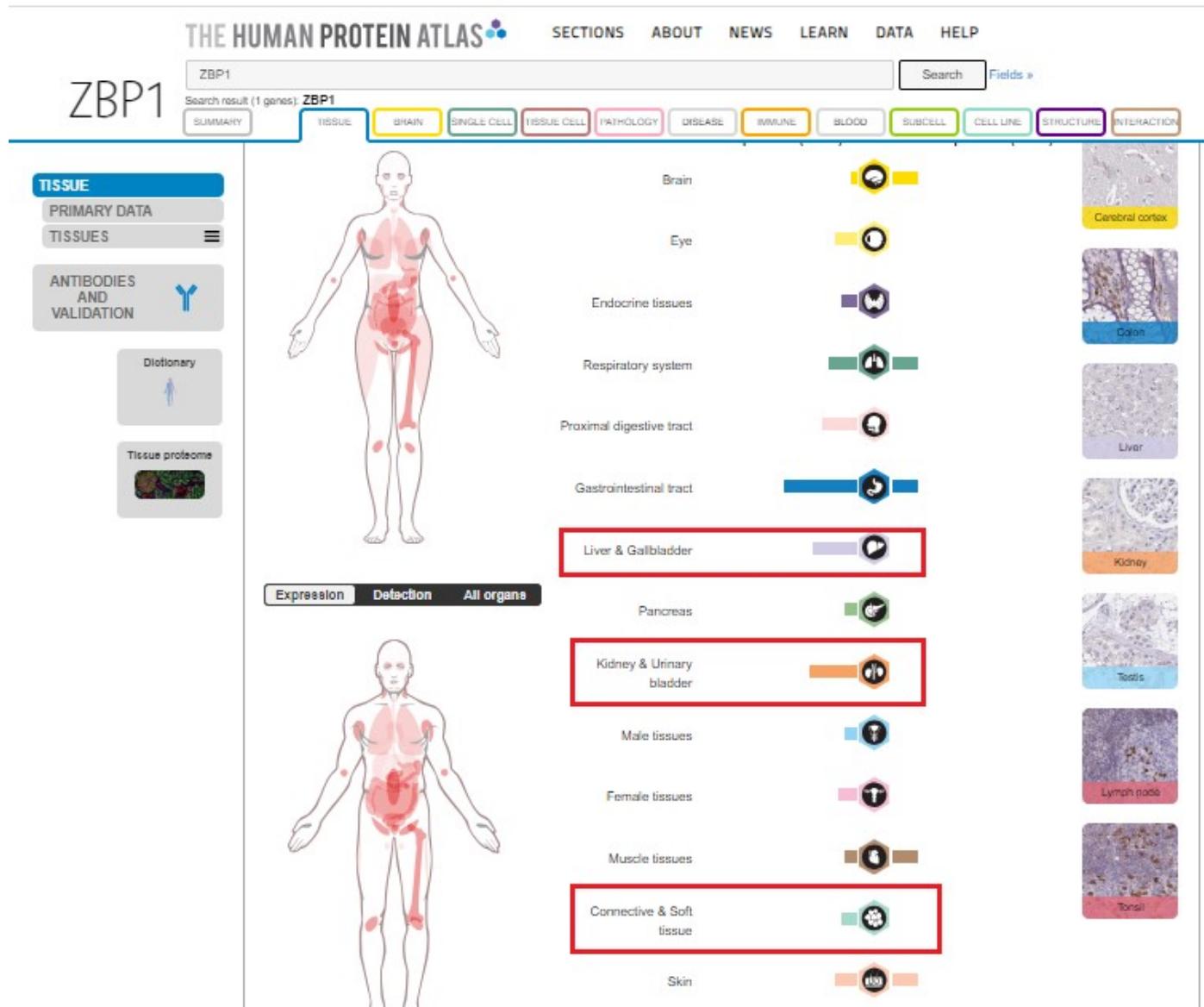


Supplementary information:

Supplementary Figures:

S1 Figures: Validation of the significant expression of the candidate mRNAs (ZBP1, STING1, and DDX58=RIG-1) in the T2DM-related tissues using THE HUMAN PROTEIN ATLAS database
<https://www.proteinatlas.org/>, Jan 2022.



