**Article**

**Construction of a ceRNA Network Related to Rheumatoid Arthritis**

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**Abstract:** (1) Background: Rheumatoid arthritis (RA) is a common systemic autoimmune disease affecting many people and has an unclear and complicated physiological mechanism. The competing endogenous RNA (ceRNA) network plays an essential role in the development and occurrence of various human physiological processes. This study aimed to construct a ceRNA network related to RA. (2) Methods: We explored the GEO database for peripheral blood mononuclear cell (PBMC) samples and then analyzed the RNA of 52 samples (without treatment) to obtain lncRNAs (DELs), miRNAs (DEM), and mRNAs (DEGs), which can be differentially expressed with statistical significance in the progression of RA. Next, a ceRNA network was constructed, based on the DELs, DEMs, and DEGs. At the same time, the Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) analysis were used to validate the possible function of the ceRNA network. (3) Results: Through our analysis, 389 DELs, 247 DEMs, and 1081 DEGs were screened. After this, a ceRNA network was constructed for further statistical comparisons, including 16 lncRNAs, 1 miRNA, and 15 mRNAs. According to the GO and KEGG analysis, the ceRNA network was mainly enriched in the mTOR pathway, the dopaminergic system, and the Wnt signaling pathway. (4) Conclusions: The novel ceRNA network related to RA that we constructed offers novel insights into and targets for the underlying molecular mechanisms of the mTOR pathway, the dopaminergic system, and the Wnt signaling pathway. (4) Conclusions: The novel ceRNA network related to RA that we constructed offers novel insights into and targets for the underlying molecular mechanisms of the mTOR pathway, the dopaminergic system, and the Wnt signaling pathway (both classic and nonclassic pathways) that affect the level of the genetic regulator, which might offer novel ways to treat RA.

**Keywords:** ceRNA; RA; mTOR pathway; dopaminergic system; Wnt signaling pathway

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**1. Introduction**

Rheumatoid arthritis (RA) is a systemic autoimmune disease with chronic inflammation of the joints, synovial cell proliferation, and invasive destruction of cartilage and bone, leading to various complications. According to statistics, RA may affect about 1% of the population [1]. Many researchers have shown a variety of signaling pathways [2,3] and candidate genes [4] that are related to RA, but the underlying mechanism is still unclear. Based on this, it is of great significance to analyze the intrinsic mechanisms within RA for offering novel ideas for the treatment of RA.

Currently, many studies have explored the underlying mechanisms within RA. They have indicated that the formation of RA stems from the complex and extensive signal transduction network of various processes, including the disordered function of the autoimmune response, inflammation, and tumor-like cell changes [5]. Moreover, the development of cutting-edge technology and the study of this complex network have enabled a transition from the macroscale, i.e., the macromolecules of biology, to the microscale, i.e., the gene level [6,7]. However, as RA is an autoimmune disease, the related studies are still mostly focused on inflammatory factors [8–10], such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and granulocyte-macrophage colony stimulating factor (GM-CSF), and pathways to explore the possibility of alleviating RA [11]. Therefore, we
thought the construction of a ceRNA network, the network linking the genetic factors and signaling pathways, could be a novel direction.

At the genetic level, the use of noncoding RNAs (ncRNAs) to alleviate RA is a research hotspot [12–14]. To be specific, noncoding RNAs (ncRNA) are RNAs that lack the ability to translate into proteins and can be further divided into miRNAs, IncRNAs, and circle RNAs [15], which regulate the expression of mRNA at the level of both transcription and post-transcription [16]. Among them, IncRNAs and miRNAs have been studied more widely. For miRNA, Xu et al. found that exosome-encapsulated miR-6089 interferes with an inflammatory response in RA through targeting the TLR4 included in the signaling pathways of TLRs/NF-κB [17]. Meanwhile, the viability, proliferation, apoptosis, and migration of fibroblast-like synoviocytes (FLS) were found to be regulated by miR-338-5p within RA via targeting NFAT5 [18].

For lncRNA, Zhang et al. documented that the lncRNA HOTAIR can target downstream miR-138 to inhibit the activation of the NF-κB pathway in LPS-treated chondrocytes, which could alleviate the progression of RA, which indicates the importance of IncRNA–miRNA interactions in RA pathogenesis [19]. Furthermore, some evidence has suggested that the function of ncRNA can be more comprehensively discussed within the ceRNA network through an lncRNA–miRNA–mRNA axis within autoimmune diseases [20–24]. According to this principle, Zhang et al. found that the overexpression of the lncRNA ENST00000494760 may sponge up miR-654-5p, promoting the expression of C1QC in RA patients. This novel ceRNA axis can be used as a biomarker [25]. Yang et al. found that CIRCrna_09505 can act as a miR-6089 sponge to interfere with inflammation through the miR-6089/AKT1/NF-κB axis in CIA mice (an animal model of RA) [26]. Therefore, constructing an RA-related ceRNA network based on the lncRNA–miRNA–mRNA axis has great potential significance for RA research. We assumed that an analysis of the related ceRNA network could provide novel targets for treating RA.

To construct the ceRNA network, we downloaded the microarray data of the lncRNAs, miRNAs, and mRNAs of PBMC samples (GSE101193 and GSE124373). We first screened the DELs, DEMs, and DEGs in these two datasets through GEO2R analysis. We then used the ggalluvial R package to construct lncRNA–miRNA–mRNA triplets with miRcode, miRDB, miRTarBase, and TargetScan based on DELs, DEMs, and DEGs. Finally, the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway and Gene Ontology (GO) analysis were used by the clusterProfiler R package to explore the possible functions of the ceRNA network.

This study discriminated among human RA-related lncRNA, miRNAs, mRNAs, and possible signaling pathways with high statistical significance, which might offer a novel approach to identify pathological mechanisms and potential targets for RA.

2. Materials and Methods

2.1. Data Download

Firstly, we searched the GEO database (Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo, accessed on 1 January 2020) for datasets related to rheumatoid arthritis (RA) by using the keywords “rheumatoid arthritis” and “peripheral blood mononuclear cells”. Next, we searched databases that focused on comparing the genetic factors within PBMCs between the RA and control groups that had relatively sufficient samples from humans. Therefore, GSE101193 and GSE124373 were downloaded. For lncRNA expression profiling, 27 PBMC samples from RA patients and 27 PBMC samples from the healthy control were included in the GSE101193 dataset (platform: GPL21827 Agilent-079487 Arraystar Human LncRNA microarray V4). For miRNA expression profiling, 28 PBMC samples from RA patients and 18 PBMC samples from a healthy control were included in the GSE124373 dataset (platform: GPL21572 Affymetrix Multispecies miRNA-4 Array). For gene/mRNA expression profiling, we used the GSE101193 dataset.
2.2. DELs/DEMs/DEGs Screening

This study used GEO2R, a software platform that automatically performs deviation control analysis for differential expression analysis. Firstly, the differentially expressed lncRNAs (DELs, adj.P.Val < 0.05 and |log FC| > 1.5) between RA and normal samples were screened. At the same time, differentially expressed miRNAs (DEMs) between RA and normal samples were screened, with the cutoff criteria of a p-value of < 0.05. In addition, differentially expressed mRNAs (DEGs) between RA and normal samples were screened based on adj.P.Val < 0.05 and |log FC| > 1.5. Next, the DELs, DEMs, and DEGs were used for subsequent analysis.

2.3. CeRNA Network Construction

We used the ggalluvial R package to construct lncRNA–miRNA–mRNA triplets with miRcode (Version 11; http://www.mircode.org/mircode/, accessed on 1 January 2020), miRDB (Version 7.0; http://mirdb.org/, accessed on 1 January 2020), miRTarBase (http://mirTarbase.mbc.nctu.edu.tw/index.html, accessed on 1 January 2020) and TargetScan (Version 7.2; http://targetscan.org/vert_72/, accessed on 1 January 2020) from the DELs, DEMs and DEGs.

