doi: 10.3978/j.issn.2095-6959.2020.05.011
**View this article at:** http://dx.doi.org/10.3978/j.issn.2095-6959.2020.05.011

# 类风湿关节炎患者滑膜组织 lncRNA 表达及基于 CeRNA 网络的生物信息学分析

肖剑伟，蔡旭，陈新鹏，曾苗雨，郭粉莲，洪易炜，叶志中

(深圳市福田区风湿病专科医院风湿免疫科，广东 深圳 518000)

[摘　要]　**目的：**通过生物信息学分析来识别类风湿关节炎(rheumatoid arthritis，RA)滑膜组织病变进展相关的差异表达基因。**方法：**通过NCBI GEO数据库获取GSE55235和GSE55457的基因表达谱。采用Perl语言对下载的数据进行样本数据合并及基因重注释；采用R语言进行批次矫正及差异分析，根据差异长链非编码RNA(lncRNA)和mRNA构建竞争性内源RNA(ceRNA)网络及进行GO富集分析和KEGG通路分析；使用cytoHubba插件筛选*Hub*基因，分析与差异LncRNA的相关性。**结果：**分析显示与正常滑膜组织对比，RA患者滑膜组织143个mRNA、3个lncRNA存在明显差异表达。根据差异基因构建lncRNA-miRNA-mRNA互作网络，网络由2个LncRNA节点，16个miRNA节点、17个mRNA节点以及44个边组成。GO功能富集分析主要集中在细胞死亡的正调控、成纤维细胞增殖的调节、免疫应答调节细胞表面受体信号通路等功能。KEGG通路分析显示35条通路被富集，其中涉及IL-17代谢通路、MAPK信号通路、WNT信号通路、TNF信号通路等。其中*Hub*基因MYC，CDKN1A，JUN，FOS与LncRNA MEG3在RA滑膜组织中均呈低表达，且lncRNA MEG3与MYC，CDKN1A，JUN，FOS表达具有相关性。**结论：**通过生物信息学网络分析，lncRNA MEG3可能作为ceRNA在RA的疾病发展中发挥着重要作用，为RA提供一些新的候选诊断生物标志物或潜在的治疗靶点。

[关键词]　类风湿关节炎；生物信息学分析；lncRNA；ceRNA；Perl语言

# Expression of LncRNA in synovial tissues of patients with rheumatoid arthritis and bioinformatics analysis based on CeRNA network

XIAO Jianwei, CAI Xu, CHEN Xinpeng, ZENG Miaoyu, GUO Fenlian, HONG Yiwei, YE Zhizhong

*(Department of Rhumatology, Shenzhen Futian Hospital for Rheumatic Diseases, Shenzhen Guangdong 518000, China)*

**Abstract**　**Objective:** To identify differentially expressed genes related to the progression of synovial tissue lesions in rheumatoid arthritis (RA) by bioinformatics analysis. **Methods:** Gene expression profiles of GSE55235 and

**收稿日期 (Date of reception)：**2019–07–16

**通信作者 (Corresponding author)：**叶志中，Email: yezhizhong0823@163.com

**基金项目 (Foundation item)：**深圳市医疗卫生三名工程 (SZSM201602087)；深圳市福田区卫生公益性科研项目 (FTWS20180)。This work was supported by the Sanming Project of Medicine in Shenzhen (SZSM201602087) and Shenzhen Futian Medical Science and Technology Research Fund (FTWS2018066), China.

GSE55457 were acquired from the NCBI GEO database. Data were combined and re-annotated in Perl; Batch correction and identify differentially expressed genes were performed using R; the competing endogenous RNA (ceRNA) network was constructed based on the differential long non-coding RNA (lncRNA) and mRNA. The Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis was performed. The *Hub* gene was screened using the cytoHubba plugin and analyzed for the correlation between differential lncRNA. **Results:** Compared with normal synovial tissue, 143 mRNA and 3 LncRNA in synovial tissue of RA patients were significantly different. The LncRNA-miRNA-mRNA interaction network was constructed based on the differential gene. The network consisted of two LncRNA nodes, 16 miRNA nodes, 17 mRNA nodes and 44 edges. GO functional enrichment analysis mainly were significantly enhanced in positive regulation of programmed cell death, regulation of fibroblast proliferation and immune response-regulating cell surface receptor signaling pathway. KEGG pathway analysis showed that pathways associated with IL-17 signaling pathway, MAPK signaling pathway, Wnt signaling pathway, and TNF signaling pathway. *Hub* gene MYC, CDKN1A, JUN, FOS and LncRNA MEG3 were down-regulated in RA synovial tissue, and LncRNA MEG3 was correlated with the expression of MYC, CDKN1A, JUN and FOS. **Conclusion:** The bioinformatics network analysis showed that LncRNA MEG3 may play an important role in the development of RA in ceRNA and providing some new candidate diagnostic biomarkers or potential therapeutic targets for RA.

**Keywords** rheumatoid arthritis; bioinformatics analysis; lncRNA; ceRNA; Perl

类风湿关节炎(rheumatoid arthritis，RA)是一种全身性、自身免疫性疾病，它以慢性炎症、滑膜增生、关节肿胀及压痛为主要临床特征。RA主要发生在20~50岁的人群中，女性RA的发病率是男性的2~3倍。这些病理变化包括多个炎症性级联所定义的多种疾病亚型，其最终的共同途径是持续的滑膜炎症导致关节软骨和基础骨的损伤[1-3]，导致功能限制、工作障碍和生活质量低下。

研究[4-5]表明滑膜炎症在RA发病机制中发挥着重要的作用。滑膜细胞主要有成纤维细胞样细胞(fibroblast-like cells，FLS)和巨噬细胞样滑膜细胞。类风湿滑膜中上调的炎性细胞因子可导致巨噬细胞样滑膜细胞的发育。而滑膜成纤维细胞(rheumatoid arthritis synovial fibroblasls，RASF)可能参与RA患者关节的局部损伤。Pap等[6]报道小鼠RA模型的研究结果，发现成纤维细胞样滑膜细胞和软骨的共同植入与成纤维细胞侵入软骨导致关节破坏有关。而RA的炎症滑膜与疼痛和关节功能减退密切相关[7]。

超过70%的人类基因组是有效转录的，但只有1%~2%能够编码蛋白质[8-9]，其余部分产生非编码RNA(ncRNA)。NcRNA根据其长度可分为长链ncRNA(lncRNA)或短链ncRNA，包括microRNA(miRNA)和siRNA[10]，其中，lncRNA是一类转录本长度超过200个碱基的长序列非编码RNA分子。既往研究[11-12]主要集中于miRNA在RA发病及机制中的作用。而越来越多的研究[13-14]也表明：LncRNA通过多种机制在免疫反应、炎症反应、细胞发育和代谢等基本生物学过程中发挥重要作用。包括Hotair，H19，C5T1lncRNA，LOC100652951等在内的多种lncRNA参与了RA的调控[15-18]。