STING1

STING1

Search result (2 genes: STING1 | STEEP1)

 Fields »

SUMMARY

TISSUE

BRAIN

SINGLE CELL

TISSUE CELL

PATHOLOGY

DISEASE

IMMUNE

BLOOD

SUBCELL

CELL LINE

STRUCTURE

INTERACTION

TISSUE

PRIMARY DATA

TISSUES

RNA AND PROTEIN EXPRESSION SUMMARY¹ANTIBODIES
AND
VALIDATION

Dictionary



Expression Detection All organs

RNA expression (nTPM)¹ Protein expression (score)¹

Brain

Eye

Endocrine tissues

Respiratory system

Proximal digestive tract

Gastrointestinal tract

Liver & Gallbladder

Pancreas

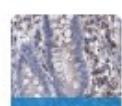
Kidney & Urinary bladder

Male tissues

Female tissues

Muscle tissues

Connective & Soft tissue



RIGI

DDX58

Search result (2 genes): RIGI | ARL16

SUMMARY

TISSUE

BRAIN

SINGLE CELL

TISSUE CELL

PATHOLOGY

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IMMUNE

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CELL LINE

STRUCTURE

INTERACTION

Search

Fields »

RNA AND PROTEIN EXPRESSION SUMMARY¹

TISSUE

PRIMARY DATA

TISSUES



ANTIBODIES AND VALIDATION



Dictionary

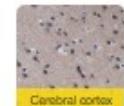
Tissue proteome



Expression | Detection All organs

RNA expression (nTPM)¹

Brain



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



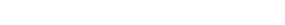
Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex



Cerebral cortex

Cerebral cortex

S2 Figures: Validation of the implication of the candidate mRNAs (ZBP1, STING1, and DDX58=RIG-1) in the development of diabetes, and kidney and liver diseases using DisGeNET database (<https://www.disgenet.org/home/>), the Expression Atlas database (<https://www.ebi.ac.uk/gxa/home>) and diseases database (<https://diseases.jensenlab.org/Search>), Jan 2022.

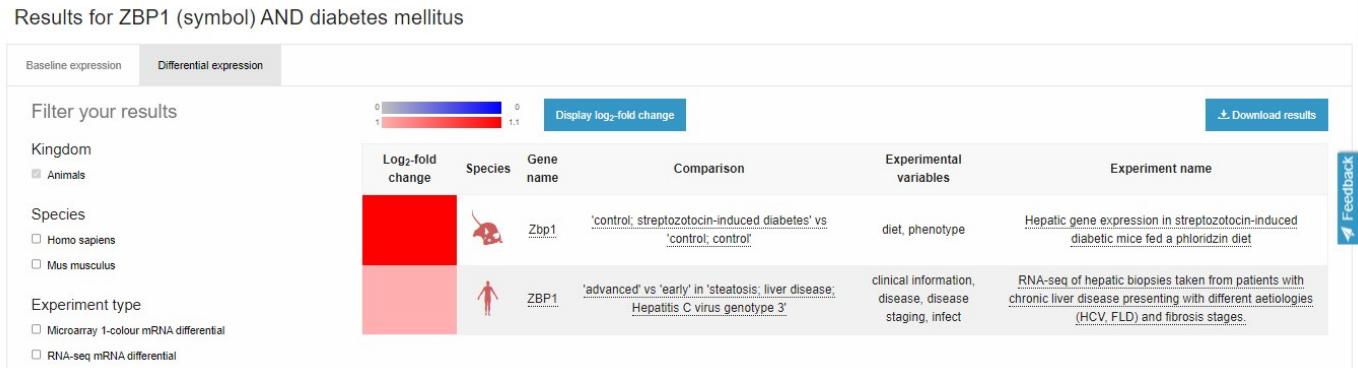
The screenshot shows the DisGeNET Diseases interface. At the top, it says "DISEASES" and "Disease-gene associations mined from literature". Below that are three buttons: "Search", "Downloads", and "About". The main content area is titled "ZBP1 disease associations". It shows a table of disease associations with columns for Name, Z-score, and Confidence. Diseases listed include Adult respiratory distress syndrome, Human immunodeficiency virus infectious disease, Listeriosis, Cowpox, Decoyoning disease, Diabetes, Pancreatitis, Liver disease, Kidney disease, and Chickenpox. The rows for Diabetes, Pancreatitis, Liver disease, and Kidney disease are highlighted with a red border.