MiRcode provides miRNA target predictions of the entire human genome, including more than 10,000 lncRNAs. miRDB can provide miRNA targets and functional annotations in the human genome [27,28]. TargetScan can predict miRNA binding sites, and it is very effective in predicting miRNA binding sites in mammals. MiRTarBase specializes in collecting miRNA–mRNA targeting relationships supported by experimental evidence. All databases have sufficient experimental and computational support and are similar in function but different in propensity, so their combined use can improve the quality of research.

Firstly, we predicted the miRNA targeted by the DELs and constructed the lncRNA–miRNA pairs with the miRcode database based on DELs and DEMs. Next, the target genes of these miRNA signatures were acquired using the miRDB, miRTarBase, and TargetScan databases. Genes that existed in all three databases were treated as target genes of these miRNAs. Finally, through a comparison of predicted target genes with essential genes consisting of DEGs, only the remaining overlapped genes and their interaction pairs were used to construct the lncRNA–miRNA–mRNA triplets (the ceRNA network).

2.4. GO and KEGG Enrichment Analysis of the ceRNA Network

In order to explore the possible functions of the ceRNA network, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway and Gene Ontology (GO) analyses were performed by the clusterProfiler R package. For GO analysis, a p-value of < 0.05 indicates statistical significance, and the GO analysis involved three categories, namely molecular function (MF), biological processes (BP), and cellular components (CC). For KEGG analysis, a p-value of < 0.05 was used as the cutoff criterion. The workflow of this study is shown in Figure 1.
Figure 1. Workflow of this study.

3. Results

3.1. DELs/DEMs/DEGs

As we know, lncRNA–miRNA pairs and miRNA–mRNA pairs can form lncRNA–miRNA–mRNA triplets. miRNA can bind to a targeted mRNA to promote mRNA degradation, while an lncRNA can bind to a targeted miRNA to inhibit mRNA degradation. The data were analyzed separately. As shown in Figure 2, 389 DELs (52 upregulated and 337 downregulated) were screened in GSE101193, 247 DEMs (71 upregulated and 176 downregulated) in GSE124373, and 1081 DEGs (97 upregulated and 984 downregulated) were screened in GSE101193. These DELs, DEMs, and DEGs were selected for subsequent analysis.

3.2. The ceRNA Network

As shown in Figure 3A, a ceRNA network, including 16 lncRNAs (especially for hnRNPU, MALAT1, and NEAT1), 1 miRNA (miR-142-3p), and 15 mRNAs (especially for ACSL4, APC, CLOCK, and ROCK), was constructed with p-values smaller than 0.05. Fifteen of the lncRNAs were downregulated and all 15 mRNAs were downregulated in RA (Figure 3B,C).
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Figure 3. (A) The ceRNA network. (B) Heatmap of lncRNAs in the ceRNA network. (C) Heatmap of mRNAs in the ceRNA network.

3.3. GO and KEGG Enrichment Analysis of the ceRNA Network

A GO functional annotation analysis was carried out further to test the underlying biological functions of the ceRNA network. We identified 156 significant GO-BP terms, 14 GO-CC terms, and 38 GO-MF terms (Table 1) with a \( p \)-value of <0.05. The top 15 significant GO terms are shown in Figure 4A. For the GO-BP analysis of the ceRNA network, the Wnt signaling pathway (peptidyl–serine, phosphorylation, peptidyl–serine modification, protein localization to the centrosome, protein localization to the microtubule organizing center) showed significance in RA. In GO-CC analysis, the most enriched terms indicated the significance of the mTOR pathway (TORC2 complex, TOR complex) and the canonical Wnt signaling pathway (\( \beta \)-catenin destruction complex, Wnt signalosome). Meanwhile, the Wnt signaling pathway, especially for nonclassic pathways (Rho GTPase binding), had significance in RA according to the GO-MF terms. In addition, as exhibited in Figure 4B, the KEGG pathway enrichment analysis of the ceRNA network indicated that they were predominately enriched in 10 KEGG pathways (Table 2) based on a \( p \)-value of <0.05. The dopaminergic system (dopaminergic synapse, circadian rhythm) and the Wnt pathway were significantly enriched.

Figure 2. DELs/DEMs/DEGs screening.

Figure 3. Cont.
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Table 1. GO enrichment analysis of the ceRNA network.

