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MicroRNAs and metabolic programming

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Talk overview

- **Introduction to non-coding RNAs**
- **Introduction to microRNAs and their roles in metabolism**
- **miRNAs in Metabolic Syndrome and related conditions**
- **Conclusions**

The complex and diverse world of RNA molecules: before seq

Long RNA

mRNA pseudogenes lncRNA rRNA ribozyme

Intermediate RNA

RNU RMRP snRNA LTR RPPH1 SINE
LINE
snoRNA rRNA
tRNA ribozyme

Small RNA

Courtesy of Dr. Sethupathy

The complex and diverse world of RNA molecules: after seq

Long RNA

mRNA pseudogenes lncRNA eRNA rRNA ribozyme

Intermediate RNA

TERRA RNU RMRP snRNA Ro LTR RPPH1 SINE
SNAR SCARNA LINE PASR TASR rRNA
pyknon vtRNA snoRNA T-UCR ribozyme
tRNA

Small RNA

tDR svRNA sdRNA TSS-miRNA PASR TASR srRNA Y
Exo-siRNA qiRNA sbRNA hc-siRNA tasiRNA diRNA usRNA
tiRNA tRH tRF natsiRNA casiRNA tasiRNA
miRNA Endo-siRNA dsRNA crasiRNA scnRNA tel-sRNA piRNA

List of major classes of small ncRNAs, including their abbreviations, size range and function

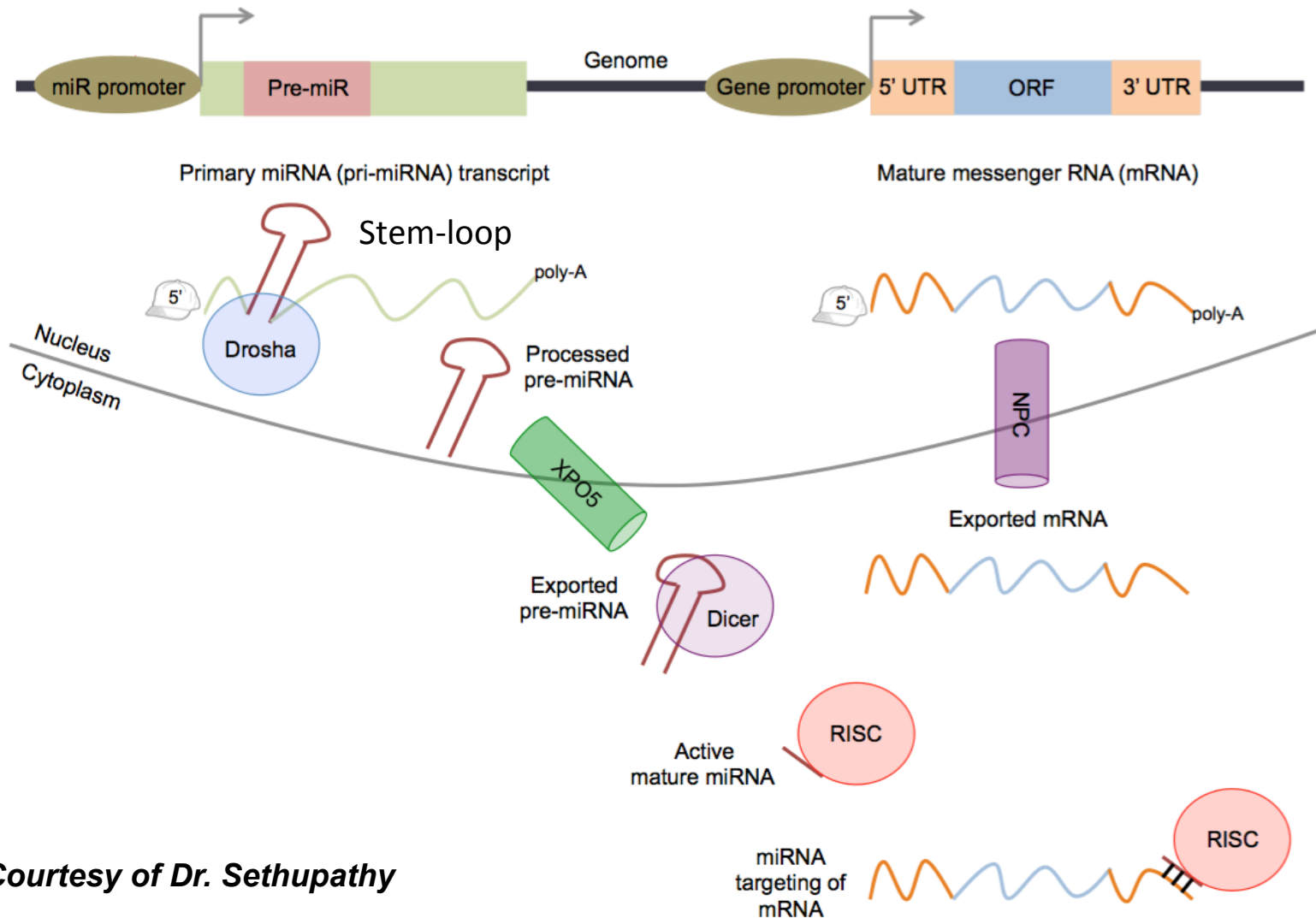
<i>Name</i>	<i>Abbreviation</i>	<i>Size</i>	<i>Function(s)</i>
transfer RNA	tRNA	73–93nt	Transfers amino acids to the ribosome during translation of mRNA to protein
ribosomal RNA	rRNA	120–5035nt	Translation of mRNA to protein
small nuclear RNA	snRNA	90–220nt	RNA splicing
small nucleolar RNA	snoRNA	C/D box-70–120nt H/ACA-100–200nt	Guide the modification and maturation of other ncRNAs
long non-coding RNA/long intergenic non-coding RNA	lncRNA/lincRNA	>200nt	Epigenetic gene regulation
microRNA	miRNA	21–22nt	Translation inhibition; binds mRNA to block translation
short/small interfering RNA	siRNA	21–25nt	Translation inhibition; binds mRNA to signal cleavage

