

1 **miRNAs responsive to the diabetic microenvironment in the human beta cell line**
2 **EndoC- β H1 may target genes in the FOXO, HIPPO and Lysine degradation pathways.**

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25 **Keywords:** Animal Free Research; miRNA; beta cells; Type 2 Diabetes, ncRNA regulation

26 **Highlights**

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28 • The diabetic microenvironment causes changes in the MicroRNA milieu

29 • Some miRNAs demonstrate dysregulation across multiple diabetomimetic stimuli

30 • Affected miRNAs target genes in FOXO1, HIPPO and Lysine degradation pathways

31 • This has potential to result in attenuation of beta cell survival or beta cell fate

Abstract33
34

35 Altered expression of miRNAs is evident in the islets of diabetic human donors, but the effects
36 of specific aspects of the diabetic microenvironment and identity of gene ontology pathways
37 demonstrating target gene enrichment in response to each is understudied.

38

39 We assessed changes in the miRNA milieu in response to high/low glucose, hypoxia,
40 dyslipidaemia and inflammatory factors in a humanised EndoC- β H1 beta cell culture system
41 and performed miRPath analysis for each treatment individually. The 10 miRNAs
42 demonstrating the greatest dysregulation across treatments were then independently
43 validated and Gene Set Enrichment Analysis to confirm targeted pathways undertaken.

44

45 171 of 392 miRNAs displayed altered expression in response to one or more cellular stressors.
46 miRNA changes were treatment specific, but their target genes were enriched in conserved
47 pathways. 5 miRNAs (miR-136-5p, miR299-5p, miR-454-5p, miR-152 and miR-185) were
48 dysregulated in response to multiple stressors and survived validation in independent samples
49 ($p=0.008$, 0.002 , 0.012 , 0.005 and 0.024 respectively). Target genes of dysregulated miRNAs
50 were clustered into FOXO1, HIPPO and Lysine degradation pathways ($p= 0.02$, $p= 5.84 \times 10^{-5}$
51 and $p =3.00 \times 10^{-3}$ respectively).

52

53 We provide evidence that the diabetic microenvironment may induce changes to the
54 expression of miRNAs targeting genes enriched in pathways involved in cell stress response
55 and cell survival.

56 Introduction

57 Cellular stresses are known to be associated with the pathogenesis of several common,
58 chronic diseases, such as type 2 diabetes, cancer and neurodegenerative disorders. Stressful
59 stimuli such as chronic hyperglycaemia, dyslipidaemia, inflammation and hypoxia contribute
60 to insulin resistance and dysregulated insulin secretion (1-3) and are also associated with
61 tumorigenesis, where chronic inflammation is suggested to be instrumental in loss of
62 regulatory control over cell proliferation, migration and cell-cell interactions (4). Likewise in
63 neurodegenerative conditions such as Alzheimer's disease, oxidative stress is a feature of the
64 disease process, contributing to initiation of inflammatory responses (5, 6).

65

66 The biosynthesis, regulation, recruitment and interaction of microRNAs with their targets are
67 integral to the cellular stress response (7-9). MicroRNAs (miRNA) are a class of small non-
68 coding RNAs, which regulate gene expression by mRNA degradation and/or translational
69 repression (10-12). Previous studies have shown that various components of stress response
70 pathways such as the DNA damage response protein p53 have been shown to regulate the
71 biosynthesis of microRNAs following exposure to damaging stimuli (13). As part of this, stress
72 granule formation is also associated with the regulation of miRNA synthesis along with
73 recruitment of proteins such as Argonaute that are involved in miRNA trafficking and the RISC
74 complex (14). MicroRNA synthesis can also be affected in response to oxidative stress, which
75 has been shown to contribute to reduced expression of Dicer, essential for miRNA synthesis,
76 (15) and to be linked to reduced stress tolerance in cells (15, 16). Alongside the impact of
77 cellular stress responses on miRNA synthesis, miRNAs themselves contribute to coordination
78 of the cellular stress response by regulating the levels of components of the unfolded protein
79 response, such as the negative regulation of *XBP1* during endoplasmic reticulum stress, which
80 is regulated by miR-214. (17, 18). Cellular stress is also thought to dysregulate
81 microRNA:mRNA target interactions by virtue of the system becoming overwhelmed as a
82 result of large increases in the expression of mRNA targets (8).

83 The cellular microenvironment brought about by type 2 diabetes (T2D) is stressful for
84 pancreatic beta cells. We therefore aimed to characterise changes in the beta cell miRNA
85 repertoire in response to diabetes-related cellular stressors. We exposed the human
86 EndoC β H1 beta cell line to disrupted glycaemia, altered lipids, hypoxia or proinflammatory
87 cytokines, and then characterised effects on the miRNA milieu in a single sample consisting
88 of 3 pooled replicates to identify the miRNAs with the largest consistent fold changes across
89 assays for validation. 368 miRNAs were expressed in EndoC β H1 cells, of which 171 showed
90 evidence of altered expression upon treatment with one or more diabetes-associated factors.
91 The 10 most dysregulated miRNAs across all treatments were then validated in 3 biological
92 and 3 technical replicates to allow assessment of statistical significance. Their targets were
93 then predicted using bioinformatics and validated using qRT-PCR. GSEA gene ontology
94 analysis revealed that the FOXO1 and HIPPO pathways, known to be important in
95 maintenance of beta cell fate and function (19, 20), were enriched in target genes of
96 dysregulated miRNAs. These results suggest that the cellular microenvironment can induce
97 changes in the expression of miRNAs in human beta cells, and that these miRNAs may target
98 genes involved in cell survival.

99

100 **Research Design and Methods**

101

102 *Culture and treatment of EndoC- β H1 cells*

103

104 EndoC- β H1 cells at passage <25 were plated in 24-well plates at a density of 6.0×10^5 cells/
105 ml and maintained according to a modified humanised culture protocol as previously described
106 for 72 hrs prior to treatment (21). Cells were then treated with low (2.5 mM) or high glucose
107 (25 mM) for 24, 36 or 48 hrs to mimic disrupted glycaemia, with 0.5 mM palmitic acid, 0.5 mM
108 oleic acid or 0.5 mM palmitic acid/0.5 mM oleic acid for 12, 24 and 48 hrs to mimic
109 dyslipidaemia, with TNF α (1000 U/ mL), INF γ (750 U/ mL) and IL1 β (75 U/ mL) for 12, 24 and

110 36 hrs to mimic inflammatory changes or were grown in 1%, 3% or 21% O₂ for a period of 24,
111 36 or 48 hrs to mimic hypoxia. We did not measure insulin secretion or other functional
112 parameters, because the responses of this cell line are already well documented in this regard
113 (22-24).

114

115 *RNA extraction and reverse transcription*

116

117 Treated cells were washed in Dulbecco's phosphate buffered saline (D-PBS) before RNA
118 extraction using TRI[®] reagent to harvest both the small RNA (<200bp) and mRNA/lncRNA
119 fractions (Sigma-Aldrich, Steinheim, Germany). RNA concentrations were adjusted to 100 ng/
120 μ L prior to reverse transcription. For miRNA assessment, cDNA synthesis was carried out in
121 20 μ L reactions using the Taqman[®] Advanced miRNA Assay kit (Thermo Fisher, Waltham,
122 MA USA) according to the manufacturer's instructions. For assessment of mRNA target levels,
123 cDNA synthesis was carried out using EvoScript Universal cDNA master (Roche life science,
124 Burgess Hill, UK). Samples were normalised to 100 ng/ μ L RNA prior to reverse transcription.

125

126 *Large-scale miRNA screen*

127

128 The miRNA milieu of treated and endogenous control cells was assessed using Taqman[®]
129 Advanced miRNA (miR) Open Arrays on the Thermo Fisher 12K OpenArray Flex platform
130 (Thermo Fisher, Waltham, MA USA). These arrays contain unique probes to 754 miR targets
131 (plate IDs available from Thermo Fisher, Advanced microRNA panel, Waltham, MA, USA).
132 Data were analysed using Thermo Fisher 'Connect You' lab software (Thermo Fisher
133 Connect[™], Thermo Fisher, Waltham, MA USA, (<https://www.thermofisher.com>). Target
134 microRNAs demonstrating the largest fold changes across the treatments were selected for
135 follow up (supplementary table S1 and S2).

136

137 *miRNA pathway enrichment analysis for individual treatments*

138

139 To assess pathway and gene targets for miRNAs dysregulated in response to individual
140 aspects of the diabetic microenvironment, we used the DNA intelligent analysis (DIANA)
141 mirPath v3.0 database and the DIANA-micro-T-CDS v 5.0 algorithm (25, 26). The DIANA
142 mirPath database focuses on the identification of miRNA targeted cell pathways, the algorithm
143 performs gene set enrichment analysis (GSEA) using a Fisher's exact test to determine the
144 statistical significance of microRNA gene targets in KEGG pathways, Benjamini Hochberg
145 false discovery rate p value threshold set to 0.05. We first used this platform to carry out GSEA
146 using the top 5 upregulated and the top 5 down-regulated miRNAs for each individual
147 component of the diabetic microenvironment (high glucose, low glucose, hypoxia,
148 inflammatory factors and palmitic acid).

149

150 *Validation of dysregulated miRNAs*

151

152 The top 10 miRNAs demonstrating dysregulation across 4 or more treatments were validated
153 using Taqman[®] advanced miR assays (Thermo Fisher, Waltham, MA USA). The three
154 miRNAs with the most stable expression patterns under test conditions in our initial analysis
155 (miR 106b-3p, miR-191-3p and miR103-3p) were selected for use as endogenous controls.
156 qRTPCR reaction mixes included 2.5 μ L Taqman[®] Universal PCR mastermix II (no
157 AmpErase[®] UNG) (Thermo Fisher, Waltham, MA, USA), 1.75 μ L dH₂O, 0.5 μ L cDNA and 0.25
158 μ L Taqman[®] gene assay (Thermo Fisher, Foster City USA) in a 5 μ L reaction volume. Cycling
159 conditions were: 50 °C for 2 min, 95 °C for 10 min and 50 cycles of 15 seconds at 95 °C for
160 30 s and 1 minute at 60 °C. Reactions were carried out in 3 biological replicates and 3 technical
161 replicates. MicroRNA assay identifiers are given in supplementary table S2. The relative
162 expression of each target miRNA was determined by the comparative Ct approach (27, 28)
163 and were calculated relative to the geometric mean of the endogenous control genes. We also
164 carried out an analysis relative to the global mean of expression across all transcripts tested
165 as a separate validation. Expression levels were then normalised to the median level of

166 expression seen in untreated EndoC- β H1 cells. Differences in gene expression levels
167 between mock-treated and treated EndoC- β H1 cells were compared to the same time point
168 controls for each condition and investigated for statistical significance by student independent
169 t-test carried out using SPSS version 23 (IBM, North Castle, NY, USA). Data were presented
170 as means \pm S.E.M.

171

172 *Pathway enrichment analysis for miRNAs responsive to 4 or more treatments*

173

174 Following validation of the 10 miRNAs showing evidence of dysregulation in response to >4
175 of the diabetomimetic stimuli tested, we then carried out a miRNA pathway enrichment
176 analysis to more closely examine the gene ontology pathways that may be enriched in the
177 target genes of miRNAs responsive to multiple aspects of the diabetic microenvironment. The
178 p value was set to 0.050 and MicroT threshold to 0.8. Each predicted target was given a
179 microRNA target (MITG) score which predicts the probability of the microRNA targeting that
180 gene.

181

182 *Validation of miRNA target gene mRNA levels*

183

184 Target genes for miRNAs demonstrating dysregulation in response to 4 or more of the cellular
185 stressors tested were selected for validation were based on the MITG scores from the DIANA-
186 microT-CDS v5.0 algorithm (25). The MITG score is the predictive score, where the higher the
187 score the higher the probability that the gene in question is a target of the miRNA on the basis
188 of complementarity (29). A panel of 10 mRNAs were selected on the basis of highest MITG
189 score, most statistically significant p value, number of genes predicted and number of miRNAs
190 targeting the top 5 pathways showing enrichment for targets of dysregulated miRNAs.

191

192 Target gene expression levels were then measured directly using quantitative RT-PCR
193 performed using IDT mini primetime™ gene expression assays (Integrated DNA

194 Technologies, Skokie, Illinois, USA) as detailed in supplementary table S3. Reactions were
195 carried out in triplicate on 384 well plates, using one assay per plate containing all samples.
196 Each reaction included 2.5 μ L Taqman[®] Universal PCR mastermix II (no AmpErase[®] UNG)
197 (Thermo Fisher, Waltham, MA, USA), 1.75 μ L dH₂O, 0.5 μ L cDNA and 0.25 μ L Taqman[®] gene
198 assay (Thermo Fisher, Foster City USA) in a 5 μ L reaction volume. Cycling conditions were:
199 50 °C for 2 min, 95 °C for 10 min and 50 cycles of 15 seconds at 95 °C for 30 s and 1 minute
200 at 60 °C. Associations between miRNA and mRNA target expression were assessed using
201 independent t tests carried out using SPSS v23 (IBM, North Castle, NY, USA). We identified
202 correlations by integrating miRNA expression data with mRNA target expression to assess
203 expression changes that occurred in response to the same cellular stresses. This method was
204 used to assess relationships between the miRNA and mRNA, particularly where the predicted
205 miRNA target gene expression was contrary to that of the miRNA (30-32). To account for
206 comparisons between time points and controls we also carried out ANOVA using SPSS v24
207 (IBM, North Castle, NY, USA).

208

209

210 **Results**

211

212 *Dysregulation of miRNAs in response to aspects of the diabetic microenvironment*

213

214 391 out of 757 miRNAs tested were expressed in untreated EndoC- β H1 human beta cells.
215 170 of these demonstrated altered expression with greater than 2x fold change upon treatment
216 with high (25mM) or low (2.5mM) glucose, palmitic acid (0.5mM), hypoxia (<3% O₂) or
217 cytokines (TNF α , IFN γ , IL1 β) (Supplementary table S1). This equates to 23% of the miRNome
218 tested.

219

220 *Overlap in the pathways enriched in target genes of miRNAs dysregulated by different*
221 *treatments*

222

223 Although each treatment generally caused dysregulation of a specific and unique set of
224 miRNAs (Supplementary table S1), the KEGG pathways that mRNA targets of those miRNAs
225 were clustered in displayed surprising conservation (table 1). Despite the differing identity of
226 miRNAs showing expression differences in response to the different tissues, the HIPPO
227 pathway, the 'Lysine degradation' pathway, the 'Proteoglycans in cancer' and the 'ErbB
228 signalling pathway' were all enriched in targets of dysregulated miRNAs for 4/5 of the
229 treatments (table 1).

230

231 *Validation of miRNAs demonstrating evidence of dysregulation in response to 4 or more*
232 *treatments*

233

234 Independent validation of the miRNAs demonstrating the largest fold changes in response to
235 at least 4 treatments demonstrated that 5 miRNAs survived independent validation, see table
236 2 and figure 1). MicroRNA miR-136-5p was altered in response to 25 mM high glucose and
237 inflammatory factors TNF α , IL1- β and INF γ ($p=0.008$ mean diff 0.782, $p=0.01$ mean diff 1.047
238 and $p=0.002$ mean diff -0.634 respectively). miR-299-5p showed altered expression in
239 response to changes in glycaemia and hypoxia ($p= 0.002$ mean diff -0.619 and 0.01 mean diff
240 -0.685 respectively). miR-454-5p responded to 2.5 mM low glucose ($p= 0.012$ mean diff
241 4.145). Both miR-152 and miR-185 responded to 25 mM high glucose ($p=0.005$ mean diff
242 0.536 and $p=0.024$ mean diff -2.221 respectively). To assess the changes in relation to the
243 timepoints we carried further analysis by ANOVA which showed the same statistical hits as
244 were identified by the t-tests (Supplementary table S4).