| Ontology | ID       | Description                                                                 | BgRatio | p-Value  | P. Adjust | Q-Value     | Gene ID                  | Count |
|----------|----------|------------------------------------------------------------------------------|---------|----------|-----------|-------------|--------------------------|-------|
| BP       | GO:0018105 | peptidyl-serine phosphorylation                                                | 310/18,866 | 0.00000846 | 0.027603925 | 0.016408959 | SMG1/ROCK2/RICTOR/INPP5F | 4     |
| BP       | GO:0018209 | peptidyl-serine modification                                                   | 333/18,866 | 0.00011566 | 0.027603925 | 0.016408959 | SMG1/ROCK2/RICTOR/INPP5F | 4     |
| BP       | GO:2000114 | regulation of the establishment of cell polarity                              | 373/18,866 | 0.000172687 | 0.027603925 | 0.016408959 | ROCK2/RICTOR             | 2     |
| BP       | GO:1902903 | regulation of supramolecular fiber organization                                | 25/18,866  | 0.000175152 | 0.027603925 | 0.016408959 | ROCK2/RICTOR/APC/TWF1    | 4     |
| BP       | GO:0071539 | protein localization to the centrosome                                        | 31/18,866  | 0.000270738 | 0.027724176 | 0.01640441 | CEP192/APC               | 2     |
| BP       | GO:1905508 | protein localization to the microtubule organizing center                      | 33/18,866  | 0.000307137 | 0.027724176 | 0.01640441 | CEP192/APC               | 2     |
| BP       | GO:0046486 | glycerolipid metabolic process                                                | 434/18,866 | 0.000308239 | 0.027724176 | 0.01640441 | SMG1/IPMK/INPP5F/ACSL4   | 4     |
| BP       | GO:0033144 | negative regulation of the intracellular steroid hormone receptor signaling pathway | 35/18,866  | 0.000345793 | 0.027724176 | 0.01640441 | CLOCK/STRN3              | 2     |
| BP       | GO:0018105 | regulation of insulin secretion                                               | 181/18,866 | 0.00036301  | 0.027724176 | 0.01640441 | CLOCK/ACSL4/KIF5B        | 3     |
| BP       | GO:0046488 | phosphatidylinositol metabolic process                                        | 185/18,866 | 0.000387013 | 0.027724176 | 0.01640441 | SMG1/IPMK/INPP5F         | 3     |
| BP       | GO:0033073 | insulin secretion                                                             | 213/18,866 | 0.000584074 | 0.035403862 | 0.021045576 | CLOCK/ACSL4/KIF5B        | 3     |
| BP       | GO:0090276 | regulation of peptide hormone secretion                                       | 213/18,866 | 0.000584074 | 0.035403862 | 0.021045576 | CLOCK/ACSL4/KIF5B        | 3     |
| BP       | GO:0072698 | protein localization to the microtubule cytoskeleton                           | 53/18,866  | 0.000794252 | 0.044560949 | 0.026488942 | CEP192/APC               | 2     |
| BP       | GO:0044380 | protein localization to the cytoskeleton                                       | 57/18,866  | 0.000918215 | 0.044560949 | 0.026488942 | CLOCK/ACSL4/KIF5B        | 3     |
| BP       | GO:0046854 | phosphatidylinositol phosphorylation                                          | 57/18,866  | 0.000918215 | 0.044560949 | 0.026488942 | SMG1/IPMK                | 2     |
| BP       | GO:0033073 | peptide hormone secretion                                                     | 257/18,866 | 0.001070381 | 0.044560949 | 0.026488942 | CLOCK/ACSL4/KIF5B        | 3     |
| BP       | GO:0003170 | heart valve development                                                       | 61/18,866  | 0.001050909 | 0.044560949 | 0.026488942 | ROCK2/HECTD1             | 2     |
| BP       | GO:0046883 | regulation of hormone secretion                                               | 267/18,866 | 0.001124321 | 0.044560949 | 0.026488942 | CLOCK/ACSL4/KIF5B        | 3     |
| BP       | GO:0030258 | lipid modification                                                            | 271/18,866 | 0.001173562 | 0.044560949 | 0.026488942 | SMG1/IPMK/INPP5F         | 3     |
| BP       | GO:00110053| regulation of actin filament organization                                     | 278/18,866 | 0.001262989 | 0.044560949 | 0.026488942 | ROCK2/RICTOR/TWF1        | 3     |
| BP       | GO:0051298 | centrosome duplication                                                        | 68/18,866  | 0.00130984  | 0.044560949 | 0.026488942 | CEP192/ROCK2             | 2     |
| BP       | GO:1901880 | negative regulation of protein depolymerization                              | 71/18,866  | 0.001420519 | 0.044560949 | 0.026488942 | APC/TWF1                 | 2     |
| BP       | GO:0000281 | mitotic cytokinesis                                                           | 72/18,866  | 0.001460434 | 0.044560949 | 0.026488942 | ROCK2/ACSL4/KIF5B        | 2     |
| BP       | GO:0046834 | lipid phosphorylation                                                         | 72/18,866  | 0.001460434 | 0.044560949 | 0.026488942 | ROCK2/ACSL4/KIF5B        | 2     |
| BP       | GO:0032024 | positive regulation of insulin secretion                                      | 74/18,866  | 0.001541868 | 0.044560949 | 0.026488942 | ACSL4/KIF5B              | 2     |
| BP       | GO:0051258 | protein polymerization                                                        | 300/18,866 | 0.001571818 | 0.044560949 | 0.026488942 | CEP192/ROCK2/TWF1        | 3     |
| Ontology ID | Description                                                                 | BgRatio | p-Value    | P. Adjust | Q-Value    | Gene ID                  | Count |
|------------|------------------------------------------------------------------------------|---------|------------|-----------|------------|--------------------------|-------|
| GO:0033143 | regulation of the intracellular steroid hormone receptor signaling pathway | 75/18,866 | 0.001583384 | 0.044560949 | 0.026488942 | CLOCK/STRN3              | 2     |
| GO:0070830 | bicellular tight junction assembly                                             | 77/18,866 | 0.001668011 | 0.04500111  | 0.02675093  | ROCK2/APC                | 2     |
| GO:0120192 | tight junction assembly                                                       | 79/18,866 | 0.00175476  | 0.04500111  | 0.02675093  | ROCK2/APC                | 2     |
| GO:0046879 | hormone secretion                                                             | 314/18,866 | 0.001791068 | 0.04500111  | 0.02675093  | CLOCK/ACSL4/KIF5B        | 3     |
| GO:0043242 | negative regulation of protein-containing complex disassembly                 | 81/18,866 | 0.001843624 | 0.04500111  | 0.02675093  | APC/TWF1                 | 2     |
| GO:0120193 | tight junction organization                                                    | 82/18,866 | 0.001888848 | 0.04500111  | 0.02675093  | ROCK2/APC                | 2     |
| GO:0009914 | hormone transport                                                            | 323/18,866 | 0.001941672 | 0.04500111  | 0.02675093  | CLOCK/ACSL4/KIF5B        | 3     |
| GO:0043297 | apical junction assembly                                                      | 85/18,866 | 0.002027676 | 0.045181911 | 0.027214999 | ROCK2/APC                | 2     |
| GO:0032984 | protein-containing complex disassembly                                        | 330/18,866 | 0.002064148 | 0.045181911 | 0.027214999 | KIF5B/APC/TWF1           | 3     |
| GO:1901879 | regulation of protein depolymerization positive regulation of cellular protein localization | 88/18,866 | 0.002171223 | 0.045827103 | 0.030055499 | ROCK2/APC/TWF1          | 2     |
| GO:1903829 | regulation of protein secretion                                               | 338/18,866 | 0.002209936 | 0.045827103 | 0.027214999 | ROCK2/KIF5B/APC          | 3     |
| GO:0006650 | glycerophospholipid metabolic process regulation of actin                     | 343/18,866 | 0.002304246 | 0.046557591 | 0.027675832 | SMG1/IMPK/INPP5F         | 3     |
| GO:0050708 | regulation of protein secretion                                               | 352/18,866 | 0.00248028  | 0.048861513 | 0.029045383 | CLOCK/ACSL4/KIF5B        | 3     |
| GO:0032956 | regulation of actin regulation of peptide kinase activity                      | 360/18,866 | 0.002643621 | 0.050560779 | 0.030055499 | ROCK2/RICTOR/TWF1       | 3     |
| GO:0090277 | regulation of the intracellular steroid hormone receptor signaling pathway     | 99/18,866 | 0.002737614 | 0.050560779 | 0.030055499 | ACSL4/KIF5B              | 2     |
| GO:0061640 | cytoskeleton-dependent cytokinesis                                             | 100/18,866 | 0.002792202 | 0.050560779 | 0.030055499 | ROCK2/APC                | 2     |
| GO:0018108 | peptidyl-tyrosine phosphorylation                                             | 374/18,866 | 0.00294531  | 0.050560779 | 0.030055499 | RICTOR/INPP5F/TWF1       | 3     |
| GO:0018212 | peptidyl-tyrosine modification                                                | 377/18,866 | 0.003016219 | 0.050560779 | 0.030055499 | RICTOR/INPP5F/TWF1       | 3     |
| GO:0003300 | cardiac muscle hypertrophy negative regulation of phosphatase activity        | 104/18,866 | 0.003015681 | 0.050560779 | 0.030055499 | ROCK2/INPP5F             | 2     |
| GO:0010923 | regulation of peptide secretion                                               | 104/18,866 | 0.003015681 | 0.050560779 | 0.030055499 | CEP192/ROCK2             | 2     |
| GO:0002791 | regulation of peptide secretion                                               | 381/18,866 | 0.003103842 | 0.05054736  | 0.03089684  | CLOCK/ACSL4/KIF5B        | 3     |
