



# Exploration of microRNA profiles in human colostrum

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**Background:** Colostrum is well known to have excellent nutritional value for newborns. The aim of this study was to investigate the dynamic expression pattern of microRNA in human colostrum and mature milk. Furthermore, we identified the specific microRNA in human colostrum and analyzed the regulatory function of human colostrum.

**Methods:** We collected breast milk samples from 18 lactating volunteers. The expression of microRNA in breast milk was detected by microarray analysis. The expression differences were characterized by log<sub>2</sub>FC ( $|\log_2\text{fold change}| > 1.58$ ) and associated P values ( $P < 0.05$ ). Furthermore, the prediction of microRNA targets, bioinformatics analysis and network generation were carried out using network database.

**Results:** Our results showed that during the human lactation process, the composition of microRNAs in human milk changes dynamically. Compared to the microRNA expression profile in human mature milk, the expression levels of 49 microRNAs were significantly different and 67 microRNAs were specifically expressed in human colostrum. Based on the results of Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis, the predicted target mRNAs of the identified colostrum-specific microRNAs were involved in the regulation of distinct biological processes, such as signal transduction, positive regulation of GTPase activity, and protein phosphorylation. Moreover, the predicted mRNA targets were from large spectrums of signaling pathways, such as the MAPK, Ras, Hippo, Wnt, and mTOR signaling pathways, as well as the longevity regulating pathway.

**Conclusions:** Our study illuminates the landscape of microRNA expressions in human colostrum and mature milk, and emphasizes the value of microRNAs as nutritional additives in milk-related commercial products.

**Keywords:** MicroRNAs (miRNAs); colostrum; mature milk; microarray

Submitted Jul 16, 2020. Accepted for publication Sep 01, 2020.

doi: 10.21037/atm-20-5709

View this article at: <http://dx.doi.org/10.21037/atm-20-5709>

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## Introduction

Breastfeeding has many nutritional, immune, physical, developmental, and psychological benefits, which makes human breast milk the best food for newborns, as well as the most natural. A large prospective cohort study in Brazil reported the total duration of breastfeeding and predominant breastfeeding to be positively associated with intelligence quotient, educational attainment, and income (1). The World Health Organization recommends that infants should be exclusively breastfed for the first 6 months of life. Human breast milk contains at least 415 proteins. These proteins are involved in all aspects of metabolism and various functions of the body (2). Colostrum contains more nutrients than mature milk, making it more beneficial for babies.

MicroRNAs (miRNAs) are endogenous non-coding RNAs of 18–25 nt in length. They are important regulators of many biological processes, such as organogenesis, body development, cellular metabolism, and cell differentiation (3). Moreover, miRNAs have unique stable expression patterns in various body fluids, including saliva (4), serum (5,6), plasma (7), and urine (8). Therefore, miRNAs can be used as non-invasive or minimally invasive biomarkers for a range of diseases, as well as potential indicators for the quality of food products (9). Exogenous miRNAs derived from diet can regulate the expressions of target genes and be used to identify specific tissue cells (10). MiR-168a, for instance, is abundant in rice and among the most highly enriched exogenous plant miRNAs in sera of Chinese populations (11). Previous functional studies have demonstrated that miR-168a binds to the mRNA of human/mouse low-density lipoprotein receptor adapter protein 1 and inhibits its protein expression in the liver; consequently, causing impairment in removal of low-density lipoprotein from plasma (10,11).

Exogenous miRNAs are stable in the blood of mammals. In recent years, studies on the functional properties and potential applications of miRNAs in the food field have increased. MiRNAs are involved in mammary gland development and milk ingredient synthesis (12). MiRNAs also comprise the nutritive indexes of fluid milk and powdered-formula milk (13). To date, the unique miRNA expression profiles in human colostrum and mature milk have rarely been reported. In the current study, we aimed to investigate dynamic miRNA expression patterns in human colostrum compared with mature milk in order to identify miRNAs specifically expressed in human colostrum. For the

first time, this study shines a light on miRNA expression in human colostrum and mature milk, and emphasizes the value of miRNAs as nutritional additives in milk-related commercial products.

We present the following article in accordance with the MDAR reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-5709>).

## Methods

### *Sample collection*

Human milk samples were collected from 18 lactating volunteers (age  $30\pm 4$  y, pregnancy  $40\pm 3$  w). Breast milk produced on days 7 and 14 after birth is defined as transition milk. Previous reports have clearly shown that nutritional compositions of breast milk vary throughout lactation period (14,15). Colostrum is rich in growth factors and immunologic compounds (16), whereas components in mature milk is most likely stable without further fluctuations (17). The Nutritional components of colostrum are obviously different from those of mature milk. Therefore, we collected samples of colostrum (1–7 days) and mature milk (14 days) to perform our analysis. All human milk samples ( $n=18$ , 8 colostrum samples and 10 mature milk samples), were expressed by hand between 8 a.m. and 11 a.m., and stored at  $-80$  °C. Two colostrum and two mature milk samples were subjected to microarray analysis. All participants were Han Chinese from Tianjin, China, and were healthy, with no hypertension, diabetes, or other diseases. None of the participants were smokers or drinkers, and none of them were pregnant. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Ethics Committee of the second hospital of Tianjin Medical University (No. KY2020K055) and informed consent was taken from all the patients.

### *MiRNA functional enrichment analyses*

Microarray analyses were performed at Shanghai Biotechnology Corporation (Shanghai, China), using Agilent SurePrint Human miRNA 8×60K V21.0 microarray (Agilent Technologies, USA). Expression differences were characterized by  $\log_2$ FC ( $|\log_2$ fold change|  $>1.58$ ) and P values ( $P<0.05$ ). The analyses were performed using the R package of edgeR (18).

**Table 1** Primer sequences for quantitative RT-PCR

Gene name	Primer sequences (5'-3')
<i>hsa-miR-623</i>	Stemloop: GTCGTATCCAGTGCAGGGTCCGAGGTATTTCGCACTGGATACGACACCCAA Forward: GGTCCATCCCTTGCAGGGGCTG
<i>hsa-miR-885-5p</i>	Stemloop: GTCGTATCCAGTGCAGGGTCCGAGGTATTTCGCACTGGATACGACAGAGGC Forward: GGTCCCTCCATTACTACTACCCTG
<i>hsa-miR-429</i>	Stemloop: GTCGTATCCAGTGCAGGGTCCGAGGTATTTCGCACTGGATACGACACGGTT Forward: GGTCCCTAATACTGTCTGGTAAA
<i>hsa-miR-511-3p</i>	Stemloop: GTCGTATCCAGTGCAGGGTCCGAGGTATTTCGCACTGGATACGACTCTGTC Forward: GGTCCGTGTAGCAAAGACAGA
<i>hsa-miR-29c-3p</i>	Stemloop: GTCGTATCCAGTGCAGGGTCCGAGGTATTTCGCACTGGATACGACTAACC Forward: GGTCCACCATTGAAATCGGTAA
<i>hsa-miR-183-5p</i>	Stemloop: GTCGTATCCAGTGCAGGGTCCGAGGTATTTCGCACTGGATACGACATACCG Forward: GGTCCAAGATGGTCACGGTAT
<i>hsa-miR-30b-5p</i>	Stemloop: GTCGTATCCAGTGCAGGGTCCGAGGTATTTCGCACTGGATACGACAGCTGA Forward: GGTCCATCCTACTACTCAGCT
<i>cel-miR-39</i>	Stemloop: GTCGTATCCAGTGCAGGGTCCGAGGTATTTCGCACTGGATACGACCAAGCT Forward: GGTCCGTGTAAATCAGCTTG
Universal reverse	CCAGTGCAGGGTCCGAGGT

RT-PCR, real-time polymerase chain reaction.

