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Supplemental Information

Adenosine-to-Inosine Editing of Vasoactive MicroRNAs Alters Their Targetome and Function in Ischemia

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SUPPLEMENTAL INFORMATION

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SUPPLEMENTAL FIGURES AND FIGURE LEGENDS

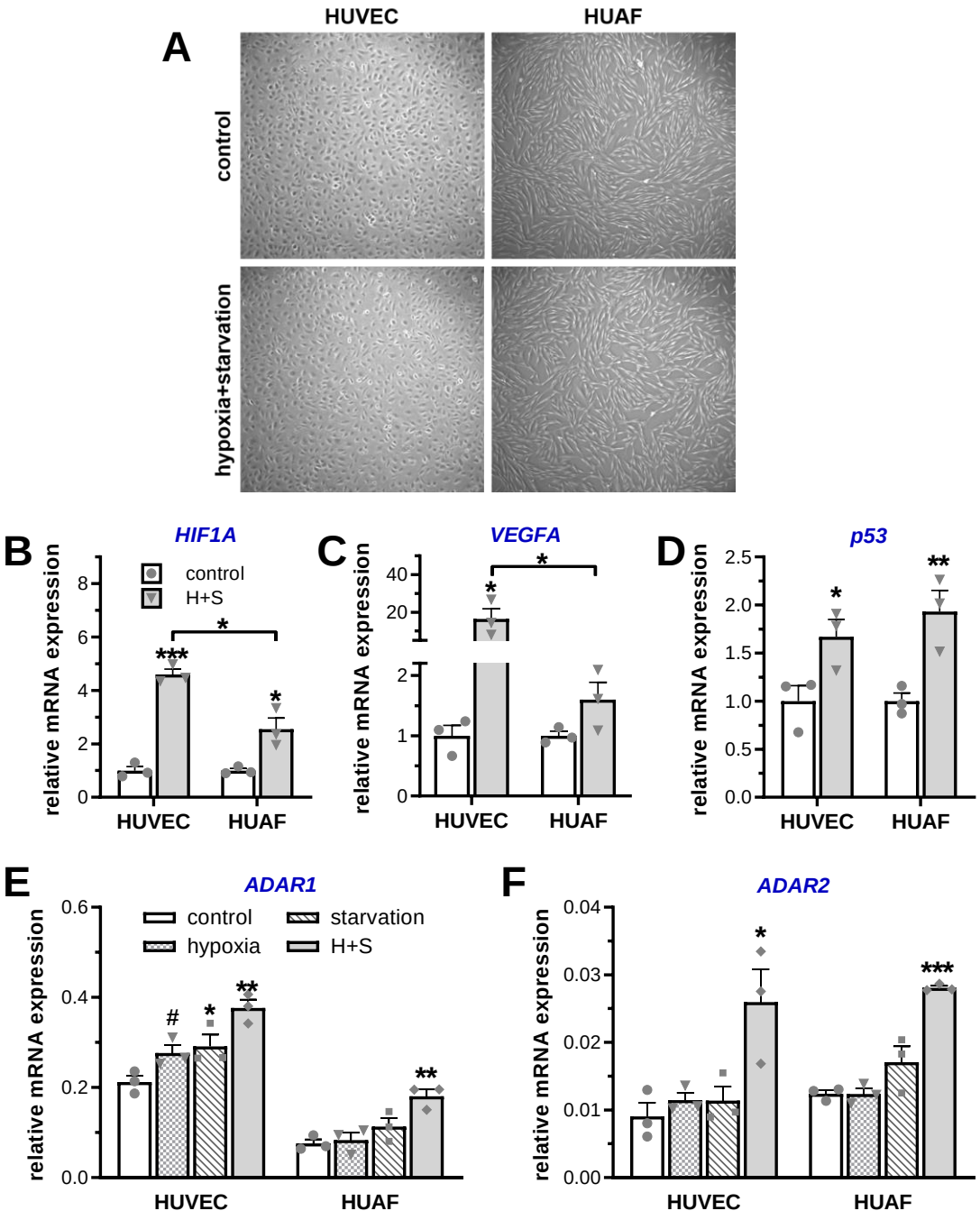

Figure S1: In vitro ischemia conditions induce HIF1A, VEGFA, p53, ADAR1 and ADAR2 expression. (**A**)Primary human umbilical vascular endothelial cells (HUVECs) and human umbilical arterial fibroblasts (HUAFs) were cultured either under normal or ischemic culture conditions, mimicked using a combination of hypoxia and serum starvation (H+S). Expression of hypoxia-inducible genes HIF1A (**B**) and VEGFA (**C**) and p53 (**D**) were successfully increased upon H+S culture conditions. (**D**-**E**) Regulation of ADAR1 (**D**) and ADAR2 (**E**) expression in response to either only serum starvation or hypoxia or the combination. All data are presented as mean ±SEM (n=3). #P<0.1, *P<0.05, **P<0.01, ***P<0.001; versus control condition unless otherwise indicated by 2-sided Student t test.

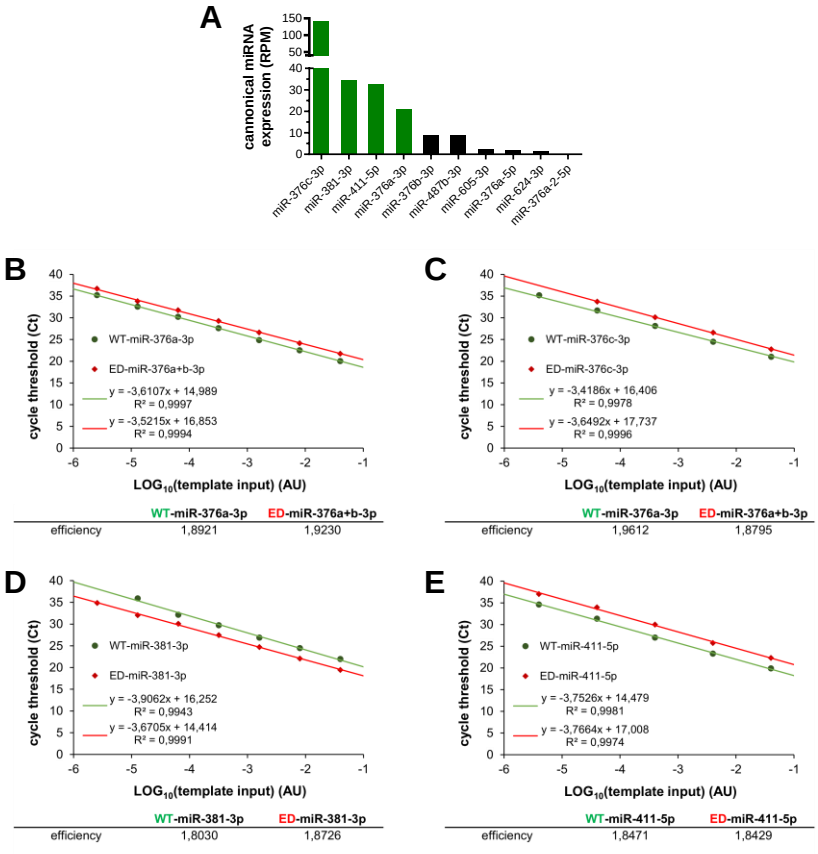

Figure S2: MicroRNA expression and characterization of the microRNA qRT-PCR assays. (**A**) Overall mature miRNA expression in reads per million (RPM) of microRNAs found edited at pri-miRNA level in vascular cells. Data are displayed in descending order and were extrapolated from miRbase.org (only canonical miRNA sequence reads were included). (**B**-**E**) Characterization of PCR efficiency of TaqMan WT-miRNA and custom ED-miRNA qRT-PCR kits by serial dilution of cDNA from HUAF samples transfected with 0.1 pg of the miRNA. To do so, cycle threshold was plotted versus the logarithmic function of the relative input. The equation: efficiency = $10^{(-1/\text{slope})}$ was usedto calculate the corresponding real-time PCR efficiencies[1].

