SUPPLEMENTARY MATERIAL

NAFLD and Vitamin D: Evidence for Intersection of MicroRNA Regulated Pathways

Zhang Z, Moon R, Thorne JL and Moore JB[1]

[1]Corresponding Author: J. Bernadette Moore j.b.moore@leeds.ac.uk

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Supplementary Table 1 miRNAs dysregulated in liver from NAFLD patients and their functional/pathophysiological effects

miRNA	**Summary**	**Functional/pathophysiological effects and/or genetic targets of dysregulated miRNA**
miR-33	**Up** in NASH (n=22) or SS (n=18) vs. NL(n=22) [MO women]; **up** in NASH (n=12) vs. NL (n=9) [ModO women][1]	Hepatic *SREBP2* and *ABCG1* mRNAs: **up** in NASH (n=22) vs. controls (n=22) [MO women]; hepatic *SREBP2*, *ABCG1*, *SREBP1c*, *CPT1a* and *ACC1* mRNAs: **up** in NASH (n=12) vs steatosis (n=9) and NL (n=9) of ModO women[1]
	Up *(miR-33a)* in NASH (n=38) vs. normal histology (n=10) [bariatric surgery patients][2]	Not investigated
	Down *(miR-33a-5p)* in NAFLD (n=58) vs. non-NAFLD (n=37), [postmortem samples, CSD and NCSD][3]	Not investigated
miR-141	**Up** *(miR-141)* in NASH fatty liver (n=20) vs. NASH non-fatty liver(n=15) and normal histology (n=10) [liver tissue bank][4]	Not investigated
	Up *(miR-141)* in steatosis (n=4) vs. non-steatosis (n=4) [liver tissue bank][5]	Not investigated
miR-155	**Up** *(miR-155)* in steatosis (n=4) vs. non-steatosis (n=4) [liver tissue bank][5]	Not investigated
	Down *(miR-155)* in NAFLD (n=11) vs. HCs (n=11) [biopsy consenting NAFLD and HCs][6]	Hepatic *SREBP1c*, *FAS* and *ACC1* mRNA: **up** in NAFLD (n=11) vs. HCs (n=11) **Target:** *LXRα*[6]
miR-199	**Up** (*miR-199a-5p*) in steatosis (n=7) vs. HCs (n=7); [commercial liver tissue bank][7]	Hepatic *CAV1* and *PPARα* mRNA: **down** in steatosis (n=7) vs. HCs (n=7) **Targets:** *CAV1*[7]

Supplementary Table 1 miRNAs dysregulated in liver from NAFLD patients and their functional/pathophysiological effects

miRNA	**Summary**	**Functional/pathophysiological effects and/or genetic targets of dysregulated miRNA**
miR-199	**Up** (*miR-199a-5p*) in NAFLD (n=5) vs. HCs (n=6); liver steatosis score: **up** in NAFLD vs. HCs; [diagnosis and treatment of gallstone disease][8]	Hepatic *MST1* mRNA: **down** in NAFLD (n=5) vs. HCs (n=6)[8]
miR-223	**Up** *(miR-223)* in NASH (n=10) vs. controls (n=14) [NIH liver tissue repository][9]	Hepatic *CXCL10, TAZ, SERPINB9, DOCK11* and *GOLM1* mRNA: **up** in NASH (n=10) vs. HCs (n=14); **up** in steatosis (n=10) vs. HCs; hepatic *GPC3*, *CXCL10* and *TAZ* mRNA: **up** in NASH vs. HCs **Targets:** *CXCL10* and *TAZ* [9]
	Up *(miR-223)* in steatosis (n=4) vs. non-steatosis (n=4) [liver tissue bank][5]	Not investigated
miR-378	**Up** *(miR-378)* in NASH (n=24) vs. normal histology (n=19) [liver transplantation biopsies][10]	*Ppargc1β* mRNA: **down** in NASH (n=24) vs. HCs (n=19); LXRα targets miR-378 promoter[10]
	Up *(miR-378)* in NASH (n=38) vs. normal histology (n=24) [liver transplantation biopsies][11]	*Prkag2* mRNA and protein: **down** in NASH (n=38) vs. HCs (n=24) **Target:** *Prkag2*[11]
	Down (*miR-378i*) in NAFLD with severe fibrosis or cirrhosis (n=15) vs. NAFLD without fibrosis (n=15) [bariatric surgery patients][12]	Not investigated

ABCG1, ATP binding cassette subfamily G member 1; ACC1, acetyl-CoA carboxylase; CAV, caveolin1; CPT1a, carnitine palmitoyltransferase 1a; CSD, cardiac sudden death; CXCL10, C-X-C motif chemokine 10; DOCK11, dedicator of cytokinesis 11; FAS, fatty acid synthase; GOLM1, Golgi membrane protein 1; GPC3, glypican-3; HCs, healthy controls; LXRα, liver X receptorα; MO, morbidly obese; ModO, moderately boese; MST1, mammalian sterile 20-like kinase 1; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NCSD, non-cardiac sudden death; PPARα; Ppargc1β, peroxisome proliferator-activated receptor γ coactivator 1-beta; Prkag2, protein kinase AMP-activated non-catalytic subunit gamma 2; SREBP1c, sterol regulatory element-binding protein 1c; SREBP2, sterol regulatory element-binding protein 2; SERPINB9, Serpin family B member 9; TAZ, transcriptional coactivator with PDZ-binding motif.

