**Supplementary Table 1:** Circulatory miRNA identified in multiple studies to be important in the regulation of key aspects of cardiometabolic diseases

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | miRNAs | Expression | Experimental model | Potential Targets | Disease | Ref. |
| 1 | miR-15a-5p | Downregulated | Human Plasma | Angiogenesis/B-cell function | Atherosclerosis/Obesity | [1,2][3,4] |
| 2 | miR-16 | Downregulated | Cell culture | Inflammation | Atherosclerosis | [5][6] |
| 3 | miR-17-5p | Downregulated | Mice | Glucose metabolism/inflammation | Obesity/T2DM | [7][8] |
| 4 | miR-21 | DownregulatedUpregulatedUpregulated | Human PlasmaPBMCsHuman Plasma | Lipid MetabolismInflammation(Treg Cells)Apoptosis/proliferation | NAFLDCHDCHD with T2DM | [9][10][11][12] |
| 5 | miR-126 | Downregulated | Mice/ Human Plasma | Inflammation | Atherosclerosis/ T2DM | [13][14][15][16][17] |
| 6 | miR-222 | DownregulatedUpregulated | MouseHuman Plasma/Amniotic Fluid | Beta Cell proliferationAdipogenesis | Insulin deficientObesity | [18][19] |
| 7 | miR-320a | Upregulation | Human plasma | Insulin Pathway | T2DM/obesity | [20][21][22] |
| 8 | miR-370-3p | Upregulated | Human Plasma | Lipid metabolism | T2DM/Diabetic cardiomyopathy | [23–25] |
| 9 | miR-375 | Upregulated | Human Serum | Beta cell apoptosis | T2DM | [26][27] |
| 10 | miR-451a | Downregulated  | Human Liver/serum/Cell culture/Rat | Inflammation/glucose homeostasis | NAFLD/T2DM | [28–30] |

**Supplementary Table 2**: Primer sequences of analysed genes

|  |  |  |
| --- | --- | --- |
| Gene | Forward Primer Sequence | Reverse Primer Sequence |
| *VCP*  | AAACTCATGGCGAGGTGGAG | TGTCAAAGCGACCAAATCGC |
| *EMC7*  | GGGCTGGACAGACTTTCTAATG | CTCCATTTCCCGTCTCATGTCAG |
| *CHMP2A*  | CGCTATGTGCGCAAGTTTGT | GGGGCAACTTCAGCTGTCTG |
| *C1orf43*  | CTATGGGACAGGGGTCTTTGG | TTTGGCTGCTGACTGGTGAT |
| *VEGF*  | TCTTCAAGCCATCCTGTGT | CTTTCTTTGGTCTGCATTC |
| *PPAR-α* | CGCGGCCCAGGCTGAA | ACCAGATGGTGCTGGTTGTG |
| *CPT1a* | TTTGGACCGGTTGCTGATGAC | GCTTCTTTCAGGTGCCTTCC |
| *Mfn-2* | TGATGCAGACGGAAAAGCACT | GTACAACGCTCCATGTGCTG |
| *CD36* | GGTAAAAGGAATCTGTCCTATTGGG | AAAGGTGGAAATGAGGCTGC |
| *mTOR* | GAATTGGCACAGGTTAGTGGC | CAACTGTCCCAGGGTCCAC |
| *ACOX-1* | TATGCCCAGACAGAGATGGGT | TGAAGTCTTTCCAAGCCCAC |
| *SMAD-3* | ACCACCAGATGAACCACAGC | TAACTGGCTGCAGGTCCAAG |
| *TNF-α* | AGCCCATGTTGTAGCAAACC | TGAGGTACAGGCCCTCTGAT |
| *IL-6* | TCAATGAGGAGACTTGCCTGG | GGGTCAGGGGTGGTTATTGC |
| *IL-8* | ACCGGAAGGAACCATCTCAC | GGCAAAACTGCACCTTCACAC |

**Supplementary table 3**: Overrepresentation analysis of genes targeted by differentially expressed miRNAs (miR-15a-5p, and -17-5p) identifies significant enrichment in Gene Ontology (GO)

