Identification and characteristics of postnatal development-related long non-coding RNAs under microbiota dependent condition

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Abstract

Background

The interplay of long-non coding RNAs (lncRNAs) and the intestinal microbiota may serve as an essential role in intestinal development and homeostasis. Microbiota could regulate a large numbers of lncRNAs expression in intestinal epithelial cells. However, the associations between lncRNAs and microbiota during early postnatal development stages are still need to understand.

Methods

In present study, the microbial effects on lncRNA of intestinal epithelial cells (IECs) during postnatal development stage were investigated.

Results

We identified gut microbiota-specific lncRNAs in diverse postnatal development stages including week 1, week 4 and week 12/16 of mice. A large proportion of gut microbiota-specific lncRNAs only were differential expressed in a single postnatal development stage. Up- and down-regulated gut microbiota-specific lncRNAs both showed consistent expression pattern. We also constructed gut microbiota-specific lncRNAs and coding genes interacted co-expressed networks. Functional analysis indicated that gut microbiota-specific lncRNAs were associated with ABC transporters.

Conclusions

In summary, the present study characterizes the landscape of lncRNAs associated with gut microbiota in different postnatal development stages. It provide assistance for exploring the relationships among lncRNAs, gut microbiota and postnatal development stages.

Background

Postnatal development is a key period in which the interaction between an individual and the environment has a lifelong impact on health and well-being, and it is an extension of the concept of "fetal origin of health and disease" [1]. Combined action of metabolic, complex functional and structural mechanisms contribute to infant growth during the early postnatal period [2]. The organism did not fully mature at birth, so the process of maturation continued for some time after birth [3, 4]. More and more studies reveal that early postnatal development is associated with risk of disease in adulthood based on human and animal studies [5]. Many factors such as immune, nutrition, hormones and so on all can influence postnatal development [1, 6, 7]. Development of mammalian gastrointestinal is an important and essential part of postnatal development. Intestinal epithelial cells (IECs) play a central role in gastrointestinal [8]. Thus, ongoing researches should be need to explore the potential mechanism of postnatal development.

Over time, bacteria and other microorganisms have evolved together with their multicellular hosts to form a unique micro ecosystem, namely microbiota [9]. The human body is not a closed and sterile system. Microorganisms can be implanted into skin [10], gastrointestinal tract [11], respiratory tract [12], urogenital tract and other open surfaces, and develop into a local microbial community with unique characteristics. Gut microbiota is also an essential influenced factor in postnatal development. Many kinds of metabolic processes including energy homeostasis, glucose metabolism and lipid metabolism are regulated by gut microbiota [13, 14]. Imbalance of gut microbiota is related to metabolic perturbations during postnatal development process. In recent years, a trickle of studies have examined that lack of contact with environmental microbiota during early development stage maybe contribute to immune deficiency and advanced autoimmune diseases [15–17]. However, the functions of gut microbiota in postnatal development are still need to study.

Long non-coding RNA (lncRNA) is considered as an important type of non-coding RNA follow a series of researches [18, 19]. The biological function and molecular mechanisms of lncRNA in many kinds of human diseases in particular are constantly revealed [20, 21]. Besides diseases, the role of lncRNA in development also has been reported [22]. LncRNAs have been reported that not expressed at each certain stages in development. Expression of a lncRNA in a specific development stage indicate that it may have an important biological function at that time [23, 24]. For example, Phillip Grote et al. report that lncRNA locus Handsdown (Hdn) is active in early heart cells and essential for murine development [25]. The lncRNA Pnky is a trans-acting regulator of cortical development in vivo [26]. Wang et al. demonstrate that conserved lncRNAs at the nonimprinting regions in brain are essential for zebrafish development [27]. Although there are some evidences suggest that the important biological function and molecular mechanisms of lncRNA in postnatal development, their global ans systematic functions in development including gastrointestinal development remains largely unexplored. The associations among gut microbiota, development and lncRNA are also need to be in depth description and exploration.

In present study, lncRNAs could become as specific biomarkers for dividing mice samples of diverse postnatal development stages. Gut microbiota-specific lncRNAs were identified and analyzed in diverse postnatal development stages. Most of these gut microbiota-specific lncRNAs only differential expressed in a single postnatal development stage. Up- and down-regulated gut microbiota-specific lncRNAs showed consistent expression pattern. Gut microbiota-specific lncRNAs and coding genes interacted co-expressed networks were constructed. These gut microbiota-specific lncRNAs were associated with ABC transporters. Collectively, the results of the present study indicated that gut microbiota-specific lncRNAs could serve as essential roles in postnatal development stages.