ZBP1 disease associations

ZBP1 [ENSP00000360215]
Z-DNA-binding protein 1. Participates in the detection by the host's innate immune system of DNA from viral, bacterial or even host origin. Plays a role in host defense against tumors and pathogens. Acts as a cytosolic DNA sensor which, when activated, induces the recruitment of TBK1 and IRF3 to its C-terminal region and activates the downstream interferon regulatory factor (IRF) and NF-kappa B transcription factors, leading to type-I interferon production. ZBP1-induced NF-kappa B activation probably involves the recruitment of the IKK containing kinases RIPK1 and RIPK3 (By similarity).
Synonyms: ZBP1, ZBP1p, ZBP1, HOY01, Q9H171 ...
Linkouts: STRING Pharos UniProt OMIM

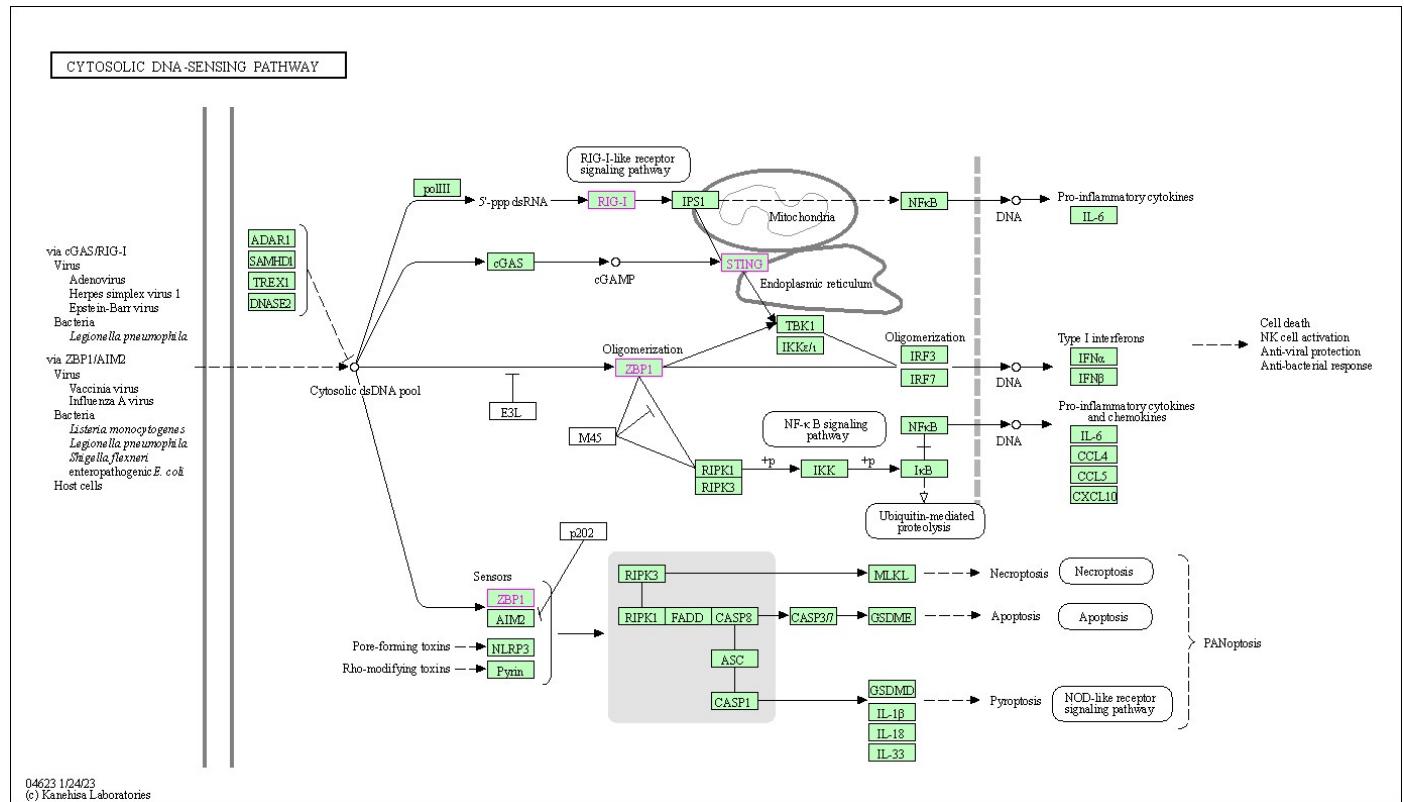
Name	Z-score	Confidence
Adult respiratory distress syndrome	2.3	★★★★★
Human immunodeficiency virus infectious disease	2.2	★★★★★
Listeriosis	2.1	★★★★★
Cowpox	2.1	★★★★★
Decoyoning disease	2.1	★★★★★
Diabetes	2.1	★★★★★
Pancreatitis	2.1	★★★★★
Liver disease	2.1	★★★★★
Kidney disease	2.1	★★★★★
Chickenpox	2.0	★★★★★