<i>Name</i>	<i>Abbreviation</i>	<i>Size</i>	<i>Function(s)</i>
endoribonuclease-prepared short interfering RNA	esiRNA	20–25 nt	RNA interference
repeat-associated small interfering RNA*previous name for piRNAs	rasiRNA	24–29 nt	Silencing of retrotransposons in the germline
piwi-interacting RNA	piRNA	26–31 nt	Silencing of retrotransposons in the germline
centromere repeat-associated small interacting RNA	crasiRNA	35–42 nt	Centromere identity and function
small RNAs derived from snoRNAs	sdRNA	17–19, >27 nt	Gene regulation and alternative splicing
transcription initiation RNA	tiRNA	18 nt	Unclear; may function in transcription regulation
splice site RNA	spliRNA	17–18 nt	Unclear; generated from the donor splice site in animal internal exons
tRNA-derived RNA fragments	tRFs	18–22 nt, 30–35 nt	miRNA-like functions; gene regulation

MicroRNAs (miRNAs):

- Approximately 22 nt length.
- 1-3% of genome.
 - ~2500 miRNAs in human.
- Tissue specific.
- Highly stable.
- Regulate gene expression (multiple genes).
- Their sequence is used to predict potential targets.
- Genetic variation may influence miRNA activity.
- Conserved across species.
- Involved in development, differentiation, cell proliferation, metabolism, and inflammation as well as in human diseases.

Canonical microRNA (miRNA) biogenesis and function



Courtesy of Dr. Sethupathy

Mechanisms of action.

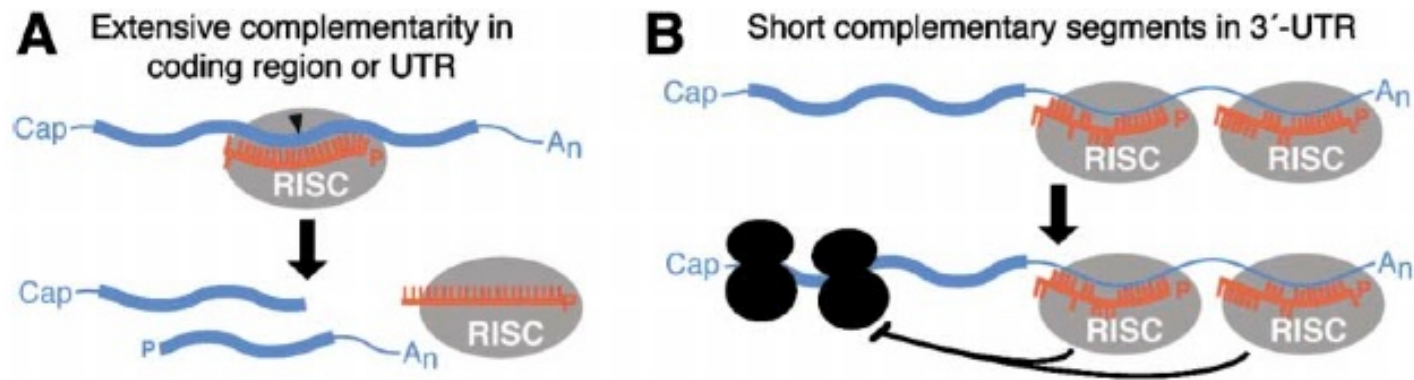


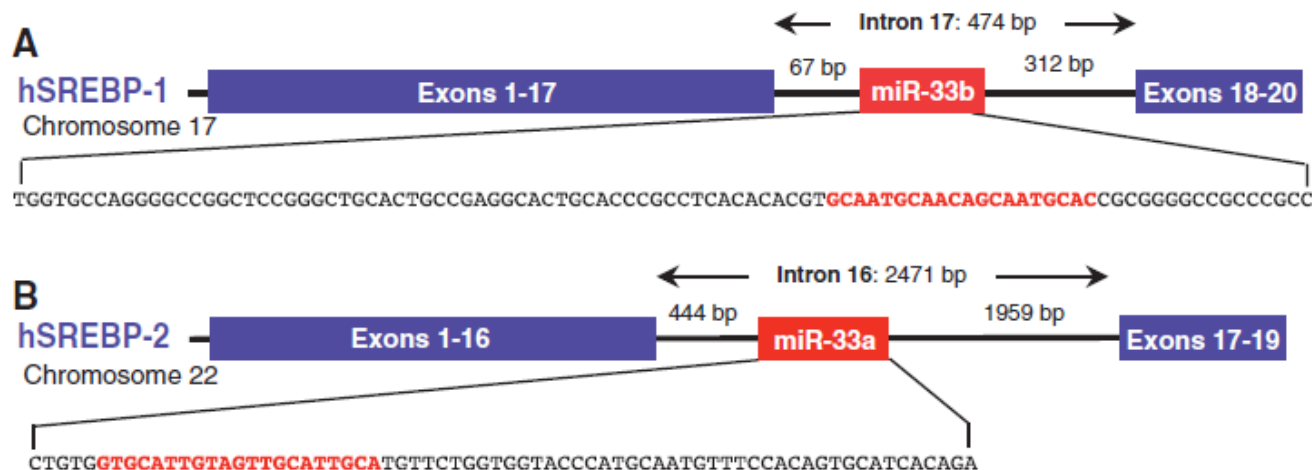
Figure 3. The Actions of Small Silencing RNAs