245

246 *The Lysine degradation, HIPPO and FOXO pathways are enriched in genes targeted by*
247 *dysregulated miRNAs*

248

249 Given the conservation of pathways enriched in targets of dysregulated miRNAs, we then
250 determined the gene ontology pathways enriched for genes targeted by miRNAs
251 demonstrating common effects across treatments. The top 5 pathways targeted by these
252 miRNAs were: Lysine degradation ($p=3.0 \times 10^{-3}$) with 9 gene targets predicted, HIPPO
253 signalling pathway ($p=5.84 \times 10^{-5}$) with 17 predicted gene targets, FOXO signalling pathway
254 ($p=0.02$) with 18 predicted gene targets, TGF β - oestrogen ($p=0.02$) with 9 predicted gene
255 targets and Pathways in Central Cancer ($p=3.0 \times 10^{-3}$) with 9 predicted gene targets, see table
256 3.

257

258 *Correlation of miRNA and mRNA target expression*

259

260 To validate miRNA:target relationships, we correlated the mRNA expression level of the most
261 highly predicted target gene from each of the top three pathways, with its respective miRNA
262 as previously described (30-32). We found that changes in the expression of miR-136-5p,
263 miR299-5p and miR-454-5p negatively correlated with expression changes in their respective
264 target genes, *MAPK1/ DLG2*, *PDK1* and *MAPK1* in response to the cellular stressors tested,
265 (table 4; figure 2). A positive correlation between miRNA and mRNA expression was also
266 noted for miR-185 and *MAPK1* in response to 25 mM glucose.

267

268 **Discussion**

269

270 Cellular stresses such as those produced by diabetes or other metabolic disturbance are
271 known to influence features of beta cell function (2) and affect the miRNA milieu (33-35). In
272 the work described here, we present evidence that exposure to some features of the type 2
273 diabetic microenvironment; altered glycaemia, dyslipidaemia, hypoxia and inflammatory
274 agents, was associated with dysregulation of miRNA expression for five miRNAs including
275 miR-136-5p, miR299-5p, miR-454-5p, miR-152 and miR-185. GSEA analysis revealed that
276 predicted targets of these miRNAs may be clustered in FOXO, HIPPO, Lysine Degradation

277 and Central carbon in cancer pathways. We also demonstrated that whilst the specific miRNAs
278 showing expression differences in response to different treatments were different, the
279 pathways that were enriched in their targets showed surprising conservation. Gene target
280 validation showed negative correlations between 3 miRNAs and their respective gene targets,
281 miR-136-5p and *MAPK1/ DLG2*, miR299-5p and *PDK1* and miR-454-5p and its predicted
282 target *MAPK1*. These findings are consistent with previous studies reporting associations of
283 specific miRNA with beta cell dysfunction and survival in human and rodent model systems
284 and in our previous work in ex vivo human islets (34, 36-41).

285

286 MicroRNAs have previously been implicated in cellular stress response; changes to the
287 expression of the mir-375 (42) and the miR-200 families (43) have been demonstrated by
288 others to have involvement in the regulation of apoptosis in response to oxidative stress (44)
289 and in response to inflammatory factors (34, 45). Well-defined roles have also been described
290 for miRNAs in glucose homeostasis (46, 47); miR-124, and miR-187 are known to target genes
291 involved in beta cell proliferation (47, 48), whereas miR-375 and miR-7 are known to play roles
292 in cell proliferation, differentiation and insulin production and secretion (47, 49, 50).
293 MicroRNAs also have involvement in mediation of the unfolded folded response (51). The
294 cross-regulatory relationship between cellular stress and miRNA expression renders these
295 small non-coding RNA regulators uniquely poised to interface between the cellular
296 microenvironment and beta cell function (8, 9, 34, 52, 53). A number of studies have
297 demonstrated that exposure to these cellular stressors is also associated with disrupted beta
298 cell function, particularly in relation to glucose sensitive insulin secretion (22, 54, 55).

299

300 We found altered expression of miRNAs 136-5p, 299-5p, 152 and 185 which have been
301 implicated in beta cell responses to cellular stress (12, 36, 37, 56-58). Reduced expression of
302 miR-136-5p has been found in the islets of patients with T2D (59) with altered miR-299-5p

303 expression associated with beta cell failure and apoptosis in response to diabetes related
304 stresses (12). Increased levels of miR-185 have recently been suggested to enhance insulin
305 secretion and be protective from apoptosis, improving proliferation and viability (58). Bao *et al*
306 note that miR-185 is downregulated in both patients with T2D and mouse models of the
307 disease (36). Elevated levels of miR-152 have been seen in islets from patients with T2D (37)
308 and it is known to be upregulated in hyperglycaemia as well as impaired glucose sensitive
309 insulin secretion (GSIS) (35, 37, 46). These findings are consistent with a model whereby
310 hyperglycaemia could result in impaired insulin secretion via miRNA regulation of key targets
311 in beta cell function but that these miRNAs are also implicated in beta cell survival. We also
312 noted biphasic miRNA expression across timepoints, a feature which has been previously
313 described in the literature and which demonstrates how labile miRNA expression can be in
314 response to cellular stressors (60-62).

315

316 Validation of predicted targets identified from pathways analysis showed negative correlations
317 for miR-454-5p and its predicted target *MAPK1*, miR-136-5p and its predicted target *DLG2*
318 and miR-299-5p and its predicted target *PDK1*. Correlation analysis is a recognised technique
319 for identifying potential roles for miRNA in gene regulation, with negative correlations being
320 the most commonly observed phenomenon (31, 32). In the work presented here, target
321 validation from pathways may support a model where microRNAs 454-5p, 136-5p and 299-5p
322 could be influencing beta cell survival and rates of apoptosis in response to diabetes related
323 cell stresses. Low glucose conditions were associated with a marked increase in expression
324 of miR454-5p, compared to negligible levels in controls and significantly decreased expression
325 of its target, *MAPK1*. *MAPK1* signalling occurs in response to microenvironmental changes
326 affecting cellular metabolism and is implicated in the pathogenesis of metabolic syndrome
327 (38). Downregulation of *MAPK1* leads to increased apoptosis (38) and so it is possible that
328 miR-454-5p could be influencing rates of apoptosis during cellular stress (38, 39). Similarly
329 reduced levels we found of miR-136-5p, with concomitant increases in its predicted target
330 *DLG2*, associated with exposure to inflammatory factors may indicate a potential role in beta

331 cell survival. In a rat model of spinal cord injury, over expression of miR-136-5p promoted
332 generation of proinflammatory cytokines while reduced expression was shown to be protective
333 against inflammatory infiltrates (56, 59). Its target, *DLG2* is a signalling protein within the
334 HIPPO pathway (20) which is important for beta cell differentiation, survival and proliferation
335 and interacts with MAPK and PI3K-AKT pathways (20). The increased levels of expression
336 we observed are suggestive of a role for miR-136-5p in the regulation of beta cell survival
337 during inflammation.

338

339 miR-299-5p has been associated with tumorigenesis and regulation of apoptosis in colorectal
340 cancer as well as being neuroprotective via inhibition of autophagy in mouse models of
341 Alzheimers disease (12). A study using mouse models also showed that reduced expression
342 of miR-299-5p in response to glucolipototoxicity resulted in beta cell failure and apoptosis (12,
343 57). Here, exposure to <3% O₂ hypoxic conditions induced reduced expression of miR-299,
344 with increased expression of its target *PDK1* which has well established roles in beta cell
345 stress response in relation to insulin signalling, survival and apoptosis with ablation resulting
346 in a diabetic phenotype in mice (40). *PDK1* forms part of the PI3K-PDK1-AKT signalling
347 pathway, part of the central carbon metabolism in cancer KEGG pathway, which has been
348 shown in mouse models to mediate potentiation of insulin secretion and beta cell survival (41).
349 Studies in mouse models have also shown that hypoxia inducible factor HIF1 α activates
350 transcription of *PDK1* to increase lactate secretion (63), outlining its pivotal role in beta cell
351 stress response. These data suggest that miRNAs may be involved in coordinating beta cell
352 stress responses particularly in relation to beta cell survival and rates of apoptosis.

353

354 Patterns of islet miRNA expression in patients with T2D compared with euglycaemic controls
355 are comparable with the changes that we have observed in our study; our data on miR-185,
356 miR-152, miR-299-5p, miR-376a and miR-136-5p are in agreement with other studies in ex
357 vivo islet samples (10, 35, 46, 64, 65), despite the heterogeneity between studies, which may
358 arise from differences in islet handling and cell culture techniques (35). Our study differs from

359 previous work in that it uses a completely humanised culture system for assessment of effects
360 and it assesses specific subcomponents of the diabetic microenvironment in isolation.
361 Although sequence conservation between the human and rodent miRNA portfolios is
362 reasonable (66), the timing and localisation of miRNA expression is not well conserved
363 between vertebrate species (67). Accordingly, assessment of diabetes-related miRNA
364 changes has revealed differences between rodent and human datasets (34, 68). Added to
365 this, the short and degenerate nature of miRNA binding sites means that miRNA:mRNA target
366 conservation is often poor to the extent that the changing nature of miRNA target sites has
367 been suggested as a source of organismal diversity (69). This means that the predicted effects
368 of diabetes-induced miRNA dysregulation may differ between animal models and humans,
369 and care should be taken in extrapolating conclusions between species. An important next
370 step would be to follow up these findings in relation to effects on target protein levels and cell
371 signalling pathways. However, this falls outside the scope of this present study.

372

373 In conclusion, we have shown evidence that exposure to cellular stressors commonly
374 associated with a diagnosis of type 2 diabetes in a humanised Endo- β H1 culture system may
375 target genes which are enriched in a core set of pathways. The expression of three
376 dysregulated miRNAs, miR-454-5p, miR136-5p and miR-299-5p, correlate with expression
377 changes in their predicted target genes which are enriched in FOXO and MAPK pathways and
378 are known to be involved in regulation of beta cell survival in response to cell stress,
379 proliferation, differentiation and apoptosis (38, 39, 70). These data may suggest that the beta
380 cell stress response, particularly in relation to beta cell survival, could possibly be coordinated
381 by microRNAs and their dysregulated expression is likely to be important feature of T2D.

382

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384

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566

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572 **Table 1: Gene Ontology pathways enriched in targets of miRNAs dysregulated by different aspects of the diabetic microenvironment.**

573 The top 15 pathways enriched in target genes of miRNAs showing evidence of dysregulation in response to different cell treatments is given
 574 here. P values are FDR adjusted. No. Genes = Number of genes targeted in pathway. No. miRNA = number of miRNAs targeting that
 575 pathway. Pathways highlighted in italic type are common to 3 or more treatments, pathways highlighted in bold typeface are common to 4.

576

Pathway	FDR corrected p value	No. Genes	No. miRNA
25mM Glucose			
<i>TGF-beta signaling pathway</i>	1.52E-07	34	7
<i>Mucin type O-Glycan biosynthesis</i>	2.61E-07	10	5
GABAergic synapse	1.63E-06	22	8
Signaling pathways regulating pluripotency of stem cells	2.33E-06	50	9
Proteoglycans in cancer	3.40E-06	61	9
Hippo signaling pathway	8.43E-05	43	7
Lysine degradation	8.54E-05	16	7
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	9.86E-05	25	7
N-Glycan biosynthesis	0.0003	15	5
Adrenergic signaling in cardiomyocytes	0.0004	43	8
FoxO signaling pathway	0.0008	41	8
MAPK signaling pathway	0.001	73	8
Biosynthesis of unsaturated fatty acids	0.001	5	3
Morphine addiction	0.002	28	8
ErbB signaling pathway	0.002	31	9
2.5mM Glucose			
Proteoglycans in cancer	8.46E-09	75	10
<i>Mucin type O-Glycan biosynthesis</i>	2.19E-08	12	9
<i>Axon guidance</i>	6.19E-08	62	10
Nicotine addiction	3.77E-07	19	8
ErbB signaling pathway	2.09E-06	40	9
Lysine degradation	4.95E-05	20	9
Ras signaling pathway	0.0002	87	10
Glioma	0.0002	28	10
<i>Amphetamine addiction</i>	0.0005	28	9
Endometrial cancer	0.0005	25	10

N-Glycan biosynthesis	0.0007	20	7
<i>TGF-beta signaling pathway</i>	0.0007	32	9
Hippo signaling pathway	0.0007	52	9
Neurotrophin signaling pathway	0.0008	51	10
Focal adhesion	0.0008	78	10
<3% O₂			
Proteoglycans in cancer	3.52E-07	47	8
<i>TGF-beta signaling pathway</i>	5.60E-07	20	5
<i>Axon guidance</i>	6.85E-07	38	9
FoxO signaling pathway	2.50E-05	37	8
Endocytosis	5.43E-05	51	8
Neurotrophin signaling pathway	9.97E-05	35	7
Colorectal cancer	0.00012	20	6
Lysine degradation	0.0002	11	5
Hepatitis B	0.0002	29	7
RNA degradation	0.002	24	7
Protein processing in endoplasmic reticulum	0.002	38	9
MAPK signaling pathway	0.002	56	8
<i>Mucin type O-Glycan biosynthesis</i>	0.003	6	6
ErbB signaling pathway	0.004	23	7
Prolactin signaling pathway	0.004	19	7
0.5mM Palmitic Acid			
Prion diseases	4.55E-12	7	6
Lysine degradation	7.12E-05	18	7
ErbB signaling pathway	0.0002	33	9
Nicotine addiction	0.0012	14	8
Circadian entrainment	0.0011	34	10
Inflammatory mediator regulation of TRP channels	0.0013	31	9
<i>Amphetamine addiction</i>	0.0013	23	9
Morphine addiction	0.0013	28	9
Glioma	0.0013	22	9
Dopaminergic synapse	0.0012	43	10
Glutamatergic synapse	0.0023	37	10
Proteoglycans in cancer	0.003	58	10
Long-term potentiation	0.004	26	9
Hippo signaling pathway	0.004	34	7
Rap1 signaling pathway	0.004	60	10
TNFα (1000 U/ mL, INFγ (750 U/ mL) and IL1β (75 U/ mL)			

Hippo signaling pathway	0.002	35	7
Adrenergic signaling in cardiomyocytes	0.002	43	9
cGMP-PKG signaling pathway	0.002	51	10
Glutamatergic synapse	0.002	33	7
<i>Amphetamine addiction</i>	0.002	22	8
cAMP signaling pathway	0.002	57	9
Vascular smooth muscle contraction	0.002	35	10
Wnt signaling pathway	0.002	39	8
Signaling pathways regulating pluripotency of stem cells	0.004	39	8
Endocrine and other factor-regulated calcium reabsorption	0.007	15	6
<i>Axon guidance</i>	0.007	32	7
Dopaminergic synapse	0.011	38	9
Transcriptional misregulation in cancer	0.014	43	8
mRNA surveillance pathway	0.014	27	5
Estrogen signaling pathway	0.017	26	8

578 **Table 2. Targeted expression of most altered microRNAs high throughput global microRNA screen.** The p values for statistical significance
 579 as determined by independent t-test, Mean difference, Standard errors of measurement (SED) and the 95% confidence intervals are given below.
 580 Results significant below the Bonferroni threshold for correction for 4 treatments (glucose, hypoxia, dyslipidaemia and inflammatory factors) ($p =$
 581 0.013) are given in bold italic type, those showing nominal significance only are given in italic underlined type.