The screenshot shows the Expression Atlas homepage. At the top, it has a logo and the title "Expression Atlas" with the subtitle "Gene expression across species and biological conditions". On the right, there is a button "Query single cell expression" and a link "To Single Cell Expression Atlas". Below the title, there is a navigation bar with links for Home, Browse experiments, Download, Release notes, FAQ, Help, Licence, About, and Support. The main content area is titled "Results for ZBP1 (symbol) AND diabetes mellitus".



STING1, stimulator of interferon response cGAMP interactor 1, 340061 Q										<input type="button" value="Download"/>	<input type="button" value="Share"/>	
N. diseases: 159; N. variants: 6										<input type="button" value="Add/Remove filter"/>		
Source: ALL										<input type="button" value="Filter within current results: KID"/>		
Results per page <input type="button" value="200"/>												
Disease ↴	Type ↴	Disease Class ↴	Semantic Type ↴	N. genes ↴	N. SNPs ↴	Score gda ↴	EL gda ↴	EL gda ↴	N. PMIDs ↴	N. SNPs gda ↴	First Ref. ↴	Last Ref.
✓ Kidney Failure, Acute < disease	Female Urogenital Di... > Disease or Syndr... > 826			32	0.010	None	1,000	1			2019	2019
STING1, stimulator of interferon response cGAMP interactor 1, 340061 Q										<input type="button" value="Download"/>	<input type="button" value="Share"/>	
N. diseases: 159; N. variants: 6										<input type="button" value="Add/Remove filter"/>		
Source: ALL										<input type="button" value="Filter within current results: LIV"/>		
Results per page <input type="button" value="200"/>												
Disease ↴	Type ↴	Disease Class ↴	Semantic Type ↴	N. genes ↴	N. SNPs ↴	Score gda ↴	EL gda ↴	EL gda ↴	N. PMIDs ↴	N. SNPs gda ↴	First Ref. ↴	Last Ref.
✓ Non-alcoholic Fatty ... > disease	Digestive System Dis... > Disease or Syndr... > 1068			222	0.010	None	1,000	1			2018	2018
✓ Liver carcinoma	disease	Digestive System Dis... > Neoplastic Process	> 5725	942	0.010	None	1,000	1			2020	2020
✓ Fibrosis, Liver	disease	Pathological Conditi... > Disease or Syndr... > 1179		64	0.010	None	1,000	1			2018	2018

S3 Figure: The visualization of the candidate mRNAs (ZBP1, STING1, and DDX58=RIG-1) in the cGAS-STING pathway through KEGG pathway database (<https://www.genome.jp/kegg/>, Jan 2022)



S4 Figures: Validation of the implication of the selected biochemical effectors proteins (LC3B=MAP1LC3B, and TNF) in the development of diabetes, and kidney and liver diseases using DisGeNET database (<https://www.disgenet.org/home/>), Jan 2022.

