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Supplementary data

Supplementary Data 1. Extended data processing pipeline.

Bioinformatics Analysis.

Raw data were analyzed with a specific bioinformatic pipeline for the identification of known and novel miRNAs. Quality control was performed with FastQC (v.0.11.3); adapter sequences as well as low-quality base calls ($q < 20$) were trimmed with cutadapt (v.1.13) and processed with miRDeep2 (v.0.0.7). This software allows the alignment of the reads to the reference human genome (GRCh38) using the mapper.pl module based on Bowtie1. Only the alignments with zero mismatches in the seed region and those that did not map to more than five different loci in the genome were retained. Quantification of miRNAs was performed with the quantifier.pl module, which determines the expression of the corresponding known miRNAs in two steps. First, predefined mature miRNA sequences are mapped against the reference precursors in miRBase (v21), a public repository miRNA which contains 2888 human miRNAs sequences [1]. Second, sequencing reads were mapped against the precursor sequences. Reads falling into an interval of two nucleotides upstream and five nucleotides downstream of the mature miRNA sequences were determined for quantification.

Statistical analysis

For data preprocessing and exploratory analysis, first, miRNAs with low read counts were filtered out by the filterByExpr edgeR function, retaining only those miRNAs that have sufficiently large counts according to the minimum expression criterion [2]. miRNA count matrix was normalized with Trimmed Mean of M-values (TMM) and count per million (CPM) approaches for library size normalization. Then, for exploration analysis, partial least square discriminant analysis (PLS-DA) with the normalized miRNAs counts was performed.

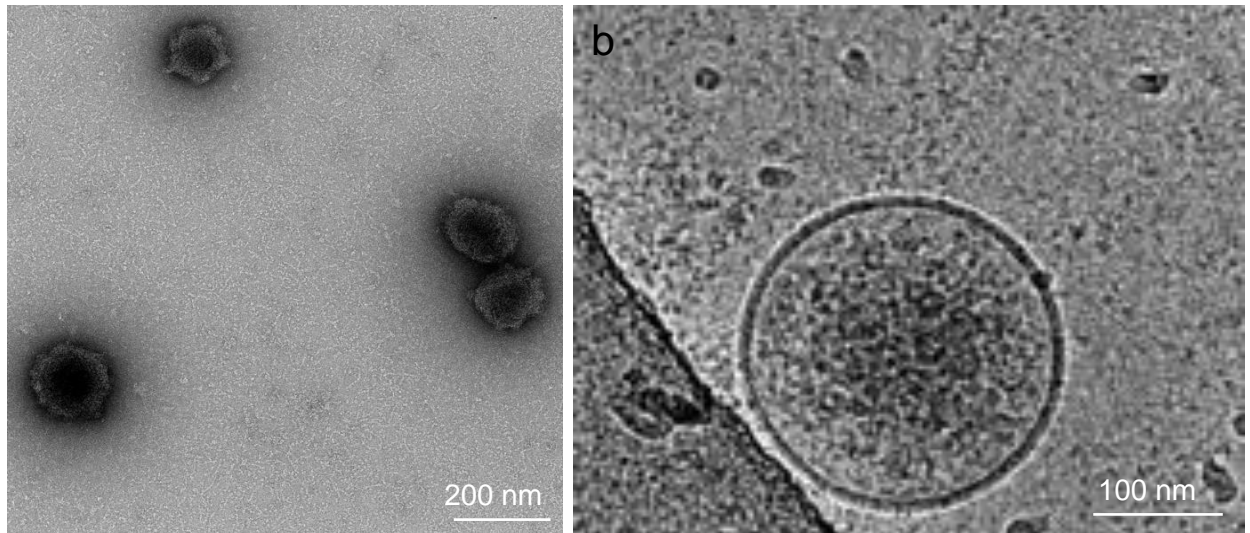
For the significant differentially expressed (SDE) miRNA analysis, miRNA expression differences between groups were analyzed using a binomial negative generalized linear model (bnGLM). MiRNAs with a fold change (FC) ≥ 1.5 and an adjusted p -value ≤ 0.05 using the false discovery rate (FDR) were considered SDE miRNAs.

miRNA-based target prediction and pathway enrichment analysis

Finally, SDE miRNA-target interactions and pathway enrichment analysis of the target genes was performed. Only experimentally validated interactions were considered. Enriched target genes were considered with at least four validated interactions with SDE miRNAs and enrichment p -values corrected for false discovery rate (FDR) ≤ 0.05 . Functional enrichment analysis of the enriched target genes were analyzed by means of three databases: GO, KEGG and REACTOME. Enrichment p -values (Fischer's exact test with hypergeometric distribution) were corrected for the false discovery rate (FDR) (q value ≤ 0.05).