Supplementary Table 2 miRNAs dysregulated in serum from NAFLD patients

miRNA	Summary
miR-16	**Up** *(miR-16)* in NAFLD (n=34) vs. HCs (n=19), **up** in steatosis and NASH vs. HCs; discriminated steatosis from HCs (AUROC=0.962)[13]
	Up *(miR-16)* in NASH (n=31) vs. HCs (n=37); positive correlation with hepatocellular ballooning and fibrosis[14]
	Up *(miR-16-5p)* in fatty liver infiltration (n=10) vs. no fatty liver infiltration (n=12) [patients with obesity and T2DM][15]
	Down *(miR-16-5p)* in SAF≥ 2 (n=50) vs. SAF<2 (n=25); **down** in NAS ≥5 (n=38) vs. NAS<5 (n=37); **down** in F>2 (n=29) vs. F≤2 (n=46); negative correlation with AST, APRI, FIB4, BARD and NAFLD fibrosis score (NAFL n=25, NASH n=50 and NL n=17)[16]
miR-20	**Up** *(miR-20a-5p/miR-20b-5p)* in NAFLD (n=52) vs. Non-NAFLD (n=48) [adults with T2DM][17]
	Down *(miR-20a)* in NAFLD (n=92) vs. HCs (n=383), **down** in severe NAFLD (n=51) vs. mild NAFLD (n=41) and HCs; in multivariate logistic regression OR=4.09 for severe NAFLD[18]
	Down (*miR-20a-5p*) in NAFLD (n=14) vs. HCs (n=13)[19]
miR-22	**Up** *(mir-22-5p)* in NAFLD (n=32) and NAFLD+fibrate (n=11) vs. HCs (n=10)[20]
	Up *(miR-22-3p)* in SAF≥ 2 (n=50) vs. SAF<2 (n=25), **up** in NAS≥5 (n=38) vs. NAS<5 (n=37); positive correlation with AST, ALT, Ferritin and APRI (NAFL n=25, NASH n=50 and HC n=17)[16]
miR-27	**Up** *(miR-27b-3p)* in NAFLD (n=103) vs. HCs (n=80); discriminated NAFLD from HCs (AUROC=0.693)[21]
	Up *(miR-27b-3p)* in SAF≥ 2 (n=50) vs. SAF<2 (n=25), **up** in NAS ≥5 (n=38) vs. NAS <5 (n=37), **up** in F>2 (n=29) vs. F≤2 (n=46); positive correlation with AST, ALT, Ferritin, APRI and FIB4 (NAFL n=25, NASH n=50 and NL n=17); discriminated NAS≥5 from NAS <5 (AUROC=0.73)[16]
	Down *(miR-27a)* in NAFLD (n=92) vs. HCs (n=383), **down** in severe NAFLD (n=51) vs. mild NAFLD (n=41) and HCs; in multivariate logistic regression OR=4.09 for severe NAFLD[18]