(A) Messenger RNA cleavage specified by a miRNA or siRNA. Black arrowhead indicates site of cleavage.

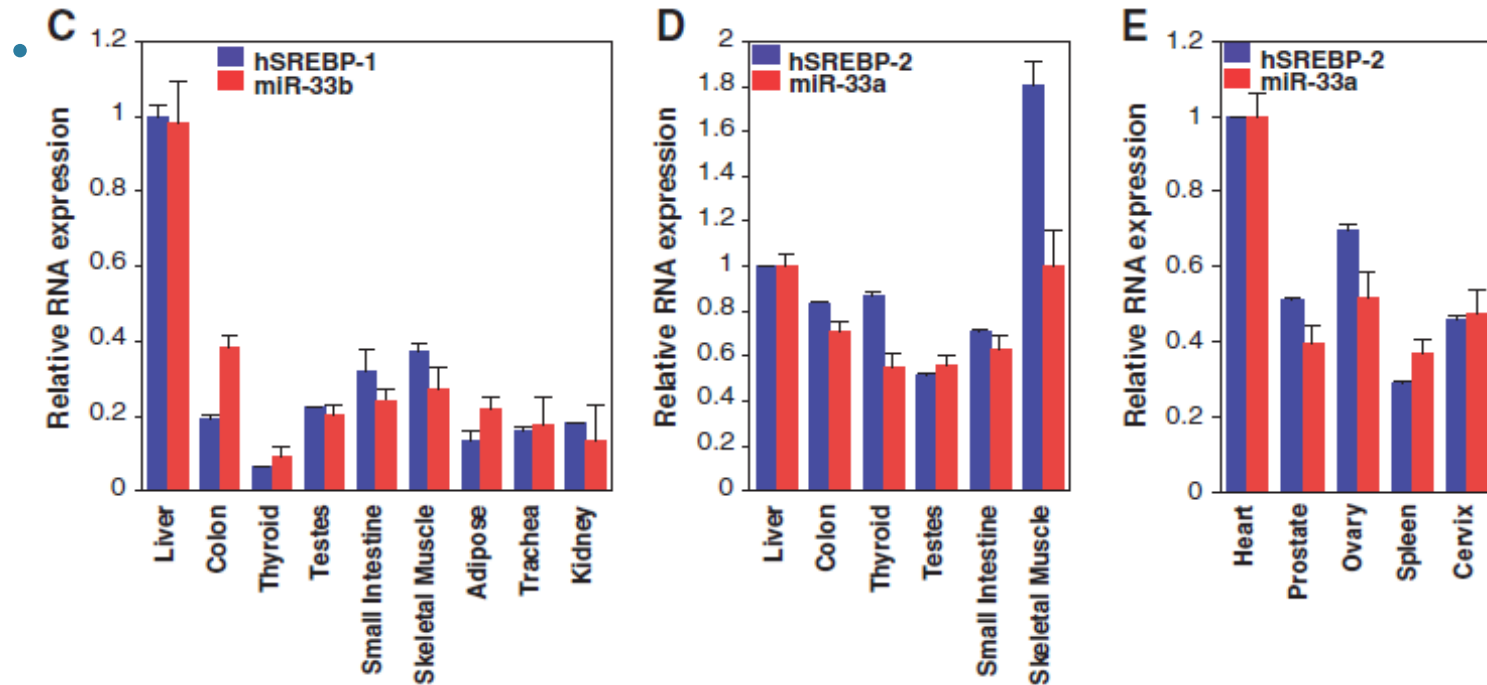
(B) Translational repression specified by miRNAs or siRNAs.

Expression of *SREBP 1* and 2

- miR-33a and miR-33b are embedded in intronic sequences in *SREBP* genes.
- Regulate expression of ABCA1



Co-expression of miRNAs and mRNAs



Nutrients and bioactive compounds that regulate miRNAs expression

EGCG, resveratrol, epicatechin.

Curcumin

Dietary fat (amount and type).