582

25 mM glucose Independent Samples Test- t- test $p = 0.016$																	
24 hrs						36 hrs						48 hrs					
	p value	Mean diff.	SED	95% CI			p value	Mean diff.	SED	95% CI			p value	Mean diff.	SED	95% CI	
				Lower	Upper					Lower	Upper					Lower	Upper
miR-185-3p	0.297	-0.743	0.675	-2.247	0.762	miR-185-3p	<u>0.024</u>	<u>-2.221</u>	<u>0.820</u>	<u>-4.076</u>	<u>-0.366</u>	miR-185-3p	<u>0.035</u>	<u>-1.629</u>	<u>0.667</u>	<u>-3.116</u>	<u>-0.142</u>
miR-885-5p	0.646	0.226	0.470	-0.886	1.338	miR-885-5p	0.98	0.007	0.272	-0.609	0.624	miR-885-5p	0.575	0.226	0.387	-0.665	1.118
miR-27b-3p	0.999	0.000	0.184	-0.411	0.411	miR-27b-3p	0.113	0.312	0.179	-0.088	0.711	miR-27b-3p	0.116	0.312	0.181	-0.091	0.715
miR-124-3p	0.206	0.296	0.219	-0.192	0.783	miR-124-3p	0.819	0.053	0.226	-0.450	0.556	miR-124-3p	0.592	-0.120	0.216	-0.601	0.362
miR-136-5p	0.252	0.318	0.262	-0.266	0.902	miR-136-5p	0.008	0.782	0.236	0.257	1.306	miR-136-5p	0.571	0.143	0.244	-0.400	0.685
miR-152-3p	0.448	-0.141	0.179	-0.539	0.257	miR-152-3p	0.005	0.536	0.148	0.206	0.866	miR-152-3p	0.111	0.288	0.165	-0.079	0.655
miR-299-5p	0.002	-0.619	0.139	-0.933	-0.304	miR-299-5p	<u>0.035</u>	<u>-0.255</u>	<u>0.103</u>	<u>-0.487</u>	<u>-0.023</u>	miR-299-5p	0.155	0.164	0.106	-0.075	0.404
miR-576-5p	0.514	-0.322	0.464	-1.456	0.813	miR-576-5p	0.101	-0.514	0.266	-1.164	0.136	miR-576-5p	<u>0.032</u>	<u>-0.683</u>	<u>0.224</u>	<u>-1.275</u>	<u>-0.091</u>
miR-93-5p	0.232	0.263	0.207	-0.197	0.724	miR-93-5p	0.097	0.395	0.216	-0.086	0.876	miR-93-5p	0.073	0.446	0.223	-0.050	0.942
2.5 mM glucose Independent Samples Test- t- test $p = 0.016$																	
24 hrs						36 hrs						48 hrs					
	p value	Mean diff.	SED	95% CI			p value	Mean diff.	SED	95% CI			p value	Mean diff.	SED	95% CI	
miR-185-3p	0.188	-1.019	0.721	-2.626	0.587	miR-185-3p	0.146	-3.828	1.737	-10.675	3.019	miR-185-3p	0.108	-5.380	2.020	-13.523	2.763
miR-885-5p	0.188	-2.368	1.677	-6.105	1.368	miR-885-5p	0.325	0.905	0.862	-1.082	2.892	miR-885-5p	0.924	-0.184	1.876	-4.365	3.997
miR-454-5p	0.62	0.781	1.529	-2.625	4.187	miR-454-5p	<u>0.033</u>	<u>3.320</u>	<u>1.346</u>	<u>0.321</u>	<u>6.318</u>	miR-454-5p	0.012	4.145	1.350	1.138	7.153
miR-27b-3p	0.188	0.311	0.220	-0.179	0.801	miR-27b-3p	0.922	0.024	0.239	-0.508	0.556	miR-27b-3p	0.349	0.211	0.215	-0.267	0.690
miR-124-3p	0.689	-0.122	0.296	-0.782	0.538	miR-124-3p	0.056	-0.614	0.284	-1.247	0.020	miR-124-3p	0.521	-0.203	0.305	-0.882	0.476
miR-136-5p	0.075	0.518	0.260	-0.062	1.097	miR-136-5p	0.84	-0.056	0.269	-0.656	0.544	miR-136-5p	0.69	0.124	0.301	-0.548	0.795

miR-152-3p	0.637	-0.125	0.257	-0.697	0.447	miR-152-3p	0.299	-0.251	0.229	-0.762	0.260	miR-152-3p	0.239	0.288	0.230	-0.225	0.800
miR-299-5p	<u>0.49</u>	<u>0.831</u>	<u>1.159</u>	<u>-1.752</u>	<u>3.414</u>	miR-299-5p	0.457	0.897	1.160	-1.687	3.482	miR-299-5p	0.539	0.739	1.161	-1.848	3.326
miR-576-5p	0.352	1.439	1.475	-1.846	4.725	miR-576-5p	0.237	1.044	0.818	-0.839	2.928	miR-576-5p	0.946	-0.117	1.676	-3.852	3.618
miR-93-5p	0.332	0.244	0.239	-0.289	0.778	miR-93-5p	0.873	-0.042	0.257	-0.614	0.530	miR-93-5p	0.551	0.145	0.235	-0.378	0.668
<3% O2 Independent Samples Test- t- test p = 0.016																	
4 hrs						12 hrs						24 hrs					
	p value	Mean diff.	SED	95% CI			p value	Mean diff.	SED	95% CI			p value	Mean diff.	SED	95% CI	
				Lower	Upper					Lower	Upper					Lower	Upper
miR-27b-3p	0.14	-0.411	0.262	-0.977	0.155	miR-27b-3p	0.387	-0.229	0.256	-0.781	0.323	miR-27b-3p	0.18	-0.353	0.249	-0.891	0.185
miR-124-3p	0.065	1.816	0.852	-0.139	3.770	miR-124-3p	0.168	1.301	0.866	-0.665	3.268	miR-124-3p	0.389	1.083	1.215	-1.542	3.708
miR-136-5p	0.52	0.441	0.668	-1.001	1.884	miR-136-5p	0.468	0.502	0.672	-0.949	1.953	miR-136-5p	0.486	0.493	0.686	-0.990	1.975
miR-152-3p	0.142	-0.336	0.209	-0.807	0.135	miR-152-3p	0.511	-0.141	0.205	-0.607	0.326	miR-152-3p	0.11	-0.472	0.276	-1.068	0.123
miR-299-5p	0.01	-0.685	0.220	-1.171	-0.200	miR-299-5p	<u>0.035</u>	<u>-0.532</u>	<u>0.221</u>	<u>-1.020</u>	<u>-0.045</u>	miR-299-5p	0.182	-0.373	0.265	-0.945	0.199
miR-93-5p	0.102	-0.396	0.217	-0.889	0.097	miR-93-5p	0.229	-0.282	0.218	-0.777	0.213	miR-93-5p	0.097	-0.483	0.270	-1.067	0.101
miR-21-3p	0.238	0.826	0.650	-0.660	2.311	miR-21-3p	0.171	0.976	0.652	-0.512	2.464	miR-21-3p	0.265	0.771	0.645	-0.710	2.253
0.5 mM Palmitic acid Independent Samples Test- t- test p = 0.016																	
12 hrs						24 hrs						48 hrs					
	p value	Mean diff.	SED	95% CI			p value	Mean diff.	SED	95% CI			p value	Mean diff.	SED	95% CI	
				Lower	Upper					Lower	Upper					Lower	Upper
miR-185-3p	0.147	2.754	1.749	-1.144	6.651	miR-185-3p	0.992	-0.017	1.772	-3.966	3.931	miR-185-3p	0.368	1.731	1.835	-2.357	5.820
miR-885-5p	0.819	0.062	0.266	-0.531	0.656	miR-885-5p	0.634	-0.146	0.297	-0.809	0.516	miR-885-5p	<u>0.046</u>	<u>-0.522</u>	<u>0.230</u>	<u>-1.034</u>	<u>-0.010</u>
miR-27b-3p	0.682	-0.184	0.435	-1.152	0.785	miR-27b-3p	0.693	0.194	0.478	-0.872	1.260	miR-27b-3p	0.454	0.341	0.438	-0.635	1.318
miR-124-3p	0.814	-0.053	0.218	-0.540	0.434	miR-124-3p	0.651	-0.103	0.220	-0.594	0.388	miR-124-3p	0.226	0.228	0.169	-0.186	0.641
miR-136-5p	0.803	-0.060	0.235	-0.583	0.463	miR-136-5p	0.79	0.110	0.401	-0.783	1.002	miR-136-5p	0.002	1.047	0.259	0.469	1.624
miR-152-3p	0.357	-0.213	0.221	-0.705	0.279	miR-152-3p	0.563	0.160	0.268	-0.437	0.757	miR-152-3p	0.17	0.450	0.305	-0.229	1.129
miR-299-5p	0.076	-0.242	0.122	-0.515	0.030	miR-299-5p	0.86	-0.055	0.305	-0.736	0.625	miR-299-5p	0.415	0.178	0.209	-0.287	0.642
miR-576-5p	0.508	-0.192	0.280	-0.816	0.432	miR-576-5p	0.368	1.650	1.440	-4.412	7.712	miR-576-5p	0.129	-0.408	0.230	-0.978	0.163
miR-93-5p	0.794	-0.112	0.417	-1.042	0.818	miR-93-5p	0.683	0.201	0.479	-0.867	1.269	miR-93-5p	0.371	0.416	0.444	-0.574	1.406
proinflammatory cytokines Independent Samples Test- t- test p = 0.016																	

	12 hrs					24 hrs					36 hrs						
	p value	Mean diff.	SED	95% CI		p value	Mean diff.	SED	95% CI		p value	Mean diff.	SED	95% CI			
				Lower	Upper				Lower	Upper				Lower	Upper		
miR-885-5p	0.993	0.004	0.380	-0.857	0.864	miR-885-5p	0.773	-0.130	0.436	-1.116	0.856	miR-885-5p	0.121	0.667	0.389	-0.214	1.547
miR-454-5p	0.583	0.198	0.342	-0.638	1.034	miR-454-5p	0.702	-0.107	0.265	-0.755	0.542	miR-454-5p	0.57	-0.166	0.278	-0.823	0.492
miR-27b-3p	0.477	0.294	0.398	-0.593	1.180	miR-27b-3p	0.706	0.155	0.400	-0.737	1.048	miR-27b-3p	0.481	0.291	0.398	-0.595	1.178
miR-124-3p	0.146	0.411	0.261	-0.170	0.992	miR-124-3p	0.336	0.254	0.251	-0.305	0.813	miR-124-3p	0.55	0.148	0.240	-0.385	0.682
miR-136-5p	0.002	-0.634	0.156	-0.982	-0.286	miR-136-5p	0.562	0.190	0.282	-0.890	1.269	miR-136-5p	0.266	-0.547	0.368	-2.020	0.926
miR-152-3p	0.674	-0.069	0.158	-0.422	0.284	miR-152-3p	0.756	-0.060	0.188	-0.480	0.360	miR-152-3p	0.544	-0.251	0.353	-1.633	1.131
miR-299-5p	0.822	0.036	0.154	-0.308	0.379	miR-299-5p	0.152	-0.302	0.194	-0.735	0.132	miR-299-5p	0.371	0.128	0.137	-0.177	0.433
miR-576-5p	0.798	0.040	0.154	-0.302	0.383	miR-576-5p	0.194	0.276	0.198	-0.165	0.717	miR-576-5p	0.157	0.269	0.176	-0.123	0.660
miR-93-5p	0.257	-0.098	0.082	-0.281	0.084	miR-93-5p	0.533	-0.243	0.328	-1.605	1.118	miR-93-5p	0.156	-0.199	0.130	-0.489	0.090

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587 **Table 3. mRNA targets identified from DIANA pathways analysis.**

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589 5 microRNAs were found to be differentially regulated upon validation and these were selected

590 for DIANA pathways analysis. Target genes were selected on the basis of pathway *p* value

591 and MITG score, which determines the probability of the microRNA targeting a specific gene.

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Gene	Pathway	FDR corrected <i>p</i>-value	MITG score(s)
<i>KMT2C</i>	Lysine degradation	3.00 x 10 ⁻³	0.97
<i>BCL2L11</i>	FOXO	0.02	0.99
<i>DLG2</i>	Hippo	5.84 x 10 ⁻⁵	0.92
<i>SP1</i>	TGFβ and Estrogen	0.02	0.99
<i>SOD</i>	FOXO	0.02	0.98
<i>MAPK1</i>	FOXO	0.02	0.90
<i>TEAD1</i>	Hippo	5.84 x 10 ⁻⁵	0.85
<i>SERPINE1</i>	Hippo	5.84 x 10 ⁻⁵	0.82
<i>MOB1A</i>	Hippo	5.84 x 10 ⁻⁵	0.82
<i>PDK1</i>	Central carbon cancer	3.00 x 10 ⁻³	0.82

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596 **Table 4. Validated of gene targets identified from DIANA pathways analysis.** The p values
 597 for statistical significance as determined by independent t-test, Mean difference, Standard
 598 errors of measurement (SED) and the 95% confidence intervals are given below. **Bold italic**
 599 ***p<0.050*** Gene list is *a priori* and single test applied so no correction for multiple testing.

