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Micro RNA sequence codes for small extracellular vesicle release and cellular retention

Ruben Garcia-Martin , 1 Guoxiao Wang , 1 Bruna B. Brandão , 1 Tamires Marques Zanotto , 1 Samah Shah , 2 Sandip Kumar Patel , 2 Birgit Schilling , 2 et C. Ronald Kahn 1

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Clara Touchard & Mathilde Le Garff
21st November 2023

UNIVERSITÀ DEGLI STUDI DI TRIESTE

Outlines

miRNAs

MicroRNAs (miRNAs) :

- short 20-24 nt
- endogenously-produced non-coding RNAs

Over **2,500** mature microRNAs have been discovered

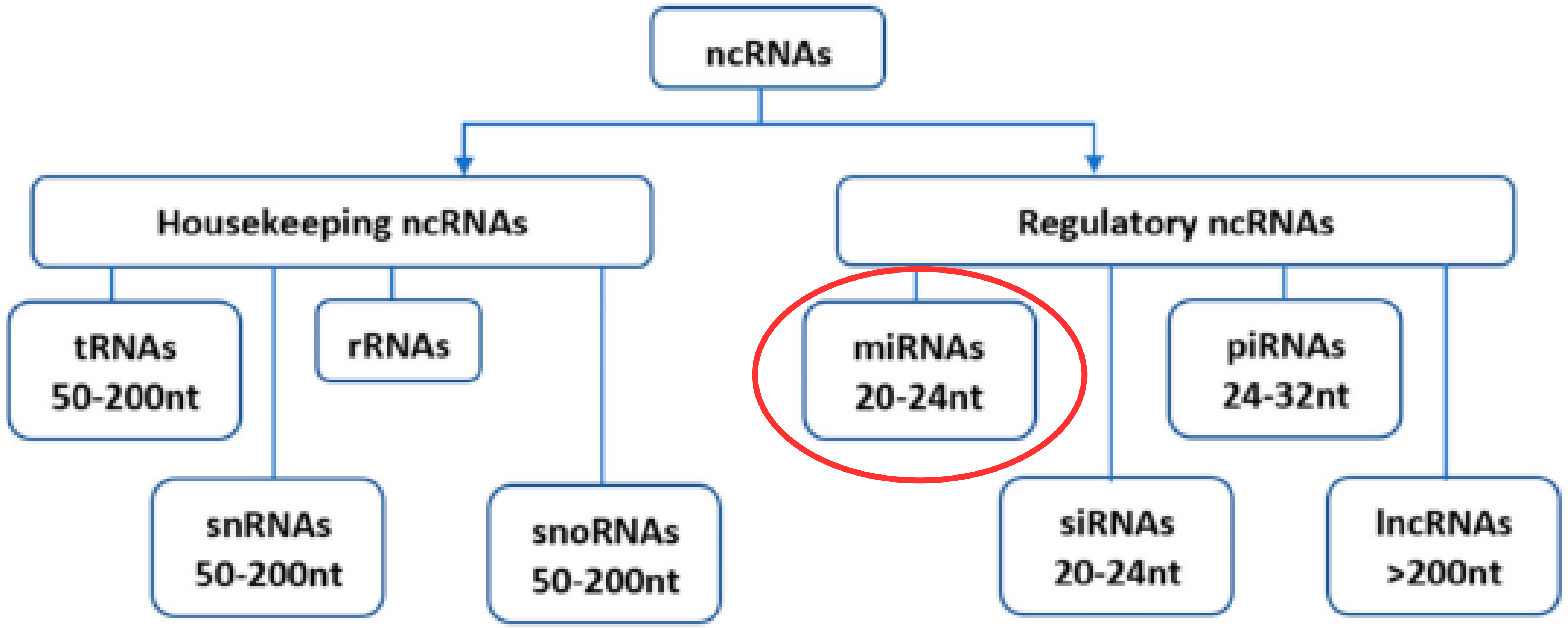


Fig 1 : suptypes of non coding RNA s [1]

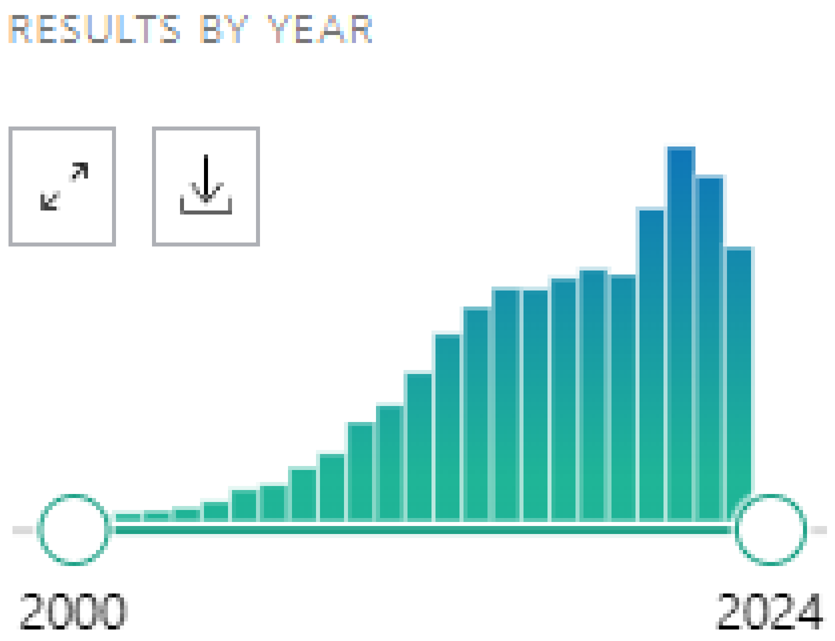


Fig 2 : Number of publications on Pubmed since 2000.

→ ***Growing interest***

miRNA Biogenesis

Actors :

1. Drosha and DGCR8
2. Exportin-5
3. Dicer, TRBP and Ago
4. RISC complex

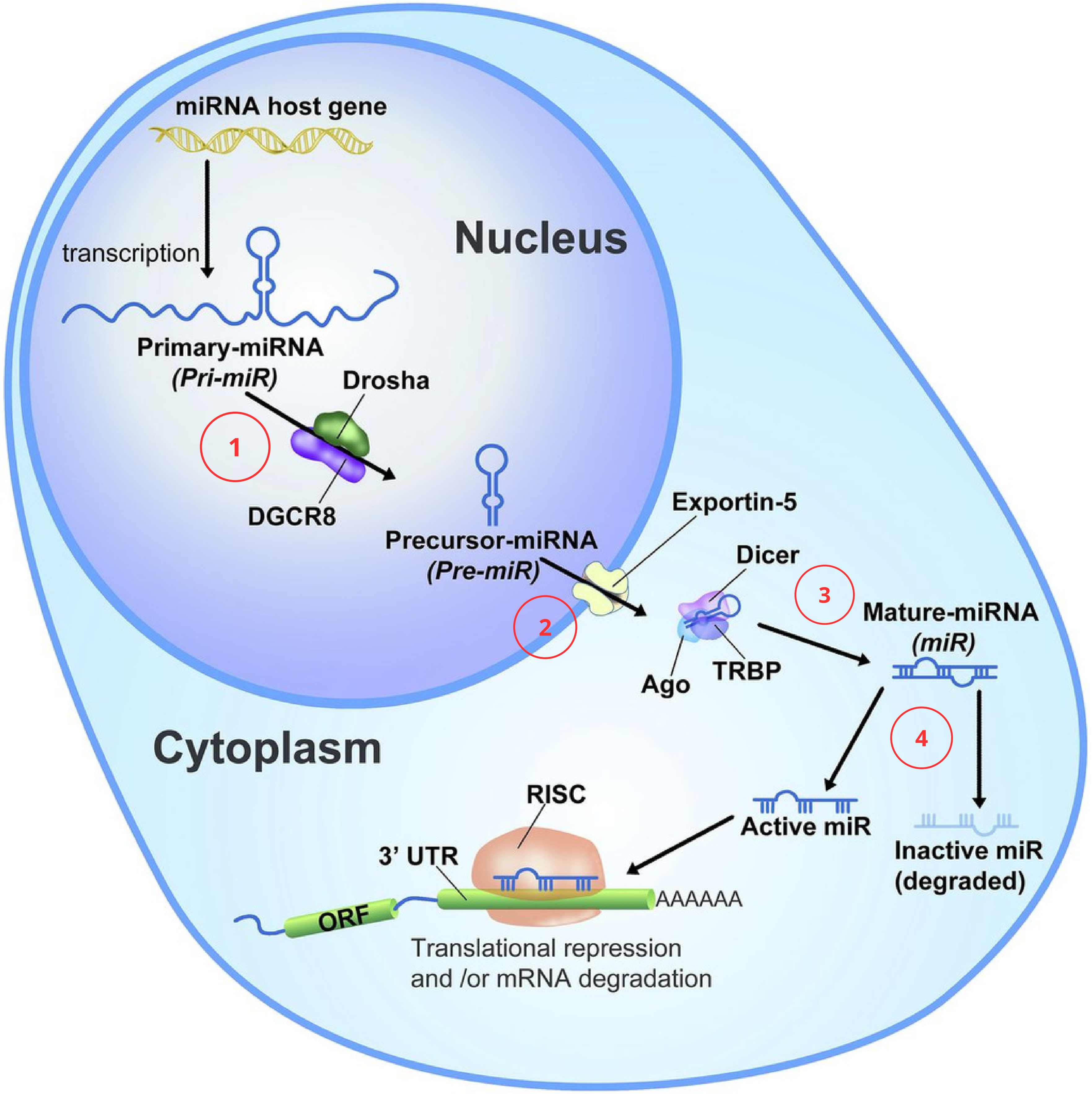


Fig 3 : Steps of miRNA biogenesis [2].

miRNA Biogenesis

Actors :

1. Drosha and DGCR8
2. Exportin-5
3. Dicer, TRBP and Ago
4. RISC complex

→ ***Action into the cytoplasm***

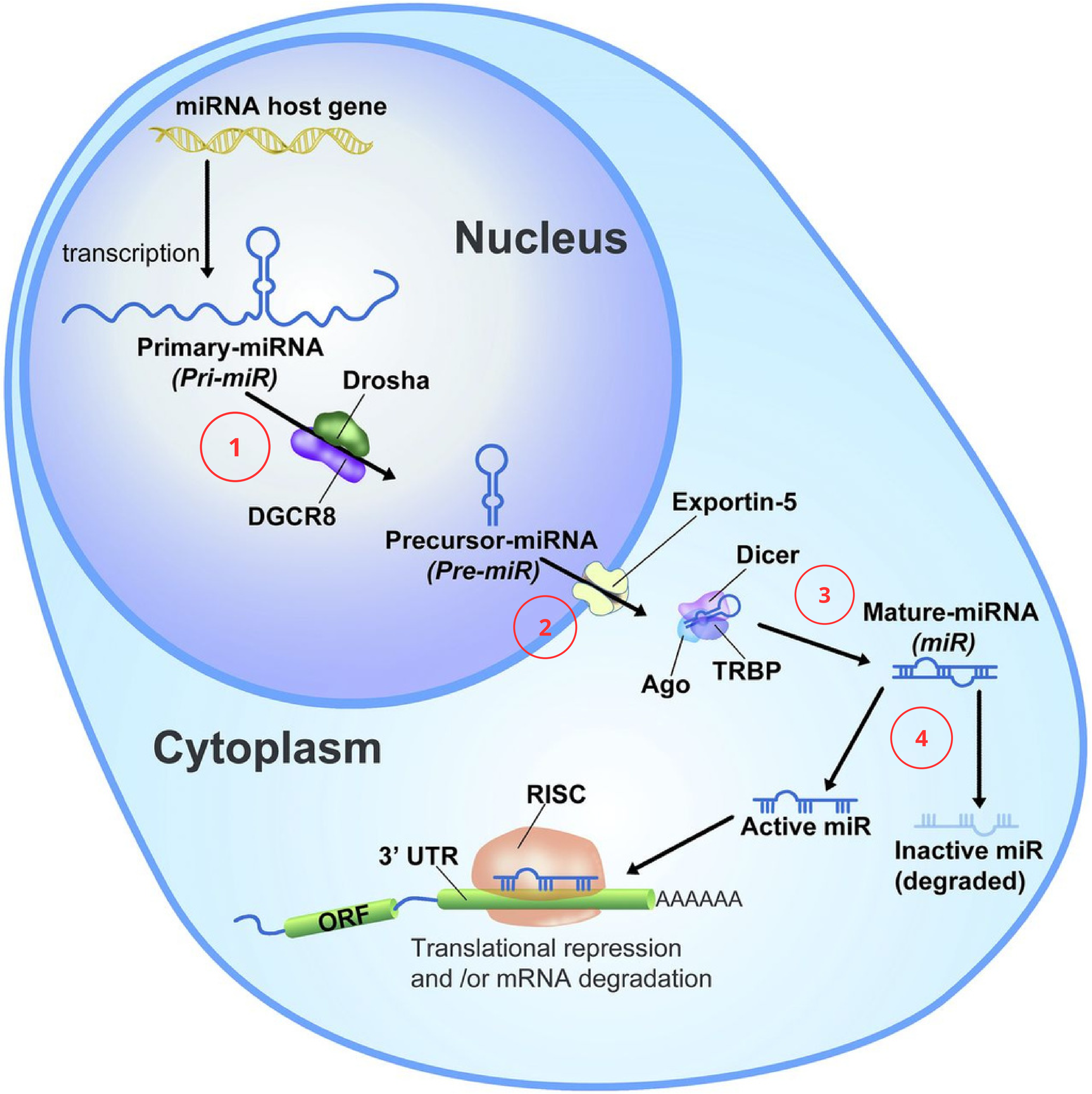


Fig 3 : Steps of miRNA biogenesis [2].

miRNA functions

miRNAs perform negative post-transcriptional gene regulation and modify the expression levels of target genes when they target mRNAs by :

- translation inhibition
- mRNA cleavage
- translation activation

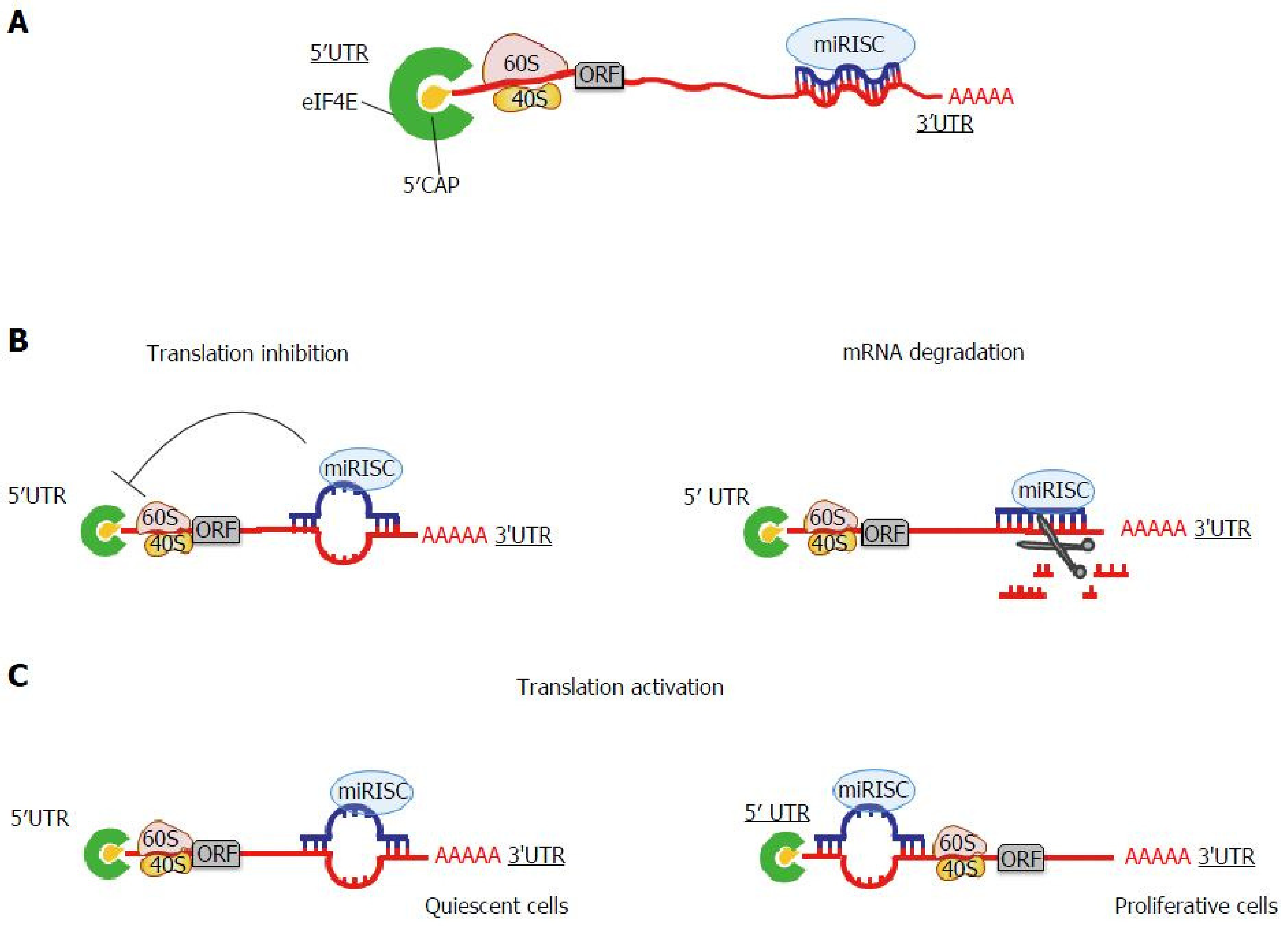


Fig 4 : Mechanisms of action of microRNAs[3].

miRNA functions

miRNAs perform negative post-transcriptional gene regulation and modify the expression levels of target genes when they target mRNAs by :