Folate

Retinoic acid

microRNAs (miRNAs) and cardiometabolic phenotypes

LETTER

doi:10.1038/nature10486

Inhibition of miR-33a/b in non-human primates raises plasma HDL and lowers VLDL triglycerides

LETTER

doi:10.1038/nature11793

Obesity-induced overexpression of miR-802 impairs glucose metabolism through silencing of *Hnf1b*

ARTICLES

nature
medicine

MicroRNA-30c reduces hyperlipidemia and atherosclerosis in mice by decreasing lipid synthesis and lipoprotein secretion

nature
medicine

**Courtesy of
Dr. Sethupathy**

MicroRNA-148a regulates LDL receptor and ABCA1 expression to control circulating lipoprotein levels

microRNAs (miRNAs) and cardiometabolic phenotypes

LETTER

doi:10.1038/nature10112

MicroRNAs 103 and 107 regulate insulin sensitivity

RESEARCH ARTICLE

FIBROSIS

MicroRNA-21 Promotes Fibrosis of the Kidney by Silencing Metabolic Pathways



Related Commentary, page 2773  Research article

*Courtesy of
Dr. Sethupathy*

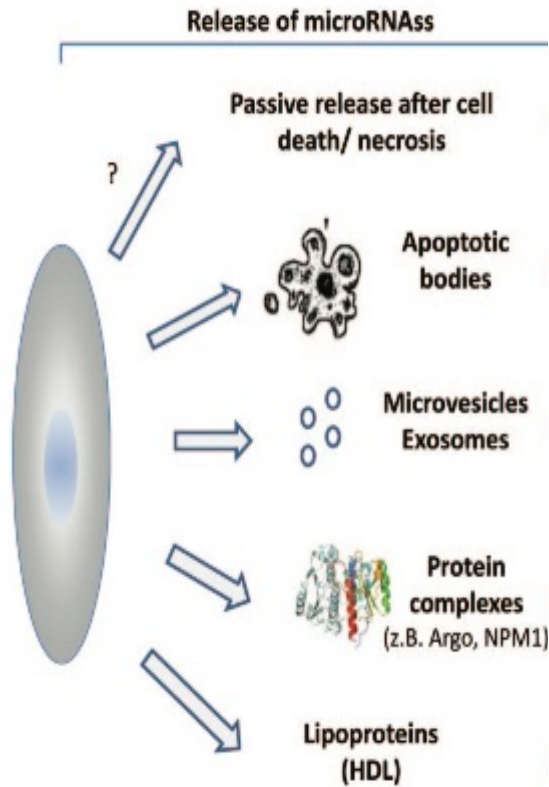
Essential metabolic, anti-inflammatory, and
anti-tumorigenic functions of miR-122 in liver

miRNAs are promising therapeutic targets

Initial <i>micro</i> RNA Development Programs		
<i>micro</i> RNA Target	anti-miR Program	Commercial Rights
miR-122	RG-101 for Hepatitis C Virus Infection*	 REGULUS THERAPEUTICS™
miR-221	Hepatocellular Carcinoma	 SANOFI
miR-10b	Glioblastoma	 REGULUS THERAPEUTICS™
RG-012 (miR-21)	Kidney Fibrosis	 SANOFI
miR-103/107	Metabolic	AstraZeneca 
miR-19	Oncology	AstraZeneca 

Courtesy of Dr. Sethupathy

Circulating miRNAs.



Blood and fluids.

Exosomes and proteins protect miRNAs-

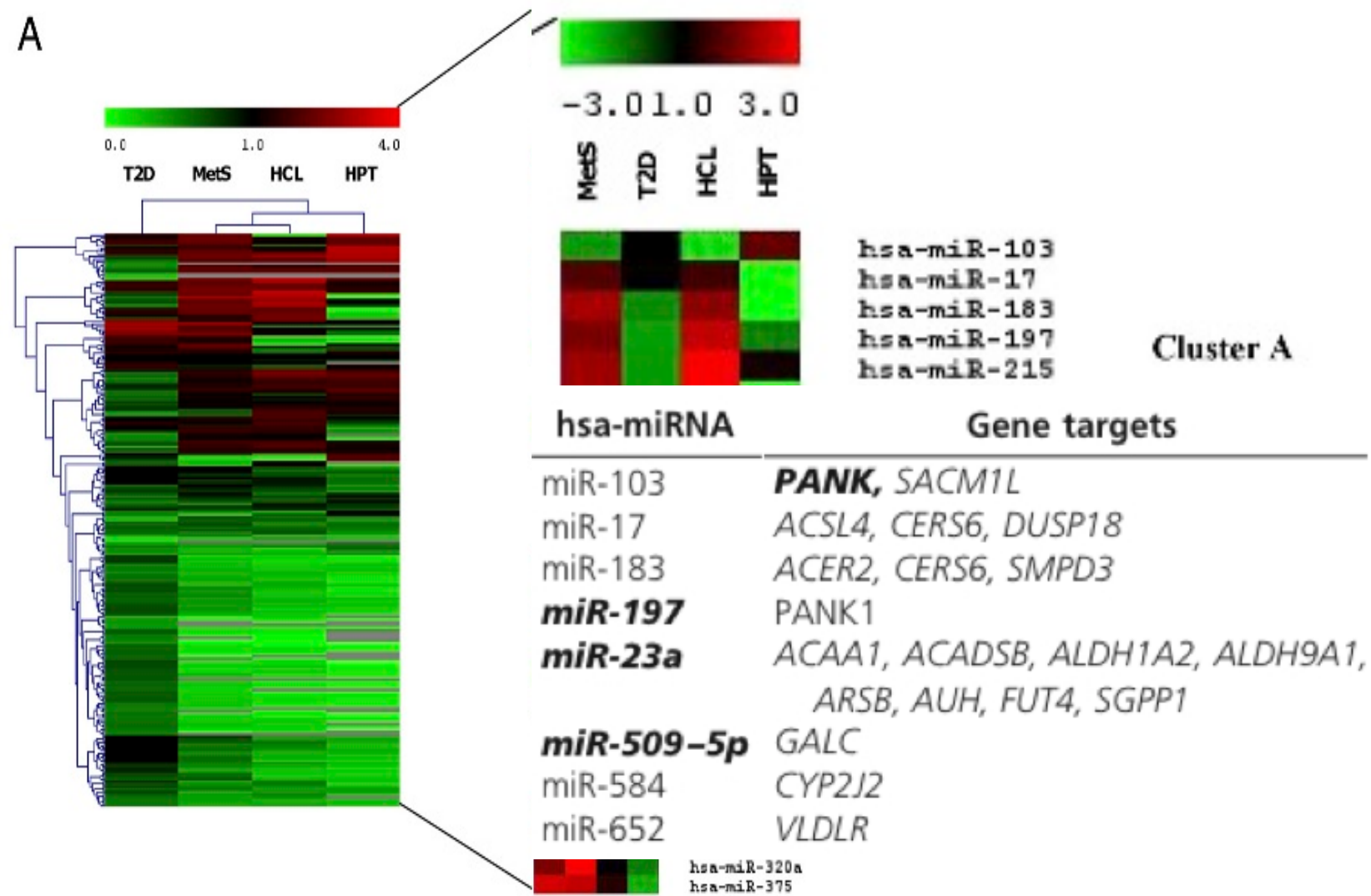
MiRNAs may have targets in other cells.

