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- A high-saturated fat meal acutely regulates miRNA expression in human leukocytes.
- This involves a higher number of upregulated (43) than downregulated (36) miRNAs.
- Multiple signalling events for cancer and other diseases are likely affected.
- A miRNA dysregulation in the postprandial state is reported for the first time.

A microRNA expression signature of the postprandial state in response to a high-saturated fat challenge

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Running title: High-fat meal on miRNAs

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Abstract

The postprandial hypertriglyceridemia is an important and largely silent disturbance involved in the genesis of numerous pathological conditions. Exaggerated and prolonged states of postprandial hypertriglyceridemia are frequently related to the ingestion of meals enriched in saturated fatty acids (SFAs). MicroRNAs are non-coding RNAs that function as gene regulators and play significant roles in both health and disease. However, differential miRNA expression between fasting and postprandial states has never been elucidated. Here we studied the impact of a high-saturated fat meal, mainly rich in palmitic acid, on the miRNA signature in peripheral blood mononuclear cells (PBMCs) of nine male healthy individuals in the postprandial period by using a two-step analysis, miRNA array and validation through qRT-PCR.

Compared with miRNA expression signature in PBMCs at fasting, 36 miRNAs were downregulated and 43 miRNAs were upregulated in PBMCs at postprandial hypertriglyceridemic peak. Six chromosomes (3, 7, 8, 12, 14, and 19) had nearly a half (48.1%) of dysregulated miRNA-gene-containing regions. Downregulated miR-300 and miR-369-3p and upregulated miR-495-3p, miR-129-5p, and miR-7-2-3p had the highest number of target genes. The differentially expressed miRNAs and their predicted target genes involved pathways in cancer, MAPK signalling pathway, endocytosis, and axon guidance. Only downregulated miRNAs notably targeted PI3K-Akt signalling pathways, whereas only upregulated miRNAs targeted focal adhesion, Wnt signalling pathway, transcriptional misregulation in cancer, and ubiquitin-mediated proteolysis. This is the first study of miRNA expression analysis of human PBMCs during postprandial hypertriglyceridemia and offers insight into new potential mechanisms by which dietary SFAs influence on health or disease.

1 Introduction

Exaggerated and prolonged states of postprandial hypertriglyceridemia due to the ingestion of multiple fat-enriched meals during the course of a day are emerging as important causes of atherosclerosis, including coronary artery disease, stroke, and subsequent sudden death [1-3]. In the current paradigm, the inflammatory disease of atherosclerosis is characterized by the initial endothelial dysfunction and monocyte recruitment, accumulation of lipids in infiltrated macrophages within the arterial wall, plaque development, and eventual plaque rupture [4]. In contrast, recent studies suggest that circulating monocytes may start interacting with postprandial triglyceride-rich lipoproteins before their migration to arterial wall, which results in transcriptional regulation of genes involved in lipid homeostasis and inflammation [5, 6]. However, the mechanisms underlying postprandial effects of dietary fats in cardiovascular and other diseases are largely unknown.

MicroRNAs (miRNAs) are a set of endogenous and small non-coding single-stranded RNAs approximately 22 nucleotides in length that comprise a novel class of gene expression regulators [7]. miRNAs bind to their target genes in the 3' untranslated regions (UTRs), thus mediating negative posttranscriptional regulation. They can also repress mRNA targets through binding to other regions, including 5'-UTRs or protein coding sequences, and in some cases may even activate translation [8]. In humans, several miRNAs have been shown implicated in controlling lipid homeostasis and inflammation [9, 10], which has led to several studies of miRNA profiling as non-invasive biomarkers for early detection of asymptomatic and symptomatic atherosclerotic lesions [11, 12]. Importantly, miRNAs are responsive to environmental factors [13] and exhibit temporal expression patterns [14], supporting the possibility of acute changes in miRNA expression during fed states. Because the consumption

of saturated fatty acids (SFAs) has been linked with larger and longer postprandial hypertriglyceridemic response [15] and increased risk for several chronic diseases such as cardiovascular disease and cancer [16, 17], the aims of this study were to explore whether a high-saturated fat meal, mainly rich in palmitic acid, could change the miRNA signature in peripheral blood mononuclear cells (PBMCs) from healthy individuals in the postprandial period and to establish the role of miRNA signature as a novel tool to predict clinical outcomes linking the postprandial metabolism of dietary SFAs with pathophysiological processes.

2 Materials and Methods

2.1 Participants and design

Nine healthy Caucasian non-smoking males, aged 18-23 y were recruited by advertising (**Table 1**). Participants were excluded if they have established coronary heart disease, renal impairment, hypothyroidism, or liver dysfunction based on clinical chemistry testing. None of the participants consumed special diets, or took medication known to alter gastric emptying or lipoprotein metabolism. The participants were reported to the Clinic Experimental Research Unit for Vascular Risk at the University Hospital Virgen del Rocio (UHVR, Seville) at 0800 in a 12-h fasted state. On arrival, a blood sample was taken (t = 0). The high-saturated meal consisted in an oral emulsion prepared according with the procedure described in the patent PCT/ES2014/070427, with 30 g of sucrose/m^2 and 50 g of cow's milk cream/m^2 of body surface area. The average total energy provided was ~800 kcal, with a macronutrient profile of 77% fat and 23% carbohydrate. The fatty acid composition of the milk cream is described in **Table 2**. The emulsion was consumed

within 10 min, and subsequently, blood samples were collected hourly over 6 h in tubes containing clot activator and gel separation for serum for the measurements of triglycerides, or sodium citrate cell preparation tubes (BD Vacutainer® CPT™) for the isolation of peripheral blood mononuclear cells (PBMCs). PBMCs were only isolated from blood samples at fasting and at hypertriglyceridemic postprandial peak (~2 h). In this study, each participant served as his own control. Prior to the beginning of the study, all participants provided their informed consent using protocols approved by the Human Clinical Commission and Ethics Committee of UHVR. The investigation conformed to the principles outlined in the Helsinki Declaration of the World Medical Association. This study was registered with clinicaltrials.gov (NCT02061267).

2.2 Fatty acid analysis of dietary fat

Fatty acid composition was determined according to the method described in EC/796/2002 [18] with a gas chromatography system (HP-5890; Hewlett-Packard, Palo Alto, CA) with a flame ionization detector and an SP-2380 (Supelco, Bellefonte, PA) fused silica capillary column (50 m × 0.25 mm internal diameter) coated with cyanopropylpolysiloxane (0.25 μm film thickness). The oven temperature program was isothermal at 165 °C for 10 min before rising to 200 °C at 1.5 °C/min. The injector and detector temperatures were 220 °C and 250 °C, respectively. Hydrogen was used as the carrier gas at a column head pressure of 130 kPa. Sample injections were performed in the split mode.

2.3 Biochemical determinations

Glucose was immediately measured using a DAX-96 autoanalyser (Bayer Diagnostics, Milan, Italy). Total cholesterol and triglycerides were determined by enzymatic methods (CHOD-PAP and GPO-PAP, respectively; Roche Diagnostics, Basel, Switzerland). HDL-cholesterol was determined after precipitation with phosphotungstic acid. LDL-cholesterol was measured using an Advia 2400 Clinical Chemistry System (Siemens Healthcare Diagnostics, Erlangen, Germany).

2.4 Peripheral blood mononuclear cell (PBMC) isolation and total RNA isolation

PBMCs were isolated by using the BD Vacutainer® CPT™ Cell Preparation Tubes according to the manufacturer's instructions. Total RNA from PBMCs was isolated by using TRIsure® and quantified with a Nanodrop ND 1000 spectrophotometer (Nanodrop Technologies, Wilmington, DE). RNA integrity and miRNA content were determined with an Agilent 2100 Bioanalyser with RNA 6000 Nano chips (Agilent Technologies, Santa Clara, CA). The RNA integrity of the samples was above 9.

2.5 miRNA microarray and data analysis

RNA samples were pooled to randomly create four (2 + 2 + 2 + 3, referred to as #1, 2, 3, 4) fasting (F1, F2, F3, F4) and postprandial (P1, P2, P3, P4) specimens. For each sample, 300 ng of total RNA were labelled using miRNA Microarray with miRNA Complete Labelling and Hyb Kit (5190-0456; Agilent Technologies). The samples were hybridized for 20 h onto a human miRNA Microarray v3.0, Release 15.0, 8×15 K containing 955 human mature miRNA probes (Agilent Technologies) and processed at the Andalusian Center for Molecular Biology and Regenerative Medicine (CABIMER) Genomics Core Facility. Data was subjected to a background

correction and quantile normalization [19], and then transformed to a linear scale for statistical analysis [20]. Only miRNA with a $p < 0.05$ and fold change <-1.2 or >1.2 were considered for further investigation. A list of putative miRNA targets was identified using the prediction algorithm DNA Intelligent Analysis (DIANA) DIANA-microT-CDS (v5.0). To explore the function of dysregulated miRNAs, the DIANA-miRPath (v2.0) was used to identify functional pathways according to Kyoto Encyclopaedia of Genes and Genomes (KEGG) [21]. The Gene Ontology (GO) analysis was performed to investigate the biological processes, cellular components, and specific molecular function of differentially expressed miRNA using DAVID (Database for Annotation, Visualization and Integrated Discovery) database.

2.6 Quantitative real time PCR (qRT-PCR)

miRNA expression levels were analysed using the BioMark 48.48 Dynamic Array Nanofluidic Chip (Fluidigm Inc, San Francisco, CA). Briefly, miRNA was reversed transcribed with the TaqMan microRNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA) and then pre-amplified using the TaqManR PreAmp Master Mix (2×) (Applied Biosystems). Following hydraulic chip priming, pre-amplified cDNA samples plus one no template standard were mixed with a mild detergent loading solution to allow capillary flow, and the samples were added to the sample inlets of the Nanofluidic Chip. Ten individual Taqman primer-probe mixtures (Applied Biosystems) specific for individual selected transcripts along with assay loading solution were also added into the above inlets, allowing a combination of each sample to mix with each primer-probe assay in every possible combination (a total of 2304 reactions). The chip was then thermo-cycled through 40 cycles and Taqman primer-probe fluorescence in the FAM (6-carboxyfluorescein) channel was detected

using the CCD (charge-coupled device) camera attached to a BioMark HD System, normalized by ROX (6-carboxy-X-rhodamine) intensity.

2.7 Statistical analysis

Statistical analysis was performed using the SPSS software v19.0 (IBM Corporation, NY). Differentially expressed miRNA (peak *vs* baseline) were obtained by paired comparisons using the Limma package [22]. For qRT-PCR analysis, a paired t-test was used to determine significant differences between peak and baseline values. The level of significance was set at 0.05.

3 RESULTS

3.1 Identification of dysregulated miRNAs on PBMCs in the postprandial state

To identify miRNAs expressed in the blood of human in the postprandial state, we conducted miRNA expression profiling in PBMCs from blood of nine healthy volunteers before and after the ingestion of a standardized high-saturated fat meal. According to the time course of changes in serum triglycerides, the serum triglyceride concentration peaked at 2 h postprandial (**Figs. S1 and 1A**). Total RNA samples of PBMCs from fasting were pooled as indicated above and the same was done with samples at 2 h postprandial. Of the total 866-screened human miRNAs, comparison of miRNA expression patterns in PBMCs between fasting and postprandial states revealed an exclusive detection of 856 miRNAs in PBMCs either at fasting or postprandial (**Table S1**). A hierarchical clustering was conducted and a combined dendrogram/heat map was generated for statistically significant and differentially regulated miRNAs (**Fig. 1B**). While 79 miRNAs with differential regulation were

expressed in both PBMCs from fasting and postprandial states, the number of downregulated miRNAs (36, 4.2% of all screened targets) was slightly lower than upregulated miRNAs (43, 5.0% of all screened targets). It is interesting to note that the ingestion of the high-saturated fat meal had a scattering effect on miRNA expression level in PBMCs, thus two different major clusters among the downregulated or upregulated miRNAs were recognized (see letters α-δ, Fig. 1B). The cluster α had more signal intensity but less fold change than the cluster β for the expression of downregulated miRNAs, whereas the cluster γ had less signal intensity but more fold change than the cluster δ for the expression of upregulated miRNAs (see also **Table S2**). Differences in the expression levels of miRNAs between the fasting and the postprandial state following the criteria of >1.2-fold under- or overexpression and statistical significance (*p* value less than 0.05) were analysed with a volcano plot (**Fig. 1C**). Based on these criteria, we identified 9 downregulated (miR-613, -629-3p, -24-2-5p, -555, -148a-5p, -621, -875-3p, -513c-5p, -1226; 25.7% of all downregulated targets) and 9 upregulated (miR-653, -19b-1-5p, -363-5p, -885-3p, -339-3p, -938, -148b-5p, -593-5p, -24-2-5p, -200b-5p; 20.9% of all upregulated targets) miRNAs in the postprandial state when compared to the fasting state (**Fig. 1D**). In addition, there were significant correlations between fasting and postprandial values for expression intensity of downregulated (**Fig. S2A**) and upregulated (**Fig. S2B**) miRNAs. Furthermore, fold change was also correlated with fasting values for expression intensity in upregulated (**Fig. S2C**) and downregulated (**Fig. S2D**) miRNAs.

Expression of randomly selected miRNAs (downregulated: miR-629-3p, -24-2-5p, -555, -621; upregulated: miR-653, -363-5p, -593-5p, -200b-5p; non-regulated: miR-103-3p, -16) was further verified by quantitative miRNA RT-PCR technology (**Table**

3). These data were consistent with the expression patterns observed by miRNA array profiling.

In order to evaluate the reproducibility and variability of the results, an exploratory multivariate analysis was applied to the dataset of the total screened human miRNAs in total RNA samples of PBMCs both at fasting (F1, F2, F3, F4) and at postprandial (P1, P2, P3, P4). Based on the Euclidean distance, **Fig. 2A** shows the hierarchical clustering dendrogram and heat map of miRNA expression, whereas **Fig. 2B** shows the 3D tree map for the hierarchical clustering of miRNAs under the first principal component for fasting and postprandial sample groups. The optimal level of division calculated indicates two clusters corresponding to the fasting (F1 to F4) and postprandial (P1 to P4) states. These clusters were also evident after a factorial correspondence analysis (**Fig. 2C**) or a principal components analysis (**Fig. 2D**) of all of the miRNAs observed.

3.2 Genome location of dysregulated miRNAs on PBMCs in the postprandial state

The miRNA genes are integral components of chromosomes. To map the chromosomal location of downregulated and upregulated miRNAs in the postprandial state, we detailed the location of each dysregulated miRNA in the geography of human chromosomes by examination of the miRBase database (http://www.mirbase.org/) and using ideograms (**Fig. 3**). Whereas chromosome 18 was not affected (chromosome Y has no reported miRNA genes), chromosomes 1, 3, 5, 6-9, 11-17, 19, 20, 22, and X had both downregulated and upregulated miRNA-gene-containing regions. However, only upregulated miRNAs were mapped in chromosomes 2, 4, 10, and 21. The chromosomal distribution of dysregulated

miRNAs was extremely biased, with 74.7% of the repertoire (35 downregulated and 24 upregulated miRNAs) focusing in the larger (q) arm of the affected chromosomes, mainly in centromere distal areas. In addition, 3p-arm-annotated miRNAs were more frequent than those derived from the 5' (5p) strand region of the mature miRNA hairpin precursors. Six chromosomes (3, 7, 8, 12, 14, and 19) had nearly a half (48.1%) of all the dysregulated miRNAs. The most affected chromosomes were 7 and 14, which had scattered 8 miRNA loci each.

Furthermore, 63 (79.8%) of the dysregulated miRNAs were individually distributed across chromosomes, including 19 single miRNAs within different cluster regions, whereas the rest (16 miRNAs, 20.2%) was grouped with at least 2 miRNAs in seven clusters on chromosomes 8, 13, 14, and 19 (**Table 4**). Three of these clusters (clusters 2, 3, and 7 on chromosomes 8, 13, and 19, respectively) comprised miRNAs with concerted dysregulation (co-upregulation). However, in the miR-875/599 cluster (cluster 1 on chromosome 8), miR-875 showed reverse directions of dysregulation in the 5p/3p species. Reverse dysregulation between miRNAs of the same cluster was also observed in the miR-665/136, -379/495, and -299/1185-1 clusters (clusters 4, 5, and 6, respectively) on chromosome 14. Genome structure analysis indicated that these seven clusters had homologous miRNAs (clusters: miR-30d/30b, -518f/521-2) and heterologous miRNAs (clusters: miR-875/599, -17/92a-1, -665/136, -379/495, -299/1185-1); non-clustered miRNAs of the same gene family were also encoded in independent transcripts located on the same chromosome (miR-1323/1283-1 and -1283-1/520c clusters of the miR-515 family on chromosome 19) or on different chromosomes, forming groups of paralogous miRNAs (miR-181a-2-3p and -181c-3p of the miR-181 family on chromosomes 9 and 19; miR-138-1-3p and -138-2-3p of the miR-138 family on chromosomes 3 and 16; miR-148a-5p and -

148b-5p of the miR-148 family on chromosomes 7 and 12, respectively) (**Fig. 4A**). The miR-17/92a-1 cluster (on chromosome 13) and its two paralogous miR-106b/25 (on chromosome 7) and -106a/363 (on chromosome X), known as oncomiR-1, were affected with the upregulation of four miRNA members (miR-18a-3p, -19b-1-5p, -25-5p, -363-5p) that contained partially homologous sequences (**Fig. 4B**).