### ***Validation of candidate miRNAs by quantitative real-time polymerase chain reaction (qRT-PCR)***

Equal volumes of the milk samples were centrifuged at 2000 g for 10 minutes at 4 °C. Then, the same volume of *Caenorhabditis elegans* miR-39 (*cel-miR-39*, UCACCGGGUGUAAAUCAGCUUG) was spiked into each milk samples as internal reference for normalization (19). MiRNAs were extracted from the milk samples using EasyPure® miRNA Kit (Transgen Biotech, China) and detected by RT-PCR with SGEExcel Fast SYBR Mixture (Sangon Biotech, Shanghai, China), according to the manufacturer's protocol. Each sample was analyzed in triplicate. The miRNA primer sequences were synthesized by Tsingke Biotech (Beijing, China) according to the miRBase database (Release 20.0) and are listed in *Table 1*. The expression levels of miRNAs were calculated using the  $2^{-\Delta\Delta C_t}$  method.

### ***Prediction of miRNA targets, bioinformatic analysis, and network generation***

The target genes of the differentially expressed miRNAs

were predicted using miRDB (<http://mirdb.org/>), TargetScan ([http://www.targetscan.org/vert\\_72/](http://www.targetscan.org/vert_72/)), and microRNA.org (<http://www.microrna.org/microrna/home.do>). Target genes that appeared in all the three databases were picked out by Cytoscape (Cytoscape 3.7.2, <https://cytoscape.org/download.html>) and incorporated into the subsequent analysis.

GO functional enrichment analysis can identify the major biological functions of differentially expressed genes. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment can also be utilized to investigate the cellular and organismal functions of tested genes. Therefore, we used GO terms and KEGG pathway analysis to determine the role of differentially expressed mRNAs.

### ***Statistical analyses***

All data were analyzed by SPSS 19.0 (SPSS, IL, USA). Data were presented as mean ± standard deviation (SD) of three independent experiments. Student's two-tailed *t*-test was used for comparison between two groups, and one-way

analysis of variance (ANOVA) was used to compare more than two groups.  $P < 0.05$  was considered to be statistically significant.

## Results

### *Dynamic miRNA expressions in human milk*

The different expression profiles of miRNAs in human colostrum and mature milk were compared using the limma package. There were 782 and 805 known miRNAs identified in colostrum and mature milk, respectively. There were 715 miRNAs in both colostrum and mature milk (Figure 1A). Only a small number of miRNAs were detected exclusively in colostrum or in mature milk: 67 colostrum-specific miRNAs were identified (Table S1), and 89 miRNAs were identified specifically in mature milk (Table S2).

Among the 715 miRNAs detected in both colostrum and mature milk, 49 miRNAs were differentially expressed between colostrum and mature milk ( $|\log_2FC| \geq 1.58$  with  $P < 0.05$ ), including 25 miRNAs that were significantly decreased and 24 miRNAs that were significantly increased in colostrum compared to mature milk (Figure 1B). Using a fold change  $\geq 3$  and  $P < 0.05$  as the cutoff threshold, the expressions of 7 miRNAs were significantly altered (Figure 1C). MiR-623 was enriched 10-fold in colostrum compared to in mature milk. In contrast, the levels of miR-30b-5p, miR-885-5p, miR-29c-3p, miR-511-3p, miR-429, and miR-183-5p in colostrum were downregulated compared to those in mature milk. Taken together, these results suggested that there are dynamic changes in the composition of miRNAs in human milk during the human lactation process.

### *Validation with RT-qPCR*

Next, the expressions of the 7 significantly altered miRNAs were validated in all 18 milk samples using RT-qPCR. After normalization using cel-miR-39 (15), the expression levels of miR-623 in colostrum were  $5.052 \pm 0.821$  times higher than those in mature milk ( $P < 0.01$ ). Meanwhile, the expression levels of miR-30b-5p, miR-885-5p, miR-29c-3p, miR-511-3p, miR-429, and miR-183-5p in colostrum were  $0.228 \pm 0.023$  ( $P < 0.01$ ),  $0.435 \pm 0.025$  ( $P < 0.01$ ),  $0.434 \pm 0.014$  ( $P < 0.01$ ),  $0.549 \pm 0.031$  ( $P < 0.01$ ),  $0.556 \pm 0.013$  ( $P < 0.01$ ), and  $0.722 \pm 0.021$  ( $P < 0.01$ ) times lower than those in mature milk, respectively (Figure 2). The results of qRT-PCR further confirmed the altered differential expressions of