| GO:0014897 | striated muscle hypertrophy                                                   | 107/18,866 | 0.00318865  | 0.051278072 | 0.030482264 | ROCK2/INPP5F             | 2     |
| GO:0014896 | muscle hypertrophy                                                           | 109/18,866 | 0.003300505 | 0.052110512 | 0.030976277 | ROCK2/INPP5F             | 2     |
| GO:0035305 | negative regulation of dephosphorylation                                      | 111/18,866 | 0.003426385 | 0.05294101  | 0.031470411 | CEP192/ROCK2             | 2     |
| GO:0051261 | protein depolymerization                                                      | 115/18,866 | 0.003672202 | 0.054416789 | 0.032347677 | APC/TWF1                 | 2     |
| GO:0032970 | regulation of an actin filament-based process                                 | 405/18,866 | 0.003687236 | 0.054416789 | 0.032347677 | ROCK2/RICTOR/TWF1        | 3     |
| GO:0030518 | intracellular steroid hormone receptor signaling pathway                      | 116/18,866 | 0.003734913 | 0.054416789 | 0.032347677 | CLOCK/STRN3              | 2     |
| Ontology ID  | Description                                                                 | BgRatio | p-Value     | P. Adjust | Q-Value     | Gene ID               | Count |
|-------------|------------------------------------------------------------------------------|---------|-------------|-----------|-------------|-----------------------|-------|
| GO:0031109  | microtubule polymerization or depolymerization                               | 117/18,866 | 0.003798126 | 0.05441679 | 0.032347677 | CEP192/APC           | 2     |
| GO:0042752  | regulation of the circadian rhythm                                            | 122/18,866 | 0.004121687 | 0.05675952 | 0.033740328 | ROCK2/CLOCK          | 2     |
| GO:0043244  | complex disassembly                                                          | 122/18,866 | 0.004121687 | 0.05675952 | 0.033740328 | APC/TWF1             | 2     |
| GO:0031929  | TOR signaling                                                                | 124/18,866 | 0.004254596 | 0.05675952 | 0.033740328 | SMG1/RICTOR          | 2     |
| GO:0007098  | centrosome cycle                                                             | 125/18,866 | 0.004321795 | 0.05675952 | 0.033740328 | CEP192/ROCK2         | 2     |
| GO:0043500  | muscle adaptation                                                            | 125/18,866 | 0.004321795 | 0.05675952 | 0.033740328 | ROCK2/INPP5F         | 2     |
| GO:0007015  | actin filament organization                                                   | 434/18,866 | 0.004735354 | 0.060184819 | 0.03576442   | ROCK2/RICKTR/TFW1    | 3     |
| GO:0046887  | positive regulation of hormone secretion                                     | 131/18,866 | 0.004862092 | 0.060814735 | 0.036150891 | ACSL4/KIF5B          | 2     |
| GO:0043434  | response to peptide hormones                                                  | 131/18,866 | 0.005093485 | 0.061934727 | 0.036816663 | ROCK2/COPI2/EP2AIP1  | 3     |
| GO:0031023  | microtubule organizing center organization                                    | 136/18,866 | 0.005108829 | 0.061934727 | 0.036816663 | CEP192/ROCK2         | 2     |
| GO:0006644  | phospholipid metabolic process                                                | 455/18,866 | 0.005314214 | 0.062148718 | 0.03693868   | CEP192/ROCK2         | 2     |
| GO:0043401  | steroid hormone-mediated signaling pathway protein secretion                  | 139/18,866 | 0.005330891 | 0.062148718 | 0.03693868   | CEP192/ROCK2         | 2     |
| GO:009306   | establishment of protein localization to the extracellular region             | 462/18,866 | 0.005363087 | 0.062148718 | 0.03693868   | CEP192/ROCK2         | 2     |
| GO:0035592  | establishment of cell polarity protein localization to the extracellular region | 463/18,866 | 0.005463792 | 0.062398087 | 0.037092104 | RICKTR/ROCK2         | 2     |
| GO:0088569  | regulation of peptidyl-serine phosphorylation                                 | 470/18,866 | 0.005591787 | 0.062947546 | 0.037418726 | ACSL4/KIF5B          | 2     |
| GO:0031335  | negative regulation of supramolecular fiber organization                     | 156/18,866 | 0.00564688  | 0.070820291 | 0.04207486   | APC/TWF1             | 2     |
| GO:0051494  | negative regulation of cytoskeleton organization                              | 163/18,866 | 0.007235545 | 0.070821752 | 0.042102702 | APC/TWF1             | 2     |
| GO:0042989  | sequestering of actin monomers                                                | 10/18,866  | 0.007924308 | 0.070821752 | 0.042102702 | RICKTR/ROCK2         | 2     |
| GO:0051418  | microtubule nucleation by the microtubule organizing center                   | 10/18,866  | 0.007924308 | 0.070821752 | 0.042102702 | RICKTR/ROCK2         | 2     |
| GO:0071394  | cellular response to testosterone stimulus                                    | 10/18,866  | 0.007924308 | 0.070821752 | 0.042102702 | RICKTR/ROCK2         | 2     |
| GO:0098935  | dendritic transport                                                           | 10/18,866  | 0.007924308 | 0.070821752 | 0.042102702 | RICKTR/ROCK2         | 2     |
| Ontology | ID        | Description                                                                 | BgRatio | p-Value       | P. Adjust       | Q-Value        | Gene ID         | Count |
|----------|-----------|-------------------------------------------------------------------------------|---------|---------------|----------------|----------------|----------------|-------|
| BP       | GO:1902946| protein localization to early endosomes regulation of protein localization to centrosomes | 10/18,866 | 0.007924308   | 0.070827152    | 0.042102702    | ROCK2          | 1     |
| BP       | GO:1904779| regulation of epithelial cell differentiation                                 | 10/18,866 | 0.007924308   | 0.070827152    | 0.042102702    | APC            | 1     |
| BP       | GO:0030856| regulation of cytokinesis                                                     | 171/18,866 | 0.007936372   | 0.070827152    | 0.042102702    | ROCK2/CLOCK    | 2     |
| BP       | GO:0000910| regulation of protein secretion regulation of actin filament polymerization   | 172/18,866 | 0.008026064   | 0.070827152    | 0.042102702    | ROCK2/APC      | 2     |
| BP       | GO:0050714| positive regulation of secretory response                                    | 172/18,866 | 0.008026064   | 0.070827152    | 0.042102702    | ACSL4/KIF5B    | 2     |
| BP       | GO:0030833| regulation of protein localization                                          | 174/18,866 | 0.008206832   | 0.070827152    | 0.042102702    | RICTOR/TWF1    | 2     |
| BP       | GO:0010921| regulation of phosphatase activity                                          | 175/18,866 | 0.008297907   | 0.070827152    | 0.042102702    | CEP192/ROCK2   | 2     |
| BP       | GO:0007028| regulation of cytokinesis                                                    | 11/18,866  | 0.008713507   | 0.070827152    | 0.042102702    | KIF5B          | 1     |
| BP       | GO:0032253| regulation of actin filament polymerization                                 | 11/18,866  | 0.008713507   | 0.070827152    | 0.042102702    | KIF5B          | 1     |
| BP       | GO:0046607| regulation of the centrosome cycle                                          | 11/18,866  | 0.008713507   | 0.070827152    | 0.042102702    | ROCK2          | 1     |
| BP       | GO:0090269| fibroblast growth factor production regulation of fibroblast growth factor production | 11/18,866  | 0.008713507   | 0.070827152    | 0.042102702    | ROCK2          | 1     |
| BP       | GO:0090270| regulation of fibroblast growth factor production                           | 11/18,866  | 0.008713507   | 0.070827152    | 0.042102702    | ROCK2          | 1     |
| BP       | GO:0099519| dense core granule cytoskeletal transport regulation of aspartic-type peptidase activity | 11/18,866  | 0.008713507   | 0.070827152    | 0.042102702    | ROCK2          | 1     |
| BP       | GO:1901950| dense core granule transport regulation of aspartic-type peptidase activity | 11/18,866  | 0.008713507   | 0.070827152    | 0.042102702    | KIF5B          | 1     |
| BP       | GO:1905245| regulation of aspartic-type peptidase activity                               | 11/18,866  | 0.008713507   | 0.070827152    | 0.042102702    | KIF5B          | 1     |
| BP       | GO:1905383| regulation of vesicle fusion protein localization to presynapses             | 11/18,866  | 0.008713507   | 0.070827152    | 0.042102702    | ROCK2          | 1     |
| BP       | GO:120032 | membrane-bounded cell projection assembly                                   | 183/18,866 | 0.009042998   | 0.070827152    | 0.042102702    | APC/TWF1       | 2     |
| BP       | GO:0068991| regulation of cell projection assembly                                       | 185/18,866 | 0.009233827   | 0.070827152    | 0.042102702    | APC/TWF1       | 2     |
| BP       | GO:0031340| regulation of vesicle fusion positive regulation of vesicle fusion           | 12/18,866  | 0.00950212    | 0.070827152    | 0.042102702    | KIF5B          | 1     |
| BP       | GO:0032957| inositol trisphosphate metabolic process positive regulation of protein localization to the endosome | 12/18,866  | 0.00950212    | 0.070827152    | 0.042102702    | ROCK2          | 1     |