600

25 mM high glucose Independent Samples Test <i>p</i> = 0.050					
Gene	p value	Mean Diff.	SED	95% CI	
				Lower	Upper
<i>BCL211</i>	0.392	0.060	0.066	-0.096	0.217
<i>DLG2</i>	0.215	0.184	0.135	-0.135	0.504
<i>KMT2C</i>	0.451	-0.069	0.087	-0.275	0.136
<i>MAPK1</i>	0.099	-0.048	0.025	-0.107	0.012
<i>MOB1A</i>	0.263	-0.075	0.061	-0.219	0.070
<i>PDK1</i>	0.373	0.094	0.099	-0.140	0.328
<i>SERPINE1</i>	0.11	0.085	0.046	-0.025	0.194
<i>SOD1-1</i>	<i>0.024</i>	<i>-0.085</i>	<i>0.030</i>	<i>-0.155</i>	<i>-0.015</i>
<i>SP1</i>	0.367	-0.064	0.067	-0.222	0.093
<i>TEAD1</i>	0.682	-0.033	0.077	-0.216	0.150
2.5 mM low glucose Independent Samples Test <i>p</i> = 0.050					
Gene	p value	Mean Diff.	SED	95% CI	
				Lower	Upper
<i>BCL211</i>	0.206	0.083	0.060	-0.058	0.225
<i>DLG2</i>	0.122	0.234	0.133	-0.080	0.549
<i>KMT2C</i>	0.259	-0.054	0.044	-0.158	0.050
<i>MAPK1</i>	<i>0.039</i>	<i>-0.117</i>	<i>0.046</i>	<i>-0.226</i>	<i>-0.007</i>
<i>MOB1A</i>	0.117	-0.103	0.057	-0.238	0.033
<i>PDK1</i>	0.179	0.151	0.101	-0.088	0.391
<i>SERPINE1</i>	0.448	0.037	0.046	-0.071	0.145
<i>SOD1-1</i>	0.957	-0.002	0.037	-0.090	0.086
<i>SP1</i>	0.475	-0.052	0.069	-0.216	0.111
<i>TEAD1</i>	0.931	-0.007	0.077	-0.190	0.176
Hypoxia Independent Samples Test <i>p</i>=0.050					
Gene	p value	Mean Diff.	SED	95% CI	
				Lower	Upper
<i>BCL211</i>	0.266	-0.088	0.072	-0.264	0.088
<i>DLG2</i>	<i>0.004</i>	<i>-0.457</i>	<i>0.091</i>	<i>-0.689</i>	<i>-0.225</i>
<i>KMT2C</i>	0.934	0.005	0.057	-0.135	0.145
<i>MAPK1</i>	0.153	0.054	0.033	-0.027	0.134
<i>MOB1A</i>	0.449	-0.058	0.072	-0.233	0.117

PDK1	0.0003	0.873	0.121	0.577	1.170
<i>SERPINE1</i>	0.285	-0.082	0.070	-0.254	0.089
<i>SOD1-1</i>	0.025	-0.077	0.025	-0.140	-0.013
<i>SP1</i>	0.95	0.005	0.083	-0.197	0.208
<i>TEAD1</i>	0.525	0.071	0.105	-0.186	0.328
0.5 mM Palmitic Acid Independent Samples Test p=0.050					
Gene	p value	Mean Diff.	SED	95% CI	
				Lower	Upper
<i>BCL211</i>	0.692	0.023	0.057	-0.110	0.157
<i>DLG2</i>	0.598	0.073	0.133	-0.240	0.387
<i>KMT2C</i>	0.06	-0.138	0.061	-0.283	0.007
<i>MAPK1</i>	0.252	-0.031	0.025	-0.090	0.028
<i>MOB1A</i>	0.13	-0.099	0.057	-0.234	0.037
PDK1	0.023	0.281	0.097	0.053	0.510
<i>SERPINE1</i>	0.423	0.043	0.050	-0.076	0.161
<i>SOD1-1</i>	0.905	0.005	0.040	-0.090	0.099
<i>SP1</i>	0.882	-0.010	0.068	-0.171	0.150
<i>TEAD1</i>	0.51	0.054	0.078	-0.130	0.237
Pro-inflammatory cytokines Independent Samples Test p=0.050					
Gene	p value	Mean Diff.	SED	95% CI	
				Lower	Upper
<i>BCL211</i>	0.766	0.015	0.049	-0.101	0.132
DLG2	0.032	0.267	0.095	0.032	0.502
<i>KMT2C</i>	0.861	-0.014	0.076	-0.193	0.165
<i>MAPK1</i>	0.729	-0.012	0.034	-0.094	0.069
<i>MOB1A</i>	0.104	-0.104	0.056	-0.236	0.028
<i>PDK1</i>	0.407	0.086	0.097	-0.144	0.315
<i>SERPINE1</i>	0.746	-0.017	0.051	-0.138	0.104
<i>SOD1-1</i>	0.741	-0.014	0.040	-0.110	0.082
<i>SP1</i>	0.273	-0.102	0.085	-0.304	0.100
<i>TEAD1</i>	0.615	0.045	0.085	-0.156	0.246

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604 **Figure Legends**

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607 **Figure 1. Targeted miRNA expression of most altered miRNAs from high throughput**
608 **global miRNA screen.** Larger dotted line shows significance $p < 0.016$. Bonferroni multiple
609 testing correction for 3 tests. Coloured shapes denote significance. Smaller dotted line shows
610 significance $p < 0.050$ no correction for multiple testing. Circles: 25 mM high glucose. Squares:
611 2.5 mM low glucose. Diamonds: $< 3\%$ O₂. Triangles: 0.5 mM palmitic acid. Stars pro-
612 inflammatory factors.

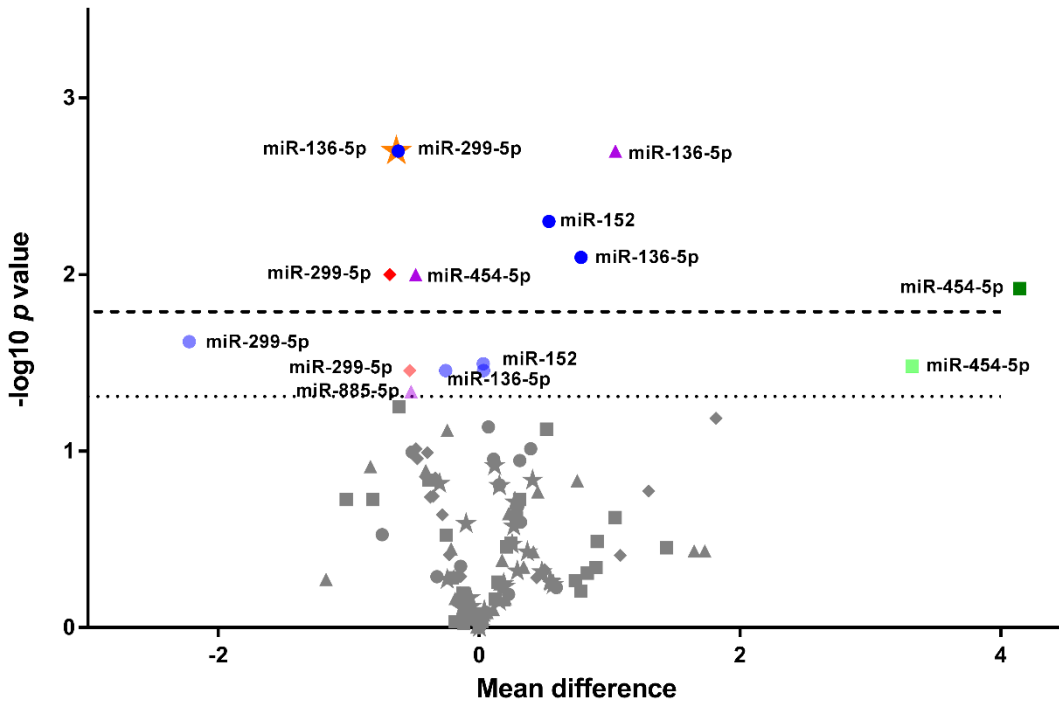
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614 **Figure 2. mRNA expression of predicted target genes from DIANA pathways analysis.**

615 Target genes are given on the X axis. Transcript expression expressed relative to endogenous
616 controls and normalised to mock treated cells given on the Y axis. Smaller dotted line shows
617 significance $p < 0.050$. Null effect given by solid line, $p = 0.05$ indicated by dotted line. Blue
618 circles: 25 mM high glucose. Green squares: 2.5 mM low glucose. Red diamonds: $< 3\%$ O₂.
619 Purple triangles: 0.5 mM palmitic acid. Inverse triangles: inflammatory factors, dark purple
620 $p = 0.050$. Pink inverse triangles: pro-inflammatory factors.

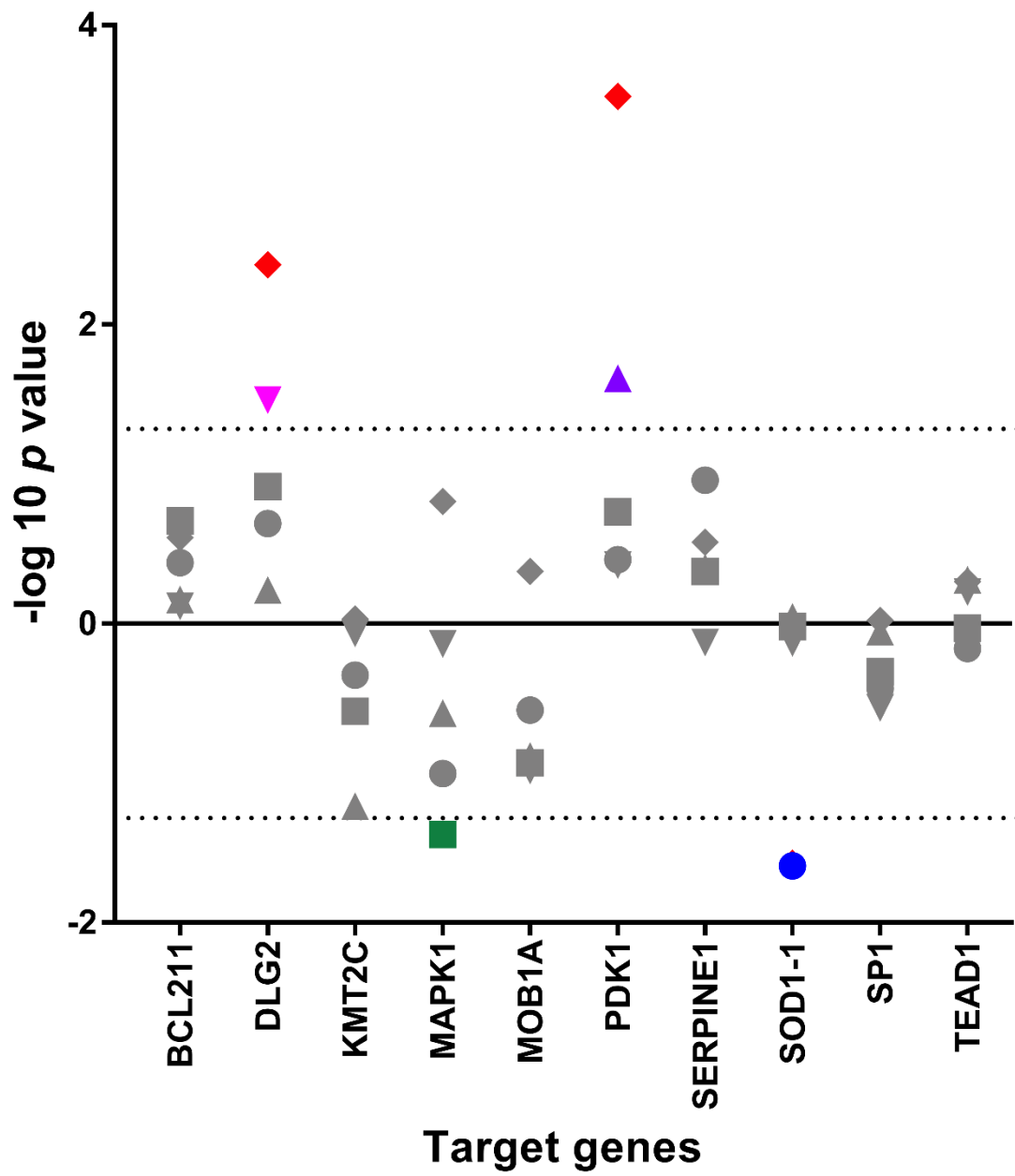
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623 Figure 1
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628 Figure 2
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631 Supplementary tables

632 **Supplementary table S1. Table showing fold changes for microRNA expression from the high throughput global screen.** Only those with
 633 fold change > 2.0 shown. MicroRNAs were selected for pathways analysis on the basis of being the most dysregulated microRNAs across 4 or
 634 more cell insult assays. Assay IDs are also given. MicroRNAs selected for experimental follow up on the basis of dysregulation in response to >
 635 stimuli are identified in bold type.

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Up regulated		
Sample name	Target name	Fold change
25 mM glucose	478532_mir_hsa-miR-23a-3p	412.56
25 mM glucose	478238_mir_hsa-miR-374a-5p	184.64
25 mM glucose	478514_mir_hsa-miR-147a	165.77
25 mM glucose	479087_mir_hsa-miR-606	156.2
25 mM glucose	478826_mir_hsa-miR-323b-5p	114.78
25 mM glucose	478620_mir_hsa-miR-101-5p	91.85
25 mM glucose	477895_mir_hsa-miR-1290	84.06
25 mM glucose	477962_mir_hsa-miR-19b-1-5p	75.86
25 mM glucose	478411_mir_ath-miR159a	71.98
25 mM glucose	477833_mir_hsa-miR-548d-3p	36.17
25 mM glucose	478790_mir_hsa-miR-296-3p	20.98
25 mM glucose	479041_mir_hsa-miR-556-3p	17.71
25 mM glucose	477913_mir_hsa-miR-144-3p	16.17
25 mM glucose	477863_mir_hsa-miR-101-3p	12.18
25 mM glucose	479067_mir_hsa-miR-585-3p	11.23
25 mM glucose	478307_mir_hsa-miR-136-5p	10.74
25 mM glucose	478065_mir_hsa-miR-365a-3p	10.42

25 mM glucose	478588_mir_hsa-miR-320b	10.29
25 mM glucose	478753_mir_hsa-miR-200b-5p	9.17
25 mM glucose	478389_mir_hsa-miR-374b-5p	8.91
25 mM glucose	477879_mir_hsa-miR-124-3p	8.42
25 mM glucose	478091_mir_hsa-miR-424-3p	8.05
25 mM glucose	478087_mir_hsa-miR-412-3p	7.35
25 mM glucose	478177_mir_hsa-miR-616-3p	6.88
25 mM glucose	478349_mir_hsa-miR-378a-3p	6.65
25 mM glucose	477951_mir_hsa-miR-191-3p	6.57
25 mM glucose	478581_mir_hsa-miR-135a-5p	6.54
25 mM glucose	479073_mir_hsa-miR-589-5p	6.4
25 mM glucose	478134_mir_hsa-miR-493-3p	6.07
25 mM glucose	478200_mir_hsa-miR-744-5p	6.06
25 mM glucose	478490_mir_hsa-miR-200a-3p	5.47
25 mM glucose	479131_mir_hsa-miR-651-5p	5.35
25 mM glucose	478745_mir_hsa-miR-196a-3p	5.2
25 mM glucose	477936_mir_hsa-miR-183-3p	4.79
25 mM glucose	479448_mir_hsa-miR-30a-5p	4.42
25 mM glucose	478691_mir_hsa-miR-1292-5p	4.38
25 mM glucose	477991_mir_hsa-miR-23b-5p	4.06
25 mM glucose	477976_mir_hsa-miR-216a-5p	3.96
25 mM glucose	477942_mir_hsa-miR-188-3p	3.96
25 mM glucose	478855_mir_hsa-miR-374a-3p	3.93
25 mM glucose	478231_mir_hsa-miR-199a-5p	3.6
25 mM glucose	479469_mir_hsa-miR-625-5p	3.52
25 mM glucose	478209_mir_hsa-miR-93-3p	3.38
25 mM glucose	479207_mir_hsa-miR-92b-5p	3.37
25 mM glucose	478951_mir_hsa-miR-500a-3p	3.27
25 mM glucose	478273_mir_hsa-miR-30a-3p	3.26