Results

Samples similarity and difference of samples based on lncRNA transcriptome under diverse postnatal development stages and condition

In order to explore similarity and difference of samples based on lncRNA transcriptome under diverse postnatal development stages and condition. Hierarchical clustering method based on the PCCs was performed. We found all the samples of week 1 were clustered together (Fig. 1A). Samples of week 4 and week 12/16 cluster together obviously and couldn't distinguish. The result indicated that samples of week 1 showed stronger similarity on lncRNA level. CONV and GF samples also could be distinguished at some extent. The results of PCA for lncRNA expression showed first three PCs had most proportion of variance (Fig. 1B). Especially, the first PC accounts for 85%. Thus, the first three PCs were analyzed and showed, separately. Samples of week1 were separated from other two stages including week 4 and week 12/16 according to both the developmental stage and microbial status based on PC1 and PC2 (Fig. 1C). It indicated that lncRNA expression changed dramatically during maturation of IECs, especially in the early postnatal period. In addition, PC2 also could distinguish CONV and GF within single developmental week 1 stage. PC3 could separated week 4 and week 12/16 (Fig. 1D, E). Thus, these first three PCs showed outperformance on distinguishing developmental stage and microbial status. All the results indicated that lncRNA expression could serve as effective biomarkers for developmental stage and microbial status.

Some lncRNAs were differential expressed between CONV and GF mice in diverse postnatal development stages

In order to further explore roles of lncRNAs for microbiota in diverse postnatal development stages, differential expressed lncRNAs between CONV and GF mice were identified. In each postnatal development stage, a certain number of differential expressed lncRNAs were identified. For example, there was 20 differential expressed lncRNAs in week 1 (Fig. 2A). In week 4 and week 12/16 CONV and GF mice, 21 and 42 differential expressed lncRNAs were identified (Fig. 2B, 2C). We also describe the interactions of differential expressed lncRNAs among three diverse kinds of postnatal development stages. We found there is little intersection between these differential expressed lncRNAs in diverse postnatal development stages (Fig. 2D). It also indicated that microbiota-specific lncRNAs showed diverse expression pattern during postnatal development. Different microbiota-related lncRNAs serve as their roles at specific postnatal development stage.

Differential expressed lncRNAs between CONV and GF mice showed specific features in respective postnatal development stage

All above results revealed that microbiota-related lncRNAs showed significant differences in diverse postnatal development stage. Thus, we further depicted the specific features of microbiota-related lncRNAs in respective postnatal development stage. We divided all the microbiota-related lncRNAs to up- and down-regulated microbiota-related lncRNAs. In mice with week 1, there were 6 and 14 up- and down-

regulated microbiota-related lncRNAs. The expression pattern of up- and down-regulated microbiota-related lncRNAs were almost consistent (Fig. 3A, B). For example, fold-change values of almost all down-regulated microbiota-related lncRNAs showed declining trend. Fold-change values of almost all down-regulated microbiota-related lncRNAs showed rising trend. Similar pattern were also present in week 4 and week 12/16 (Figure S1). We also discovered that some up- and down-regulated lncRNAs showed similar expression patterns and clustered together (Fig. 3C, D). Specially, up-regulated lncRNAs Gm13067, Gm37459, F630040K05Rik, 4930519L02Rik, Gm16137 and Gm16540 form an independent cluster, obviously. Similarly, up- and down-regulated lncRNAs in other postnatal development stages also clustered diverse groups (Figure S2). Collectively, differential expressed lncRNAs between CONV and GF mice showed specific expression in diverse postnatal development stage. However, these lncRNAs also showed similar expression pattern in respective postnatal development stage.

Gut microbiota-specific lncRNA and protein coding gene interaction networks were constructed at different postnatal development stages

In order to describe biological mechanisms of gut microbiota-specific lncRNAs, lncRNA and protein coding gene interaction networks at different postnatal development stages were constructed. All the interactions were filtered by co-expression of lncRNAs and genes. Gut microbiota-specific lncRNA and gene interaction network in week 1 contained 11 lncRNAs and 209 genes (Fig. 4A). Only a little number of lncRNAs and genes had high degree in the network (Fig. 4B, C). It maybe could serve as a degree pattern of scale-free network. In addition, Gut microbiota-specific lncRNA and gene interaction network in week 4 contained 15 lncRNAs and 562 genes (Fig. 4D). Gut microbiota-specific lncRNA and gene interaction network in week 12/16 contained 31 lncRNAs and 461 genes (Fig. 4E). The degree of genes and lncRNAs in week 4 and week 12/16 also showed similar patterns which are only a small part of genes and lncRNAs had higher degree (Figure S3). The results revealed that gut microbiota-specific lncRNA could serve their roles by interacting with some genes in diverse postnatal development stages. Moreover, these gut microbiota-specific lncRNA and protein coding gene interaction networks showed specific features of meaningful biological network.