3.3 *In silico* miRNA target prediction and pathway enrichment analysis of dysregulated miRNAs on PBMCs in the postprandial state

To establish a possible underlying biological implication with downregulated and upregulated miRNAs in the postprandial state after the ingestion of the high-saturated fat meal, DIANA-microT-CDS (for predicted target genes), DIANA-mirPath (for KEGG pathways), and DAVID (for GO categories) databases were applied. All of the dysregulated miRNAs had target genes in the database (**Table S3**). Among the downregulated miRNAs, miR-300 and -369-3p of the miR-154 family (q32.31 cluster region on chromosome 14) had the highest number of target genes (1293 and 1195, respectively), whereas miR-523-3p had only 2 target genes. Among the upregulated miRNAs, miR-495-3p of the miR-299 family (q32.31 cluster region on chromosome 14), miR-129-5p of the miR-129 family (q22.1 region on chromosome 7), and miR-7-2-3p of the miR-7 family (q26.1 cluster region on chromosome 15) had the highest number of target genes (2618, 1605, and 1448, respectively), whereas miR-181c-3p had only 4 target genes. The total number of target genes coupled with upregulated miRNAs was greater than with downregulated miRNAs (16330 *vs* 11114). **Fig. 5** shows the KEGG pathways overrepresented among these predicted target genes. It revealed the enrichment of 31 KEGG targeted categories, nine potentially affected by both downregulated and (especially by) upregulated miRNAs, five by only

downregulated miRNAs, and seventeen by only upregulated miRNAs. Most target genes of dysregulated miRNAs were enriched in the “Pathways in cancer” category, which was coupled to 6 downregulated miRNAs (miR-148a-5p, -646, -300, -369-3p, 875-3p, -1226-3p) and 8 upregulated miRNAs (miR-616-3p, -138-2-3p, -519e-3p, -665, -7-2-3p, -519d, -495-3p, -129-5p). A total of 96 target genes in the “PI3K-Akt signalling pathway” category were identified as potentially affected by only 6 downregulated miRNAs (miR-148a-5p, -302e, -646, -300, -369-3p, 629-3p). The “Focal adhesion”, “Wnt signalling pathway”, “Transcriptional misregulation in cancer”, and "Ubiquitin-mediated proteolysis" were the main enriched KEGG pathway categories by only upregulated miRNAs. The most prominent miRNAs in annotating the greater number of KEGG pathways enriched in the postprandial state were miR-495-3p, -519d, 129-5p, and -7-2-3p (all of them upregulated miRNAs). These miRNAs were respectively coupled to 20, 19, 17, and 16 KEGG pathways, mainly those associated with MAPK, TGF-beta, neurotrophin, and ErbB signalling. The total number of target genes that enriched KEGG pathways coupled with upregulated miRNAs was more than twice that with downregulated miRNAs (1130 vs 508). On the basis of the downregulated miRNAs, the five high-enrichment GO functions were PI3K cascade, VEGF receptor signalling pathway, pathways-restricted SMAD protein phosphorylation, patterning of blood vessels, and BMP signalling pathway (**Table S4**). For upregulated miRNAs, the five high-enrichment GO functions were regulation of lipid kinase activity, Wnt receptor signalling pathway through beta-catenin, regulation of erythrocyte differentiation, thymus development, and gamma-aminobutyric acid signalling pathway.

4 DISCUSSION

Here, we hypothesized that a high-saturated fat meal may have an important effect on miRNA expression profiling in human PBMCs. To test this hypothesis, we conducted what is to the best of our knowledge the first study on the microRNA expression signature in the postprandial state in humans. We compared PBMC miRNA profiles of healthy volunteers before and after the ingestion of a standardized high-fat meal enriched in SFAs, mainly palmitic acid. PBMCs were obtained from blood samples at fasting and at the postprandial time (~2 h) corresponding to the hypertriglyceridemic peak. It was noteworthy the detection of 856 miRNAs (of the total 866-screened human miRNAs), 79 of which were differently expressed (36 downregulated and 43 upregulated) between fasting and postprandial states, i.e., in only 2-3 h in response to the ingestion of a standardized high-fat meal. By setting cut off limits at absolute fold change greater than 1.2 (*p* value less than 0.05), 9 miRNAs were downregulated (miR-613, -629-3p, -24-2-5p, -555, -148a-5p, -621, -875-3p, -513c-5p, -1226) and 9 were upregulated (miR-653, -19b-1-5p, -363-5p, -885-3p, -339-3p, -938, -148b-5p, -593-5p, -24-2-5p, -200b-5p) in the postprandial state when compared to the fasting state, suggesting the relevance of these miRNAs to the acute metabolism of dietary fats in humans. These profiles were maintained in a set of randomly selected miRNAs after validation by quantitative miRNA microfluidic RT-PCR technology, indicating that our findings are reliable and not a result of the false positive characteristic of high throughput technologies. We found that dysregulated miRNAs were distributed across most chromosomes, with the exception of pair 18 (pair Y has no reported miRNAs), mainly in q arm and centromere distal regions. This observation is consistent with previous reports that transcription start sites of miRNA genes were typically associated with dense heterochromatic loci embedded in pericentromeric regions of chromosome arms [23, 24].

Recent evidence has disclosed the potential contribution of 69 miRNAs in human genomic regions associated with elevated fasting plasma concentrations of lipids by a genome-wide association meta-analysis [25]. Genetic predisposition to high fasting triglycerides was linked to 24 miRNAs, of which only 2 miRNAs (miR-148a on chromosome 7 and miR-138-2 on chromosome 16) were coincident with dysregulated miRNAs in our study. Two miRNAs (miR-629-3p on chromosome 15 and miR-25-5p on chromosome 7) of the top ten whole blood miRNAs associated with fasting triglycerides in a recent cross-sectional analysis of the Framingham Heart Study [26] were also only shared by our miRNA signature in the postprandial period. These observations suggest that fasting and postprandial triglycerides play a different regulatory role on circulating non-coding RNAs. There is indeed a growing recognition that non-fasting triglyceride concentrations may be more relevant than fasting concentrations in the assessment of some metabolic disorders [27]. Thus, it is very likely that the composition and number of plasma particles containing triglycerides in the postprandial state may otherwise regulate the miRNA genome from a clinical setting of elevated plasma triglycerides in the fasting state.

It was striking the repertoire of clustered miRNAs in the location q32.2 and q32.31 on the acrocentric chromosome 14, the most affected chromosome together with the chromosome 7 in the postprandial state. Human chromosome 14q32.2 is an imprinted region that carries paternally expressed genes including DLK1 and RTL1, and maternally expressed genes including MEG3/GTL2, MEG8, and antisense RTL1, along with the germline-derived DLK1-MEG3 intergenic differentially methylated region (IG-DMR) and the postfertilization-derived MEG3-DMR [28]. Of note, the maternally but not the paternally inherited 14q32.2 imprinted region harbours one of the largest miRNA clusters in the human genome consisting of 54 miRNAs that

response to epigenetic regulatory mechanisms [29]. The miR-665 within this cluster was upregulated in the postprandial state, suggesting that the vital region hosted at the DLK1-DIO3 locus was responsive to the ingestion of the high-saturated fat meal. Aberrant expression of miR-665 has been implicated in the chronic heart failure [30], inflammatory bowel disease [31], apoptosis of nerve cells [32], and pathogenesis of several tumours such as prostate cancer [33], breast cancer [34], and intestinal gastric adenocarcinoma [35]. We also found that 3p species of miR-136 located on DLK1-DIO3 locus was downregulated in the postprandial state. Mechanistic studies have defined miR-136 as a multifunctional regulator of innate immunity [36], tumour sensitivity [37, 38], tumour suppression [39, 40], and wound healing [41]. Regarding to the location 14q32.31, 6 intergenic miRNAs were alternating upregulation (miR-411-3p, -495-3p, -1185-1-5p) and downregulation (miR-299-3p, -300, -369-3p), giving rise to a conjugated system that connected 3 close miRNA clusters, two of them paralogous (miR-379/495, -299/1185-1) and one homologous (miR-323b/656). Based on their own unique promoters, intergenic miRNAs may be independently transcribed [42]. Interestingly, such miRNA clusters are embedded in the miR-379 miRNA megacluster that was recently associated to endoplasmic reticulum stress [43]. In addition, increased expression of miR-411 and -1185 has been involved in the pathogenesis of cardiovascular disease [44, 45] and miR-495-3p in tumour sensitivity [46]. Decreased expression of miR-299-3p and -369-3p has been linked to tumorigenesis [47, 48] and miR-300 to poor prognosis in patients with cancer [49]. We also observed discordant 5p (increasing)/3p (decreasing) regulation of miR-875. It is known that 5p and 3p miRNA species may be selectively co- or cross-regulated [50] according to differences in the sequence of 5’ and 3’ arms of the mature miRNA hairpin duplex [51]. A decreased expression of miR-875-3p has been implicated in

cardiac myopathy [52]. We further found a biased 3p-arm selection of dysregulated miRNAs, which is indicative that targets of these 3p species may be biologically prominent in the response to the ingestion of dietary SFAs.

Two miRNAs (miR-18a-3p, -19b-1-5p) from the miR-17/92a-1 polycistronic oncomiR-1 and one miRNA from each of its two paralogous miR-106b/25 (miR-25-5p) and -106a/363 (miR-363-5p) clusters were also overrepresented upon challenge with the high-saturated fat meal. Differential expression of oncomiR-1 components has been previously reported at different posttranscriptional levels by Drosha or Dicer cleavage [53], miR-19b being required to recapitulate the oncogenic properties of the entire cluster [54]. The amplification or overexpression of miR-18a-3p has been associated to the development of epidermal skin cancer [55], while miR-25-5p to the inflammatory response in several types of cancer cells [56]. However, the biological role of miR-363-5p on tumorigenesis remains unclear [57]. Previous research reported long-term regulatory effects of dietary fatty acids on several miRNAs, including miR-19b and -18a [58]. Therefore, our study indicates that oncomiR-1 cluster is also closely related to acute metabolism of dietary fatty acids, thus providing a further level of complexity and a new perspective in the epigenetic mechanisms underlying the control of circulating miRNA profile during non-fasting conditions. The oncomiR-1 cluster has been recently associated with cardiovascular system [59] and we have previously reported the critical role of the predominant class of dietary fatty acids in postprandial triglyceride-rich lipoproteins on cardiovascular risk factors [15, 60]. This lead to the hypothesis that oncomiR-1 cluster and its paralogous may serve as a potential target for exploring the role of different dietary fatty acids to fine-tune transcriptional levels of genes involved in metabolic disorders that are common to relevant degenerative diseases. An attractive possibility is the

reciprocal control of miRNA expression and peroxisome proliferator-activated receptors [61], which are a family of transcriptional factors responsive to dietary fatty acids from postprandial triglyceride-rich lipoproteins in myeloid cells [5, 62, 63].

We used several computational algorithms to establish miRNA targets and functional enrichment analysis. Most of the predicted genes (~60%) were affected by upregulated miRNAs, which suggests an increase of transcriptional gene repression in response to the ingestion of the high-saturated fat meal. Two downregulated miRNAs such as miR-300 and -369-3p located at the same chromosomal region (14q32.31) and three upregulated miRNAs such as miR-495-3p, -129-5p, and -7-2-3p at distant chromosomal regions (14q32.31, 7q22.1, and 15q26.1, respectively) had the highest number of enriched targets. Our study unveiled four major categories of pathways and biological processes (pathways in cancer, MAPK signalling pathway, endocytosis, and axon guidance) as those enriched by both downregulated and upregulated miRNAs. PI3K-Akt signalling pathway was notably targeted by only downregulated miRNAs, which is in accordance with the activation of PI3K and Akt by postprandial triglyceride-rich lipoproteins containing SFAs in human vascular smooth muscle cells [64]. The PI3K-Akt signalling pathway is frequently involved in cell proliferation, survival, migration, autophagy, and oxidative status [65]. The main enriched KEGG pathway categories impacted by only upregulated miRNAs were focal adhesion, Wnt signalling pathway, transcriptional misregulation in cancer, and ubiquitin-mediated proteolysis. Integrative focal adhesion and wnt/beta-catenin signalling pathways predicted by miRNAs have been involved in artery ischemia, brain injury, and metastasis [66]. Dysregulation of the ubiquitin-proteasome pathway by miRNAs has been shown to result in uncontrolled proliferation and genomic instability [67].

The conclusions that are drawn from the current study are limited by the small sample size and will need to be confirmed in large-scale studies. Nevertheless, the study illustrates miRNA profile differences between fasting and postprandial states by a within-subject study design that enabled the subjects to act as their own control.

In summary, we herein propose that dietary SFAs could be pivotal molecular players in acutely regulating a wide spectrum of miRNAs associated with human pathophysiology, including cancer, atherosclerosis, inflammation, immunity, epigenetic, and neural regulation. These findings on miRNA biogenesis also suggest that miRNAs may serve as biomarkers of fasting and non-fasting status, even of compliance for assessing dietary SFA intake. However, more in-depth studies are still warranted to provide further understanding of how dietary fatty acids, including others than SFAs, may cause miRNA dysregulation and this may serve to orchestrate biological processes and regulatory functions during the postprandial state, that is, each time we eat. Whether miRNAs in concert with such repetitive spikes of exogenous lipids may have consequences on any disease progression, particularly in people who suffer from pathologically exacerbated and delayed postprandial responses will be of future interest.

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LEGENDS TO FIGURES

Figure 1. A) Box-and-whisker plots of serum triglyceride concentrations at fasting and after the ingestion of a high-saturated fat meal in male healthy individuals (*n* = 9). B) Hierarchical clustering of postprandially changed (downregulated and upregulated) miRNAs. Colours represent the intensity value of each miRNA at fasting and at postprandial. C) Volcano plot of detectable miRNAs. The x-axis shows the $\log_2$ fold change in miRNAs' expression between fasting and postprandial, while the y-axis shows the $-\log_{10}$ of the adjusted *p*-value for each miRNA. D) Description of the number of downregulated (green) and upregulated (orange) miRNAs that are represented in B and the number of these miRNA that are represented in C.

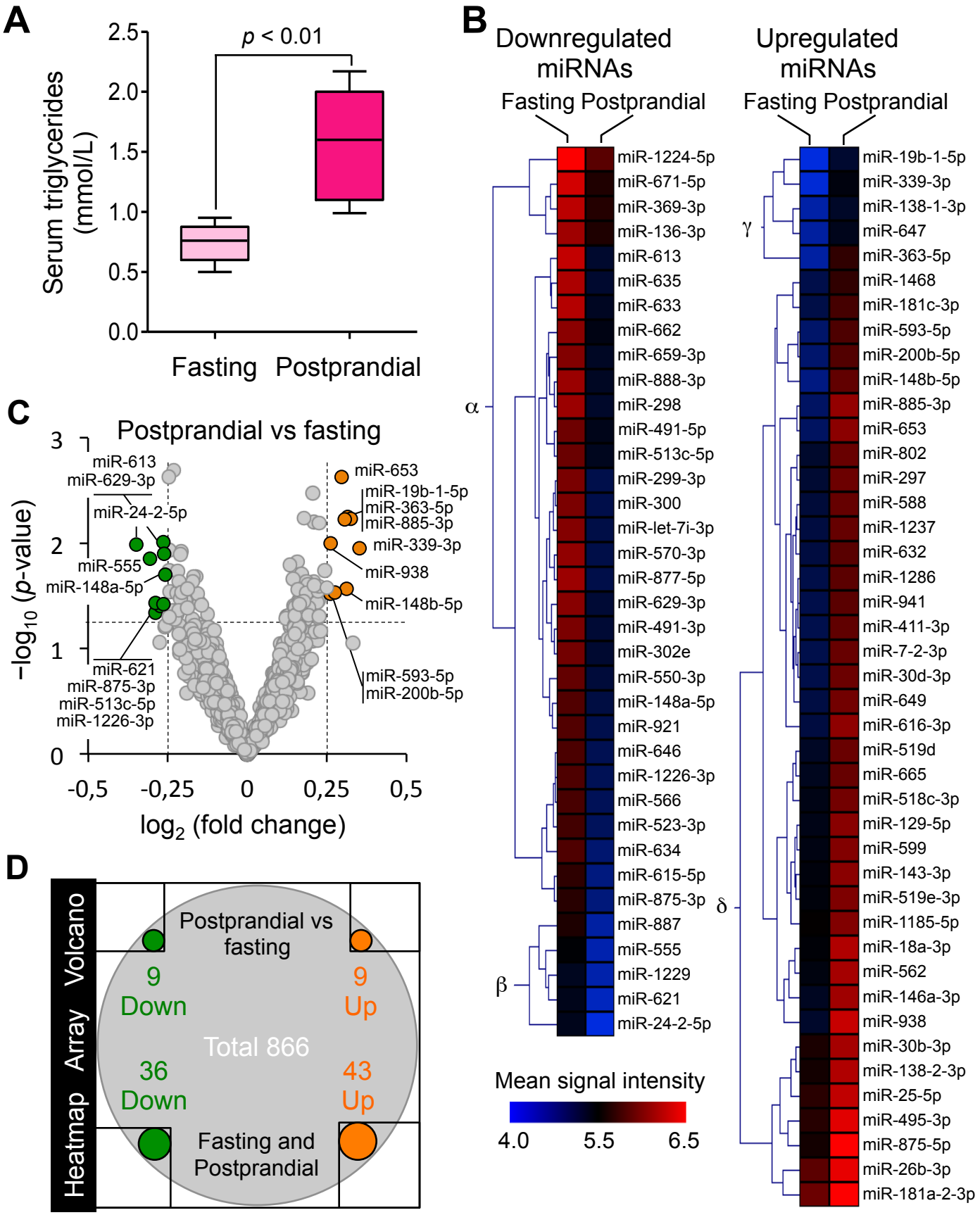
Figure 2. A) Heatmap expression of total miRNAs from fasting (F, red) and postprandial (P, black) samples #1, 2, 3, and 4. B) Three-dimensional hierarchical cluster analysis for the principal components performed after correspondence analysis (COA). Colours represent the intensity value of each miRNA at fasting and at postprandial. C) Two-dimensional factorial representation of the COA with means of the clusters. D) Scatter plot of miRNA data by principal component analysis.

Figure 3. Chromosome localization of the downregulated (green) and upregulated (orange) miRNAs in the postprandial state when compared to the fasting state.