25 mM glucose	478215_mir_hsa-miR-96-5p	3.13
25 mM glucose	478367_mir_hsa-miR-590-5p	2.95
25 mM glucose	479178_mir_hsa-miR-770-5p	2.7
25 mM glucose	478105_mir_hsa-miR-448	2.66
25 mM glucose	478827_mir_hsa-miR-32-3p	2.63
25 mM glucose	478041_mir_hsa-miR-340-3p	2.62
25 mM glucose	478132_mir_hsa-miR-491-5p	2.58
25 mM glucose	478153_mir_hsa-miR-542-3p	2.55
25 mM glucose	478142_mir_hsa-miR-501-5p	2.51
25 mM glucose	477908_mir_hsa-miR-140-3p	2.37
25 mM glucose	478755_mir_hsa-miR-202-5p	2.33
25 mM glucose	477804_mir_hsa-miR-20b-5p	2.27
25 mM glucose	478035_mir_hsa-miR-337-3p	2.23
25 mM glucose	479150_mir_hsa-miR-665	2.18
25 mM glucose	477943_mir_hsa-miR-188-5p	2.1
25 mM glucose	478655_mir_hsa-miR-1250-5p	2.05
25 mM glucose	478749_mir_hsa-miR-198	2.02
Down regulated		
Sample name	Target name	Fold change
25 mM glucose	478591_mir_hsa-miR-302b-3p	>500
25 mM glucose	479224_mir_hsa-miR-99a-3p	>500
25 mM glucose	478719_mir_hsa-miR-148b-5p	500
25 mM glucose	479003_mir_hsa-miR-454-5p	200
25 mM glucose	478786_mir_hsa-miR-25-5p	125.00
25 mM glucose	477921_mir_hsa-miR-152-3p	52.63
25 mM glucose	478732_mir_hsa-miR-185-3p	37.04
25 mM glucose	477952_mir_hsa-miR-191-5p	26.32
25 mM glucose	478439_mir_hsa-let-7d-5p	22.73
25 mM glucose	478165_mir_hsa-miR-576-5p	21.74

25 mM glucose	479186_mir_hsa-miR-876-3p	16.95
25 mM glucose	478793_mir_hsa-miR-299-5p	16.39
25 mM glucose	478207_mir_hsa-miR-885-5p	15.38
25 mM glucose	478240_mir_hsa-miR-376a-3p	14.29
25 mM glucose	478078_mir_hsa-miR-382-5p	12.05
25 mM glucose	478210_mir_hsa-miR-93-5p	11.90
25 mM glucose	478270_mir_hsa-miR-27b-3p	11.11
25 mM glucose	477980_mir_hsa-miR-219a-5p	9.62
25 mM glucose	477851_mir_hsa-miR-130a-3p	8.93
25 mM glucose	477931_mir_hsa-miR-16-2-3p	8.40
25 mM glucose	478203_mir_hsa-miR-769-5p	7.52
25 mM glucose	478068_mir_hsa-miR-369-5p	6.90
25 mM glucose	478138_mir_hsa-miR-497-5p	6.90
25 mM glucose	478060_mir_hsa-miR-363-3p	6.62
25 mM glucose	480871_mir_hsa-miR-133b	6.58
25 mM glucose	477902_mir_hsa-miR-136-3p	6.45
25 mM glucose	478779_mir_hsa-miR-222-5p	6.37
25 mM glucose	477932_mir_hsa-miR-17-3p	5.92
25 mM glucose	478788_mir_hsa-miR-26a-2-3p	5.92
25 mM glucose	478197_mir_hsa-miR-708-5p	5.65
25 mM glucose	477899_mir_hsa-miR-130b-5p	5.62
25 mM glucose	478012_mir_hsa-miR-31-3p	5.56
25 mM glucose	479024_mir_hsa-miR-548n	5.56
25 mM glucose	478690_mir_hsa-miR-1291	5.35
25 mM glucose	477929_mir_hsa-miR-15b-3p	4.95
25 mM glucose	477996_mir_hsa-miR-26b-3p	4.95
25 mM glucose	478156_mir_hsa-miR-544a	4.24
25 mM glucose	479035_mir_hsa-miR-551b-5p	4.20
25 mM glucose	478015_mir_hsa-miR-31-5p	4.18

25 mM glucose	479059_mir_hsa-miR-579-3p	4.18
25 mM glucose	477825_mir_hsa-miR-301b-3p	4.07
25 mM glucose	478139_mir_hsa-miR-499a-5p	3.97
25 mM glucose	477959_mir_hsa-miR-197-3p	3.88
25 mM glucose	478544_mir_hsa-miR-129-2-3p	3.77
25 mM glucose	479229_mir_hsa-miR-29c-3p	3.56
25 mM glucose	478584_mir_hsa-miR-18b-5p	3.50
25 mM glucose	477928_mir_hsa-miR-15a-3p	3.46
25 mM glucose	477824_mir_hsa-miR-148b-3p	3.41
25 mM glucose	478422_mir_hsa-miR-486-3p	3.41
25 mM glucose	478181_mir_hsa-miR-628-3p	3.40
25 mM glucose	478159_mir_hsa-miR-551b-3p	3.22
25 mM glucose	478511_mir_hsa-miR-133a-3p	3.13
25 mM glucose	478003_mir_hsa-miR-29b-2-5p	3.09
25 mM glucose	478317_mir_hsa-miR-20a-3p	3.08
25 mM glucose	478626_mir_hsa-miR-1179	3.08
25 mM glucose	478326_mir_hsa-miR-370-3p	3.03
25 mM glucose	478889_mir_hsa-miR-431-5p	3.00
25 mM glucose	477887_mir_hsa-miR-126-3p	2.99
25 mM glucose	478479_mir_hsa-miR-33b-5p	2.93
25 mM glucose	479002_mir_hsa-miR-545-3p	2.93
25 mM glucose	478128_mir_hsa-miR-486-5p	2.83
25 mM glucose	478727_mir_hsa-miR-16-1-3p	2.82
25 mM glucose	478778_mir_hsa-miR-221-5p	2.64
25 mM glucose	478157_mir_hsa-miR-548a-3p	2.58
25 mM glucose	478582_mir_hsa-miR-135b-5p	2.53
25 mM glucose	477973_mir_hsa-miR-21-3p	2.48
25 mM glucose	478583_mir_hsa-miR-181b-5p	2.48
25 mM glucose	478126_mir_hsa-miR-485-5p	2.46

25 mM glucose	478178_mir_hsa-miR-624-5p	2.45
25 mM glucose	478418_mir_hsa-miR-26b-5p	2.44
25 mM glucose	478576_mir_hsa-let-7b-5p	2.42
25 mM glucose	477971_mir_hsa-miR-2110	2.35
25 mM glucose	478028_mir_hsa-miR-328-3p	2.30
25 mM glucose	478347_mir_hsa-miR-33a-5p	2.28
25 mM glucose	478342_mir_hsa-miR-766-3p	2.26
25 mM glucose	478653_mir_hsa-miR-1248	2.21
25 mM glucose	478058_mir_hsa-miR-362-3p	2.19
25 mM glucose	478683_mir_hsa-miR-1282	2.19
25 mM glucose	478043_mir_hsa-miR-342-3p	2.18
25 mM glucose	478999_mir_hsa-miR-541-3p	2.17
25 mM glucose	478432_mir_hsa-miR-483-5p	2.14
25 mM glucose	479235_mir_hsa-miR-30e-5p	2.14
25 mM glucose	478221_mir_hsa-let-7b-3p	2.13
25 mM glucose	477835_mir_hsa-miR-487b-3p	2.12
25 mM glucose	478135_mir_hsa-miR-494-3p	2.12
25 mM glucose	479166_mir_hsa-miR-758-3p	2.10
25 mM glucose	478641_mir_hsa-miR-1226-5p	2.09
25 mM glucose	478199_mir_hsa-miR-7-2-3p	2.04
25 mM glucose	478129_mir_hsa-miR-488-3p	2.01
25 mM glucose	478074_mir_hsa-miR-375	2
Up regulated		
Sample name	Target name	Fold change
2.5 mM glucose	477895_mir_hsa-miR-1290	413.31
2.5 mM glucose	478048_mir_hsa-miR-34a-5p	211.33
2.5 mM glucose	478177_mir_hsa-miR-616-3p	108.29
2.5 mM glucose	478270_mir_hsa-miR-27b-3p	41.39
2.5 mM glucose	478826_mir_hsa-miR-323b-5p	28.29

2.5 mM glucose	479177_mir_hsa-miR-769-3p	26.98
2.5 mM glucose	478753_mir_hsa-miR-200b-5p	22.61
2.5 mM glucose	478620_mir_hsa-miR-101-5p	16.35
2.5 mM glucose	477963_mir_hsa-miR-200b-3p	15.57
2.5 mM glucose	478793_mir_hsa-miR-299-5p	14.57
2.5 mM glucose	478065_mir_hsa-miR-365a-3p	11.67
2.5 mM glucose	479115_mir_hsa-miR-633	11.41
2.5 mM glucose	479041_mir_hsa-miR-556-3p	11.1
2.5 mM glucose	479217_mir_hsa-miR-941	10.28
2.5 mM glucose	478210_mir_hsa-miR-93-5p	9.5
2.5 mM glucose	477879_mir_hsa-miR-124-3p	8.75
2.5 mM glucose	478091_mir_hsa-miR-424-3p	7.59
2.5 mM glucose	479374_mir_hsa-miR-548k	7.17
2.5 mM glucose	477912_mir_hsa-miR-143-3p	6.66
2.5 mM glucose	478749_mir_hsa-miR-198	6.25
2.5 mM glucose	479297_mir_hsa-miR-513b-5p	5.78
2.5 mM glucose	478165_mir_hsa-miR-576-5p	5.73
2.5 mM glucose	478389_mir_hsa-miR-374b-5p	5.65
2.5 mM glucose	479067_mir_hsa-miR-585-3p	5.64
2.5 mM glucose	479469_mir_hsa-miR-625-5p	5.43
2.5 mM glucose	477852_mir_hsa-miR-550a-5p	4.88
2.5 mM glucose	478155_mir_hsa-miR-543	4.41
2.5 mM glucose	479131_mir_hsa-miR-651-5p	4.37
2.5 mM glucose	478238_mir_hsa-miR-374a-5p	3.87
2.5 mM glucose	477902_mir_hsa-miR-136-3p	3.77
2.5 mM glucose	478654_mir_hsa-miR-1249-3p	3.69
2.5 mM glucose	478855_mir_hsa-miR-374a-3p	3.62
2.5 mM glucose	479166_mir_hsa-miR-758-3p	3.58
2.5 mM glucose	478191_mir_hsa-miR-655-3p	3.49

2.5 mM glucose	478741_mir_hsa-miR-192-3p	3.39
2.5 mM glucose	478193_mir_hsa-miR-664a-3p	3.25
2.5 mM glucose	478752_mir_hsa-miR-200a-5p	3.11
2.5 mM glucose	477977_mir_hsa-miR-218-5p	3.1
2.5 mM glucose	478335_mir_hsa-miR-496	3.1
2.5 mM glucose	478253_mir_hsa-miR-103a-3p	3.08
2.5 mM glucose	478134_mir_hsa-miR-493-3p	3.04
2.5 mM glucose	478139_mir_hsa-miR-499a-5p	2.98
2.5 mM glucose	477825_mir_hsa-miR-301b-3p	2.95
2.5 mM glucose	479281_mir_hsa-let-7e-3p	2.95
2.5 mM glucose	478602_mir_hsa-miR-23b-3p	2.85
2.5 mM glucose	478040_mir_hsa-miR-339-5p	2.83
2.5 mM glucose	478951_mir_hsa-miR-500a-3p	2.82
2.5 mM glucose	479120_mir_hsa-miR-641	2.81
2.5 mM glucose	478059_mir_hsa-miR-362-5p	2.81
2.5 mM glucose	477904_mir_hsa-miR-137	2.76
2.5 mM glucose	478384_mir_hsa-miR-27a-3p	2.73
2.5 mM glucose	478318_mir_hsa-miR-212-3p	2.67
2.5 mM glucose	478439_mir_hsa-let-7d-5p	2.61
2.5 mM glucose	478494_mir_hsa-miR-10b-5p	2.58
2.5 mM glucose	477934_mir_hsa-miR-181c-5p	2.55
2.5 mM glucose	478027_mir_hsa-miR-326	2.43
2.5 mM glucose	478582_mir_hsa-miR-135b-5p	2.41
2.5 mM glucose	477976_mir_hsa-miR-216a-5p	2.4
2.5 mM glucose	478132_mir_hsa-miR-491-5p	2.39
2.5 mM glucose	479207_mir_hsa-miR-92b-5p	2.35
2.5 mM glucose	479150_mir_hsa-miR-665	2.32
2.5 mM glucose	478725_mir_hsa-miR-154-3p	2.31
2.5 mM glucose	478490_mir_hsa-miR-200a-3p	2.16

2.5 mM glucose	477943_mir_hsa-miR-188-5p	2.13
2.5 mM glucose	478130_mir_hsa-miR-489-3p	2.12
2.5 mM glucose	478143_mir_hsa-miR-503-5p	2.08
2.5 mM glucose	477853_mir_hsa-miR-323a-3p	2.08
Down regulated		
Sample name	Target name	Fold change
2.5 mM glucose	478591_mir_hsa-miR-302b-3p	>500
2.5 mM glucose	478719_mir_hsa-miR-148b-5p	>500
2.5 mM glucose	478732_mir_hsa-miR-185-3p	250
2.5 mM glucose	478207_mir_hsa-miR-885-5p	200
2.5 mM glucose	478687_mir_hsa-miR-1285-3p	200
2.5 mM glucose	478175_mir_hsa-miR-615-3p	142.86
2.5 mM glucose	479003_mir_hsa-miR-454-5p	83.33
2.5 mM glucose	477921_mir_hsa-miR-152-3p	62.5
2.5 mM glucose	478491_mir_hsa-miR-204-5p	38.46
2.5 mM glucose	478163_mir_hsa-miR-574-3p	30.3
2.5 mM glucose	478152_mir_hsa-miR-539-5p	18.18
2.5 mM glucose	477929_mir_hsa-miR-15b-3p	14.71
2.5 mM glucose	478068_mir_hsa-miR-369-5p	12.82
2.5 mM glucose	477932_mir_hsa-miR-17-3p	12.35
2.5 mM glucose	478307_mir_hsa-miR-136-5p	12.35
2.5 mM glucose	478003_mir_hsa-miR-29b-2-5p	12.2
2.5 mM glucose	478058_mir_hsa-miR-362-3p	12.2
2.5 mM glucose	478501_mir_hsa-miR-141-3p	10.42
2.5 mM glucose	478779_mir_hsa-miR-222-5p	9.52
2.5 mM glucose	477980_mir_hsa-miR-219a-5p	9.26
2.5 mM glucose	478012_mir_hsa-miR-31-3p	8.55
2.5 mM glucose	477996_mir_hsa-miR-26b-3p	8.47
2.5 mM glucose	478033_mir_hsa-miR-335-3p	7.14

