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Identification of the Coregulated mRNA and lncRNA Functional Pathways in Ovarian Cancer Using LncRNAs2Pathways by lncRNAs Based on an Integrated Network Propagation

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Abstract

Background: Ovarian Cancer is one of the most fatal female neoplasms associated with high mortality. Finding of the new mechanisms involved in the development of ovarian cancer will help us to better diagnosis and effective treatment.
Objectives: The current bioinformatics study aimed at investigating the relationship between messenger RNA (mRNA) and long non-coding RNA (lncRNA) in ovarian cancer through the LncRNAs2Pathways method.
Methods: The genome-wide lncRNA and mRNA data obtained from 185 ovarian cancer and healthy control samples originated from Michigan Medical School were downloaded and pretreated from European bioinformatics institute (EMBL-EBI) database. The interactions between miRNA and mRNA, and the intersections between lncRNA and miRNA were identified with starBase version 2.0. A long non-coding RNA-mediated ceRNA network (LMCN) was constructed by integrating lncRNA-mRNA and lncRNA-mRNA intersections. Then, the lncRNAs were mapped to the network, and these lncRNAs were regarded as source nodes, and the random walk with restart (RWR) algorithm was also applied to evaluate the effect of source nodes on protein-coding genes. Finally, the Kolmogorov-Smirnov-like statistics weighted by the propagation score was used to evaluate the enrichment value of each functional pathway.
Results: After preliminary screening, the gene expression profile including 12,437 genes was obtained. The LMCN network including 11 lncRNA and 367 mRNA were identified. A total of 11 differentially expressed lncRNAs between the normal and ovarian cancer samples by the LCMN network were identified. The LncRNAs2Pathways screened six functional pathways ($P < 0.05$) coregulated by lncRNAs related to ovarian cancer.
Conclusions: A total of six functional pathways related to lncRNA and mRNA interactions in ovarian cancer were identified. This finding is beneficial for effective diagnosis of patients with ovarian cancer, and also provides a new insight into the treatment of this disease.

Keywords: LncRNAs2Pathways Functional, Long Non-Coding, Messenger, Neoplasm, Ovarian, Pathway, RNA

1. Background

Ovarian cancer is one of the most fatal female cancers that can cause high mortality worldwide (1). If the tumor is diagnosed early, the five-year survival rate can exceed 80%. However, delayed diagnose often happens since the tumor cells may have already spread into the peritoneal cavity. Thus, the five-year reported survival rate is usually less than 40% (2). Therefore, it is necessary to understand the new mechanisms involved in the development of ovarian cancer for better diagnosis and effective treatment of this disease.

Long non-coding RNAs (lncRNAs) consist of more than 200 nucleotides and are involved in a wide range of biological processes (3, 4) such as gene expression, cell differentiation, immune response, and epigenetic regulation (5-8). Recently, more and more evidence shows that the lncRNAs play an important role in the pathology of cancer diseases (9). For example, the lncRNA overexpression is correlated with ovarian (10), breast (11), cervical (12), hepatocellular (13), and other tumor cells. Several lncRNAs play important roles in the development of ovarian cancer. For instance, human ovarian cancer-specific transcript 2 (HOST2) regulates biological behaviors of ovarian cancer through inhibition of let-7b functions (14). HOX transcript antisense RNA (HOTAIR) promotes proliferation, migration, and invasion as a competing endogenous RNA (ceRNA) in ovarian cells (15); whereas neuroblastoma associated transcript 1 (NBAT-1) could inhibit the development of ovarian cancer

and suppress tumorigenesis (16). However, all these studies just focused on the association between ovarian cancer and lncRNA alone, but the coregulation of lncRNA might play a key role in the development of ovarian cancer.

Recently, the potential coregulated disease-lncRNA associations are predicted by several methods. Jiang et al. (17) developed the lncRNA2Function to investigate the association between protein-coding genes and the lncRNAs and then, performed a hypergeometric test to functionally annotate lncRNAs. Zhao et al. (18) introduced a web-based computational tool, named co-lncRNA, for enrichment analysis of lncRNAs in Gene Ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG) pathways. Recently, Han et al. (19) developed an LncRNAs2Pathways to identify the key functional pathways related to differential expressed lncRNAs between patients with glioma, prostate, and pancreatic cancers, and normal controls based on RWR algorithm. They proved that the LncRNAs2Pathways is effective not to identify function predictor for lncRNA sets, and can provide a combinatorial effect of lncRNA in pancreatic cancers.