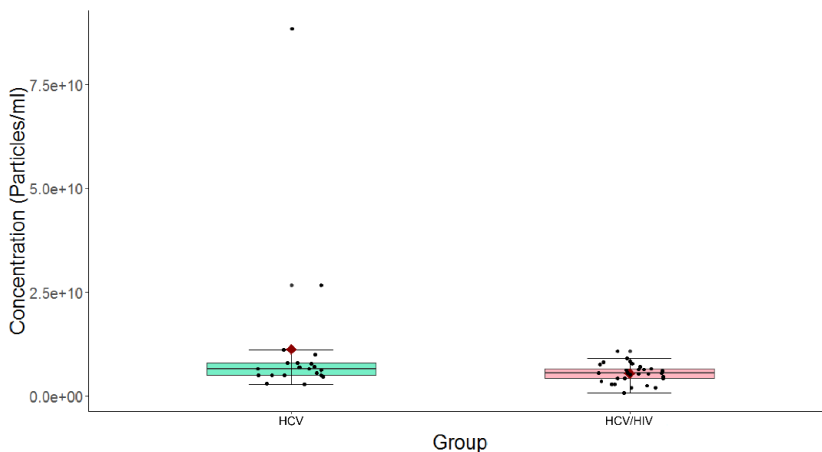
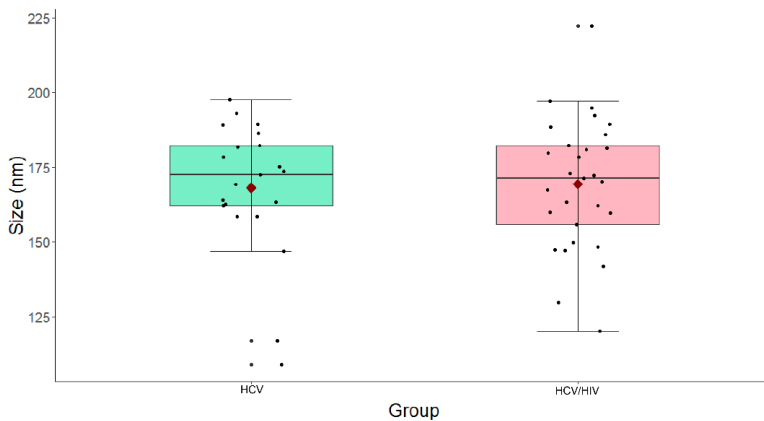
Supplementary Data 2. Microscopy characterization of plasma-derived extracellular vesicles from HCV mono-infected and HCV/HIV co-infected patients.

Representative images of the isolated plasma-derived vesicles by Transmission electron microscopy (TEM) (a) and cryo-electron microscopy (Cryo-EM) (b)



Supplementary Data 3. Size range and concentration of plasma-derived extracellular vesicles from HCV mono-infected and HCV/HIV co-infected patients.

Boxplot of particle sizes (a) and concentration (b) measured with NTA according to infection condition. HCV mono-infected group represented in light-blue and HCV/HIV co-infected in light-pink. Horizontal lines within boxes indicate medians. Horizontal lines outside the boxes represent the 5 and 95 percentiles. Mean is indicated as a dark-red diamond. The Mann-Whitney *U* test was used to compare sets of data. The table details size and concentration median (percentile 25; percentile 75) and *p*-values for the comparison between HCV mono-infected and HCV/HIV co-infected results.



NTA	Size (nm)	<i>P</i> value	Concentration (particles/ml)	<i>P</i> value
HCV samples	172.4 (160.3; 184.3)	0.888	6.5E09 (5E09;8E09)	0.064
HCV/HIV samples	171.3 (152.8; 184.1)		5.5E09 (4.1E9;7.1E09)	

Supplementary Data 4. SDE miRNAs in HCV/HIV co-infected vs HCV mono-infected samples.

Downregulated miRNAs					
miRNA	logFC	FDR	HCV counts	HCV/HIV counts	AUROC
hsa-miR-1290	-2.04944	3.06E-07	342.7 (179.2-918.2)	113.6 (63.7-175.8)	0.8571
hsa-miR-1246	-1.87948	3.51E-07	1026.0 (550.3-2319.0)	325.0 (258.6-548.1)	0.8144
hsa-miR-11400	-1.54928	1.46E-05	183.3 (74.4-214.1)	39.1 (20.5-84.7)	0.7455
hsa-miR-432-5p	-1.33714	6.58E-05	195.8 (60.8-316.5)	83.5 (40.1-101.2)	0.7635
hsa-miR-146a-5p	-1.22368	6.51E-10	13125.0 (10739.0-20933.0)	5890.0 (5428.0-6991.0)	0.9622
hsa-miR-486-3p	-1.2106	0.001654	290.6 (172.6-534.5)	240.3 (182.9-296.5)	0.6256
hsa-miR-148a-3p	-1.19943	9.11E-07	22631.0 (14810.0-38118.0)	11283.0 (9646.0-12923.0)	0.8621
hsa-miR-199a-5p	-1.19191	4.78E-08	1320.0 (797.9-1896.0)	639.9 (491.8-734.4)	0.8456
hsa-miR-381-3p	-1.10608	0.000132	438.2 (218.8-772.7)	233.7 (156.1-286.3)	0.7438
hsa-miR-221-3p	-1.10598	5.80E-10	2182.0 (1752.0-3312.0)	1036.0 (912.3-1325.0)	0.9573
hsa-miR-654-3p	-1.03753	0.007296	183.3 (76.9-329.6)	96.7 (41.3-154.3)	0.6683
hsa-miR-148b-3p	-1.0098	1.80E-07	1314.0 (691.7-1580.0)	585.7 (481.3-657.2)	0.8637
hsa-miR-584-5p	-0.95697	8.41E-06	412.7 (262.4-511.3)	176.0 (137.5-241.9)	0.8949
hsa-miR-223-5p	-0.94603	1.24E-05	1186.0 (756.9-1506.0)	601.6 (439.6-683.4)	0.8473
hsa-miR-625-3p	-0.88129	0.000455	304.5 (192.6-440.8)	157.1 (103.5-225.5)	0.8161
hsa-miR-224-5p	-0.85655	0.001422	312.1 (228.1-638.0)	217.5 (145.5-340.2)	0.7143
hsa-miR-122-5p	-0.83147	0.013329	53183.0 (31102.0-113228.0)	22100.0 (17917.0-41783.0)	0.7455
hsa-miR-151a-3p	-0.8204	5.23E-06	13079.0 (10279.0-18786.0)	8502.0 (7715.0-9591.0)	0.9146
hsa-miR-199a-3p	-0.75996	8.41E-06	1259.0 (1056.0-1492.0)	676.8 (545.5-909.0)	0.9113
hsa-miR-199b-3p	-0.75979	8.41E-06	1259.0 (1056.0-1492.0)	683.3 (536.5-909.0)	0.9080
hsa-miR-340-5p	-0.6626	0.002167	575.1 (358.5-869.3)	388.0 (320.8-543.3)	0.6831
hsa-miR-152-3p	-0.60514	0.00142	334.4 (272.3-412.7)	225.6 (143.8-287.1)	0.8161