CeRNA是一种新发现的基因调控机制，某些lncRNA，mRNA分子可以作为miRNA的“吸附海绵”，他们具有共同的miRNA结合位点，携带被命名为miRNA应答元件(MRES)的“种子序列”，可以像海绵一样吸附结合一些特定的LncRNA或mRNA，通过与miRNA竞争结合靶mRNA的3'UTR，间接抑制miRNA对靶mRNA的负向调控，最终影响到基因的表达。LncRNA与mRNA彼此之间呈正相关调控关系，互称为CeRNA[19]。在网络中，RNA分子之间彼此相互作用使机体处于稳态。但是，当网络中某个LncRNA或miRNA表达出现异常，稳态被打破，导致疾病产生。

本研究利用GEO数据库中的数据，采用Perl语言对其重新注释，获得差异lncRNA及mRNA，基于CeRNA理论，构建lncRNA-miRNA-mRNA网络，为探索RA的发病机制及靶向治疗提供新的理论依据。

## 1 资料与方法

### 1.1 数据检索

以“Rheumatoid Arthritis”“Synovial tissue”为关

键词，在GEO数据库(www.ncbi.nlm.nih.gov/geo)中搜索，检索到GSE55235，GSE55457两个数据集，以膝关节滑膜组织为研究组织，其检测平台均为GPL96，GSE55235数据集的正常滑膜组织及RA滑膜组织分别为10个和7个，GSE55235数据集则分别为7个和13个。

### 1.2 芯片数据合并、重注释及差异基因分析

采用Perl语言对下载的数据进行样本数据合并及基因重注释，将探针对应到基因上，去掉空载探针，多个探针对应同一个基因我们则选择其中中位数作为该基因的表达水平。采用R语言SVA包进行批次矫正，limma包对编码蛋白质的mRNA及lncRNA进行差异分析，取LogFC绝对值大于1，调整后$P<0.05$。

### 1.3 LncRNA，miRNA，mRNA 互作预测

从http://www.mircode.org/下载数据库，采用perl语言对筛选的差异LncRNA与miRNA的互作进行预测。根据互作预测到的miRNA，从miRDB，miRTarBase，TargetScan3个数据库预测靶基因，取3个数据库均能预测到的靶基因，与1.2步骤得到的差异mRNA取交集，得到的共同靶基因与上述靶因LncRNA、miRNA，采用perl语言得到LncRNA-miRNA-mRNA互作网络，并导入Cytoscape绘制网络互作图。

### 1.4 蛋白质相互作用网络分析及 *Hub* 基因筛选

采用R语言的clusterProfiler，org.Hs.eg.db等软件包，以$P<0.05$为筛选条件，对差异基因行GO富集分析及KEGG通路分析。采用string db数据库进行蛋白质相互作用网络分析，导入Cytoscape，使用cytoHubba插件筛选*Hub*基因，根据筛选出的*Hub*基因，分析与差异lncRNA的相关性。

## 2 结果

### 2.1 差异 mRNA 及 lncRNA

合并相同平台数据，需要进行批次矫正，采用R语言校正后，根据基因重注释结果，差异分析结果显示，与正常滑膜组织对比，RA患者滑膜组织143个mRNA存在差异表达，其中上调45个，下调98个，lncRNA上调1个(HCP5，logFC=1.188，$P$=0.001，校正$P$=0.031)，下调2个(MEG3，logFC=−1.627，$P$=0.001，校正$P$=0.027；RBFADN，logFC=−1.614，$P$=0.002，校正$P$=0.037；图1)。

### 2.2 LncRNA-miRNA-mRNA 互作网络

1.3步骤预测结果显示：与1.2步骤得到的差异mRNA取交集得到的差异mRNA一共17个(表1)，其中上调1个，下调16个。预测结果显示共有2个LncRNA纳入网络，结合差异mRNA结果，HCP5预测靶向miRNA 9个，MEG3预测靶向miRNA 12个，RBFADN虽然预测靶到miRNA 2个，但是其靶向miRNA可能结合的mRNA与1.2步骤所得的mRNA无交集，故未纳入互作网络。根据互作网络导入Cytoscape绘制LncRNA-miRNA-mRNA互作网络(图2)。

### 2.3 GO 富集分析及 KEGG 信号通路分析

GO富集分析显示：差异基因在生物过程(biological process，BP)富集于细胞死亡调控、成纤维细胞增殖调控、蛋白质磷酸化、免疫调节等方面，分子功能(molecular function，MF)富集于RNA聚合酶II转录调控区序列特异性DNA结合、R-SMAD 绑定、蛋白质丝氨酸/苏氨酸激酶抑制剂活性等方面(图3)。KEGG信号通路富集分析显示差异基因富集于肿瘤、IL-17信号通路、TNF信号通路、RA、Th1和Th2细胞分化、MAPK信号通路等(图4)。

### 2.4 蛋白质相互作用网络可视化分析

根据String数据库中的数据和Cytoscape的cytoHubba插件筛选出的*Hub*基因，前10个分别是MYC，CDKN1A，JUN，FOS，PTGS2，PMAIP1，SFRP1，SPRY2，ADM，WASL(图5)。其中，MYC，CDKN1A，JUN，FOS与lncRNA MEG3在RA滑膜组织中均呈低表达，且表达具有相关性(图6，图7)。