Lipoproteins carry miRNAs to their targets.

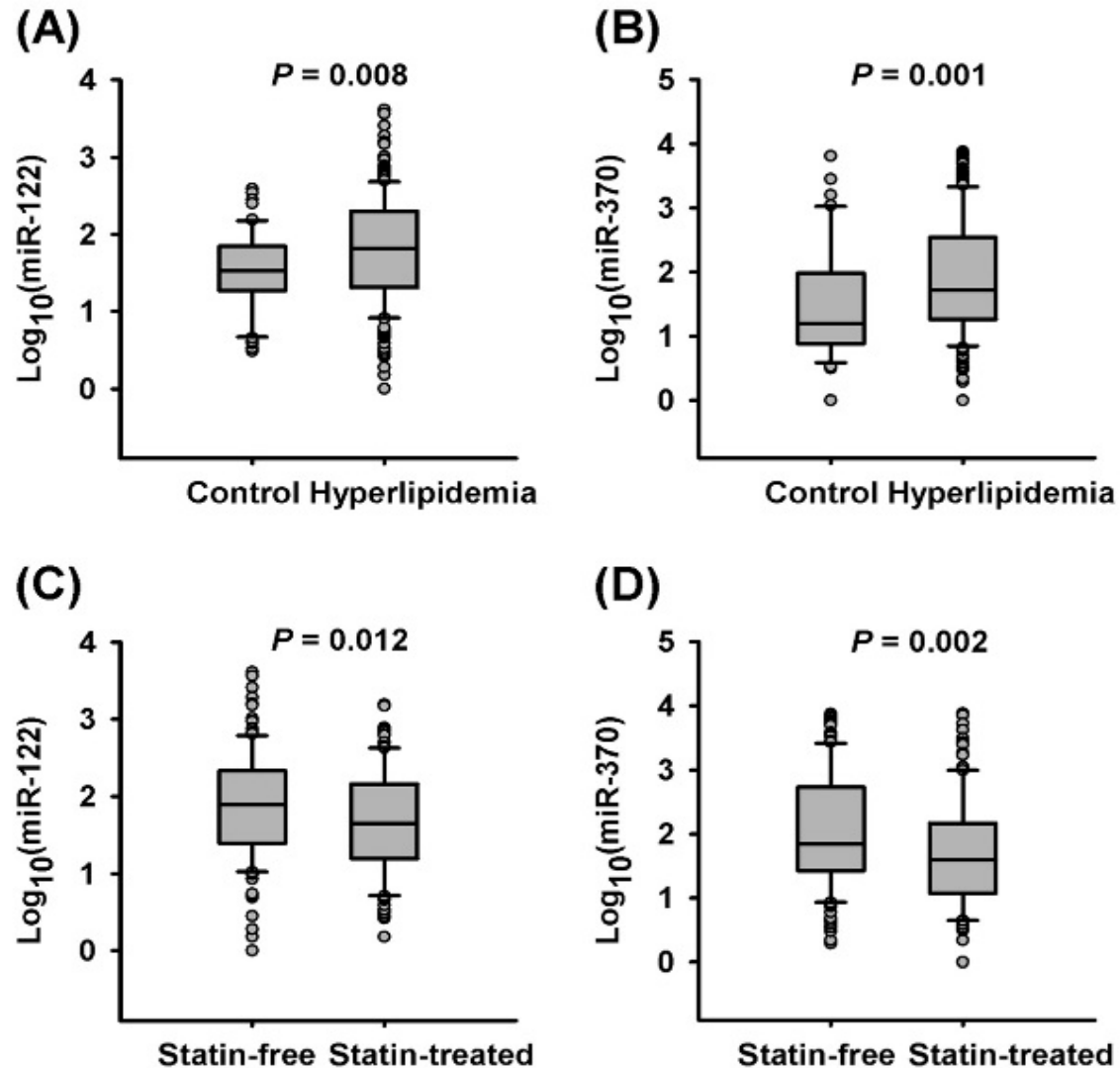
Data bases for miRNA

- Validated
 - miRWalk:
 - miRanda
 - miRDB
 - RNA22
 - TargetScan
- Predicted
 - multiMiR:
 - miRecords
 - mirTarBase
 - TarBase

miRNAs and Met S.



miRNAs and dyslipidemia.