|  |  |
| --- | --- |
| **GO categories** | **Pval** |
| Regulation of cellular protein metabolic process | 0.00 |
| Regulation of cell cycle | 0.00 |
| Negative regulation of transcription from RNA polymerase II promoter | 0.00 |
| Regulation of translation | 0.00 |
| Histone modification | 0.00 |
| Epidermal growth factor receptor signaling pathway | 0.00 |
| Interphase of mitotic cell cycle | 0.00 |
| Covalent chromatin modification | 0.00 |
| Negative regulation of cell cycle | 0.00 |
| Interphase | 0.00 |
| Cellular macromolecule catabolic process | 0.00 |
| DNA-dependent transcription, initiation | 0.00 |
| Cell cycle arrest | 0.00 |
| Regulation of transcription from RNA polymerase II promoter | 0.00 |
| Transcription initiation from RNA polymerase II promoter | 0.00 |
| Regulation of transforming growth factor beta receptor signaling pathway | 0.00 |
| Negative regulation of cellular protein metabolic process | 0.00 |
| Chromatin modification | 0.00 |
| Regulation of protein modification process | 0.00 |
| Cellular protein catabolic process | 0.00 |
| Nuclear import | 0.00 |
| G1 phase of mitotic cell cycle | 0.00 |
| Protein ubiquitination | 0.00 |
| Protein import into nucleus | 0.00 |
| Positive regulation of transcription from RNA polymerase II promoter | 0.00 |
| Viral reproductive process | 0.00 |
| Regulation of protein stability | 0.00 |
| G1/S transition of mitotic cell cycle | 0.00 |
| G1 phase | 0.00 |
| Cell division | 0.00 |
| Intrinsic apoptotic signaling pathway | 0.00 |
| Transforming growth factor beta receptor signaling pathway | 0.00 |
| Positive regulation of cellular protein metabolic process | 0.00 |
| Negative regulation of transcription, DNA-dependent | 0.00 |
| Negative regulation of transcription, DNA-dependent | 0.00 |
| Negative regulation of protein metabolic process | 0.00 |
| Apoptotic signaling pathway | 0.00 |
| Vesicle localization | 0.00 |
| Protein import | 0.00 |
| Regulation of phosphorylation | 0.00 |
| Negative regulation of RNA metabolic process | 0.00 |
| Chromatin organization | 0.00 |
| DNA damage checkpoint | 0.00 |
| Macromolecule catabolic process | 0.00 |
| Macromolecule catabolic process | 0.00 |
| Regulation of protein phosphorylation | 0.00 |
| Negative regulation of cell proliferation | 0.00 |
| Regulation of kinase activity | 0.00 |
| Regulation of protein metabolic process | 0.00 |
| Positive regulation of transcription, DNA-dependent | 0.00 |
| Cell cycle | 0.00 |
| Positive regulation of transcription, DNA-dependent | 0.00 |
| Protein catabolic process | 0.00 |
| Protein localization | 0.00 |
| Response to ionizing radiation | 0.00 |
| Cellular response to nutrient levels | 0.00 |
| Protein modification by small protein conjugation | 0.00 |
| Positive regulation of translation | 0.00 |
| Positive regulation of RNA metabolic process | 0.00 |
| Interaction with host | 0.00 |
| Positive regulation of cell cycle | 0.01 |
| Negative regulation of cellular metabolic process | 0.01 |
| Negative regulation of cellular biosynthetic process | 0.01 |
| Positive regulation of cell adhesion | 0.01 |
| Protein polyubiquitination | 0.01 |
| Ras protein signal transduction | 0.01 |
| Protein targeting | 0.01 |
| Nuclear transport | 0.01 |
| Response to hypoxia | 0.01 |
| Negative regulation of signal transduction | 0.01 |
| Response to abiotic stimulus | 0.01 |
| Regulation of protein kinase activity | 0.01 |
| Positive regulation of protein metabolic process | 0.01 |
| Transcription from RNA polymerase II promoter | 0.01 |
| Intracellular protein transport | 0.01 |
| DNA integrity checkpoint | 0.01 |
| Regulation of transferase activity | 0.01 |
| Protein phosphorylation | 0.01 |
| ER-nucleus signaling pathway | 0.01 |
| Organelle localization | 0.01 |
| Protein stabilization | 0.01 |
| Growth | 0.01 |
| Protein export from nucleus | 0.01 |
| Negative regulation of apoptotic process | 0.01 |
| Negative regulation of apoptotic process | 0.01 |
| Positive regulation of protein modification process | 0.01 |
| Positive regulation of binding | 0.01 |
| Negative regulation of biosynthetic process | 0.01 |
| Cellular response to stress | 0.01 |
| Notch signaling pathway | 0.01 |
| Protein modification process | 0.01 |
| Negative regulation of nucleobase-containing compound metabolic process | 0.01 |
| Protein autophosphorylation | 0.01 |
| Cellular response to extracellular stimulus | 0.01 |
| Nucleocytoplasmic transport | 0.01 |
| Phosphorylation | 0.01 |
| Positive regulation of nucleobase-containing compound metabolic process | 0.01 |
| Regulation of sequence-specific DNA binding transcription factor activity | 0.01 |
| Regulation of cell migration | 0.01 |
| Positive regulation of hydrolase activity | 0.01 |
| Regulation of cyclin-dependent protein kinase activity | 0.01 |
| Negative regulation of programmed cell death | 0.01 |
| Establishment of protein localization | 0.01 |
| Negative regulation of growth | 0.01 |
| Regulation of transcription, DNA-dependent | 0.01 |
| Regulation of transcription, DNA-dependent | 0.01 |
| Regulation of transcription, DNA-dependent | 0.01 |
| Positive regulation of catalytic activity | 0.01 |
| Negative regulation of cell migration | 0.01 |
| Small gtpase mediated signal transduction | 0.01 |
| Regulation of gene expression, epigenetic | 0.01 |
| Negative regulation of phosphorylation | 0.01 |
| Phosphatidylinositol-mediated signaling | 0.01 |
| Gene silencing | 0.02 |
| Morphogenesis of an epithelium | 0.02 |
| Regulation of gene expression | 0.02 |
| Viral infectious cycle | 0.02 |
| G2/M transition of mitotic cell cycle | 0.02 |
| Endoplasmic reticulum unfolded protein response | 0.02 |
| Macromolecule modification | 0.02 |
| Regulation of RNA metabolic process | 0.02 |
| Response to radiation | 0.02 |
| Protein transport | 0.02 |
| Regulation of chromosome organization | 0.02 |
| Regulation of viral reproduction | 0.02 |
| Regulation of DNA metabolic process | 0.02 |
| Positive regulation of protein phosphorylation | 0.02 |
| Positive regulation of cell differentiation | 0.02 |
| Regulation of myeloid cell differentiation | 0.02 |
| Cell cycle process | 0.02 |
| Regulation of growth | 0.02 |
| Regulation of cell adhesion | 0.02 |
| Intracellular receptor mediated signaling pathway | 0.02 |
| Positive regulation of developmental process | 0.02 |
| Regulation of mitotic cell cycle | 0.02 |
| Endosomal transport | 0.02 |
| Negative regulation of response to stimulus | 0.02 |
| Positive regulation of cell migration | 0.02 |
| Positive regulation of phosphorylation | 0.02 |
| Mitotic cell cycle | 0.02 |
| Negative regulation of translation | 0.02 |
| Myeloid cell differentiation | 0.02 |
| Viral reproduction | 0.02 |
| Response to UV | 0.02 |
| Protein folding | 0.02 |
| Positive regulation of defense response | 0.02 |
| Cell cycle checkpoint | 0.02 |
| Negative regulation of metabolic process | 0.03 |
| Homeostasis of number of cells | 0.03 |
| Regulation of catalytic activity | 0.03 |
| Positive regulation of cellular metabolic process | 0.03 |
| Response to light stimulus | 0.03 |
| Response to drug | 0.03 |
| Mitochondrial membrane organization | 0.03 |
| Androgen receptor signaling pathway | 0.04 |
| Tissue morphogenesis | 0.04 |
| Stress-activated protein kinase signaling cascade | 0.04 |
| Positive regulation of cysteine-type endopeptidase activity involved in apoptotic process | 0.04 |
| Positive regulation of cellular component organization | 0.04 |
| Positive regulation of transferase activity | 0.04 |
| Cytoskeleton-dependent intracellular transport | 0.05 |
| Regulation of organelle organization | 0.05 |
| Negative regulation of phosphate metabolic process | 0.05 |
| Intracellular transport | 0.05 |
| Regulation of molecular function | 0.05 |
| Positive regulation of I-kappab kinase/NF-kappab cascade | 0.05 |
| Gland development | 0.05 |
| Regulation of cell-cell adhesion | 0.05 |
| Positive regulation of signal transduction | 0.05 |
| Negative regulation of cellular component organization | 0.05 |
| Organelle organization | 0.05 |
| Transmembrane receptor protein serine/threonine kinase signaling pathway | 0.05 |
| Hemostasis | 0.06 |
| Positive regulation of metabolic process | 0.06 |