Figure 4. Genomic representation of dysregulated miRNAs encoded in clusters or in paralogous groups. A) Organization of precursors and mature forms of affected miRNAs. Two types of paralogous groups of miR-30 and -181 precursors can be

identified: miR-30b, -181a-2/c (light green) and miR-30d, -181b-2/d (brown). The names of miRNA precursors are denoted below de boxes. The positions of mature miRNAs are indicated by coloured boxes (aero, yellow, cyan) with labels (5p: 5p specie, 3p: 3p specie, asterisk: one arm of the hairpin) written above. Green, orange or black label means decreased, increased, or not changed expression, respectively. B) Sequence alignment of mature miRNA members of the miR-17/92a-1 cluster and its two paralogous miR-106b/25 and -106a/363 that were dysregulated. Conservation of each nucleotide position is denoted by the colour according to ClustalW software.

Figure 5. KEGG pathways enriched by the target genes of the downregulated (green) and upregulated (orange) miRNAs in the postprandial state when compared to the fasting state. The number of dysregulated miRNAs involved in each KEGG pathway is indicated in brackets.


A
p < 0.01
Serum triglycerides (mmol/L)
2.5
2.0
1.5
1.0
0.5
0.0
Fasting
Postprandial
B
Downregulated miRNAs
Upregulated miRNAs
Fasting Postprandial
miR-1224-5p
miR-671-5p
miR-369-3p
miR-136-3p
miR-613
miR-635
miR-633
miR-662
miR-659-3p
miR-888-3p
miR-298
miR-491-5p
miR-513c-5p
miR-299-3p
miR-300
miR-let-7i-3p
miR-570-3p
miR-877-5p
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α
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γ
δ
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miR-653
miR-802
miR-297
miR-588
miR-1237
miR-632
miR-1286
miR-941
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miR-7-2-3p
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miR-649
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miR-519d
miR-665
miR-518c-3p
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miR-599
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miR-519e-3p
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miR-18a-3p
miR-562
miR-146a-3p
miR-938
miR-30b-3p
miR-138-2-3p
miR-25-5p
miR-495-3p
miR-875-5p
miR-26b-3p
miR-181a-2-3p
Mean signal intensity
4.0
5.5
6.5
C
Postprandial vs fasting
−log10 (p-value)
log2 (fold change)
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1
0
-0,5
-0,25
0
0,25
0,5
miR-613
miR-629-3p
miR-24-2-5p
miR-555
miR-148a-5p
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miR-513c-5p
miR-1226-3p
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miR-339-3p
miR-938
miR-148b-5p
miR-593-5p
miR-200b-5p
D
Volcano
Array
Heatmap
Postprandial vs fasting
9
Down
9
Up
Total 866
36
Down
43
Up
Fasting and Postprandial

Figure 1

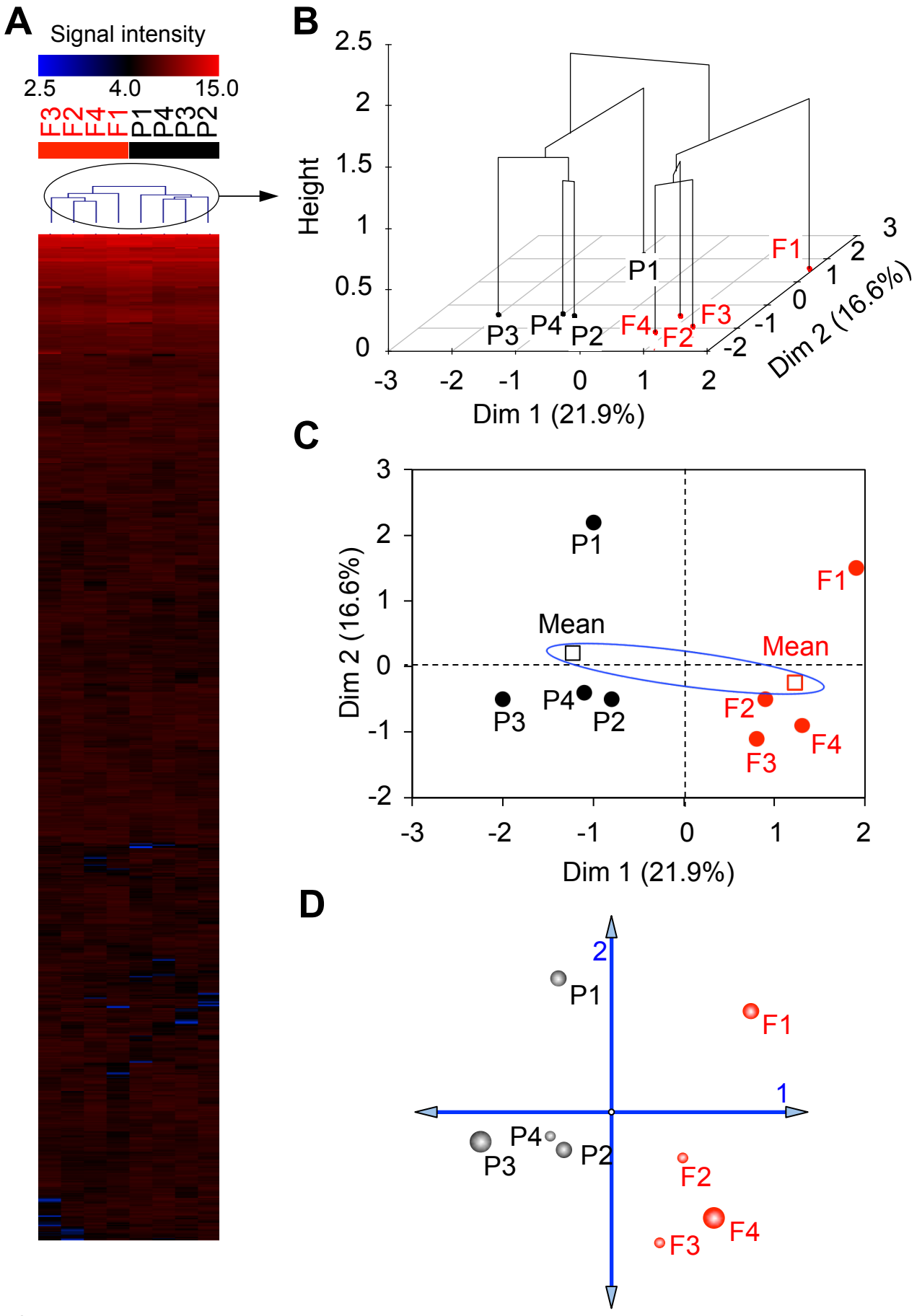
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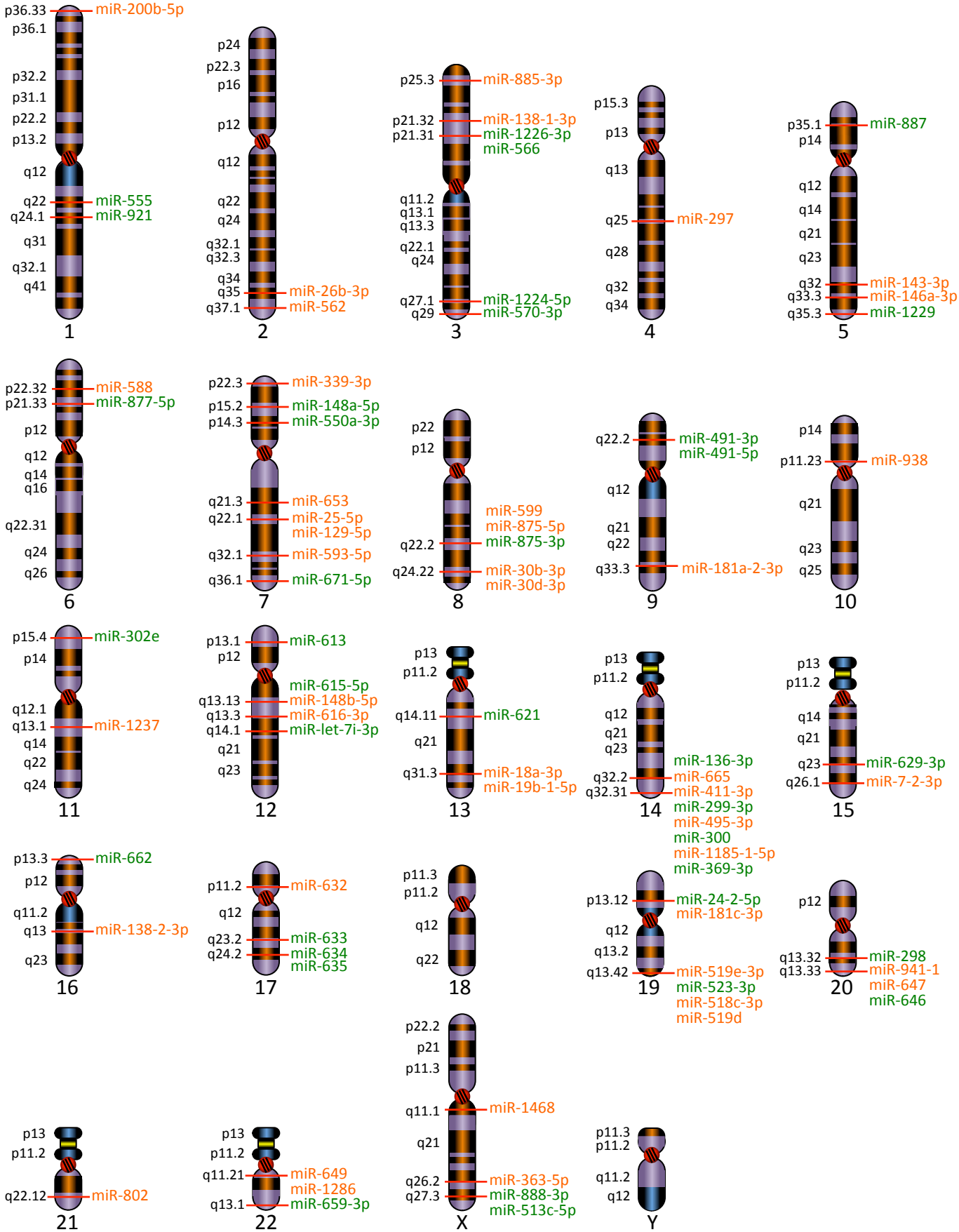
Figure 2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miR-555
miR-921
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p24
p22.3
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p12
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q32.1
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q34
q35
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miR-562
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p21.32
p21.31
q11.2
q13.1
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q22.1
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21
p13
p11.2
q11.21
q13.1
miR-649
miR-1286
miR-659-3p
22

Figure 3

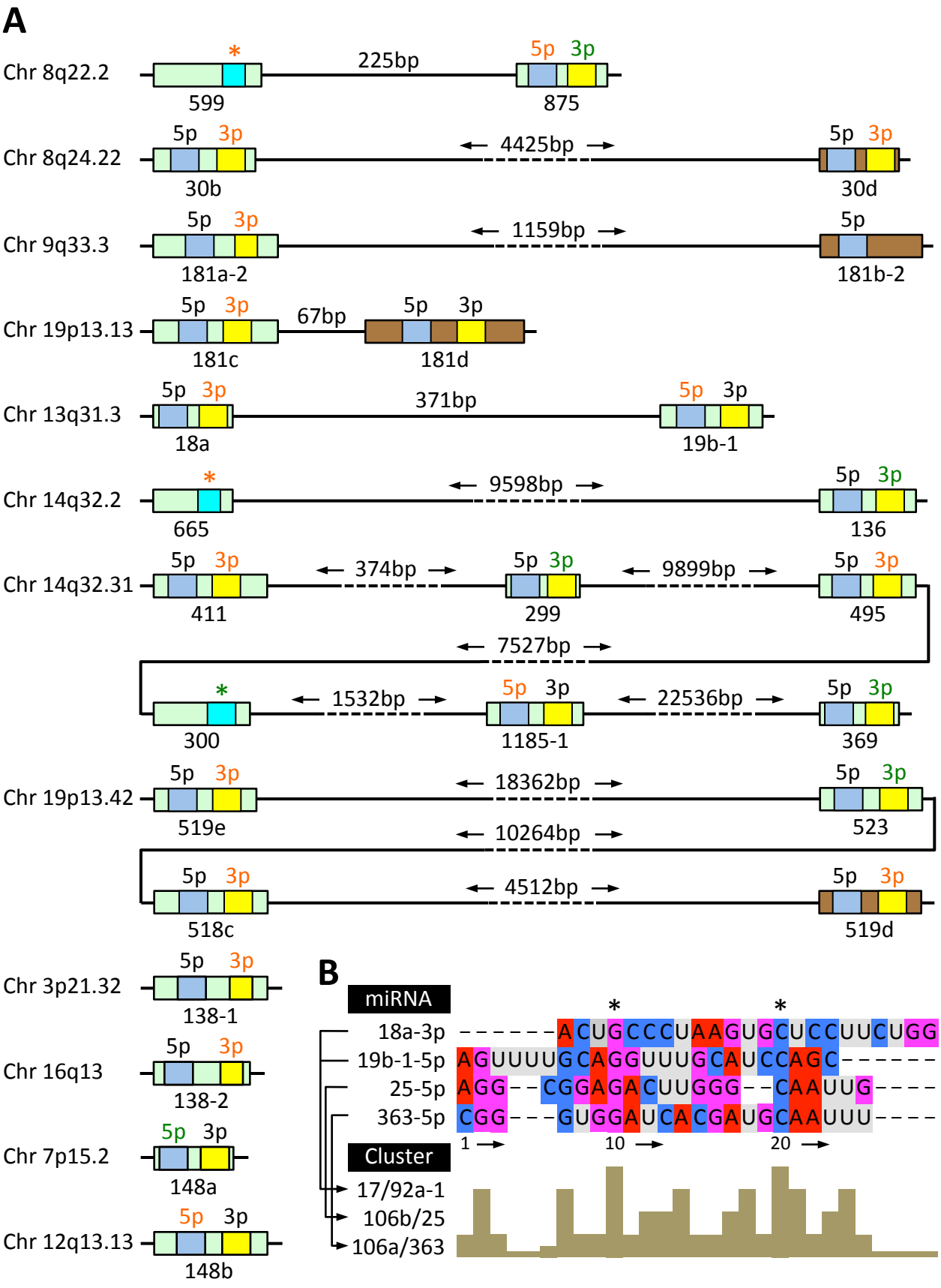
A
Chr 8q22.2
599
225bp
5p 3p
875
Chr 8q24.22
5p 3p
30b
4425bp
5p 3p
30d
Chr 9q33.3
5p 3p
181a-2
1159bp
5p
181b-2
Chr 19p13.13
5p 3p
181c
67bp
5p 3p
181d
Chr 13q31.3
5p 3p
18a
371bp
5p 3p
19b-1
Chr 14q32.2
665
9598bp
5p 3p
136
Chr 14q32.31
5p 3p
411
374bp
5p 3p
299
9899bp
5p 3p
495
7527bp
300
1532bp
5p 3p
1185-1
22536bp
5p 3p
369
Chr 19p13.42
5p 3p
519e
18362bp
5p 3p
523
10264bp
5p 3p
518c
4512bp
5p 3p
519d
Chr 3p21.32
5p 3p
138-1
Chr 16q13
5p 3p
138-2
Chr 7p15.2
5p 3p
148a
Chr 12q13.13
5p 3p
148b
B
miRNA
18a-3p
19b-1-5p
25-5p
363-5p
1
10
20
Cluster
17/92a-1
106b/25
106a/363

Figure 4

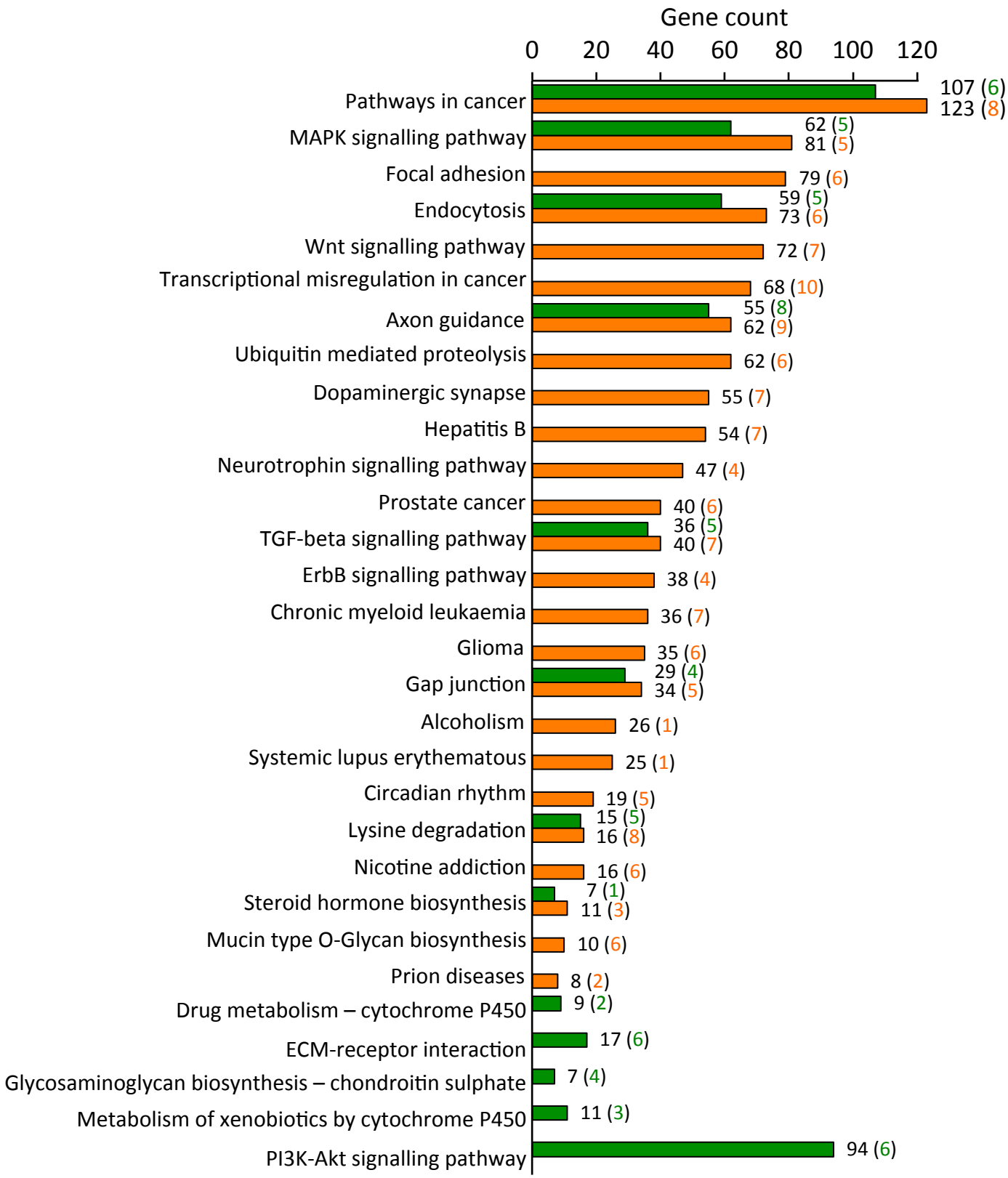
Gene count
0
20
40
60
80
100
120
Pathways in cancer
107 (6)
123 (8)
MAPK signalling pathway
62 (5)
81 (5)
Focal adhesion
79 (6)
Endocytosis
59 (5)
73 (6)
Wnt signalling pathway
72 (7)
Transcriptional misregulation in cancer
68 (10)
Axon guidance
55 (8)
62 (9)
Ubiquitin mediated proteolysis
62 (6)
Dopaminergic synapse
55 (7)
Hepatitis B
54 (7)
Neurotrophin signalling pathway
47 (4)
Prostate cancer
40 (6)
TGF-beta signalling pathway
36 (5)
40 (7)
ErbB signalling pathway
38 (4)
Chronic myeloid leukaemia
36 (7)
Glioma
35 (6)
Gap junction
29 (4)
34 (5)
Alcoholism
26 (1)
Systemic lupus erythematous
25 (1)
Circadian rhythm
19 (5)
Lysine degradation
15 (5)
16 (8)
Nicotine addiction
16 (6)
Steroid hormone biosynthesis
7 (1)
11 (3)
Mucin type O-Glycan biosynthesis
10 (6)
Prion diseases
8 (2)
Drug metabolism – cytochrome P450
9 (2)
ECM-receptor interaction
17 (6)
Glycosaminoglycan biosynthesis – chondroitin sulphate
7 (4)
Metabolism of xenobiotics by cytochrome P450
11 (3)
PI3K-Akt signalling pathway
94 (6)