- translation inhibition
- mRNA cleavage
- translation activation

miRNAs have actions within the cell... but also on neighboring cells

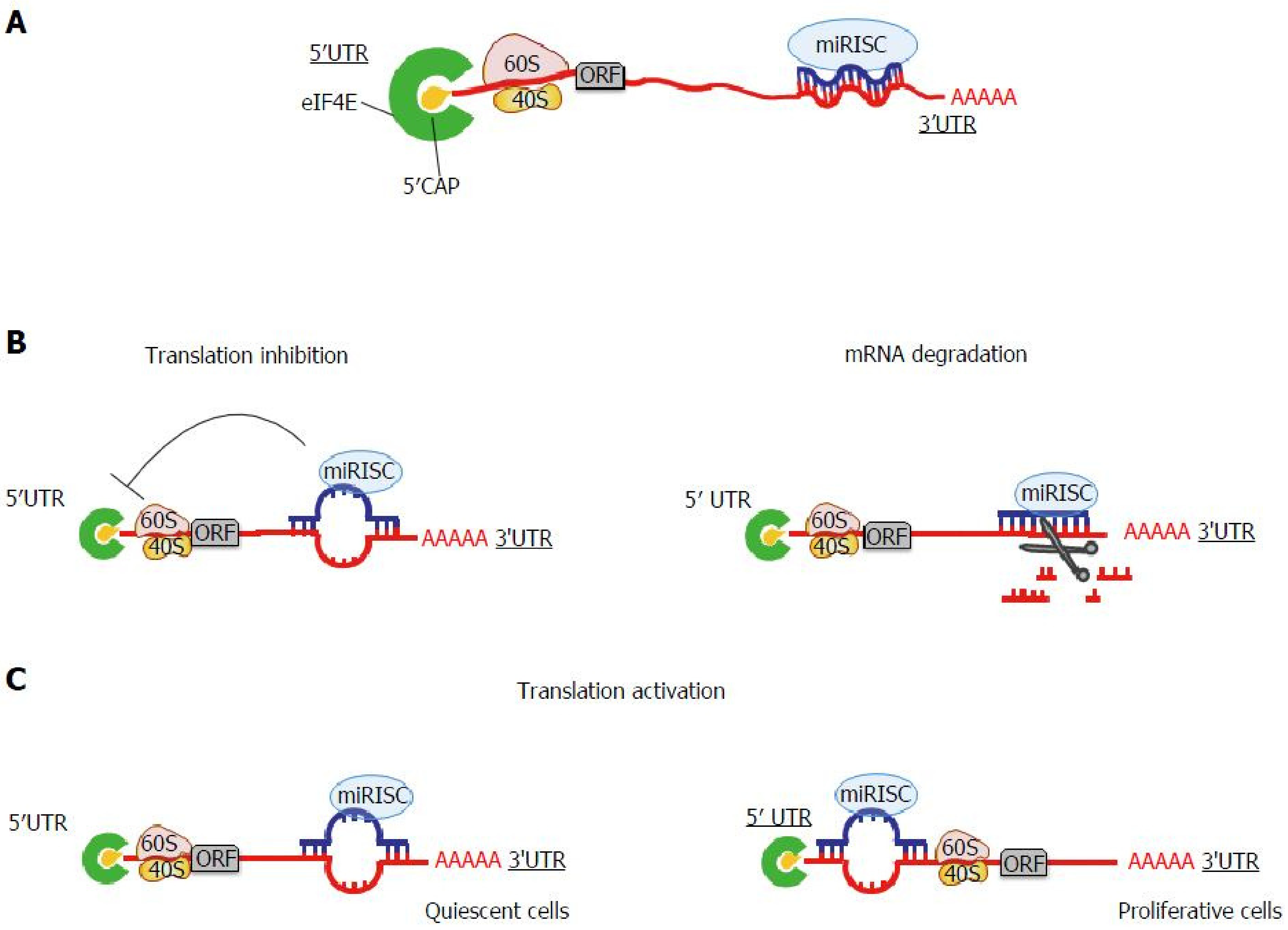


Fig 4 : Mechanisms of action of microRNAs[3].

Exosomal miRNAs

- 40–150 nm vesicles
- Lipid bilayer membrane vesicles
- Widely distributed in various body fluids
- Exosomes can be released from many cell types
- exosomes can regulate the bioactivities of recipient cells

→ ***A support for cell-cell communication***

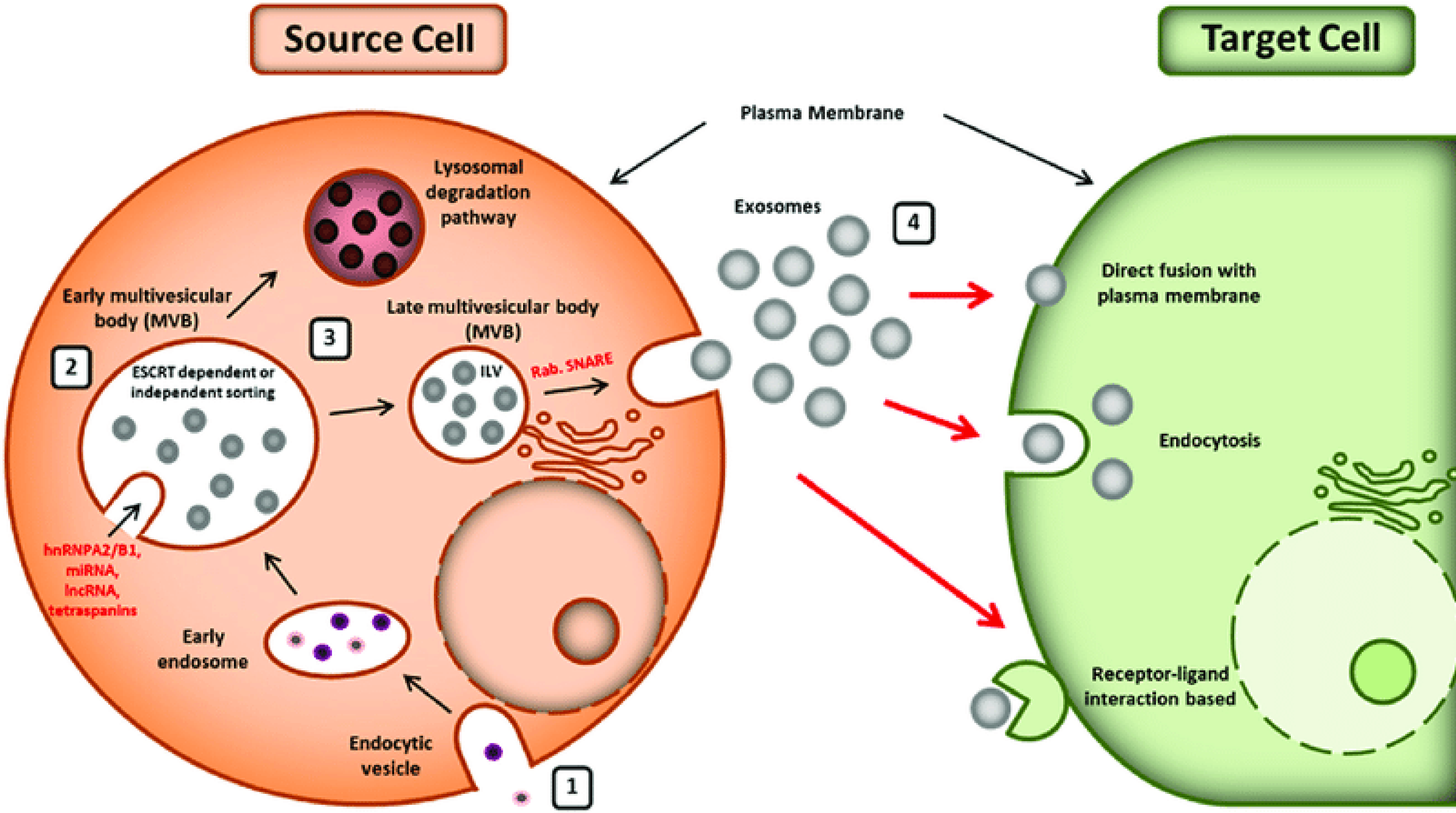


Fig 5 : Biogenesis, release, and uptake of exosomes [4].

Exosomal miRNAs

Exosomal miR-21 from tubular cells contributes to renal fibrosis by activating fibroblasts via targeting PTEN in obstructed kidneys

Sheng Zhao[1], Wei Li[2], Weimin Yu[1], Ting Rao[1], Haoyong Li[1], Yuan Ruan[1], Run Yuan[1], Chenglong Li[1], Jinzhuo Ning[1], Siqi Li[2], Wu Chen[1], Fan Cheng[1], Xiangjun Zhou[1]

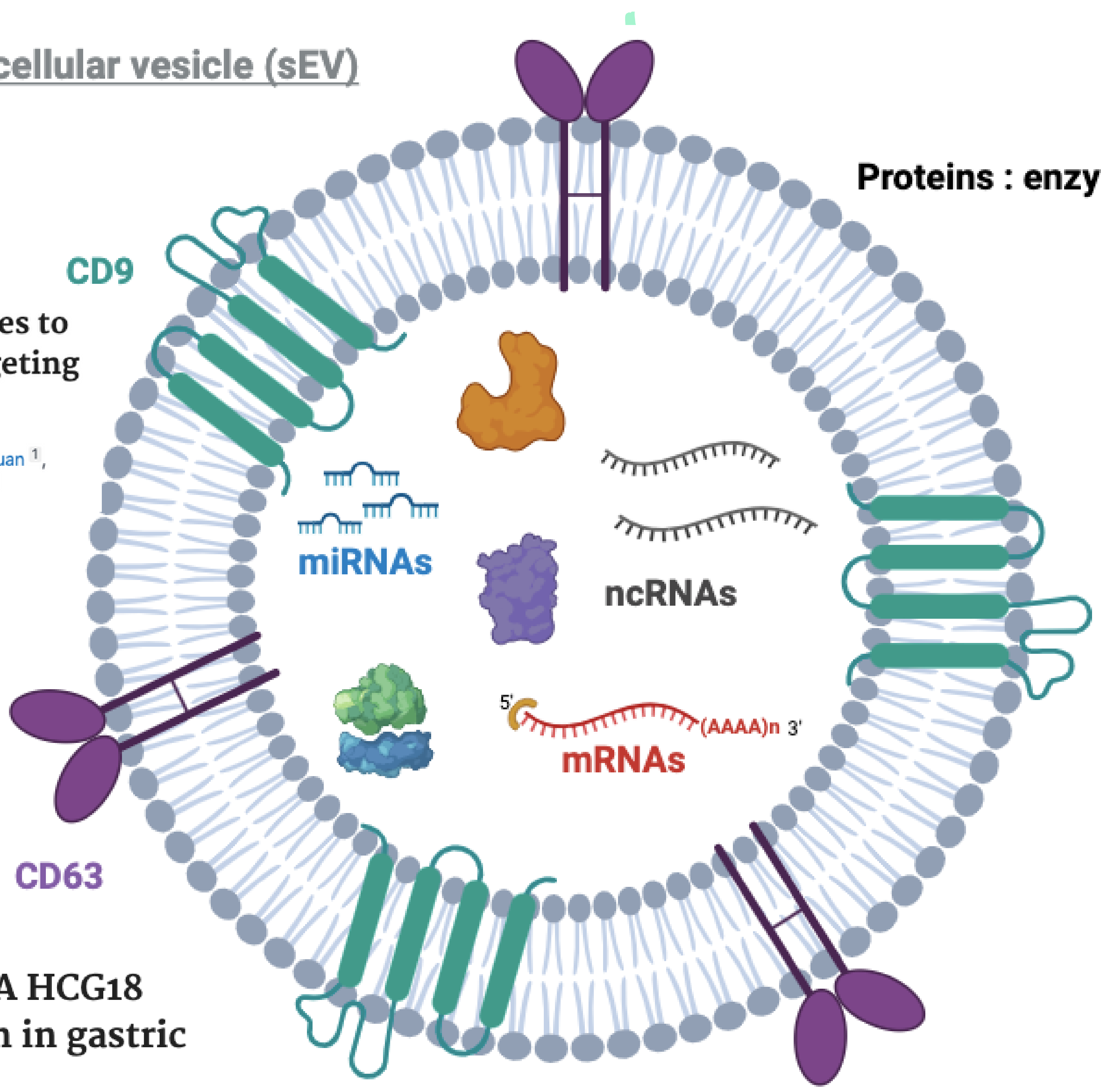


Fig.6 : Main components of an exosome

Bladder cancer-derived exosomal KRT6B promotes invasion and metastasis by inducing EMT and regulating the immune microenvironment

Qiang Song[#, 1], Hao Yu[#, 1], Yidong Cheng[#, 1], Jie Han[1], Kai Li[1], Juntao Zhuang[1], Qiang Lv[1], Xiao Yang[2], Haiwei Yang[3]

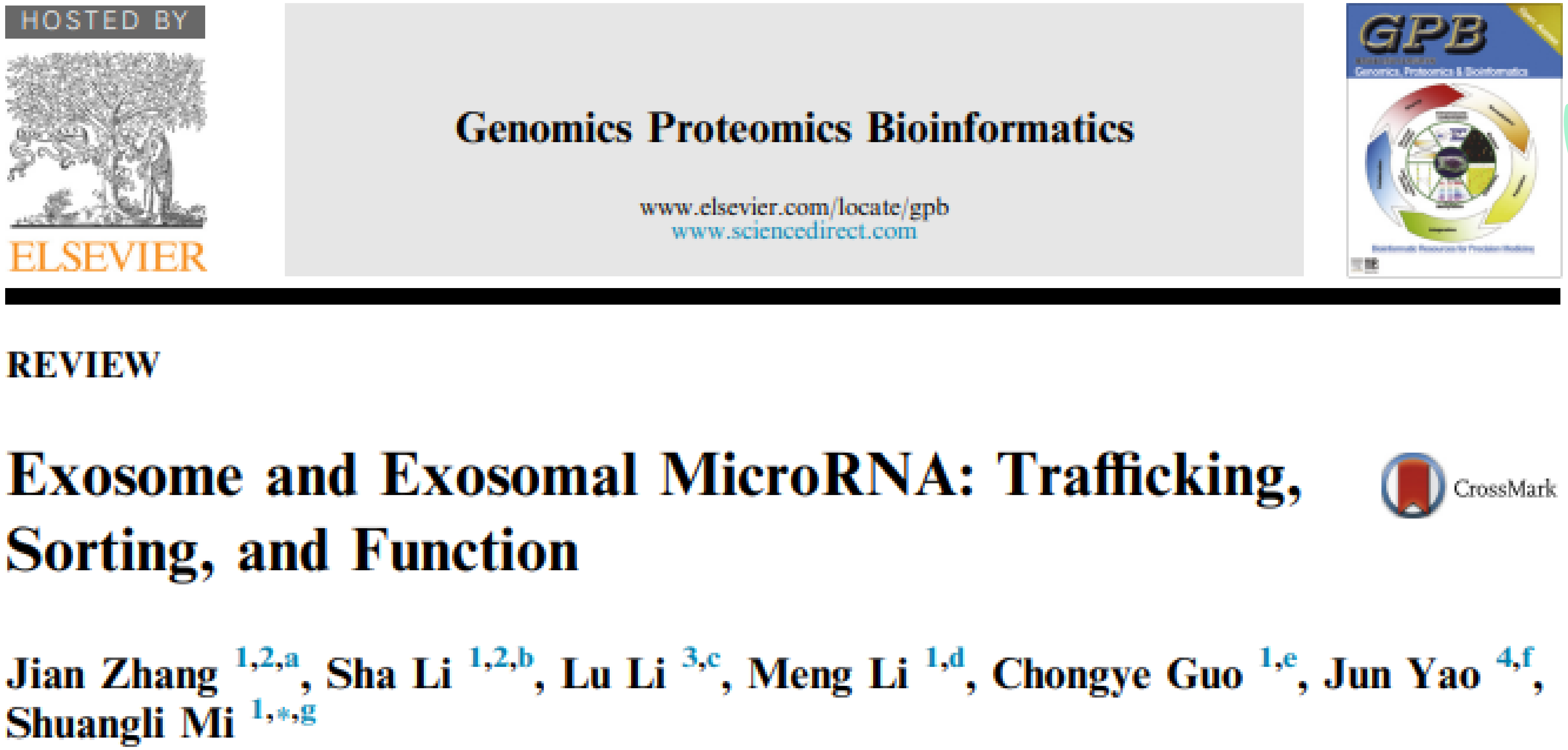
Exosome-mediated transfer of lncRNA HCG18 promotes M2 macrophage polarization in gastric cancer

Lin Xin[1], You Wu[2], Chuan Liu[2], Fei Zeng[2], Jin-Liang Wang[2], Deng-Zhong Wu[2], Ji-Ping Wu[2], Zhen-Qi Yue[2], Jin-Heng Gan[2], Hao Lu[2], Yi-Wu Yuan[2], Li-Qiang Zhou[2]

Ectodysplasin-A mRNA in exosomes released from activated hepatic stellate cells stimulates macrophage response

Emilio Marrero[1], Neha Attal[1], Ali Nimeri[1], Rachel M McGee[2], Jennifer H Benbow[2], Kyle J Thompson[1], Laura W Schrum[2], Iain H McKillop[3]