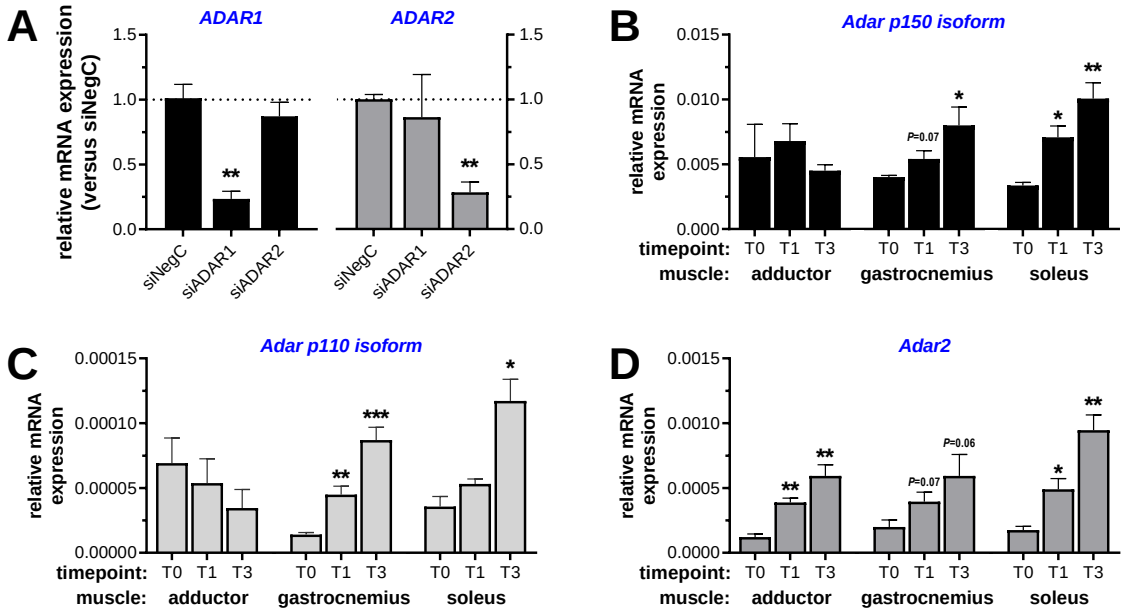

Figure S3: Expression of ADARs *in vitro* after knockdown and *in vivo* after hindlimb ischemia. (**A**) After transfecting HUAFs with a negative control, *ADAR1*-targeted or *ADAR2*-targeted siRNA (siNegC, siADAR1 and siADAR2 respectively), relative expression of *ADAR1* and *ADAR2* was measured by qRT-PCR to validate the knockdown efficiency and specificity. Data was expressed as fold change relative to siNegC and presented as mean ±SEM (n=3 per treatment). (**B**-**C**) Relative expression of Adar1 isoforms P150 (**B**) and P110 (**C**) and Adar2 (**D**) in muscles before hindlimb ischemia (T0) and 1 and 3 days after (T1 and T3 respectively) as determined by qRT-PCR. Data was expressed relative to *Rplp0* and presented as mean ±SEM (n=3 per treatment). **P*<0.05, ***P*<0.01, ****P*<0.001; versus siNegC or T0 by two-sided Student's *t*-test.

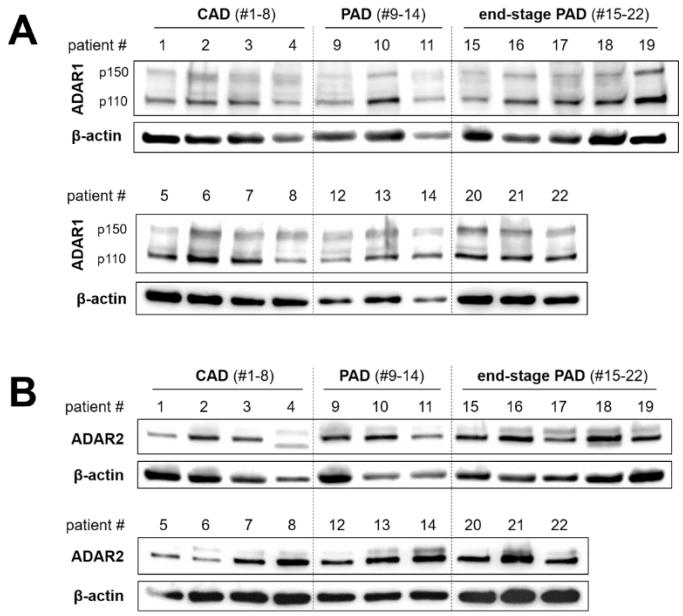

Figure S4: ADAR1 and ADAR2 expression in lower limb veins of patients with peripheral artery disease compared to coronary artery disease. Westernblots of ADAR1 (A) and ADAR2 (B) expression in lower leg vein (LLV) samples from different patient groups. Normoxic LLV samples (n=8) from patients with coronary artery disease (CAD) undergoing coronary artery bypass-surgery were compared to ischemic LLV samples (n=6) from patients with peripheral artery disease (PAD) undergoing femoral artery to popliteal artery-bypass surgery and to critically ischemic LLV samples (n=8) from patients with end-stage PAD, undergoing lower limb amputation. Stable household gene beta-actin was used to normalize expression.

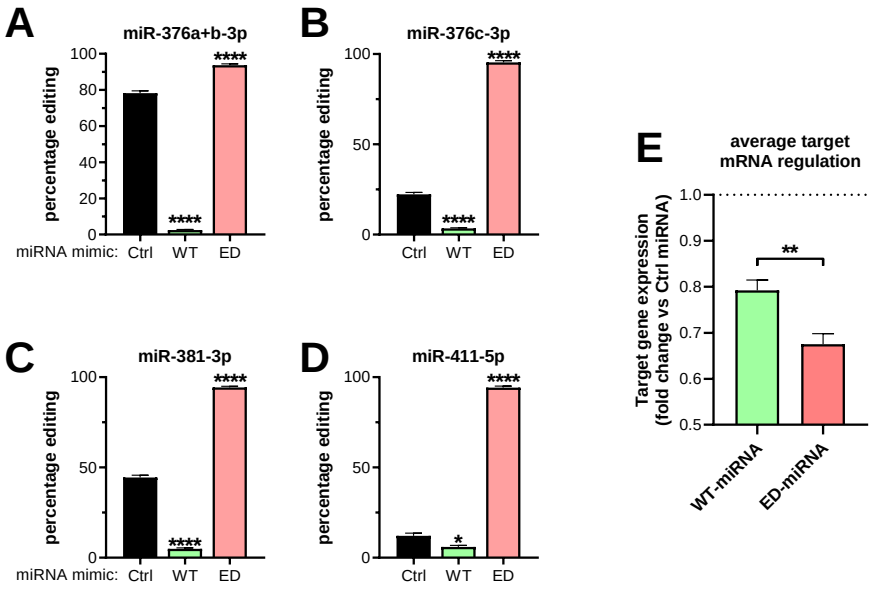

Figure S5: Regulation of percentage miRNA editing and average target mRNA regulation after overexpression of either a WT-miRNA or an ED-miRNA.
HUAF samples were transfected with 0.1 pg of either a WT-miRNA mimic (WT), an ED-miRNA mimic (ED) or a control miRNA mimic (Ctrl). (**A**-**D**) Percentage editing was calculated afterwards using version specific qRT-PCR assays. In each case, overexpression of WT-miRNA successfully reduced overall percentage editing compared to Ctrl and overexpression of ED-miRNA successfully increased percentage editing. Data are presented as mean ± SEM (n=3). **P*<0.05, *****P*<0.0001 versus Ctrl mimic by 2-sided Student *t* test. (**E**) Average expression regulation of successful regulation of WT targets by WT-miRNA overexpression and ED targets by ED-miRNA overexpression shown in Figure 7C. Data are presented as mean ± SEM. ***P*<0.001 by 2-sided Student *t* test.