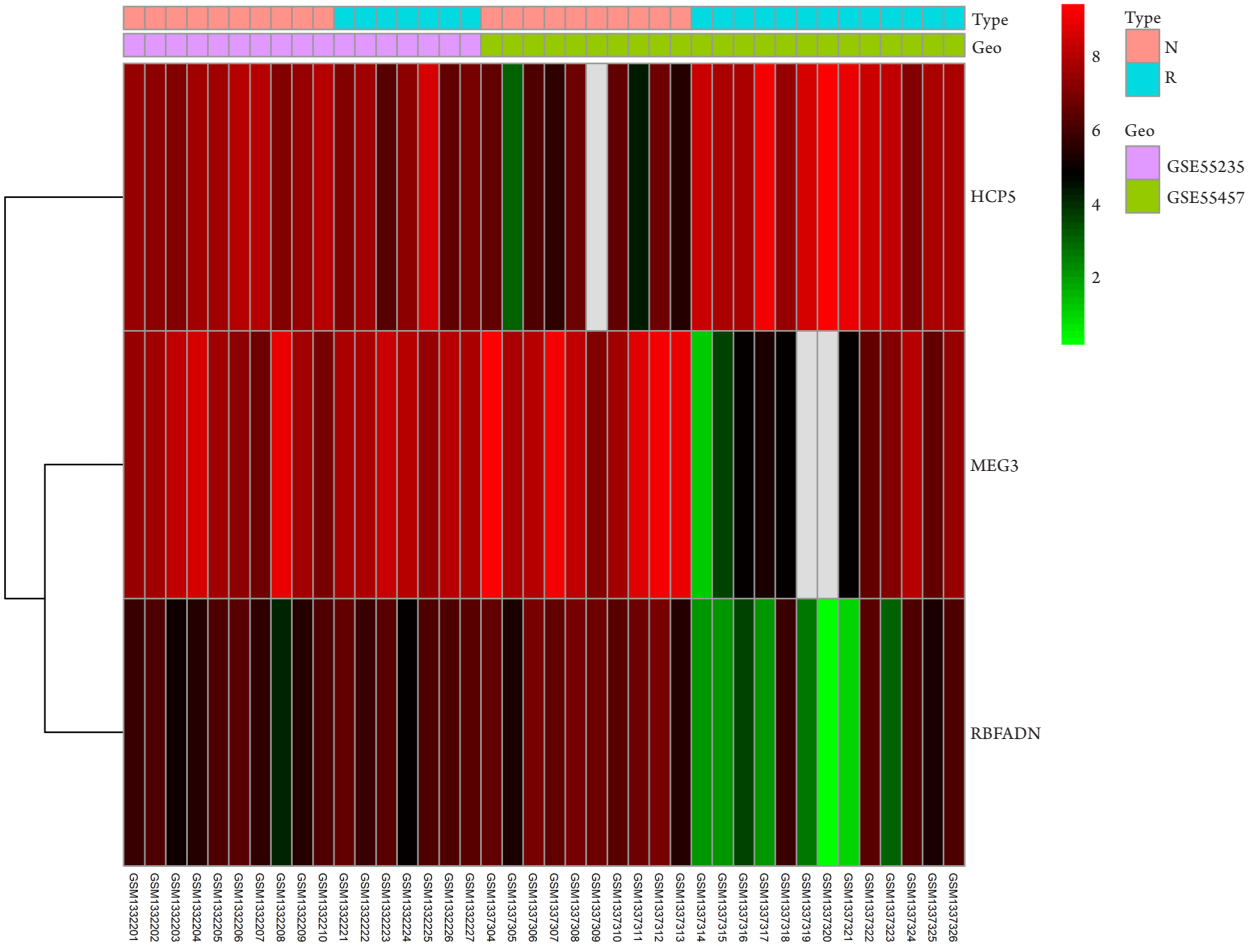


**图1 差异LncRNA在不同样本中的表达**

**Figure 1 Differential LncRNA expression in different samples**

**表1 表达差异mRNA**

**Table 1 Differential mRNA expression**

| Genes | logFC | Ave. Expr | *t* | *P* | adj. *P* | *B* |
|---|---|---|---|---|---|---|
| *PLEKHA1* | −1.119 | 8.529 | −3.399 | 0.001 | 0.034 | −1.289 |
| *PMAIP1* | −1.205 | 6.518 | −3.346 | 0.001 | 0.037 | −1.427 |
| *ADM* | −1.595 | 10.255 | −6.769 | 3.64E−08 | 3.06E−05 | 8.662 |
| *TNKS2* | −1.374 | 7.871 | −3.912 | 0.0003 | 0.014 | 0.079 |
| *PHKA1* | −1.559 | 5.069 | −4.600 | 4.26E−05 | 0.003 | 2.038 |
| *JUN* | −1.5750 | 9.856 | −5.682 | 1.26E−06 | 0.0003 | 5.335 |
| *MYC* | −1.413 | 9.965 | −6.244 | 2.01E−07 | 9.10E−05 | 7.057 |
| *CDKN1A* | −1.310 | 9.705 | −4.344 | 9.09E−05 | 0.005 | 1.320 |
| *CAMTA1* | 1.027 | 5.190 | 3.505 | 0.001 | 0.030 | −1.025 |
| *SFRP1* | −1.278 | 8.960 | −3.489 | 0.001 | 0.030 | −1.060 |
| *FOS* | −2.108 | 11.012 | −3.486 | 0.001 | 0.031 | −1.074 |

**续表1**

| Genes | logFC | Ave. Expr | *t* | *P* | adj. *P* | *B* |
|---|---|---|---|---|---|---|
| *NOVA1* | −1.359 | 7.807 | −4.169 | 0.0001 | 0.008 | 0.818 |
| *WASL* | −1.292 | 5.023 | −3.492 | 0.001 | 0.030 | −1.046 |
| *CSRNP3* | −1.124 | 3.572 | −3.819 | 0.0005 | 0.019 | −0.229 |
| *SPRY2* | −1.196 | 8.266 | −4.789 | 2.24E−05 | 0.002 | 2.630 |
| *PTGS2* | −1.878 | 6.795 | −5.293 | 4.45E−06 | 0.001 | 4.147 |
| *WASF3* | −1.003 | 8.597 | −4.565 | 4.55E−05 | 0.003 | 1.965 |