Summary of GDAs	Evidences for GDAs	Summary of VDAs	Evidences for VDAs																																																																																																
<p>MAP1LC3B, microtubule associated protein 1 light chain 3 beta, 81631 ⓘ</p> <p>< 1 - 167 of 167 results ></p> <p>Download Share Add/Remove filter</p> <p>N. diseases: 167; N. variants: 1</p> <p>Source: ALL</p> <p>Results per page 200 ▾</p> <p>Filter within current results: <input type="text"/></p> <table border="1"> <thead> <tr> <th>Disease ▲</th> <th>Type ▲</th> <th>Disease Class ▲</th> <th>Semantic Type ▲</th> <th>N. genes_d ▲ N. SNPs_d ▲</th> <th>Score_gda ▲</th> <th>EL_gda ▲</th> <th>EI_gda ▲</th> <th>N. PMIDs ▲</th> <th>N. SNPs_gda ▲</th> <th>First Ref. ▲</th> <th>Last Ref. ▲</th> </tr> </thead> <tbody> <tr> <td>Diabetes Mellitus</td> <td>group</td> <td>Nutritional and Metab... ➤ Disease or Syndr...</td> <td>2803</td> <td>824</td> <td>0.010</td> <td>None</td> <td>1.000</td> <td>1</td> <td></td> <td>2019</td> <td>2019</td> </tr> <tr> <td>Diabetic Retinopathy</td> <td>disease</td> <td>Eye Diseases; Endoc...</td> <td>645</td> <td>213</td> <td>0.020</td> <td>None</td> <td>1.000</td> <td>2</td> <td></td> <td>2017</td> <td>2019</td> </tr> </tbody> </table>				Disease ▲	Type ▲	Disease Class ▲	Semantic Type ▲	N. genes_d ▲ N. SNPs_d ▲	Score_gda ▲	EL_gda ▲	EI_gda ▲	N. PMIDs ▲	N. SNPs_gda ▲	First Ref. ▲	Last Ref. ▲	Diabetes Mellitus	group	Nutritional and Metab... ➤ Disease or Syndr...	2803	824	0.010	None	1.000	1		2019	2019	Diabetic Retinopathy	disease	Eye Diseases; Endoc...	645	213	0.020	None	1.000	2		2017	2019																																																												
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Disease ▲	Type ▲	Disease Class ▲	Semantic Type ▲	N. genes_d ▲ N. SNPs_d ▲	Score_gda ▲	EL_gda ▲	EI_gda ▲	N. PMIDs ▲	N. SNPs_gda ▲	First Ref. ▲	Last Ref. ▲																																																																																								
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Drug-Induced Liver...	phenotype	Digestive System Dis...	➤ Disease or Syndr...	537	29	0.300	None	1.000	1	2014	2014																																																																																								
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Summary of GDAs												Evidences for GDAs		Summary of VDAs		Evidences for VDAs		Home		About		Search		API		Downloads		Cytoscape		RDF		disgenet2r		Help		Biomarkers		COVID-19		Login		Signup	
TNF, tumor necrosis factor, 7124 ⓘ												< 1 - 200 of 2724 results >		Download		Share		Add/Remove filter																									
N. diseases: 2724; N. variants: 31												Source: ALL		Results per page 200		Filter within current results: diab		diab		diab		diab		diab		diab		diab		diab													

S5 Figure: Validation of the interaction between the three key mRNAs and two effector proteins with the retrieved miR-1976 from mirwalk3 (<http://mirwalk.umm.uni-heidelberg.de/>, Jan 2022)

The screenshot shows the miRWalk interface. At the top, there is a red header with the logo and the text "m²RWalk". Below the header is a navigation bar with links for HOME, FAQ, RESOURCES, and ABOUT. A circular seal is visible in the top right corner. The main content area contains a search bar with the query "hsa-miR-1976" and a dropdown menu set to "3UTR". There are also several other dropdown menus and a "set filter" button. Below the search bar is a table listing interactions for hsa-miR-1976. The columns include: miRNA, RefseqID, GeneSymbol, Duplex, Score, Position, Binding Site, Au, Me, N Pairings, Targetscan, Mirdb, and Mirtarbase. The table lists interactions with STING1, DDX58, MAP1LC3B, ZBP1, and STING1 again.