Gut Microbiota-specific Lncrnas Were Associated With Eukaryotic-type Abc Transporters

In order to further explore the biological functions of gut microbiota-specific lncRNAs in diverse postnatal development stages, functional analyses were performed for their interacted genes. In week 1, gut microbiota-specific lncRNAs were associated with key pathways including Rap1 signaling pathway, cAMP signaling pathway, Axon guidance and ATP Binding Cassette (ABC) transporters (Fig. 5A). In week 4, gut microbiota-specific lncRNAs were associated with key pathways including RNA transport, RNA

degradation, regulation of actin cytoskeleton, ABC transporters and so on (Fig. 5B). In week 12/16, gut microbiota-specific lncRNAs were associated with key pathways including tight junction, Rap1 signaling pathway, focal adhesion, ABC transporters and so on (Fig. 5C). The gut microbiota-specific lncRNAs showed different functions in diverse postnatal development stages. Notably, ABC transporters pathway was a key and common pathway which were associated with gut microbiota-specific lncRNAs in all postnatal development stages. Accumulating evidence reported that ABC transporters could regulate the absorption, distribution, metabolism, secretion and toxicity of xenobiotics [28]. Thus, we inferred that these gut microbiota-specific lncRNAs may play their role in postnatal development by participating in ABC transporters pathway. Previous study indicated that there were potential associations between ABC transporters of the intestinal epithelial cell barrier and gut microbes in health and disease [29]. Transporters belonging to the ABC superfamily couple the energy released from ATP hydrolysis to the translocation of a wide variety of substances into or out of cells and organelles [30]. ABC transporter is one of the largest known protein superfamily and there are 48 ABC transporters in humans. Yin et al. reported that there were close relationships among ABC transporters pathway, gut microbiota and obesity in chinese children and adolescents [31]. ABCA and ABCC were two major subfamilies in ABC transporters (Fig. 5D). Some key genes in these two subfamilies could interact with gut microbiota-specific lncRNAs (Fig. 5E). And, most of them showed high degree. These results indicated that gut microbiota-specific lncRNAs could influence ABC transporters pathway in postnatal development stages.

Discussion

Here, gut microbiota-specific lncRNAs at different postnatal development stages were identified and characterized. Gut microbiota-specific lncRNAs almost had no intersections among diverse postnatal development stages. These gut microbiota-specific lncRNAs showed specific expression pattern in respective postnatal development stage. Moreover, some gut microbiota-specific lncRNAs could cluster together in a postnatal development stage. Gut microbiota-specific lncRNAs were associated with eukaryotic-type ABC transporters based on genes and lncRNAs co-expressed interacted networks.

Accumulating evidence reported that gut microbiota were associated with multiple kinds of diseases including colon cancer [32], gestational diabetes [33], type 1 diabetes [34], cardiovascular disease [35] and so on. In addition, biological processes containing diet, weight [36], bone homeostasis [37] and postnatal development were also influenced by gut microbiota. Most of previous studies about gut microbiota focused on coding genes. In our work, gut microbiota-specific lncRNAs were identified in diverse postnatal development stage. Most of these lncRNAs only showed high expression in a specific postnatal development stage. Differential expressed lncRNAs almost had no intersections among diverse postnatal development stages. It revealed that most lncRNAs were time limited in postnatal development process. In addition, these lncRNAs also showed tissue specificity. The gut microbiota-specific lncRNAs and coding genes interacted networks revealed that lncRNAs served as their roles by regulating coding genes. These results enriched our understanding about biological mechanisms of gut microbiota in postnatal development.

Moreover, functional analysis indicated that gut microbiota-specific lncRNAs in diverse postnatal development stages were associated with eukaryotic-type ABC transporters. ABC transporter, a ubiquitous membrane protein superfamily, is involved in ATP driven transmembrane lipid bilayer substrate transport of cellular membranes [38]. Over the years, a large number of studies reported that ABC transporters participated in several fundamental cellular functions such as regulating cellular levels of lipids, hormones, ions by transporting peptides and cholesterol that serve as essential roles in a relevant number of genetic diseases [39, 40]. Bacteria use ABC transporters either as importers to bring nutrients and other molecules into cells or as exporters to pump toxins or other undesirable substances out of the cell. In our study, we also found gut microbiota-specific lncRNAs were also related to ABC transporters.

Conclusions

In summary, the present study identified and characterized gut microbiota-specific lncRNAs in diverse postnatal development stages. These gut microbiota-specific lncRNAs showed different expression pattern in diverse postnatal development stages. They served as roles by participating in eukaryotic-type ABC transporters in postnatal development stages. Our study could provide assistance for clarifying biological mechanisms and functions of lncRNAs in gut microbiota and postnatal development.

Materials And Methods

Collection of gut microbiota transcriptome during postnatal development stages of mice

The transcription data about small intestine of mice testing by RNA-seq technology was download from GEO (Gene Expression Omnibus, https://www.ncbi.nlm.nih.gov/geo/) database (under accession number: GSE94402, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE94402). The small intestine of mice were treated under two different conditions, conventional-raised mice (presence of microbiota, refers as CONV in our analysis) and germ-free mice (absence of microbiota, refers as GF in our analysis). All the mice were sacrificed at three different stages: 1, 4 and between 12 to 16 weeks of age. IECs were collected from the small intestine of 1-, 4- and 12 to 16-week-old mice, raised either in the presence or absence of a microbiota. The detailed information could be found in previous study [41].