Figure 5

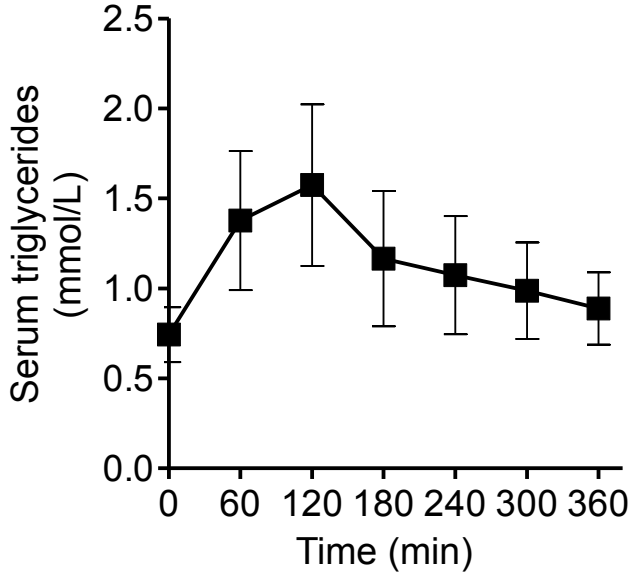

Figure S1. Mean (± SD) serum triglyceride concentration during the test meal enriched in saturated fatty acids in male healthy individuals, *n* = 9.

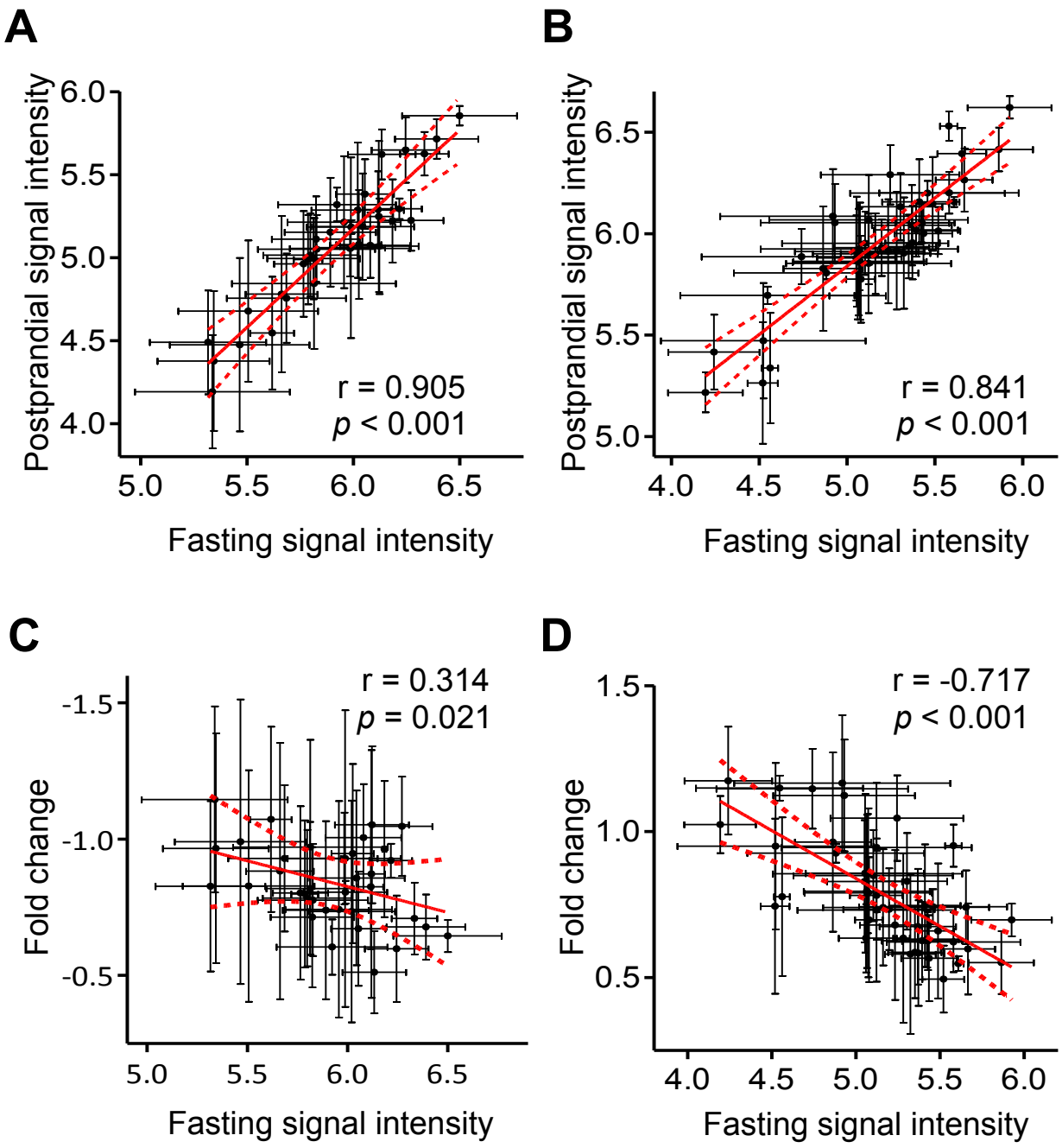

Figure S2. Pearson correlation analysis of fasting *vs* postprandial intensity values of upregulated (A) and downregulated (B) miRNAs, and fasting intensity values *vs* fold change of upregulated (C) and dowregulated (D) miRNAs.

Table 1. Subject characteristics.

Characteristic	
Age (y)	20.3 ± 1.5
Weight (kg)	72.2 ± 6.4
Waist (m)	0.9 ± 0.2
Hip (m)	0.9 ± 0.2
Body mass index (kg/m^2)	22.9 ± 1.9
Fasting glucose (mmol/L)	4.3 ± 0.5
Fasting total cholesterol (mmol/L)	3.7 ± 0.5
Fasting LDL-cholesterol	2.0 ± 0.5
Fasting HDL-cholesterol	1.3 ± 0.2
Fasting triglycerides (mmol/L)	0.8 ± 0.3

Data are expressed as mean ± SD (*n* = 9).

Table 2. Fatty acid composition of the milk cream.

Fatty acid	
4:0, butyric	0.83 ± 0.16
6:0, caproic	0.25 ± 0.02
8:0, caprylic	0.61 ± 0.07
10:0, capric	2.47 ± 0.13
12:0, lauric	3.09 ± 0.42
14:0, myristic	10.9 ± 0.91
16:0, palmitic	35.50 ± 0.82
16:1ω-7, palmitoleic	3.60 ± 0.32
18:0, stearic	11.54 ± 0.75
18:1ω-9, oleic	25.33 ± 0.71
18:2ω-6, linoleic	4.27 ± 0.82
18:3ω-3, α-linolenic	0.39 ± 0.05
Others	0.96 ± 0.42
Saturated fatty acids	65.19 ± 5.12
Monounsaturated fatty acids	28.93 ± 1.34
Polyunsaturated fatty acids	4.66 ± 0.56

Data are expressed as mean ± SD (*n* = 3 samples of the same lot).

Table 3. Validation of microarray data by qRT-PCR analysis.

hsa-miRNA	Array	Fluidigm-qRT-PCR
	Fold change	Fold change
miR-629-3p	-0.26 ± 0.15	-1.18 ± 0.20
miR-24-2-5p	-0.35 ± 0.21	-1.21 ± 0.27
miR-555	-0.32 ± 0.11	-0.78 ± 0.21
miR-621	-0.31 ± 0.23	-0.82 ± 0.24
miR-653	0.31 ± 0.17	1.41 ± 0.28
miR-363-5p	0.35 ± 0.22	0.97 ± 0.20
miR-593-5p	0.28 ± 0.13	1.64 ± 0.36
miR-200b-5p	0.26 ± 0.10	2.54 ± 0.47
miR-103-3p	-0.01 ± 0.03	0.05 ± 0.07
miR-16	0.00 ± 0.04	0.03 ± 0.04

Data are expressed as mean ± SD (*n* = 9).

Table 4. The 35 dysregulated miRNAs that were distributed either individually or grouped within chromosome cluster regions.

Cluster	Chromosome	miRNA cluster	miRNAs dysregulated in postprandial *vs* basal PBMCs	miRNA gene family
	Chr 1p36.33	miR-200b/429 (3)	miR-200b-5p	miR-8
	Chr 5q32	miR-143/145 (2)	miR-143-3p	miR-143
	Chr 7q21.3	miR-489/653 (2)	miR-653	miR-653
	Chr 7q22.1	miR-106b/25 (3)	miR-25-5p	miR-25
1	Chr 8q22.2	miR-875/599 (2)	miR-875-5p[a], miR-875-3p[a], miR-599[b]	miR-875[a], miR-599[b]
2	Chr 8q24.22	miR-30d/30b (2)	miR-30d-3p, miR-30b-3p	miR-30
	Chr 9q33.3	miR-181a-2/181b-2 (2)	miR-181a-2-3p	miR-181
	Chr 12q13.3	miR-616/6758 (2)	miR-616-3p	miR-616
3	Chr 13q31.3	miR-17/92a-1 (6)	miR-18a-3p[a], miR-19b-1-5p[b]	miR-17[a], miR-19[b]
4	Chr 14q32.2	miR-665/136 (6)	miR-665[a], miR-136-3p[b]	miR-665[a], miR-136[b]
5*	Chr 14q32.31	miR-379/495 (13)	miR-411-3p[a], miR-299-3p[b], miR-495-3p[c]	miR-379[a], miR-299[b], miR-329[c]
6*	Chr 14q32.31	miR-299/1185-1 (18)	miR-299-3p[a], miR-495-3p[b], miR-300[c], miR-1185-1-5p[c]	miR-299[a], miR-329[b], miR-154[c]
	Chr 14q32.31	miR-323b/656 (10)	miR-369-3p	miR-154
	Chr 15q26.1	miR-1179/3529 (3)	miR-7-2-3p	miR-7
	Chr 19p13.12	miR-23a/24-2 (3)	miR-24-2-5p	miR-24
	Chr 19p13.12	miR-181c/118d (2)	miR-181c-3p	miR-181
	Chr 19q13.42	miR-1323/1283-1 (9)	miR-519e-3p	miR-515
	Chr 19q13.42	miR-1283-1/520c (11)	miR-523-3p	miR-515
7	Chr 19q13.42	miR-518f/521-2 (10)	miR-518c-3p[a], miR-519d[a]	miR-515[a]
	Chr 20q13.32	miR-298/296 (2)	miR-298	miR-298
	Chr 20q13.33	miR-941-1/941-5 (5)	miR-941-1	miR-941
	Chr 20q13.33	miR-647/1914 (2)	miR-647	miR-647
	Chr 22q13.1	miR-659/658 (2)	miR-659-3p	?
	Chr Xq26.2	miR-106a/363 (6)	miR-363-5p	miR-363
	Chr Xq27.3	miR-891b/892c (6)	miR-888-3p	miR-743
	Chr Xq27.3	miR-513b/513c (2)	miR-513c-5p	miR-506

Cluster genes that share miRNAs are indicated with asterisks. The number of members in each miRNA cluster (<10 kb) is indicated in brackets. The same lowercase superscript letter is used to indicate membership of each miRNA with its corresponding miRNA gene family. Downregulated miRNAs are depicted in green colour, while upregulated miRNAs in orange colour.

Table S1. Detected miRNAs in PBMCs of healthy volunteers at fasting and after the ingestion of a standardized high-saturated fat meal.

miRNA	At fasting		At postprandial	
	Signal intensity	SD	Signal intensity	SD
hsa-let-7a-5p	12.20	0.18	12.24	0.23
hsa-let-7a-3p	6.27	0.18	5.73	0.48
hsa-let-7b-5p	10.08	0.31	10.18	0.38
hsa-let-7b-3p	5.54	0.33	5.97	0.55
hsa-let-7c-5p	9.25	0.25	9.33	0.31
hsa-let-7c-3p	6.16	0.25	5.39	0.65
hsa-let-7d-5p	10.46	0.16	10.59	0.34
hsa-let-7d-3p	5.41	0.45	5.76	0.88
hsa-let-7e-5p	6.92	0.36	6.63	0.37
hsa-let-7e-3p	5.12	0.80	5.52	0.83
hsa-let-7f-1-5p	10.52	0.61	10.60	0.73
hsa-let-7f-1-3p	5.86	0.60	5.39	0.20
hsa-let-7f-2-3p	5.54	0.34	5.85	0.25
hsa-let-7g-5p	12.77	0.21	12.95	0.18
hsa-let-7g-3p	5.09	0.57	5.62	0.53
hsa-let-7i-5p	10.69	0.25	10.46	0.21
hsa-let-7i-3p	5.96	0.53	5.21	0.79
hsa-miR-1-3p	5.75	0.37	5.58	1.06
hsa-miR-100-5p	5.79	0.48	6.04	0.15
hsa-miR-100-3p	5.73	0.59	5.31	0.68
hsa-miR-101-3p	9.68	0.16	9.55	0.24
hsa-miR-101-5p	6.01	0.54	5.77	0.51
hsa-miR-103a-3p	11.60	0.14	11.53	0.23
hsa-miR-103b	6.16	0.53	5.70	0.29
hsa-miR-105-5p	5.35	0.72	6.05	0.33
hsa-miR-105-3p	5.93	0.36	5.47	1.12
hsa-miR-106a-3p	5.63	0.37	6.06	0.33
hsa-miR-106b-5p	10.69	0.10	10.73	0.23
hsa-miR-106b-3p	6.09	0.39	5.54	0.83
hsa-miR-107	9.64	0.27	9.72	0.44
hsa-miR-10a-5p	6.48	0.32	6.21	0.42
hsa-miR-10a-3p	6.14	0.39	5.69	0.31
hsa-miR-10b-5p	5.95	0.23	5.92	0.44
hsa-miR-10b-3p	5.91	0.33	5.52	0.20
hsa-miR-1178-3p	5.82	0.35	5.33	0.27
hsa-miR-1179	6.05	0.36	5.99	0.35
hsa-miR-1180-3p	5.73	0.44	5.49	0.46
hsa-miR-1181	5.95	0.44	5.48	0.31
hsa-miR-1182	5.64	0.55	5.84	0.27