Upregulated miRNAs					
miRNA	logFC	FDR	HCV counts	HCV/HIV counts	AUROC
hsa-miR-184	3.856673	6.79E-05	35.20 (15.6-73.4)	47 (20.9-290.9)	0.5928
hsa-chr9_24472	2.693477	1.01E-05	135.3 (75.7-194.4)	291.4 (167.8-1739.0)	0.8325
hsa-miR-144-5p	1.382283	4.78E-08	548.3 (372.7-1013.0)	1582.0 (1329.0-1924.0)	0.9458
hsa-miR-1-3p	1.353063	0.010282	104.5 (74.4-223.4)	379.6 (94.2-561.7)	0.7028
hsa-miR-144-3p	1.180373	1.10E-05	1023.0 (650.9-1704.0)	2308.0 (1757.0-3223.0)	0.8571
hsa-miR-363-3p	1.031806	3.51E-07	3332.0 (2764.0-3884.0)	6166.0 (4581.0-7550.0)	0.9146
hsa-miR-92a-3p	0.942827	1.17E-07	6334.0 (4740.0-7342.0)	11965.0 (9459.0-13858.0)	0.9179
hsa-miR-183-5p	0.908059	0.000838	584.5 (304.8-949.8)	1301.0 (806.0-1502.0)	0.8259
hsa-miR-32-5p	0.86405	0.000931	143.6 (105.9-223.0)	229.7 (178.6-356.8)	0.7668
hsa-miR-424-3p	0.826871	8.95E-05	134.7 (75.7-163.5)	204.2 (157.4-234.8)	0.8325
hsa-miR-1180-3p	0.809772	0.002199	91.4 (63.7-151.2)	162.2 (122.3-203.1)	0.7553
hsa-miR-139-5p	0.648897	0.012625	2555.0 (1506.0-3683.0)	4224.0 (3351.0-5385.0)	0.7816
hsa-miR-20b-5p	0.641284	0.009494	119.2 (97.8-209.2)	216.2 (151.3-281.4)	0.6897
hsa-miR-374a-5p	0.616556	0.002355	344.5 (235.7-446.2)	500.5 (361.4-653.3)	0.7241
hsa-miR-7-5p	0.610916	0.000407	2399.0 (2086.0-2932.0)	3365.0 (2608.0-3981.0)	0.7668

Each column represent: the SDE miRNA identifier (miRBase format), the LogFC indicating the expression fold change between HCV/HIV co-infected and HCV mono-infected group, the adjusted *p*-value (FDR, corrected for multiple testing with the Benjamini– Hochberg

procedure), abundance of miRNA for HCV and HCV/HIV samples expressed as median count (percentile 25; percentile 75) and area under the ROC curves (AUROC).

Supplementary Data 5. Novel miRNAs predicted by miRDeep.

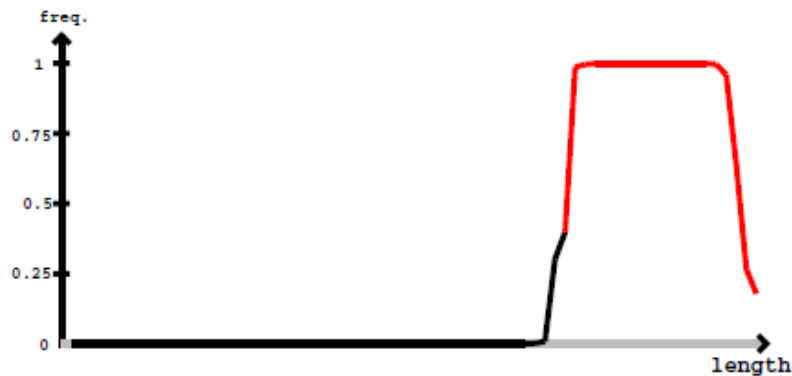
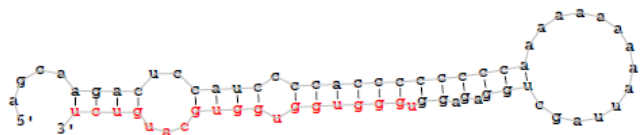
Details of the putative *de novo* miRNAs.

Provisional id	miRDeep2 score	Estimated probability that the miRNA candidate is a true positive	Mature read count	Star read count	Significant randfold p-value	Consensus mature sequence
chr9_24472	4.9	28 +/- 11%	591	0	yes	ugggugguggugcaugucu

Column 1 represents the identifier generated by mirdeep2 according to the genomic location of the identified *de novo* RNAs; column 2-6 represent parameters estimated by miRDeep2 according to the probability of being a true miRNA, its counts, the RANDFOLD test (calculates the free energy of folding [secondary structure] of the miRNA to determine the possibility of being a miRNA) and its sequence.