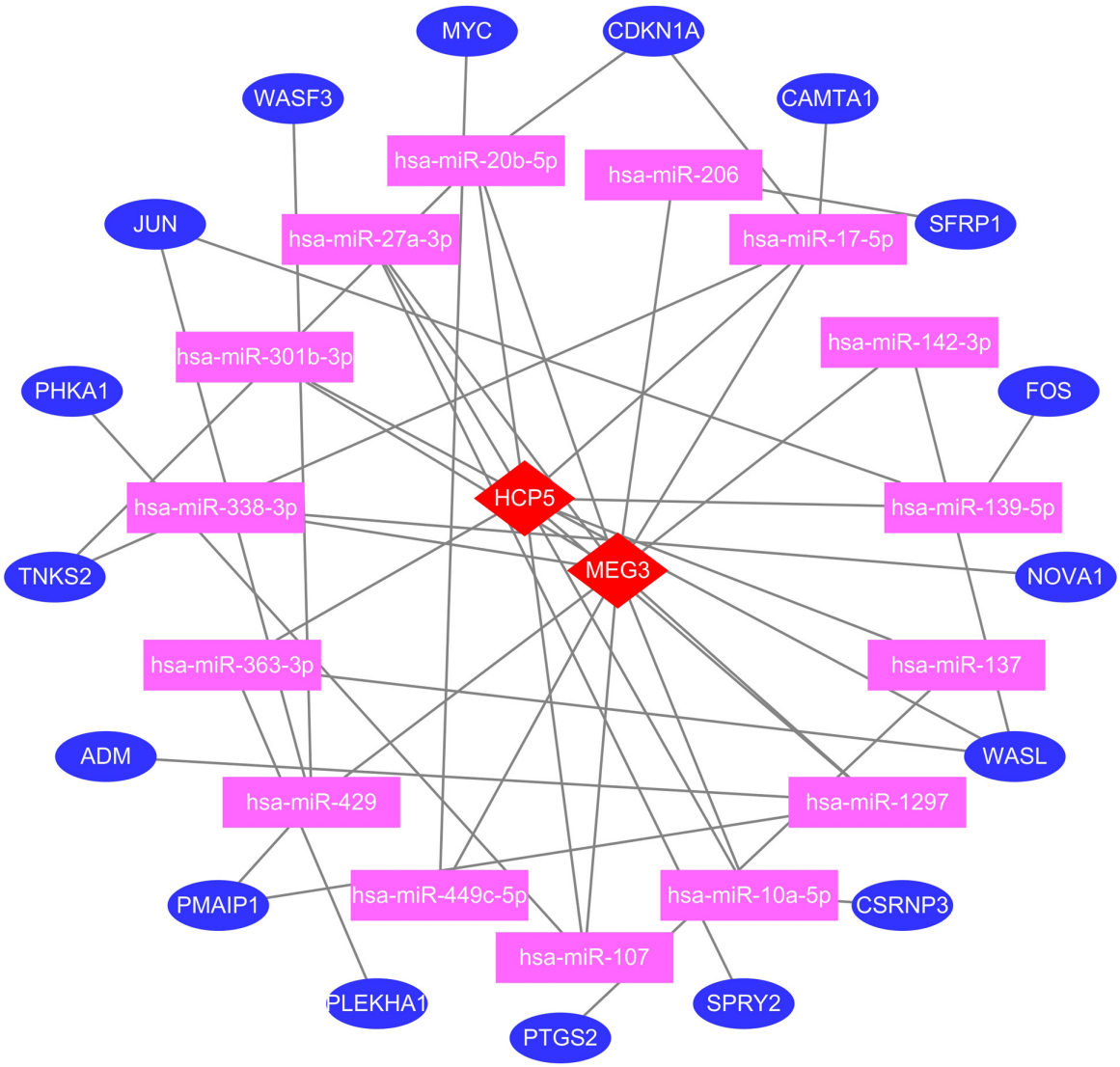


**图2 基于差异表达LncRNA 构建的ceRNA 调控网络**

**Figure 2 ceRNA regulatory network based on differentially expressed LncRNA**

菱形代表lncRNA，矩形代表miRNA，椭圆代表mRNA。

Diamond for lncRNA, rectangle for miRNA, oval for mRNA.