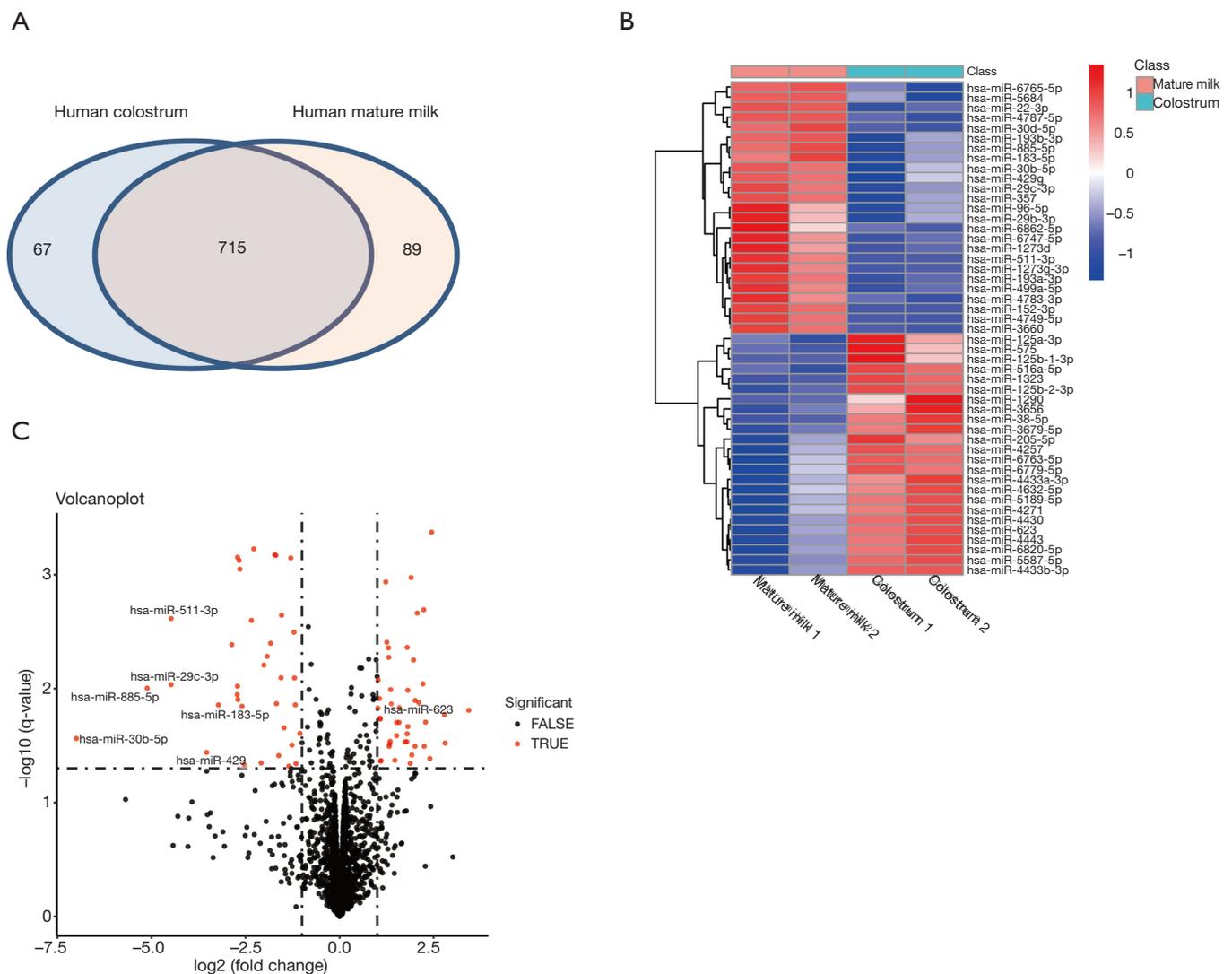
miRNAs between human colostrum and mature milk.

### *Predicted target genes of the colostrum-specific miRNAs*

To verify the functions of the identified colostrum-specific miRNAs (Table S1), their target genes were predicted using miRDB, TargetScan, and microRNA.org. The total number of targets predicted by the three databases is 2,134 targets. Using a reliability score (string)  $\geq 99\%$  as a cutoff threshold, 10 miRNAs were identified along with 260 targets (Figure 3). This miRNA-mRNA network illustrated the key regulatory functions of the identified miRNAs and their target genes. Briefly, all 10 miRNAs had specific predicted targets. At the same time, different miRNAs have common targets. For instance, miR-3666 and miR-130a-3p had more targets than the other 8 miRNAs. Among these predicted target genes, KCNA4 was the common target gene of 4 miRNAs (miR-3666, miR-130a-3p, miR-6766-3p, and miR-145-5p); UXS1, BTF3L4, and YTHDF2 were the common target genes of 3 miRNAs (miR-3666, miR-6766-3p, and miR-145-5p); SKP1 was the common target gene of miR-3666 and miR-145-5p; NEUROD1 was the common target gene of miR-3666 and miR-378; and CXXC5 was the common target gene of miR-6766-3p and miR-28-3p. These results suggested that the colostrum-specific miRNAs might have unique regulatory functions, but they may also potentially share some similar regulatory functions.

### *Functional annotation of target genes of the colostrum-specific miRNAs*

Systematic GO analysis of the target genes of the identified colostrum-specific miRNAs indicated that the colostrum-specific miRNAs were involved in the regulation of distinct biological processes. Molecular and functional analysis revealed that most of the targeted mRNAs were related to protein serine/threonine kinase activity (17.67%), chromatin binding (17.47%), ubiquitin-protein transferase activity (14.66%), and nucleotide binding (14.66%). Other targeted mRNAs were related to ubiquitin protein ligase activity (9.64%), SH3 domain binding (7.83%), and  $\beta$ -catenin binding (6.02%). Cellular component analysis showed that mRNA targeted by the miRNAs were mainly in the nucleus (22.82%), cytoplasm (22.35%), and cytosol (14.48%). Others were in the membrane (9.53%) and the Golgi apparatus (4.34%). Biological process analysis showed that mRNA targeted by the miRNAs were involved in signal transduction (24.36%), positive regulation of GTPase



**Figure 1** miRNA expressions in human milk. (A) Venn diagram of differentially expressed miRNAs between human colostrum and mature milk. (B) Human colostrum versus human mature milk. Changes in miRNA expression  $\log_2\text{FC} > 1.58$ , and  $P < 0.05$  are illustrated by heat map; blue indicates a relatively low expression and red indicates a relatively high expression. (C) Volcano plot of differentially expressed miRNAs between human colostrum and human mature milk.

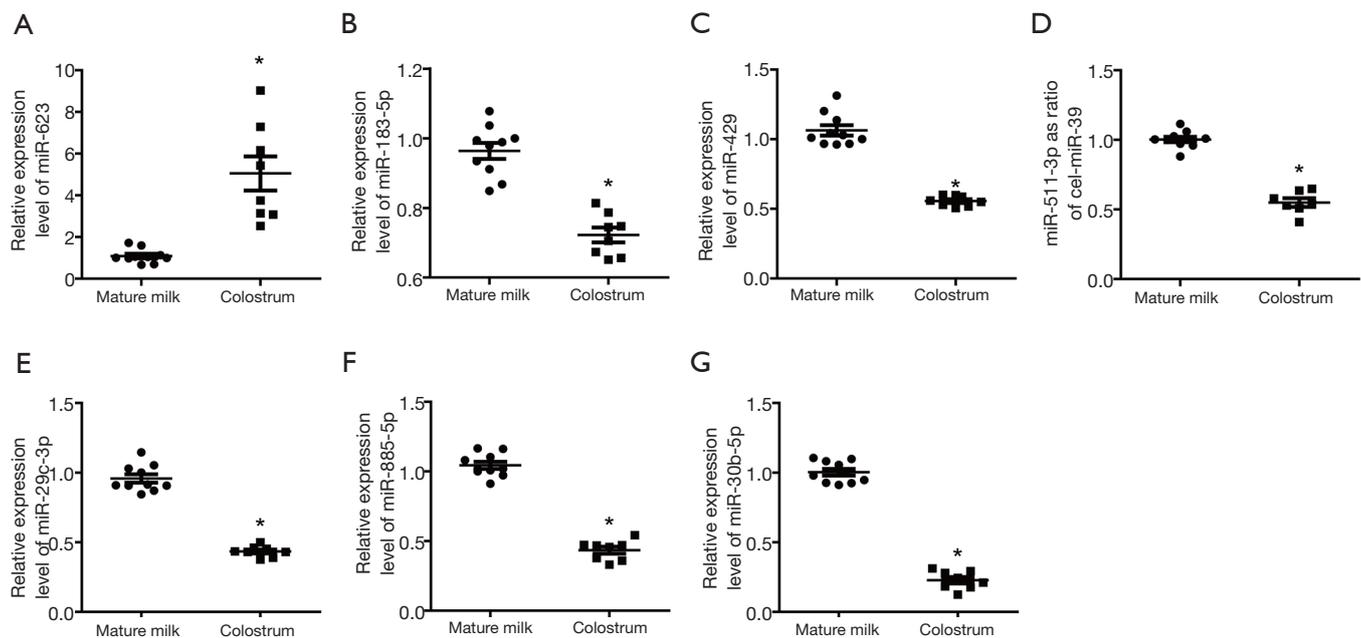
activity (12.24%), protein phosphorylation (10.9%), intracellular signal transduction (9.23%), nervous system development (7.23%), MAPK cascades (6.79%), and Wnt signaling (5.34%) (Figure 4).