The current study cited the algorithm reported by Han et al. (19) to verify the effect of this method to identify key functional pathways related to ovarian cancer and investigate their coregulation. The current study results help to identify the coregulated effect of functional pathways on ovarian cancer, which provides a new insight ino the treatment of this disease.

2. Methods

2.1. Data Extraction

In the current bioinformatics study, the genome-wide lncRNA and mRNA data were derived from a recent study published in Journal of Buon (20), which included samples from Michigan Medical School. The data of expression profile were collected from 185 patients with ovarian cancer and 10 age- and gender-matched healthy control subjects in the EMBL-EBI database (https://www.ebi.ac.uk/). These microarray datasets were extracted under accession number E-GEOD-26712, existed on A-AFFY-33-Affymetrix GeneChip Human Genome HG-U133A [HG-U133A]. After background correction and data standardization by the robust multichip average method to eliminate the influence of nonspecific hybridization, the expression values of lncRNA/mRNA were evaluated by summarizing the background-corrected intensity of the probes mapped to this gene. The gene expression profile was obtained.

The interactions between miRNA and mRNA (n = 423,975), and the intersections between lncRNA and miRNA (n = 10,212) were identified with starBase version 2.0 (21).

All genes in the expression profile were intersected with mRNA from the miRNA-mRNA and lncRNA from the lncRNA-miRNA intersections, respectively. As a result, a new gene profile was obtained.

To obtain new miRNA-mRNA and lncRNA-miRNA intersections, the mRNA and lncRNA in the new profile were again intersected with those of the miRNA-mRNA and lncRNA-miRNA intersections, respectively.

2.2. Identification of miRNA-mediated ceRNA Regulatory Networks

To construct the long non-coding RNA-mediated ceRNA network (LMCN), first the enrichment of miRNAs related to both lncRNA and mRNA was assessed by hypergeometric test Formula 1. Where N is the total number of miRNAs, K and M indicate the numbers of miRNAs associated with the current lncRNA and mRNA, respectively, and x represents the common miRNA number shared by the lncRNA and mRNA (22).

$$P=1-\sum_{t=0}^{x}\frac{\binom{K}{0ptt}\binom{N-K}{0ptM-t}}{\binom{N}{0ptM}} \quad (1)$$

Then, the Pearson correlation coefficient of the interactions was calculated and transformed to Z by the following Formula 2:

$$Z=0.5\left[ln\left(1+r\right)-ln\left(1-r\right)\right] \quad (2)$$

Finally, all the lncRNA-mRNA interaction pairs with $|z| > 0.7$ were screened to construct LMCN. The nodes of competitive lncRNA in LMCN network were regarded as the source nodes.

2.3. Evaluation of the Effect of lncRNAs on Protein-Coding Genes

The current study cited the RWR algorithm to prioritize the protein-coding genes related to lncRNAs as follows:

$$p\hat{}t+1=(1-r)\,Mp^{t}+rp^{0} \quad (3)$$

where M is the column-normalized adjacency matrix of the LMCN network, p^t is the node vector at the time step t, and p^0 is the initial probability vector of nodes. Each walker has the same probability to begin from each source node. The r parameter is a probability for walk in every time step at the source nodes, which was set at 0.7. The larger the probability of a protein-coding gene, the closer the location to the source nodes; and thereby influenced a lot by the source nodes. Then, the probabilities of the protein-coding genes were normalized to their square roots and defined as propagation scores. Finally, a ranked gene list L was obtained by ranking the protein-coding genes based on their propagation scores in the LMCN network.