Circulating miRNAs in subjects with metabolic syndrome and controls.

- Metabolic syndrome (SM).
 - Hypertension, hyperglycemia, dyslipidemia and obesity.
 - Prevalence in Mexico: 36.8%
 - 42.2% in women y 30.3% in men.
 - **Low HDL-C: 43.6%**
 - Hypertriglyceridemia: 30%

GeneChip miRNA 3.0



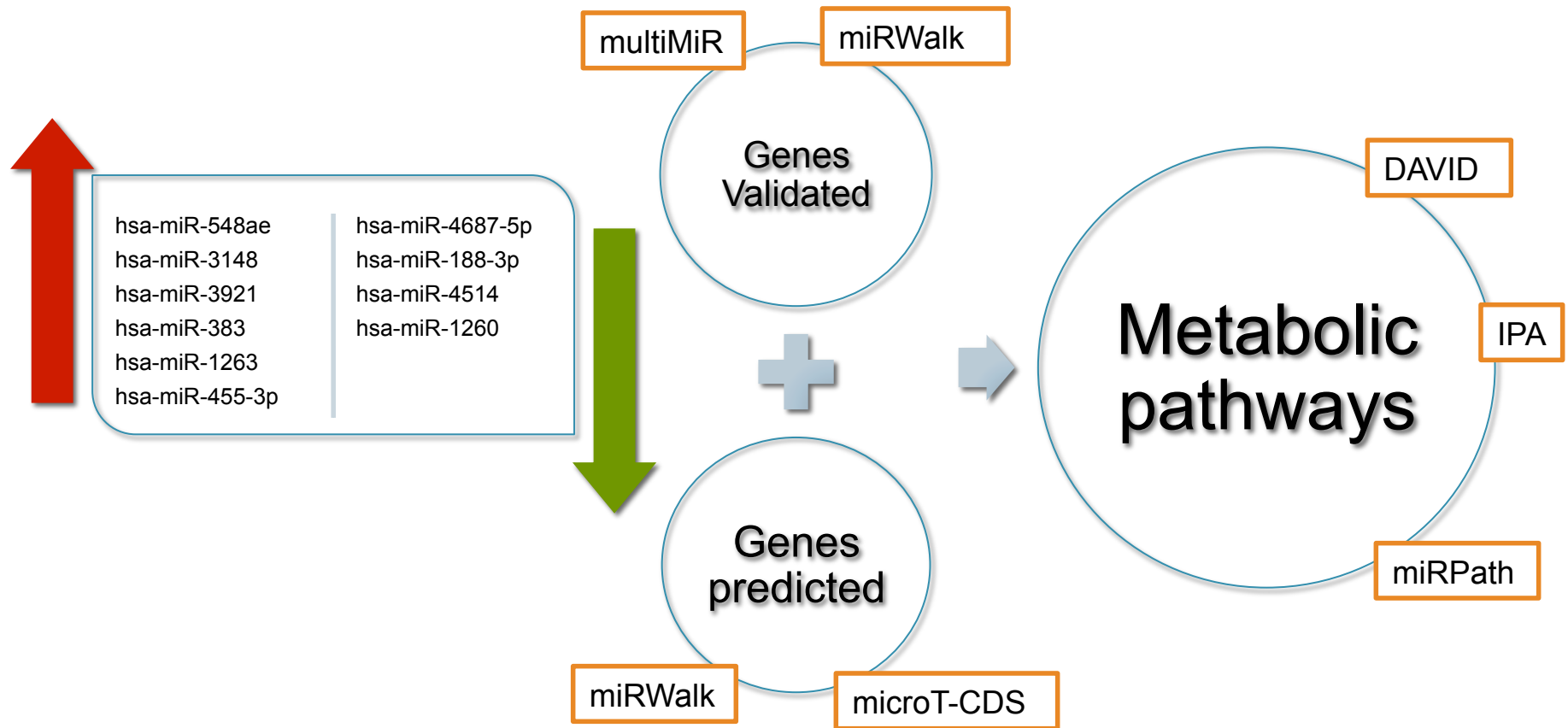
Mapping using miRBase v 17

- 153 organisms
- 5,639 human probes
 - **1733 miRNA**
 - 1658 stem-loop
 - 1674 snoRNA
 - 347 CDBox
 - 163 HacaBox
 - 32 scaRNA
 - 22 Spike-in controls
 - 10 rRNA 5.8s