In the pathway analysis, the targets of these differentially expressed miRNAs were found to be involved in a wide variety of pathways, including MAPK, PI3K-Akt, endocytic, focal adhesion, and Ras signaling. However, several other relevant pathways were also enriched, such as Rap1, FoxO, Hippo, Wnt, mTOR, and autophagy signaling, as well as

longevity regulating pathway (Figure 5). Taken together, these results suggest that human colostrum possesses unique functions compared to mature milk.

## Discussion

Breast milk is the best and most nutritious food for infants. It contains all of the nutrients that babies need for growth and development, and can be easily digested and absorbed. Moreover, since breast milk plays an important



**Figure 2** Validation by RT-qPCR. The expression levels of seven randomly selected miRNAs were verified by RT-qPCR, including (A) one up-regulated miRNA (miR-623) and (B,C,D,E,F,G) six down-regulated miRNAs. The relative expression levels of miRNAs were normalized to cel-miR-39 and shown as mean  $\pm$  SD.

role in immune system enhancement and systemic disease resistance in infants, breastfeeding can reduce the risks of morbidity and mortality in infants (20).

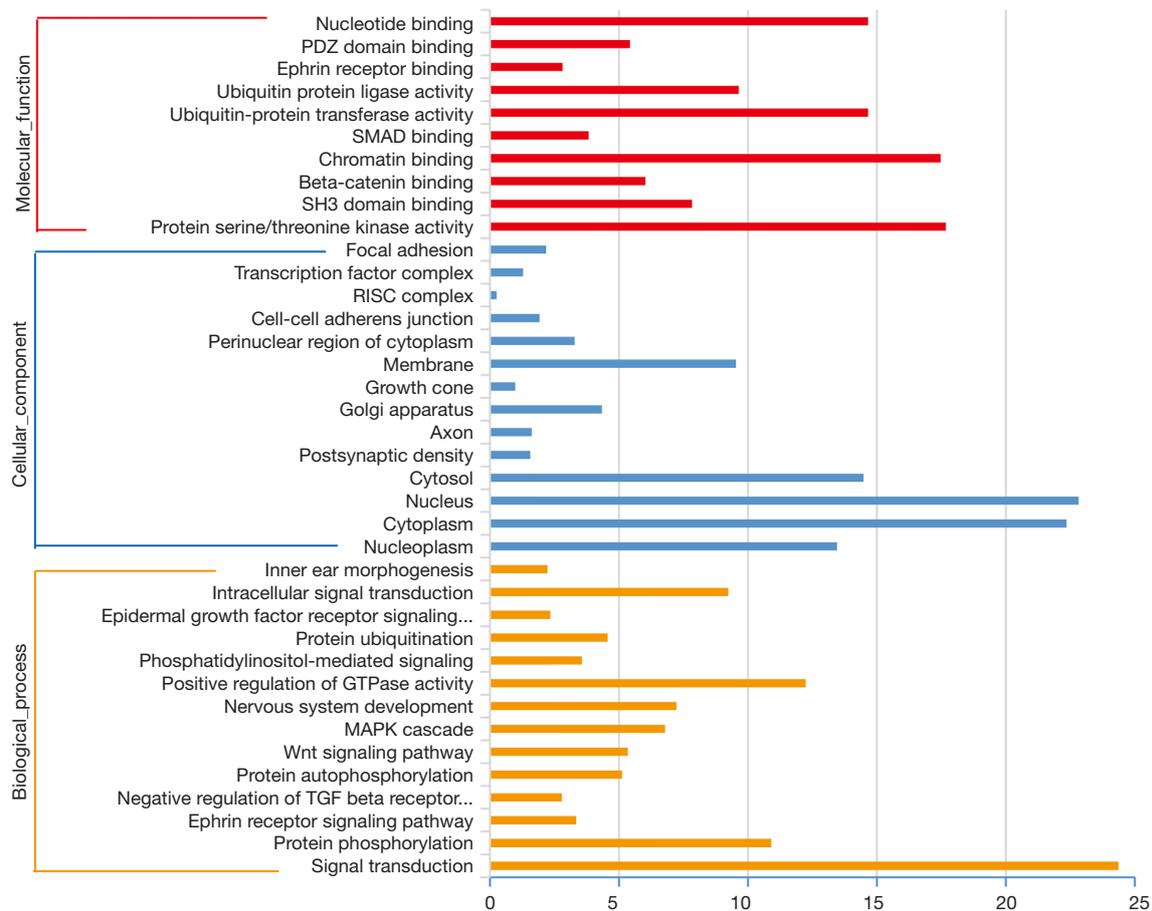
There are three stages of human lactation: colostrum, transitional milk, and mature milk. Colostrum refers to milk lactated within the 7 days after birth; transitional milk is lactated 7–14 days after birth; and mature milk is lactated from 2 weeks after birth. The nutritional components of colostrum are obviously different from those of mature milk. Some immunity-related proteins, such as immunoglobulin A, lactoferrin, and lysozyme, are more abundant in colostrum milk than in transitional or mature milk. Many studies have proved that colostrum and its products have many physiological functions, such as regulating immunity, improving gastrointestinal function, promoting growth and development, promoting resistance to pathogenic microorganisms, eliminating fatigue, and delaying aging.

MiRNAs play important roles in the post transcriptional regulation of genes. Multiple miRNAs may regulate the expression of a single specific mRNA, and a single miRNA may also regulate multiple target genes. Moreover, miRNAs have stage-specific and tissue-specific expression patterns. For instance, miR-2285t can target TGFBR1,

RRAS2, RNF111, BMP2, and ACVR2A molecules in TGF- $\beta$  signaling pathway, and many target genes of miR-29b are enriched in PTEN, PI3K/AKT, and JAK/Stat signaling pathways. MiRNA in breast milk remains stable under severe degradation conditions and can be used as a regulatory mediator in early immune system development and improvement in infants (21). In 2012, Zhou *et al.* used the SoieXa platform to study the miRNA transcriptome encapsulated by exosomes in human milk. They found 639 mature miRNAs, including 98 immune-related miRNAs (22). Another study showed that the miRNA expression spectrum in pig milk was significantly enriched in immune-related miRNAs. These immune related miRNAs can enhance the immunity of infants (23). Furthermore, miRNAs in breast milk may promote adaptation to early dietary changes through regulating infant metabolism (24).