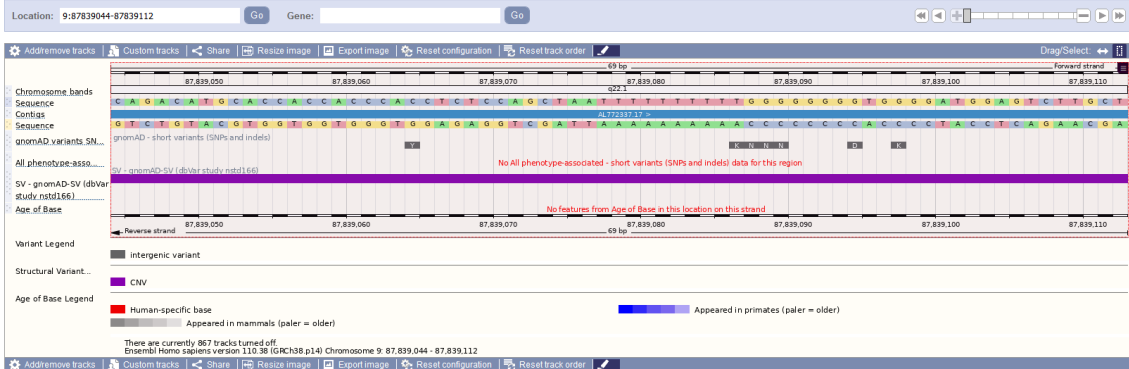
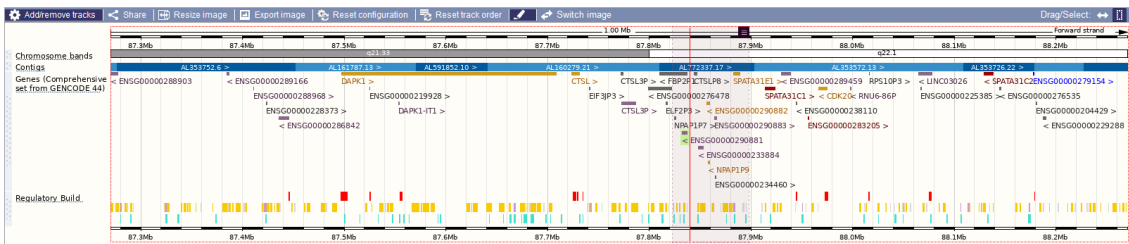
Secondary structure of the microRNA *de novo* chr9_24472 determined with mirdeep2.

miRBase precursor : chr9_24472
 Total read count : 2080
 chr9_24472 read count : 2062
 remaining reads : 18

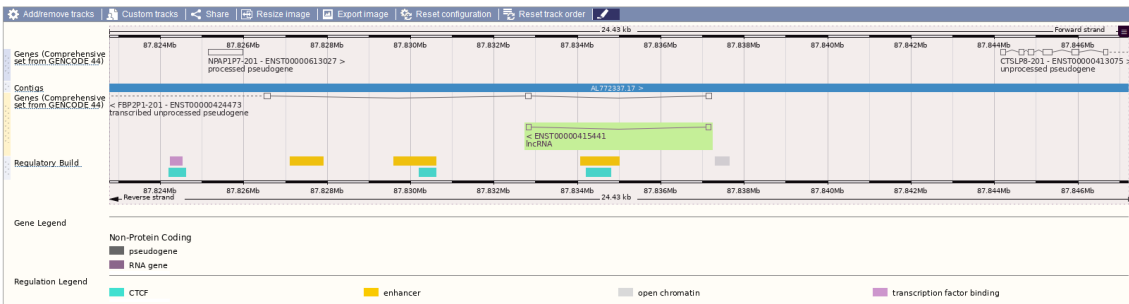


chr9_24472
 5'- agcaagacuccaaucccccccccccccaaaaaaaaauuagcuggagaggugggugguggugcaugucu -3'
(((((((.....))))))))) reads

This putative miRNA is located at the q22.1 arm of chromosome 9 [chr9:87839044-87839112 (GRCh38/hg38)] within the intron 1 of the fructose-bisphosphatase 2 pseudogene 1 (FBP2P1), coincident with an enhancer (ENSR00001151034) and a CTCF binding site.



Zoom in into this region:



Images from http://www.ensembl.org/Homo_sapiens

Supplementary Data 6. MicroRNA-gene target enrichment analysis.

Top 50 genes according to the FDR obtained in the target-enrichment analysis for the SDE miRNAs.

Gene symbol	Function involved	Number of interactions	miRNAs	FDR
USP28	DNA damage response/ Cancer	7	hsa-miR-122-5p / hsa-miR-221-3p / hsa-miR-363-3p / hsa-miR-340-5p / hsa-miR-32-5p / hsa-miR-92a-3p / hsa-miR-20b-5p	3.2344E-05
WNT1	Developmental processes/ Inflammation/ Cancer	5	hsa-miR-122-5p / hsa-miR-152-3p / hsa-miR-148a-3p / hsa-miR-148b-3p / hsa-miR-139-5p	3.2344E-05
PHLDB2	Cytoskeleton organization/ Embryonic development regulation/ Cancer	5	hsa-miR-1-3p / hsa-miR-432-5p / hsa-miR-148a-3p / hsa-miR-148b-3p / hsa-miR-152-3p	3.6609E-05
BAX	Apoptosis	5	hsa-miR-148b-3p / hsa-miR-122-5p / hsa-miR-1-3p / hsa-miR-7-5p / hsa-miR-148a-3p	5.4864E-05
MAP3K4	Cancer	5	hsa-miR-148a-3p / hsa-miR-92a-3p / hsa-miR-199a-3p / hsa-miR-199b-3p / hsa-miR-144-3p	5.4864E-05
MET	Cellular survival/ Embryogenesis/ Cellular migration and invasion/ Cancer	7	hsa-miR-1-3p / hsa-miR-199a-3p / hsa-miR-340-5p / hsa-miR-148a-3p / hsa-miR-144-3p / hsa-miR-139-5p / hsa-miR-144-5p	5.4864E-05
RAB12	Cellular response to insulin stimulus/ Autophagy/ Cancer	5	hsa-miR-148a-3p / hsa-miR-20b-5p / hsa-miR-152-3p / hsa-miR-148b-3p / hsa-miR-223-5p	5.4864E-05
ROCK1	Cytoskeleton organization/ Angiogenesis regulation/ cellular motility and invasion/ Cancer	6	hsa-miR-146a-5p / hsa-miR-584-5p / hsa-miR-148b-3p / hsa-miR-148a-3p / hsa-miR-340-5p / hsa-miR-144-5p	5.4864E-05
FMN1	Cytoskeleton organization	6	hsa-miR-432-5p / hsa-miR-340-5p / hsa-miR-92a-3p / hsa-miR-363-3p / hsa-miR-32-5p / hsa-miR-122-5p	0.00012102
STAMPB	Endosome-lysosome pathway/ Stability of cell substrates/ Cell growth/ Cytokine-mediated signaling/ Cell cycle progression/ Cancer	6	hsa-miR-221-3p / hsa-miR-139-5p / hsa-miR-584-5p / hsa-miR-1-3p / hsa-miR-432-5p / hsa-miR-144-3p	0.00012102
BAZ2B	Human hematopoietic cells reprogramming control	6	hsa-miR-92a-3p / hsa-miR-32-5p / hsa-miR-363-3p / hsa-miR-152-3p / hsa-miR-148b-3p / hsa-miR-148a-3p	0.00026214
CNEP1R1	Triacylglycerol synthesis	6	hsa-miR-32-5p / hsa-miR-92a-3p / hsa-miR-363-3p / hsa-miR-199a-3p / hsa-miR-199b-3p / hsa-miR-144-3p	0.00026214
CNOT4	Transcriptional regulation	7	hsa-miR-152-3p / hsa-miR-148b-3p / hsa-miR-148a-3p / hsa-miR-92a-3p / hsa-miR-363-3p / hsa-miR-32-5p / hsa-miR-20b-5p	0.00026214