2.4. Calculation of Pathway Enrichment Scores According to the Propagation Scores

The related pathways were downloaded from the KEGG database (23). To improve the reliability of the current study, the pathways with less than 15 protein-coding genes and more than 500 protein-coding genes were excluded. The protein-coding genes in each pathway were mapped to the ranked gene list L. If a protein-coding gene ranked at the top of the gene list L, the pathway it enriched was more possible to be influenced by the combinatorial effects of lncRNAs.

The ESs is calculated by the Kolmogorov-Smirnov-like statistics weighted by the propagation score. Higher ESs of a pathway indicated that the protein-coding genes might be ranked higher at the gene list L. The fraction of the genes in the pathway (F_{InP}) and that of the genes not in the pathway (F_{NotP}) were evaluated according to the below formulas (19):

$$\begin{aligned} \text{F\_InP}(i) &= \sum_{\substack{gj \epsilon P \\ j \le i}} \frac{|t_j|^P}{N_R},\ where\ N_R \\ &= \sum_{gj \epsilon P} |t_j|^P \end{aligned} \tag{4}$$

$$\text{F\_NotP}(i) = \sum_{\substack{gj \notin P \\ j \le i}} \frac{1}{N_{NotP}} \tag{5}$$

where t_j is the propagation score of gene j, N_R is the number of genes listed in L, and P is the propagation scores of the genes in different pathways set to 1 in this formula. When position i was walking down the L list, F_{InP} - F_{NotP} was calculated by adding it when a gene was screened in the pathway and discarding it when a gene was not in the pathway. The ESs was defined by the following formula:

$$\text{ES}(P) = max_{i \epsilon L} \{F_{InP}(i) - F_{NotP}(i)\} \tag{6}$$

2.5. Statistical Analysis of Enriched Pathways

The same account of lncRNAs equal to the number of source nodes was randomly selected from lncRNA-miRNA intersections (identified based on LMCN network) to construct the new LMCN network. Then, the propagation scores of the protein-coding genes in the LMCN network were recounted. The ESs of the pathways was also recomputed as well. The null distribution of the ESs (named ES_{null}) was generated after performing 1000 permutations. Then, the ES_{null} we compared with ES (P) to evaluate the value of P, which was P Value = M/N, where N represented the number of permutations, and M meant the number of ES_{null} greater than ES (P).

The P value was adjusted by false discovery rate (FDR). The pathways with P < 0.05 were regarded as competitive lncRNAs coregulated pathways in ovarian cancer.

3. Results

3.1. Identification of Competitive lncRNAs Related to the Ovarian Cancer

After preliminary screening, the gene expression profile including 12,437 genes was obtained. Then, all these genes were intersected with mRNA and lncRNA from the miRNA-mRNA interactions and lncRNA-miRNA intersection, and new profiles including 8377 genes related to 8351 mRNA and 26 lncRNA were identified. After further screening, a regulatory relationship consisted of 275,902 miRNA-mRNA and 601 lncRNA-miRNA intersections were identified.

3.2. Construction of LMCN Network

The LMCN network was constructed by a hypergeometric test with FDR correction for enrichment analysis of miRNAs that interacted with both lncRNA and mRNA. After FDR correction, the lncRNA-mRNA intersections with P values less than 0.01 were identified. The network included 26 lncRNA, 7244 mRNA, and 19,756 lncRNA- mRNA interactions.

Then, the correlation coefficient of lncRNA-mRNA interactions was calculated by Pearson analysis to screen coexpression network. As a result, the network including 11 lncRNA and 367 mRNA was constructed.

3.3. Identification of Source Nodes

In the current study, a total of 11 differentially expressed lncRNAs between the normal and ovarian cancer samples were identified by the LCMN network (Figure 1); they were: HCG18, TTTY15, LINC00663, LINC00652, PVT1, DGCR5, RHPN1-AS1, LINC00667, MAPKAPK5-AS1, TUG1, and ENTPD1-AS1.

3.4. Identification of Biological Pathway Coregulated by lncRNAs

To identify the biological pathways, the ES (p) value of LMCN network was compared with the ES_{null}. With an FDR < 0.05 pathway significance threshold, six biological pathways coregulated by lncRNAs related to ovarian cancer were identified (Table 1); they were the hematopoietic cell lineage pathway (P = 0), glycolysis gluconeogenesis pathway (P = 0.02), ERBB signaling pathway (P = 0.02), RNA degradation pathway (P = 0.036), endocytosis pathway (P = 0.036), and glycerophospholipid metabolism pathway (P = 0.04) (Figure 2).