Our results showed that the composition of miRNAs in human breast milk changes dynamically during lactation process. A total of 782 and 805 known miRNAs were identified in human colostrum and mature milk, respectively; of these miRNAs, 715 were detected in both human colostrum and mature milk. The expression levels of 49 of these 715 miRNAs detected in common were



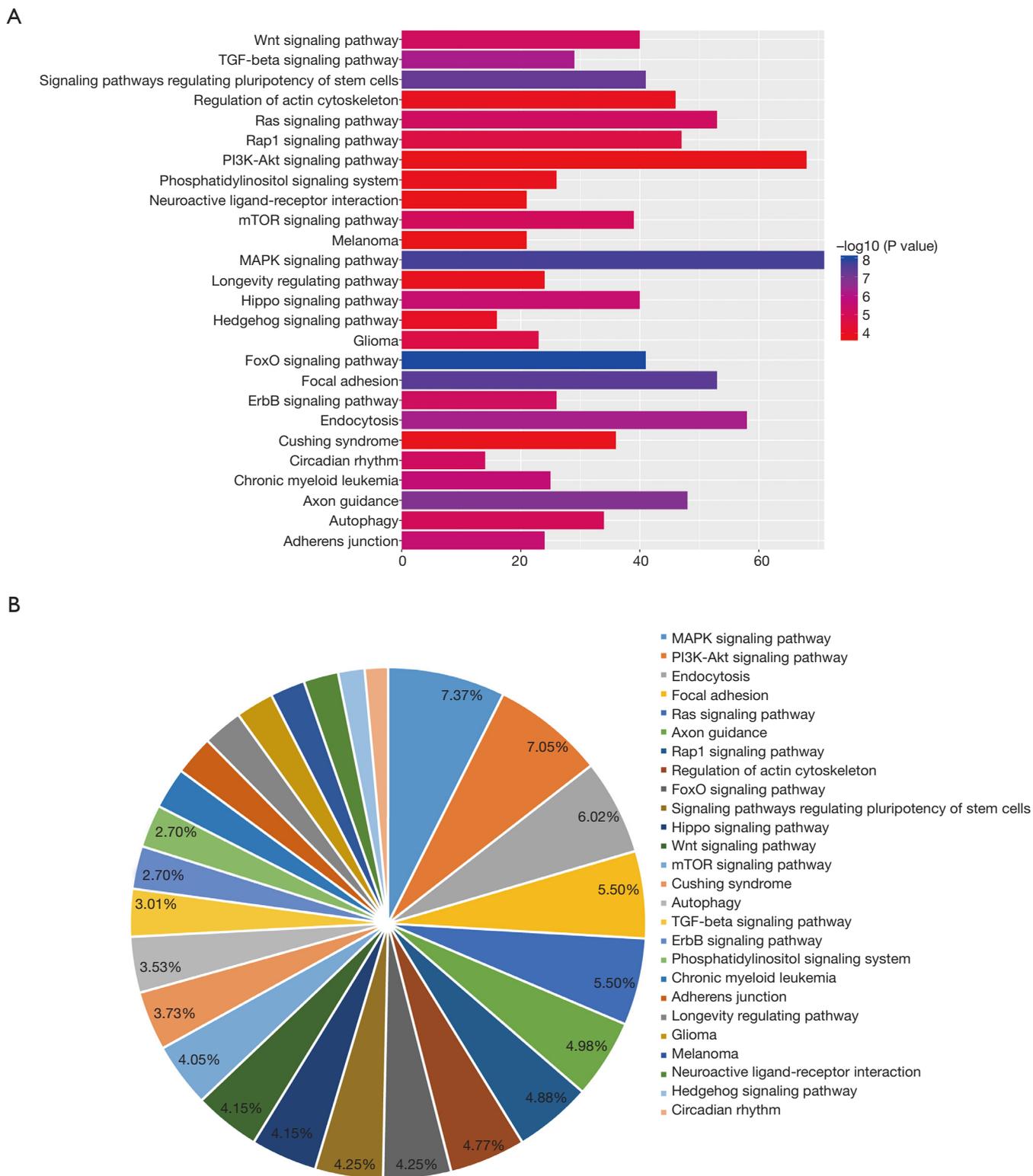


**Figure 4** GO analysis of human colostrum-specific miRNA targets. The mRNAs targeted by differentially expressed miRNAs are described in three categories: biological processes, molecular functions, and cellular components. GO, Gene Ontology; miRNAs, microRNAs.

significantly different between colostrum and mature milk. We used qRT-PCR to detect several differentially expressed microRNAs in the collected milk samples. The results of qRT-PCR confirmed the differential expressions of the miRNAs, which were consistent with the results of microarray analysis.

In conclusion, our study identified 67 colostrum-specific miRNAs. The predicted target genes of these miRNAs are closely related to molecular function regulation and binding. KEGG pathway analysis indicated that these targeted mRNAs are closely related to the oxidative stress system, inflammation, development, and longevity. Thus, colostrum might play an important role in the development and even the lifespan of infants. There have been evidence that biologically effective amounts of miRNAs can be absorbed from nutritionally relevant doses of bovine milk, and human gene expression is regulated by physiologic

concentrations of milk miRNAs in cell cultures and *in vivo* (25,26). Moreover, exosomes, a particularly important class of extracellular vesicles, acts as a vehicle to protect and transport labile cargos. For example, milk miRNAs are encapsulated in exosomes to avoid degradation by low pH in the stomach (27), to resist digestion by enzymes in the gastrointestinal tract (28), and to be specifically transported to receptor cells for local enrichment (29). Taken together, our results indicate that colostrum-specific miRNAs have important functions. These miRNAs could be used as nutritional additives in dairy products to benefit the development and growth of infants and young children. However, expression of miRNA in human milk is influenced by some maternal factors, such as maternal age, dietary habits, and health condition (30), and also by maternal living environment (31). Collections for more human milk samples are needed in future research and also



**Figure 5** KEGG analysis of human colostrum-specific miRNA targets. (A) shows the enriched pathways and (B) shows the percentage of pathways of the differentially expressed miRNAs using the target mRNAs. KEGG, Kyoto Encyclopedia of Genes and Genomes; miRNAs, microRNAs.

stratified analysis according to maternal health risk factors are important.

## Acknowledgments

*Funding:* This work was supported by grants from National Natural Science Foundation of China (81502828, 81872377) and Natural Science Foundation of Tianjin City (18JCZDJC35500, 18JCYBJC25600).