Obtain of lncRNA profile in mice with and without gut microbiota during diverse postnatal development stages

We got lncRNA annotation file of mice from GENCODE database (vM23, https://www.gencodegenes.org/) [42], and subtracted lncRNA read counts information from the transcription data provided by previous dataset GSE94402. We calculated FPKM expression level according to the covering reads and lncRNA length. During this process, the lncRNAs that are expressed in at least half samples were retained. All the expression values of lncRNAs were transformed by log2 to satisfy the normal distribution.

Explore similarity and difference of samples based on lncRNA transcriptome under diverse postnatal development stages and condition

We evaluated sample similarity by Pearson correlation method using lncRNAs expression profiles. Then, we clustered samples to divide diverse groups using hierarchical clustering method based on the Pearson Correlation Coefficients (PCCs). This process was performed by pheatmap package as implemented in R program. Principle component analysis (PCA) was also performed for mice using lncRNAs expression level. We used the first 3 principle components (PCs) to visualize sample distribution.

Identification of differential expressed lncRNAs between CONV and GF mice

For each age state of mice, T test and fold change methods were performed to identify differential expressed lncRNAs by comparing the lncRNA expression profiles of CONV and GF mice. LncRNAs with $p < 0.01$ and $|\log2(CONV/GF)| > 1$ were identified as differential expressed lncRNAs. Intersections of differentially expressed lncRNAs sets in each stage were got.

Altering features of differential expressed lncRNAs between CONV and GF mice in diverse postnatal development stages

According to the lncRNA expression changes between CONV and GF condition, we divided lncRNAs into up- ($\log2(CONV/ GF) > 1$) and down-regulated ($\log2(CONV/ GF) < 1$) sets. For the up/down-regulated lncRNAs in each postnatal development stage, we calculated spearman correlation coefficients using fold levels ($\log2(CONV/ GF)$) of lncRNA expression, and clustered lncRNAs using hierarchical clustering method in pheatmap package as implemented in R program.

Construction of gut microbiota-specific lncRNA and protein coding gene interaction networks at different postnatal development stages

The experimentally validated and computationally predicted RNA and protein interacted data was collected from RNAInter repository (RNA Interactome Database, http://www.rna-society.org/raid/) [43]]. We extracted interactied entries which RNA type annotated as “lncRNA” and species type annotated as “Mus musculus”. Then, we mapped our identified differentially expressed lncRNAs into the obtained lncRNA-protein relationships. For the relationships at each postnatal development stage, we tested

lncRNA and the corresponding mRNA correlations by pearson correlation test using expression profiles. The significant correlated lncRNA-protein pairs ($p < 0.01$) were retained and visualized by cytoscape 3.3.0 software (https://cytoscape.org/).

Functional enrichment analysis of differential expressed lncRNAs in diverse postnatal development stages

For each postnatal development stage, functional enrichment analysis was performed using the lncRNA correlated proteins by enrichr web server (http://amp.pharm.mssm.edu/Enrichr/) [44], and get significant enriched pathways in mouse ($p < 0.01$). Enriched pathways were visualized by bubble plots. LncRNA and protein relationships in all postnatal development stages of the interested pathways were also visualized using cytoscape software.

Declarations

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZMM conceived and designed the experiments, ZBB, ZYB, and HBZ analyzed the data, ZMM and STT validated the work, and ZMM wrote the manuscript.

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Not applicable.

Disclosure of interest

The authors declare that they have no competing interest.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Consent for publication