Exosomal miRNAs



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REVIEW

Exosome and Exosomal MicroRNA: Trafficking, Sorting, and Function

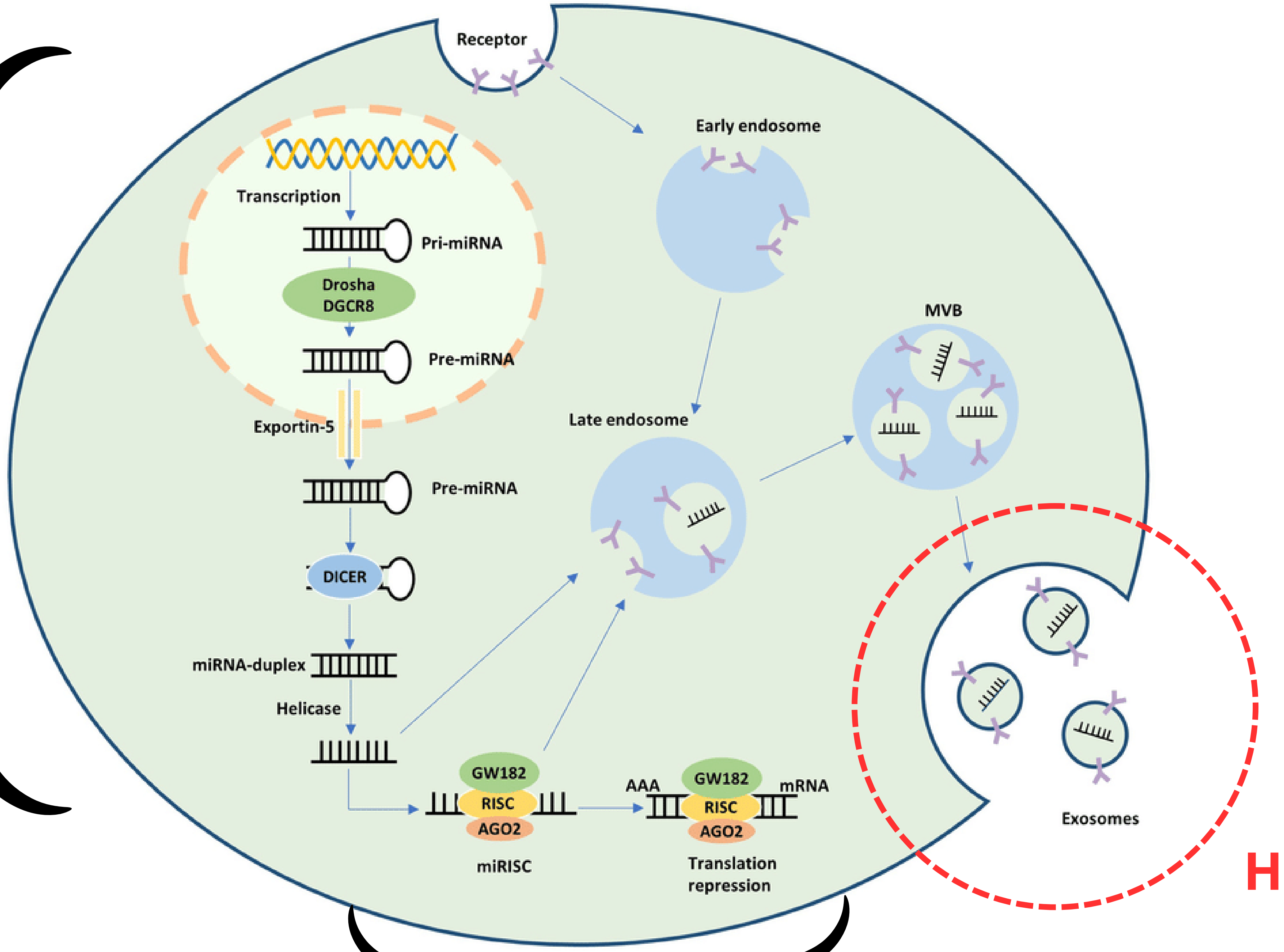
CrossMark

Jian Zhang [1,2,a], Sha Li [1,2,b], Lu Li [3,c], Meng Li [1,d], Chongye Guo [1,e], Jun Yao [4,f], Shuangli Mi [1,*,g]

Exosomal miR-92a(fromK562 cells), significantly reduced the expression of integrin a5 in the HUVEC cells and enhanced endothelial cell migration and tube formation

Exosomal miR-214, derived from the cell line HMEC-1 : stimulated migration and angiogenesis in neighboring cells .

Exosomal miRNAs



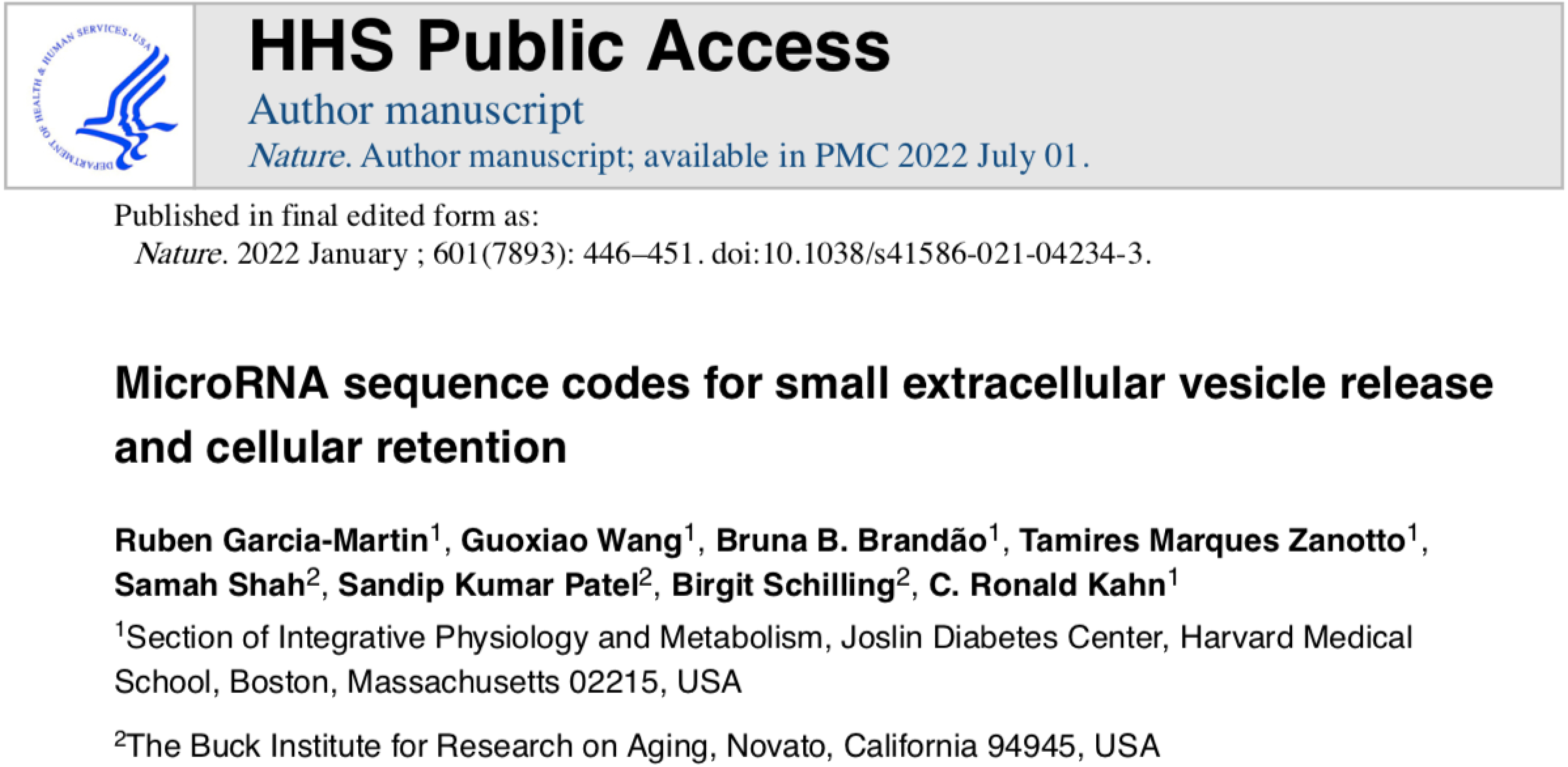
miRNA genesis

miRNA cell function

How are miRNAs excreted ?

Fig 7 : miRNA fate [5]

How are miRNAs excreted ?



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MicroRNA sequence codes for small extracellular vesicle release and cellular retention

Ruben Garcia-Martin[1], **Guoxiao Wang**[1], **Bruna B. Brandão**[1], **Tamires Marques Zanotto**[1], **Samah Shah**[2], **Sandip Kumar Patel**[2], **Birgit Schilling**[2], **C. Ronald Kahn**[1]

[1]Section of Integrative Physiology and Metabolism, Joslin Diabetes Center, Harvard Medical School, Boston, Massachusetts 02215, USA

[2]The Buck Institute for Research on Aging, Novato, California 94945, USA

Questions

1- Is exosomal miRNA secretion cell type-specific?

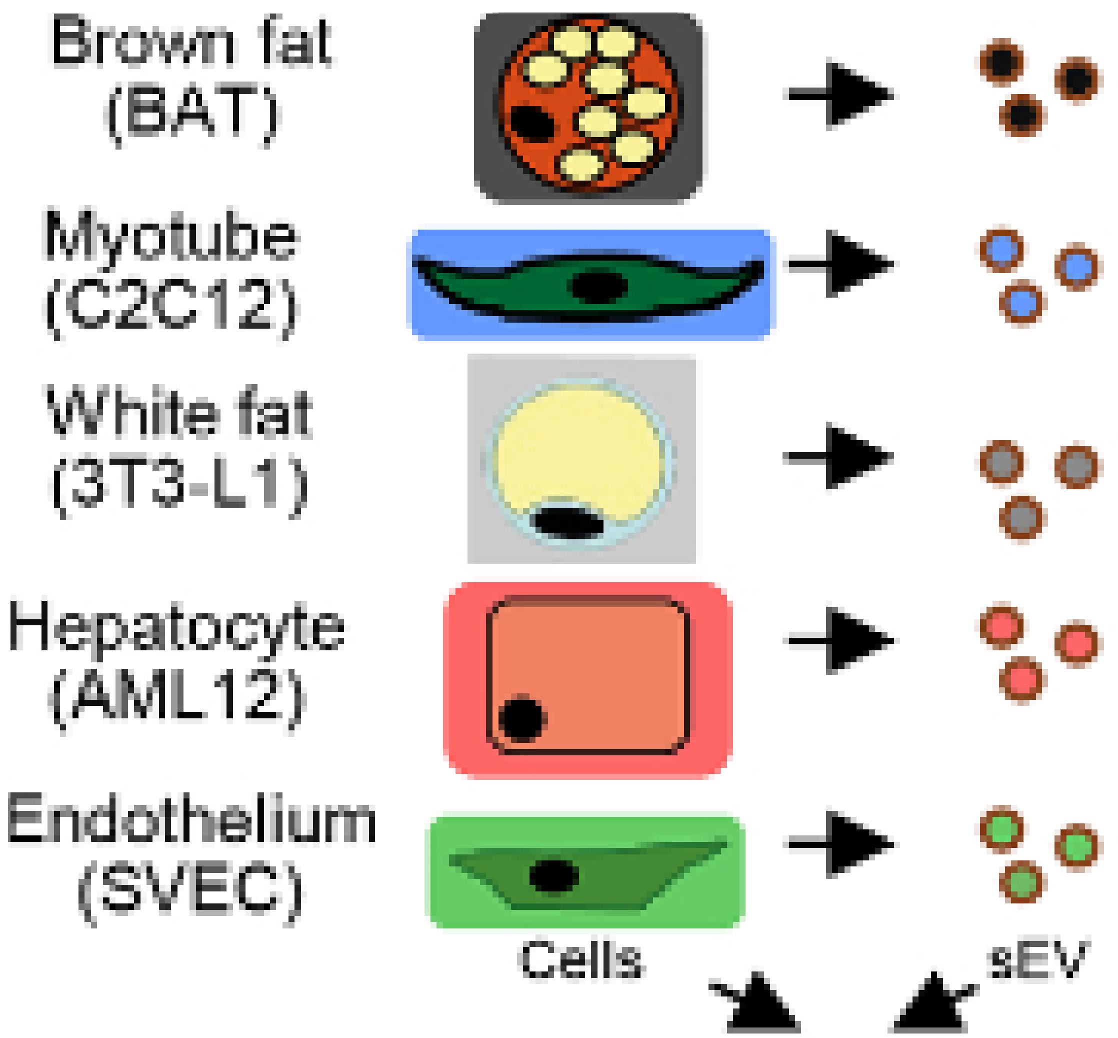
2- Is there a code that decides which miRNA will be loaded in the exosome ?

3- Do these motifs interact with specific miRNA binding proteins ?

4- can EXOmotif be used to modify gene expression in neighboring cells ?

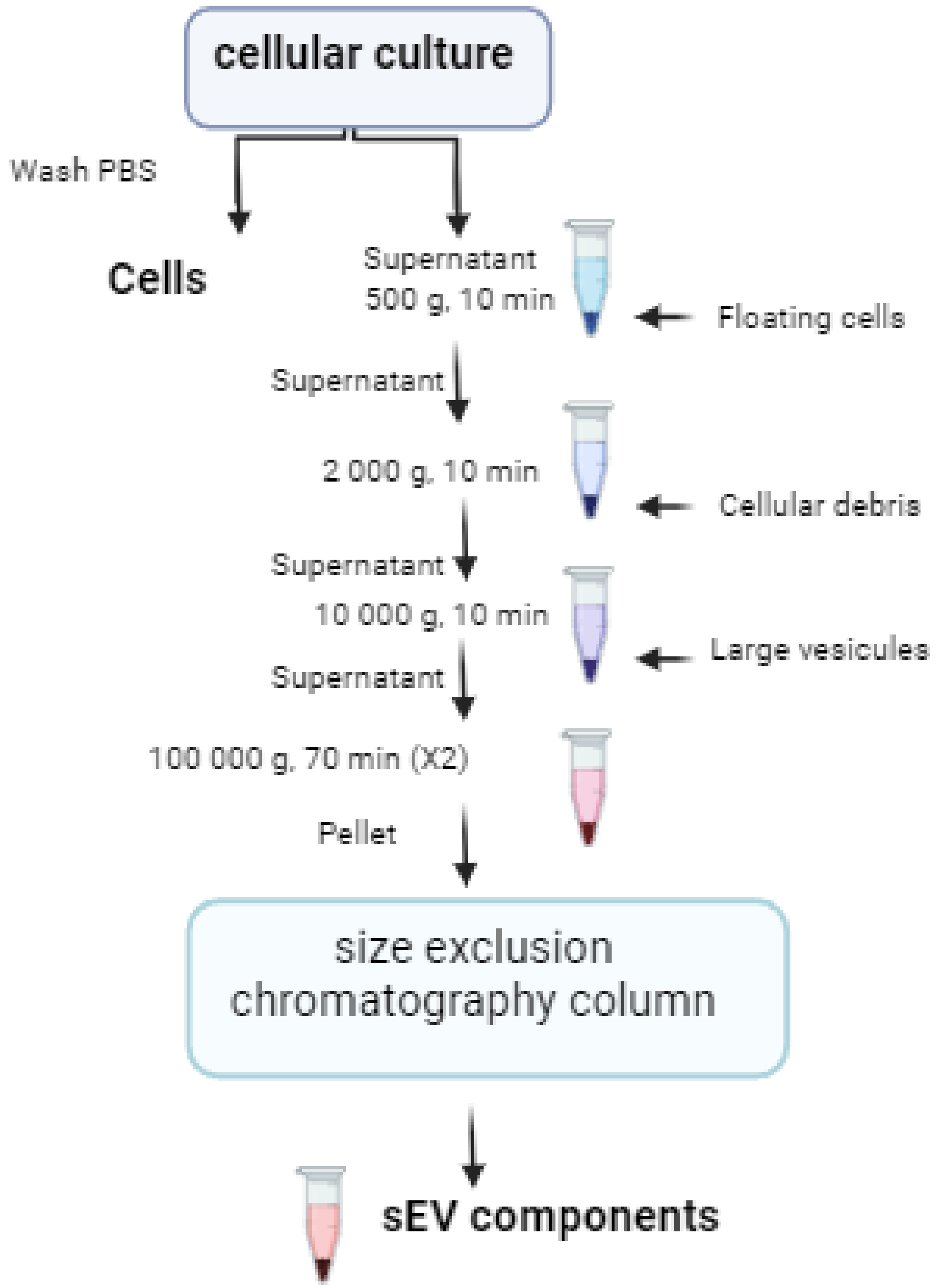
1- Is exosomal miRNA secretion cell type-specific?

The study models and method



(small extracellular vesicles)

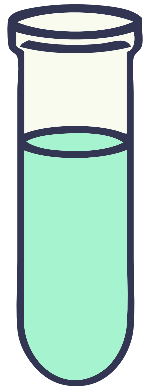
miRNA profiling



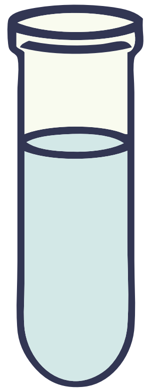
1- Is exosomal miRNA secretion cell type-specific?