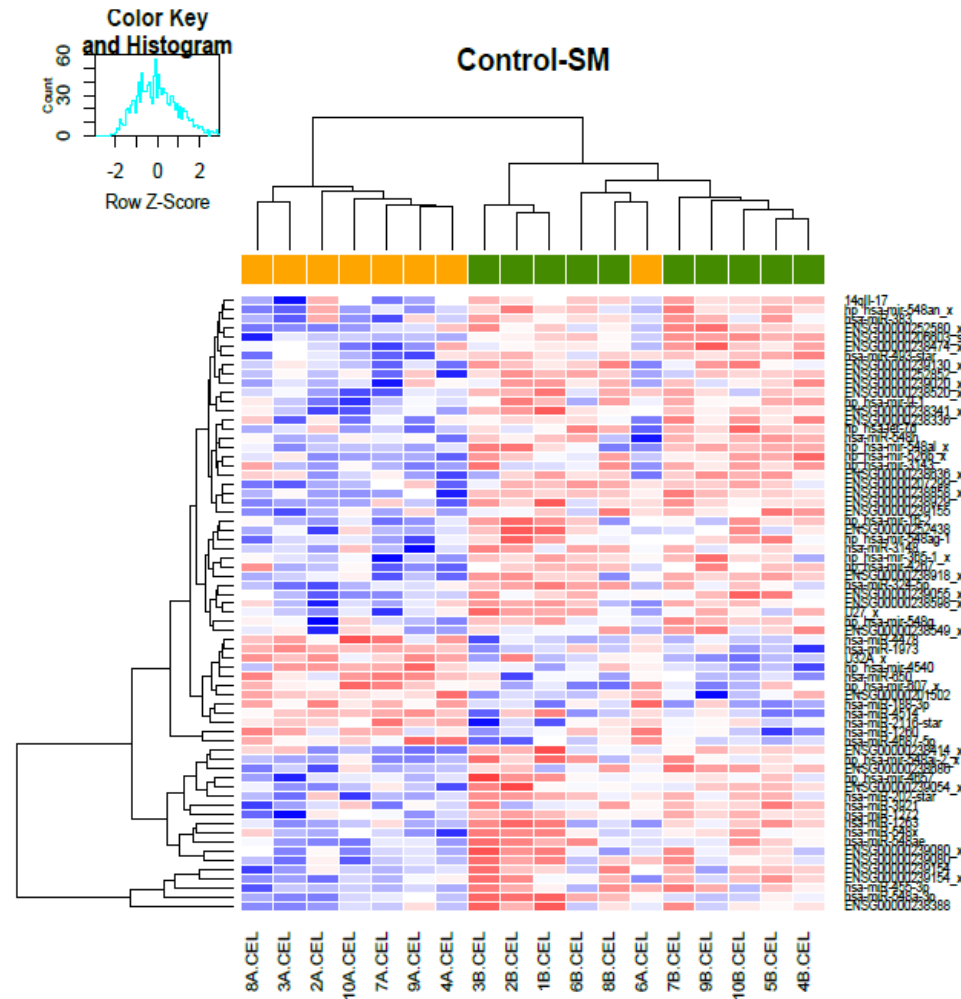
Participants characteristics.

Trait	Mean (SD) n=10	Mean (SD) n=10	p
Age (years)	38.8 (2.09)	40.25 (3.01)	0.249
Systolic blood systolic (mmHg)	106 (12.42)	124.5 (15.82)	0.013*
Diastolic blood pressure (mmHg)	68 (6.28)	83.87 (10.34)	0.001*
Body weight (kg)	57.97 (7.49)	82.3 (10.71)	<0.001*
BMI (kg/m ²)	25.97 (2.74)	35.25 (2.81)	<0.001*
Waist circumference (cm)	81.7 (3.34)	102.37 (4.3)	<0.001*
Cholesterol HDL (mg/dL)	47.24 (8.6)	38.37 (5.97)	0.025*
Triglycerides (mg/dL)	93.16 (23.33)	217.75 (71.64)	<0.001*
Glucose (mg/dL)	88.02 (11.7)	91.0 (10.5)	0.582

in silico analysis



Expression profile



Cases
Controls

Validation of findings

- Analysis by qPCR of 10 miRNAs.
- Independent sample with similar characteristics.
- Inclusion criteria.
- Consistent results.