hsa-miR-1183	6.11	0.58	5.77	0.49
hsa-miR-1184	5.42	0.46	5.63	0.58
hsa-miR-1185-5p	5.52	0.25	6.01	0.23
hsa-miR-1197	6.02	0.48	5.68	0.24
hsa-miR-1200	5.38	0.26	5.48	0.31
hsa-miR-1201	5.99	0.41	5.76	0.48
hsa-miR-1202	8.50	0.52	8.14	0.47
hsa-miR-1203	5.56	0.48	5.51	0.25
hsa-miR-1204	5.46	0.25	5.87	0.37
hsa-miR-1205	6.02	0.32	5.79	0.45
hsa-miR-1206	5.95	0.25	6.20	0.13
hsa-miR-1207-3p	5.10	0.24	4.63	0.44
hsa-miR-1207-5p	8.14	0.59	8.04	0.43
hsa-miR-1208	5.55	0.79	5.93	0.50
hsa-miR-122-5p	6.08	0.41	5.79	0.42
hsa-miR-122-3p	5.30	0.21	5.64	0.44
hsa-miR-1224-3p	5.09	0.47	4.26	1.12
hsa-miR-1224-5p	6.50	0.54	5.86	0.12
hsa-miR-1225-3p	5.82	0.52	5.56	0.33
hsa-miR-1225-5p	7.90	0.58	7.55	0.13
hsa-miR-1226-3p	5.47	0.66	4.48	1.05
hsa-miR-1226-5p	6.41	0.32	6.55	0.36
hsa-miR-1227-3p	5.74	0.59	5.38	0.78
hsa-miR-1228-3p	6.49	0.17	6.35	0.22
hsa-miR-1228-5p	5.68	0.41	6.10	0.27
hsa-miR-1229-3p	5.32	0.55	4.49	0.63
hsa-miR-1231	5.19	0.44	5.49	0.32
hsa-miR-1233-3p	5.20	0.32	5.46	0.14
hsa-miR-1234-3p	6.05	0.35	6.30	0.19
hsa-miR-1236-3p	5.27	0.79	5.91	0.40
hsa-miR-1237-3p	5.12	0.31	5.90	0.30
hsa-miR-1238-3p	6.12	0.49	6.46	0.08
hsa-miR-124-3p	5.51	0.61	5.05	0.67
hsa-miR-124-5p	5.36	0.61	5.79	0.47
hsa-miR-1243	5.79	0.45	6.20	0.33
hsa-miR-1244	5.75	0.32	6.10	0.62
hsa-miR-1245a	5.84	0.22	5.54	0.39
hsa-miR-1246	7.49	0.70	6.95	0.37
hsa-miR-1247-5p	5.49	0.38	4.99	0.40
hsa-miR-1248	6.31	0.19	5.80	0.19
hsa-miR-1249-3p	5.50	0.21	5.64	0.09
hsa-miR-1250-5p	5.82	0.11	5.67	0.69
hsa-miR-1251-5p	5.69	0.25	5.12	0.44
hsa-miR-1252-5p	6.01	0.39	5.81	0.38
hsa-miR-1253	5.88	0.20	5.35	0.38
hsa-miR-1254	5.65	0.16	5.39	0.16

hsa-miR-1255a	5.69	0.43	6.08	0.46
hsa-miR-1255b-5p	5.65	0.43	5.86	0.67
hsa-miR-1256	5.63	0.51	5.72	0.45
hsa-miR-1257	5.82	0.28	5.66	0.08
hsa-miR-1258	5.89	0.24	5.70	0.35
hsa-miR-1259	5.83	0.34	6.30	0.17
hsa-miR-125a-3p	6.63	0.31	6.75	0.40
hsa-miR-125a-5p	7.09	0.26	6.93	0.22
hsa-miR-125b-5p	6.00	0.70	6.03	0.26
hsa-miR-125b-1-3p	5.15	0.49	5.85	0.59
hsa-miR-125b-2-3p	5.65	0.02	5.79	0.39
hsa-miR-126-3p	9.07	0.46	9.00	0.62
hsa-miR-126-5p	6.44	0.54	6.55	0.45
hsa-miR-1260a	12.61	0.53	12.55	0.55
hsa-miR-1261	6.06	0.42	5.77	0.38
hsa-miR-1262	5.99	0.47	6.20	0.24
hsa-miR-1263	5.51	0.34	5.17	0.35
hsa-miR-1264	5.59	0.44	5.94	0.28
hsa-miR-1265	5.53	0.09	5.99	0.33
hsa-miR-1266-5p	6.05	0.44	5.51	0.38
hsa-miR-1267	5.59	0.23	5.92	0.47
hsa-miR-1268a	7.11	0.35	6.91	0.23
hsa-miR-1269a	5.77	0.15	5.44	0.19
hsa-miR-1270	5.71	0.51	5.88	0.33
hsa-miR-1271-5p	5.34	0.57	5.00	0.56
hsa-miR-1272	5.51	0.49	5.86	0.40
hsa-miR-1273a	5.59	0.59	6.03	0.20
hsa-miR-127-3p	5.99	0.49	5.74	0.47
hsa-miR-1274a	10.19	0.47	10.36	0.47
hsa-miR-1274b	12.55	0.48	12.57	0.32
hsa-miR-1275	7.27	0.18	6.94	0.32
hsa-miR-127-5p	5.51	0.24	6.14	0.50
hsa-miR-1276	5.74	0.44	5.51	0.46
hsa-miR-1277-3p	6.23	0.11	6.23	0.12
hsa-miR-1278	5.53	0.43	5.96	0.27
hsa-miR-1279	5.56	0.38	5.84	0.26
hsa-miR-128-3p	6.96	0.15	6.78	0.13
hsa-miR-1280	9.78	0.35	9.88	0.54
hsa-miR-1281	6.64	0.23	6.09	0.35
hsa-miR-1282	5.73	0.15	6.07	0.21
hsa-miR-1283	6.13	0.39	5.65	0.37
hsa-miR-1284	5.07	0.97	5.52	0.46
hsa-miR-1285-3p	5.71	0.49	6.06	0.32
hsa-miR-1286	5.07	0.76	5.86	0.58
hsa-miR-1287-5p	6.04	0.40	5.96	0.29
hsa-miR-1288-3p	7.24	0.40	7.22	0.34

hsa-miR-1289	5.66	0.11	5.46	0.68
hsa-miR-129-1-3p	5.29	0.92	5.59	0.77
hsa-miR-1290	6.62	0.20	6.40	0.24
hsa-miR-1291	5.47	0.52	5.91	0.13
hsa-miR-1292-5p	5.57	0.26	5.35	0.26
hsa-miR-1293	6.00	0.46	5.80	0.27
hsa-miR-129-2-3p	5.02	0.33	5.38	0.43
hsa-miR-1294	5.93	0.26	6.05	0.45
hsa-miR-1295a	6.05	0.30	5.85	0.50
hsa-miR-129-5p	5.37	0.45	6.04	0.40
hsa-miR-1296-5p	5.48	0.56	5.33	0.30
hsa-miR-1297	5.76	0.65	6.32	0.33
hsa-miR-1298-5p	5.51	0.37	5.71	0.39
hsa-miR-1299	6.01	0.34	5.96	0.44
hsa-miR-1301-3p	5.44	0.42	5.65	0.44
hsa-miR-1302	5.78	0.33	6.06	0.57
hsa-miR-1303	5.67	0.42	5.80	0.41
hsa-miR-1304-5p	5.82	0.44	5.61	0.44
hsa-miR-1305	8.62	0.56	8.50	0.48
hsa-miR-1306-3p	6.07	0.46	5.76	0.25
hsa-miR-1307-3p	5.47	0.61	5.95	0.29
hsa-miR-1308	8.06	1.57	7.10	0.35
hsa-miR-130a-3p	9.03	0.17	8.80	0.30
hsa-miR-130a-5p	5.58	0.49	6.12	0.51
hsa-miR-130b-3p	7.12	0.16	7.04	0.18
hsa-miR-130b-5p	5.37	0.61	4.89	0.53
hsa-miR-132-3p	6.27	0.57	6.40	0.24
hsa-miR-132-5p	5.59	0.35	5.68	0.46
hsa-miR-1321	5.90	0.30	6.11	0.18
hsa-miR-1322	4.99	0.78	5.63	0.22
hsa-miR-1323	5.72	0.30	5.96	0.28
hsa-miR-1324	5.57	0.35	6.11	0.21
hsa-miR-133a-3p	4.85	1.05	5.46	0.29
hsa-miR-133b	5.38	0.35	5.51	0.40
hsa-miR-134-5p	6.29	0.59	6.11	0.34
hsa-miR-135a-5p	6.28	0.12	5.97	0.25
hsa-miR-135a-3p	5.76	0.23	5.10	0.35
hsa-miR-135b-5p	6.04	0.27	6.36	0.32
hsa-miR-135b-3p	5.15	0.35	5.64	0.34
hsa-miR-136-5p	6.65	0.23	6.46	0.33
hsa-miR-136-3p	6.13	0.32	5.62	0.30
hsa-miR-137	6.15	0.24	5.63	0.33
hsa-miR-138-5p	5.74	0.53	5.54	0.42
hsa-miR-138-1-3p	4.52	0.17	5.26	0.60
hsa-miR-138-2-3p	5.58	0.79	6.20	0.21
hsa-miR-139-3p	6.61	0.27	6.46	0.30

hsa-miR-139-5p	6.39	0.34	6.17	0.36
hsa-miR-140-3p	8.17	0.37	7.96	0.30
hsa-miR-140-5p	8.45	0.30	8.53	0.38
hsa-miR-141-3p	6.92	0.18	6.53	0.54
hsa-miR-141-5p	6.00	0.40	5.43	0.43
hsa-miR-142-3p	12.72	0.54	12.73	0.48
hsa-miR-142-5p	11.30	0.39	11.18	0.14
hsa-miR-143-3p	5.43	0.31	6.05	0.20
hsa-miR-143-5p	5.58	0.30	5.69	0.34
hsa-miR-144-3p	6.48	0.23	6.16	0.35
hsa-miR-144-5p	5.49	0.37	5.84	0.49
hsa-miR-145-5p	5.98	0.53	6.21	0.16
hsa-miR-145-3p	5.86	0.27	5.90	0.36
hsa-miR-1468-5p	5.06	0.32	5.69	0.23
hsa-miR-1469	5.30	0.23	5.03	0.20
hsa-miR-146a-5p	9.87	0.42	9.94	0.51
hsa-miR-146a-3p	5.30	0.48	6.13	0.33
hsa-miR-146b-3p	5.70	0.32	5.45	0.31
hsa-miR-146b-5p	8.90	0.48	9.11	0.63
hsa-miR-147a	6.20	0.17	5.91	0.23
hsa-miR-1470	5.40	0.13	5.62	0.43
hsa-miR-1471	5.82	0.40	5.48	0.25
hsa-miR-147b	5.45	0.54	6.21	0.40
hsa-miR-148a-3p	7.59	0.31	7.69	0.12
hsa-miR-148a-5p	5.69	0.56	4.76	0.54
hsa-miR-148b-3p	6.59	0.27	6.34	0.43
hsa-miR-148b-5p	4.74	1.14	5.89	0.27
hsa-miR-149-5p	5.41	0.26	5.63	0.23
hsa-miR-149-3p	6.06	0.16	5.70	0.41
hsa-miR-150-5p	14.15	0.56	13.98	0.18
hsa-miR-150-3p	6.38	0.54	6.10	0.41
hsa-miR-151-3p	7.51	0.25	7.56	0.32
hsa-miR-151a-5p	9.14	0.31	9.10	0.29
hsa-miR-152-3p	5.41	0.63	5.51	0.24
hsa-miR-153-3p	5.69	0.37	5.37	0.28
hsa-miR-1537-3p	5.97	0.38	5.57	0.20
hsa-miR-1538	5.67	0.61	5.87	0.46
hsa-miR-1539	5.31	0.36	5.77	0.53
hsa-miR-154-5p	6.01	0.39	6.31	0.21
hsa-miR-154-3p	5.68	0.37	5.71	0.39
hsa-miR-155-5p	8.66	0.16	8.35	0.93
hsa-miR-155-3p	5.26	0.46	5.95	0.38
hsa-miR-15a-5p	11.47	0.36	11.38	0.24
hsa-miR-15a-3p	6.12	0.29	5.67	0.54
hsa-miR-15b-5p	11.06	0.24	10.92	0.25
hsa-miR-15b-3p	5.48	0.32	5.88	0.42

hsa-miR-16-5p	12.88	0.17	12.91	0.28
hsa-miR-16-1-3p	5.74	0.27	5.38	0.10
hsa-miR-16-2-3p	6.05	0.24	5.93	0.61
hsa-miR-17-5p	7.60	0.37	7.68	0.37
hsa-miR-17-3p	6.34	0.22	6.09	0.48
hsa-miR-181a-5p	8.63	0.49	8.79	0.59
hsa-miR-181a-3p	6.61	0.14	6.29	0.44
hsa-miR-181a-2-3p	5.93	0.48	6.62	0.11
hsa-miR-181b-5p	7.82	0.29	7.74	0.11
hsa-miR-181c-5p	6.83	0.19	7.02	0.15
hsa-miR-181c-3p	5.08	0.16	5.78	0.43
hsa-miR-181d-5p	6.11	0.63	6.25	0.46
hsa-miR-182-5p	5.65	0.58	5.88	0.35
hsa-miR-182-3p	5.76	0.44	6.17	0.27
hsa-miR-1825	5.91	0.48	5.83	0.41
hsa-miR-1826	6.25	0.42	6.08	0.63
hsa-miR-1827	6.03	0.44	5.62	0.58
hsa-miR-183-5p	5.86	0.27	5.25	1.44
hsa-miR-183-3p	4.72	1.15	5.08	0.47
hsa-miR-184	6.04	0.42	5.53	0.58
hsa-miR-185-5p	8.05	0.28	8.15	0.51
hsa-miR-185-3p	4.99	0.92	5.66	0.48
hsa-miR-186-5p	8.03	0.53	8.18	0.70
hsa-miR-186-3p	5.28	0.57	5.54	0.32
hsa-miR-187-3p	4.64	0.71	5.34	0.76
hsa-miR-187-5p	5.42	0.58	4.84	0.23
hsa-miR-188-3p	5.80	0.60	5.33	0.58
hsa-miR-188-5p	6.65	0.55	6.49	0.35
hsa-miR-18a-5p	6.92	0.26	6.91	0.40
hsa-miR-18a-3p	5.46	0.88	6.20	0.12
hsa-miR-18b-5p	5.78	0.49	5.48	0.52
hsa-miR-18b-3p	4.70	0.87	5.47	0.61
hsa-miR-190a-5p	5.88	0.80	6.26	0.22
hsa-miR-1908-5p	5.47	0.38	5.34	0.90
hsa-miR-1909-3p	5.54	0.87	5.90	0.48
hsa-miR-1909-5p	5.57	0.17	5.26	0.13
hsa-miR-190b	5.91	0.35	5.39	0.39
hsa-miR-191-5p	6.11	0.39	5.34	0.51
hsa-miR-191-3p	6.34	0.19	5.91	0.86
hsa-miR-1910-5p	4.93	0.25	5.33	0.38
hsa-miR-1911-5p	5.45	0.24	5.28	0.42
hsa-miR-1911-3p	5.52	0.32	5.64	0.23
hsa-miR-1912	5.98	0.24	5.52	0.08
hsa-miR-1913	5.46	0.77	5.53	0.40
hsa-miR-1914-5p	5.08	0.19	5.39	0.18
hsa-miR-1914-3p	7.30	0.33	7.38	0.25

hsa-miR-1915-3p	7.07	0.49	6.75	0.35
hsa-miR-1915-5p	5.18	0.24	5.48	0.62
hsa-miR-192-5p	7.70	0.21	7.82	0.15
hsa-miR-192-3p	5.56	0.93	5.85	0.29
hsa-miR-193a-3p	5.65	0.58	5.37	0.27
hsa-miR-193a-5p	6.18	0.11	5.86	0.46
hsa-miR-193b-3p	5.53	0.38	5.37	0.20
hsa-miR-193b-5p	5.54	0.80	5.99	0.57
hsa-miR-194-5p	6.37	0.29	6.24	0.12
hsa-miR-194-3p	5.42	0.46	5.80	0.08
hsa-miR-195-5p	5.72	0.13	5.95	0.35
hsa-miR-195-3p	4.98	0.96	5.51	0.34
hsa-miR-196a-5p	5.89	0.27	6.09	0.16
hsa-miR-196a-3p	5.05	0.78	5.85	0.44
hsa-miR-196b-5p	6.45	0.32	6.41	0.43
hsa-miR-197-3p	6.90	0.27	7.08	0.43
hsa-miR-198	6.18	0.39	5.76	0.28
hsa-miR-199a-3p	9.00	0.25	8.83	0.41
hsa-miR-199a-5p	8.31	0.73	8.00	0.89
hsa-miR-19a-3p	10.36	0.19	10.17	0.20
hsa-miR-19a-5p	6.07	0.64	5.41	0.82
hsa-miR-19b-3p	11.96	0.31	11.67	0.84
hsa-miR-19b-1-5p	4.19	0.43	5.22	0.20
hsa-miR-19b-2-5p	6.22	0.68	5.68	0.60
hsa-miR-200a-3p	5.55	0.29	5.87	0.27
hsa-miR-200a-5p	5.87	0.21	5.66	0.13
hsa-miR-200b-3p	6.01	0.47	6.20	0.32
hsa-miR-200b-5p	4.86	0.45	5.83	0.61
hsa-miR-200c-3p	5.72	0.36	5.41	0.15
hsa-miR-200c-5p	5.48	0.64	5.97	0.51
hsa-miR-202-3p	6.27	0.25	6.05	0.72
hsa-miR-202-5p	5.61	0.41	5.79	0.48
hsa-miR-203-3p	6.23	0.25	6.00	0.51
hsa-miR-204-5p	5.44	0.22	5.72	0.25
hsa-miR-205-5p	5.56	0.38	5.23	0.36
hsa-miR-206	5.86	0.36	6.09	0.34
hsa-miR-208a-3p	5.87	0.38	5.75	0.34
hsa-miR-208b-3p	6.05	0.38	6.21	0.28
hsa-miR-20a-5p	11.19	0.18	11.11	0.13
hsa-miR-20a-3p	5.87	0.08	6.11	0.35
hsa-miR-20b-5p	7.82	0.15	7.92	0.39
hsa-miR-20b-3p	5.52	0.49	4.94	0.64
hsa-miR-21-5p	13.79	0.36	13.51	0.61
hsa-miR-21-3p	7.44	0.22	7.51	0.24
hsa-miR-210	6.01	0.33	5.83	0.37
hsa-miR-211-5p	5.46	0.04	5.28	0.22

