and organ damage by alternative inflammasome activation. Nat Immunol 2020;21:30-41.

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