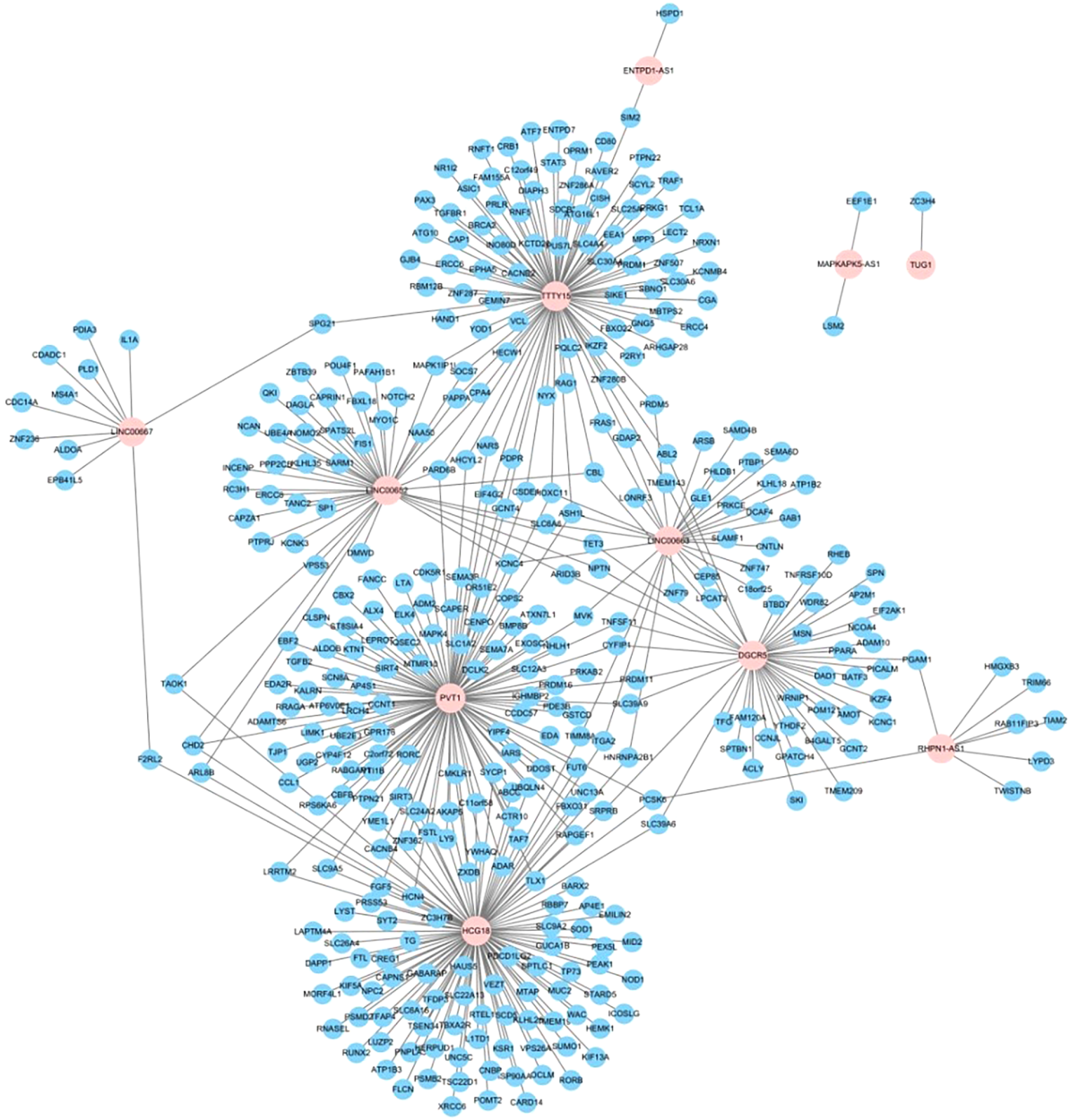

Figure 1. The ceRNA network constructed in the study. The red color indicates differentially expressed lncRNAs between the normal samples and the samples with ovarian cancer; the blue color indicates that the nodes were connected to the hub lncRNAs.