Supplementary Table 2 miRNAs dysregulated in serum from NAFLD patients

miRNA	Summary
miR-29	**Up** *(miR-29a-3p)* in NAFLD (n=32) and NAFLD+fibrate (n=11) vs. HCs (n=10)[20]
	Up *(miR-29b-3p but **no change** in miR-29a-3p or miR-29b-3p)* in multivariate logistic regression OR=1.49 for NAFLD [non-T2D NAFLD (n=73) and non-T2D non-NAFLD (n=68)]; positive correlation with intrahepatic lipid content [N=99][22]
	Down *(miR-29a)* in NAFLD (n=58) vs. HCs (n=34); discriminated NAFLD from HCs (AUROC=0.679)[23]
miR-99	**Down** *(miR-99a)* in NAFLD (n=20) vs. HCs (n=20); negative correlation with GGT; discriminated NAFLD from HCs (AUROC=0.76)[24]
	Down *(miR-99a)* in NAFLD (n=210) vs. Controls (n=90), **down** in NASH (n=86) vs. steatosis (n=124); negative correlation with ALT, activity, inflammation, ballooning and fibrosis; discriminated NAFLD from HCs (AUROC=0.73) and NASH vs. steatosis (AUROC=0.91)[25]
miR-125	**Up** (*miR-125b-5p*) in NAFLD (n=29) vs. HCs (n=24); ALT: **up** in NALFD vs. HCs; serum TNFAIP3 mRNA: **down** in NAFLD vs. HCs[26]
	Down (*miR-125b-5p*) in NAFLD (n=34) vs HCs (n=20); serum ITGA8 mRNA: **up** in NAFLD vs. HCs[27]
miR-181	**Up** *(miR-181b-3p)* in NAFLD (n=25) vs. HCs (n=21)[28]
	Up *(miR-181a-5p)* in NAFLD (n=30) vs. HCs (n=30)[29]
	Down *(miR-181d)* in NAFLD (n=20) vs. HCs (n=20); negative correlation with GGT; discriminated NAFLD from HCs (AUROC=0.86)[24]
miR-192	**Up** *(miR-192-5p)* in NAFLD (n=103) vs. HCs (n=80); discriminated NAFLD from HCs (AUROC=0.652)[21]
	Up *(miR-192)* in NASH (n=87) vs. NAFL (n=50) and HCs (n=61); positive correlation with ALT, steatosis and serum CK18-Asp396[30]
	Up *(miR-192)* in NASH (n=47) vs. steatosis (n=30) and HCs (n=19); positive correlation with AST, GGT; discriminated histological severity (AUROC range 0.676-0.709)[31]

Supplementary Table 2 miRNAs dysregulated in serum from NAFLD patients

miRNA	Summary
miR-192	**Up** *(miR-192)* in NASH (n=31) vs. NAFL (n=17) and HCs (n=37), **up** in NAFL (n=17) vs HCs (n=37); positive correlation with histological severity but not fibrosis[14]
	Up *(miR-192)* in circulating exosomes in advanced stage NAFLD (n=3) vs. early stage NAFLD (n=3)[32]
	Up *(miR-192-5p)* in SAF≥ 2 (n=50) vs. SAF>2 (n=25), **up** in NAS≥5 (n=38) vs. NAS<5 (n=37); positive correlation with AST, ALT, Ferritin, APRI and BARD (NAFL n=25, NASH n=50 and NL n=17)[16]
	Up *(miR-192-5p)* in NASH (n=31) vs. HCs (n=37), up in NAFL (n=17) vs. HCs, positive correlation with ALT, AST, steatosis, activity, ballooning and inflammation[33]
	Up *(miR-192-5p)* with increasing fibrosis severity (n=132 NAFLD patients); in multivariate analyses, positive correlation with steatosis, fibrosis, and the PNPLA3 I148M and TM6SF2 E167K variants[34]
	Down *(miR-192-5p)* in NASH (n=60) vs. HCs (n=60); discriminated NAFD vs. HCs (AUROC=0.791)[35]
miR-197	**Down** *(miR-197)* in NAFLD (n=20) vs. HCs (n=20); negative correlation with inflammation; discriminated NAFLD from HCs (AUROC=0.77)[24]
	Down *(miR-197-3p)* in SAF≥ 2 (n=50) vs. SAF<2 (n=25)[16]
miR-375	**Up** *(miR-375)* in NASH (n=47) vs. steatosis (n=30) and HCs (n=19); discriminated NAS>5 from NAS<5 (AUROC=0.72)[31]
	Up *(miR-375-3p)* in fatty liver infiltration (n=10) vs. no fatty liver infiltration (n=12) [patients with obesity and T2DM][15]
miR-379	**Up** *(miR-379)* in Steatosis (n=10) vs. HCs, **Down** in NASH (n=10) vs. HCs; discriminate steatosis and NASH from HCs (AUROC=0.92)[36]
	Up *(miR-379)* in NAFLD (n=79) vs. HCs (n=10); discriminated: NAFLD from HC (AUROC= 0.72)[37]
miR-451	**Up** *(miR-451)* in NAFLD (n=48) vs. HCs (n=90) [adult males][38]
	Down *(miR-451)* in NAFLD (n=20) vs. HCs (n=20); serum MIF mRNA: **up** in NAFLD vs. HCs[39]

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ALT, alanine aminotransferase; APOE, apolipoprotein E; APTI, AST to platelet ratio index; AST, aspartate transaminase; AUROC, the area under the receiver operating characteristic; CK18, cytokeratin-18; eLP-IR, enhanced lipo-protein insulin-resistance index; F, fibrosis%; FIB4, fibrosis 4; FPG, fasting plasma glucose; GGT, gamma-glutamyl transpeptidase; HC, healthy control; γ-GT, γ-glutamyl transpeptidase; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; NNL, near normal liver; NS, not specified; PNPLA3, patatin-like phospholipase domain containing protein 3; SIRT1, sirtuin 1; SAF, steatosis, activity, fibrosis score; T2DM, type 2 diabetes mellitus; TG, triglyceride

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