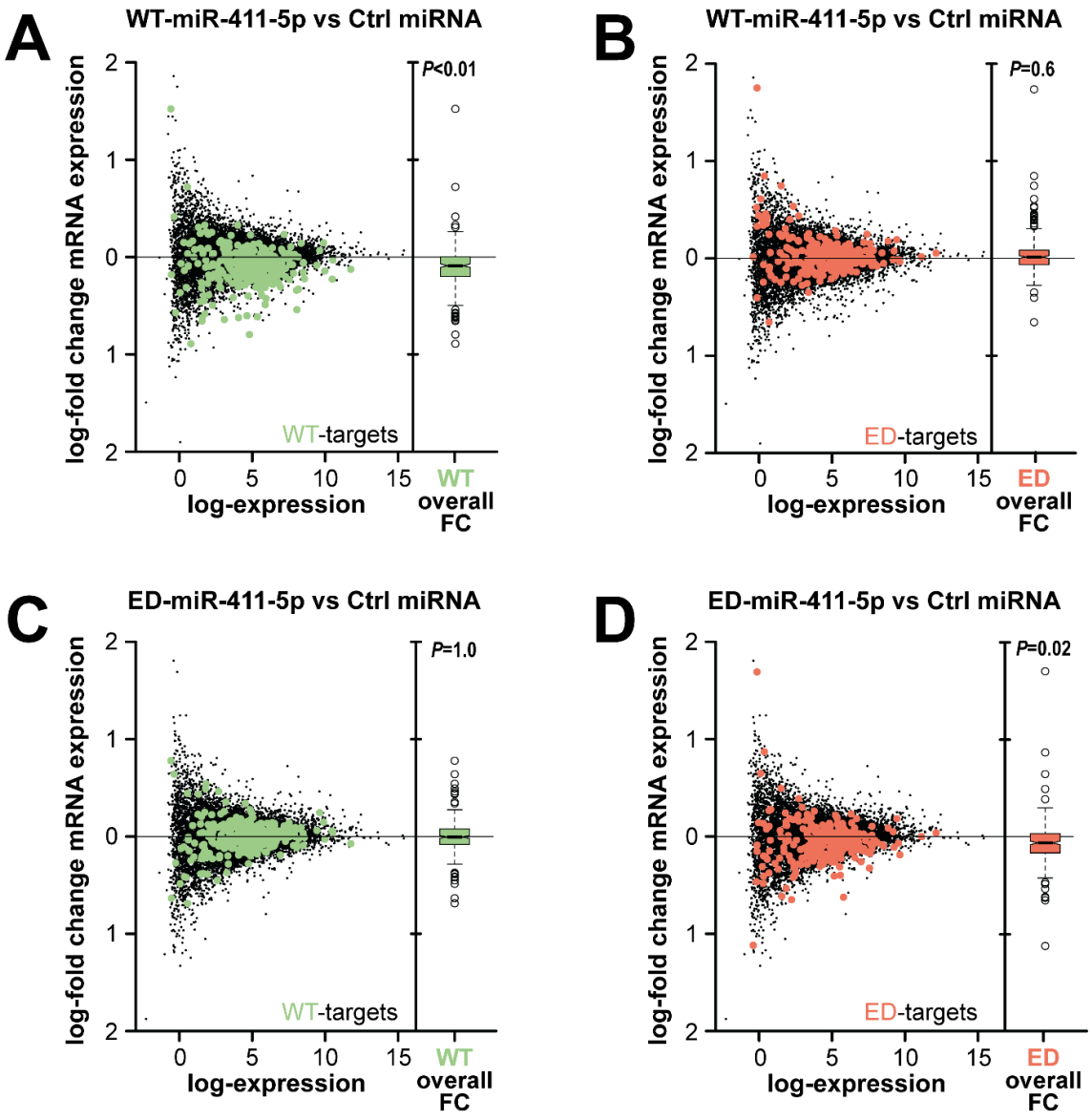

Figure S6: Overall target gene regulation after overexpression of WT-miR-411-5p or ED-miR-411-5p. The log-fold changes (FC) of mRNA expression calculated from RNA-seq data obtained after overexpression of WT-miR-411-5p (**A**&**B**) or ED-miR-411-5p (**C**&**D**) compared to overexpression of a non-targeting control microRNA (Ctrl miRNA) in HUAFs. Data represent averages of 3 independent experiments and are visualized using mean-difference plots, highlighting the predicted target genes (with a 0.5 binding score threshold to minimize false positives, see Supplemental Table VI) that were uniquely targeted by the WT-miR-411-5p (green, **A**&**C**) or ED-miR-411-5p (red, **B**&**D**). The overall distribution of the logFC per targetome is shown in the boxplots. Differential expression of each targetome was tested using ROAST[2].

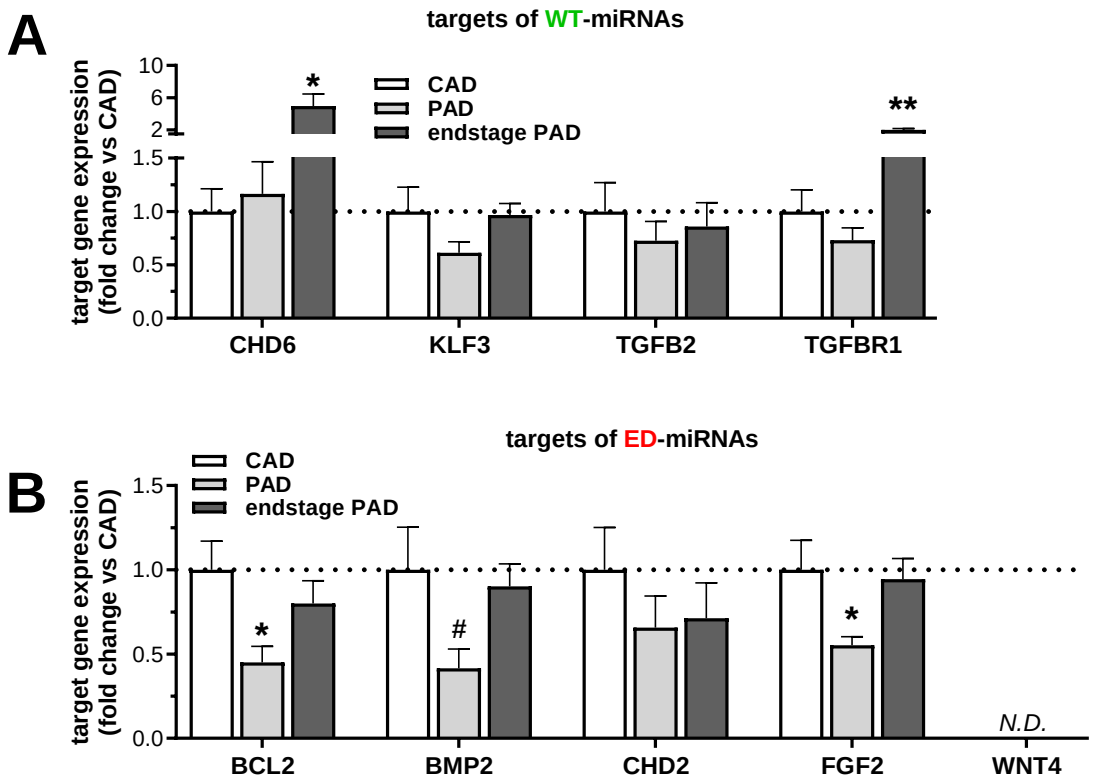

Figure S7: Expression of validated WT-miRNA and ED-miRNA target gene in lower limb veins of patients with and without peripheral artery disease. (**A**&**B**) Relative mRNA expression of genes we validated (see Figure 7B&C) to be targeted by the four selected WT-miRNAs (**A**) or ED-miRNAs (**B**) in lower leg vein (LLV) samples from different patient groups. LLV samples from patients with coronary artery disease (CAD) but not peripheral artery disease (PAD) (n=8) were compared to LLV samples from patients with severe PAD (n=6) and LLV samples from patients with end-stage PAD (n=8). Expression was normalized to stable household gene RPLP0 and expressed as fold change of the CAD group. Expression of WNT4 was not detected (N.D.) in these samples. Data is presented as mean ±SEM. *P<0.05, **P<0.01; by 2-sided Student t test versus CAD.