GFPT2	Insulin resistance	5	hsa-miR-32-5p / hsa-miR-92a-3p / hsa-miR-363-3p / hsa-miR-199b-3p / hsa-miR-199a-3p	0.00026214
MECP2	Mammalian embryonic development/ Neurologic disorder	8	hsa-miR-199a-3p / hsa-miR-122-5p / hsa-miR-199a-5p / hsa-miR-148b-3p / hsa-miR-92a-3p / hsa-miR-340-5p / hsa-miR-432-5p / hsa-miR-20b-5p	0.00026214
ZIC5	Transcriptional repression/ Cancer	8	hsa-miR-340-5p / hsa-miR-7-5p / hsa-miR-152-3p / hsa-miR-148b-3p / hsa-miR-148a-3p / hsa-miR-92a-3p / hsa-miR-363-3p / hsa-miR-32-5p	0.00026214
MYLIP	Cholesterol homeostasis	9	hsa-miR-20b-5p / hsa-miR-92a-3p / hsa-miR-340-5p / hsa-miR-32-5p / hsa-miR-363-3p / hsa-miR-221-3p / hsa-miR-224-5p / hsa-miR-374a-5p / hsa-miR-654-3p	0.00031364
SMAD4	Cell growth regulation/ Angiogenesis/ Apoptosis/ Cell invasion/ Cancer	8	hsa-miR-92a-3p / hsa-miR-146a-5p / hsa-miR-224-5p / hsa-miR-199a-5p / hsa-miR-183-5p / hsa-miR-20b-5p / hsa-miR-144-3p / hsa-miR-144-5p	0.00038023
LHFPL2	Predicted to be involved in development of primary sexual characteristics	7	hsa-miR-221-3p / hsa-miR-32-5p / hsa-miR-374a-5p / hsa-miR-223-5p / hsa-miR-92a-3p / hsa-miR-363-3p / hsa-miR-224-5p	0.00038404
TRAM2	Reticulum endoplasmic posttranslational secretory control	6	hsa-miR-122-5p / hsa-miR-7-5p / hsa-miR-424-3p / hsa-miR-92a-3p / hsa-miR-363-3p / hsa-miR-32-5p	0.00038404
PLPP4	Cancer	4	hsa-miR-199a-5p / hsa-miR-152-3p / hsa-miR-148b-3p / hsa-miR-148a-3p	0.00038794
ACTC1	Cell motility/ Cardiomyopathy	7	hsa-miR-1-3p / hsa-miR-139-5p / hsa-miR-32-5p / hsa-miR-340-5p / hsa-miR-363-3p / hsa-miR-7-5p / hsa-miR-92a-3p	0.00042088
ITGA5	Tumor invasion/ Cancer	5	hsa-miR-92a-3p / hsa-miR-148b-3p / hsa-miR-183-5p / hsa-miR-152-3p / hsa-miR-148a-3p	0.00042088
REV3L	DNA synthesis/damage	5	hsa-miR-340-5p / hsa-miR-183-5p / hsa-miR-32-5p / hsa-miR-92a-3p / hsa-miR-363-3p	0.00046578
SESN3	Blood glucose regulation/ Insulin resistance/ lipid storage in obesity	9	hsa-miR-374a-5p / hsa-miR-363-3p / hsa-miR-92a-3p / hsa-miR-32-5p / hsa-miR-20b-5p / hsa-miR-584-5p / hsa-miR-148a-3p / hsa-miR-148b-3p / hsa-miR-152-3p	0.00046578
UHRF1	Gene expression regulation/ p53-dependent DNA damage checkpoint/ Cancer	4	hsa-miR-1-3p / hsa-miR-146a-5p / hsa-miR-7-5p / hsa-miR-221-3p	0.00046578
CCT6A	Cancer	5	hsa-miR-32-5p / hsa-miR-148a-3p / hsa-miR-152-3p / hsa-miR-148b-3p / hsa-miR-625-3p	0.00051727
ATP7A	Copper transportation	5	hsa-miR-148b-3p / hsa-miR-122-5p / hsa-miR-32-5p / hsa-miR-92a-3p / hsa-miR-223-5p	0.00059278
SLC7A11	Mediator of Kaposi sarcoma-associated herpesvirus fusion	8	hsa-miR-122-5p / hsa-miR-148b-3p / hsa-miR-340-5p / hsa-miR-32-5p / hsa-miR-92a-3p / hsa-miR-363-3p / hsa-miR-223-5p /	0.00060268