The study models and method :

- **Cell sample**



- **sEV sample**



Small RNA sequencing

1. RNA isolation
2. cDNA library
3. sequencing

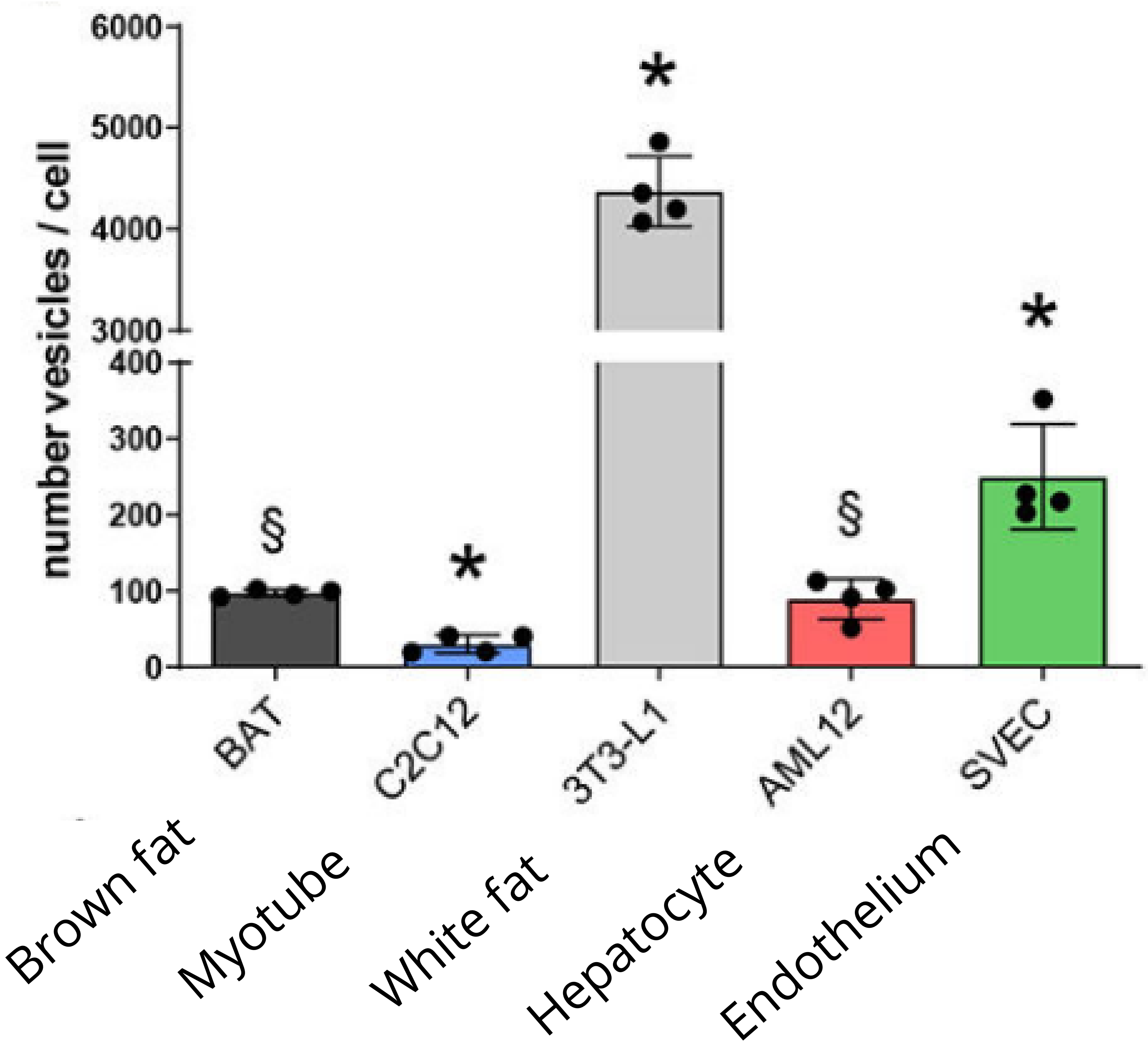
for sequencing only miRNA :
Qiagen miRNA workflow kit
(ref : 331502) , miRNA specific library

All miRNAs sequences from :

- **sEV sample**
- **Cell sample**

1- Is exosomal miRNA secretion cell type-specific?

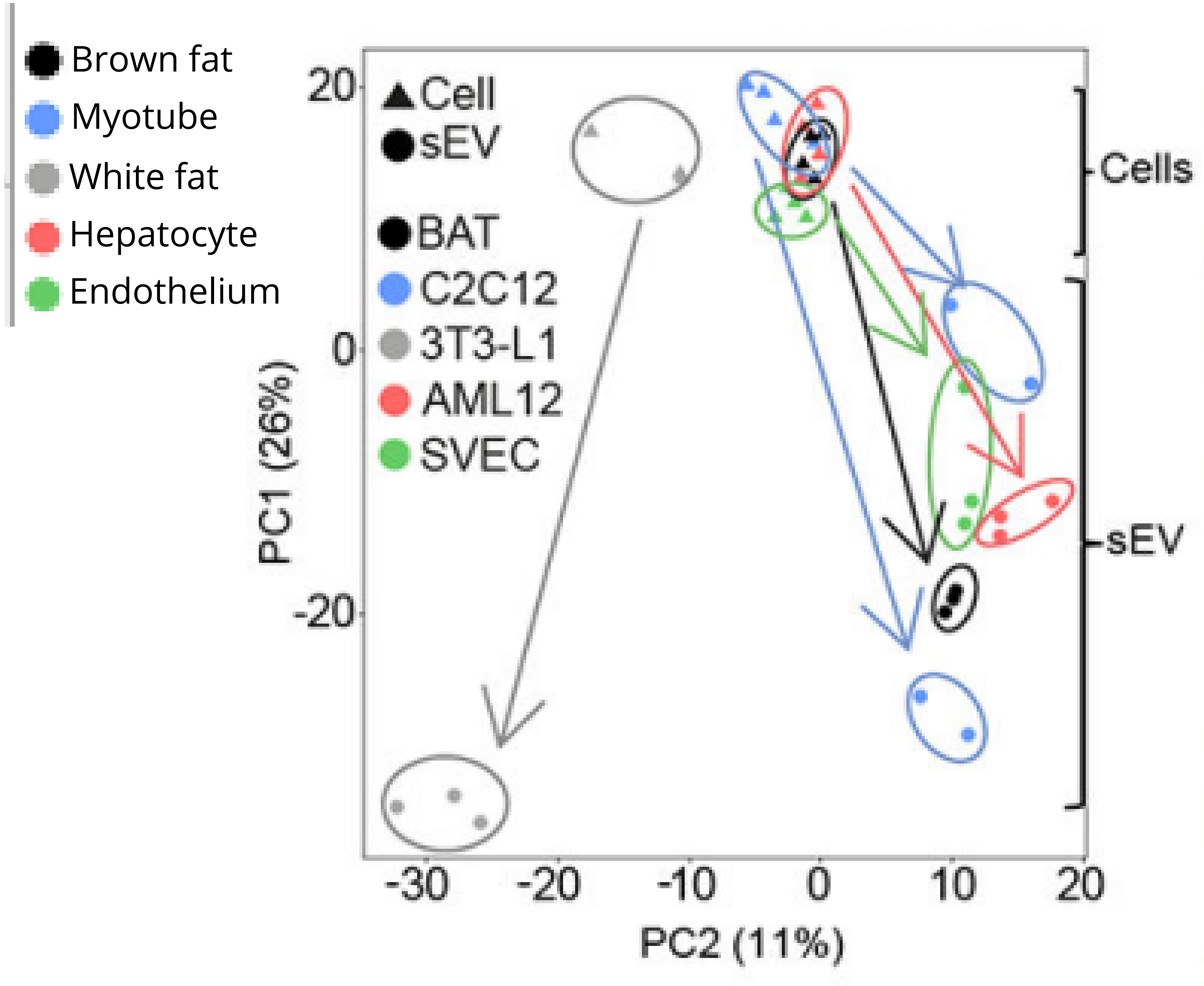
The number of vesicles is specific to each cell type



- **depending on cell type, different numbers of exosomes are observed**
- **White fat (3T3-L1) have a highest production / release rate per cell**

White adipose tissue exerts its functions (energy storage or dissipation…) via different methods of communication [6].

1- Is exosomal miRNA secretion cell type-specific?



Principal component analysis (PCA)

<u>miRNA profile into the cell</u> :

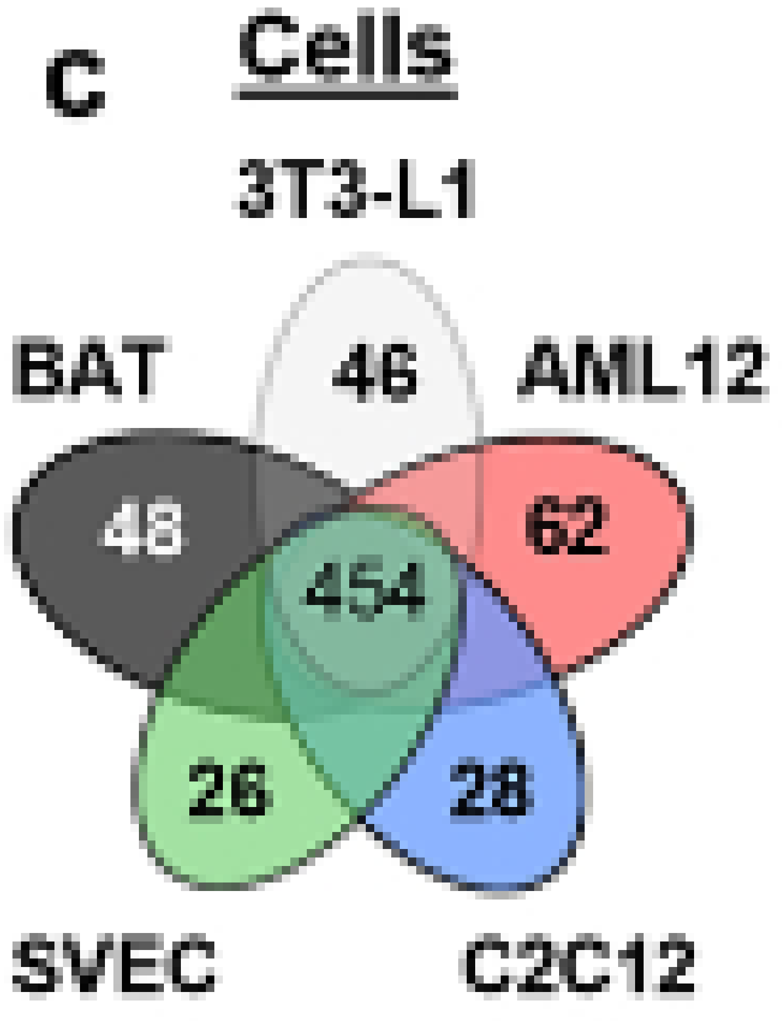
- brown fat and hepatocyte cells are clustered together (overlap).
- White fat is most distinct.

<u>miRNA profile into vesicles</u> :

- Each cell type have a very different miRNA secretion profile

→ ***Specific nature of miRNA secretion***

1- Is exosomal miRNA secretion cell type-specific?

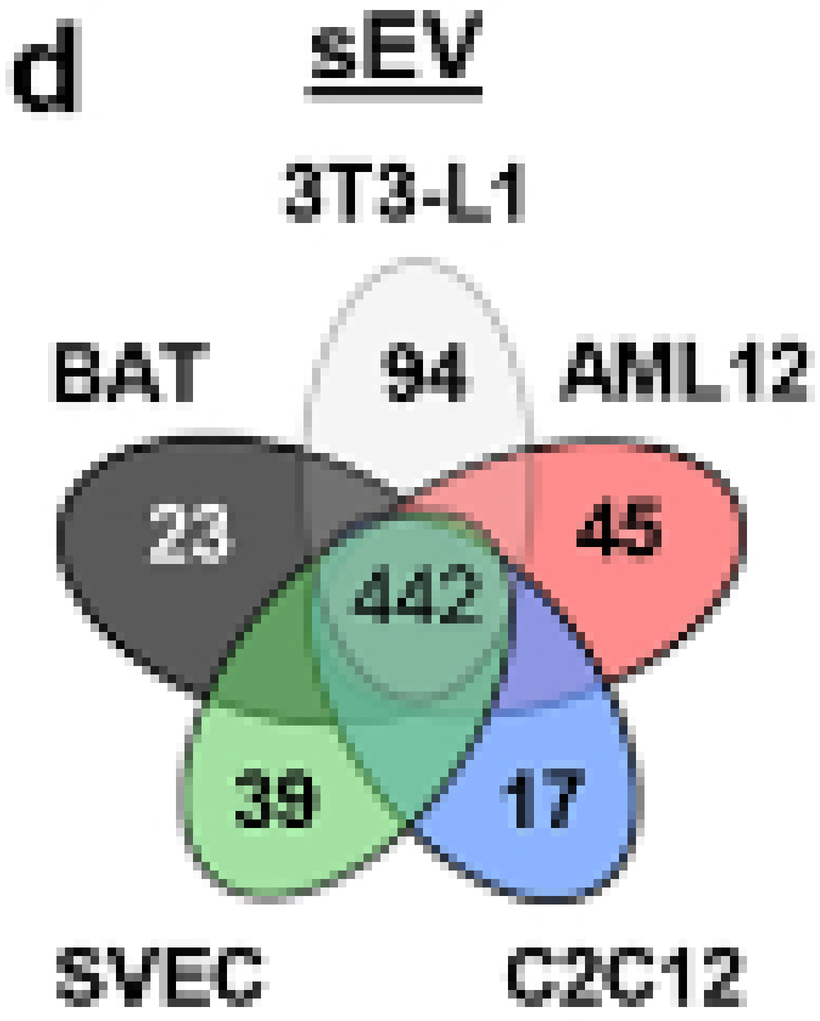


Venn Diagram

- Of the 664 miRNA analyzed in the cell bodies :

210 were significantly more highly expressed in one cell-type compared to the other four.

Cell type specificity

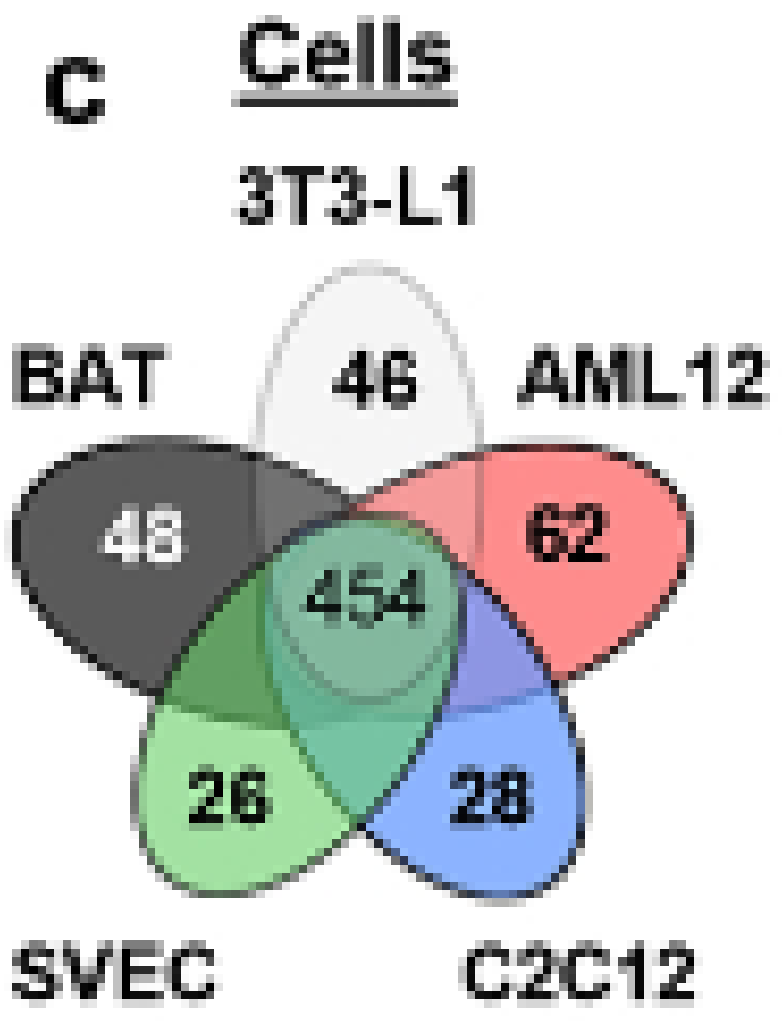


- Of the 660 miRNA analyzed in the vesicle :

218 were enriched in the vesicles from one cell-type compared to the vesicles from the other .

Cell-specific secretion

1- Is exosomal miRNA secretion cell type-specific?



Venn Diagram

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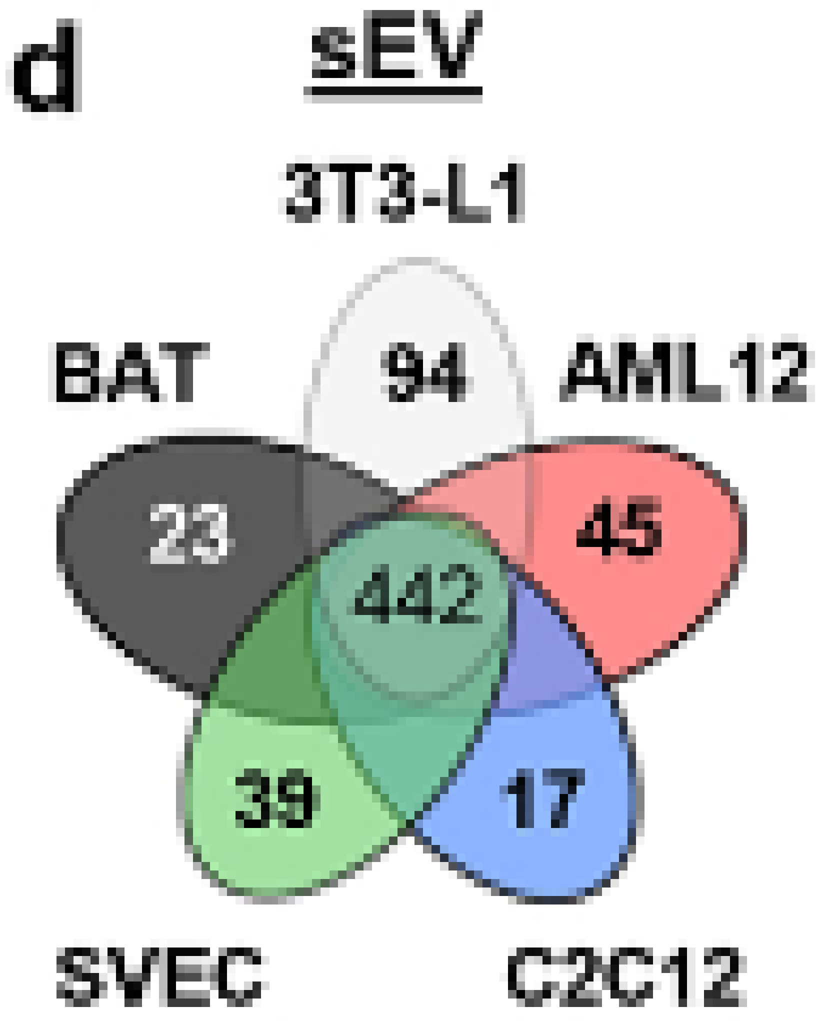
Cell type specificity



- Of the 660 miRNA analyzed in the vesicle :

218 were enriched in the vesicles from one cell-type compared to the vesicles from the other .