## Footnote

*Reporting Checklist:* The authors have completed the MDAR reporting checklist. Available at <http://dx.doi.org/10.21037/atm-20-5709>

*Data Sharing Statement:* Available at <http://dx.doi.org/10.21037/atm-20-5709>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-5709>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Ethics Committee of the second hospital of Tianjin Medical University (No. KY2020K055) and informed consent was taken from all the patients.

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**Cite this article as:** Wu F, Zhi X, Xu R, Liang Z, Wang F, Li X, Li Y, Sun B. Exploration of microRNA profiles in human colostrum. *Ann Transl Med* 2020;8(18):1170. doi: 10.21037/atm-20-5709

**Table S1** The colostrum-specific miRNAs identified uniquely in human colostrum

SystematicName	Colostrum1	Colostrum2	active_sequence	chr	mirbase_accession_No
hsa-miR-1180-3p	2.32296	2.92182	ACACACCCACGCG	chr17	MIMAT0005825
hsa-miR-1199-5p	2.54510	3.10266	CTGCGCGGCC	chr19	MIMAT0031119
hsa-miR-1229-3p	2.62540	3.07745	CTGTGGGAGGGC	chr5	MIMAT0005584
hsa-miR-1237-3p	2.55619	2.72214	CTGGGGGACGG	chr11	MIMAT0005592
hsa-miR-1254	2.20128	3.20950	ACTGCAGGCTCCAGC	chr10	MIMAT0005905
hsa-miR-1266-3p	2.59962	2.94387	TCCCTCAGGGCATAGA	chr15	MIMAT0026742
hsa-miR-1295a	2.11806	4.17877	TCACCCAGATCTGCG	chr1	MIMAT0005885
hsa-miR-1304-3p	2.98629	2.68252	GGGGTTCGAGGCT	chr11	MIMAT0022720
hsa-miR-130a-3p	3.67398	2.18873	ATGCCCTTTAACATTGCA	chr11	MIMAT0000425
hsa-miR-145-5p	2.71837	2.20168	AGGGATTCTGGGAAAAC	chr5	MIMAT0000437
hsa-miR-17-3p	2.50705	2.73279	CTACAAGTGCCCTCAC	chr13	MIMAT0000071
hsa-miR-1825	3.02946	2.38080	GGAGAGGAGGGCAC	chr20	MIMAT0006765
hsa-miR-184	2.35008	3.04543	ACCCTTATCAGTTCTCCGTCCA	chr15	MIMAT0000454
hsa-miR-2277-3p	1.97716	2.90604	GAGCCAGGCAGGG	chr5	MIMAT0011777
hsa-miR-28-3p	3.14458	2.74099	TCCAGGAGCTCACA	chr3	MIMAT0004502
hsa-miR-298	2.05152	2.66207	TGGGAGAACCTCCCTG	chr20	MIMAT0004901
hsa-miR-3130-3p	2.30457	2.63398	TTACCCAGTCTCCGG	chr2	MIMAT0014994
hsa-miR-3163	2.21398	3.49302	GTCTTACTGCCCTCATT	chr11	MIMAT0015037
hsa-miR-3170	2.07935	2.95889	ACTGTCTGTCTCAGAACC	chr13	MIMAT0015045
hsa-miR-3180-5p	2.86044	2.93355	CGACGTGGGGCG	chr16	MIMAT0015057
hsa-miR-3182	2.64436	1.98775	GACTACACTACAGAAGC	chr16	MIMAT0015062
hsa-miR-3187-5p	2.16980	2.88324	CCTCAGCCACACG	chr19	MIMAT0019216
hsa-miR-3651	2.76310	1.98912	TCATGTACCAGCGACC	chr9	MIMAT0018071
hsa-miR-3653-3p	1.99244	2.84147	CTTCAGTCAACTTCTTAG	chr22	MIMAT0018073
hsa-miR-3666	2.14131	2.86701	TCGGCATCTACACTTGC	chr7	MIMAT0018088
hsa-miR-3679-3p	2.11051	2.43942	GATGAAGATTACTGGGGG	chr2	MIMAT0018105
hsa-miR-3689a-5p	3.54821	3.36309	TCCCAGGAACCATGAT	chr9	MIMAT0018117
hsa-miR-3689f	3.92421	3.86609	TCCCAGGAAGCACG	chr9	MIMAT0019010
hsa-miR-378e	2.29603	2.43965	TCCTGACTCCAAGTCC	chr5	MIMAT0018927
hsa-miR-3934-3p	3.11223	3.03074	TCCCAGCTGTGCAAC	chr6	MIMAT0022975
hsa-miR-4265	3.97453	2.44913	CCCAGAGCTGAGCC	chr2	MIMAT0016891
hsa-miR-4282	3.95189	3.86366	TCCTGGATGCAAATTTTA	chr6	MIMAT0016912
hsa-miR-431-5p	2.19106	2.57381	TGCATGACGGCCTGC	chr14	MIMAT0001625
hsa-miR-4446-3p	2.13045	3.12006	ACCCATGTCACTGCC	chr3	MIMAT0018965
hsa-miR-4489	2.39445	3.03111	CGTCCTGCATCACTAG	chr11	MIMAT0019023
hsa-miR-4492	2.15679	2.80300	GGCGCGCGCC	chr11	MIMAT0019027
hsa-miR-4510	2.59543	2.87916	AACCATACATCCTACTCCC	chr15	MIMAT0019047
hsa-miR-4533	2.17802	2.77478	AGCGTCCGGCAAC	chr20	MIMAT0019072
hsa-miR-4636	1.96493	4.79457	CTAAAGGCTTTGAACACG	chr5	MIMAT0019693
hsa-miR-4715-5p	2.42423	3.20679	CCACCTTAACTGCAGC	chr15	MIMAT0019824
hsa-miR-4717-3p	2.27863	2.40895	AGGCCACAGCCACC	chr16	MIMAT0019830
hsa-miR-4731-3p	2.40021	2.70453	AGTGTGGGGGCCA	chr17	MIMAT0019854
hsa-miR-4773	2.43453	3.21978	GCCTTTCTATGCTCCTG	chr2	MIMAT0019928
hsa-miR-509-3-5p	1.87485	2.65251	CATGATTGCCACGTCTG	chrX	MIMAT0004975
hsa-miR-509-5p	2.01383	3.08984	TGATTGCCACTGTCTGC	chrX	MIMAT0004779
hsa-miR-510-3p	2.39686	2.80545	TCCACTCTTAGAGTTTC	chrX	MIMAT0026613
hsa-miR-513c-3p	2.27689	2.71956	TCTTCTCAGAAAGGTGAA	chrX	MIMAT0022728
hsa-miR-516a-3p	2.20430	2.50209	ACCCTCTGAAAGGAAGCA	chr19	MIMAT0006778
hsa-miR-598-5p	1.89566	3.08960	GCTCACACCATCGG	chr8	MIMAT0026620
hsa-miR-639	1.88307	2.10263	ACAGCGCTCGCAACCGC	chr19	MIMAT0003309
hsa-miR-658	2.13478	2.09188	ACCAACGGACCTACTTCCCT	chr22	MIMAT0003336
hsa-miR-663b	1.97456	2.87451	CCTCAGGCACGGC	chr2	MIMAT0005867
hsa-miR-664a-3p	3.06870	2.17013	TGTAGGCTGGGGATAAA	chr1	MIMAT0005949
hsa-miR-6722-5p	2.01272	2.81332	GCATGTGGTCCGGT	chr9	MIMAT0025853
hsa-miR-6737-3p	2.89093	2.48512	CTGGGTAGGGGTGA	chr1	MIMAT0027376
hsa-miR-6752-3p	2.33123	2.44844	CTGGGAGTATGGGGG	chr11	MIMAT0027405
hsa-miR-6763-3p	2.44360	2.85405	CTGGGGGCAGAGG	chr12	MIMAT0027427
hsa-miR-6766-3p	2.53711	2.83010	TGAGGGTGGGGGAA	chr15	MIMAT0027433
hsa-miR-6771-5p	2.46932	2.96786	GCCTGGCCCATGC	chr16	MIMAT0027442
hsa-miR-6795-5p	2.12781	3.19112	ACAGCCTCTCATCCTG	chr19	MIMAT0027490
hsa-miR-6871-5p	2.26893	3.55816	GCAACCACCCCGA	chr20	MIMAT0027642
hsa-miR-7157-5p	2.16873	2.70452	TCTCTGGTGCCAATGA	chr2	MIMAT0028224
hsa-miR-7854-3p	2.14090	2.81021	TTCCCATCTGCGGTC	chr16	MIMAT0030429
hsa-miR-8052	2.29522	2.84037	GCTCATGCCCTCTACA	chr11	MIMAT0030979
hsa-miR-8075	1.91768	3.67316	CAGACCCGACATCTG	chr13	MIMAT0031002
hsa-miR-8078	1.94227	2.57651	GAGTCTCTACCGGG	chr18	MIMAT0031005
hsa-miR-873-3p	2.52308	2.71775	TCCCGGGAACCTCATC	chr9	MIMAT0022717