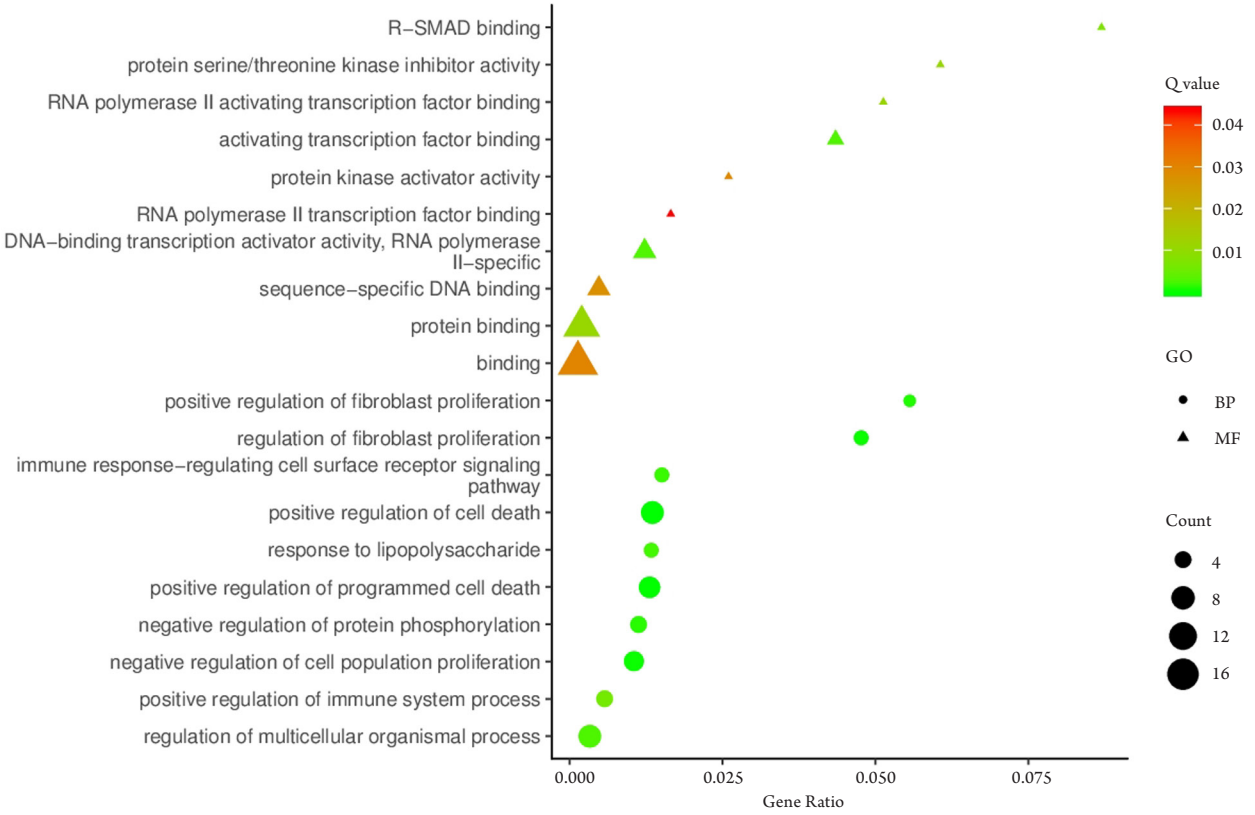


**图3 差异表达基因GO富集分析结果(BP，MF)**

**Figure 3 Results of GO enrichment analysis of differentially expressed genes (BP, MF)**

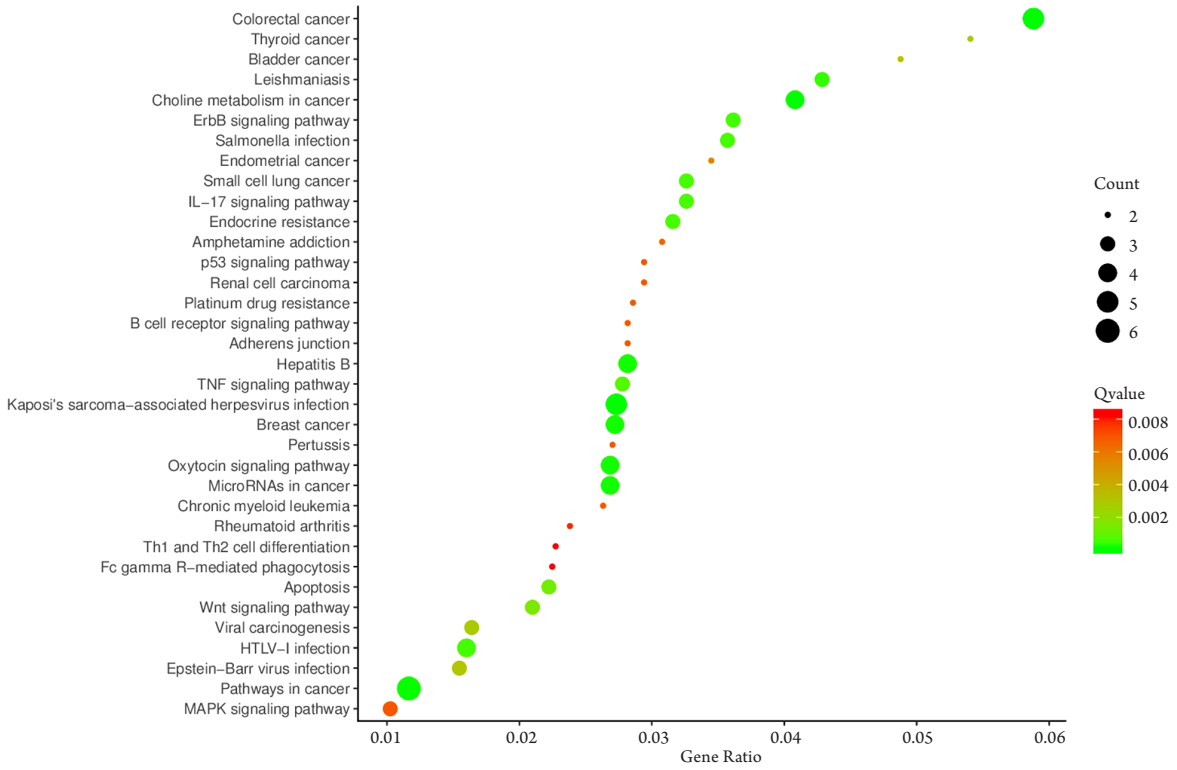


**图4 差异表达基因KEGG分析结果**

**Figure 4 KEGG analysis results of differentially expressed genes**

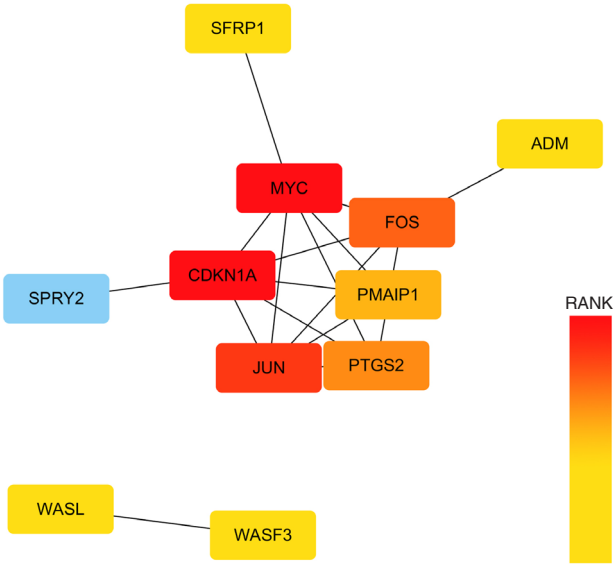


图5 PPI网络差异编码基因中的*Hub*基因

**Figure 5 *Hub* gene in the differentially encoded gene of PPI network**

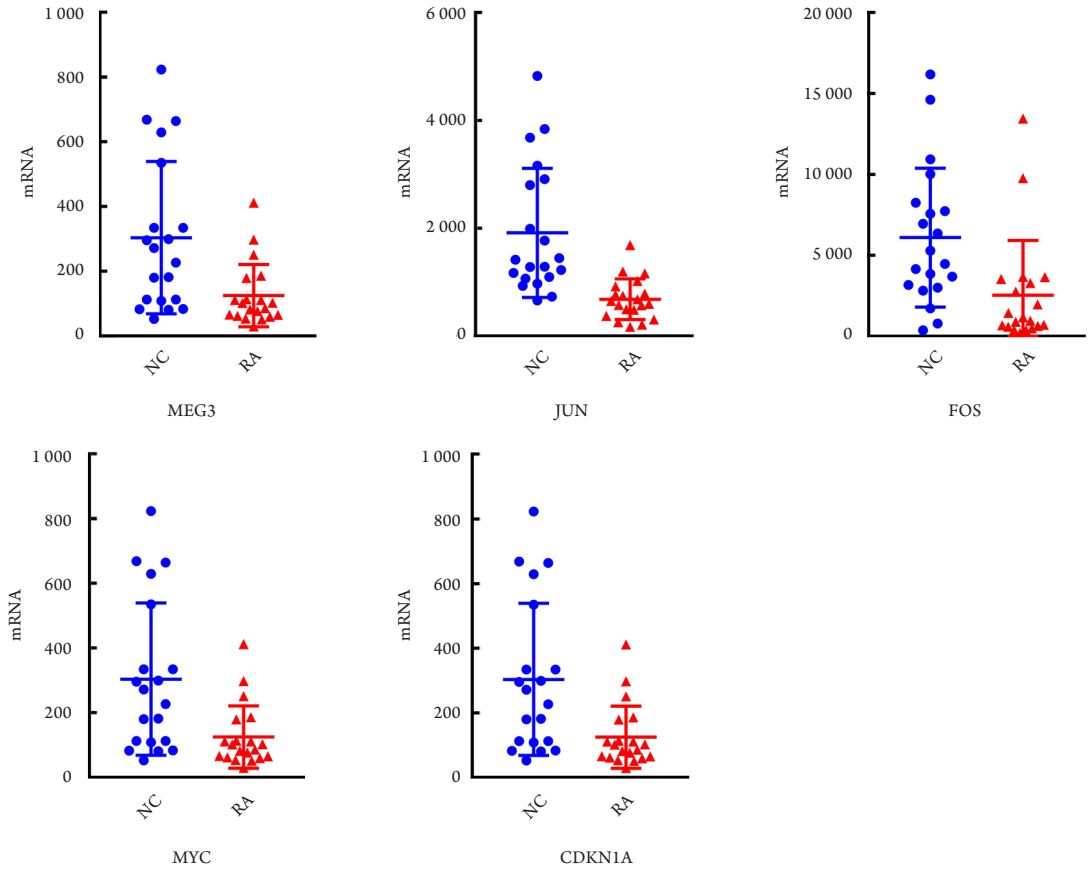


图6 LncRNA MEG3，MYC，CDKN1A，JUN，FOS在正常滑膜组织中呈高表达，RA滑膜组织中均呈低表达，均$P<0.01$

**Figure 6 LncRNA MEG3, MYC, CDKN1A, JUN, FOS were high expression in normal synovial tissue, and low expression in RA synovial tissue, $P<0.01$**

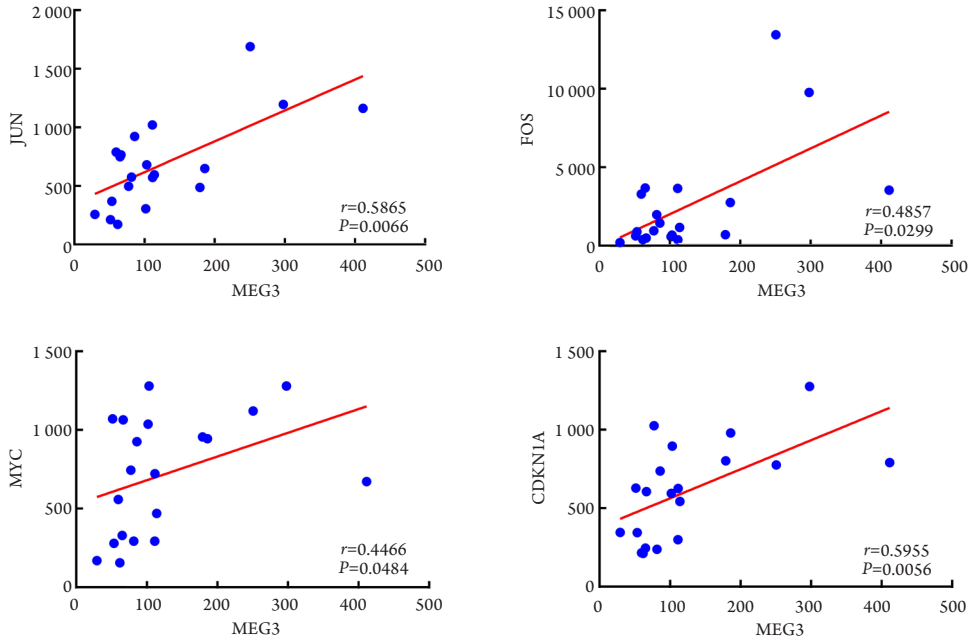


**图7 LncRNA MEG3与MYC，CDKN1A，JUN，FOS在RA滑膜组织中的表达呈正相关**

**Figure 7 LncRNA MEG3 was positively correlated with the expression of MYC, CDKN1A, JUN and FOS in RA synovial tissue**

## 3 讨论

RA是一种病因不明的自身免疫性疾病。既往对RA分子机制的研究[20-22]主要集中在蛋白质编码基因和miRNA上，而越来越多的研究[23-28]表明lncRNA参与了调节自身免疫和炎症相关的过程，包括NK-κB和TOLL样受体的信号转导、细胞因子表达以及免疫细胞的增殖和分化等。现已经在胃癌、膀胱癌等多种肿瘤中对CeRNA网络进行了系统分析，推断lncRNA的潜在功能的一个有效方法是研究其与miRNA和mRNA的关系。因此，深入研究lncRNA在RA发生发展中的作用及其调控机制，并探讨其在RA诊断及治疗中的潜在意义是非常重要的。