Cell-specific secretion

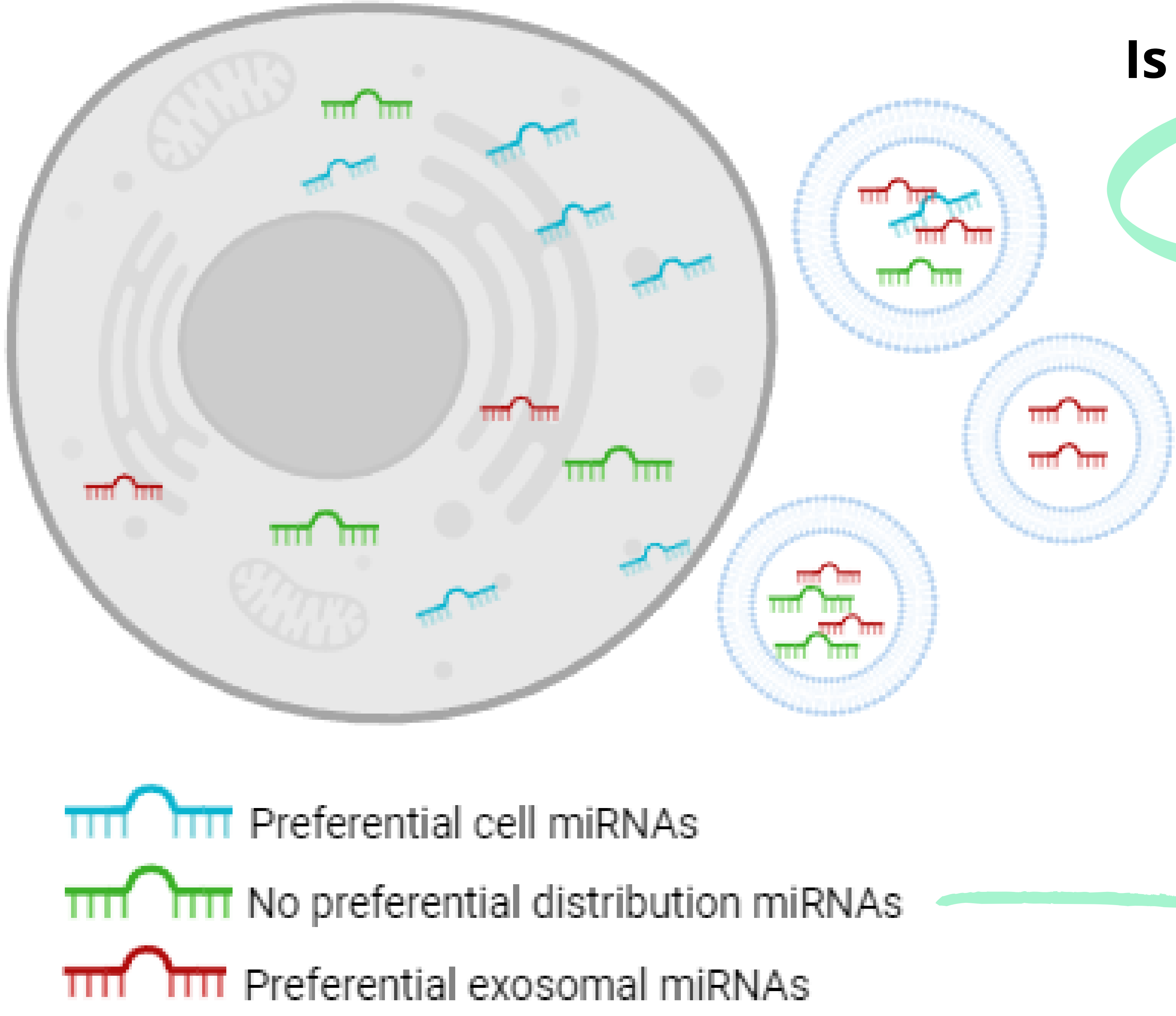
Suggesting a cell specific sorting mechanism

Take home messages :

- **The numbers of exosomes vary between cell type.**
- **White fat is the major contributor to circulating exosomes.**
- **Specific nature of miRNA secretion**

2-What signal induces miRNA fate?

In silico method



Is the sequence and a preference for a localization due to chance?

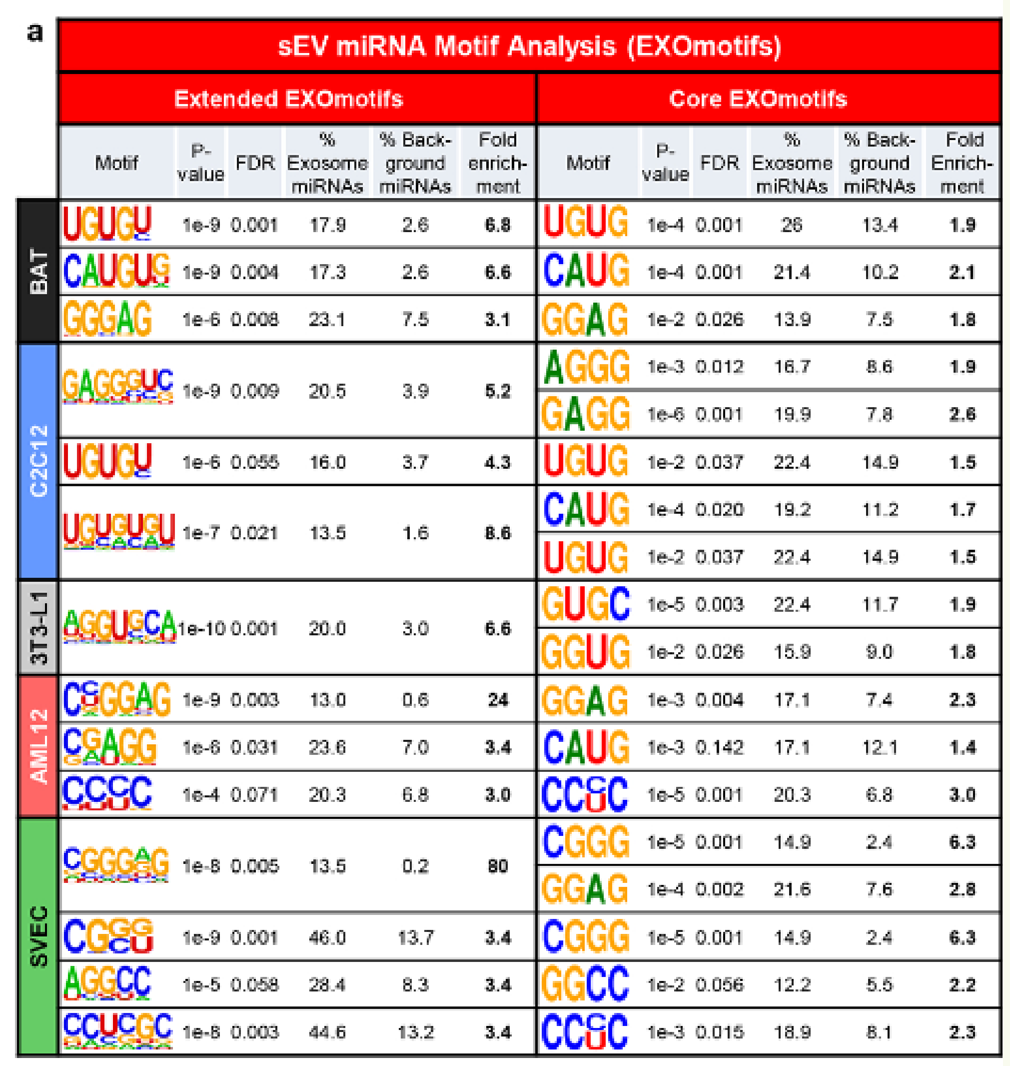
Hypergeometric Optimization of Motif EnRichment (**HOMER**)

Searching over- represented motifs found in the sequence of preferential cell miRNAs/exosomal miRNAs with a preferential exosomal miRNAs/cell miRNAs or with no preferential distribution

2-What signal induces miRNA fate?

Criteria

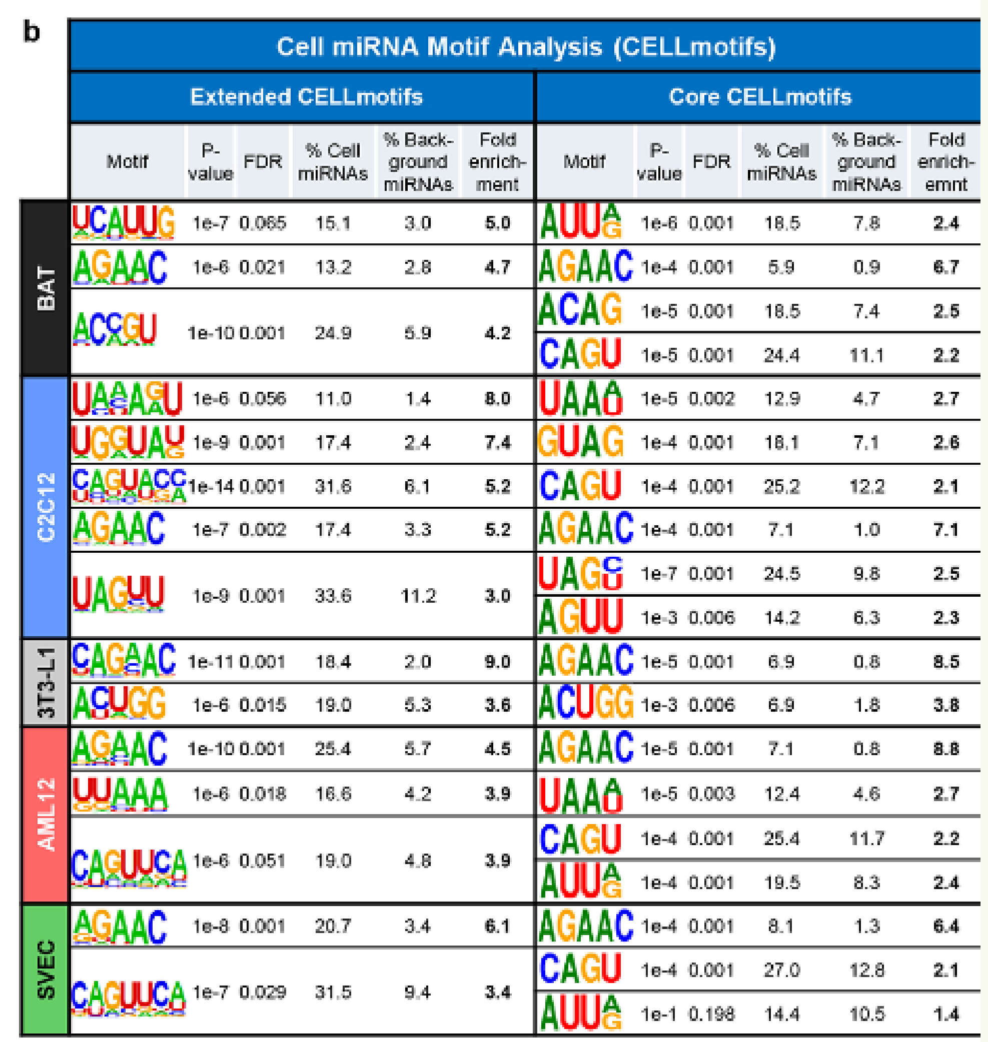
- selection of miRNAs enriched at least 3-fold compared to no preferential localization miRNAs
- motif length : 4 to 7 nucleotides
- motif that present at least 10% of miRNAs



a

sEV miRNA Motif Analysis (EXOmotifs)

	Extended EXOmotifs						Core EXOmotifs					
	Motif	P-value	FDR	% Exosome miRNAs	% Background miRNAs	Fold enrichment	Motif	P-value	FDR	% Exosome miRNAs	% Background miRNAs	Fold Enrichment
BAT	UGUGU	1e-9	0.001	17.9	2.6	**6.8**	UGUG	1e-4	0.001	26	13.4	**1.9**
	CAUGUG	1e-9	0.004	17.3	2.6	**6.6**	CAUG	1e-4	0.001	21.4	10.2	**2.1**
	GGGAG	1e-6	0.008	23.1	7.5	**3.1**	GGAG	1e-2	0.026	13.9	7.5	**1.8**
C2C12	GAGGGUC	1e-9	0.009	20.5	3.9	**5.2**	AGGG	1e-3	0.012	16.7	8.6	**1.9**
							GAGG	1e-6	0.001	19.9	7.8	**2.6**
	UGUGU	1e-6	0.055	16.0	3.7	**4.3**	UGUG	1e-2	0.037	22.4	14.9	**1.5**
	UGUGUGU	1e-7	0.021	13.5	1.6	**8.6**	CAUG	1e-4	0.020	19.2	11.2	**1.7**
							UGUG	1e-2	0.037	22.4	14.9	**1.5**
3T3-L1	AGGUGCA	1e-10	0.001	20.0	3.0	**6.6**	GUGC	1e-5	0.003	22.4	11.7	**1.9**
							GGUG	1e-2	0.026	15.9	9.0	**1.8**
AML12	CCGGAG	1e-9	0.003	13.0	0.6	**24**	GGAG	1e-3	0.004	17.1	7.4	**2.3**
	CGAGG	1e-6	0.031	23.6	7.0	**3.4**	CAUG	1e-3	0.142	17.1	12.1	**1.4**
	CCCC	1e-4	0.071	20.3	6.8	**3.0**	CCGC	1e-5	0.001	20.3	6.8	**3.0**
SVEC	CGGGAG	1e-8	0.005	13.5	0.2	**80**	CGGG	1e-5	0.001	14.9	2.4	**6.3**
							GGAG	1e-4	0.002	21.6	7.6	**2.8**
	CGGG	1e-9	0.001	46.0	13.7	**3.4**	CGGG	1e-5	0.001	14.9	2.4	**6.3**
	AGGCC	1e-5	0.058	28.4	8.3	**3.4**	GGCC	1e-2	0.056	12.2	5.5	**2.2**
	CCUCGC	1e-8	0.003	44.6	13.2	**3.4**	CCGC	1e-3	0.015	18.9	8.1	**2.3**



b

Cell miRNA Motif Analysis (CELLmotifs)

	Extended CELLmotifs						Core CELLmotifs					
	Motif	P-value	FDR	% Cell miRNAs	% Background miRNAs	Fold enrichment	Motif	P-value	FDR	% Cell miRNAs	% Background miRNAs	Fold enrichemnt
BAT	UCAUUG	1e-7	0.065	15.1	3.0	**5.0**	AUUA	1e-6	0.001	18.5	7.8	**2.4**
	AGAAC	1e-6	0.021	13.2	2.8	**4.7**	AGAAC	1e-4	0.001	5.9	0.9	**6.7**
	ACCGU	1e-10	0.001	24.9	5.9	**4.2**	ACAG	1e-5	0.001	18.5	7.4	**2.5**
							CAGU	1e-5	0.001	24.4	11.1	**2.2**
C2C12	UAAAGU	1e-6	0.056	11.0	1.4	**8.0**	UAAA	1e-5	0.002	12.9	4.7	**2.7**
	UGGUAU	1e-9	0.001	17.4	2.4	**7.4**	GUAG	1e-4	0.001	18.1	7.1	**2.6**
	CAGUACC	1e-14	0.001	31.6	6.1	**5.2**	CAGU	1e-4	0.001	25.2	12.2	**2.1**
	AGAAC	1e-7	0.002	17.4	3.3	**5.2**	AGAAC	1e-4	0.001	7.1	1.0	**7.1**
	UAGUU	1e-9	0.001	33.6	11.2	**3.0**	UAGC	1e-7	0.001	24.5	9.8	**2.5**
							AGUU	1e-3	0.006	14.2	6.3	**2.3**
3T3-L1	CAGAAC	1e-11	0.001	18.4	2.0	**9.0**	AGAAC	1e-5	0.001	6.9	0.8	**8.5**
	ACUGG	1e-6	0.015	19.0	5.3	**3.6**	ACUGG	1e-3	0.006	6.9	1.8	**3.8**
AML 12	AGAAC	1e-10	0.001	25.4	5.7	**4.5**	AGAAC	1e-5	0.001	7.1	0.8	**8.8**
	UUAAA	1e-6	0.018	16.6	4.2	**3.9**	UAAA	1e-5	0.003	12.4	4.6	**2.7**
	CAGUUCA	1e-6	0.051	19.0	4.8	**3.9**	CAGU	1e-4	0.001	25.4	11.7	**2.2**
							AUUA	1e-4	0.001	19.5	8.3	**2.4**
SVEC	AGAAC	1e-8	0.001	20.7	3.4	**6.1**	AGAAC	1e-4	0.001	8.1	1.3	**6.4**
	CAGUUCA	1e-7	0.029	31.5	9.4	**3.4**	CAGU	1e-4	0.001	27.0	12.8	**2.1**
							AUUA	1e-1	0.198	14.4	10.5	**1.4**

- **EXOmotif** sequence of 4-7 nt enriched with CG
- **CELLmotif** Sequence of 4-5 nt low in CG content

2-What signal induces miRNA fate?