**Table S2** The miRNAs identified specifically in human mature milk

SystematicName	Mature1	Mature2	active_sequence	chr	mirbase_accession_No
hsa-miR-10a-3p	1.98751	2.63176	TATCCCCCTAGATACGAA	chr17	MIMAT0004555
hsa-miR-1203	2.24244	2.85905	GAGCTGCATCCTGGC	chr17	MIMAT0005866
hsa-miR-1207-3p	2.25352	2.56912	GAAATGAGGGCCAGC	chr8	MIMAT0005872
hsa-miR-1237-5p	2.33949	2.57669	CGCGCTTCGGCC	chr11	MIMAT0022946
hsa-miR-1261	2.65172	2.48569	AAGCCAAAGCCTTATCC	chr11	MIMAT0005913
hsa-miR-1273d	4.68993	5.83660	ACTGCAGCCTCAACC	chr1	MIMAT0015090
hsa-miR-1273g-5p	2.38639	3.44264	ACTTACTGCAGCCTCAA	chr1	MIMAT0020602
hsa-miR-1273h-3p	2.62297	2.54658	GCCTGGGAGGTGCG	chr16	MIMAT0030416
hsa-miR-1273h-5p	2.07145	2.68090	ACTGCAGCCTTGACC	chr16	MIMAT0030415
hsa-miR-128-3p	2.46776	2.53820	AAAGAGACCGGTTCACTGT	chr3	MIMAT0000424
hsa-miR-1285-3p	1.90388	2.40571	AGGTCTCACTTTGTTGC	chr7	MIMAT0005876
hsa-miR-1287-5p	2.65848	2.65860	GACTCGAACCCTGAT	chr10	MIMAT0005878
hsa-miR-129-5p	2.64066	2.11382	GCAAGCCCAGACCGC	chr7	MIMAT0000242
hsa-miR-138-5p	2.17710	3.01523	CGGCCTGATTACA	chr3	MIMAT0000430
hsa-miR-150-5p	2.01261	2.34502	CACTGGTACAAGGGTTGG	chr19	MIMAT0000451
hsa-miR-152-3p	3.64082	3.90271	CCAAGTTCTGTCATGC	chr17	MIMAT0000438
hsa-miR-182-5p	2.19165	2.30981	AGTGTGAGTTCTACCAT	chr7	MIMAT0000259
hsa-miR-183-3p	2.39574	2.31177	TTATGGCCCTTCGGT	chr7	MIMAT0004560
hsa-miR-185-5p	2.74797	3.14207	TCAGGAAGTGCCTTTCT	chr22	MIMAT0000455
hsa-miR-18a-5p	2.12542	2.38964	CTATCTGCACTAGATGCA	chr13	MIMAT0000072
hsa-miR-1910-3p	2.52924	2.68037	TGTCATCCTGCTTCTGC	chr16	MIMAT0026917
hsa-miR-1972	2.53313	2.76746	TGAGCCACTGTGCC	chr16	MIMAT0009447
hsa-miR-1973	2.71066	2.94558	TATGCTACCTTTGCACG	chr4	MIMAT0009448
hsa-miR-199a-3p	2.33512	2.71778	TAACCAATGTGCAGACTACT	chr19	MIMAT0000232
hsa-miR-210-5p	2.91142	2.65243	CAGTGTGCGGTGGG	chr11	MIMAT0026475
hsa-miR-22-5p	3.42928	2.99324	TAAAGCTTGCCACTGAAG	chr17	MIMAT0004495
hsa-miR-29c-5p	3.11572	4.41128	GAACACCAGGAGAAATCGGT	chr1	MIMAT0004673
hsa-miR-30e-3p	2.62255	2.72617	GCTGTAAACATCCGACTG	chr1	MIMAT0000693
hsa-miR-3150b-5p	2.82997	2.15772	GCTGGGGAGATCCTC	chr8	MIMAT0019226
hsa-miR-3159	2.16115	3.25306	GTGGCCGACACTTG	chr11	MIMAT0015033
hsa-miR-3164	2.30669	2.91856	CGCCATTTCCCTTAAA	chr11	MIMAT0015038
hsa-miR-3174	2.16155	2.95890	GGCTCTGCATCTCTAAC	chr15	MIMAT0015051
hsa-miR-3177-3p	2.82184	2.49063	ACGTGTCCCCAGTGC	chr16	MIMAT0015054
hsa-miR-324-5p	2.50719	2.63198	ACACCAATGCCCTAGGG	chr17	MIMAT0000761
hsa-miR-338-3p	2.13770	2.52962	CAACAAAATCACTGATGCTGG	chr17	MIMAT0000763
hsa-miR-339-3p	2.58758	3.10585	CGGCTCTGTCGTGCG	chr7	MIMAT0004702
hsa-miR-340-5p	2.43818	3.20849	AATCAGTCTCATTGCTTTA	chr5	MIMAT0004692
hsa-miR-3619-3p	2.01330	2.78057	CCACAGCAGGCAGG	chr22	MIMAT0019219
hsa-miR-365b-5p	2.95847	2.68694	ACAGCTGCCCTGA	chr17	MIMAT0022833
hsa-miR-3935	2.42008	2.59386	GTGGCTGGTGCTCG	chr16	MIMAT0018350
hsa-miR-4267	3.09477	3.92122	GTGCCACCGAGCT	chr2	MIMAT0016893
hsa-miR-4284	3.91543	2.18863	ATGGGGTGATGTGAGC	chr7	MIMAT0016915
hsa-miR-4291	3.18635	4.27236	AGTGTTCTGCTGAA	chr9	MIMAT0016922
hsa-miR-4418	2.50637	2.67114	CTGCTGAGTCCTGCA	chr1	MIMAT0018930