| BP       | GO:05668  | regulation of endocytic recycling or depolymerization regulation of actin polymerization or depolymerization | 12/18,866  | 0.00950212    | 0.070827152    | 0.042102702    | INPP5F         | 1     |
| BP       | GO:008064 | regulation of actin polymerization or depolymerization                      | 190/18,866 | 0.009718813   | 0.070827152    | 0.042102702    | RICTOR/TWF1    | 2     |
| BP       | GO:0070507| regulation of microtubule cytoskeleton organization                          | 190/18,866 | 0.009718813   | 0.070827152    | 0.042102702    | ROCK2/APC      | 2     |
| BP       | GO:0030832| regulation of actin filament length                                          | 191/18,866 | 0.009817161   | 0.070827152    | 0.042102702    | RICTOR/TWF1    | 2     |
| Ontology | ID         | Description                                                                 | BgRatio     | p-Value          | P. Adjust       | Q-Value         | Gene ID               | Count |
|----------|------------|------------------------------------------------------------------------------|-------------|------------------|----------------|----------------|-----------------------|-------|
| BP       | GO:002793  | positive regulation of peptide secretion actin filament polymerization       | 193/18,866  | 0.010015204      | 0.070827152    | 0.042102702    | ACSL4/KIF5B           | 2     |
| BP       | GO:0030041 | positive regulation of pseudopodium assembly                                 | 193/18,866  | 0.010015204      | 0.070827152    | 0.042102702    | RICTOR/TWF1           | 2     |
| BP       | GO:0031274 | positive regulation of synaptic transmission, GABAergic                      | 13/18,866   | 0.010290147      | 0.070827152    | 0.042102702    | APC                   | 1     |
| BP       | GO:0032230 | negative regulation of the intracellular estrogen receptor signaling pathway | 13/18,866   | 0.010290147      | 0.070827152    | 0.042102702    | KIF5B                 | 1     |
| BP       | GO:0033147 | glucocorticoid receptor signaling pathway                                     | 13/18,866   | 0.010290147      | 0.070827152    | 0.042102702    | STRN3                 | 1     |
| BP       | GO:0042921 | regulation of attachment of spindle microtubules to kinetochores            | 13/18,866   | 0.010290147      | 0.070827152    | 0.042102702    | CLOCK                 | 1     |
| BP       | GO:0051988 | axo-dendritic protein transport regulation of protein localization to endosomes | 13/18,866   | 0.010290147      | 0.070827152    | 0.042102702    | KIF5B                 | 1     |
| BP       | GO:1905666 | corticosteroid receptor signaling pathway                                     | 13/18,866   | 0.010290147      | 0.070827152    | 0.042102702    | ROCK2                 | 1     |
| BP       | GO:0009755 | hormone-mediated signaling pathway                                            | 200/18,866  | 0.010722411      | 0.070827152    | 0.042102702    | CLOCK/STRN3           | 2     |
| BP       | GO:001921  | positive regulation of receptor recycling                                    | 14/18,866   | 0.011077589      | 0.070827152    | 0.042102702    | INPP5F                | 1     |
| BP       | GO:0031272 | regulation of pseudopodium assembly                                          | 14/18,866   | 0.011077589      | 0.070827152    | 0.042102702    | APC                   | 1     |
| BP       | GO:0031958 | angiotensin-activated signaling pathway                                       | 14/18,866   | 0.011077589      | 0.070827152    | 0.042102702    | ROCK2                 | 1     |
| BP       | GO:0048681 | negative regulation of axon regeneration response to redox state             | 14/18,866   | 0.011077589      | 0.070827152    | 0.042102702    | INPP5F                | 1     |
| BP       | GO:0051775 | response to interleukin-15                                                   | 14/18,866   | 0.011077589      | 0.070827152    | 0.042102702    | CLOCK                 | 1     |
| BP       | GO:0070672 | positive regulation of connective tissue replacement                          | 14/18,866   | 0.011077589      | 0.070827152    | 0.042102702    | ACSL4                 | 1     |
| BP       | GO:1905205 | positive regulation of peptide secretion                                       | 206/18,866  | 0.011345864      | 0.070827152    | 0.042102702    | CLOCK/STRN3           | 2     |
| BP       | GO:0071383 | cellular response to steroid hormone stimulus                                 | 206/18,866  | 0.011345864      | 0.070827152    | 0.042102702    | ROCK2/KIF5B           | 2     |
| BP       | GO:1902905 | positive regulation of supramolecular fiber organization                     | 208/18,866  | 0.011557199      | 0.070827152    | 0.042102702    | ROCK2/RICTOR          | 2     |
| BP       | GO:0035303 | regulation of dephosphorylation                                              | 209/18,866  | 0.011663523      | 0.070827152    | 0.042102702    | CEP192/ROCK2          | 2     |
| BP       | GO:0045216 | cell-cell junction organization                                              | 210/18,866  | 0.011770283      | 0.070827152    | 0.042102702    | ROCK2/ROCK1           | 2     |
| BP       | GO:0032252 | secretory granule localization                                                | 15/18,866   | 0.011864447      | 0.070827152    | 0.042102702    | KIF5B                 | 1     |
| BP       | GO:0070571 | negative regulation of neuron projection regeneration                         | 15/18,866   | 0.011864447      | 0.070827152    | 0.042102702    | INPP5F                | 1     |
| Ontology | ID       | Description                                           | BgRatio | p-Value      | P. Adjust   | Q-Value    | Gene ID       | Count |
|----------|----------|-------------------------------------------------------|---------|--------------|-------------|------------|---------------|-------|
| BP       | GO:1900037 | regulation of the cellular response to hypoxia       | 15/18,866 | 0.011864447  | 0.070827152 | 0.042102702 | ROCK2        | 1     |
| BP       | GO:1901550 | regulation of endothelial cell development            | 15/18,866 | 0.011864447  | 0.070827152 | 0.042102702 | ROCK2        | 1     |
| BP       | GO:1903140 | regulation of establishment of the endothelial barrier | 15/18,866 | 0.011864447  | 0.070827152 | 0.042102702 | ROCK2        | 1     |
| BP       | GO:1905203 | regulation of connective tissue replacement           | 15/18,866 | 0.011864447  | 0.070827152 | 0.042102702 | ROCK2        | 1     |
| BP       | GO:0007623 | circadian rhythm                                      | 218/18,866 | 0.01264001   | 0.072503172 | 0.043099   | ROCK2/CLOCK  | 2     |
| BP       | GO:0031269 | pseudopodium assembly                                 | 16/18,866 | 0.01265072   | 0.072503172 | 0.043099   | APC           | 1     |
| BP       | GO:0042532 | negative regulation of tyrosine phosphorylation of STAT protein | 16/18,866 | 0.01265072   | 0.072503172 | 0.043099   | INPP5F        | 1     |
| BP       | GO:0045725 | positive regulation of the glycogen biosynthetic process | 16/18,866 | 0.01265072   | 0.072503172 | 0.043099   | EPM2AIP1      | 1     |
| BP       | GO:2000651 | positive regulation of sodium ion transmembrane transporter activity | 16/18,866 | 0.01265072   | 0.072503172 | 0.043099   | KIF5B         | 1     |
| BP       | GO:0000075 | establishment or maintenance of cell polarity         | 219/18,866 | 0.012750671  | 0.072503172 | 0.043099   | CLOCK/APC    | 2     |
| BP       | GO:0007163 | epithelial cell development                            | 220/18,866 | 0.012861762  | 0.072503172 | 0.043099   | ROCK2/RICTOR | 2     |
| BP       | GO:0002064 | actin polymerization or depolymerization              | 221/18,866 | 0.012973283  | 0.072503172 | 0.043099   | ROCK2/CLOCK  | 2     |
| BP       | GO:0008154 | cellular protein complex disassembly                  | 221/18,866 | 0.012973283  | 0.072503172 | 0.043099   | RICTOR/TWF1  | 2     |
| BP       | GO:0043624 | pseudopodium organization                             | 17/18,866 | 0.013436409  | 0.073527015 | 0.04370617 | APC/TWF1      | 2     |
| BP       | GO:0031268 | positive regulation of glycogen metabolic process     | 17/18,866 | 0.013436409  | 0.073527015 | 0.04370617 | EPM2AIP1      | 1     |
| BP       | GO:0051495 | positive regulation of cytoskeleton organization      | 230/18,866 | 0.013996188  | 0.076026045 | 0.045214547 | ROCK2/RICTOR | 2     |
| BP       | GO:0032271 | regulation of protein polymerization                  | 231/18,866 | 0.014111968  | 0.076165963 | 0.045276321 | RICTOR/TWF1  | 2     |
| BP       | GO:0035338 | long-chain fatty acyl-CoA biosynthetic process         | 19/18,866 | 0.015006037  | 0.080140524 | 0.047817303 | ACSL4         | 1     |
| BP       | GO:0032886 | regulation of microtubule-based process               | 240/18,866 | 0.015172917  | 0.080780576 | 0.04802358 | ROCK2/APC     | 2     |
| BP       | GO:0003323 | type B pancreatic cell development                    | 20/18,866 | 0.015789976  | 0.080795463 | 0.048028294 | CLOCK         | 1     |
| BP       | GO:0008900 | retrograde axonal transport                           | 20/18,866 | 0.015789976  | 0.080795463 | 0.048028294 | KIF5B         | 1     |
| BP       | GO:0045019 | negative regulation of a nitric oxide biosynthetic process | 20/18,866 | 0.015789976  | 0.080795463 | 0.048028294 | ROCK2        | 1     |
Table 1. Cont.