4. Discussion

Increasing evidence shows that the aberrant expression of lncRNAs plays an essensial role in the tumor malignancy (24, 25). As well, more and more lncRNAs are involved in the development of ovarian cancer (26, 27). However, these studies just focus on separate lncRNAs, which might contribute to the misapprehension of the ovarian cancer mechanism. The current study discovered several lncRNAs related key pathways involved in ovarian cancer by LncRNAs2Pathways algorithm. The current study results provided the key pathways in ovarian cancer development and a new algorithm for further investigation of key biological pathways. The key pathways involved in ovarian

Table 1. Biological Pathway Coregulated by lncRNAs Related to Ovarian Cancer

Gene Set Name	Enrichment Scores	P Value	FDR
KEGG_HEMATOPOIETIC_CELL_LINEAGE	0.89367	0	0
KEGG_GLYCOLYSIS_GLUCONEOGENESIS	0.82526	0.01	0.02
KEGG_ERBB_SIGNALING_PATHWAY	0.8481	0.01	0.02
KEGG_RNA_DEGRADATION	0.91531	0.03	0.036
KEGG_ENDOCYTOSIS	0.66622	0.03	0.036
KEGG_GLYCEROPHOSPHOLIPID_METABOLISM	0.83586	0.04	0.04

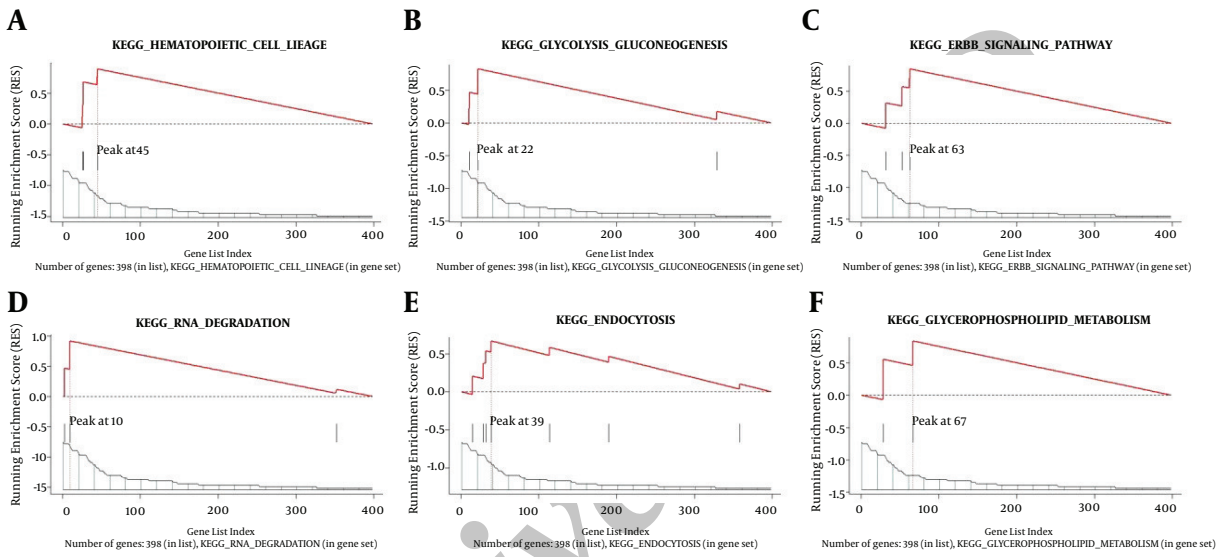

Figure 2. Protein-coding genes were mapped to the ranked protein-coding gene list, and the value of enrichment score was calculated. A, Enrichment score for hematopoietic cell lineage; B, Enrichment score for glycolysis gluconeogenesis; C, Enrichment score for ERBB signaling pathway; D, Enrichment score for endocytosis; E, Enrichment score for glycerophospholipid metabolism.

cancer discovered in the current study were hematopoietic cell lineage pathway, glycolysis gluconeogenesis pathway, ERBB signaling pathway, RNA degradation pathway, endocytosis, and glycerophospholipid metabolism pathway.