Not applicable

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Figures

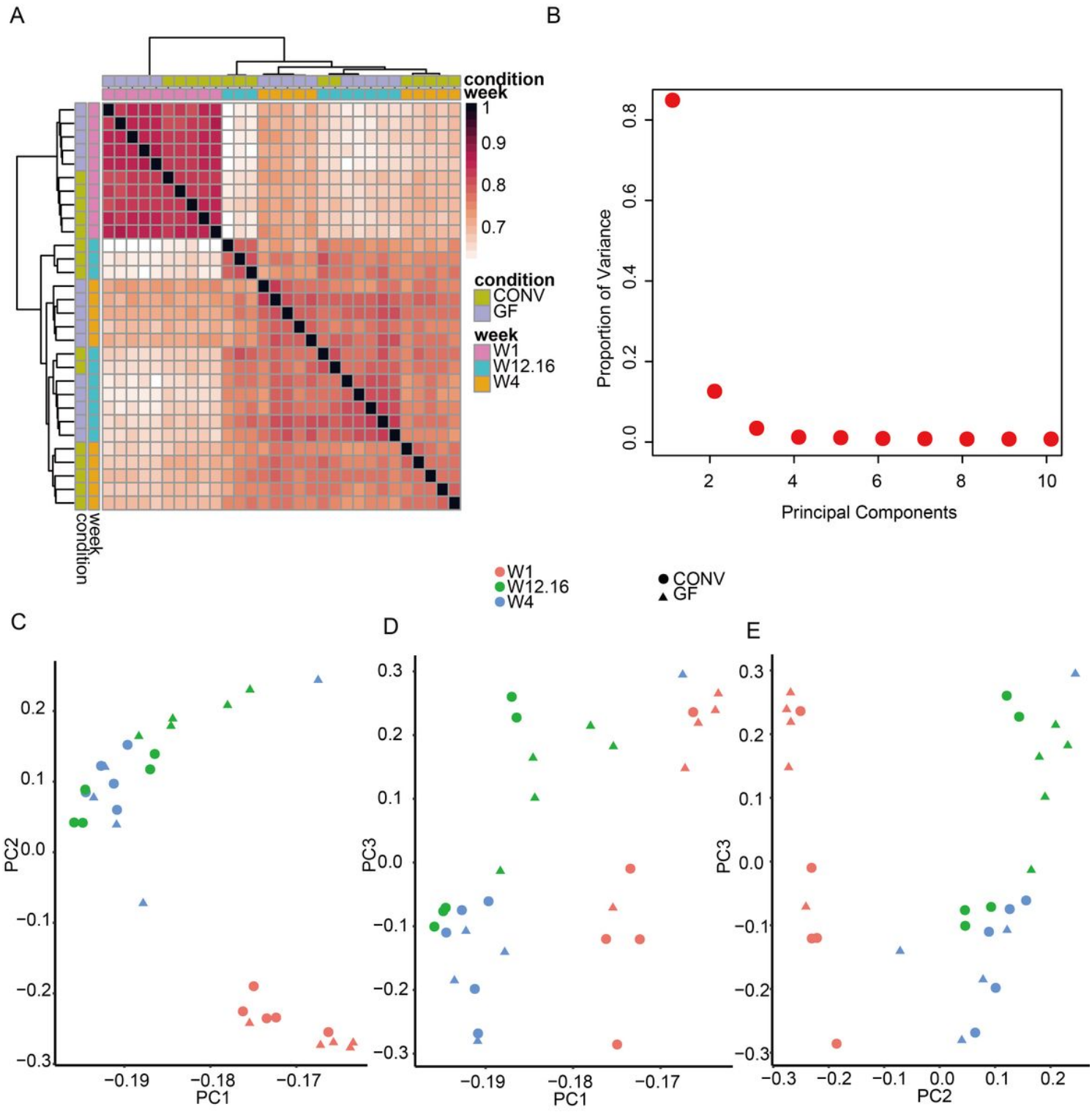

Figure 1

Samples similarity and difference of samples based on lncRNA transcriptome under diverse postnatal development stages and condition. (A) Hierarchical clustering of samples similarity between CONV and GF in the three developmental stages based on lncRNAs. (B) The point plot shows proportion of principal components. (C-E) Multidimensional scaling analysis plot displaying the overall lncRNA profile between CONV and GF in the three developmental stages.