为寻找可能成为RA临床诊断和治疗靶点的新的生物标志物的关键lncRNA，本研究通过对NCBI GEO数据的分析，构建lncRNA-miRNA-mRNA互作网络，网络由2个lncRNA节点，16个miRNA节点、17个mRNA节点以及44个边组成。而GO功能富集分析显示其主要集中在细胞死亡的正调控、成纤维细胞增殖的调节、免疫应答调节细胞表面受体信号通路等功能，且多数为RA中低表达的基因。KEGG通路分析进一步表明：35条通路被富集，其中涉及IL-17代谢通路、MAPK信号通路、WNT信号通路、TNF信号通路等，这些通路在RA中都起着重要的作用[29-31]。

本研究通过分析得到2个处于关键的节点lncRNA(HCP5，MEG3)，其中lncRNA MEG3连接的mRNA在GO和通路分析中显示与RA高度相关。这些结果表明：在RA的发生发展的过程中，lncRNA MEG3可能发挥重要的作用。研究[32]表明：在RA患者成纤维滑膜细胞中，MEG3表达下调并激活STAT3和PI3K/AKT通路，促进FLS增殖和侵袭，然而对其具体的机制尚不清楚。RA患者的滑膜成纤维细胞，其类肿瘤样的异常增殖是滑膜组织增生的主要原因。根据CeRNA调控机制，当lncRNA下调时，mRNA相应的下调而miRNA应该上调。在预测到的16个miRNA中，MEG3可能调控的miRNA为12个。研究[33-36]表明：miR-17-5p，miR-301b-3p，miR-1297，miR-449c-5p过表达显著增强宫颈癌细胞、前列腺癌细胞等多种肿瘤细胞的增殖和转移。miR-206在RA患者中表达升高，且与血清IL-16和IL-17具有正相关[37]。而miR-142-3p，miR-20b-5p，miR-429，miR-27a-3p，miR-107，miR-338-3p，miR-10a-5p在多种肿瘤细胞中均下调，与CeRNA调控作用机制不一致，提示其作用机制可能并非通过CeRNA。根据MEG3-miRNA-mRNA网络，我们推测LncRNA MEG3可能通过miR-17-5p，miR-301b-3p，miR-1297，miR-449c-5p，miR-206的相互竞争作用改变mRNA的表达。根据上述预测结果显示：miR-17-5p可能靶向CDKN1A。而Gang等[38]研究表明：在RASF中，CDKN1A表达较正常滑膜组织是明显下调的，