2.5 mM glucose	477961_mir_hsa-miR-199a-3p	6.94
2.5 mM glucose	478317_mir_hsa-miR-20a-3p	6.94
2.5 mM glucose	477933_mir_hsa-miR-181c-3p	6.62
2.5 mM glucose	478214_mir_hsa-miR-9-5p	6.29
2.5 mM glucose	478032_mir_hsa-miR-331-5p	6.17
2.5 mM glucose	477824_mir_hsa-miR-148b-3p	5.95
2.5 mM glucose	479035_mir_hsa-miR-551b-5p	5.81
2.5 mM glucose	479057_mir_hsa-miR-577	5.05
2.5 mM glucose	478225_mir_hsa-miR-106a-5p	5
2.5 mM glucose	478178_mir_hsa-miR-624-5p	4.93
2.5 mM glucose	478179_mir_hsa-miR-625-3p	4.93
2.5 mM glucose	478750_mir_hsa-miR-19a-5p	4.83
2.5 mM glucose	478683_mir_hsa-miR-1282	4.74
2.5 mM glucose	478153_mir_hsa-miR-542-3p	4.42
2.5 mM glucose	479421_mir_hsa-miR-374b-3p	4.1
2.5 mM glucose	478309_mir_hsa-miR-500a-5p	3.89
2.5 mM glucose	478778_mir_hsa-miR-221-5p	3.86
2.5 mM glucose	478060_mir_hsa-miR-363-3p	3.7
2.5 mM glucose	479224_mir_hsa-miR-99a-3p	3.64
2.5 mM glucose	478827_mir_hsa-miR-32-3p	3.45
2.5 mM glucose	478156_mir_hsa-miR-544a	3.34
2.5 mM glucose	478138_mir_hsa-miR-497-5p	3.31
2.5 mM glucose	478578_mir_hsa-let-7f-5p	3.31
2.5 mM glucose	477971_mir_hsa-miR-2110	3.27
2.5 mM glucose	478513_mir_hsa-miR-146b-5p	3.24
2.5 mM glucose	478028_mir_hsa-miR-328-3p	3.15
2.5 mM glucose	478197_mir_hsa-miR-708-5p	3.07
2.5 mM glucose	478422_mir_hsa-miR-486-3p	3.05
2.5 mM glucose	479055_mir_hsa-miR-573	3.03

2.5 mM glucose	477931_mir_hsa-miR-16-2-3p	2.92
2.5 mM glucose	478917_mir_hsa-miR-452-3p	2.89
2.5 mM glucose	478859_mir_hsa-miR-376a-5p	2.85
2.5 mM glucose	477928_mir_hsa-miR-15a-3p	2.82
2.5 mM glucose	478329_mir_hsa-miR-454-3p	2.78
2.5 mM glucose	478674_mir_hsa-miR-1271-5p	2.75
2.5 mM glucose	477954_mir_hsa-miR-193a-5p	2.74
2.5 mM glucose	479517_mir_hsa-miR-181d-5p	2.72
2.5 mM glucose	478181_mir_hsa-miR-628-3p	2.65
2.5 mM glucose	479229_mir_hsa-miR-29c-3p	2.65
2.5 mM glucose	478690_mir_hsa-miR-1291	2.64
2.5 mM glucose	478476_mir_hsa-miR-1260a	2.63
2.5 mM glucose	478041_mir_hsa-miR-340-3p	2.6
2.5 mM glucose	478784_mir_hsa-miR-24-1-5p	2.5
2.5 mM glucose	477857_mir_hsa-miR-181a-5p	2.45
2.5 mM glucose	478199_mir_hsa-miR-7-2-3p	2.43
2.5 mM glucose	477890_mir_hsa-miR-1275	2.39
2.5 mM glucose	478159_mir_hsa-miR-551b-3p	2.37
2.5 mM glucose	478168_mir_hsa-miR-590-3p	2.33
2.5 mM glucose	479526_mir_hsa-miR-411-3p	2.33
2.5 mM glucose	478215_mir_hsa-miR-96-5p	2.32
2.5 mM glucose	479228_mir_hsa-miR-19a-3p	2.28
2.5 mM glucose	477962_mir_hsa-miR-19b-1-5p	2.23
2.5 mM glucose	478362_mir_hsa-miR-548e-3p	2.2
2.5 mM glucose	478231_mir_hsa-miR-199a-5p	2.18
2.5 mM glucose	479003_mir_hsa-miR-545-5p	2.16
2.5 mM glucose	478581_mir_hsa-miR-135a-5p	2.14
2.5 mM glucose	478587_mir_hsa-miR-29a-3p	2.12
2.5 mM glucose	477850_mir_hsa-let-7g-3p	2.11

2.5 mM glucose	478653_mir_hsa-miR-1248	2.11
2.5 mM glucose	477899_mir_hsa-miR-130b-5p	2.11
2.5 mM glucose	478043_mir_hsa-miR-342-3p	2.08
2.5 mM glucose	478705_mir_hsa-miR-132-5p	2.07
2.5 mM glucose	478131_mir_hsa-miR-490-3p	2.06
2.5 mM glucose	477973_mir_hsa-miR-21-3p	2.02
2.5 mM glucose	479235_mir_hsa-miR-30e-5p	2.02
Up regulated		
Sample name	Target name	Fold change
< 3% O2	478179_mir_hsa-miR-625-3p	66.28
< 3% O2	478225_mir_hsa-miR-106a-5p	65.47
< 3% O2	478210_mir_hsa-miR-93-5p	49.17
< 3% O2	478788_mir_hsa-miR-26a-2-3p	46.85
< 3% O2	478732_mir_hsa-miR-185-3p	26.11
< 3% O2	479067_mir_hsa-miR-585-3p	24.27
< 3% O2	477913_mir_hsa-miR-144-3p	20.59
< 3% O2	478163_mir_hsa-miR-574-3p	16.69
< 3% O2	478058_mir_hsa-miR-362-3p	15.41
< 3% O2	477896_mir_hsa-miR-129-5p	15.18
< 3% O2	478317_mir_hsa-miR-20a-3p	14.66
< 3% O2	479177_mir_hsa-miR-769-3p	14.24
< 3% O2	478494_mir_hsa-miR-10b-5p	12.27
< 3% O2	478830_mir_hsa-miR-330-5p	11.83
< 3% O2	478165_mir_hsa-miR-576-5p	11.74
< 3% O2	479002_mir_hsa-miR-545-3p	10.88
< 3% O2	478152_mir_hsa-miR-539-5p	10.64
< 3% O2	478778_mir_hsa-miR-221-5p	10.21
< 3% O2	478491_mir_hsa-miR-204-5p	9.01
< 3% O2	478630_mir_hsa-miR-1197	7.77

< 3% O2	477902_mir_hsa-miR-136-3p	7.41
< 3% O2	477922_mir_hsa-miR-153-3p	7.23
< 3% O2	478439_mir_hsa-let-7d-5p	6.72
< 3% O2	479448_mir_hsa-miR-30a-5p	6.12
< 3% O2	478307_mir_hsa-miR-136-5p	6
< 3% O2	477995_mir_hsa-miR-26a-5p	5.28
< 3% O2	478743_mir_hsa-miR-194-3p	5.15
< 3% O2	477885_mir_hsa-miR-125b-5p	5.05
< 3% O2	479072_mir_hsa-miR-589-3p	5.04
< 3% O2	479187_mir_hsa-miR-876-5p	5.02
< 3% O2	480870_mir_hsa-miR-548d-5p	4.99
< 3% O2	478641_mir_hsa-miR-1226-5p	4.97
< 3% O2	478197_mir_hsa-miR-708-5p	4.89
< 3% O2	477883_mir_hsa-miR-125a-3p	4.62
< 3% O2	478041_mir_hsa-miR-340-3p	4.54
< 3% O2	477951_mir_hsa-miR-191-3p	3.92
< 3% O2	478191_mir_hsa-miR-655-3p	3.71
< 3% O2	477855_mir_hsa-miR-122-5p	3.54
< 3% O2	477928_mir_hsa-miR-15a-3p	3.49
< 3% O2	479131_mir_hsa-miR-651-5p	3.48
< 3% O2	477877_mir_hsa-miR-1233-3p	3.44
< 3% O2	479228_mir_hsa-miR-19a-3p	3.41
< 3% O2	478859_mir_hsa-miR-376a-5p	3.38
< 3% O2	478136_mir_hsa-miR-495-3p	3.23
< 3% O2	479121_mir_hsa-miR-642a-5p	3.22
< 3% O2	477982_mir_hsa-miR-222-3p	3.21
< 3% O2	478691_mir_hsa-miR-1292-5p	3.17
< 3% O2	478644_mir_hsa-miR-1228-5p	3.15
< 3% O2	479101_mir_hsa-miR-618	3.12

< 3% O2	478384_mir_hsa-miR-27a-3p	3.05
< 3% O2	478157_mir_hsa-miR-548a-3p	3.03
< 3% O2	477850_mir_hsa-let-7g-3p	3.02
< 3% O2	478720_mir_hsa-miR-149-3p	3.01
< 3% O2	477952_mir_hsa-miR-191-5p	2.93
< 3% O2	478238_mir_hsa-miR-374a-5p	2.92
< 3% O2	478490_mir_hsa-miR-200a-3p	2.92
< 3% O2	478690_mir_hsa-miR-1291	2.83
< 3% O2	478181_mir_hsa-miR-628-3p	2.81
< 3% O2	478015_mir_hsa-miR-31-5p	2.77
< 3% O2	478133_mir_hsa-miR-492	2.75
< 3% O2	478084_mir_hsa-miR-409-3p	2.7
< 3% O2	478138_mir_hsa-miR-497-5p	2.7
< 3% O2	478126_mir_hsa-miR-485-5p	2.65
< 3% O2	477987_mir_hsa-miR-22-5p	2.64
< 3% O2	477980_mir_hsa-miR-219a-5p	2.56
< 3% O2	479055_mir_hsa-miR-573	2.53
< 3% O2	478230_mir_hsa-miR-196a-5p	2.51
< 3% O2	479137_mir_hsa-miR-656-3p	2.49
< 3% O2	478324_mir_hsa-miR-335-5p	2.47
< 3% O2	478293_mir_cel-miR-39-3p	2.39
< 3% O2	478389_mir_hsa-miR-374b-5p	2.38
< 3% O2	478752_mir_hsa-miR-200a-5p	2.37
< 3% O2	478306_mir_hsa-miR-193a-3p	2.32
< 3% O2	479003_mir_hsa-miR-545-5p	2.29
< 3% O2	478155_mir_hsa-miR-543	2.27
< 3% O2	478368_mir_hsa-miR-654-5p	2.27
< 3% O2	478088_mir_hsa-miR-421	2.26
< 3% O2	478342_mir_hsa-miR-766-3p	2.24

< 3% O2	478215_mir_hsa-miR-96-5p	2.24
< 3% O2	478023_mir_hsa-miR-324-3p	2.24
< 3% O2	479517_mir_hsa-miR-181d-5p	2.23
< 3% O2	478158_mir_hsa-miR-551a	2.23
< 3% O2	477801_mir_hsa-let-7f-1-3p	2.22
< 3% O2	477820_mir_hsa-miR-1-3p	2.2
< 3% O2	478192_mir_hsa-miR-660-5p	2.16
< 3% O2	478583_mir_hsa-miR-181b-5p	2.14
< 3% O2	478388_mir_hsa-miR-30e-3p	2.13
< 3% O2	479530_mir_hsa-miR-518d-5p	2.12
< 3% O2	478586_mir_hsa-miR-20a-5p	2.12
< 3% O2	477862_mir_hsa-let-7i-3p	2.11
< 3% O2	477961_mir_hsa-miR-199a-3p	2.09
< 3% O2	478205_mir_hsa-miR-874-3p	2.09
< 3% O2	477956_mir_hsa-miR-194-5p	2.04
< 3% O2	479000_mir_hsa-miR-541-5p	2.03
< 3% O2	479405_mir_hsa-miR-181a-3p	2.01
< 3% O2	478128_mir_hsa-miR-486-5p	2.01
< 3% O2	478193_mir_hsa-miR-664a-3p	2
Down regulated		
Sample name	Target name	Fold change
< 3% O2	478025_mir_hsa-miR-325	>500
< 3% O2	478237_mir_hsa-miR-302d-3p	>500
< 3% O2	478860_mir_hsa-miR-376b-3p	>500
< 3% O2	478995_mir_hsa-miR-525-3p	>500
< 3% O2	478207_mir_hsa-miR-885-5p	>500
< 3% O2	479003_mir_hsa-miR-454-5p	76.92
< 3% O2	477921_mir_hsa-miR-152-3p	66.67
< 3% O2	478307_mir_hsa-miR-136-5p	24.39

< 3% O2	478214_mir_hsa-miR-9-5p	15.15
< 3% O2	477879_mir_hsa-miR-124-3p	14.49
< 3% O2	478793_mir_hsa-miR-299-5p	14.29
< 3% O2	478270_mir_hsa-miR-27b-3p	11.76
< 3% O2	479053_mir_hsa-miR-570-3p	10.75
< 3% O2	477929_mir_hsa-miR-15b-3p	10.53
< 3% O2	478339_mir_hsa-miR-597-5p	9.62
< 3% O2	477963_mir_hsa-miR-200b-3p	9.52
< 3% O2	477973_mir_hsa-miR-21-3p	9.52
< 3% O2	479073_mir_hsa-miR-589-5p	8.93
< 3% O2	478240_mir_hsa-miR-376a-3p	8.2
< 3% O2	477959_mir_hsa-miR-197-3p	7.63
< 3% O2	478177_mir_hsa-miR-616-3p	6.9
< 3% O2	478544_mir_hsa-miR-129-2-3p	6.37
< 3% O2	478687_mir_hsa-miR-1285-3p	6.1
< 3% O2	478273_mir_hsa-miR-30a-3p	4.65
< 3% O2	478035_mir_hsa-miR-337-3p	4.24
< 3% O2	479022_mir_hsa-miR-548j-5p	3.82
< 3% O2	478620_mir_hsa-miR-101-5p	3.77
< 3% O2	478130_mir_hsa-miR-489-3p	3.66
< 3% O2	478139_mir_hsa-miR-499a-5p	3.5
< 3% O2	478725_mir_hsa-miR-154-3p	3.48
< 3% O2	479035_mir_hsa-miR-551b-5p	3.48
< 3% O2	478479_mir_hsa-miR-33b-5p	3.46
< 3% O2	478087_mir_hsa-miR-412-3p	3.45
< 3% O2	477899_mir_hsa-miR-130b-5p	3.36
< 3% O2	478581_mir_hsa-miR-135a-5p	3.32
< 3% O2	477895_mir_hsa-miR-1290	3.21
< 3% O2	479207_mir_hsa-miR-92b-5p	3.21