Validation CELL and EXOmotif *in vivo*

Preferential exosomal miRNA → **CELLmotif inclusion** →

Preferential cell miRNA → **CELLmotif removal** →

Preferential cell miRNA → **EXOmotif inclusion** →

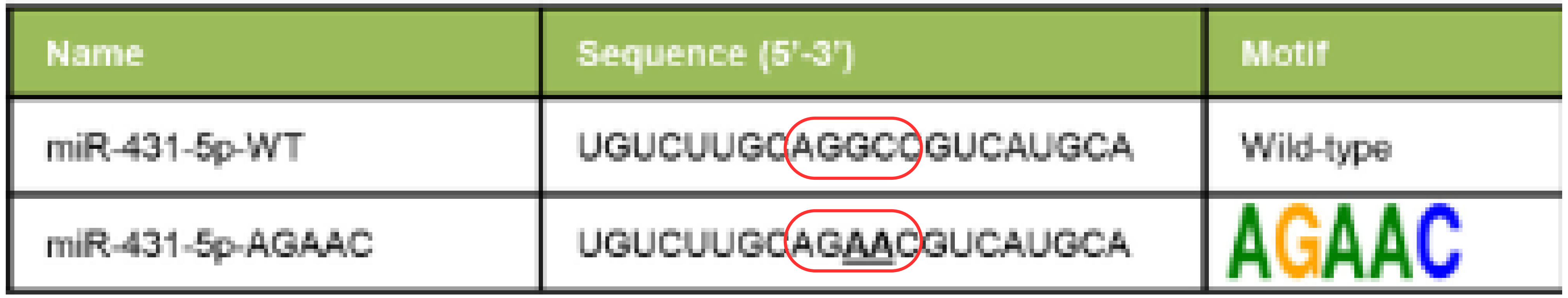
miRNA enrichment in the exosome

(*Motifs are cloned in Lentiviral vector*)

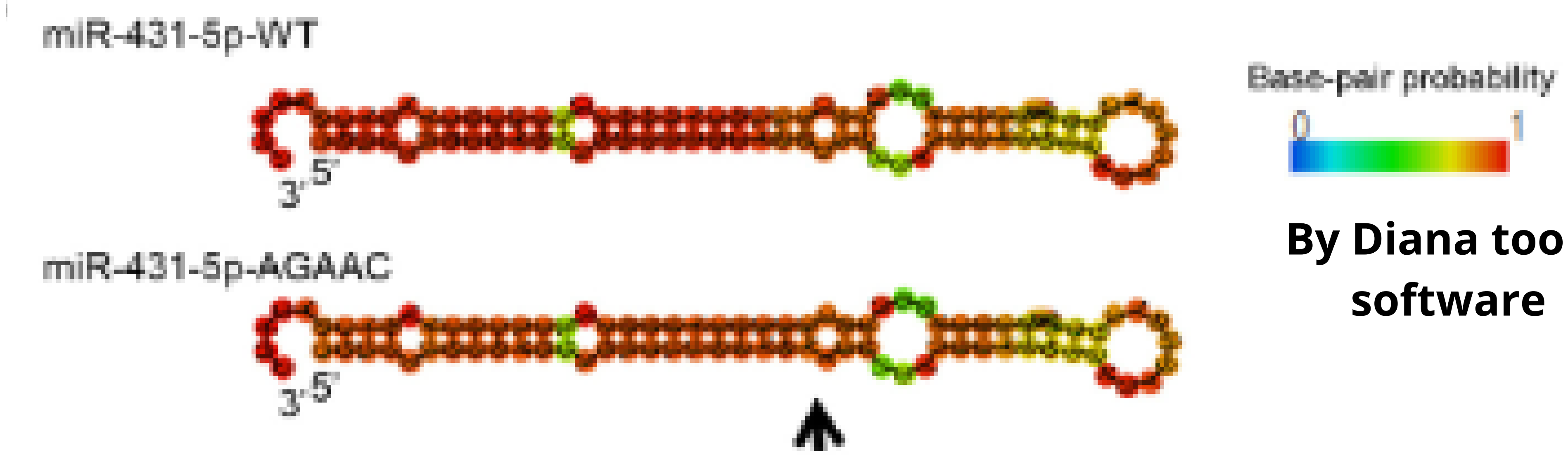
2-What signal induces miRNA fate?

Validation CELL and EXOmotif *in vivo*

CELLmotif inclusion

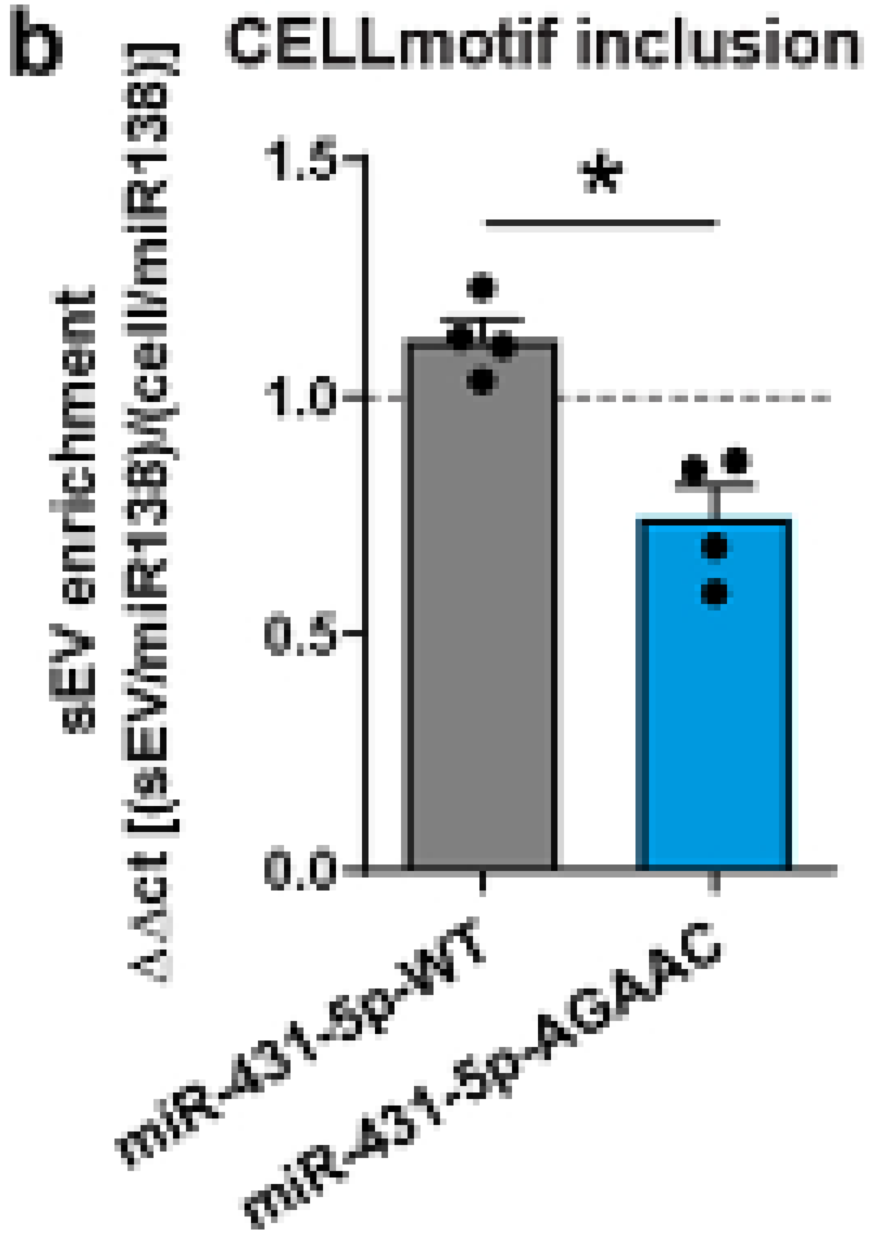


Name	Sequence (5'-3')	Motif
miR-431-5p-WT	UGUCUUGCAGGCCGUCAUGCA	Wild-type
miR-431-5p-AGAAC	UGUCUUGCAGAACGUCAUGCA	AGAAC



By Diana tools software

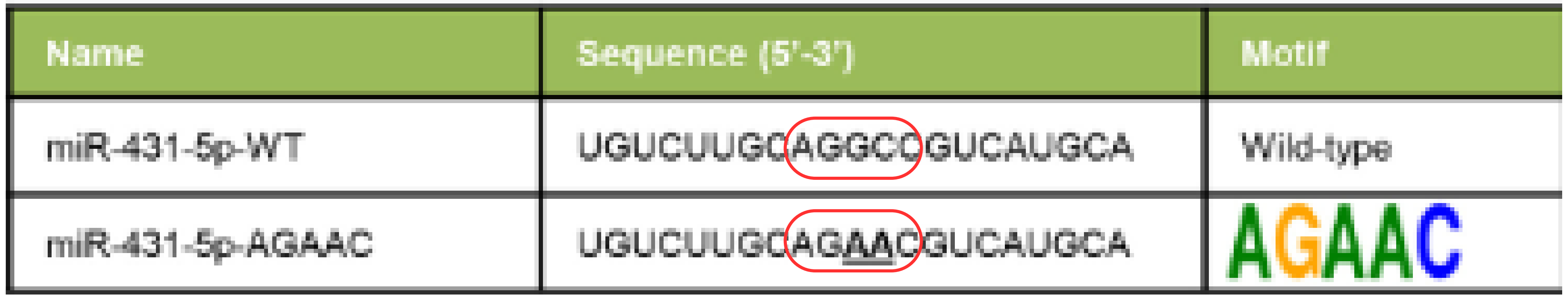
Cell type : AML12 hepatocytes



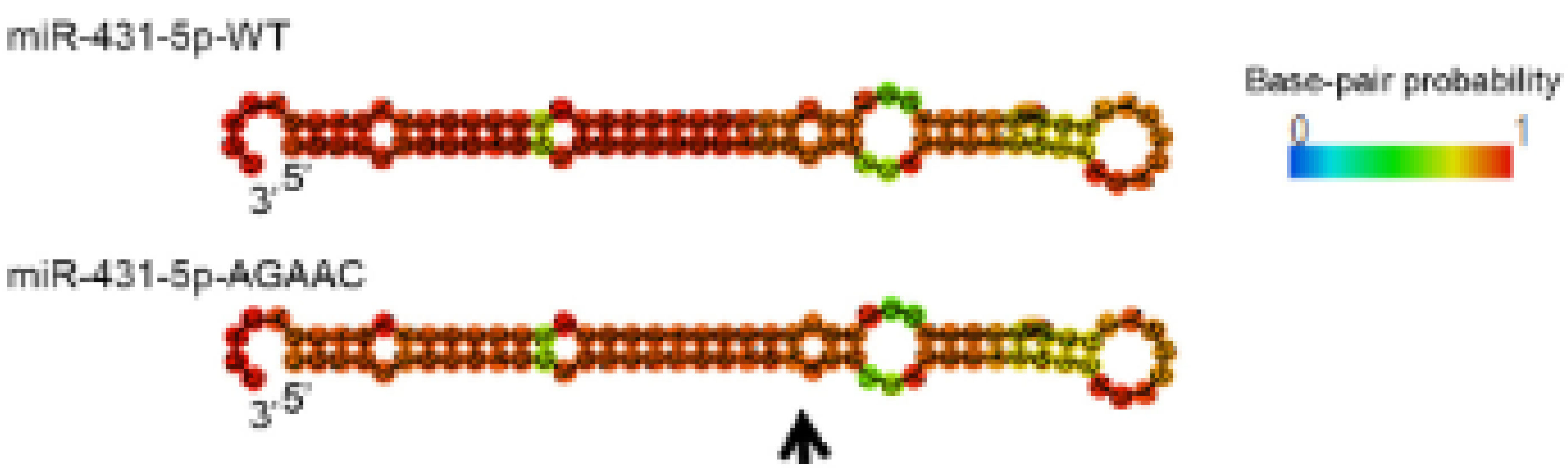
2-What signal induces miRNA fate?

Validation CELL and EXOmotif *in vivo*

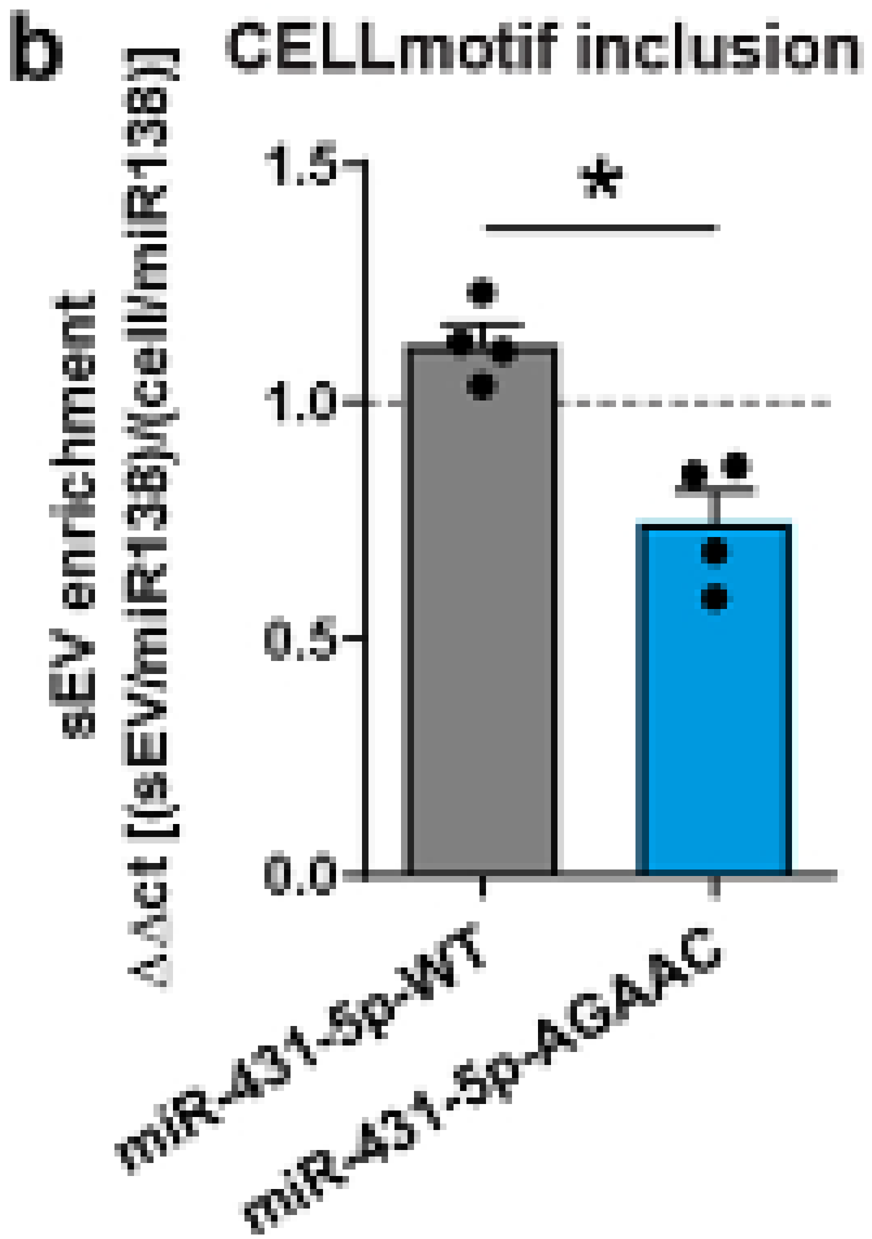
CELLmotif inclusion



Name	Sequence (5'-3')	Motif
miR-431-5p-WT	UGUCUUGCAGGCCGUCAUGCA	Wild-type
miR-431-5p-AGAAC	UGUCUUGCAGAACGUCAUGCA	AGAAC



Cell type : AML12 hepatocytes

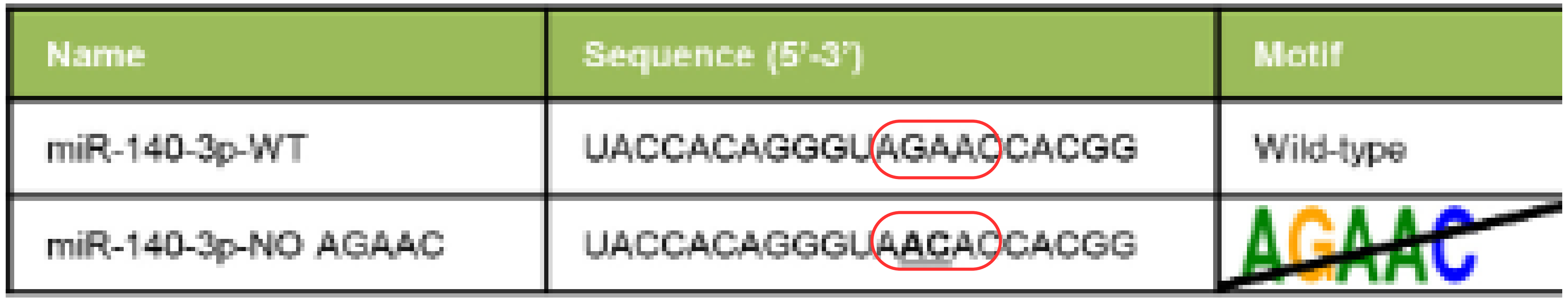


→ ***Inclusion of a CELLmotif into the preferentially exosomal miR-431 leads to its cell retention.***

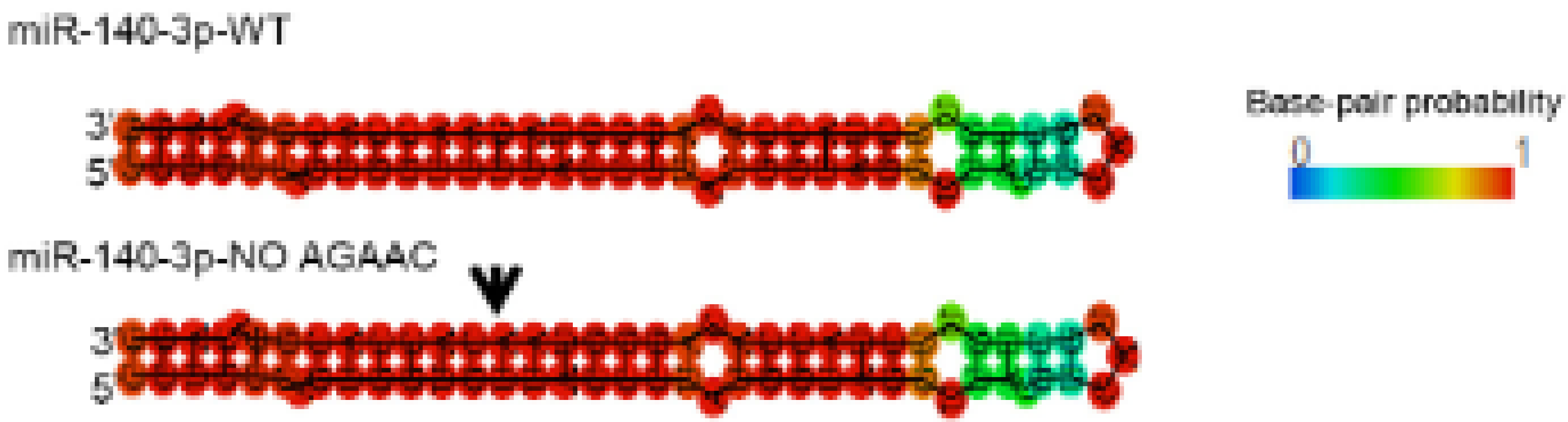
2-What signal induces miRNA fate?