hsa-miR-212-3p	6.74	0.53	6.23	1.10
hsa-miR-214-3p	5.51	0.33	5.70	0.71
hsa-miR-214-5p	5.36	0.44	5.72	0.57
hsa-miR-215-5p	6.52	0.24	6.75	0.21
hsa-miR-216a-5p	5.83	0.22	5.20	0.58
hsa-miR-216b-5p	4.99	1.24	5.48	0.40
hsa-miR-217	5.24	0.63	5.82	0.68
hsa-miR-218-5p	5.94	0.32	6.09	0.22
hsa-miR-218-1-3p	5.28	0.53	5.59	0.38
hsa-miR-218-2-3p	4.71	1.38	5.19	0.92
hsa-miR-219-1-3p	5.75	0.39	5.17	0.52
hsa-miR-219-2-3p	5.54	0.42	5.68	0.46
hsa-miR-219-5p	6.17	0.41	5.81	0.43
hsa-miR-22-3p	8.98	0.44	9.06	0.51
hsa-miR-22-5p	5.96	0.19	6.19	0.32
hsa-miR-220a	5.16	0.13	5.71	0.36
hsa-miR-220b	4.93	0.89	5.58	0.72
hsa-miR-220c	6.00	0.21	5.59	0.22
hsa-miR-221-3p	8.62	0.53	8.55	0.72
hsa-miR-221-5p	6.76	0.08	6.42	0.28
hsa-miR-222-3p	7.77	0.37	7.80	0.66
hsa-miR-222-5p	5.53	0.68	5.83	0.60
hsa-miR-223-3p	12.76	0.38	12.64	0.34
hsa-miR-223-5p	6.44	0.70	6.76	0.17
hsa-miR-224-5p	6.11	0.48	6.28	0.30
hsa-miR-23a-3p	10.11	0.49	10.17	0.66
hsa-miR-23a-5p	5.98	0.26	6.56	0.34
hsa-miR-23b-3p	8.58	0.31	8.68	0.24
hsa-miR-23b-5p	6.07	0.43	5.88	0.18
hsa-miR-24-3p	10.88	0.33	10.95	0.38
hsa-miR-24-1-5p	5.72	0.44	5.83	0.29
hsa-miR-24-2-5p	5.34	0.73	4.19	0.68
hsa-miR-25-3p	8.41	0.55	8.60	0.62
hsa-miR-25-5p	5.67	0.32	6.26	0.31
hsa-miR-26a-5p	10.50	0.49	10.59	0.74
hsa-miR-26a-1-3p	5.91	0.46	5.43	0.85
hsa-miR-26a-2-3p	5.34	0.30	5.81	1.05
hsa-miR-26b-5p	11.46	0.16	11.07	0.74
hsa-miR-26b-3p	5.86	0.39	6.41	0.22
hsa-miR-27a-3p	9.85	0.33	9.90	0.49
hsa-miR-27a-5p	5.36	0.43	5.96	0.31
hsa-miR-27b-3p	7.70	0.36	7.70	0.44
hsa-miR-27b-5p	5.30	0.47	5.97	0.26
hsa-miR-28-3p	5.80	0.55	5.11	0.72
hsa-miR-28-5p	7.27	0.10	7.34	0.18
hsa-miR-296-3p	5.59	0.59	4.79	1.15

hsa-miR-296-5p	5.49	0.53	5.80	0.36
hsa-miR-297	5.20	0.54	5.93	0.28
hsa-miR-298	6.12	0.13	5.25	0.91
hsa-miR-299-3p	5.92	0.55	5.32	0.20
hsa-miR-299-5p	5.90	0.29	5.40	0.24
hsa-miR-29a-3p	12.53	0.16	12.55	0.14
hsa-miR-29a-5p	5.52	0.91	5.93	0.14
hsa-miR-29b-3p	9.32	0.36	9.36	0.30
hsa-miR-29b-1-5p	6.42	0.40	6.71	0.22
hsa-miR-29b-2-5p	5.70	0.64	4.77	1.00
hsa-miR-29c-3p	11.76	0.24	11.85	0.23
hsa-miR-29c-5p	5.85	0.25	5.74	0.53
hsa-miR-300	5.98	0.56	5.05	0.34
hsa-miR-301a-3p	6.86	0.46	6.61	0.34
hsa-miR-301b-3p	6.20	0.60	6.00	0.62
hsa-miR-302a-3p	5.89	0.35	6.01	0.28
hsa-miR-302a-5p	5.81	0.34	6.27	0.30
hsa-miR-302b-3p	5.67	0.60	5.44	0.79
hsa-miR-302b-5p	5.79	0.26	6.13	0.47
hsa-miR-302c-3p	5.26	0.47	5.08	0.32
hsa-miR-302c-5p	5.29	0.22	5.59	0.55
hsa-miR-302d-3p	5.86	0.40	6.11	0.49
hsa-miR-302d-5p	5.77	0.45	5.22	0.19
hsa-miR-302e	5.99	0.42	5.18	0.08
hsa-miR-302f	5.84	0.50	5.57	0.74
hsa-miR-30a-5p	6.06	0.37	6.01	0.38
hsa-miR-30a-3p	5.77	0.34	5.96	0.38
hsa-miR-30b-5p	11.32	0.23	11.14	0.23
hsa-miR-30b-3p	5.61	0.06	6.16	0.05
hsa-miR-30c-5p	8.18	0.66	8.29	0.69
hsa-miR-30c-1-3p	5.71	0.45	5.31	0.86
hsa-miR-30c-2-3p	6.00	0.33	5.63	0.82
hsa-miR-30d-5p	8.91	0.27	8.58	0.36
hsa-miR-30d-3p	5.07	1.12	5.93	0.41
hsa-miR-30e-5p	8.79	0.46	8.88	0.58
hsa-miR-30e-3p	7.45	0.19	7.53	0.26
hsa-miR-31-5p	6.96	0.33	7.07	0.26
hsa-miR-31-3p	6.00	0.08	5.70	0.48
hsa-miR-32-5p	5.26	0.23	5.38	0.41
hsa-miR-32-3p	6.03	0.43	6.37	0.22
hsa-miR-320a	7.18	0.25	7.26	0.29
hsa-miR-320b	7.78	0.04	7.54	0.48
hsa-miR-320c	6.99	0.14	6.93	0.22
hsa-miR-320d	9.88	0.12	9.98	0.08
hsa-miR-323a-3p	5.87	0.42	5.62	0.28
hsa-miR-323a-5p	5.67	0.24	5.98	0.57

hsa-miR-324-3p	9.01	0.24	9.08	0.42
hsa-miR-324-5p	6.98	0.25	6.82	0.44
hsa-miR-325	5.30	0.33	5.69	0.58
hsa-miR-326	5.63	0.77	6.02	0.67
hsa-miR-328-3p	5.03	0.39	5.49	0.36
hsa-miR-329-3p	5.98	0.30	5.83	0.46
hsa-miR-330-3p	6.09	0.36	5.91	0.42
hsa-miR-330-5p	5.83	0.31	5.37	0.37
hsa-miR-331-3p	8.92	0.26	8.95	0.08
hsa-miR-331-5p	5.39	0.22	4.94	1.47
hsa-miR-335-5p	7.03	0.31	6.90	0.09
hsa-miR-335-3p	5.72	0.56	5.33	0.15
hsa-miR-337-3p	5.94	0.31	6.08	0.42
hsa-miR-337-5p	5.66	0.57	6.21	0.37
hsa-miR-338-3p	6.56	0.35	6.68	0.34
hsa-miR-338-5p	6.72	1.07	6.51	1.25
hsa-miR-339-3p	4.24	0.52	5.42	0.37
hsa-miR-339-5p	5.67	0.23	5.09	0.94
hsa-miR-33a-5p	6.21	0.31	5.85	0.37
hsa-miR-33a-3p	4.83	0.53	4.23	1.11
hsa-miR-33b-5p	5.63	0.40	5.97	0.40
hsa-miR-33b-3p	5.55	0.93	5.98	0.63
hsa-miR-340-5p	7.66	0.29	7.72	0.31
hsa-miR-340-3p	6.99	0.24	6.66	0.45
hsa-miR-342-3p	11.99	0.19	12.08	0.14
hsa-miR-342-5p	8.89	0.12	8.97	0.27
hsa-miR-345-5p	5.98	0.56	5.28	0.34
hsa-miR-346	5.43	0.09	4.92	1.26
hsa-miR-34a-5p	6.28	0.31	5.95	0.55
hsa-miR-34a-3p	5.69	0.15	5.42	0.34
hsa-miR-34b-3p	5.48	0.26	5.66	0.28
hsa-miR-34b-5p	5.98	0.21	6.19	0.39
hsa-miR-34c-3p	5.27	0.37	4.55	0.77
hsa-miR-34c-5p	6.19	0.41	5.84	0.22
hsa-miR-361-3p	8.30	0.35	8.22	0.28
hsa-miR-361-5p	8.26	0.39	8.36	0.46
hsa-miR-362-3p	6.99	0.38	6.82	0.57
hsa-miR-362-5p	6.50	0.29	6.01	0.22
hsa-miR-363-3p	8.08	0.37	8.22	0.49
hsa-miR-363-5p	4.55	0.99	5.70	0.09
hsa-miR-365-3p	7.14	0.12	7.05	0.25
hsa-miR-367-3p	6.08	0.27	5.35	1.21
hsa-miR-367-5p	5.56	0.62	6.04	0.42
hsa-miR-369-3p	6.25	0.32	5.65	0.39
hsa-miR-369-5p	5.83	0.16	6.03	0.12
hsa-miR-370-3p	5.67	0.45	5.88	0.31

hsa-miR-371a-3p	5.32	0.78	5.71	0.50
hsa-miR-371a-5p	6.23	0.47	6.40	0.46
hsa-miR-372-3p	5.65	0.44	5.45	0.22
hsa-miR-373-3p	5.85	0.30	5.73	0.23
hsa-miR-373-5p	5.57	0.36	5.64	0.63
hsa-miR-374a-5p	9.29	0.33	9.27	0.42
hsa-miR-374a-3p	5.99	0.52	5.31	0.62
hsa-miR-374b-5p	8.39	0.14	8.20	0.28
hsa-miR-374b-3p	6.20	0.37	5.94	0.34
hsa-miR-375	5.14	0.26	5.45	0.35
hsa-miR-376a-3p	6.11	0.36	6.21	0.23
hsa-miR-376a-5p	6.02	0.24	6.24	0.39
hsa-miR-376b-3p	5.58	0.47	5.71	0.78
hsa-miR-376c-3p	7.10	0.30	6.82	0.38
hsa-miR-377-3p	6.90	0.31	6.83	0.27
hsa-miR-377-5p	5.64	0.49	4.87	0.84
hsa-miR-378a-3p	7.35	0.16	7.29	0.18
hsa-miR-378a-5p	5.90	0.27	6.25	0.39
hsa-miR-379-5p	5.89	0.45	5.65	0.19
hsa-miR-379-3p	5.84	0.17	5.41	0.54
hsa-miR-380-3p	5.85	0.32	5.97	0.44
hsa-miR-380-5p	5.74	0.40	5.10	0.76
hsa-miR-381-3p	6.16	0.46	5.69	0.46
hsa-miR-382-5p	5.55	0.21	5.86	0.56
hsa-miR-383-5p	5.70	0.69	5.99	0.39
hsa-miR-384	5.97	0.15	5.95	0.18
hsa-miR-409-3p	6.20	0.32	6.13	0.48
hsa-miR-409-5p	5.90	0.72	5.46	1.38
hsa-miR-410-3p	6.11	0.50	5.87	0.34
hsa-miR-411-5p	5.84	0.42	5.47	0.30
hsa-miR-411-3p	5.05	0.45	5.88	0.42
hsa-miR-412-3p	6.10	0.51	5.38	0.64
hsa-miR-421	5.98	0.40	6.23	0.16
hsa-miR-422a	6.11	0.29	5.51	0.80
hsa-miR-423-3p	6.39	0.27	6.72	0.33
hsa-miR-423-5p	6.66	0.14	6.59	0.20
hsa-miR-424-5p	7.17	0.28	7.10	0.19
hsa-miR-424-3p	5.68	0.44	5.83	0.48
hsa-miR-425-5p	9.36	0.26	9.40	0.26
hsa-miR-425-3p	6.06	0.34	6.15	0.12
hsa-miR-429	5.74	0.18	6.03	0.19
hsa-miR-431-5p	6.32	0.23	6.00	0.33
hsa-miR-431-3p	6.17	0.22	5.58	0.50
hsa-miR-432-5p	6.12	0.22	6.37	0.16
hsa-miR-432-3p	5.00	1.10	4.36	0.27
hsa-miR-433-3p	6.01	0.34	5.77	0.28

hsa-miR-448	5.48	0.61	5.10	0.87
hsa-miR-449a	6.12	0.19	6.20	0.20
hsa-miR-449b-5p	5.40	0.92	6.00	0.60
hsa-miR-450a-5p	6.16	0.17	5.59	0.43
hsa-miR-450b-3p	5.39	0.44	5.93	0.37
hsa-miR-450b-5p	5.46	0.38	6.03	0.61
hsa-miR-451a	9.03	1.16	8.73	0.84
hsa-miR-452-5p	5.94	0.22	5.63	0.58
hsa-miR-452-3p	5.89	0.58	5.56	0.57
hsa-miR-453	5.07	0.65	5.55	0.43
hsa-miR-454-3p	5.97	0.42	6.33	0.28
hsa-miR-454-5p	5.09	0.98	5.66	0.50
hsa-miR-455-3p	5.54	0.41	5.47	0.80
hsa-miR-455-5p	5.63	0.40	5.34	0.64
hsa-miR-483-3p	5.31	0.38	4.88	0.58
hsa-miR-483-5p	6.82	0.52	6.30	0.14
hsa-miR-484	7.36	0.17	7.37	0.43
hsa-miR-485-3p	6.15	0.15	5.76	0.15
hsa-miR-485-5p	5.63	0.62	5.86	0.23
hsa-miR-486-3p	5.84	0.42	5.32	0.78
hsa-miR-486-5p	6.86	0.16	6.66	0.23
hsa-miR-487a-3p	5.91	0.27	5.54	0.32
hsa-miR-487b-3p	6.54	0.46	6.67	0.43
hsa-miR-488-3p	5.69	0.24	6.16	0.39
hsa-miR-488-5p	5.47	0.15	5.32	0.42
hsa-miR-489-3p	5.74	0.22	5.58	0.42
hsa-miR-490-3p	5.33	0.72	5.50	0.25
hsa-miR-490-5p	5.19	0.66	5.63	0.49
hsa-miR-491-3p	6.04	0.48	5.19	0.64
hsa-miR-491-5p	5.94	0.31	5.35	0.32
hsa-miR-492	5.81	0.55	5.94	0.73
hsa-miR-493-3p	5.58	0.08	5.09	0.65
hsa-miR-493-5p	6.14	0.57	6.28	0.23
hsa-miR-494-3p	9.27	1.28	8.71	0.95
hsa-miR-495-3p	5.65	0.28	6.39	0.25
hsa-miR-496	4.91	0.76	5.40	0.60
hsa-miR-497-5p	5.78	0.20	5.48	0.32
hsa-miR-497-3p	5.52	0.83	6.28	0.12
hsa-miR-498	6.02	0.28	5.85	0.29
hsa-miR-499a-3p	5.54	0.62	4.98	0.94
hsa-miR-499a-5p	5.91	0.21	5.94	0.23
hsa-miR-500a-5p	6.91	0.27	6.47	0.17
hsa-miR-500a-3p	6.18	0.23	5.91	0.38
hsa-miR-501-3p	5.11	0.22	5.68	1.03
hsa-miR-501-5p	6.97	0.14	6.41	0.40
hsa-miR-502-3p	6.59	0.24	6.32	0.28

hsa-miR-502-5p	5.48	0.58	5.87	0.42
hsa-miR-503-5p	5.54	0.67	6.02	0.38
hsa-miR-504-5p	5.86	0.35	5.17	0.87
hsa-miR-505-3p	5.88	0.36	6.17	0.48
hsa-miR-505-5p	5.70	0.44	6.04	0.39
hsa-miR-506-3p	5.94	0.23	5.42	0.90
hsa-miR-507	5.86	0.61	5.65	0.23
hsa-miR-508-3p	5.96	0.11	6.12	0.36
hsa-miR-508-5p	6.04	0.52	5.81	0.34
hsa-miR-509-3-5p	5.56	0.36	5.37	0.64
hsa-miR-509-3p	5.51	0.48	5.76	0.21
hsa-miR-509-5p	5.66	0.42	5.24	0.46
hsa-miR-510-5p	5.50	0.39	5.18	0.97
hsa-miR-511-5p	5.77	0.68	6.25	0.36
hsa-miR-512-3p	5.91	0.37	5.64	0.33
hsa-miR-512-5p	5.69	0.19	5.43	0.64
hsa-miR-513a-3p	6.04	0.18	5.66	0.79
hsa-miR-513a-5p	6.54	0.73	6.13	0.54
hsa-miR-513b-5p	6.54	0.29	5.83	0.59
hsa-miR-513c-5p	6.12	0.37	5.07	0.58
hsa-miR-514-3p	5.88	0.44	5.48	0.52
hsa-miR-515-3p	6.03	0.23	5.83	0.50
hsa-miR-515-5p	5.10	1.25	5.75	0.51
hsa-miR-516a-3p	5.54	0.29	6.13	0.35
hsa-miR-516a-5p	5.44	0.25	5.94	0.38
hsa-miR-516b-5p	5.88	0.11	6.08	0.18
hsa-miR-517-5p	5.76	0.25	5.47	0.53
hsa-miR-517a-3p	5.90	0.43	5.53	0.11
hsa-miR-517b-3p	5.58	0.48	5.92	0.35
hsa-miR-517c-3p	5.60	0.36	5.80	0.39
hsa-miR-518a-3p	5.63	0.09	5.34	0.65
hsa-miR-518a-5p	5.73	0.49	5.59	0.38
hsa-miR-518b	5.26	0.41	5.77	0.41
hsa-miR-518c-3p	5.37	0.31	5.96	0.36
hsa-miR-518c-5p	6.08	0.23	5.67	0.31
hsa-miR-518d-3p	5.17	0.49	5.36	0.26
hsa-miR-518e-3p	5.39	0.25	5.64	0.26
hsa-miR-518e-5p	5.85	0.44	6.18	0.27
hsa-miR-518f-3p	5.47	0.65	5.68	0.47
hsa-miR-518f-5p	5.91	0.36	5.84	0.44
hsa-miR-519b-3p	6.13	0.29	5.67	0.35
hsa-miR-519c-3p	6.32	0.45	5.89	0.53
hsa-miR-519d-3p	5.28	0.08	5.92	0.58
hsa-miR-519e-3p	5.43	0.33	6.00	0.29
hsa-miR-519e-5p	6.04	0.21	5.60	0.24
hsa-miR-520a-3p	5.78	0.50	5.95	0.41