< 3% O2	477825_mir_hsa-miR-301b-3p	3.17
< 3% O2	478076_mir_hsa-miR-378a-5p	3.03
< 3% O2	478159_mir_hsa-miR-551b-3p	2.99
< 3% O2	479526_mir_hsa-miR-411-3p	2.99
< 3% O2	477954_mir_hsa-miR-193a-5p	2.87
< 3% O2	478369_mir_hsa-miR-29b-3p	2.78
< 3% O2	478594_mir_hsa-miR-320a	2.75
< 3% O2	478718_mir_hsa-miR-148a-5p	2.66
< 3% O2	477944_mir_hsa-miR-18a-3p	2.6
< 3% O2	478168_mir_hsa-miR-590-3p	2.53
< 3% O2	478203_mir_hsa-miR-769-5p	2.51
< 3% O2	478683_mir_hsa-miR-1282	2.49
< 3% O2	478113_mir_hsa-miR-455-5p	2.46
< 3% O2	478914_mir_hsa-miR-450b-5p	2.42
< 3% O2	478026_mir_hsa-miR-32-5p	2.4
< 3% O2	477937_mir_hsa-miR-183-5p	2.35
< 3% O2	479212_mir_hsa-miR-937-3p	2.29
< 3% O2	477991_mir_hsa-miR-23b-5p	2.28
< 3% O2	477890_mir_hsa-miR-1275	2.22
< 3% O2	478262_mir_hsa-miR-192-5p	2.22
< 3% O2	478033_mir_hsa-miR-335-3p	2.14
< 3% O2	478134_mir_hsa-miR-493-3p	2.12
< 3% O2	479178_mir_hsa-miR-770-5p	2.11
< 3% O2	478060_mir_hsa-miR-363-3p	2.1
< 3% O2	477866_mir_hsa-miR-106b-3p	2.09
< 3% O2	478326_mir_hsa-miR-370-3p	2.09
< 3% O2	477816_mir_hsa-miR-381-3p	2.05
Up regulated		
Sample name	Target name	Fold change

0.5 mM Palmitic Acid	478513_mir_hsa-miR-146b-5p	443.64
0.5 mM Palmitic Acid	478913_mir_hsa-miR-450b-3p	364.07
0.5 mM Palmitic Acid	477936_mir_hsa-miR-183-3p	82.6
0.5 mM Palmitic Acid	478273_mir_hsa-miR-30a-3p	65.08
0.5 mM Palmitic Acid	478384_mir_hsa-miR-27a-3p	52.77
0.5 mM Palmitic Acid	478065_mir_hsa-miR-365a-3p	47.34
0.5 mM Palmitic Acid	478210_mir_hsa-miR-93-5p	42.43
0.5 mM Palmitic Acid	478785_mir_hsa-miR-24-2-5p	35.22
0.5 mM Palmitic Acid	478432_mir_hsa-miR-483-5p	17.63
0.5 mM Palmitic Acid	478179_mir_hsa-miR-625-3p	14.78
0.5 mM Palmitic Acid	478293_mir_cel-miR-39-3p	14.23
0.5 mM Palmitic Acid	478793_mir_hsa-miR-299-5p	10.98
0.5 mM Palmitic Acid	479115_mir_hsa-miR-633	9.19
0.5 mM Palmitic Acid	478200_mir_hsa-miR-744-5p	8.52
0.5 mM Palmitic Acid	479374_mir_hsa-miR-548k	7.6
0.5 mM Palmitic Acid	479041_mir_hsa-miR-556-3p	7.36
0.5 mM Palmitic Acid	478165_mir_hsa-miR-576-5p	7.05
0.5 mM Palmitic Acid	479281_mir_hsa-let-7e-3p	7.01
0.5 mM Palmitic Acid	477933_mir_hsa-miR-181c-3p	6.81
0.5 mM Palmitic Acid	477879_mir_hsa-miR-124-3p	6.67
0.5 mM Palmitic Acid	478183_mir_hsa-miR-629-5p	6.56
0.5 mM Palmitic Acid	478155_mir_hsa-miR-543	6.43
0.5 mM Palmitic Acid	478145_mir_hsa-miR-505-3p	6.16
0.5 mM Palmitic Acid	478164_mir_hsa-miR-576-3p	5.84
0.5 mM Palmitic Acid	478191_mir_hsa-miR-655-3p	5.56
0.5 mM Palmitic Acid	478126_mir_hsa-miR-485-5p	5.46
0.5 mM Palmitic Acid	477863_mir_hsa-miR-101-3p	5.27
0.5 mM Palmitic Acid	478594_mir_hsa-miR-320a	5.11
0.5 mM Palmitic Acid	478790_mir_hsa-miR-296-3p	4.72

0.5 mM Palmitic Acid	477976_mir_hsa-miR-216a-5p	4.58
0.5 mM Palmitic Acid	478602_mir_hsa-miR-23b-3p	4.52
0.5 mM Palmitic Acid	477851_mir_hsa-miR-130a-3p	4.34
0.5 mM Palmitic Acid	477918_mir_hsa-miR-150-5p	4.32
0.5 mM Palmitic Acid	478029_mir_hsa-miR-329-3p	4.04
0.5 mM Palmitic Acid	479176_mir_hsa-miR-767-5p	4.01
0.5 mM Palmitic Acid	478544_mir_hsa-miR-129-2-3p	3.79
0.5 mM Palmitic Acid	477963_mir_hsa-miR-200b-3p	3.7
0.5 mM Palmitic Acid	478476_mir_hsa-miR-1260a	3.62
0.5 mM Palmitic Acid	479059_mir_hsa-miR-579-3p	3.61
0.5 mM Palmitic Acid	478579_mir_hsa-let-7e-5p	3.5
0.5 mM Palmitic Acid	477952_mir_hsa-miR-191-5p	3.3
0.5 mM Palmitic Acid	477826_mir_hsa-miR-487a-3p	3.17
0.5 mM Palmitic Acid	477942_mir_hsa-miR-188-3p	2.98
0.5 mM Palmitic Acid	479121_mir_hsa-miR-642a-5p	2.96
0.5 mM Palmitic Acid	478580_mir_hsa-let-7g-5p	2.92
0.5 mM Palmitic Acid	477835_mir_hsa-miR-487b-3p	2.87
0.5 mM Palmitic Acid	478619_mir_hsa-miR-100-3p	2.84
0.5 mM Palmitic Acid	477943_mir_hsa-miR-188-5p	2.83
0.5 mM Palmitic Acid	478362_mir_hsa-miR-548e-3p	2.81
0.5 mM Palmitic Acid	478327_mir_hsa-miR-423-3p	2.78
0.5 mM Palmitic Acid	478023_mir_hsa-miR-324-3p	2.74
0.5 mM Palmitic Acid	478389_mir_hsa-miR-374b-5p	2.73
0.5 mM Palmitic Acid	478101_mir_hsa-miR-432-5p	2.67
0.5 mM Palmitic Acid	478578_mir_hsa-let-7f-5p	2.64
0.5 mM Palmitic Acid	478576_mir_hsa-let-7b-5p	2.62
0.5 mM Palmitic Acid	478720_mir_hsa-miR-149-3p	2.61
0.5 mM Palmitic Acid	478575_mir_hsa-let-7a-5p	2.58
0.5 mM Palmitic Acid	478203_mir_hsa-miR-769-5p	2.42

0.5 mM Palmitic Acid	479131_mir_hsa-miR-651-5p	2.4
0.5 mM Palmitic Acid	478626_mir_hsa-miR-1179	2.38
0.5 mM Palmitic Acid	477957_mir_hsa-miR-195-5p	2.29
0.5 mM Palmitic Acid	478314_mir_hsa-miR-193b-3p	2.27
0.5 mM Palmitic Acid	478375_mir_hsa-let-7i-5p	2.22
0.5 mM Palmitic Acid	478494_mir_hsa-miR-10b-5p	2.15
0.5 mM Palmitic Acid	478349_mir_hsa-miR-378a-3p	2.14
0.5 mM Palmitic Acid	478318_mir_hsa-miR-212-3p	2.1
0.5 mM Palmitic Acid	477994_mir_hsa-miR-25-3p	2.09
0.5 mM Palmitic Acid	478789_mir_hsa-miR-27b-5p	2.09
0.5 mM Palmitic Acid	477921_mir_hsa-miR-152-3p	2.07
0.5 mM Palmitic Acid	477904_mir_hsa-miR-137	2.04
0.5 mM Palmitic Acid	478028_mir_hsa-miR-328-3p	2.02
0.5 mM Palmitic Acid	477992_mir_hsa-miR-24-3p	2.02
0.5 mM Palmitic Acid	478030_mir_hsa-miR-330-3p	2.01
0.5 mM Palmitic Acid	478078_mir_hsa-miR-382-5p	2.01
0.5 mM Palmitic Acid	478691_mir_hsa-miR-1292-5p	2
Down regulated		
Sample name	Target name	Fold change
0.5 mM Palmitic Acid	477962_mir_hsa-miR-19b-1-5p	>500
0.5 mM Palmitic Acid	478168_mir_hsa-miR-454-5p	142.86
0.5 mM Palmitic Acid	477913_mir_hsa-miR-144-3p	90.91
0.5 mM Palmitic Acid	478917_mir_hsa-miR-452-3p	83.33
0.5 mM Palmitic Acid	478270_mir_hsa-miR-27b-3p	30.3
0.5 mM Palmitic Acid	478732_mir_hsa-miR-185-3p	27.03
0.5 mM Palmitic Acid	478831_mir_hsa-miR-33a-3p	22.22
0.5 mM Palmitic Acid	478307_mir_hsa-miR-136-5p	15.38
0.5 mM Palmitic Acid	478329_mir_hsa-miR-454-3p	11.36
0.5 mM Palmitic Acid	478660_mir_hsa-miR-1254	9.8

0.5 mM Palmitic Acid	478207_mir_hsa-miR-885-5p	9.35
0.5 mM Palmitic Acid	478240_mir_hsa-miR-376a-3p	9.35
0.5 mM Palmitic Acid	478138_mir_hsa-miR-497-5p	8.7
0.5 mM Palmitic Acid	479166_mir_hsa-miR-758-3p	8.62
0.5 mM Palmitic Acid	479000_mir_hsa-miR-541-5p	7.52
0.5 mM Palmitic Acid	478158_mir_hsa-miR-551a	7.14
0.5 mM Palmitic Acid	479055_mir_hsa-miR-573	7.14
0.5 mM Palmitic Acid	477931_mir_hsa-miR-16-2-3p	6.9
0.5 mM Palmitic Acid	478264_mir_hsa-miR-19b-3p	6.8
0.5 mM Palmitic Acid	478754_mir_hsa-miR-200c-5p	6.58
0.5 mM Palmitic Acid	479134_mir_hsa-miR-653-5p	6.54
0.5 mM Palmitic Acid	477961_mir_hsa-miR-199a-3p	5.62
0.5 mM Palmitic Acid	479002_mir_hsa-miR-545-3p	5.52
0.5 mM Palmitic Acid	478113_mir_hsa-miR-455-5p	5.41
0.5 mM Palmitic Acid	479469_mir_hsa-miR-625-5p	5.38
0.5 mM Palmitic Acid	479205_mir_hsa-miR-92a-1-5p	5.26
0.5 mM Palmitic Acid	478163_mir_hsa-miR-574-3p	5.24
0.5 mM Palmitic Acid	478197_mir_hsa-miR-708-5p	5.24
0.5 mM Palmitic Acid	478705_mir_hsa-miR-132-5p	5.13
0.5 mM Palmitic Acid	478178_mir_hsa-miR-624-5p	5.05
0.5 mM Palmitic Acid	478369_mir_hsa-miR-29b-3p	4.98
0.5 mM Palmitic Acid	478784_mir_hsa-miR-24-1-5p	4.95
0.5 mM Palmitic Acid	477932_mir_hsa-miR-17-3p	4.83
0.5 mM Palmitic Acid	478068_mir_hsa-miR-369-5p	4.69
0.5 mM Palmitic Acid	478181_mir_hsa-miR-628-3p	4.59
0.5 mM Palmitic Acid	478193_mir_hsa-miR-664a-3p	4.57
0.5 mM Palmitic Acid	479530_mir_hsa-miR-518d-5p	4.52
0.5 mM Palmitic Acid	478341_mir_hsa-miR-7-5p	4.37
0.5 mM Palmitic Acid	478804_mir_hsa-miR-30b-3p	4.29

0.5 mM Palmitic Acid	477959_mir_hsa-miR-197-3p	3.82
0.5 mM Palmitic Acid	479003_mir_hsa-miR-545-5p	3.75
0.5 mM Palmitic Acid	478199_mir_hsa-miR-7-2-3p	3.57
0.5 mM Palmitic Acid	478216_mir_hsa-miR-99b-3p	3.57
0.5 mM Palmitic Acid	478003_mir_hsa-miR-29b-2-5p	3.53
0.5 mM Palmitic Acid	478015_mir_hsa-miR-31-5p	3.37
0.5 mM Palmitic Acid	478674_mir_hsa-miR-1271-5p	3.34
0.5 mM Palmitic Acid	479187_mir_hsa-miR-876-5p	3.33
0.5 mM Palmitic Acid	477973_mir_hsa-miR-21-3p	3.28
0.5 mM Palmitic Acid	477823_mir_hsa-miR-92b-3p	3.18
0.5 mM Palmitic Acid	478238_mir_hsa-miR-374a-5p	3.04
0.5 mM Palmitic Acid	477804_mir_hsa-miR-20b-5p	3.03
0.5 mM Palmitic Acid	478587_mir_hsa-miR-29a-3p	2.99
0.5 mM Palmitic Acid	478792_mir_hsa-miR-299-3p	2.97
0.5 mM Palmitic Acid	478826_mir_hsa-miR-323b-5p	2.95
0.5 mM Palmitic Acid	478622_mir_hsa-miR-105-3p	2.92
0.5 mM Palmitic Acid	479229_mir_hsa-miR-29c-3p	2.88
0.5 mM Palmitic Acid	477939_mir_hsa-miR-185-5p	2.87
0.5 mM Palmitic Acid	478630_mir_hsa-miR-1197	2.85
0.5 mM Palmitic Acid	479150_mir_hsa-miR-665	2.85
0.5 mM Palmitic Acid	478491_mir_hsa-miR-204-5p	2.83
0.5 mM Palmitic Acid	477887_mir_hsa-miR-126-3p	2.8
0.5 mM Palmitic Acid	477982_mir_hsa-miR-222-3p	2.77
0.5 mM Palmitic Acid	478196_mir_hsa-miR-675-5p	2.65
0.5 mM Palmitic Acid	477901_mir_hsa-miR-134-5p	2.62
0.5 mM Palmitic Acid	478752_mir_hsa-miR-200a-5p	2.61
0.5 mM Palmitic Acid	479532_mir_hsa-miR-518f-5p	2.6
0.5 mM Palmitic Acid	478209_mir_hsa-miR-93-3p	2.6
0.5 mM Palmitic Acid	478055_mir_hsa-miR-361-3p	2.57