Until now, the functional analysis of lncRNAs is performed by several valuable ceRNA resources through computer programs such as starBase, miRSponge, and lncACTdb (21, 28, 29). The current study systematically evaluated a set of lncRNAs based on a network propagation strategy. The data were collected from patients with ovarian cancer and healthy control subjects in EMBL-EBI database. This database is an integration tool for proteomics and structural biology and is the largest one that included scientific experiments data (30). First, an LMCN network was constructed by integrating lncRNA-mRNA and lncRNA-mRNA intersections; then, the lncRNAs were mapped to the network and were regarded as source nodes; and the RWR algorithm was applied to evaluate the effect of source nodes on protein-coding genes. Finally, the Kolmogorov-Smirnov-like statistics was used weighted by the propagation score to evaluate the enrichment value of each functional pathway. Based on the scale of the network, only the coexpressed gene pairs with a cutoff of three datasets were retained. By combining P values across multiple databases, the gene coexpressed relationships were also extracted (31). Therefore, this method can be applied by researchers who only use a software package.

The "glycolysis effect" in cancer cells was suggested by Warbug that found the phenomenon of damaged respiration and the production of increased lactate (32). Therefore, the glycolysis pathway is a common pathway that happens in most cancer cells, ovarian cancer is no exception. The current study found that this pathway was a key one that might play an essensial role in the development of ovarian cancer.

The function of lncRNAs in glycolysis pathway gained

much attention in recent research. For example, Rupaimoole et al. (33) demonstrated that the lncRNAs ceruloplasmin modulated the metabolism of ovarian cancer by binding a partner between the signal transducer and activator of transcription 1 and RNA polymerase II, leading to upregulation of glucose-6-phosphate isomerase (35). Another study performed by Luo et al. (34) showed that the metastasis-associated lung adenocarcinoma transcript 1 could enhance the glycolysis through hypoxia-inducible factor (HIF)-1α stabilization in hepatic L-02 cells. Liu et al. (35) reported that the MiR-186 inhibited aerobic glycolysis in gastric cancer via HIF-1α regulation; in their further study, a novel role for HIF transcriptional pathway is proposed in gastric cancer by regulation of adenocarcinoma associated, positive CD44 regulator, long intergenic noncoding RNA (36). In ovarian cancer, it is also suggested that HIF-1α upregulates its downstream gene (such as glucose transport protein 1) to enhance glycolytic ability (37). Therefore, it was assumed that the glycolysis might be associated with coregulation of lncRNAs in ovarian cancer, which confirmed the results that the glycolysis was one of the top altered pathways in ovarian cancer.

The ERBB signaling pathway detected in the current study is involved in the tumor development and progression. In ovarian cancer, *ERBB2* was one of the oncogenes, which negatively regulated the apoptosis in an integrated hierarchical network of ovarian cancer (38). Glycerophospholipid metabolism pathway detected in the current study was also identified before (39). As it is already known, the glycerophospholipids are the components of the cell membrane. They are involved in the fatty acid synthesis, which is indispensable for highly proliferating cancer cells (40). Therefore, it was hypothesized that the glycerophospholipid metabolism pathway detected in the current study reflected abnormal proliferation of ovarian cancer. Therefore, the glycerophospholipids might be used as biomarkers to distinguish the patients with ovarian cancer from the healthy individuals, and provide a new means for diagnosis.

The current study had several limitations, which should be pointed out. First, the LncRNAs2Pathways did not consider the association degree between lncRNAs and ovarian cancer, thus the other network-based algorithms should be modified for better performance. Second, the results of the current study were not verified by basic experiments.

In conclusion, the LncRNAs2Pathways is effective to identify key functional pathways in ovarian cancer, and convenient to understand the coregulated relationships among these pathways.

Footnote

Authors' Contribution: Lu-yun Qu and Hai-yang Jiang are co-first authors.

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