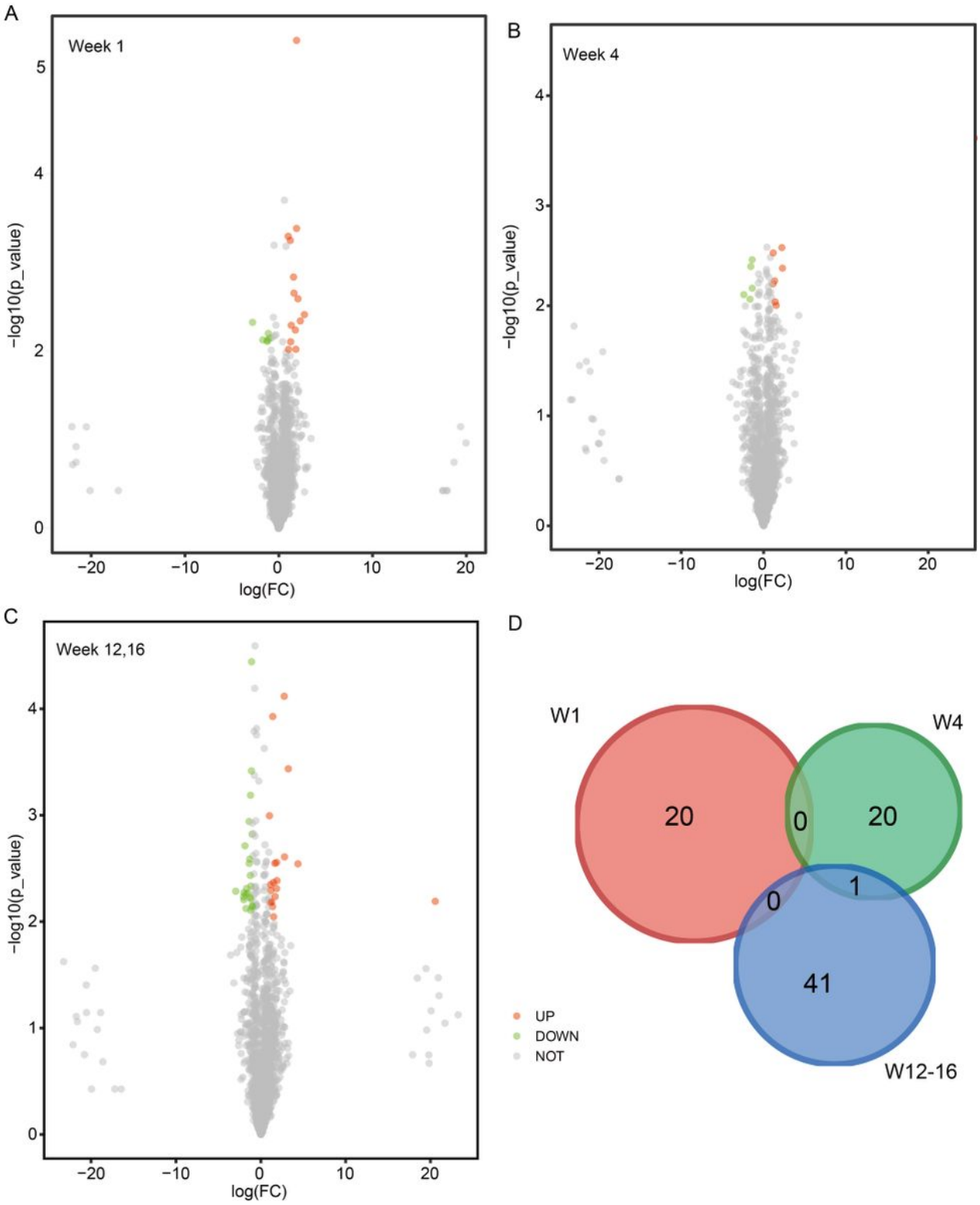

Figure 2

Some lncRNAs were differential expressed between CONV and GF mice in diverse postnatal development stages. (A) Volcano plots show differential expressed lncRNAs in week 1, (B) week 2 and (C) week 12/16. Orange, green and gray represent up-regulated, down-regulated and non-differential expressed lncRNAs. (D) The venn diagram shows intersection of differential expressed lncRNAs among week 1, week 4 and week 12/16.