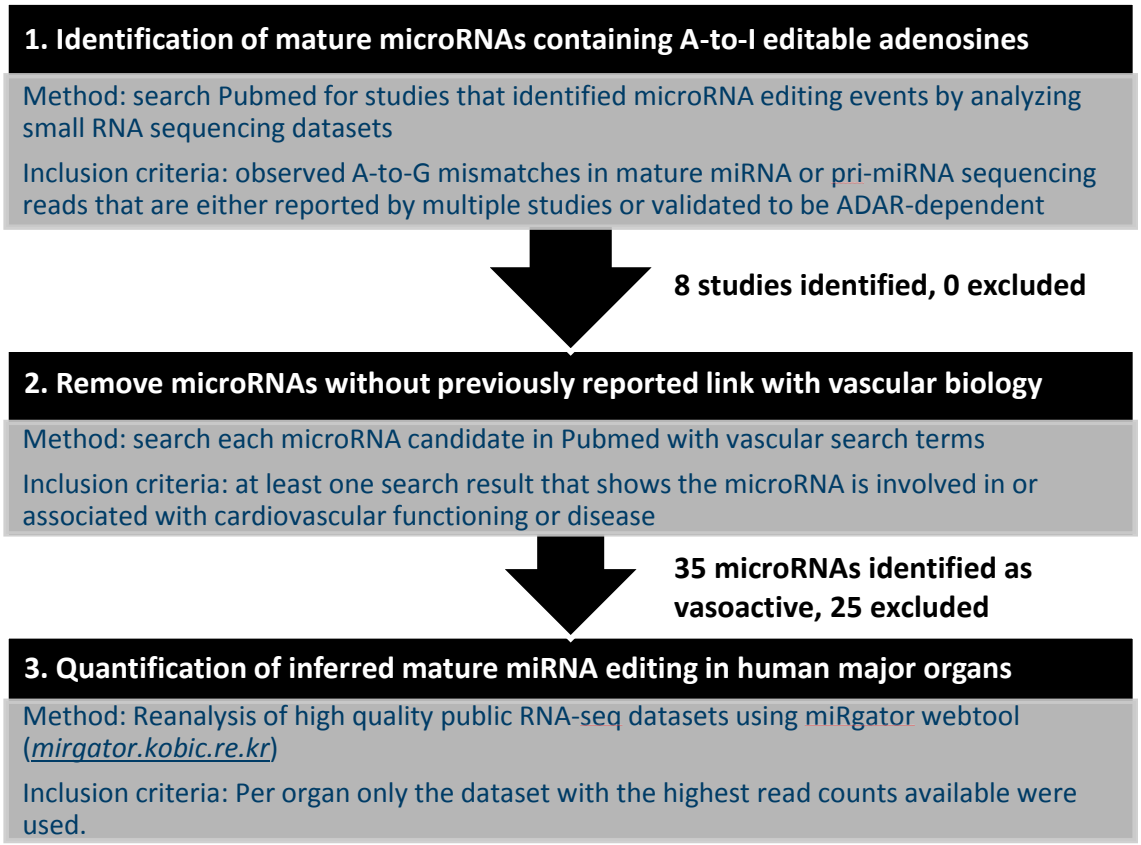

Figure S8: Identification of vasoactive microRNAs containing tissue specific A-to-I editing. A schematic overview of the steps taken to identify vasoactive microRNAs that can be A-to-I edited in a tissue and context dependent manner, using manual literature curation and reanalysis of public RNA-seq datasets.