CDKN1A过表达显著抑制RASF的增殖和侵袭，下调肿瘤坏死因子α和IL-6的表达。预测结果显示miR-206可能靶向SFRP1。研究[39-40]显示：在RA患者滑膜液中，SFRP1升高，且与滑膜液中滑液中IL-17水平呈正相关。miR-449c-5p，miR-301b-3p，miR-1297分别靶向MYC，WASL，PMAIP1，然而多项研究[41-42]表明：在RASF中，MYC均明显升高，与预测结果相反，而WASL，PMAIP1在RA发病中的作用尚未见有报告，因而尚需试验进一步明确。上述结果表明：lncRNA MEG3作为ceRNA可能通过MEG3-miR-17-5p-CDKN1A以及MEG3-miR-206-SFRP1这两个ceRNA调控网络在RA的疾病发展中发挥重要作用。

本研究构建了两个lncRNA-miRNA-mRNA网络，分析lncRNA相关的ceRNA介导的基因在RA发生发展中的作用，有助于从lncRNA的角度进一步了解RA的发病机制，并为RA提供一些新的候选诊断生物标志物或潜在的治疗靶点。然而，与大多数的生物信息分析研究一样，研究也存在一些局限性。如研究样本量较小，也没有消除某些可能改变滑膜组织基因表达的药物，包括甲氨蝶呤、生物制剂、激素、非甾体抗炎药的使用，这个局限性表现为在分析中MYC，JUN，FOS基因是下调的，而之前研究表明这些基因在RASF中是上调的，这个结果可能因受到药物等因素的影响，需要进一步研究明确。另外本研究差异表达的基因和它相关的通路没有通过体外研究或其他功能研究得到证实，因此需要进一步通过使用类风湿滑膜组织样本行蛋白质印迹法和聚合酶链反应检测来验证。

## 参考文献


1. Ammari M, Presumey J, Ponsolles C, et al. Delivery of mir-146a to ly6c(high) monocytes inhibits pathogenic bone erosion in inflammatory Arthritis[J]. Theranostics, 2018, 8(21): 5972-5985.
2. Tanner MR, Pennington MW, Chauhan SS, et al. KCa1.1 and Kv1.3 channels regulate the interactions between fibroblast-like synoviocytes and T lymphocytes during rheumatoid arthritis[J]. Arthritis Res Ther, 2019, 21(1): 6.
3. Fassio A, Adami G, Gatti D, et al. Inhibition of tumor necrosis factor-alpha (TNF-alpha) in patients with early rheumatoid arthritis results in acute changes of bone modulators[J]. Int Immunopharmacol, 2019, 67: 487-489.
4. Li R, Li X, Yu B, et al. Comparison of leukocyte esterase testing of synovial fluid with synovial histology for the diagnosis of periprosthetic joint infection[J]. Med Sci Monit, 2017, 23: 4440-4446.
5. Huang QL, Zhou FJ, Wu CB, et al. Circulating biomarkers for predicting infliximab response in rheumatoid arthritis: a systematic bioinformatics analysis[J]. Med Sci Monit, 2017, 23: 1849-1855.
6. Pap T, Aupperle KR, Gay S, et al. Invasiveness of synovial fibroblasts is regulated by p53 in the SCID mouse in vivo model of cartilage invasion[J]. Arthritis Rheum, 2001, 44(3): 676-681.
7. Tolboom TC, van der Helm-Van Mil AH, Nelissen RG, et al. Invasiveness of fibroblast-like synoviocytes is an individual patient characteristic associated with the rate of joint destruction in patients with rheumatoid arthritis[J]. Arthritis Rheum, 2005, 52(7): 1999-2002.
8. Djebali S, Davis CA, Merkel A, et al. Landscape of transcription in human cells[J]. Nature, 2012, 489(7414): 101-108.
9. Mehler MF, Mattick JS. Noncoding RNAs and RNA editing in brain development, functional diversification, and neurological disease[J]. Physiol Rev, 2007, 87(3): 799-823.
10. Kowalczyk MS, Higgs DR, Gingeras TR. Molecular biology: RNA discrimination[J]. Nature, 2012, 482(7385): 310-311.
11. Long L, Yu P, Liu Y, et al. Upregulated microRNA-155 expression in peripheral blood mononuclear cells and fibroblast-like synoviocytes in rheumatoid arthritis[J]. Clin Dev Immunol, 2013, 2013: 296139.
12. Pauley KM, Satoh M, Chan AL, et al. Upregulated miR-146a expression in peripheral blood mononuclear cells from rheumatoid arthritis patients[J]. Arthritis Res Ther, 2008, 10(4): R101.
13. Ponting CP, Oliver PL, Reik W. Evolution and functions of long noncoding RNAs[J]. Cell, 2009, 136(4): 629-641.
14. Wang KC, Chang HY. Molecular mechanisms of long noncoding RNAs[J]. Mol Cell, 2011, 43(6): 904-914.
15. Song J, Kim D, Han J, et al. PBMC and exosome-derived Hotair is a critical regulator and potent marker for rheumatoid arthritis[J]. Clin Exl Med, 2015, 15(1): 121-126.
16. Stuhlmüller B, Kunisch E, Franz J, et al. Detection of oncofetal H19 RNA in rheumatoid arthritis synovial tissue[J]. Am J Patho, 2003, 163(3): 901-911.
17. Messemaker TC, Frank-Bertoncelj M, Marques RB, et al. A novel long non-coding rna in the rheumatoid arthritis risk locus traf1-c5 influences c5 mRNA levels[J]. Genes Immun, 2016, 17(2): 85-92.
18. Lu MC, Yu HC, Yu CL, et al. Increased expression of long noncoding RNAs LOC100652951 and LOC100506036 in T cells from patients with rheumatoid arthritis facilitates the inflammatory responses[J]. Immunol Res, 2016, 64(2): 576-583.
19. Salmena L, Poliseno L, Tay Y, et al. A ceRNA hypothesis: the rosetta stone of a hidden RNA language?[J]. Cell, 2011, 146(3): 353-358.
20. Van Loosdregt J, Rossetti M, Spreafico R, et al. Increased autophagy in CD4(+) T cells of rheumatoid arthritis patients results in T-cell

hyperactivation and apoptosis resistance[J]. Eur J Immunol, 2016, 46(12): 2862-2870.