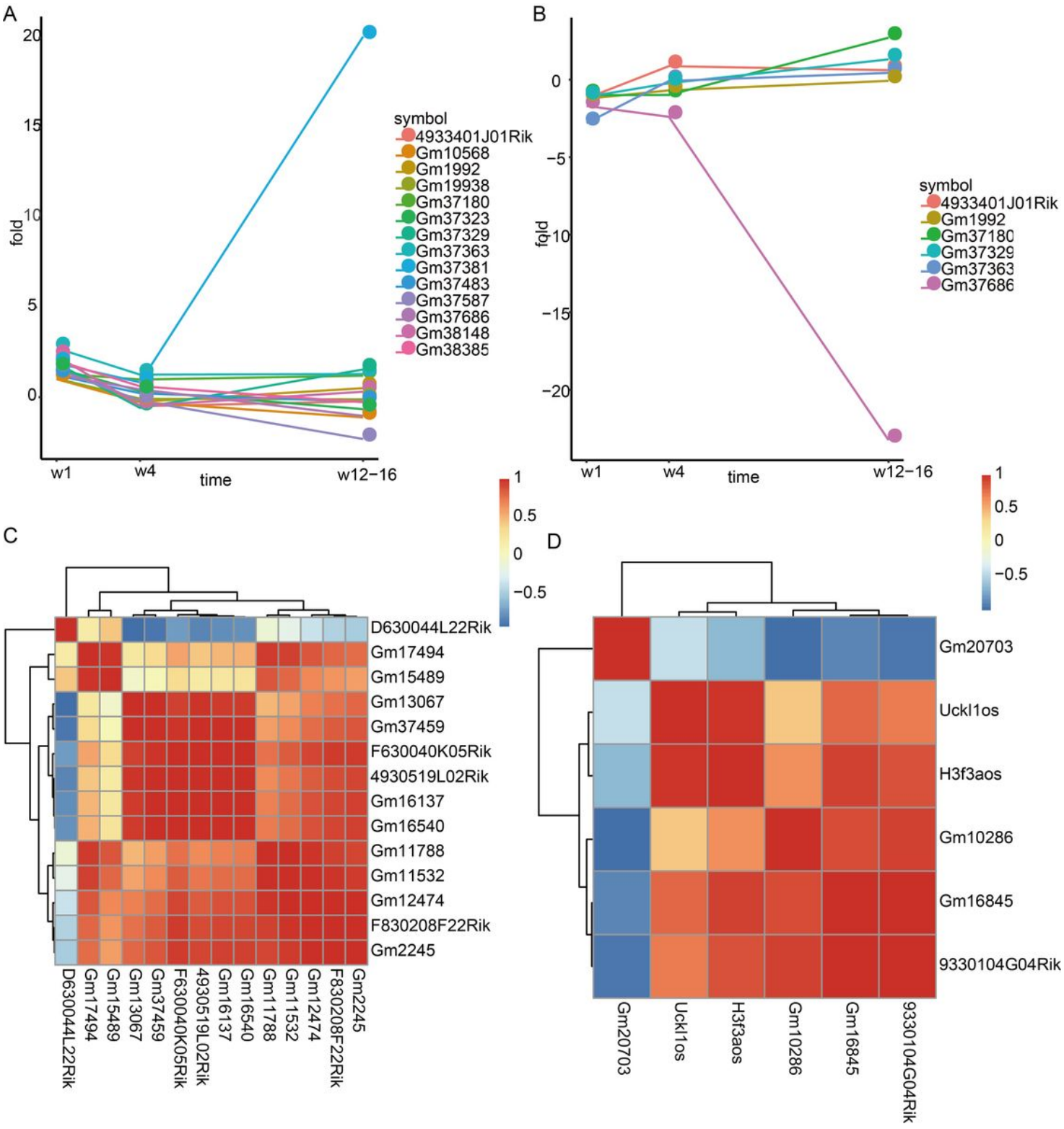

Figure 3

Differential expressed lncRNAs between CONV and GF mice showed specific features in respective postnatal development stage. (A) The line plots show fold-change values of up-regulated and (B) down-regulated lncRNAs in different postnatal development stage. (C) Hierarchical clustering of up-regulated and (D) down-regulated lncRNAs similarity.

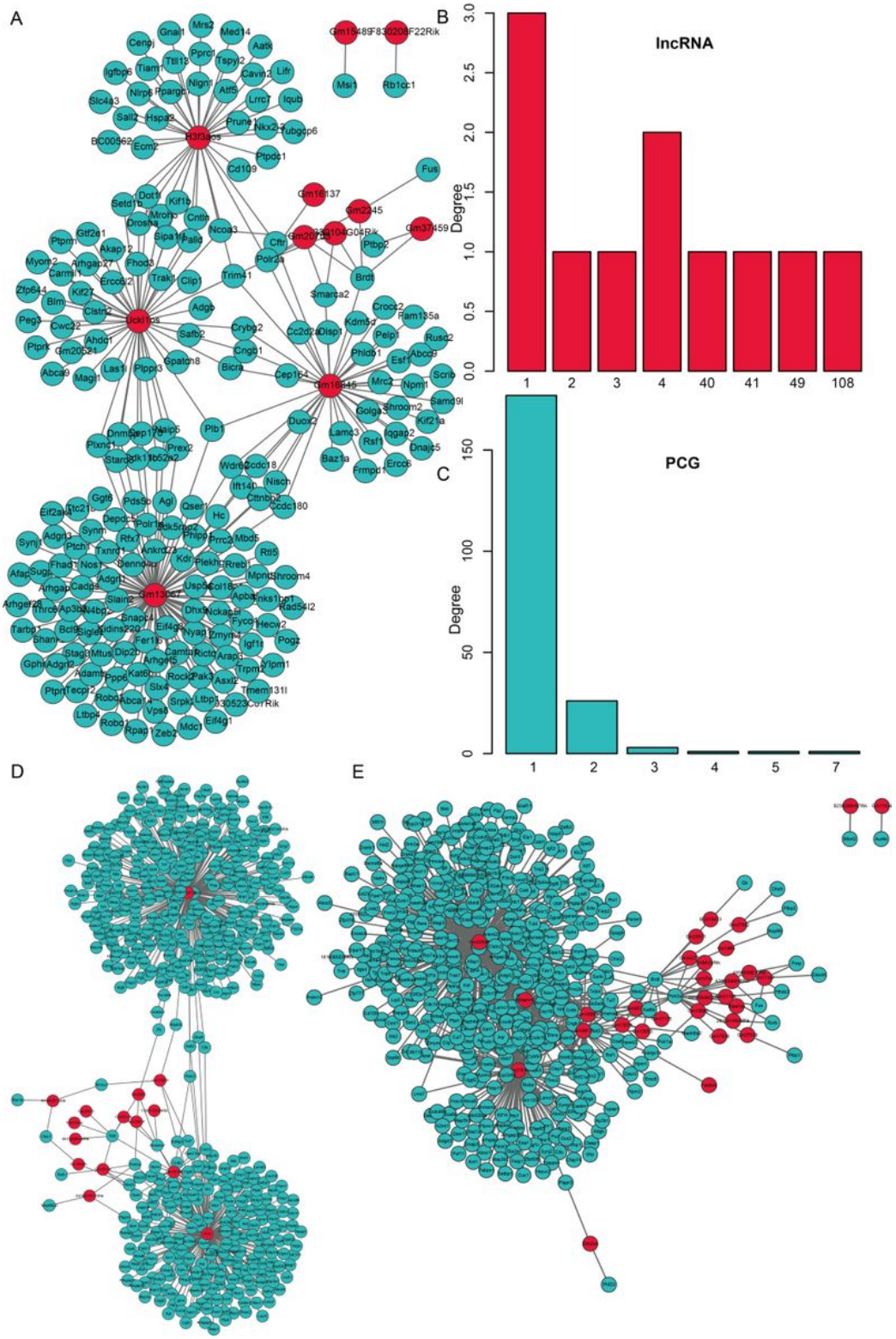

Figure 4

Gut microbiota-specific lncRNA and protein coding gene interaction networks were constructed at different postnatal development stages. (A) The Gut microbiota-specific lncRNA and gene interacted network for week 1. Green and red represent genes and lncRNAs. (B-C) Bar plots show degree of lncRNAs and genes. (D-E) The gut microbiota-specific lncRNA and gene interacted network for week 4 and week 12/16.