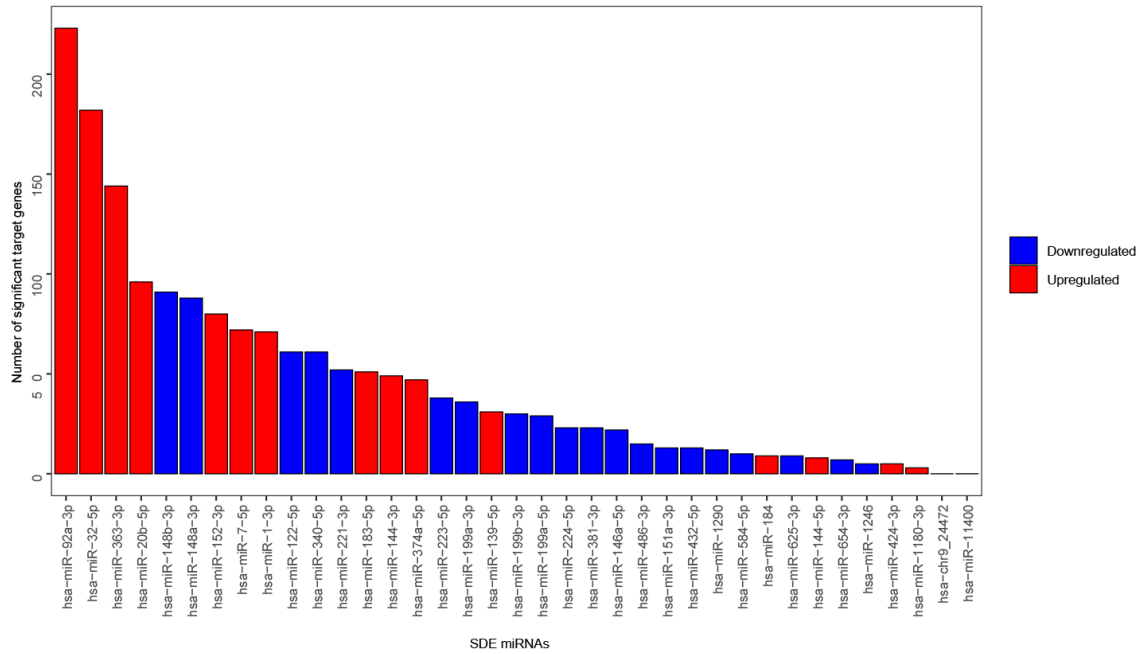
			hsa-miR-20b-5p	
ANKIB1	Proteasomal ubiquitin-dependent protein catabolic process Regulation	4	hsa-miR-1-3p / hsa-miR-20b-5p / hsa-miR-32-5p / hsa-miR-92a-3p	0.00062965
PIK3CD	Immune response	5	hsa-miR-7-5p / hsa-miR-199a-5p / hsa-miR-32-5p / hsa-miR-363-3p / hsa-miR-92a-3p	0.00062965
PPARD	Transcriptional repression and nuclear receptor signaling/ Cancer	4	hsa-miR-92a-3p / hsa-miR-148a-3p / hsa-miR-148b-3p / hsa-miR-152-3p	0.00062965
ATXN1	Immunomodulation/ Neurodegenerative disorders	9	hsa-miR-340-5p / hsa-miR-221-3p / hsa-miR-32-5p / hsa-miR-92a-3p / hsa-miR-374a-5p / hsa-miR-1290 / hsa-miR-144-3p / hsa-miR-20b-5p / hsa-miR-7-5p	0.0006793
BCL11A	Fetal hemoglobin silencing in adult cells/ B-cell malignancies	4	hsa-miR-148b-3p / hsa-miR-340-5p / hsa-miR-32-5p / hsa-miR-486-3p	0.00070532
NFKB1	Wide variety of biological functions/ Immune cell development/ the immediate-early response to viral infection	4	hsa-miR-146a-5p / hsa-miR-92a-3p / hsa-miR-199a-5p / hsa-miR-139-5p	0.00070532
SLC39A6	Protein, nucleic acid, carbohydrate, and lipid metabolism/ Gene transcription control/ Growth, development/ Cell differentiation	4	hsa-miR-32-5p / hsa-miR-139-5p / hsa-miR-144-3p / hsa-miR-92a-3p	0.00070532
ZCCHC2	Predicted to have nucleic acid binding activity and zinc ion binding activity	6	hsa-miR-148b-3p / hsa-miR-340-5p / hsa-miR-122-5p / hsa-miR-92a-3p / hsa-miR-144-3p / hsa-miR-374a-5p	0.00070532
MCOLN2	Predicted to have cation channel activity	5	hsa-miR-32-5p / hsa-miR-92a-3p / hsa-miR-199b-3p / hsa-miR-199a-3p / hsa-miR-363-3p	0.00070659
FXR1	Organ development; muscle fiber development; and somitogenesis	7	hsa-miR-32-5p / hsa-miR-92a-3p / hsa-miR-7-5p / hsa-miR-148a-3p / hsa-miR-148b-3p / hsa-miR-151a-3p / hsa-miR-152-3p	0.00079126
HIVEP1	Transcriptional regulation of both HIV and cellular genes	4	hsa-miR-221-3p / hsa-miR-32-5p / hsa-miR-363-3p / hsa-miR-92a-3p	0.00079126
MORC3	Epigenetic gene silencing/ Developmental abnormalities/ Cancers	4	hsa-miR-32-5p / hsa-miR-584-5p / hsa-miR-92a-3p / hsa-miR-144-3p	0.00079126
SNAPIN	insulin secretion regulation/ Lysosomes and autophagy maintenance in macrophages	5	hsa-miR-1-3p / hsa-miR-7-5p / hsa-miR-148a-3p / hsa-miR-152-3p / hsa-miR-148b-3p	0.00079126
GAS1	Tumor suppression	5	hsa-miR-183-5p / hsa-miR-148a-3p / hsa-miR-152-3p / hsa-miR-148b-3p / hsa-miR-184	0.00083771
DNAJC27	Predicted to be involved in intracellular protein transport and positive regulation of MAPK cascade	4	hsa-miR-7-5p / hsa-miR-32-5p / hsa-miR-92a-3p / hsa-miR-20b-5p	0.00090638
MAPK9	Proliferation, differentiation, transcription regulation and	4	hsa-miR-199a-3p / hsa-miR-7-5p / hsa-miR-92a-3p / hsa-miR-20b-5p	0.00090638