| Ontology | ID          | Description                                      | BgRatio | p-Value     | P. Adjust   | Q-Value     | Gene ID  | Count |
|----------|-------------|--------------------------------------------------|---------|-------------|-------------|-------------|----------|-------|
| BP       | GO:0097709  | connective tissue replacement                    | 20/18,866 | 0.015789976 | 0.080795463 | 0.048028294 | ROCK2   | 1     |
| BP       | GO:1902004  | positive regulation of amyloid-β formation       | 20/18,866 | 0.015789976 | 0.080795463 | 0.048028294 | ROCK2   | 1     |
| BP       | GO:1904406  | negative regulation of a nitric oxide metabolic process | 20/18,866 | 0.015789976 | 0.080795463 | 0.048028294 | ROCK2   | 1     |
| BP       | GO:1902307  | positive regulation of sodium ion transmembrane transport | 21/18,866 | 0.016573334 | 0.083716582 | 0.049764733 | KIF5B   | 1     |
| BP       | GO:1904886  | β-catenin destruction complex disassembly         | 21/18,866 | 0.016573334 | 0.083716582 | 0.049764733 | APC      | 1     |
| CC       | GO:0031932  | TORC2 complex                                    | 12/19,559 | 3.13E-05    | 0.00178885  | 0.001098438 | SMG1/RICTOR | 2     |
| CC       | GO:0038201  | TOR complex                                       | 15/19,559 | 4.97E-05    | 0.00178885  | 0.001098438 | SMG1/RICTOR | 2     |
| CC       | GO:0032587  | ruffle membrane                                   | 95/19,559 | 0.002045063 | 0.049081508 | 0.03137768  | APC/TWF1 | 2     |
| CC       | GO:0031256  | leading edge membrane                             | 175/19,559 | 0.006749208 | 0.070207508 | 0.043109873 | APC/TWF1 | 2     |
| CC       | GO:0001726  | ruffle                                            | 179/19,559 | 0.007050656 | 0.070207508 | 0.043109873 | APC/TWF1 | 2     |
| CC       | GO:0035253  | ciliary rootlet                                   | 11/19,559 | 0.007847494 | 0.070207508 | 0.043109873 | KIF5B   | 1     |
| CC       | GO:0030877  | β-catenin destruction complex                     | 12/19,559 | 0.008585059 | 0.070207508 | 0.043109873 | APC      | 1     |
| CC       | GO:1990909  | Wnt signalosome                                   | 12/19,559 | 0.008585059 | 0.070207508 | 0.043109873 | APC      | 1     |
| CC       | GO:0033919  | chromatoid body                                   | 13/19,559 | 0.009268152 | 0.070207508 | 0.043109873 | CLOCK    | 1     |
| CC       | GO:0098554  | cytoplasmic side of the endoplasmic reticulum membrane | 15/19,559 | 0.010689622 | 0.070207508 | 0.043109873 | EPM2AIP1 | 1     |
| CC       | GO:004233   | mitochondria-associated endoplasmic reticulum membrane | 16/19,559 | 0.011395599 | 0.070207508 | 0.043109873 | ACSL4    | 1     |
| CC       | GO:0036464  | cytoplasmic ribonucleoprotein granule             | 233/19,559 | 0.011701251 | 0.070207508 | 0.043109873 | ROCK2/CLOCK | 2     |
| CC       | GO:0035770  | ribonucleoprotein granule                         | 243/19,559 | 0.012677658 | 0.070214721 | 0.043114302 | ROCK2/CLOCK | 2     |
| CC       | GO:0000242  | pericentriolar material                           | 21/19,559 | 0.014931918 | 0.07692722  | 0.047153426 | CEP192   | 1     |
| MF       | GO:0017048  | Rho GTPase binding                               | 162/18,352 | 0.007540672 | 0.065516951 | 0.030425828 | ROCK2/STRN3 | 2     |
| MF       | GO:0070016  | armadillo repeat domain binding                   | 10/18,352 | 0.008145489 | 0.065516951 | 0.030425828 | STRN3    | 1     |
| MF       | GO:0102391  | decanooate-CoA ligase activity                    | 10/18,352 | 0.008145489 | 0.065516951 | 0.030425828 | ACSL4    | 1     |
| MF       | GO:0031956  | medium-chain fatty acid-CoA ligase activity       | 11/18,352 | 0.008956623 | 0.065516951 | 0.030425828 | ACSL4    | 1     |
| MF       | GO:0047676  | arachidonate-CoA ligase activity                  | 11/18,352 | 0.008956623 | 0.065516951 | 0.030425828 | ACSL4    | 1     |
| MF       | GO:0034595  | phosphatidylinositol phosphate                    | 12/18,352 | 0.009767138 | 0.065516951 | 0.030425828 | INPP5F   | 1     |
| MF       | GO:0035004  | phosphatidylinositol 3-kinase activity            | 12/18,352 | 0.009767138 | 0.065516951 | 0.030425828 | APC      | 1     |
| Ontology ID | Description                                                                 | BgRatio | p-Value      | P. Adjust     | Q-Value      | Gene ID       | Count |
|------------|------------------------------------------------------------------------------|---------|--------------|---------------|--------------|---------------|-------|
| GO:0004467 | long-chain fatty acid-CoA ligase activity                                     | 13/18,352 | 0.010577034 | 0.065516951 | 0.030425828 | ACSL4         | 1     |
| GO:0052745 | inositol phosphate phosphatase activity                                       | 13/18,352 | 0.010577034 | 0.065516951 | 0.030425828 | INPP5F        | 1     |
| GO:0019902 | phosphatase binding                                                          | 194/18,352 | 0.010631345 | 0.065516951 | 0.030425828 | CEP192/STRN3 | 2     |
| GO:0003996 | acyl-CoA ligase activity                                                      | 16/18,352 | 0.013003014 | 0.065516951 | 0.030425828 | ACSL4         | 1     |
| GO:0008574 | ATP-dependent microtubule motor activity, plus-end-directed phosphatidylinositol monophosphate phosphatase activity | 16/18,352 | 0.013003014 | 0.065516951 | 0.030425828 | KIF5B         | 1     |
| GO:0052744 | microtubule plus-end binding                                                 | 20/18,352 | 0.016229019 | 0.065516951 | 0.030425828 | APC           | 1     |
| GO:0050321 | tau-protein kinase activity                                                  | 22/18,352 | 0.017838328 | 0.065516951 | 0.030425828 | ROCK2         | 1     |
| GO:0070840 | dynnein complex binding                                                      | 23/18,352 | 0.018642061 | 0.065516951 | 0.030425828 | APC           | 1     |
| GO:0008017 | microtubule binding                                                          | 265/18,352 | 0.019269691 | 0.065516951 | 0.030425828 | KIF5B/APC     | 2     |
| GO:0003785 | actin monomer binding                                                         | 28/18,352 | 0.022651526 | 0.070013807 | 0.032514152 | TWF1          | 1     |
| GO:0016878 | acid-thiol ligase activity                                                   | 30/18,352 | 0.024251027 | 0.071232516 | 0.033080116 | KIF5B         | 1     |
| GO:0051721 | protein phosphatase 2A binding                                               | 32/18,352 | 0.025848084 | 0.071232516 | 0.033080116 | STRN3         | 1     |
| GO:0052866 | ATP-dependent microtubule motor activity                                      | 33/18,352 | 0.026645697 | 0.071232516 | 0.033080116 | INPP5F        | 1     |
| GO:0009039 | telemere DNA binding                                                         | 36/18,352 | 0.029034882 | 0.071232516 | 0.033080116 | SMG1          | 1     |
| GO:0045296 | cadherin binding                                                             | 323/18,352 | 0.029331036 | 0.071232516 | 0.033080116 | KIF5B/TWF1    | 2     |
| GO:0016877 | ligase activity, forming carbon-sulfur bonds                                  | 40/18,352 | 0.032211948 | 0.075531465 | 0.039076532 | ACSL4         | 1     |
| GO:0015631 | tubulin binding                                                              | 365/18,352 | 0.034916716 | 0.079144557 | 0.03675438 | KIF5B/APC     | 2     |
| GO:0048156 | tau protein binding                                                          | 45/18,352 | 0.036169837 | 0.079398484 | 0.036845131 | ROCK2         | 1     |
| GO:0070888 | E-box binding                                                                | 50/18,352 | 0.040112215 | 0.085238458 | 0.039584423 | ROCK2         | 1     |
| GO:0004402 | histone acetyltransferase activity                                           | 55/18,352 | 0.044039733 | 0.085703637 | 0.039800451 | CLOCK         | 1     |
| GO:0017016 | Ras GTPase binding                                                           | 415/18,352 | 0.044107496 | 0.085703637 | 0.039800451 | ROCK2/STRN3   | 2     |
| GO:0043022 | ribosome binding                                                             | 57/18,352 | 0.045606543 | 0.085703637 | 0.039800451 | RICTOR        | 1     |
| GO:0061733 | peptidyl-serylesterase activity                                              | 57/18,352 | 0.045606543 | 0.085703637 | 0.039800451 | CLOCK         | 1     |
| GO:0031267 | small GTPase binding                                                         | 428/18,352 | 0.046632861 | 0.085703637 | 0.039800451 | ROCK2/STRN3   | 2     |
| GO:0004674 | protein serine/threonine kinase activity                                      | 435/18,352 | 0.048014931 | 0.085921455 | 0.039901604 | SMG1/ROCK2    | 2     |
signaling pathway (inositol phosphate metabolism, phosphatidylinositol signaling system, Wnt signaling pathway) were dominant.