Validation CELL and EXOmotif i*n vivo*

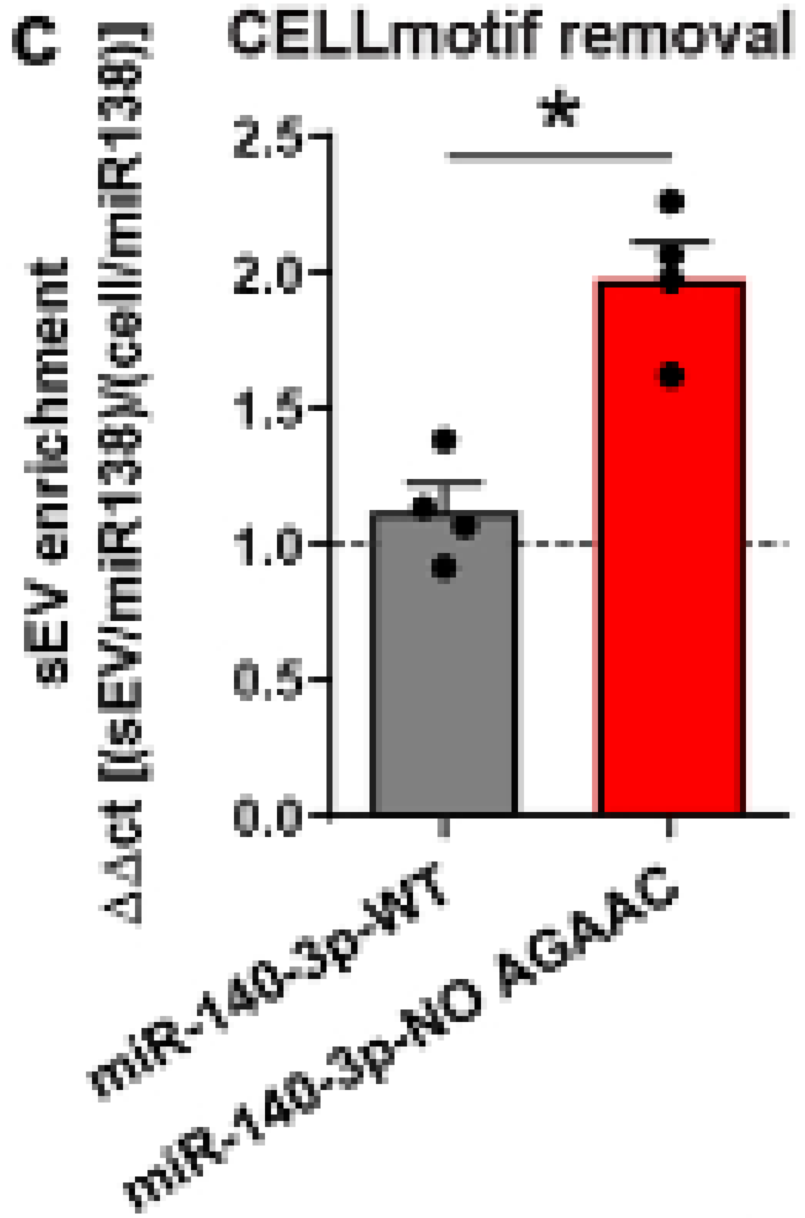
CELLmotif removal



Name	Sequence (5'-3')	Motif
miR-140-3p-WT	UACCACAGGGUAGAACCACGG	Wild-type
miR-140-3p-NO AGAAC	UACCACAGGGUAACACCACGG	~~AGAAC~~



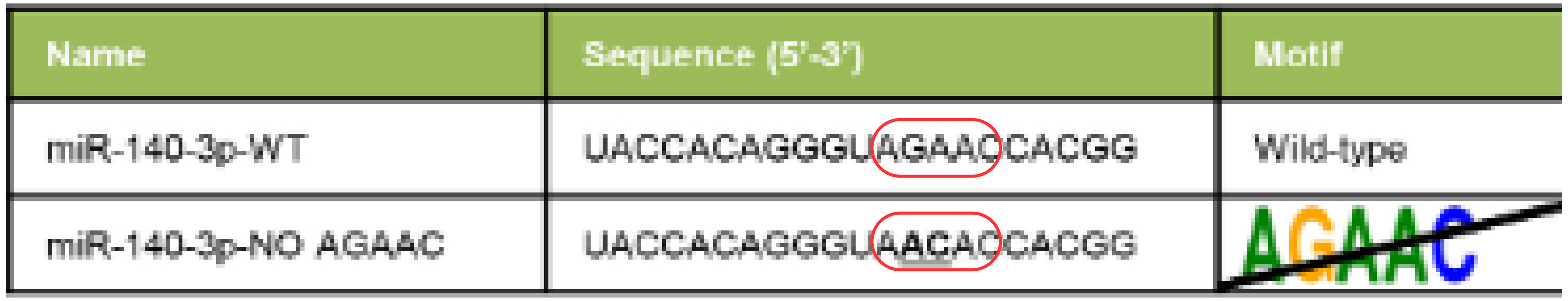
Cell type : Brown adipocytes



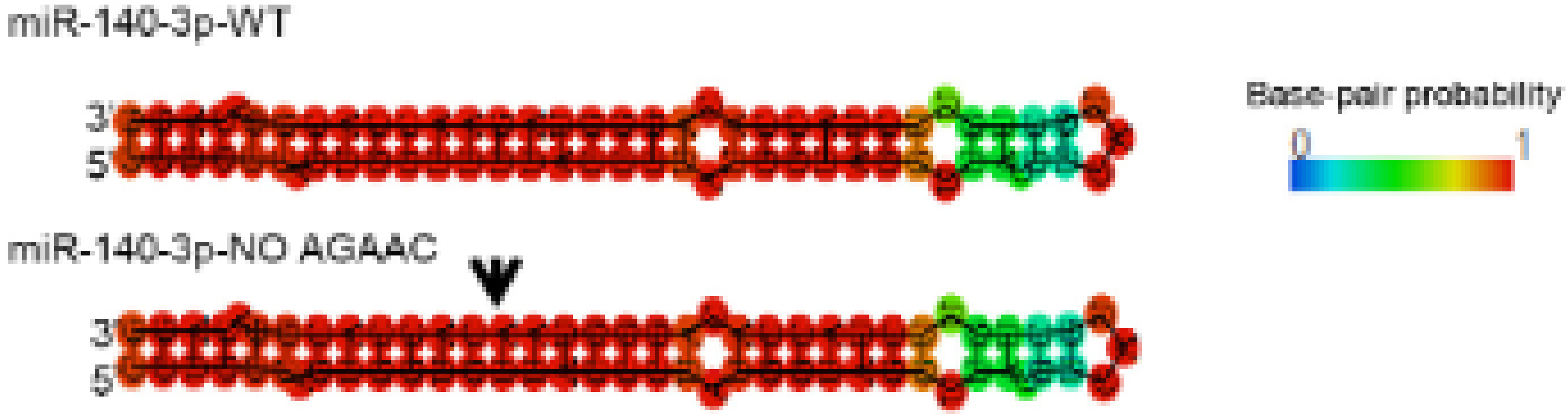
2-What signal induces miRNA fate?

Validation CELL and EXOmotif i*n vivo*

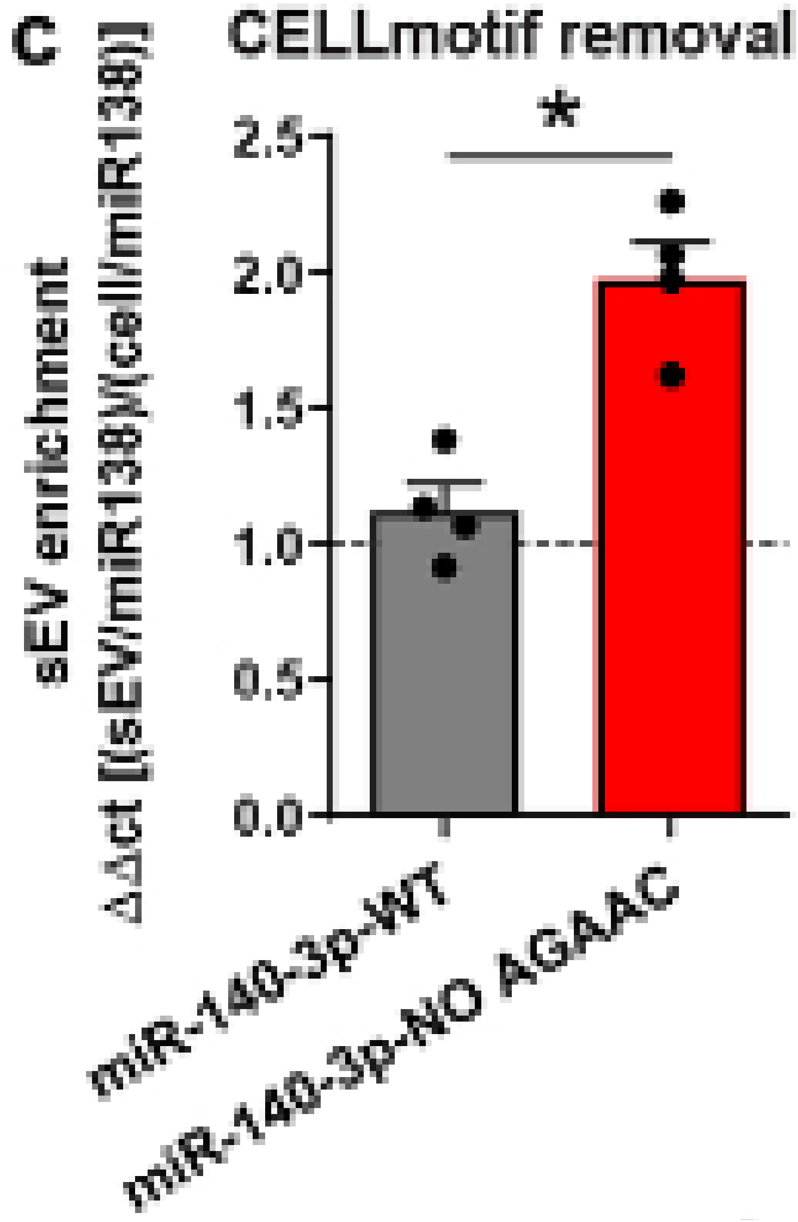
CELLmotif removal



Name	Sequence (5'-3')	Motif
miR-140-3p-WT	UACCACAGGGUAGAACCACGG	Wild-type
miR-140-3p-NO AGAAC	UACCACAGGGUAACACCACGG	~~AGAAC~~



Cell type : Brown adipocytes

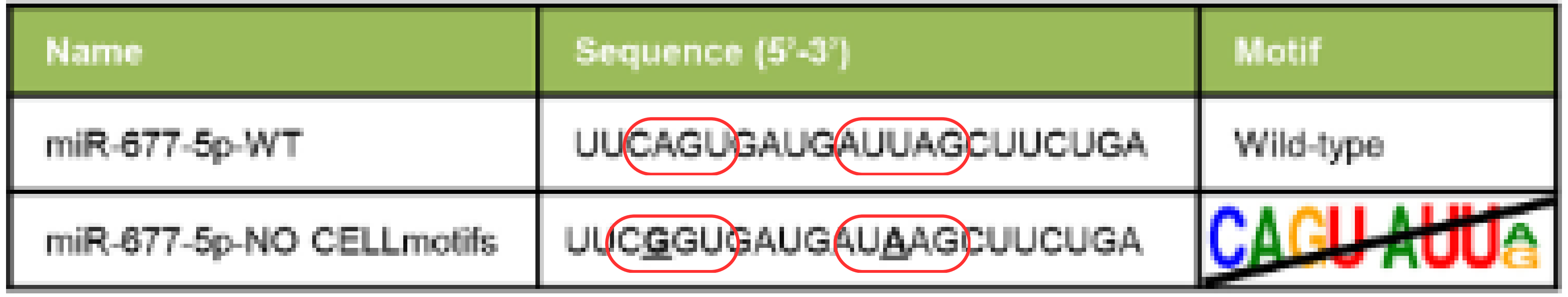


The modification of CELLmotif induces the enrichment of miR-140 into exosomes.

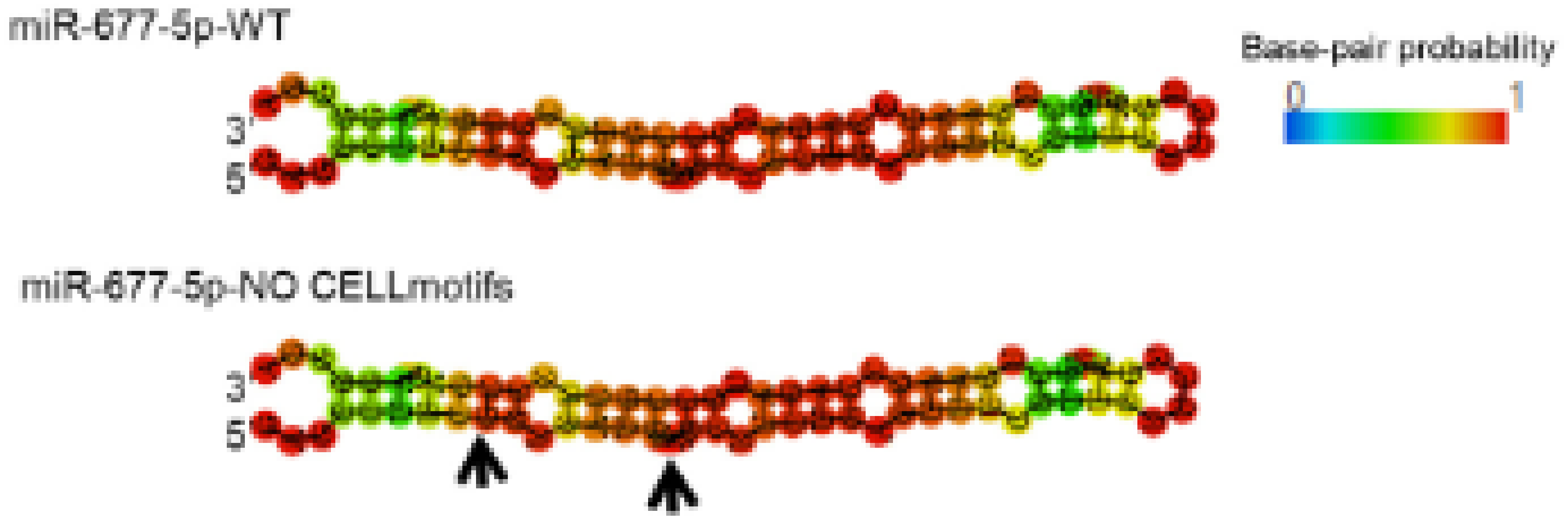
2-What signal induces miRNA fate?

Validation CELL and EXOmotif *in vivo*

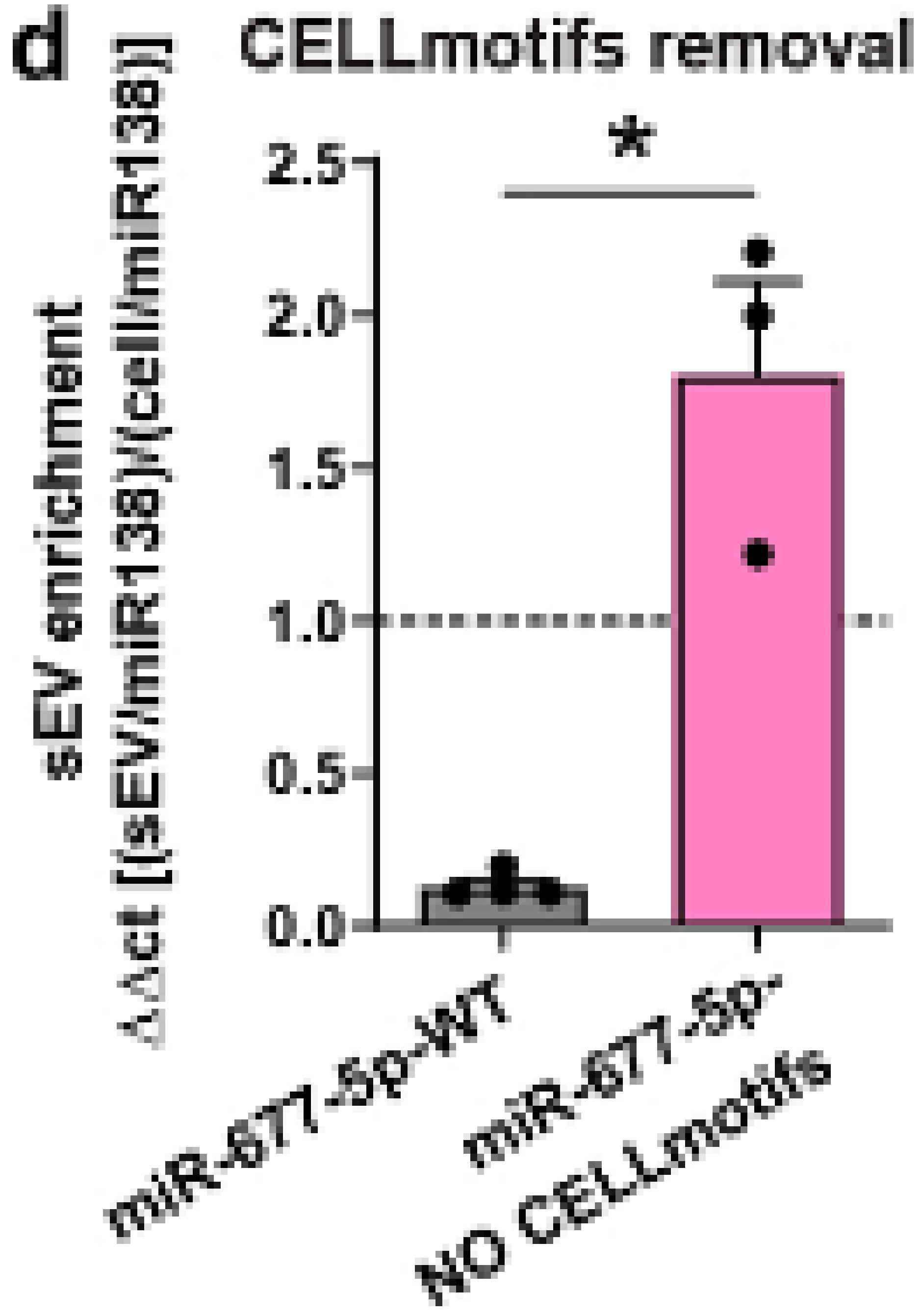
CELLmotif **removal**



Name	Sequence (5’-3’)	Motif
miR-677-5p-WT	UUCAGUGAUGAUUAGCUUCUGA	Wild-type
miR-677-5p-NO CELLmotifs	UUCGGUGAUGAUAAGCUUCUGA	~~CAGU AUUA~~