	development/ Cell death			
SOS2	Positive regulation of ras proteins	4	hsa-miR-1-3p / hsa-miR-152-3p / hsa-miR-148b-3p / hsa-miR-148a-3p	0.00090638
PMEPA1	Androgens and transforming growth factor beta induction/ Cancer	6	hsa-miR-7-5p / hsa-miR-654-3p / hsa-miR-374a-5p / hsa-miR-92a-3p / hsa-miR-32-5p / hsa-miR-363-3p	0.00096528
PTAR1	Predicted to have protein prenyltransferase activity	6	hsa-miR-1-3p / hsa-miR-7-5p / hsa-miR-374a-5p / hsa-miR-32-5p / hsa-miR-363-3p / hsa-miR-92a-3p	0.00096528
B4GALT7	Glycosaminoglycan synthesis	6	hsa-miR-152-3p / hsa-miR-148b-3p / hsa-miR-148a-3p / hsa-miR-32-5p / hsa-miR-363-3p / hsa-miR-92a-3p	0.00097395
HECTD1	Organ development/ Negative regulation of protein localization to plasma membrane; and protein autoubiquitination	4	hsa-miR-221-3p / hsa-miR-374a-5p / hsa-miR-32-5p / hsa-miR-92a-3p	0.00097395

Each column represent: the target gene symbol (Gene symbol), function involved, the number of SDE miRNAs that modulate each enriched gene (Number of interactions), the miRNA identifier in miRBase format and the adjusted p -value (FDR, corrected p -value for multiple testing performed with the Benjamini–Hochberg procedure).

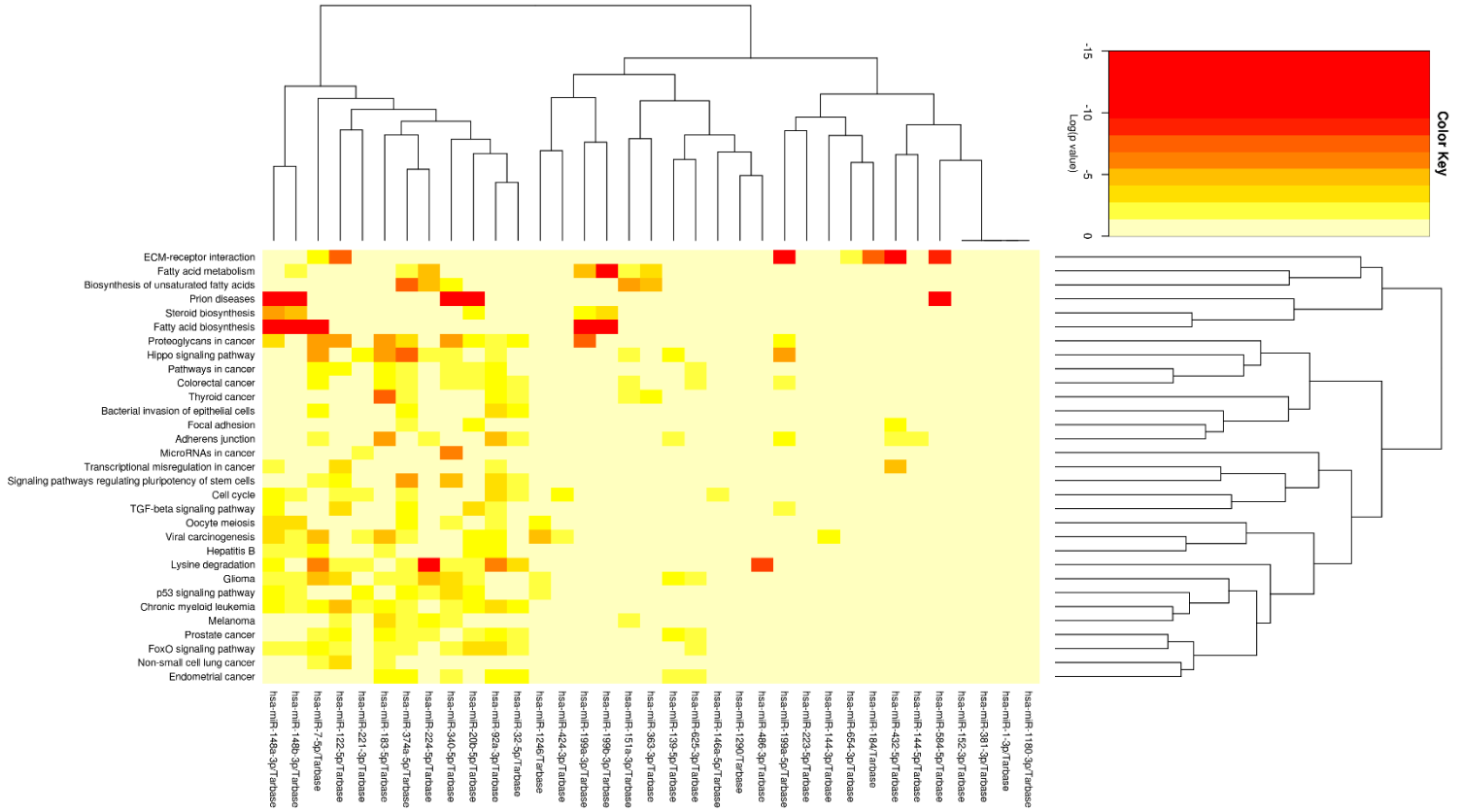
Supplementary Data 7. Barplot of the number of target genes by the SDE miRNAs in HCV/HIV co-infected patients.

Upregulated miRNAs are represented in red and downregulated miRNAs in blue.



Supplementary Data 8. Heatmap of pathway enrichment analysis.

The significance of the association of SDE miRNAs with “Kyoto Encyclopedia of Genes and Genomes” categories is displayed in color (see color key), as identified applying the “pathways intersection” method.