This screenshot shows the same miRWalk interface as the first one, but with a different search query. The search bar now contains "hsa-miR-1976" and the dropdown menu is set to "5UTR". The table below shows interactions for hsa-miR-1976 with TNF.

miRNA	RefseqID	GeneSymbol	Duplex	Score	Position	Binding Site	Au	Me	N Pairings	Targetscan	Mirdb	Mirtarbase
hsa-miR-1976	NM_001367258	STING1	details	1.00	3UTR	1667,1693	0.43	-5.481	18	—	—	—
hsa-miR-1976	NM_198282	STING1	details	1.00	3UTR	1894,1920	0.43	-5.481	18	—	—	—
hsa-miR-1976	NM_014314	DDX58	details	0.92	3UTR	4343,4393	0.43	-4.171	15	—	—	—
hsa-miR-1976	NM_014314	DDX58	details	1.00	3UTR	4002,4020	0.47	-12.956	14	—	—	—
hsa-miR-1976	NM_022818	MAP1LC3B	details	0.92	3UTR	1298,1314	0.59	-6.675	11	—	—	—
hsa-miR-1976	NM_001160418	ZBP1	details	0.92	3UTR	1627,1656	0.41	-5.495	18	—	—	—
hsa-miR-1976	NM_001301738	STING1	details	1.00	3UTR	1707,1733	0.43	-5.481	18	—	—	—

S6 Figure: The association of miR-1976 with cGAS-STING-related pathways through DIANA tools mirPath 3 (<http://www.microrna.gr/miRPathv3>, Jan 2022)

mirPath v.3

New search
Help

KEGG analysis
GO analysis

Species: Human
Reverse Search

Gene filter: determine genes (optional)

Add miRNAs: TarBase v7.0 or upload a file
Run example

Show lists added

Show Heatmap
Show microRNA/Pathway Clusters
 Significance Clusters/Heatmap
 Targeted Pathways Clusters/Heatmap

#	KEGG pathway	p-value	#genes	#miRNAs	download results
1.	Inflammatory mediator regulation of TRP channels (hsa04750)	9.69830767779e-05	67	see genes	1 details
	hsa-miR-1976 microT-CDS		67	see genes	
2.	Adrenergic signaling in cardiomyocytes (hsa04261)	0.000977928936086	93	see genes	1 details
3.	Glycosphingolipid biosynthesis - lacto and neolacto series (hsa00601)	0.00159704188411	17	see genes	1 details
4.	Hippo signaling pathway	0.00159704188411	91	see genes	1 details
12.	NF-kappa B signaling pathway (hsa04064)	0.0166282728639	54	see genes	1 details
	hsa-miR-1976 microT-CDS		54	see genes	
13.	alpha-Linolenic acid metabolism (hsa00592)	0.0195002319172	20	see genes	1 details
14.	Rap1 signaling pathway (hsa04015)	0.0195002319172	130	see genes	1 details
15.	Dilated cardiomyopathy (hsa05414)	0.0219132229455	58	see genes	1 details
35.	NOD-like receptor signaling pathway (hsa04621)	0.0924986641088	35	see genes	1 details
	hsa-miR-1976 microT-CDS		35	see genes	
36.	Phosphatidylinositol signaling system (hsa04070)	0.0947286655195	50	see genes	1 details

Figure S7: Retrieval of AC074117.2 lncRNA from DIANA Tools database (<https://diana.e-ce.uth.gr/lncbasev3>, Jan 2022)

miRNA
IncRNA

Keyword
Location

Clear All

Execute Search
Clear All
Download ▾

Interactions: 38, Experiments 1 (low: 0 , high: 1) Cell lines: 1, Tissues: 1, Publications: 1

Filters ▾
Reset

Tissue
Select Tissues ▾

Cell Type
Select Cell Types ▾

Method
Select Methods ▾

Validated As
Select Validated as ▾

Validation Type
Select Validation Types ▾

miRNA Conf. Level
Select Confidence Levels ▾

Biotypes
Select Biotypes ▾

Species
Select Species ▾

lncRNA Source
Select lncRNA Sources ▾

Variants
All ▾ | With ▾ | Without ▾

Gene name ▾
miRNA name ▾
Experiments ▾
Publications ▾
Cell Lines ▾
Tissues ▾
miRNA Conf. ▾
DIANA Links