0.5 mM Palmitic Acid	479451_mir_hsa-miR-1296-5p	2.57
0.5 mM Palmitic Acid	479405_mir_hsa-miR-181a-3p	2.56
0.5 mM Palmitic Acid	477922_mir_hsa-miR-153-3p	2.55
0.5 mM Palmitic Acid	477866_mir_hsa-miR-106b-3p	2.53
0.5 mM Palmitic Acid	477885_mir_hsa-miR-125b-5p	2.53
0.5 mM Palmitic Acid	478159_mir_hsa-miR-551b-3p	2.53
0.5 mM Palmitic Acid	480871_mir_hsa-miR-133b	2.5
0.5 mM Palmitic Acid	478221_mir_hsa-let-7b-3p	2.49
0.5 mM Palmitic Acid	477951_mir_hsa-miR-191-3p	2.48
0.5 mM Palmitic Acid	480872_mir_hsa-miR-548am-5p	2.48
0.5 mM Palmitic Acid	478033_mir_hsa-miR-335-3p	2.46
0.5 mM Palmitic Acid	478192_mir_hsa-miR-660-5p	2.39
0.5 mM Palmitic Acid	478052_mir_hsa-miR-34c-5p	2.34
0.5 mM Palmitic Acid	478368_mir_hsa-miR-654-5p	2.33
0.5 mM Palmitic Acid	478060_mir_hsa-miR-363-3p	2.29
0.5 mM Palmitic Acid	479217_mir_hsa-miR-941	2.28
0.5 mM Palmitic Acid	478342_mir_hsa-miR-766-3p	2.27
0.5 mM Palmitic Acid	478253_mir_hsa-miR-103a-3p	2.24
0.5 mM Palmitic Acid	478048_mir_hsa-miR-34a-5p	2.22
0.5 mM Palmitic Acid	477824_mir_hsa-miR-148b-3p	2.2
0.5 mM Palmitic Acid	478106_mir_hsa-miR-450a-5p	2.2
0.5 mM Palmitic Acid	478175_mir_hsa-miR-615-3p	2.19
0.5 mM Palmitic Acid	478412_mir_hsa-miR-106b-5p	2.16
0.5 mM Palmitic Acid	477899_mir_hsa-miR-130b-5p	2.15
0.5 mM Palmitic Acid	478185_mir_hsa-miR-636	2.09
0.5 mM Palmitic Acid	479135_mir_hsa-miR-654-3p	2.07
0.5 mM Palmitic Acid	478067_mir_hsa-miR-369-3p	2.06
0.5 mM Palmitic Acid	478132_mir_hsa-miR-491-5p	2
Up regulated		

Sample name	Target name	Fold change
cytokine treatment	479530_mir_hsa-miR-518d-5p	>500
cytokine treatment	477933_mir_hsa-miR-181c-3p	215.01
cytokine treatment	477936_mir_hsa-miR-183-3p	73.72
cytokine treatment	478793_mir_hsa-miR-299-5p	41.94
cytokine treatment	478183_mir_hsa-miR-629-5p	23.86
cytokine treatment	478691_mir_hsa-miR-1292-5p	21.08
cytokine treatment	477921_mir_hsa-miR-152-3p	19.5
cytokine treatment	478318_mir_hsa-miR-212-3p	18.71
cytokine treatment	478432_mir_hsa-miR-483-5p	18.4
cytokine treatment	478913_mir_hsa-miR-450b-3p	13.88
cytokine treatment	479067_mir_hsa-miR-585-3p	13.03
cytokine treatment	478683_mir_hsa-miR-1282	12.96
cytokine treatment	477929_mir_hsa-miR-15b-3p	11.4
cytokine treatment	479057_mir_hsa-miR-577	10.78
cytokine treatment	479115_mir_hsa-miR-633	9.67
cytokine treatment	478513_mir_hsa-miR-146b-5p	9.53
cytokine treatment	478153_mir_hsa-miR-542-3p	8.76
cytokine treatment	478790_mir_hsa-miR-296-3p	7.61
cytokine treatment	479131_mir_hsa-miR-651-5p	6.97
cytokine treatment	478753_mir_hsa-miR-200b-5p	6.74
cytokine treatment	479421_mir_hsa-miR-374b-3p	6.49
cytokine treatment	478587_mir_hsa-miR-29a-3p	6.13
cytokine treatment	478065_mir_hsa-miR-365a-3p	5.56
cytokine treatment	478590_mir_hsa-miR-98-5p	5.44
cytokine treatment	478389_mir_hsa-miR-374b-5p	4.79
cytokine treatment	479374_mir_hsa-miR-548k	4.67
cytokine treatment	478041_mir_hsa-miR-340-3p	4.19
cytokine treatment	477896_mir_hsa-miR-129-5p	4.02

cytokine treatment	479134_mir_hsa-miR-653-5p	3.61
cytokine treatment	479212_mir_hsa-miR-937-3p	3.54
cytokine treatment	478191_mir_hsa-miR-655-3p	3.47
cytokine treatment	477963_mir_hsa-miR-200b-3p	3.45
cytokine treatment	477976_mir_hsa-miR-216a-5p	3.29
cytokine treatment	478214_mir_hsa-miR-9-5p	3.28
cytokine treatment	477863_mir_hsa-miR-101-3p	3.2
cytokine treatment	478145_mir_hsa-miR-505-3p	3.11
cytokine treatment	477804_mir_hsa-miR-20b-5p	3.04
cytokine treatment	477931_mir_hsa-miR-16-2-3p	3.04
cytokine treatment	479176_mir_hsa-miR-767-5p	2.89
cytokine treatment	477980_mir_hsa-miR-219a-5p	2.8
cytokine treatment	477895_mir_hsa-miR-1290	2.8
cytokine treatment	479207_mir_hsa-miR-92b-5p	2.74
cytokine treatment	478038_mir_hsa-miR-338-5p	2.63
cytokine treatment	477918_mir_hsa-miR-150-5p	2.5
cytokine treatment	478752_mir_hsa-miR-200a-5p	2.5
cytokine treatment	478602_mir_hsa-miR-23b-3p	2.44
cytokine treatment	478494_mir_hsa-miR-10b-5p	2.43
cytokine treatment	478544_mir_hsa-miR-129-2-3p	2.24
cytokine treatment	478325_mir_hsa-miR-339-3p	2.24
cytokine treatment	478773_mir_hsa-miR-217	2.16
cytokine treatment	478743_mir_hsa-miR-194-3p	2.12
cytokine treatment	478155_mir_hsa-miR-543	2.05
cytokine treatment	477952_mir_hsa-miR-191-5p	2.02
Down regulated		
Sample name	Target name	Fold change
cytokine treatment	479064_mir_hsa-miR-582-3p	333.33
cytokine treatment	478914_mir_hsa-miR-450b-5p	200

cytokine treatment	477913_mir_hsa-miR-144-3p	166.67
cytokine treatment	478177_mir_hsa-miR-616-3p	142.86
cytokine treatment	478307_mir_hsa-miR-136-5p	66.67
cytokine treatment	478827_mir_hsa-miR-32-3p	62.5
cytokine treatment	478207_mir_hsa-miR-885-5p	55.56
cytokine treatment	479059_mir_hsa-miR-579-3p	35.71
cytokine treatment	479041_mir_hsa-miR-556-3p	32.26
cytokine treatment	478131_mir_hsa-miR-490-3p	27.78
cytokine treatment	478270_mir_hsa-miR-27b-3p	22.73
cytokine treatment	478139_mir_hsa-miR-499a-5p	21.28
cytokine treatment	477879_mir_hsa-miR-124-3p	16.67
cytokine treatment	478210_mir_hsa-miR-93-5p	14.29
cytokine treatment	478060_mir_hsa-miR-363-3p	12.35
cytokine treatment	478329_mir_hsa-miR-454-3p	11.49
cytokine treatment	479003_mir_hsa-miR-545-5p	11.49
cytokine treatment	478831_mir_hsa-miR-33a-3p	10.75
cytokine treatment	478306_mir_hsa-miR-193a-3p	10.1
cytokine treatment	478152_mir_hsa-miR-539-5p	9.9
cytokine treatment	478491_mir_hsa-miR-204-5p	9.01
cytokine treatment	479405_mir_hsa-miR-181a-3p	8.93
cytokine treatment	477962_mir_hsa-miR-19b-1-5p	8.2
cytokine treatment	478199_mir_hsa-miR-7-2-3p	7.87
cytokine treatment	478015_mir_hsa-miR-31-5p	6.76
cytokine treatment	478532_mir_hsa-miR-23a-3p	6.37
cytokine treatment	478025_mir_hsa-miR-325	5.99
cytokine treatment	477937_mir_hsa-miR-183-5p	5.95
cytokine treatment	479047_mir_hsa-miR-562	5.92
cytokine treatment	478179_mir_hsa-miR-625-3p	5.62
cytokine treatment	477853_mir_hsa-miR-323a-3p	5.41

cytokine treatment	477888_mir_hsa-miR-126-5p	5.15
cytokine treatment	478804_mir_hsa-miR-30b-3p	5.1
cytokine treatment	478113_mir_hsa-miR-455-5p	5.05
cytokine treatment	478012_mir_hsa-miR-31-3p	5.05
cytokine treatment	478349_mir_hsa-miR-378a-3p	5
cytokine treatment	478888_mir_hsa-miR-431-3p	4.81
cytokine treatment	478826_mir_hsa-miR-323b-5p	4.74
cytokine treatment	478586_mir_hsa-miR-20a-5p	4.69
cytokine treatment	478002_mir_hsa-miR-29a-5p	4.65
cytokine treatment	478657_mir_hsa-miR-1251-5p	4.61
cytokine treatment	479032_mir_hsa-miR-550a-3p	4.46
cytokine treatment	477814_mir_hsa-miR-148a-3p	4.42
cytokine treatment	478209_mir_hsa-miR-93-3p	4.2
cytokine treatment	477959_mir_hsa-miR-197-3p	4.17
cytokine treatment	480871_mir_hsa-miR-133b	4.07
cytokine treatment	478102_mir_hsa-miR-433-3p	3.91
cytokine treatment	477909_mir_hsa-miR-140-5p	3.89
cytokine treatment	477991_mir_hsa-miR-23b-5p	3.89
cytokine treatment	477900_mir_hsa-miR-132-3p	3.88
cytokine treatment	478240_mir_hsa-miR-376a-3p	3.73
cytokine treatment	478238_mir_hsa-miR-374a-5p	3.69
cytokine treatment	479150_mir_hsa-miR-665	3.68
cytokine treatment	477901_mir_hsa-miR-134-5p	3.57
cytokine treatment	478033_mir_hsa-miR-335-3p	3.57
cytokine treatment	479024_mir_hsa-miR-548n	3.32
cytokine treatment	478134_mir_hsa-miR-493-3p	3.29
cytokine treatment	478068_mir_hsa-miR-369-5p	3.27
cytokine treatment	477862_mir_hsa-let-7i-3p	3.19
cytokine treatment	477971_mir_hsa-miR-2110	3.17

cytokine treatment	477917_mir_hsa-miR-149-5p	3.12
cytokine treatment	477982_mir_hsa-miR-222-3p	3.12
cytokine treatment	478143_mir_hsa-miR-503-5p	3.09
cytokine treatment	477843_mir_hsa-let-7f-2-3p	2.99
cytokine treatment	477824_mir_hsa-miR-148b-3p	2.98
cytokine treatment	477816_mir_hsa-miR-381-3p	2.96
cytokine treatment	477887_mir_hsa-miR-126-3p	2.88
cytokine treatment	477939_mir_hsa-miR-185-5p	2.79
cytokine treatment	478511_mir_hsa-miR-133a-3p	2.79
cytokine treatment	477849_mir_hsa-miR-429	2.79
cytokine treatment	477922_mir_hsa-miR-153-3p	2.75
cytokine treatment	477902_mir_hsa-miR-136-3p	2.67
cytokine treatment	477961_mir_hsa-miR-199a-3p	2.65
cytokine treatment	479451_mir_hsa-miR-1296-5p	2.65
cytokine treatment	479517_mir_hsa-miR-181d-5p	2.65
cytokine treatment	478164_mir_hsa-miR-576-3p	2.62
cytokine treatment	477944_mir_hsa-miR-18a-3p	2.6
cytokine treatment	478476_mir_hsa-miR-1260a	2.59
cytokine treatment	478551_mir_hsa-miR-18a-5p	2.56
cytokine treatment	477857_mir_hsa-miR-181a-5p	2.46
cytokine treatment	477912_mir_hsa-miR-143-3p	2.44
cytokine treatment	477811_mir_hsa-miR-151b	2.42
cytokine treatment	478158_mir_hsa-miR-551a	2.41
cytokine treatment	477925_mir_hsa-miR-154-5p	2.38
cytokine treatment	479217_mir_hsa-miR-941	2.38
cytokine treatment	478005_mir_hsa-miR-29c-5p	2.38
cytokine treatment	478128_mir_hsa-miR-486-5p	2.37
cytokine treatment	478855_mir_hsa-miR-374a-3p	2.37
cytokine treatment	479229_mir_hsa-miR-29c-3p	2.36

cytokine treatment	477866_mir_hsa-miR-106b-3p	2.34
cytokine treatment	478348_mir_hsa-miR-502-3p	2.29
cytokine treatment	478999_mir_hsa-miR-541-3p	2.28
cytokine treatment	478654_mir_hsa-miR-1249-3p	2.26
cytokine treatment	479166_mir_hsa-miR-758-3p	2.25
cytokine treatment	479165_mir_hsa-miR-744-3p	2.23
cytokine treatment	478043_mir_hsa-miR-342-3p	2.23
cytokine treatment	478172_mir_hsa-miR-598-3p	2.21
cytokine treatment	477956_mir_hsa-miR-194-5p	2.16
cytokine treatment	478193_mir_hsa-miR-664a-3p	2.16
cytokine treatment	478253_mir_hsa-miR-103a-3p	2.14
cytokine treatment	478125_mir_hsa-miR-485-3p	2.13
cytokine treatment	477987_mir_hsa-miR-22-5p	2.12
cytokine treatment	479281_mir_hsa-let-7e-3p	2.12
cytokine treatment	478459_mir_hsa-miR-376c-3p	2.1
cytokine treatment	478313_mir_hsa-miR-15b-5p	2.07
cytokine treatment	478040_mir_hsa-miR-339-5p	2.06
cytokine treatment	477941_mir_hsa-miR-187-3p	2.05
cytokine treatment	478026_mir_hsa-miR-32-5p	2.05
cytokine treatment	478027_mir_hsa-miR-326	2.04
cytokine treatment	478090_mir_hsa-miR-423-5p	2.04
cytokine treatment	478362_mir_hsa-miR-548e-3p	2.04

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642 **Supplemental table S2. Selected 10 most dysregulated microRNA assay IDs**

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Assay name	Assay ID
hsa-miR-185-3p	478732_mir
hsa-miR-885-5p	478207_mir
hsa-miR-576-5p	478165_mir
hsa-miR-27b-3p	478270_mir
hsa-miR-124-3p	477879_mir
hsa-miR-136-5p	478307_mir
hsa-miR-152-3p	477921_mir
hsa-miR-299-5p	478793_mir
hsa-miR-93-5p	478210_mir
hsa-miR-454-5p	478919_mir

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648**Supplemental table S3. Assay IDs for predicted mRNA targets.**

Gene	Assay ID	RefSeq
<i>PPIA</i>	Hs.PT.58v.38887593.g	NM_021130
<i>HPRT1</i>	Hs.PT.58.2145446	NM_000194
<i>IDH3B</i>	Hs.PT.19660618	NM_174855
<i>MOB1A</i>	Hs.PT.58.1530191	NM_018221
<i>PDK1</i>	Hs.PT.58.19794808	NM_002610
<i>SOD1</i>	Hs.PT.58.20593019	NM_000454
<i>SP1</i>	Hs.PT.58.19745651	NM_138473
<i>KMT2C</i>	Hs.PT.19586130	NM_170606
<i>DLG2</i>	Hs.PT.58.28262784	NM_001142702
<i>BCL2L1</i>	Hs.PT.56a.39595693.g	NM_138578
<i>MAPK1</i>	Hs.PT.58.39782850	NM_138957
<i>SERPINE1</i>	Hs.PT.58.3938488.g	NM_000602
<i>TEAD1</i>	Hs.PT.58.22785339	NM_021961

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