Supplementary Data 9. Top 25 pathways obtained in the pathway-enrichment analysis target genes of SDE miRNAs.

ID	Description	FDR
KEGG		
hsa05205	Proteoglycans in cancer	2.59E-14
hsa05206	MicroRNAs in cancer	6.41E-14
hsa05215	Prostate cancer	4.19E-13
hsa01522	Endocrine resistance	4.78E-12
hsa05210	Colorectal cancer	4.78E-12
hsa05165	Human papillomavirus infection	6.39E-12
hsa05224	Breast cancer	7.81E-12
hsa01521	EGFR tyrosine kinase inhibitor resistance	9.28E-12
hsa04151	PI3K/AKT Signaling in Cancer	2.74E-11
hsa05167	Kaposi sarcoma-associated herpesvirus infection	2.98E-11
hsa05226	Gastric cancer	6.07E-11
hsa05163	Human cytomegalovirus infection	9.29E-11
hsa05218	Melanoma	2.52E-10
hsa05225	Hepatocellular carcinoma	5E-10
hsa05212	Pancreatic cancer	5E-10
hsa05207	Chemical carcinogenesis - receptor activation	8.91E-10
hsa05161	Hepatitis B	1.61E-09
hsa05223	Non-small cell lung cancer	2.35E-09
hsa04933	AGE-RAGE signaling pathway in diabetic complications	2.35E-09
hsa04071	Sphingolipid signaling pathway	3.7E-09
hsa05214	Glioma	3.7E-09
hsa05160	Hepatitis C	5.32E-09
hsa04550	Signaling pathways regulating pluripotency of stem cells	7.87E-09
hsa04068	FoxO signaling pathway	1.43E-08
hsa04722	Neurotrophin signaling pathway	2.54E-08
REACTOME		
R-HSA-5663202	Diseases of signal transduction by growth factor receptors and second messengers	4.8E-07
R-HSA-6785807	Interleukin-4 and Interleukin-13 signaling	4.8E-07
R-HSA-8848021	Signaling by PTK6	3.41E-06
R-HSA-9006927	Signaling by Non-Receptor Tyrosine Kinases	3.41E-06
R-HSA-9634638	Estrogen-dependent nuclear events downstream of ESR-membrane signaling	8.83E-05
R-HSA-449147	Signaling by Interleukins	8.83E-05
R-HSA-9009391	Extra-nuclear estrogen signaling	8.83E-05
R-HSA-2219528	PI3K/AKT Signaling in Cancer	0.000181
R-HSA-9006925	Intracellular signaling by second messengers	0.000255
R-HSA-1257604	PIP3 activates AKT signaling	0.000354
R-HSA-2559585	Oncogene Induced Senescence	0.000428
R-HSA-8878166	Transcriptional regulation by RUNX2	0.000815
R-HSA-109606	Intrinsic Pathway for Apoptosis	0.001093
R-HSA-199418	Negative regulation of the PI3K/AKT network	0.001465
R-HSA-8939211	ESR-mediated signaling	0.001465

R-HSA-166520	Signaling by NTRKs	0.001722
R-HSA-4420097	VEGFA-VEGFR2 Pathway	0.002711
R-HSA-3858494	Beta-catenin independent WNT signaling	0.00357
R-HSA-9006931	Signaling by Nuclear Receptors	0.003698
R-HSA-2559583	Cellular Senescence	0.003852
R-HSA-1227986	Signaling by ERBB2	0.003852
R-HSA-5628897	TP53 Regulates Metabolic Genes	0.004158
R-HSA-194138	Signaling by VEGF	0.004211
R-HSA-3700989	Transcriptional Regulation by TP53	0.004298
R-HSA-452723	Transcriptional regulation of pluripotent stem cells	0.004954

GO

GO:0036293	response to decreased oxygen levels	3.83E-09
GO:0001666	response to hypoxia	4.81E-09
GO:0070482	response to oxygen levels	6.75E-09
GO:0003158	endothelium development	1.14E-08
GO:0048732	gland development	1.36E-08
GO:0036294	cellular response to decreased oxygen levels	7.67E-08
GO:0071456	cellular response to hypoxia	1.9E-07
GO:0048608	reproductive structure development	1.9E-07
GO:0071453	cellular response to oxygen levels	1.9E-07
GO:0061458	reproductive system development	1.9E-07
GO:0061614	pri-miRNA transcription by RNA polymerase II	3.63E-07
GO:0045446	endothelial cell differentiation	3.63E-07
GO:0009791	post-embryonic development	5.67E-07
GO:1901653	cellular response to peptide	9.81E-07
GO:0018209	peptidyl-serine modification	2.69E-06
GO:0030900	forebrain development	2.69E-06
GO:0018105	peptidyl-serine phosphorylation	3.12E-06
GO:0010810	regulation of cell-substrate adhesion	6.05E-06
GO:0021543	pallium development	7.22E-06
GO:0002064	epithelial cell development	7.22E-06
GO:0006352	DNA-templated transcription, initiation	8.12E-06
GO:0050678	regulation of epithelial cell proliferation	1.03E-05
GO:0051893	regulation of focal adhesion assembly	1.49E-05
GO:0090109	regulation of cell-substrate junction assembly	1.49E-05
GO:0048569	post-embryonic animal organ development	1.49E-05

Each column represent: the pathway ID in each database format, the description of the pathway and the adjusted p -value (FDR, corrected p -value for multiple testing performed with the Benjamini-Hochberg procedure).

References

1. Kozomara, A. and S. Griffiths-Jones, *miRBase: annotating high confidence microRNAs using deep sequencing data*. *Nucleic Acids Res*, 2014. **42**(Database issue): p. D68-73.
2. Chen, Y., A.T. Lun, and G.K. Smyth, *From reads to genes to pathways: differential expression analysis of RNA-Seq experiments using Rsubread and the edgeR quasi-likelihood pipeline*. *F1000Res*, 2016. **5**: p. 1438.