SUPPLEMENTAL TABLES

Table S1. MicroRNAs containing A-to-I editable adenosines

#	A-to-I editable miRNAs	Chromo some	Dominant side of miRNA duplex	Sequence and editable adenosines (A)	Reported A-to-I edited in:	Linked to vascular functioning
1	**miR-376a1-3p**	14	3p	A**UCAUAGA**GGAAAAUCCACGU	3-5	yes[6]
2	**miR-376a2-3p**	14	3p	A**UCAUAGA**GGAAAAUCCACGU	3-5	yes[6]
3	**miR-376b-3p**	14	3p	A**UCAUAGA**GGAAAAUCCAUGUU	4,5,7-9	yes[10]
4	**miR-376c-3p**	14	3p	A**ACAUAGA**GGAAAUUCCACGU	3-5,7-9,11,12	yes[13]
5	**miR-381-3p**	14	3p	U**AUACAAG**GGCAAGCUCUCUGU	4,5,7,8,11,12	yes[14]
6	**miR-411-5p**	14	5p	U**AGUAGAC**CGUAUAGCGUACG	3-5,7-9,11,12	yes[15]
7	**miR-376a2-5p**	14	3p	G**UAGAUUU**UCCUUCUAUGGU	4,5,8,9,11,12	yes[16]
8	**miR-605-3p**	10	3p	A**GAAGGCA**CUAUGAGAUUUAGA	4,5	yes[17]
9	**miR-624-3p**	14	5p	C**ACAAGGU**AUUGGUAUUACCU	4,5	yes[18]
10	**miR-487b-3p**	14	3p	A**AUCGUAC**AGGGUCAUCCACUU	4,19	yes[20]
11	Let-7c-5p	21	5p	U**GAGGUAG**UAGGUUGU**A**UGGUU	4,5	yes[21]
12	Let-7d-3p	9	5p	C**UAUACGA**CCUGCUGCCUUUCU	4,5,8	yes[21]
13	Let-7e-3p	19	5p	C**UAUACGG**CCUCCUAGCUUUCC	4,5,8	yes[22]
14	miR-24-2-5p	19	3p	U**GCCUACU**GAGCUGAAACACAG	4,5	yes[23]
15	miR-27a-5p	19	3p	**AGGGCUUA**GCUGCUUGUGAGCA	4,5,11	yes[24]
16	miR-27a-3p	19	3p	U**UCACAGU**GGCUAAGUUCCGC	4,5,8,11	yes[21]
17	miR-98-5p	X	5p	U**GAGGUAG**UA**A**GUUGUAUUGUU	4,5	yes[25]
18	miR-99a-5p	21	5p	**AACCCGUA**GAUCCGAUCUUGUG	4,5,8,11,12	yes[26]
19	miR-130b-3p	22	3p	C**AGUGCAA**UGAUGAAAGGGC**A**U	4,5	yes[27]
20	miR-151a-3p	8	5p	C**UAGACUG**AAGCUCCUUGAGG	4,5,8,11,12	yes[18]
21	miR-200b-3p	1	3p	U**AAUACUG**CCUGGUAAUGAUGA	4,5,8,11,12	yes[21]
22	miR-337-3p	14	3p	C**UCCUAUA**UGAUGCCUUUCUUC	4,5,7,12	yes[28]
23	miR-376a1-5p	14	3p	G**UAGAUUC**UCCUUCUAUGAGUA	4,5,8,9,11,12	yes[16]
24	miR-377-3p	14	3p	A**UCACACA**A**A**GGCAACUUUUGU	4,5	yes[16]
25	miR-378a-3p	5	3p	A**CUGGACU**UGGAGUC**A**GAAGGC	3-5,7	yes[21]
26	miR-379-5p	14	5p	U**GGUAGAC**UAUGGAACGUAGG	4,5,7-9,11,12	yes[16]
27	miR-421-3p	X	3p	A**UCAACAG**ACAUU**A**AUUGGGCGC	4,5,7,8	yes[29]
28	miR-455-5p	9	3p	U**AUGUGCC**UUUGGACU**A**UCG	4,5,8	yes[30]
29	miR-494-3p	14	3p	U**GAAACAU**ACACGGGAA**A**CCUC	4,31	yes[20]
30	miR-497-5p	17	5p	C**AGCAGCA**CACUGUGGUUUGU	4,5,7,8,11,12	yes[32]
31	miR-497-3p	17	5p	C**AAACCAC**ACUGUGGUGUU**A**	3-5,7	yes[21]
32	miR-503-5p	X	5p	U**AGCAGCG**GGAACAGUUCUGCAG	4,5	yes[23]
33	miR-539-5p	14	3p	A**GAAAUU**A**A**UCCUUGGUGUG	4,5,8	yes[33]
34	miR-589-3p	7	5p	U**CAGAAC**A**A**AUGCCGGUUCCCAGA	4,5,8,12	yes[34]
35	miR-1260b-5p	11	5p	A**UCCCACC**A**A**CUGCCACCAU	4,5	yes[35]
36	miR-1251-5p	12	5p	A**CUCUAGC**UGCCAAAGGCGCU	4,5,7,12	no
37	miR-1295b-3p	1	5p	A**AUAGGCC**A**A**CGGAUCUGGGCAA	4,12	no
38	miR-1301-3p	2	3p	U**UGCAGCU**GCCUGGGAGUGACUUC	4,5,12	no
39	miR-1304-3p	11	5p	U**CUCACUG**UAGCCUCGAACCCC	4,5,12	no
40	miR-301a-3p	17	3p	C**AGUGCAA**UAGUAUUGUCA**A**AGC	4,5	no
41	miR-301b-3p	22	3p	C**AGUGCAA**UGAUAUUGUCA**A**AGC	4,5	no
42	miR-3144-3p	6	5p	A**UAUACCU**GUUCGGUCUCUUUA	4,12	no
43	miR-3157-3p	10	5p	C**UGCCCUA**GUCU**A**GCUGAAGCU	4,5	no
44	miR-3167-3p	11	5p	A**GGAUUUCA**GAAAUACUGGUGU	4,5	no
45	miR-3622a-3p	8	5p	U**CACCUGA**CCUCCCAUGCCUGU	4,5,12	no
46	miR-3681-5p	2	unclear	U**AGUGGAU**GAUGCACUCUGUGC	4,5	no
47	miR-378b-3p	3	3p	A**CUGGACU**UGGAGGCAGAA**A**	3-5	no
48	miR-378c-5p	10	5p	A**CUGGACU**UGGAGUCAGAAG**A**GUGG	4,5	no
49	miR-4510-5p	15	5p	U**GAGGGAG**UAGG**A**UGUAUGGUU	4,5	no
50	miR-4662a-5p	8	5p	U**UAGCCAA**UUGUCCAUCUUUAG	4,5	no
51	miR-488-3p	1	3p	U**UGAAAGG**CUAUUUCUUGGUC	4,5	no
52	miR-532-5p	X	3p	C**AUGCCUU**GAGUGU**A**GGACCGU	4,5	no
53	miR-556-3p	1	5p	A**UAUUACC**AUUAGCUCAUCUUU	4,5	no
54	miR-561-3p	2	5p	C**AAAGUUU**A**A**GAUCCUUGAAGU	4,5	no
55	miR-598-3p	8	3p	U**ACGUCAU**CGUUGUCAUCGUCA	4,5,8	no
56	miR-625-3p	14	5p	G**ACUAUAG**AACUUUCCCCCUCA	4,5	no
57	miR-6503-3p	11	unclear	G**GGACUAG**GAUGCAGACCUCC	3-5,12	no
58	miR-664a-5p	1	3p	A**CUGGCUA**GGGAAAAUGAUUGGAU	4,5,11,12	no
59	miR-944-3p	21	3p	A**AAUUAUU**GUACAUCGGAUGAG	4,5,11	no
60	miR-99b-3p	19	5p	C**AAGCUCG**UGUCUGUGGGUCCG	4,5	no

MicroRNAs located in the 14q32 microRNA cluster have their chromosome number highlighted in blue.
The seed sequence of each microRNA is highlighted in **bold**.

Table S2. Seed sequence analysis of A-to-I edited pri-miRNAs

miRNA	WT-miRNA sequence and pri-miRNA A-to-I editing location	WT-miRNA seed	Seed sequence shared by	ED-miRNA seed	Seed sequence shared by
miR-376a1-5p	G**UAGAUUC**UCCUUCUAUGAGUA	UAGAUUC	none	U**G**GAUUC	none
miR-376a1-3p	A**UCAUAGA**GGAAAAUCCACGU	UCAUAGA	miR-376a2+b-3p	UCAU**G**GA	none
miR-376a2-5p	G**GUAGAUU**UUCCUUCUAUGGU	GUAGAUU	none	GU**G**GAUU	*miR-8056**
miR-376a2-3p	A**UCAUAGA**GGAAAAUCCACGU	UCAUAGA	miR-376a1+b-3p	UCAU**G**GA	none
miR-376b-3p	A**UCAUAGA**GGAAAAUCCAUGUU	UCAUAGA	miR-376a1+a2-3p	UCAU**G**GA	none
miR-376c-3p	A**ACAUAGA**GGAAAUUCCACGU	ACAUAGA	none	ACAU**G**GA	*miR-4802-3P**
miR-381-3p	U**AUACAAG**GGCAAGCUCUCUGU	AUACAAG	miR-300-3p	AU**G**CAAG	none
miR-411-5p	U**AGUAGAC**CGUAUAGCGUACG	AGUAGAC	none	AGU**G**GAC	none
miR-605-3p	A**GAAGGCA**CUAUGAGAUUUAGA	GAAGGCA	none	GA**G**GGCA	*miR-3616-3p**
miR-624-3p	C**ACAAGGU**AUUGGUAUUACCU	ACAAGGU	none	ACA**G**GGU	none
miR-487b-3p[†]	A**AUCGUAC**AGGGUCAUCCACUU	AUCGUAC	none	**G**UCGUAC	none

* unvalidated microRNA according to Targetscan[36].
[†] characterized previously by Van der Kwast et al. 2018[19].

Table S3. Overview of the findings per selected microRNA

	Experiment	Figure	Tissue	miR-376a&b-3p			miR-376c-3p			miR-381-3p			miR-411-5p		
				WT	ED	% editing	WT	ED	% editing	WT	ED	% editing	WT	ED	% editing
regulation after 24h ischemia	primary miRNA editing	2	HUVECs	≈	++	+	+	+	+	++	+	-	+	++	+
			HUAFs	≈	++	+	++	++	+	+	++	+	+	++	+
	mature miRNA editing	3	HUVECs	≈	+	≈	≈	+	+	+	≈	-	+	+	≈
			HUAFs	+	++	+	++	++	+	+	+	≈	+	+	≈
	AGO2 IP		HUAFs	+	++	+	++	++	+	+	++	+	+	+	≈
	hindlimb ischemia (adductor remains relatively normoxic)	5	adductor	excluded because edited adenosine is not conserved in the murine mmu-miR-376a-3p			+	≈/-	-	≈/+	-	-	++	≈	≈/-
			gastrocnemius				++	+	-	+	++	≈	+	+	≈
			soleus				≈	++	+	++	++	≈	≈/+	+	+
	ex vivo culture	6	IMA	+	++	+	+	+	≈/+	+	+	≈	+	+	≈/+
			VSM	≈/+	+	≈/+	≈	+	+	≈	++	+	+	+	≈/+
ischemic LLVs (PAD patients) versus normoxic LLVs (CAD patients		6	PAD patient LLVs	++	++	≈/+	+	+	+	+	+	+	++	++	≈/+
			end-stage PAD patient LLVs	+	++	≈/+	+	++	++	+	++	++	+	++	+
role of ADARs	primary miRNA editing	4	HUAFs siADAR1	≈	-	≈	-	--	-	≈/-	--	-	-	--	-
			HUAFs siADAR2	+	-	-	-	-	≈	-	-	≈	-	≈/-	≈
	mature miRNA editing		HUAFs siADAR1	-	≈/-	+	-	--	-	-	--	-	-	-	≈
			HUAFs siADAR2	≈/-	-	-	-	-	≈	≈/-	≈/-	≈	≈	≈	≈
				WT mimic	ED mimic	effect of editing	WT mimic	ED mimic	effect of editing	WT mimic	ED mimic	effect of editing	WT mimic	ED mimic	effect of editing
in vitro angio-genesis	wound healing	8	HUAFs	-	+	++	-	-	≈	≈/-	+	+	≈/-	+	+
	tube formation		HUVECs	≈/-	≈/-	≈	-	≈/+	++	≈/-	+	+	≈/-	+	+
	neovessel sprouting		aortic segments	not conserved in mmu-miR-376a			≈/-	+	++	≈/+	+	+	≈	+	++