Figure 4. (A) GO and (B) KEGG enrichment analyses of the ceRNA network.

Table 2. KEGG enrichment analysis of the ceRNA network.

| ID         | Description                                      | BgRatio | p-Value     | P. Adjust   | Q-Value     | Gene ID     | Count |
|------------|--------------------------------------------------|---------|-------------|-------------|-------------|-------------|-------|
| hsa00562   | inositol phosphate metabolism                    | 73/8104 | 0.002765887 | 0.128071623 | 0.109375964 | IPMK/INPP5F | 2     |
| hsa04070   | phosphatidylinositol signaling system            | 97/8104 | 0.004832891 | 0.128071623 | 0.109375964 | IPMK/INPP5F | 2     |
| hsa04728   | dopaminergic synapse                              | 132/8104| 0.008794936 | 0.155377197 | 0.132695521 | CLOCK/KIF5B | 2     |
| hsa04310   | Wnt signaling pathway                            | 166/8104| 0.013659929 | 0.180994061 | 0.154572882 | ROCK2/APC  | 2     |
| hsa00061   | fatty acid biosynthesis                           | 18/8104 | 0.019823143 | 0.202227639 | 0.172706822 | ACSL4      | 1     |
| hsa04810   | regulation of the actin cytoskeleton             | 218/8104| 0.022893695 | 0.202227639 | 0.172706822 | ROCK2/APC  | 2     |
| hsa05132   | Salmonella infection                              | 249/8104| 0.029353631 | 0.22248917  | 0.18980543  | ROCK2/KIF5B | 2     |
| hsa04710   | circadian rhythm                                 | 31/8104 | 0.033921832 | 0.224732137 | 0.191926155 | CLOCK      | 1     |
| hsa04216   | ferroptosis                                      | 41/8104 | 0.044644012 | 0.24791126  | 0.211721632 | ACSL4      | 1     |
| hsa00071   | fatty acid degradation                            | 43/8104 | 0.046775709 | 0.24791126  | 0.211721632 | ACSL4      | 1     |

4. Discussion

This study constructed an RA-related ceRNA network, screened out the factors related to RA at the gene level as comprehensively as possible, and further inferred the possible
pathways from the influence of related genes on RA by GO and KEGG analysis. Mounting experiments have shown that mistakenly expressed ncRNAs, such as lncRNAs and miRNAs, may be dominant contributors to RA's pathogenesis and progression [19–24]. Moreover, according to the ceRNA theory [29], accumulating evidence has also showed that ceRNA networks participate in regulating the viability, proliferation, migration, and apoptosis of fibroblast-like synoviocytes (FLS) within RA [30], providing novel ideas for the clinical treatment of RA progression. For instance, the lncRNA MEG3 can alleviate RA through miR-141 and inactivation of the AKT/mTOR signaling pathway [13]. The lncRNA HOTAIR can alleviate the progression of RA by targeting miR-138 and inhibiting the NF-κB pathway [19]. The lncRNA GAS5 can alleviate RA by regulating the miR-222-3p/Sirt1 signaling axis [31]. Therefore, this study might provide new guidance for the treatment of RA.

However, given that bioinformatics is a relatively new concept in the field of RA, the sample size for gene comparisons is insufficient, which may have resulted in certain false positive or false negative results. On this basis, we found that in our constructed ceRNA network, three lncRNAs (hnRNPU, MALAT1, and NEAT1), one miRNA (miR-142-3p), and four mRNAs (ACSL4, APC, CLOCK, and ROCK) were directly associated with RA [32–46]. In addition, six lncRNAs (QKI, EPC1, TNFSF10, DDX3X, RC3H1-IT1, and BRWD1-IT1) and six mRNAs (SMG1, LCOR, IPMK, RICTOR, KIF5B, and HECTD1) were confirmed to play a role in the destruction of cartilage or the promotion of inflammation [47–58], which indirectly supports their association with RA. These pieces of evidence are compatible with the findings of this research to a certain extent. Moreover, additional novel genes screened in this article (lncRNAs: ZFR, CLK4, FAM98A, ZEB2, DLEU1, LINCO0184, and LINCO0342; mRNAs: CEP192, INPP5F, STRN3, EPM2AIP1, and TWF1) might provide new targets for treating RA.