AC007619.2 ⓘ | hsa-miR-1976 ⓘ | 1 | 1 | 1 | 1 | Low | IncRNA Expr UCSC ↗ mT TB InP mP |

AC012123.2 ⓘ | hsa-miR-1976 ⓘ | 1 | 1 | 1 | 1 | Low | IncRNA Expr UCSC ↗ mT TB InP mP |

AC012531.1 ⓘ | hsa-miR-1976 ⓘ | 1 | 1 | 1 | 1 | Low | IncRNA Expr UCSC ↗ mT TB InP mP |

AC013404.1 ⓘ | hsa-miR-1976 ⓘ | 1 | 1 | 1 | 1 | Low | IncRNA Expr UCSC ↗ mT TB InP mP |

AC074117.2 ⓘ | hsa-miR-1976 ⓘ | 1 | 1 | 1 | 1 | Low | IncRNA Expr UCSC ↗ mT TB InP mP |

Publication
Methods
Tissue
Cell Type
Tested Cell Line
Category
Experimental Condition

Karginov FV et al. 2013 | IP ⓘ | Kidney | 293S | NA | Embryonic/Fetal | No treatment (control) |

Activate Windows

Figure S8: lncRNA AC074117.2 / miR-1976 interaction using IntaRNA 2.0 tool.

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IntaRNA - Results

Input and runtime details for job 0986262 submitted on 03.11.2023 at 17:42 CET

[Show Input Parameters](#)
[Show Job Execution Details](#)

Output
[zip]

Downloadable files

IntaRNA result table: [csv]

Identified Interactions

Sort by selecting a column name.

Target	Start(T)	End(T)	Query	Start(Q)	End(Q)	Energy
AC074117.2	355	373	hsa-miR-1976	8	20	-16.4

Details of Selected Interaction Download Interaction Details

Energy	-16.4 kcal/mol	Position - Target	355 – 373
Hybridization Energy	-19.95 kcal/mol	Position - Query	8 – 20
Unfolding Energy - Target	3.26 kcal/mol	Position Seed - Target	367 – 373
Unfolding Energy - Query	0.29 kcal/mol	Position Seed - Query	8 – 14

Sequence : AUAUCAACAUAGAUAGAAGAACCCUCUCUGU
Structure : ((((((.....(((((((((.....)))))))))))
StartIndex : 355@8

Position-wise minimal energy profile

The following plots provide insights into the overall RNA-RNA interaction abundance. To this end, a minimal energy profile is provided for both sequences of each query-target pair considered. It visualizes for a given pair of sequences for each sequence position the minimal energy of any RNA-RNA interaction that can be formed between these two RNAs.

Furthermore, a combined plot that visualizes the minimal energy for each intermolecular index pair is provided in a heatmap style to track where interactions can potentially be formed (existing interaction regions) or in conjunction.

Note, since IntaRNA uses a heuristic to enable the low runtime, the provided energies are (close) upper bounds. Note further, only RNA-RNA interactions featuring a seed (according to the user parameters) are considered. Only interaction energies below or equal to 0 are visualized and missing data (subsequences without predicted interactions) are also depicted with an energy of 0.

Query sequence

Target sequence

Minimal energy per query-target index pair

Supplementary Tables:

Table S4: Primers used for qPCR.

Primer name	Gene ID	Cat.no.	Tm	Product size
<i>TMEM173 (STING1)</i>	NM_198282	249900 Gene Globe ID: QT00055440	70 °C	125 bp
<i>ZBP1</i>	NM_001160418	249900 Gene Globe ID: QT00029631	70 °C	83 bp
<i>DDX58</i>	NM_014314	249900 Gene Globe ID: QT00040509	70 °C	114 bp
<i>GAPDH</i>	NM_002046	249900 Gene Globe ID: QT00079247	70°C	95 bp
<i>miR_1976</i>	MIMAT0009451	339350 Gene Globe ID: ZP00000388	75 °C	85 bp
<i>AC074117.2</i>	ENST00000417130	Gene Globe ID: UPFH0284997	58.8 °C	82 bp