Table S4. Enriched pathways within putative targetomes*

	Total genes mapped to pathway	# of mapped genes in target set	Expected # of genes targeted	Fold Enrichment	*P* value
WT-miR-376a+b-3p					
-					
ED-miR-376a+b-3p					
Cadherin signalling pathway	158	24	8.06	2.98	0.0007
Wnt signalling pathway	312	34	15.91	2.14	0.0062
WT-miR-376c-3p					
-					
ED-miR-376c-3p					
Cadherin signalling pathway	158	27	11.87	2.27	0.0395
WT-miR-381-3p					
-					
ED-miR-381-3p					
Cadherin signalling pathway	158	25	9.83	2.54	0.0046
Wnt signalling pathway	312	43	19.41	2.22	0.0010
WT-miR-411-5p					
Cadherin signalling pathway	158	23	4.94	4.66	0.0000
Wnt signalling pathway	312	31	9.76	3.18	0.0000
ED-miR-411-5p					
-					

* Putative targetomes were analyzed by the PANTHER pathway algorithm[37]. Only pathway enrichments with $P<0.05$ after Bonferroni correction are reported.

Table S5. Putative targets of WT-miRNAs or ED-miRNAs involved in one or more selected processes related to the response to ischemia
See separate supplemental file.

Table S6: Number of miR-411-5p targets detected using RNA-seq and regulation of the unique targets

Targe-tome	>0.5 binding score	Detected in RNA-seq	Unique to either targetome	Fraction down regulated	Fraction up regulated	Direction	P-Value	FDR
WT-miR-411-5p overexpression vs Ctrl microRNA overexpression								
WT	464	348	**300**	0.3133	0.0300	Down	0.002	0.003
ED	407	315	**274**	0.0547	0.0876	Up	0.579	0.579
ED-miR-411-5p overexpression vs Ctrl microRNA overexpression								
WT	464	348	**300**	0.0733	0.0767	Down	0.987	0.987
ED	407	315	**274**	0.2299	0.0657	Down	0.022	0.043
ED-miR-411-5p overexpression vs WT-miR-411-5p overexpression								
WT	464	348	**300**	0.0300	0.3333	Up	0.001	0.001
ED	407	315	**274**	0.2482	0.0438	Down	0.013	0.013

Overall regulation of unique targets was examined using limma's roast function[38]

Table S7: Number of targets within each targetome and fractions conserved in mice and detected by microarray

			no cutoff				0.5 score cutoff			
			conserved		detected		conserved		detected	
microRNA	target set	human	in mouse		in array		in mouse		in array	
miR-376c	WT only	879	590	*67%*	406	*69%*	218	*37%*	157	*39%*
	ED only	1200	854	*71%*	609	*71%*	266	*31%*	190	*31%*
	shared	326	207	*63%*	146	*71%*	45	*22%*	36	*25%*
miR-381	WT only	1259	959	*76%*	698	*73%*	509	*53%*	376	*54%*
	ED only	886	557	*63%*	391	*70%*	169	*30%*	125	*32%*
	shared	387	248	*64%*	185	*75%*	68	*27%*	51	*28%*
miR-411	WT only	557	256	*46%*	176	*69%*	58	*23%*	43	*24%*
	ED only	590	307	*52%*	218	*71%*	67	*22%*	49	*22%*
	shared	85	37	*44%*	28	*76%*	1	*3%*	1	*4%*

Table S8: Primer sequences and purpose

Primer	Used for:	Sequence (5' to 3')
pri-miR-let7c_F	amplification & sequencing	TTGGAGGAGCTGACTGAAGAT
pri-miR-let7c_R		ATGAAGAATTCCTCGACGGCT
pri-miR-let7d_F	amplification & sequencing	TTTGAAGTGCATCTGCCAAGT
pri-miR-let7d_R		GCAAGGAAACAGGTTATCGGT
pri-miR-let7e_F	amplification & sequencing	TGGTCCCTGTCTGTCTGTCT
pri-miR-let7e_R		TAAGGGTCCCTGAGTGGGG
pri-miR-1260b_F	amplification & sequencing	CAGGTGCTTACCGCAATCAG
pri-miR-1260b_R		CTCCCAAGCAGCAGCAACAG
pri-miR-130b_F	amplification & sequencing	AGCCTGCATTCCAGGTCTCAG
pri-miR-130b_R		AGGCAGCAAGCTCCCTTTCC
pri-miR-151a_F	amplification & sequencing	CTACAGTAGCTGAGCCTGGT
pri-miR-151a_R		AGGTTTGGGCAACACCGA
pri-miR-200b_F	amplification & sequencing	CAGCTACTGAGCTTCCCAGC
pri-miR-200b_R		TCGGCCGGTCGCTGC
pri-miR-24-2_F	amplification & sequencing	CCGCCTGTCCCCTGC
pri-miR-24-2_R		CAGCCCACCCAGGGAAG
pri-miR-27a_F	amplification & sequencing	CTGAGCTCTGCCACCGAG
pri-miR-27a_R		GCAAGGCCAGAGGAGGTGAG
pri-miR-337_F	amplification & sequencing	ATCCGAGCGCTTGCACTG
pri-miR-337_R		AAGGGTGCAGAGGAGGGTC
pri-miR-376a1_F	amplification; qPCR & sequencing	TTTCTGATGACTCAAGCACAGG
pri-miR-376a1_R		CGTCCTCCGAGGTTTTCAAAG
pri-miR-376a2_F	amplification & sequencing	TTGTGTTTGATGGATTGTACTTAGG
pri-miR-376a2_R		CCTGATGGTGGCTTCAGTCC
pri-miR-376b_F	amplification & sequencing	ACTGTGTTCAGATTTGTCCTTTCC
pri-miR-376b_R		TCAGGCCCTACGGTCTCTTC
pri-miR-376c_F	amplification & sequencing	ATTTTGATAGATTGTGCTTAGGTTC
pri-miR-376c_R		AGGAATGTTTCCAAGCAGCA
pri-miR-377_F	amplification & sequencing	GGCATCTCGGTGTGTTCTTG
pri-miR-377_R		GGGGTGTAGATGCCCCTGAG
pri-miR-378a_F	amplification & sequencing	GGAGTGAGCGGCTTGTATGG
pri-miR-378a_R		GTGGGGAAGGTGACTCCACT
pri-miR-379_F	amplification & sequencing	GTGACGCCAACTTCAGGGG
pri-miR-379_R		GTTGGCAACACCTCCAGGAA
pri-miR-381_F	amplification & sequencing	CCGTGAATGATAGTGAGAAC
pri-miR-381_R		ACACATACCGCATCCCTTG
pri-miR-411_F	amplification; qPCR & sequencing	AAGGCCTTGGAGGGCTTTCTG
pri-miR-411_R		GACAGCGTTGTTTCCAGGAGC
pri-miR-487b_F	amplification; qPCR & sequencing	GAAGACGTACCAAGTCCACCC
pri-miR-487b_R		GCTCCAGAGTCTGCGCTCTT
pri-miR-494_F	amplification & sequencing	TTCGGCAGTTCTGTTTTGAT
pri-miR-494_R		TCCAGGGTGGGATTTGATACT
pri-miR-497_F	amplification & sequencing	TGGGGTCTTCCCAGCACT
pri-miR-497_R		TCCCAGGGCCAAGCCTC
pri-miR-503_F	amplification & sequencing	TATTCCTGGCTAGGCTGGGG
pri-miR-503_R		ACTTACCTGCTGGGTAGGC
pri-miR-539_F	amplification & sequencing	TCACCATCTAACCTTGAGCCAAA
pri-miR-539_R		ATGGCGTCCAGGAAGTCTGC
pri-miR-589_F	amplification & sequencing	AGCCTGAGAGACCGACCCT
pri-miR-589_R		GCAGAAGGCAGGAATCCAGAG
pri-miR-605_F	amplification & sequencing	GAACTTTGGTAGAACTTTCACAGC
pri-miR-605_R		CTGTAACATAGGTAACCTGTATCTG
pri-miR-624_F	amplification & sequencing	GGTTTTGTGTTCTTGTAATGAAAAA
pri-miR-624_R		ATCTTGTTCACTGAAACCACTT