hsa-miR-4421	2.09017	2.85002	TAGCTCCTTTCCACAGA	chr1	MIMAT0018934
hsa-miR-4458	2.36574	2.61123	TTCTTCCACACCTACCT	chr5	MIMAT0018980
hsa-miR-4475	2.03341	2.51302	ATAATGAATGCTTGGTCCC	chr9	MIMAT0019002
hsa-miR-4479	2.60301	2.53507	CTGCTCCGAGCACG	chr9	MIMAT0019011
hsa-miR-4482-3p	2.46688	3.25644	GAGCCCCACTGAGA	chr10	MIMAT0020958
hsa-miR-4494	2.51388	3.01822	CCTCTGGTCAGCCA	chr12	MIMAT0019029
hsa-miR-4526	2.09555	2.37480	AGCGGCCAGCCC	chr18	MIMAT0019065
hsa-miR-4638-5p	2.05626	2.75095	ACTTGTCCACCGCAG	chr5	MIMAT0019695
hsa-miR-4657	2.36918	3.14834	ATGCCTCAGACCACTT	chr7	MIMAT0019724
hsa-miR-4694-3p	2.14011	2.68527	AGGTGTTATCCTGTCCA	chr11	MIMAT0019787
hsa-miR-4725-5p	2.83625	2.59880	GGTGGGAAGGCTGC	chr17	MIMAT0019843
hsa-miR-4727-3p	2.18564	2.82298	GAATCTGCCAGCTTCC	chr17	MIMAT0019848
hsa-miR-4746-5p	2.50482	2.71830	TCTGCAGTTCTCCTG	chr19	MIMAT0019880
hsa-miR-4768-3p	2.30560	2.87099	ATTCTCTCTGGATCTCCT	chrX	MIMAT0019921
hsa-miR-484	3.18353	3.33444	ATCGGGAGGGGACTGA	chr16	MIMAT0002174
hsa-miR-499a-5p	3.89492	4.44918	AAACATCACTGCAAGTCTTAA	chr20	MIMAT0002870
hsa-miR-5003-5p	2.48713	2.62131	TCTACCCTGCAAGGTT	chr5	MIMAT0021025
hsa-miR-501-3p	2.07789	2.63682	AGAATCCTTGCCCGGG	chrX	MIMAT0004774
hsa-miR-5093	2.62512	2.40514	GCTCCTAGCCAGCC	chr16	MIMAT0021085
hsa-miR-5096	2.05944	3.04100	GCCTGACCAACATGG	chr4	MIMAT0020603
hsa-miR-511-3p	5.81124	6.95428	TCTGTCTTTTGCTACACA	chr10	MIMAT0026606
hsa-miR-517a-3p	3.93271	1.99377	ACACTCTAAAGGGATGCAC	chr19	MIMAT0002852
hsa-miR-517c-3p	2.82146	2.00449	ACACTCTAAAAGGATGCAC	chr19	MIMAT0002866
hsa-miR-518a-5p	2.04188	2.55783	GAAAGGGCTTCCCTT	chr19	MIMAT0005457
hsa-miR-522-3p	3.31805	1.92379	ACACTCTAAAGGGAACCATT	chr19	MIMAT0002868
hsa-miR-541-3p	2.21166	2.54955	AGTCCAGATTCTGTGCC	chr14	MIMAT0004920
hsa-miR-574-3p	3.71477	3.03704	TGTGGGTGTGTGCATG	chr4	MIMAT0003239
hsa-miR-593-5p	1.85946	2.61223	GCTGAGCAATGCCTG	chr7	MIMAT0003261
hsa-miR-629-3p	2.27893	2.78905	GCTGGGCTTACGTTGG	chr15	MIMAT0003298
hsa-miR-6508-5p	2.91166	2.97465	GGTGGGTGCATGCATT	chr21	MIMAT0025472
hsa-miR-652-3p	2.41564	2.60999	CACAACCCTAGTGCC	chrX	MIMAT0003322
hsa-miR-664a-5p	2.34364	2.45058	ATCCAATCATTTCCCTAGC	chr1	MIMAT0005948
hsa-miR-664b-5p	2.13124	3.56128	TACCCAATCATCTCCCT	chrX	MIMAT0022271
hsa-miR-6726-5p	2.91249	2.72714	ACCTGCAGACCCCA	chr1	MIMAT0027353
hsa-miR-6753-3p	2.84822	3.51372	GTGCCAGGGCAGA	chr11	MIMAT0027407
hsa-miR-6813-3p	2.63163	2.32766	CTGGGGAGAGGGG	chr20	MIMAT0027527
hsa-miR-6855-5p	1.93228	2.44027	GCAATGTCTGCACCC	chr9	MIMAT0027610
hsa-miR-6868-5p	1.99168	2.49615	GCTGCTTCAGTGTCT	chr17	MIMAT0027636
hsa-miR-6884-5p	4.09949	3.50563	CAACATCACCTTCTCAG	chr17	MIMAT0027668
hsa-miR-7114-3p	2.68504	2.54284	CTGGTGGAGAGGGG	chr9	MIMAT0028126
hsa-miR-766-3p	3.02450	2.87476	GCTGAGGCTGTGGGGCT	chrX	MIMAT0003888
hsa-miR-7856-5p	3.52941	3.85569	GATCCCTCAGTGCCT	chr1	MIMAT0030431
hsa-miR-8077	2.31582	2.82875	GGAGTCAGAACCCEA	chr19	MIMAT0031004
hsa-miR-885-3p	2.12362	2.12247	TATCCACTACACCCCG	chr3	MIMAT0004948
hsa-miR-921	2.76696	2.55530	GAATCCTGGTTCTGTCC	chr1	MIMAT0004971
hsa-miR-96-5p	3.52452	4.40404	AGCAAAAATGTGCTAGTGCCAA	chr7	MIMAT0000095