21. Smigielska-Czepiel K, van den Berg A, Jellema P, et al. Comprehensive analysis of miRNA expression in T-cell subsets of rheumatoid arthritis patients reveals defined signatures of naive and memory Tregs[J]. Genes Immun, 2014, 15(2): 115-125.
22. 高登文, 钱龙. 微小RNA在免疫系统和类风湿关节炎中的作用[J].中华风湿病学杂志, 2011, 15(6): 416-420.
GAO Dengwen, QIAN Long. The role of microRNAs in the immune system and rheumatoid arthritis[J]. Chinese Journal of Rheumatology, 2011, 15(6): 416-420.
23. Müller N, Döring F, Klapper M, et al. Interleukin-6 and tumour necrosis factor-α differentially regulate lincRNA transcripts in cells of the innate immune system in vivo in human subjects with rheumatoid arthritis[J]. Cytokine, 2014, 68(1): 65-68.
24. Aune TM, Crooke PS 3rd, Patrick AE, et al. Expression of long non-coding RNAs in autoimmunity and linkage to enhancer function and autoimmune disease risk genetic variants[J]. J Autoimmun, 2017, 81: 99-109.
25. Xia M, Liu J, Liu S, et al. Ash1l and lnc-Smad3 coordinate Smad3 locus accessibility to modulate iTreg polarization and T cell autoimmunity[J]. Nat Commun, 2017, 8: 15818.
26. Zemmour D, Pratama A, Loughhead SM, et al. Flicr, a long noncoding RNA, modulates Foxp3 expression and autoimmunity[J]. Proc Natl Acad Sci U S A, 2017, 114(17): E3472-E3480.
27. Liu ML, Williams KJ, Werth VP. Microvesicles in autoimmune diseases[J]. Adv Clin Chem, 2016, 77: 125-175.
28. Wang J, Peng H, Tian J, et al. Upregulation of long noncoding RNA TMEVPG1 enhances T helper type 1 cell response in patients with Sjögren syndrome[J]. Immunol Res, 2016, 64(2): 489-496.
29. Ganesan R, Rasool M. Interleukin 17 regulates SHP-2 and IL-17RA/STAT-3 dependent Cyr61, IL-23 and GM-CSF expression and RANKL mediated osteoclastogenesis by fibroblast-like synoviocytes in rheumatoid arthritis[J]. Mol Immunol, 2017, 91: 134-144.
30. Sujitha S, Rasool M. MicroRNAs and bioactive compounds on TLR/MAPK signaling in rheumatoid arthritis[J]. Clin Chim Acta, 2017, 473: 106-115.
31. Miao CG, Yang YY, He X, et al. Wnt signaling pathway in rheumatoid arthritis, with special emphasis on the different roles in synovial inflammation and bone remodeling[J]. Cell Signal, 2013, 25(10): 2069-2078.
32. Lu X, Qian J. Downregulated meg3 participates in rheumatoid arthritis via promoting proliferation of fibroblast-like synoviocytes[J]. Exp Ther Med, 2019, 17(3): 1637-1642.
33. Cai N, Cai N, Hu L, et al. MiR-17-5p promotes cervical cancer cell proliferation and metastasis by targeting transforming growth factor-β receptor 2[J]. Eur Rev Med Pharmacol Sci, 2018, 22(7): 1899-1906.
34. Zheng H, Bai L. Hypoxia induced microRNA-301b-3p overexpression promotes proliferation, migration and invasion of prostate cancer cells by targeting LRP1B[J]. Exp Mol Pathol, 2019, 20(8): 104301.
35. Chen Z, Zhang M, Qiao Y, et al. MicroRNA-1297 contributes to the progression of human cervical carcinoma through PTEN[J]. Artif Cells Nanomed Biotechnol, 2018, 46(sup2): 1120-1126.
36. Jiang L, Wu CL, Wu JZ, et al. Microarray-based measurement of microRNA-449c-5p levels in hepatocellular carcinoma and bioinformatic analysis of potential signaling pathways[J]. Pathol Res Pract, 2019, 215(1): 68-81.
37. Elatta AA, Ali Y, Bassyouni I, et al. Correlation of myoMir-206 and proinflammatory cytokines (IL-16 and IL-17) in patients with rheumatoid arthritis[J]. Reumatologia, 2019, 57(2): 72-77.
38. Gang X, Xu H, Si L, et al. Treatment effect of CDKN1A on rheumatoid arthritis by mediating proliferation and invasion of fibroblast-like synoviocytes cells[J]. Clin Exp Immunol, 2018, 194(2): 220-230.
39. Imai K, Morikawa M, D'Armiento J, et al. Differential expression of WNTs and FRPs in the synovium of rheumatoid arthritis and osteoarthritis[J]. Biochem Biophys Res Commun, 2006, 345(4): 1615-1620.
40. Lee YS, Lee KA, Yoon HB, et al. The Wnt inhibitor secreted frizzled-related protein 1 (sFRP1) promotes human Th17 differentiation[J]. Eur J Immunol, 2012, 42(10): 2564-2573.
41. 孟明, 顾立刚, 张前, 等. 类风湿关节炎大鼠滑膜细胞的类肿瘤样增生与相关基因表达的关系[J]. 细胞与分子免疫学杂志, 2005, 21(4): 411-414.
MENG Ming, GU Ligang, ZHANG Qian, et al. The study on the relationship between the tumor-like proliferation of synoviocytes and the expression of c-myc and ODC genes in adjuvant arthritis rats[J]. Journal of Cellular and Molecular Immunology, 2005, 21(4): 411-414.
42. Pap T, Nawrath M, Heinrich J, et al. Cooperation of Ras- and c-Myc-dependent pathways in regulating the growth and invasiveness of synovial fibroblasts in rheumatoid arthritis[J]. Arthritis Rheum, 2004, 50(9): 2794-2802.

**本文引用：** 肖剑伟, 蔡旭, 陈新鹏, 曾苗雨, 郭粉莲, 洪易炜, 叶志中. 类风湿关节炎患者滑膜组织lncRNA表达及基于CeRNA网络的生物信息学分析[J]. 临床与病理杂志, 2020, 40(5): 1144-1153. doi: 10.3978/j.issn.2095-6959.2020.05.011

***Cite this article as:*** XIAO Jianwei, CAI Xu, CHEN Xinpeng, ZENG Miaoyu, GUO Fenlian, HONG Yiwei, YE Zhizhong. Expression of LncRNA in synovial tissues of patients with rheumatoid arthritis and bioinformatics analysis based on CeRNA network[J]. Journal of Clinical and Pathological Research, 2020, 40(5): 1144-1153. doi: 10.3978/j.issn.2095-6959.2020.05.011