pri-miR-98_F pri-miR-98_R	amplification & sequencing	AAAGAGTCTGTCACCATGTAAAA TGCTAAGACTAAGTGTGAATATGCC
pri-miR-99a_F pri-miR-99a_R	amplification & sequencing	TTTTGACTCTTAATTGCATCAGATA GCACTGTGTATAGCATTTTGTCA
pri-miR-376a2_F pri-miR-376a2_R	qPCR	CGTGCTTTCCGGGATGAAAC CAGTCCAGCCATGATCCCAA
pri-miR-376b_F pri-miR-376b_R	qPCR	CAGAGCCCAGTCCTTCTTTG CCTACGGTCTCTTCCAGAAACA
pri-miR-376c_F pri-miR-376c_R	qPCR	GGTTCATGCTTTCCAGGACTCA TCTTCCCTGATGGTGGTTTCAG
pri-miR-381_F pri-miR-381_R	qPCR	AACCTGCCCAGTGCTATTGTT ACACACATACCGCATCCCTT
pri-miR-605_F pri-miR-605_R	qPCR	TGTCTCTAGCCCTAGCTTGGTT AGCAATATACCTGTGGCTGTCA
pri-miR-624_F pri-miR-624_R	qPCR	AAAGTGGTTTTGTGTTCTTGTAATG ACCACTTAGGTGTAATGCTATCTCA
U6-F U6-R	qPCR	AGAAGATTAGCATGGCCCCT ATTTTGCGTGTCATCCTTGCG
ADAR1_human_F ADAR1_human_R	qPCR	GCTTGGGAACAGGGAATCGC CGCAGTCTGGGAGTTGTATTTC
ADAR2_human_F ADAR2_human_R	qPCR	GGAAGCTGCCTTGGGATCAG GCTGCTGGAACTCATGTTTTCTTC
RPLP0_human_F RPLP0_human_R	qPCR	TCCTCGTGGAAGTGACATCG TGTCTGCTCCCACAATGAAAC
p53_F p53_R	qPCR	TGACACGCTTCCCTGGATTG TTTTCAGGAAGTAGTTTCCATAGGT
VEGFa_F VEGFa_R	qPCR	ATCACCATGCAGATTATGCGG CCCCTTTCCCTTTCCTCGAAC
HIF1A_F HIF1A_R	qPCR	TGTCTCTAGCCCTAGCTTGGTT AGCAATATACCTGTGGCTGTCA
Adar1p150_mouseF Adar1p150_mouseR	qPCR	GGCACTATGTCTCAAGGGTTC CCTGTGGCTGCGGGTATC
Adar1p110_mouseF Adar1p110_mouseR	qPCR	TCACCAATCTGCGCCCTAAC GTGTCTGGTGAGGGAACACC
Adar2_mouse_F Adar2_mouse_R	qPCR	GCTTGCCCTGAAGGAGTTTTG CAGTGCTGCTGGAACTCATATTC
Rplp0_mouse_F Rplp0_mouse_R	qPCR	GCGACCTGGAAGTCCAACTA ATCTGCTGCATCTGCTTGG
ANGPT2_3'UTR_F ANGPT2_3'UTR_R	construct cloning (WT-376a&b site)	CTCTCTCGAGTATCAACAGAAACGTGCCAT CTGCGGCCGCGGGTGAATCTTGAGACATATAGC
WNT4_3'UTR_F WNT4_3'UTR_R	construct cloning (ED-376a&b site)	CTCTCTCGAGCTGAAGTCCCACCCTAGAACC CTGCGGCCGCGTTTGTCTGCTTCCCAGGACT
TGFBR2_3'UTR_F TGFBR2_3'UTR_R	construct cloning (WT-376c site)	CTCTCTCGAGACTGTTCTATAGTTTTTCAGGATCT CTGCGGCCGCATTCAAACATGACCATGCTAATAA
CHD2_3'UTR_F CHD2_3'UTR_R	construct cloning (ED-376c site)	CTCTCTCGAGGGGGGATGAGACCATGAGATT CTGCGGCCGCTGTGCTAAGAACTTTTCTCCCT
KLF3_3'UTR_F KLF3_3'UTR_R	construct cloning (WT-381 site)	CTCTCTCGAGATGAAGTTGCTCCGAGCTGTC CTGCGGCCGCTCCCATTGGACTACAGAGTAGAAAC
CHD6_3'UTR_F CHD6_3'UTR_R	construct cloning (WT-411 site)	CTCTCTCGAGTCTAAAAAGTCATGATTCCCCCACT CTGCGGCCGCCGGCTCTGTTGGGCTAACG
TGFB2_3'UTR_F TGFB2_3'UTR_R	construct cloning (WT-411 site)	CTCTCTCGAGTTTGCCACATCATTGCAGAAG CTGCGGCCGCCCTATCTGAGAGGAAAATGTCTGC
FGF2_3'UTR_F FGF2_3'UTR_R	construct cloning (ED-411 site)	CTCTCTCGAGTATTGCATCTGCTGTTACCCAG CTGCGGCCGCCGTCCTGAGTATTCGGCAAC
ANGPT2_F ANGPT2_R	qPCR	CAGCCCCTACGTGTCCAATG GCCGTCTGGTTCTGTACTGC

BMP2_F	qPCR	CCAGACCACCGGTTGGAG
BMP2_R		AAACTCCTCCGTGGGGATAG
WNT4_F	qPCR	GCTCCACACTCGACTCCTTG
WNT4_R		CCCATGCACTGTCCTGTCAC
TGFBR1_F	qPCR	TCCTCGAGATAGGCCGTTTG
TGFBR1_R		CCAGTTCCACAGGACCAAGG
CHD2_F	qPCR	ATGCAAGACTGGATTTCCTGAAG
CHD2_R		TCTCACGGCATACACCATGC
BCL2_F	qPCR	AACATCGCCCTGTGGATGAC
BCL2_R		GGGCCAAACTGAGCAGAGTC
KLF3_F	qPCR	TGACCCAGTTCCTGTCAAGC
KLF3_R		TGTATTCCGTGCGACAGACC
CHD6_F	qPCR	GCTCTGGTTGCCATCCTTCTG
CHD6_R		CCACCTTCGTCGTTGTAACTG
TGFB2_F	qPCR	CCCTGCTGCACTTTTGTACC
TGFB2_R		AGGAGATGTGGGGTCTTCCC
FGF2_F	qPCR	ACCTGGCTATGAAGGAAGATGG
FGF2_R		CGTTTCAGTGCCACATACCAAC