**Supplementary table 4**: Overrepresentation analysis of shared genes between the differentially expressed miRNAs highlights target genes involved in metabolic related pathways.

|  |  |
| --- | --- |
| GO Categories | P-val |
| Mitotic cell cycle | 0.02 |
| Cellular protein catabolic process | 0.02 |
| Interphase | 0.02 |
| Interphase of mitotic cell cycle | 0.02 |
| G1/S transition of mitotic cell cycle | 0.02 |
| Protein catabolic process | 0.03 |
| G1 phase of mitotic cell cycle | 0.03 |
| B cell differentiation | 0.03 |
| Protein modification process | 0.03 |
| G1 phase | 0.03 |
| Macromolecule modification | 0.03 |
| Regulation of cell cycle | 0.04 |
| Apoptotic signaling pathway | 0.04 |
| Small gtpase mediated signal transduction | 0.04 |
| Ras protein signal transduction | 0.04 |
| Regulation of mitotic cell cycle | 0.04 |
| Response to UV | 0.04 |
| Regulation of catabolic process | 0.04 |
| Dephosphorylation | 0.04 |
| Regulation of protein modification process | 0.04 |
| Regulation of protein stability | 0.04 |
| Regulation of cellular protein metabolic process | 0.04 |
| Cellular macromolecule catabolic process | 0.04 |
| Cellular protein metabolic process | 0.04 |
| Positive regulation of cell cycle | 0.04 |
| Regulation of protein phosphorylation | 0.05 |

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