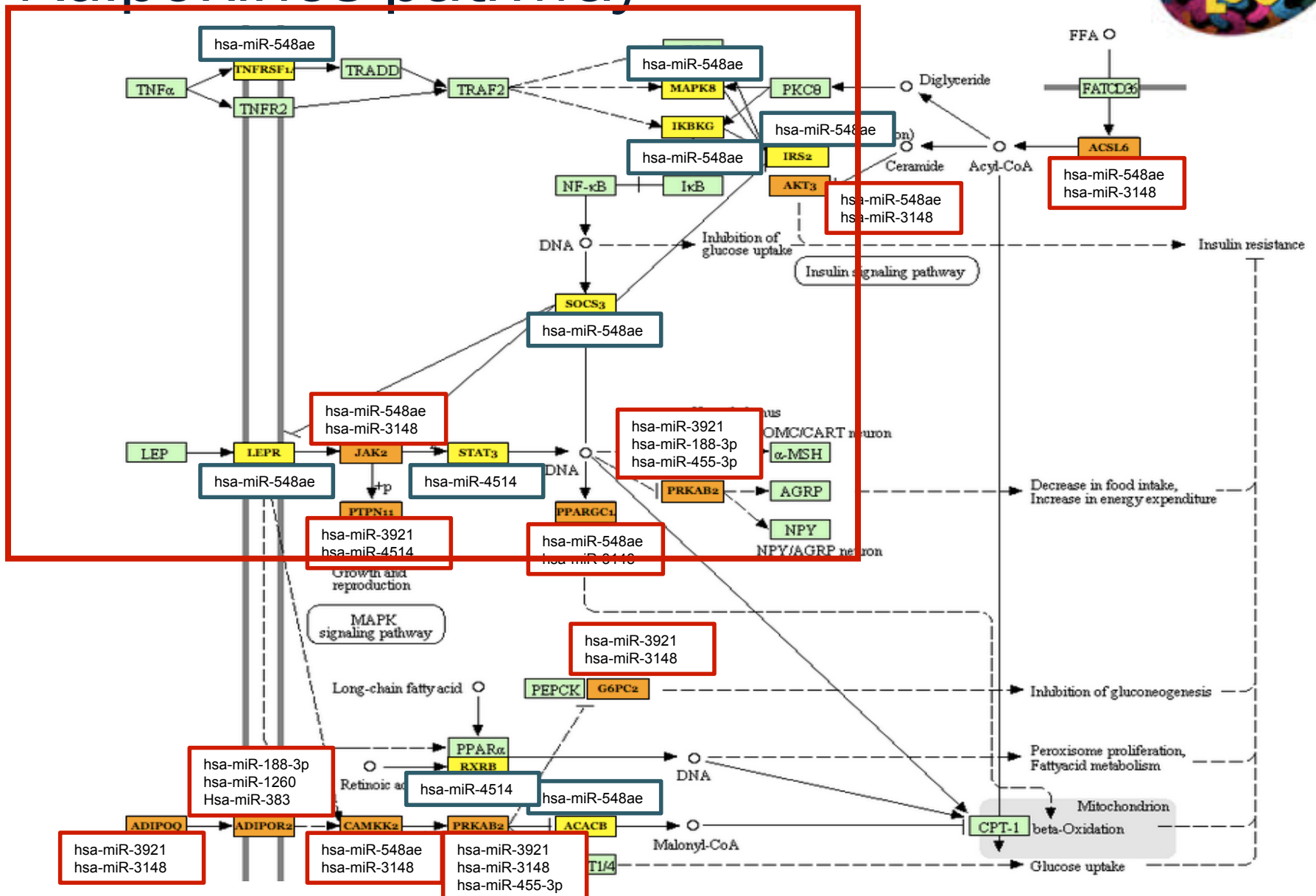
Genes regulated by miRNAs

miRNA	Target genes
hsa-miR-548ae	<i>IRS2, ACACB, PANK3, PANK1, ACSL3, LEPR, ACSL6</i>
hsa-miR-4687-5p	<i>ACACA</i>
hsa-miR-3148	<i>PPARGC1A, PANK1, ADIPOQ, ACSL1, ACSL6</i>
hsa-miR-3921	<i>ACACA, ADIPOQ</i>
hsa-miR-4514	<i>PANK4, ACSL3</i>
hsa-miR-188-3p	<i>ADIPOR2, ABCB1, DHCR24, FABP4, HMGA2</i>
hsa-mir-383	<i>ADIPOR2</i>
hsa-miR-1260a	<i>ADIPOR2, ACACB</i>
hsa-miR-455-3p	<i>ACAD8, ADIPOR1</i>
hsa-miR-1263	<i>IL1A, ABCC1, LEPR</i>

Metabolic pathways related to miRNAs

KEGG pathway	p-value	#genes	#miRNAs
PI3K-Akt signaling pathway	1.62E-11	111	8
Insulin signaling pathway	6.40E-10	51	8
MAPK signaling pathway	1.59E-09	87	8
p53 signaling pathway	7.05E-09	28	4
TGF-beta signaling pathway	9.29E-09	33	6
Wnt signaling pathway	3.97E-08	59	10
Adipocytokine signaling pathway	1.73E-06	27	8
HIF-1 signaling pathway	1.88E-06	40	7
Jak-STAT signaling pathway	3.53E-06	51	7
VEGF signaling pathway	9.49E-05	24	7
mTOR signaling pathway	0.000379892	23	7
D-Glutamine and D-glutamate metabolism	0.02971806	2	3
Type II diabetes mellitus	0.03749052	16	5
Pantothenate and CoA biosynthesis	0.04082202	6	3

Adipokines pathway



Summary of findings

- Differences in plasma levels of 67 H/ACA Box, snoRNA C/D Box snoRNAs, miRNAs y pre-miRNAs were found in the study.
- 21 are miRNAs.
- Hsa-miR-455-3p, hsamiR-383 y hsa-miR-650 have been reported.
- Validated targets participate in adipogenesis and fatty acid metabolism.
- The predicted genes belong to metabolic pathways that are relevant for the MS.

Conclusions

- miRNAs are involved in the regulation of many metabolic disease pathways.
- They are responsive to dietary compounds and may be critical mediators of the effects of nutrients.
- The profile of plasma miRNAs differed between subjects with metabolic síndrome and controls.
- The identified miRNAs may influence metabolic pathways related to inflammation.

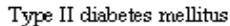
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Insulin signaling pathway