hsa-miR-520a-5p	5.61	0.29	5.66	0.46
hsa-miR-520b	6.13	0.09	5.74	0.38
hsa-miR-520c-3p	5.96	0.23	6.07	0.43
hsa-miR-520d-3p	5.75	0.56	6.06	0.55
hsa-miR-520e	5.42	0.42	5.71	0.19
hsa-miR-520f-3p	5.90	0.55	6.04	0.19
hsa-miR-520g-3p	5.58	0.25	6.07	0.15
hsa-miR-520h	6.21	0.19	5.83	0.23
hsa-miR-521	5.60	0.43	5.82	0.26
hsa-miR-522-3p	6.16	0.20	5.93	0.23
hsa-miR-523-3p	5.81	0.44	4.99	0.49
hsa-miR-524-3p	5.75	0.37	5.37	0.47
hsa-miR-525-3p	5.24	0.43	5.57	0.82
hsa-miR-525-5p	5.63	0.61	6.09	0.09
hsa-miR-526b-5p	5.79	0.52	5.90	0.42
hsa-miR-526b-3p	5.63	0.29	5.87	0.22
hsa-miR-532-3p	5.81	0.41	5.73	0.61
hsa-miR-532-5p	6.42	0.27	6.50	0.27
hsa-miR-539-5p	5.77	0.19	6.15	0.24
hsa-miR-541-3p	5.92	0.16	5.44	0.88
hsa-miR-541-5p	5.70	0.41	5.30	0.50
hsa-miR-542-3p	6.01	0.82	6.47	0.25
hsa-miR-542-5p	6.32	0.20	6.22	0.23
hsa-miR-543	5.89	0.31	5.98	0.56
hsa-miR-544a	5.36	0.50	5.60	0.66
hsa-miR-545-3p	5.43	0.49	6.03	0.08
hsa-miR-545-5p	6.51	0.39	6.02	0.59
hsa-miR-548a-3p	5.55	0.57	5.78	0.71
hsa-miR-548a-5p	5.88	0.67	6.24	0.29
hsa-miR-548b-3p	6.06	0.54	5.73	0.89
hsa-miR-548b-5p	6.47	0.11	6.00	0.20
hsa-miR-548c-3p	5.88	0.86	5.08	1.20
hsa-miR-548c-5p	6.36	0.22	5.99	0.75
hsa-miR-548d-3p	5.69	0.42	5.12	0.97
hsa-miR-548d-5p	6.30	0.17	6.11	0.35
hsa-miR-548e-3p	5.90	0.39	5.97	0.27
hsa-miR-548f-3p	5.78	0.26	5.81	0.41
hsa-miR-548g-3p	5.73	0.49	5.63	0.64
hsa-miR-548h-5p	5.33	0.78	4.87	0.42
hsa-miR-548i	5.70	0.32	6.11	0.31
hsa-miR-548j-5p	5.76	0.44	6.07	0.61
hsa-miR-548k	5.19	0.42	5.35	0.31
hsa-miR-548l	5.60	0.22	5.87	0.25
hsa-miR-548m	6.11	0.17	5.94	0.33
hsa-miR-548n	6.03	0.32	6.20	0.44
hsa-miR-548o-3p	5.46	0.45	5.90	0.32

hsa-miR-548p	6.00	0.56	5.87	0.20
hsa-miR-549a	5.28	0.64	5.96	0.41
hsa-miR-550-5p	5.48	0.45	5.75	0.65
hsa-miR-550-3p	5.89	0.43	5.15	0.65
hsa-miR-551a	5.13	0.75	5.80	0.81
hsa-miR-551b-3p	6.47	0.10	5.92	0.65
hsa-miR-551b-5p	5.20	1.24	5.88	0.32
hsa-miR-552-3p	5.85	0.36	5.42	0.48
hsa-miR-553	6.17	0.39	6.00	0.40
hsa-miR-554	5.48	0.60	5.00	0.68
hsa-miR-555	5.62	0.21	4.55	0.68
hsa-miR-556-3p	5.09	0.62	5.78	0.56
hsa-miR-556-5p	5.44	0.93	6.00	0.40
hsa-miR-557	6.33	0.21	5.89	0.12
hsa-miR-558	5.57	0.27	5.91	0.49
hsa-miR-559	5.82	0.51	5.15	0.39
hsa-miR-561-3p	5.74	0.69	5.95	0.45
hsa-miR-562	5.41	0.42	6.16	0.42
hsa-miR-563	4.89	1.15	5.74	0.30
hsa-miR-564	6.76	0.14	6.38	0.29
hsa-miR-566	5.80	0.44	5.02	0.50
hsa-miR-567	5.72	0.30	5.33	0.39
hsa-miR-568	6.18	0.30	5.95	0.44
hsa-miR-569	6.12	0.43	5.55	0.70
hsa-miR-570-3p	5.99	0.32	5.06	1.09
hsa-miR-571	5.68	0.37	5.60	0.26
hsa-miR-572	5.68	0.88	6.32	0.14
hsa-miR-573	5.55	0.45	4.58	1.48
hsa-miR-574-3p	6.82	0.21	6.68	0.22
hsa-miR-574-5p	6.94	0.18	6.58	0.29
hsa-miR-575	7.48	0.33	7.58	0.23
hsa-miR-576-3p	5.68	0.64	6.12	0.18
hsa-miR-576-5p	5.72	0.15	6.22	0.40
hsa-miR-577	6.12	0.07	5.67	0.64
hsa-miR-578	5.64	0.42	5.30	0.51
hsa-miR-579-3p	5.83	0.49	6.30	0.11
hsa-miR-580-3p	5.67	1.05	5.50	0.62
hsa-miR-581	5.05	1.55	5.81	0.52
hsa-miR-582-3p	5.52	0.42	5.67	0.21
hsa-miR-582-5p	6.99	0.20	6.70	0.32
hsa-miR-583	5.88	0.37	5.50	0.46
hsa-miR-584-5p	6.15	0.34	5.90	0.48
hsa-miR-585-3p	5.87	0.63	6.06	0.47
hsa-miR-586	5.47	0.82	5.98	0.41
hsa-miR-587	5.76	0.36	4.92	1.16
hsa-miR-588	5.16	0.71	5.90	0.40

hsa-miR-589-5p	5.46	0.36	5.95	0.60
hsa-miR-589-3p	4.84	0.86	5.65	0.45
hsa-miR-590-3p	6.68	0.13	6.16	0.72
hsa-miR-590-5p	7.42	0.16	7.47	0.10
hsa-miR-591	5.27	0.58	5.64	0.46
hsa-miR-592	6.06	0.35	5.52	0.80
hsa-miR-593-3p	5.38	0.49	5.95	0.39
hsa-miR-593-5p	4.88	1.05	5.81	0.06
hsa-miR-595	5.59	0.26	6.19	0.48
hsa-miR-596	5.39	0.73	5.00	0.42
hsa-miR-597-5p	5.25	0.14	5.64	0.08
hsa-miR-598-3p	5.80	0.22	5.65	0.51
hsa-miR-599	5.39	0.48	6.02	0.26
hsa-miR-600	5.96	0.44	5.36	0.55
hsa-miR-601	6.56	0.32	6.08	0.14
hsa-miR-602	5.85	0.29	5.72	0.42
hsa-miR-603	5.74	0.29	6.22	0.33
hsa-miR-604	5.69	0.57	5.77	0.48
hsa-miR-605-5p	5.29	0.54	5.56	0.43
hsa-miR-606	5.96	0.40	5.24	1.23
hsa-miR-607	5.33	0.79	5.73	0.49
hsa-miR-608	5.38	0.21	5.53	0.11
hsa-miR-609	5.48	0.81	6.11	0.41
hsa-miR-610	5.23	1.02	5.76	0.42
hsa-miR-611	5.12	0.30	5.43	0.25
hsa-miR-612	5.82	0.24	5.19	1.35
hsa-miR-613	6.27	0.31	5.22	0.36
hsa-miR-614	5.92	0.47	6.05	0.53
hsa-miR-615-3p	5.43	0.26	5.66	0.39
hsa-miR-615-5p	5.76	0.28	4.96	0.64
hsa-miR-616-3p	5.12	1.13	6.07	0.44
hsa-miR-616-5p	5.86	0.62	5.38	0.99
hsa-miR-617	5.40	0.42	4.93	1.25
hsa-miR-618	5.76	0.69	5.52	0.15
hsa-miR-619-3p	5.71	0.86	5.96	0.11
hsa-miR-620	6.02	0.14	5.73	0.15
hsa-miR-621	5.34	0.53	4.38	0.84
hsa-miR-622	5.95	0.44	6.34	0.48
hsa-miR-623	6.10	0.53	5.86	0.13
hsa-miR-624-3p	5.31	0.45	5.63	0.91
hsa-miR-624-5p	5.43	0.33	5.88	0.56
hsa-miR-625-5p	7.52	0.10	7.67	0.22
hsa-miR-625-3p	5.47	0.70	6.00	0.34
hsa-miR-626	5.68	0.48	6.10	0.30
hsa-miR-627-5p	6.12	0.56	6.52	0.07
hsa-miR-628-3p	6.05	0.38	5.40	0.85

hsa-miR-628-5p	5.80	0.50	6.21	0.45
hsa-miR-629-5p	5.89	0.64	5.42	0.52
hsa-miR-629-3p	6.08	0.38	5.07	0.39
hsa-miR-630	5.79	0.55	5.85	0.31
hsa-miR-631	5.63	0.30	5.13	0.41
hsa-miR-632	5.12	0.94	5.85	0.49
hsa-miR-633	6.22	0.21	5.29	0.12
hsa-miR-634	5.79	0.13	4.99	0.54
hsa-miR-635	6.18	0.02	5.22	0.50
hsa-miR-636	5.24	0.31	5.64	0.45
hsa-miR-637	5.61	0.56	4.83	0.56
hsa-miR-638	7.98	0.71	7.42	0.31
hsa-miR-639	5.93	0.49	5.51	0.25
hsa-miR-640	5.91	0.28	5.43	0.49
hsa-miR-641	5.52	0.43	5.18	0.58
hsa-miR-642a-5p	5.97	0.45	5.65	0.38
hsa-miR-643	5.22	0.68	5.83	0.15
hsa-miR-644	4.65	1.25	4.99	1.03
hsa-miR-645	5.64	0.61	5.27	0.61
hsa-miR-646	5.83	0.55	5.05	0.41
hsa-miR-647	4.56	0.09	5.34	0.54
hsa-miR-648	4.78	0.94	5.33	0.53
hsa-miR-649	5.10	0.95	5.95	0.31
hsa-miR-650	5.53	0.49	5.78	0.48
hsa-miR-651-5p	5.87	0.40	6.16	0.26
hsa-miR-652-3p	6.17	0.21	6.00	0.38
hsa-miR-653-5p	4.93	0.84	6.05	0.38
hsa-miR-654-3p	6.17	0.33	6.31	0.54
hsa-miR-654-5p	5.27	0.59	5.91	0.23
hsa-miR-655-3p	5.59	0.56	6.24	0.29
hsa-miR-656-3p	5.67	0.34	6.11	0.24
hsa-miR-657	5.26	0.68	5.74	0.52
hsa-miR-658	5.72	0.15	5.45	0.74
hsa-miR-659-3p	6.02	0.43	5.29	0.81
hsa-miR-660-5p	7.79	0.24	7.82	0.36
hsa-miR-661	5.69	0.41	5.17	0.44
hsa-miR-662	6.05	0.27	5.38	0.42
hsa-miR-663a	5.44	0.50	5.17	0.68
hsa-miR-663b	5.21	0.30	5.45	0.47
hsa-miR-664-3p	6.95	0.26	6.85	0.44
hsa-miR-664-5p	5.91	0.25	6.17	0.26
hsa-miR-665	5.32	0.30	5.90	0.55
hsa-miR-668-3p	5.19	0.69	4.90	0.56
hsa-miR-671-3p	5.22	0.47	5.75	0.53
hsa-miR-671-5p	6.33	0.23	5.63	0.26
hsa-miR-675-5p	5.05	0.21	5.53	0.91

hsa-miR-675-3p	5.61	0.26	5.25	0.25
hsa-miR-7-5p	7.27	0.26	7.42	0.30
hsa-miR-708-5p	5.56	0.67	5.97	0.61
hsa-miR-708-3p	5.79	0.34	5.43	0.29
hsa-miR-7-1-3p	6.68	0.19	6.61	0.27
hsa-miR-7-2-3p	5.05	0.70	5.91	0.54
hsa-miR-720	14.52	0.67	14.30	0.26
hsa-miR-744-5p	6.39	0.38	6.00	0.39
hsa-miR-744-3p	5.30	0.56	4.83	0.66
hsa-miR-758-3p	6.04	0.47	5.38	0.45
hsa-miR-760	5.82	0.40	6.16	0.52
hsa-miR-765	6.23	0.47	5.92	0.20
hsa-miR-766-3p	5.85	0.67	5.05	1.21
hsa-miR-767-3p	5.09	0.51	5.47	0.43
hsa-miR-767-5p	5.70	0.36	6.07	0.44
hsa-miR-769-3p	5.99	0.38	5.52	0.40
hsa-miR-769-5p	6.80	0.10	6.40	0.24
hsa-miR-770-5p	6.02	0.57	5.52	0.64
hsa-miR-802	5.23	0.42	5.91	0.51
hsa-miR-873-5p	5.90	0.46	5.69	0.40
hsa-miR-874-3p	6.94	0.29	6.65	0.14
hsa-miR-875-3p	5.81	0.77	4.84	0.79
hsa-miR-875-5p	5.58	0.10	6.53	0.14
hsa-miR-876-3p	5.62	0.97	5.96	0.57
hsa-miR-876-5p	5.58	0.64	5.93	0.26
hsa-miR-877-5p	6.03	0.21	5.08	0.66
hsa-miR-877-3p	5.69	0.91	5.99	0.31
hsa-miR-885-3p	4.92	1.28	6.09	0.47
hsa-miR-885-5p	5.31	0.23	5.68	0.46
hsa-miR-886-3p	5.66	0.14	6.08	0.21
hsa-miR-886-5p	5.49	0.19	6.15	0.46
hsa-miR-887-3p	5.66	0.34	4.78	0.94
hsa-miR-888-5p	5.29	0.79	5.65	0.30
hsa-miR-888-3p	6.12	0.12	5.29	0.46
hsa-miR-889-3p	6.05	0.52	5.53	0.74
hsa-miR-890	5.41	0.50	5.19	0.38
hsa-miR-891a-5p	5.50	0.16	5.35	0.91
hsa-miR-891b	5.47	0.32	5.30	0.49
hsa-miR-892a	5.77	0.08	6.02	0.28
hsa-miR-892b	7.22	0.54	7.47	0.44
hsa-miR-9-5p	5.84	0.39	6.03	0.29
hsa-miR-9-3p	5.75	0.26	6.10	0.32
hsa-miR-920	5.66	0.55	5.43	0.28
hsa-miR-921	5.82	0.42	5.11	0.51
hsa-miR-922	5.45	0.54	5.93	0.44
hsa-miR-923	11.31	1.32	10.94	1.56

hsa-miR-924	5.69	0.90	5.95	0.37
hsa-miR-92a-3p	10.15	0.22	10.24	0.49
hsa-miR-92a-1-5p	5.60	0.31	6.22	0.22
hsa-miR-92a-2-5p	5.44	0.83	5.82	0.52
hsa-miR-92b-3p	5.12	0.70	5.58	0.13
hsa-miR-92b-5p	5.73	0.34	5.34	0.13
hsa-miR-93-5p	9.77	0.26	9.84	0.40
hsa-miR-93-3p	5.06	0.68	5.43	0.72
hsa-miR-933	5.24	0.79	5.66	0.40
hsa-miR-934	5.08	0.33	5.48	0.47
hsa-miR-935	4.67	0.85	4.82	0.80
hsa-miR-936	5.90	0.43	6.07	0.24
hsa-miR-937-3p	4.53	1.22	5.13	0.41
hsa-miR-938	5.24	0.79	6.29	0.29
hsa-miR-939-5p	7.75	0.48	7.61	0.35
hsa-miR-940	8.10	0.38	7.97	0.38
hsa-miR-941	5.06	0.75	5.86	0.53
hsa-miR-942-5p	5.41	0.24	5.03	0.93
hsa-miR-943	5.48	0.74	5.79	0.64
hsa-miR-944	5.98	0.63	5.59	0.35
hsa-miR-95-3p	6.07	0.49	6.29	0.20
hsa-miR-96-5p	5.91	0.45	5.63	0.20
hsa-miR-96-3p	5.48	0.66	5.66	0.45
hsa-miR-98-5p	7.96	0.29	7.79	0.27
hsa-miR-99a-5p	6.69	0.26	6.50	0.67
hsa-miR-99a-3p	5.56	1.16	5.87	0.46
hsa-miR-99b-5p	5.97	0.28	5.82	0.32
hsa-miR-99b-3p	6.15	0.49	5.49	0.49

SD, standard deviation (*n* = 4).