Further, we analyzed the downstream pathways of the ceRNA network by GO and KEGG analysis, and found that the mTOR pathway, the dopaminergic system, and the Wnt signaling pathway may play important roles in RA. On this basis, we also explored the significance of these pathways in existing studies. To be specific, for the mTOR pathway, which has with prominent statistical significance in Figure 4, Kun Chen carried out a study that showed that metformin arrests the G2/M cell cycle of FLS by downregulating the IGF-IR/PI3K/AKT/mTOR pathway, thereby inhibiting the proliferation of FLS and alleviating the progression of RA [59]. In addition, a study has shown that moxibustion can also produce similar effects by inhibiting the mTOR pathway [60]. Moreover, artemisin can alleviate the progression of RA by downregulating the PI3K/AKT/mTOR pathway to inhibit chondrocyte proliferation and accelerate FLS apoptosis and autophagy [61]. This evidence indicates the significance of the mTOR pathway in RA. However, the exciting finding is that the upstream TLR4-MyD88-MAPK signaling and the downstream NF-κB pathway of the mTOR signaling pathway [62] have been regarded as target pathways for treating RA in many studies [63,64]. Most of these articles paid more attention to whether a particular drug could modify the target signaling pathway to decrease the abnormal production of pro-inflammatory cytokines and alleviate RA instead of studying the pathways that might be influenced, such as the mTOR pathway. In this case, the mTOR pathway might play an underlying role in of how MAPK signaling and the NF-κB pathway can slow down the progression of RA. Clinically, Bruyn et al. found that the combination of everolimus (mTOR inhibitor) and trexate (MTX) was better than MTX alone, possibly due to the enhanced inhibition of the mTOR pathway [65,66]. However, treatment with mTOR blockers may have unnecessary pro-inflammatory side effects, such as increased levels of inflammatory markers in RA patients treated with everolimus [65]. Therefore, our screening of targets in this pathway may provide guidance for reducing side effects and clues for precision diagnosis and treatment.

For the dopaminergic system (Figure 4), potential dopamine functions in RA have been widely considered in recent decades [67]. Dopamine can indirectly affect the immune system through prolactin [68–70] or can directly affect immune cells through the dopamine
receptors (DR) expressed by immune cells [71]. The effects of dopamine are exerted on the basis of the dose-dependent differences and different states (activated and nonactivated) of cells [67], resulting in the different roles of dopamine in the physiologic and pathologic environment. In general, dopamine is believed to inhibit the production of prolactin by stimulating D2-like DR, thus treating RA. Based on a comparison between RA patients and the control group, it was found that the number of D2DR+ B cells in the synovial tissue of RA patients is higher [72] and the number of D3DR+ mast cells is negatively correlated with the progression of the disease [73]. In blood, the number of D2DR+ B cells is positively correlated with the level of TNF in RA, suggesting that D2DR+ B cells are also involved in the systemic inflammatory response [72]. These suggest a link between dopamine and RA, but the experimental results based on this have been inconsistent or even contradictory when it comes to drug therapy. Studies have been conducted on cabergoline, a D2-like agonist, by Mobini et al. [74] and Erb et al. [75]; bromocriptine, a D2-like agonist, by McMurray [76] and Figueroa et al. [77]; and quinagolide, a D2-like agonist, by Eijsbouts et al. [78]. The different results in these experiments are likely due to the universality of the drug’s effects; i.e., the effects of the drug on RA do not necessarily affect the dopamine system alone. Therefore, the current experimental verification cannot accurately explain the specific connection between dopamine and RA. Clinically, abatacept (CTLA-4Ig), a biologic commonly used in RA patients, was found to be dependent on the Wnt pathway by Rosser-Page et al. [79,80]. However, prudent treatment should be exercised in patients with immune insufficiency, otherwise unexpected bone formation may result from a lack of T cells or Wnt-10b [79]. Considering precision medicine at the genetic level has a chance to ameliorate this side effect, target screening based on this pathway has certain significance. In addition, through a clinical trial, Briot et al. found that two commonly used RA treatment drugs anakinra (IL-1 receptor antagonist) and tocilizumab (anti-IL-6 monoclonal antibody) might also depend on the Wnt pathway to function [81]. In this study, we found that two mRNAs, CLOCK and KIF5B, related to RA can regulate the dopaminergic system so that by interfering with these two mRNAs, researchers can more precisely explore the mechanism of action between dopamine and RA, which might provide novel ideas for treating RA.

For the Wnt signaling pathway, RA treatment through the canonical Wnt/β-catenin pathway has been primarily described [82]. Xiao Wang et al. found that capsules of the traditional Chinese medicine compound huangqin qingre chubi may alleviate the progression of RA by inhibiting the CUL4B/Wnt pathway [83]. However, in this study (Figure 4), the protein functions related to noncanonical signaling pathways (protein localization to the microtubule organizing center, rho GTPase binding, the TORC2 complex, the TOR complex, the phosphatidylinositol signaling system) showed more considerable statistical significance than the protein functions related to the canonical signaling pathways (β-catenin destruction complex), which suggests that the noncanonical signaling pathways may be even more critical for RA than canonical signaling pathways, or at least as necessary. This study also indicated the upstream regulators (miRNA and lncRNA) of the Wnt signaling pathway (Figure 3), which might be used as novel targets for treating RA. Among these, the only screened miRNA, miR-142-3p, may be of great research value. It has been shown that upregulation of miR-142-3p alters the effects of the NF-κB pathway and plays a role in the progression of RA [84]. In addition, the NF-κB pathway has been shown to interact with the Wnt pathway to mediate inflammatory responses [85]. Therefore, we suggest that the relationship between these two pathways and miR-142-3p is worthy of further study. Clinically, drugs used to treat RA through the dopamine system mainly focus on cabergoline and bromocriptine [74,75,86,87]. However, clinical evidence in recent years has found that the regulation of the dopamine pathway seems to regulate the progression of RA to a certain extent, but there is no definite treatment mechanism [69]. Therefore, further analysis from the genetic perspective is meaningful.

This study has some limitations because of the lack of experimental verification. Moreover, DEMs and DEGs were screened on the basis of a p-value smaller than 0.05 instead of an adj.P.Value smaller than 0.05 because if adj.P.Val < 0.05 were used as the screening
condition, the DEMs and DEGs that can be screened are very few, which would have been insufficient for constructing a ceRNA network. However, this does not necessarily mean that the DEMs and DEGs screened in this study do not have sufficient significance. In fact, when the screening conditions are very strict, the probability of false negatives occurring will also increase. Therefore, we appropriately increased the scope of screening, and discussed the screened miRNA and mRNA in line with previous experiments [59–82] and found that they have a certain physiological significance. Overall, this study illustrated the significant and novel factors from the gene level to the protein level, which may be regarded as experimental targets for treating RA. Furthermore, it described the possible pathways, which may suggest potential experiments on the corresponding genes and proteins. Hence, this research is of great significance for the design of experiments and the better treatment of RA.

5. Conclusions

Our study used public databases to systematically analyze mRNA-miRNA–lncRNA expression profiles related to RA. In total, 16 lncRNAs (especially for hnRNPU, MALAT1, and NEAT1), 1 miRNA (miR-142-3p), and 15 mRNAs (especially for ACSL4, APC, CLOCK, and ROCK) were identified as being involved in the RA PBMC samples, which may imply three RA-related pathways including the mTOR pathway, the dopaminergic system, and the Wnt signaling pathway (both classic pathways and nonclassic pathways). On this basis, the possibility of treating RA based on the ceRNA network and related pathways was discussed. Therefore, our study might provide novel targets for treating RA.

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