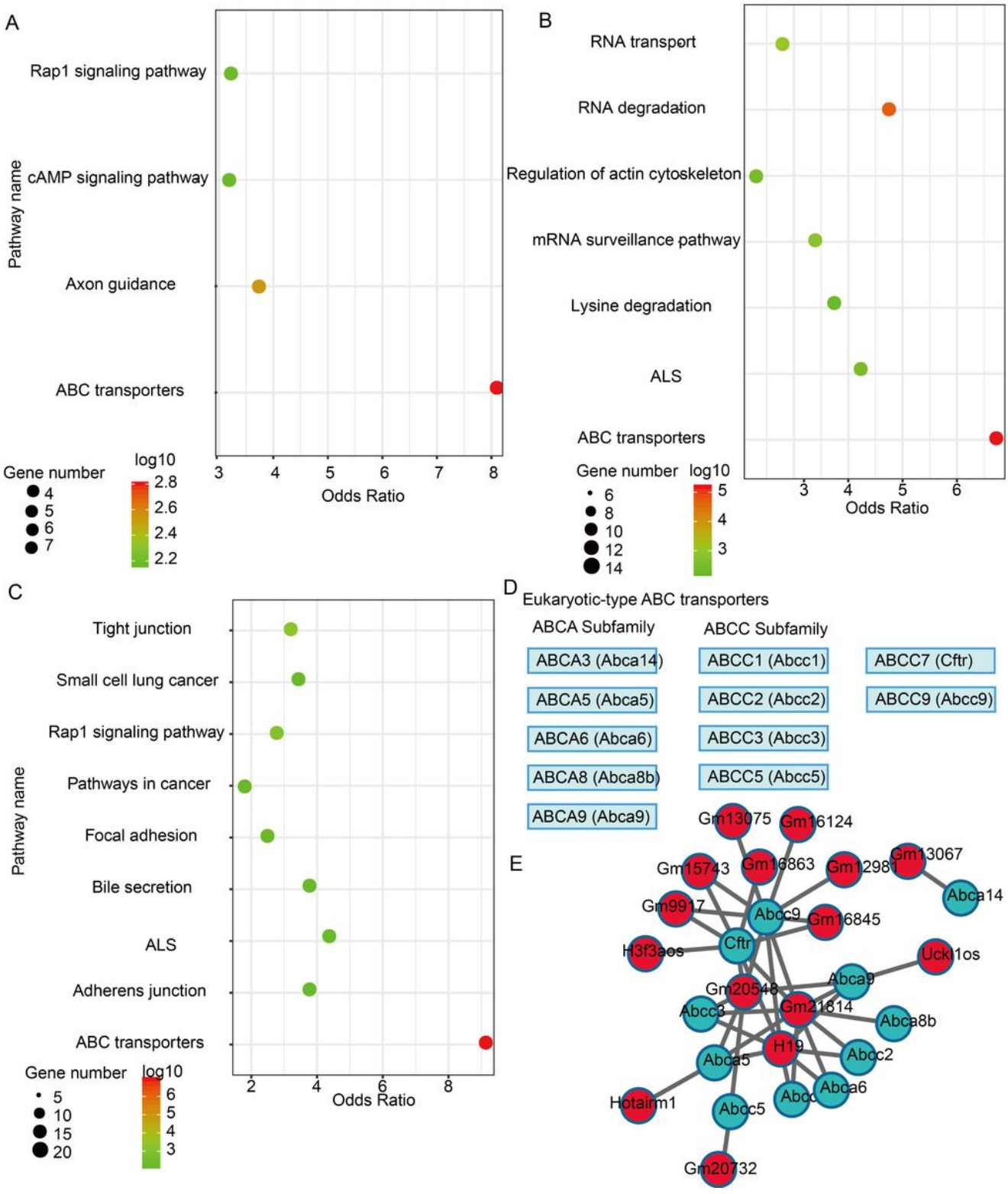

Figure 5

Functional enrichment analysis of gut microbiota-specific lncRNAs in postnatal development. (A) Points plots show enrichment pathways of gut microbiota-specific lncRNAs in week 1, (B) week 4 and (C) week 12/16. The size of nodes represent numbers of enrichment genes. Red and green represent higher and lower enrichment P-values. (D) ABCA and ABCC subfamilies in eukaryotic-type ABC transporters. (E) gut microbiota-specific lncRNA and ABC transporters-related gene interacted network.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FigureS2.tif
- FigureS1.tif
- FigureS3.tif