Table S2. Differentially affected miRNAs in PBMCs of healthy volunteers at fasting and after the ingestion of a standardized high-saturated fat meal.

hsa-miRNA	At fasting (F)		At postprandial (P)		P *vs* F		
	Signal intensity	SD	Signal intensity	SD	Fold change	SD	*p*-value
Downregulation							
let-7i-3p	5.96	0.53	5.21	0.79	-0.20	0.25	0.036
miR-24-2-5p	5.34	0.73	4.19	0.68	-0.35	0.31	0.049
miR-136-3p	6.13	0.32	5.62	0.30	-0.13	0.11	0.049
miR-148a-5p	5.69	0.56	4.76	0.54	-0.26	0.21	0.006
miR-298	6.12	0.13	5.25	0.91	-0.24	0.28	0.049
miR-299-3p	5.92	0.55	5.32	0.20	-0.15	0.15	0.047
miR-300	5.98	0.56	5.05	0.34	-0.24	0.17	0.006
miR-302e	5.99	0.42	5.18	0.08	-0.21	0.10	0.041
miR-369-3p	6.25	0.32	5.65	0.39	-0.15	0.12	0.048
miR-491-3p	6.04	0.48	5.19	0.64	-0.23	0.21	0.025
miR-513c-5p	6.12	0.37	5.07	0.58	-0.28	0.19	0.029
miR-523-3p	5.81	0.44	4.99	0.49	-0.22	0.18	0.016
miR-550-3p	5.89	0.43	5.15	0.65	-0.20	0.21	0.041
miR-555	5.62	0.21	4.55	0.68	-0.32	0.21	0.003
miR-566	5.80	0.44	5.02	0.50	-0.21	0.19	0.006
miR-570-3p	5.99	0.32	5.06	1.09	-0.27	0.34	0.030
miR-613	6.27	0.31	5.22	0.36	-0.26	0.12	0.046
miR-615-5p	5.76	0.28	4.96	0.64	-0.22	0.20	0.035
miR-621	5.34	0.53	4.38	0.84	-0.30	0.33	0.033
miR-629-3p	6.08	0.38	5.07	0.39	-0.26	0.15	0.020
miR-633	6.22	0.21	5.29	0.12	-0.23	0.06	0.039
miR-634	5.79	0.13	4.99	0.54	-0.22	0.16	0.011
miR-635	6.18	0.02	5.22	0.50	-0.25	0.14	0.023
miR-646	5.83	0.55	5.05	0.41	-0.21	0.18	0.006
miR-659-3p	6.02	0.43	5.29	0.81	-0.20	0.25	0.028
miR-662	6.05	0.27	5.38	0.42	-0.17	0.13	0.041
miR-671-5p	6.33	0.23	5.63	0.26	-0.17	0.09	0.030
miR-875-3p	5.81	0.77	4.84	0.79	-0.27	0.31	0.015
miR-877-5p	6.03	0.21	5.08	0.66	-0.25	0.19	0.027
miR-887-3p	5.66	0.34	4.78	0.94	-0.27	0.33	0.035
miR-888-3p	6.12	0.12	5.29	0.46	-0.21	0.13	0.036
miR-921	5.82	0.42	5.11	0.51	-0.19	0.18	0.022
miR-1224-5p	6.50	0.54	5.86	0.12	-0.15	0.12	0.018
miR-1226-3p	5.47	0.66	4.48	1.05	-0.31	0.39	0.023
miR-1229-3p	5.32	0.55	4.49	0.63	-0.25	0.25	0.048

Upregulation							
miR-7-2-3p	5.05	0.70	5.91	0.54	0.23	0.24	0.037
miR-18a-3p	5.46	0.88	6.20	0.12	0.20	0.25	0.03
miR-19b-1-5p	4.19	0.43	5.22	0.20	0.32	0.16	0.049
miR-25-5p	5.67	0.32	6.26	0.31	0.15	0.11	0.036
miR-26b-3p	5.86	0.39	6.41	0.22	0.13	0.11	0.002
miR-30b-3p	5.61	0.06	6.16	0.05	0.13	0.02	0.049
miR-30d-3p	5.07	1.12	5.93	0.41	0.25	0.36	0.044
miR-129-5p	5.37	0.45	6.04	0.40	0.17	0.15	0.020
miR-138-1-3p	4.52	0.17	5.26	0.60	0.21	0.18	0.044
miR-138-2-3p	5.58	0.79	6.20	0.21	0.16	0.21	0.010
miR-143-3p	5.43	0.31	6.05	0.20	0.16	0.09	0.025
miR-1468-5p	5.06	0.32	5.69	0.23	0.17	0.11	0.047
miR-146a-3p	5.30	0.48	6.13	0.33	0.21	0.15	0.014
miR-148b-5p	4.74	1.14	5.89	0.27	0.35	0.40	0.002
miR-181a-2-3p	5.93	0.48	6.62	0.11	0.16	0.12	0.046
miR-181c-3p	5.08	0.16	5.78	0.43	0.18	0.12	0.029
miR-200b-5p	4.86	0.45	5.83	0.61	0.26	0.20	0.029
miR-297	5.20	0.54	5.93	0.28	0.20	0.17	0.038
miR-339-3p	4.24	0.52	5.42	0.37	0.36	0.21	0.027
miR-363-5p	4.55	0.99	5.70	0.09	0.35	0.32	0.013
miR-411-3p	5.05	0.45	5.88	0.42	0.22	0.16	0.048
miR-491-5p	5.35	0.32	5.94	0.31	0.15	0.11	0.038
miR-495-3p	5.65	0.28	6.39	0.25	0.18	0.09	0.047
miR-518c-3p	5.37	0.31	5.96	0.36	0.15	0.12	0.006
miR-519d-3p	5.28	0.08	5.92	0.58	0.16	0.14	0.021
miR-519e-3p	5.43	0.33	6.00	0.29	0.14	0.11	0.026
miR-562	5.41	0.42	6.16	0.42	0.19	0.15	0.012
miR-588	5.16	0.71	5.90	0.40	0.20	0.23	0.039
miR-593-5p	4.88	1.05	5.81	0.06	0.28	0.33	0.012
miR-599	5.39	0.48	6.02	0.26	0.16	0.14	0.037
miR-616-3p	5.12	1.13	6.07	0.44	0.27	0.36	0.023
miR-632	5.12	0.94	5.85	0.49	0.21	0.31	0.030
miR-647	4.56	0.09	5.34	0.54	0.22	0.15	0.013
miR-649	5.10	0.95	5.95	0.31	0.24	0.28	0.010
miR-653-5p	4.93	0.84	6.05	0.38	0.31	0.27	0.023
miR-665	5.32	0.30	5.90	0.55	0.15	0.16	0.006
miR-802	5.23	0.42	5.91	0.51	0.18	0.17	0.010
miR-875-5p	5.58	0.10	6.53	0.14	0.23	0.04	0.002
miR-885-3p	4.92	1.28	6.09	0.47	0.35	0.45	0.038
miR-886-5p	5.49	0.19	6.15	0.46	0.16	0.12	0.018
miR-938	5.24	0.79	6.29	0.29	0.27	0.23	0.041
miR-941	5.06	0.75	5.86	0.53	0.22	0.26	0.034
miR-1185-5p	5.52	0.25	6.01	0.23	0.12	0.08	0.028
miR-1237-3p	5.12	0.31	5.90	0.30	0.21	0.12	0.018
miR-1286	5.07	0.76	5.86	0.58	0.22	0.27	0.035

SD, standard deviation (*n* = 4). Downregulated miRNAs are depicted in green colour, while upregulated miRNAs in orange colour.

Table S3. Number of target genes for differentially affected miRNAs in PBMCs of healthy volunteers at fasting and after the ingestion of a standardized high-saturated fat meal.

hsa-miRNA	Putative target gene number	hsa-miRNA	Putative target gene number
Downregulation		Upregulation	
let-7i-3p	7	miR-1185-5p	108
miR-1224-5p	271	miR-1237	741
miR-1226-3p	479	miR-1286	334
miR-1229	216	miR-129-5p	1605
miR-136-3p	106	miR-138-1-3p	167
miR-148a-5p	567	miR-138-2-3p	398
miR-24-2-5p	111	miR-143-3p	531
miR-298	361	miR-1468	23
miR-299-3p	253	miR-146a-3p	539
miR-300	1293	miR-148b-5p	427
miR-302e	626	miR-181a-2-3p	220
miR-369-3p	1195	miR-181c-3p	4
miR-491-3p	179	miR-18a-3p	48
miR-491-5p	296	miR-19b-1-5p	156
miR-513c-5p	166	miR-200b-5p	251
miR-523-3p	2	miR-25-5p	26
miR-550a-3p	214	miR-26b-3p	214
miR-555	64	miR-297	80
miR-566	7	miR-30b-3p	495
miR-570-3p	568	miR-30d-3p	226
miR-613	398	miR-339-3p	27
miR-615-5p	114	miR-363-5p	122
miR-621	61	miR-411-3p	655
miR-629-3p	587	miR-495-3p	2618
miR-633	172	miR-518c-3p	10
miR-634	250	miR-519d-3p	852
miR-635	218	miR-519e-3p	167
miR-646	660	miR-562	376
miR-659-3p	379	miR-588	625
miR-662	62	miR-593-5p	241
miR-671-5p	377	miR-599	174
miR-875-3p	454	miR-616-3p	185
miR-877-5p	142	miR-632	271
miR-887	10	miR-647	434
miR-888-3p	189	miR-649	228
miR-921	60	miR-653	316

miR-665	341
miR-7-2-3p	1448
miR-802	99
miR-875-5p	214
miR-885-3p	107
miR-938	198
miR-941	29

Total affected downregulated and upregulated genes were 11114 and 16330, respectively. Downregulated miRNAs are depicted in green colour, while upregulated miRNAs in orange colour.

Table S4. Overrepresented GO terms by dysregulated miRNAs[a].

Downregulated miRNAs				
Category	Term	Description	FDR	Genes (the five most involved)
BP	GO:0014065	PI3K cascade	0.02640344	IGF1R, ERBB3, ERBB2, NF1, PIK3R1
BP	GO:0048010	VEGF receptor signalling pathway	0.00838648	VEGFC, NRP1, PDGFRA, BMPR2, PDGFRB
BP	GO:0060389	Pathway-restricted SMAD protein phosphorylation	0.01407007	BMP2, SMAD7, GDF6, TGFBR1, TGFBR2
BP	GO:0001569	Patterning of blood vessels	0.00115075	SEMA5A, FLT1, NRP1, CXCR4, TGFBR2
BP	GO:0030509	BMP signalling pathway	2.61E-10	BMP2, NOG, SMAD9, SMAD7, SMAD6
BP	GO:0001952	Regulation of cell-matrix adhesion	4.98E-04	BCL2, CSF1, NF1, SMAD3, CDK6
BP	GO:0018105	Peptidyl-serine phosphorylation	9.20E-04	AKT1, GSK3B, BCL2, NLK, TGFBR1
BP	GO:0008543	Fibroblast growth factor receptor signalling pathway	9.20E-04	FGFR2, FGFR1, FGF5, FGF18, FGF7
BP	GO:0018108	Peptidyl-tyrosine phosphorylation	1.68E-07	FLT1, ERBB4, ERBB3, ERBB2, KIT
BP	GO:0045732	Positive regulation of protein catabolic process	0.00767994	AKT1, CBLB, SMAD7, IFNG, MDM2
BP	GO:0018212	Peptidyl-tyrosine modification	3.04E-07	FLT1, ERBB4, ERBB3, ERBB2, KIT
BP	GO:0045778	Positive regulation of ossification	0.04793414	ACVR2A, BMP2, BMPR2, SMAD3, BMPR1B
BP	GO:0042476	Odontogenesis	1.14E-07	BMP2, ERBB4, ERBB3, CSF1, LEF1
BP	GO:0030199	Collagen fibril organization	0.01290553	TGFBR1, NF1, COL1A2, COL2A1, COL1A1
BP	GO:0030335	Positive regulation of cell migration	7.12E-14	EGFR, FLT1, ERBB4, MAP2K1, PDGFA
BP	GO:0050679	Positive regulation of epithelial cell proliferation	1.22E-04	EGFR, VEGFC, NOG, FGF7, ERBB4
BP	GO:0032388	Positive regulation of intracellular transport	0.01645978	SMO, GSK3B, TGFBR1, RHOA, SMAD4
BP	GO:0051272	Positive regulation of cell motion	4.15E-15	ERBB4, PDGFA, CSF1, RPS6KB1, KIT
BP	GO:0040017	Positive regulation of locomotion	4.15E-15	ERBB4, PDGFA, CSF1, FGF10, RPS6KB1
BP	GO:0018209	Peptidyl-serine modification	9.35E-04	AKT1, GSK3B, BCL2, NLK, TGFBR1
BP	GO:0051781	Positive regulation of cell division	9.35E-04	VEGFC, FGF5, FGF7, FGF9, PDGFA
BP	GO:0001541	Ovarian follicle development	0.00147656	INHBB, CCNE1, INHBA, FGF7, CCND2
BP	GO:0050678	Regulation of epithelial cell proliferation	4.89E-08	EGFR, NOG, FGF7, ERBB4, FGF9
BP	GO:0031346	Positive regulation of cell projection organization	4.90E-04	CDC42, LIMK1, ROBO1, TGFBR1, RAC1
BP	GO:0048638	Regulation of developmental growth	4.90E-04	COL4A4, NOG, NRP1, FGF9, LIMK1

BP	GO:0045667	Regulation of osteoblast differentiation	0.00227003	ACVR2A, BMP2, SMAD5, BMPR2, SMAD3
BP	GO:0042176	Regulation of protein catabolic process	1.31E-04	HSP90AB1, AKT1, CBLB, SMAD7, RELA

Upregulated miRNAs

Category	Term	Description	FDR	Genes (the five most involved)
BP	GO:0043550	Regulation of lipid kinase activity	1.61E-03	CDC42, VAV3, RBL1, RAC1, RB1
BP	GO:0060070	Wnt receptor signalling pathway through beta-catenin	0.00488947	TBL1XR1, CCND1, GSK3B, LRP6, TBL1X
BP	GO:0045646	Regulation of erythrocyte differentiation	0.00771607	ACVR2A, INHBA, ETS1, STAT5A, STAT5B
BP	GO:0048538	Thymus development	2.82E-03	CRKL, BCL2, TGFBR1, SIX1, PBX1
BP	GO:0007214	Gamma-aminobutyric acid signalling pathway	1.75E-02	GABRG1, GABRA2, GABRA1, GABRA4, GABRA3
BP	GO:0030509	BMP signalling pathway	1.5383E-08	SMAD9, SMAD7, SMAD6, GDF6, SMAD5
BP	GO:0000209	Protein polyubiquitination	0.00100132	ERCC8, HUWE1, UBE4A, MAP3K1, PPIL2
BP	GO:0006512	Ubiquitin cycle	0.00603251	UBE2D2, UBE3A, SOCS3, UBE2W
BP	GO:0045778	Positive regulation of ossification	6.03E-03	ACVR2A, ADRB2, BMPR2, TGFB3, BMP7
BP	GO:0045669	Positive regulation of osteoblast differentiation	0.00855149	ACVR2A, JUND, SMAD5, BMPR2, BMP7
BP	GO:0048730	Epidermis morphogenesis	0.00855149	NOTCH1, FGF7, BCL2, FST, COL1A2
BP	GO:0000082	G1/S transition of mitotic cell cycle	7.1443E-10	CAMK2G, SKP2, RB1, PPP1CB, CUL3
BP	GO:0048661	Positive regulation of smooth muscle cell proliferation	0.00049576	PRKCA, PTGS2, PDGFB, EREG, STAT5B
BP	GO:0048146	Positive regulation of fibroblast proliferation	0.01190695	BMI1, CDKN1A, PDGFB, EREG, PDGFA
BP	GO:0051781	Positive regulation of cell division	5.6928E-05	FGF5, FGF7, PDGFB, PDGFA, FGF9
BP	GO:0001657	Ureteric bud development	0.00176651	EYA1, RET, BDNF, BCL2, SIX1
BP	GO:0030856	Regulation of epithelial cell differentiation	0.02930361	CCND1, NOTCH1, CDKN2B, STAT5A, TGFBR1
BP	GO:0007179	TGF beta receptor signalling pathway	3.22E-07	SMAD9, PDGFB, FUT8, PDGFA, NLK
BP	GO:0030178	Negative regulation of Wnt receptor signalling pathway	3.85E-02	DKK2, CCND1, FGF9, NLK, LRP6
BP	GO:0051302	Regulation of cell division	6.3266E-05	FGF5, FGF7, PDGFB, PDGFA, FGF9
BP	GO:0001656	Metanephros development	2.54E-04	RET, NF1, SMAD4, GLI3, SHH
BP	GO:0048754	Branching morphogenesis of a tube	1.4214E-07	NRP1, TGFBR2, SMAD4, IGF1, GLI3
BP	GO:0007178	Transmembrane receptor protein serine/threonine	2.00E-13	FUT8, PDGFB, PDGFA, GDF6, FST

		kinase signalling pathway		
BP	GO:0051272	Positive regulation of cell motion	2.7978E-12	ERBB4, PDGFB, PDGFA, BCAR1, STAT5B
BP	GO:0045216	Cell-cell junction organization	1.62E-02	CDC42, PARD6B, TJP1, SMAD7, TGFB3
BP	GO:0030111	Regulation of Wnt receptor signalling pathway	4.34E-04	FGF9, NLK, PPM1A, CXXC4, SENP2
BP	GO:0045667	Regulation of osteoblast differentiation	1.72E-03	ACVR2A, JUND, SMAD5, BMPR2, CDK6
BP	GO:0032355	Response to estradiol stimulus	4.67E-05	PRKCA, PDGFB, PTGS2, SOCS3, PDGFA
BP	GO:0001763	Morphogenesis of a branching structure	1.7947E-07	NRP1, TGFBR2, SMAD4, IGF1, GLI3
BP	GO:0045787	Positive regulation of cell cycle	9.876E-05	SMAD6, STAT5A, STAT5B, IGF1, BRCA2

BP, biological process; GO, gene ontology; PI3K, phosphoinositide 3-kinase; FDR, false discovery rate correction value; VEGF, vascular endothelial growth factor; SMAD, similar to the Drosophila gene mothers against decapentaplegic; BMP, bone morphogenetic protein; TGF, transforming growth factor.

[a] This information was generated by the team of DAVID database.