Gray highlighted sequences are primer extensions to flank the amplicon restriction enzyme sites

Table S9. Sequences of custom ED-miRNA specific qRT-PCR assays

Assay target	Component	Sequence
ED-miR-376a+b-3p	hairpin RT primer	GTGCTAACGTGTGCAGGGACGGAGGACACGTTAGCACACGTGG
	qPCR primers	CCGGCGATCATGGAGGAAAATC
		TGCAGGGACGGAGGA
	qPCR probe	<VIC>ACGTTAGCACACGTGGAT<MGB>
ED-miR-376c-3p	hairpin RT primer	GTCGTATCCAGTGCAGGGACCGAGGACTGGATACGACACGTGG
	qPCR primers	CCGGCGAACATGGAGGAAATTC
		TGCAGGGACCGAGGA
	qPCR probe	<VIC>CTGGATACGACACGTGGAA<MGB>
ED-miR-381-3p	hairpin RT primer	GGCGTTGGCAGTGCAGGGTCCGAGGTCTGCCAACGCCACAGAG
	qPCR primers	GCCGTATGCAAGGGCAAGC
		GTGCAGGGTCCGAGG
	qPCR probe	<VIC>CCAACGCCACAGAGAG<MGB>
ED-miR-411-5p	hairpin RT primer	GTCGTATCCAGTGCAGGGACCGAGGACTGGATACGACCGTACGC
	qPCR primers	CCGCCTAGTGGACCGTATAGC
		TGCAGGGACCGAGGA
	qPCR probe	<VIC>CTGGATACGACCGTACGCT<MGB>

<VIC>, VIC fluorophore
<MGB>, minor groove binder

Table S10: Sequences of siRNA and synthesized endogenous 3'UTRs

siRNA	targets	sequence
siADAR1	ADAR1	5′-GCUAUUUGCUGUCGUGUCA(dT)(dT)-3′
siADAR2	ADAR2	5′-GAUCGUGGCCUUGCAUUAA(dT)(dT)-3′
siRNA control:	nothing	5′-UCUCUCACAACGGGCAU(dT)(dT)-3′

3'UTR from	sequence
BMP2 (ED-miR-376a+b-3p binding site)	CTCTCTCTCGAGGGAAAAAAATAGCTAATTTGTATTTATATGTAATCAAAAGAAGTATCGGGTTTGTACA TAATTTTCCAAAAATTGTAGTTGTTTTCAGTTGTGTGTATTTAAGATGAAAAGTCTACATGGAAGGTTAC TCTGGCAAAGTGCTTAGCACGTTTGCTTTTTTGCAGTGCTACTGTTGAGTTCACAAGTTCAAGTCCAGAA AAAAAAAGTGGATAATCCACTCTGCTGACTTTCAAGATTATTATATTATTCAATTCTCAGGAATGTTGCA GAGTGATTGTCCAA**TCCATGA**GAATTTACATCCTTATTAGGTGGAATATTTGGATAAGAACCAGACATTG CTGATCTATTATAGAAACTCTCCTCCTGCCCCTTAATTTACAGAAAGAATAAAGCAGGATCCATAGAAAT AATTAGGAAAACGATGAACCTGCAGGAAAGTGAATGATGGTTTGTTGTTCTTCTTTCCTAAATTAGTGAT CCCTTCAAAGGGGCTGATCTGGCCAAAGTATTCAATAAAACGTAAGATTTCTTCATTATTGATATTGTGG TCATATATATTTGCGGCCGCCTTCC
BCL2 (ED-miR-376c-3p binding sites)	CTCTCTCGAGTTTTTACATTATTAAGAAAAAAAGATTTATTTATTTAAGACAGTCCCATCAAAACTCCTG TCTTTGGAAATCCGACCACTAATTGCCAAGCACCGCTTCGTGTGGCTCCACCTGGATGTTCTGTGCCTGT AAACATAGATTCGCTT**TCCATGT**TGTTGGCCGGATCACCATCTGAAGAGCAGACGGATGGAAAAAGGACC TGATCATTGGGGAAGCTGGCTTTCTGGCTGCTGGAGGCTGGGGAGAAGGTGTTCATTCACTTGCATTTCT TTGCCCTGGGGATATTTAATGACAACCTTCTGGTTGGTAGGGACATCTGTTTCTAAATGTTTATTATGTA CAATACAGAAAAAAATTTTATAAAATTAAGCAATGTGAAACTGAATTGGAGAGTGATAATACAAGTCCTT TAGTCTTACCCAGTGAATCATTCTGT**TCCATGT**CTTTGGACAACCATGACCTTGGACAATCATGAAATAT GCATCTCACTGGATGCAAAGAAAATCAGATGGAGCATGAATGGTACTGTACCGGTTCATCTGGACTGCCC CAGAAAAATAACTTCAAGCAAACATCCTATGCGGCCGCAG
BCL2 (ED-miR-381-3p binding sites)	CTCTCTCTCGAGTATCATTTATTTTTTACATTATTAAGAAAAAAAGATTTATTTATTTAAGACAGTCCCA TCAAAACTCCTGTCTTTGGAAATCCGACCACTAATTGCCAAGCACCGCTTCGTGTGGCTCCACCTGGATG TTCTGTGCCTGTAAACATAGATTCGCTTTCCATGTTGTTGGCCGGATCACCATCTGAAGAGCAGACGGAT GGAAAAAGGACCTGATCATTGGGGAAGCTGGCTTTCTGGCTGCTGGAGGCTGGGGAGAAGGTGTTCATTC A**CTTGCAT**TTCTTTGCCCTGGGGGCTGTGATATTAACAGAGGGAGGGTTCCTGTGGGGGGAAGTCCATGC CTCCCTGGCCTGAAGAAGAGACTCT**TTGCATA**TGACTCACATGA**TGCATA**CCTGGTGGGAGGAAAAGAGT TGGGAACTTCAGATGGACCTAGTACCCACTGAGATTTCCACGCCGAAGGACAGCGATGGGAAAAATGCCC TTAAATCATAGGAAAGTATTTTTTTAAGCTACCAATTGTGCCGAGAAAAGCATTTTAGCAATTTATACAA TATCATCCAGTACCTTAAGCCCTGATTGCGGCCGCCTTCC
ANGPT2 (ED-miR-381-3p binding sites)	CTCTCTCGAGACATCCCAGTCCACCTGAGGAACTGTCTCGAACTATTTTCAAAGACTTAAGCCCAGTGCA CTGAAAGTCACGGCTGCGCACTGTGTCCTCTTCCACCACAGAGGGCGTGTGCTCGGTGCTGACGGGACCC ACATGCTCCAGATTAGAGCCTGTAAACTTTATCACTTAAA**CTTGCAT**CACTTAACGGACCAAAGCAAGAC CCTAAACATCCATAATTGTGATTAGACAGAACACCTATGCAAAGATGAACCCGAGGCTGAGAATCAGACT GACAGTTTACAGACGCTGCTGTCACAACCAAGAATGTTATGTGCAAGTTTATCAGTAAATAACTGGAAAA CAGAACACTTTATTATACATTTATTAGCCTTAGCAGGCAATAAACCAAGAATCACTTTGAAGACACAGCA AAAAGTGATACACTCCGCAGATCTGAAATAGATGTGTTCTCAGACAACAAAGTCCCTTCAGAATCTTCAT G**TTGCAT**AAATGTTATGAATATTAAcAAgAAGTTGATTGAGAAAGCGGCCGCAG

Gray highlighted sequences are non-endogenous extensions containing restriction enzyme sites for cloning. Colored highlights indicate miRNA binding sites.

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