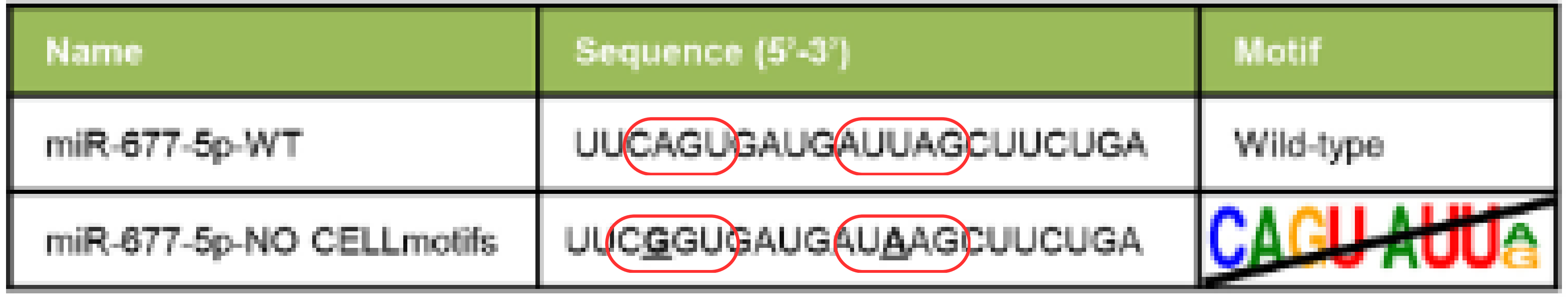
Cell type : hepatocytes



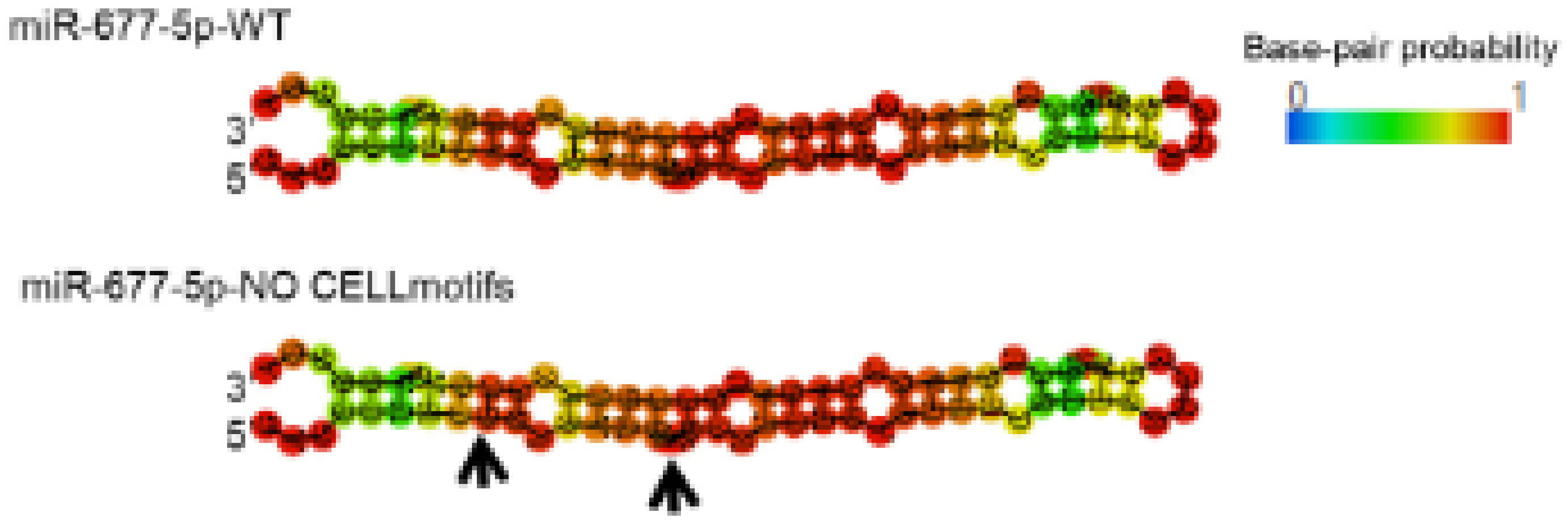
2-What signal induces miRNA fate?

Validation CELL and EXOmotif i*n vivo*

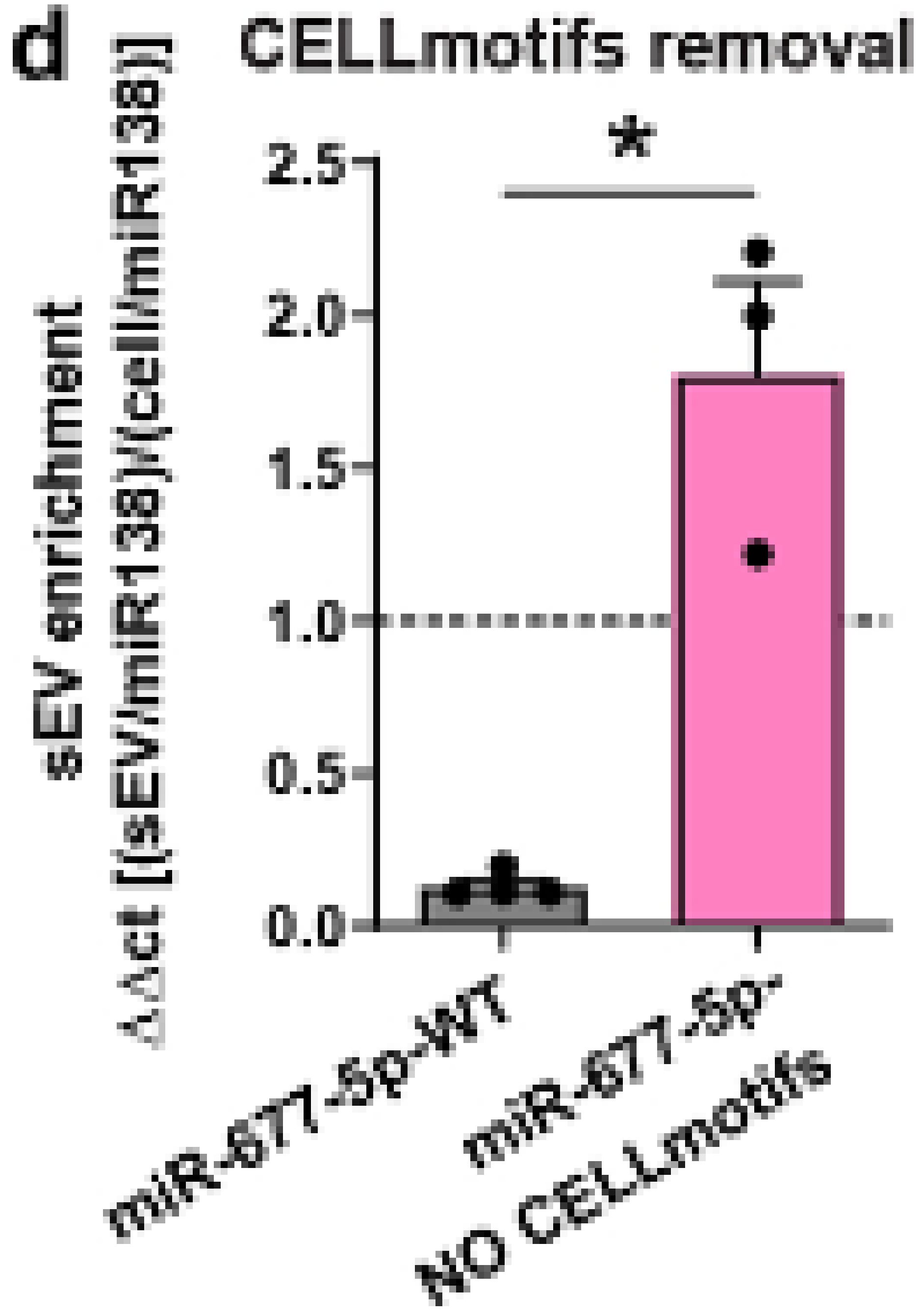
CELLmotif removal



Name	Sequence (5'-3')	Motif
miR-677-5p-WT	UUCAGUGAUGAUUAGCUUCUGA	Wild-type
miR-677-5p-NO CELLmotifs	UUCGGUGAUGAUAAGCUUCUGA	~~CAGU AUUAG~~



Cell type : hepatocytes

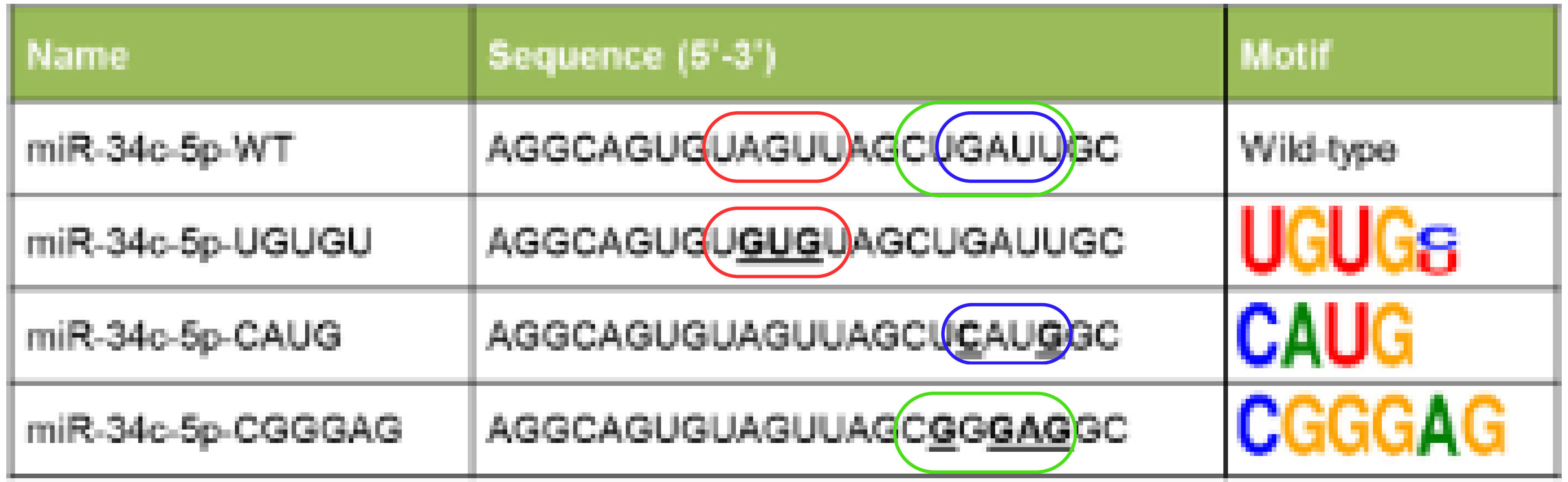


Modifications of several CELLmotifs on the same miRNAs induce the enrichment of miR-677 into exosomes.

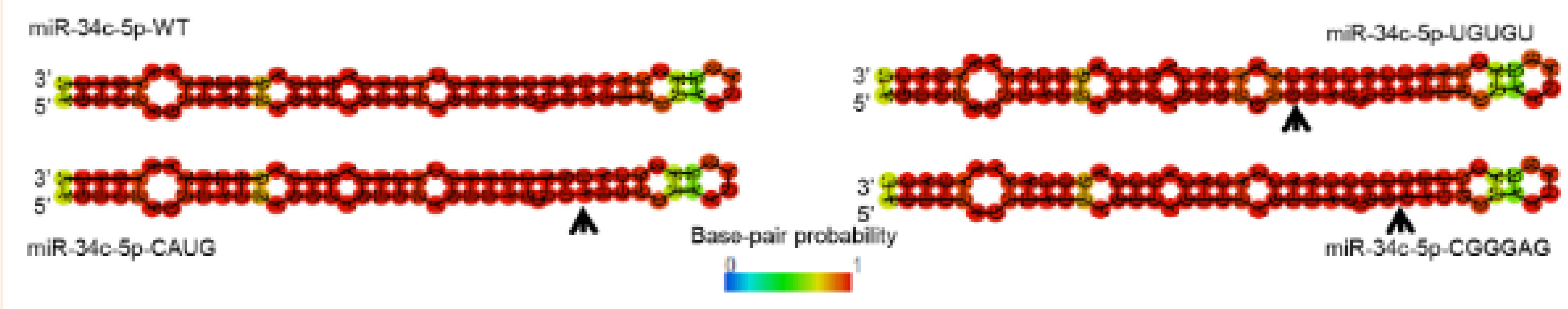
2-What signal induces miRNA fate?

Validation CELL and EXOmotif i*n vivo*

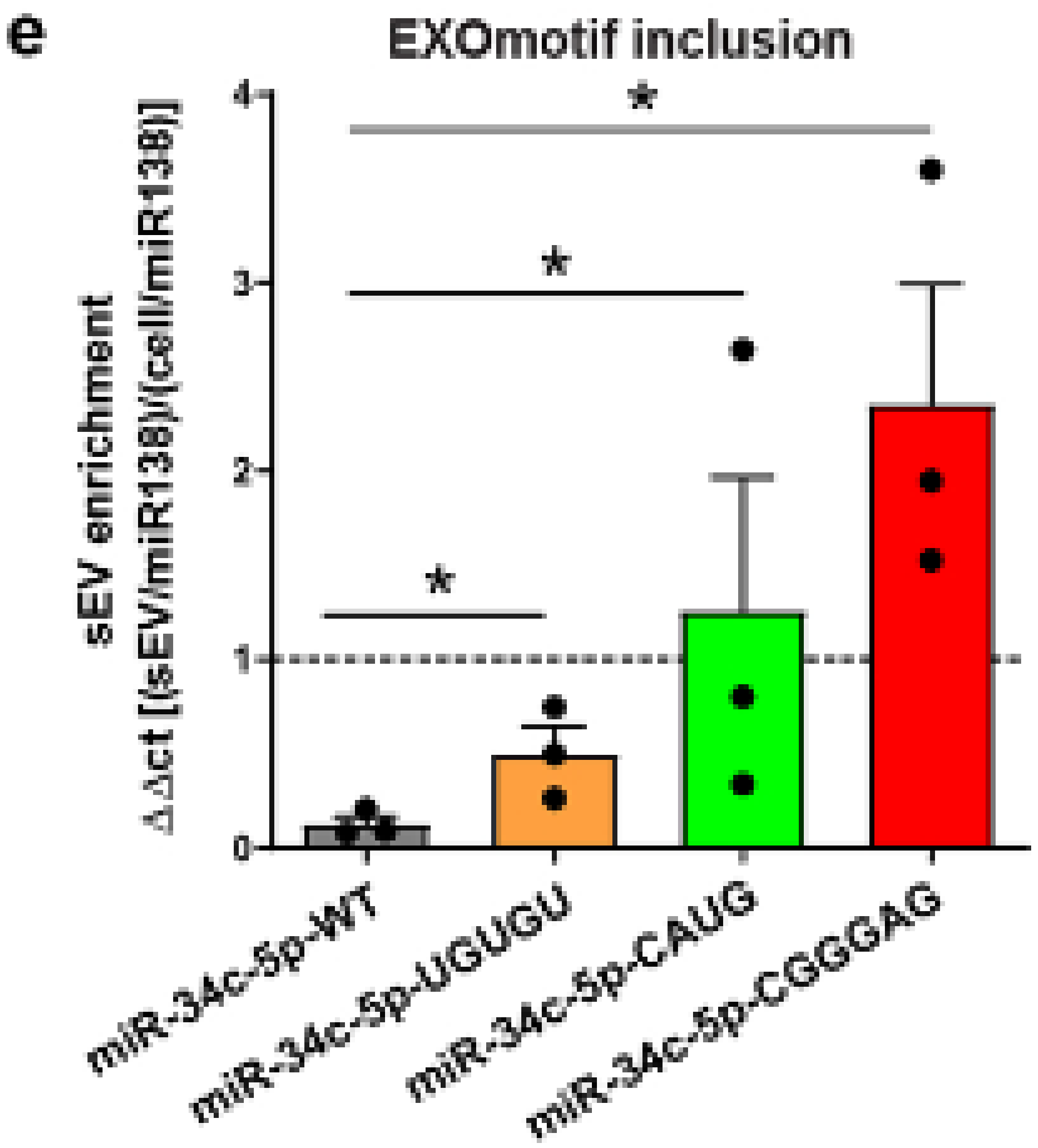
EXOmotif inclusion



Name	Sequence (5'-3')	Motif
miR-34c-5p-WT	AGGCAGUGUAGUUAGCUGAUUGC	Wild-type
miR-34c-5p-UGUGU	AGGCAGUGUGUGUAGCUGAUUGC	UGUGS
miR-34c-5p-CAUG	AGGCAGUGUAGUUAGCUCAUGGC	CAUG
miR-34c-5p-CGGGAG	AGGCAGUGUAGUUAGCGGGAGGC	CGGGAG



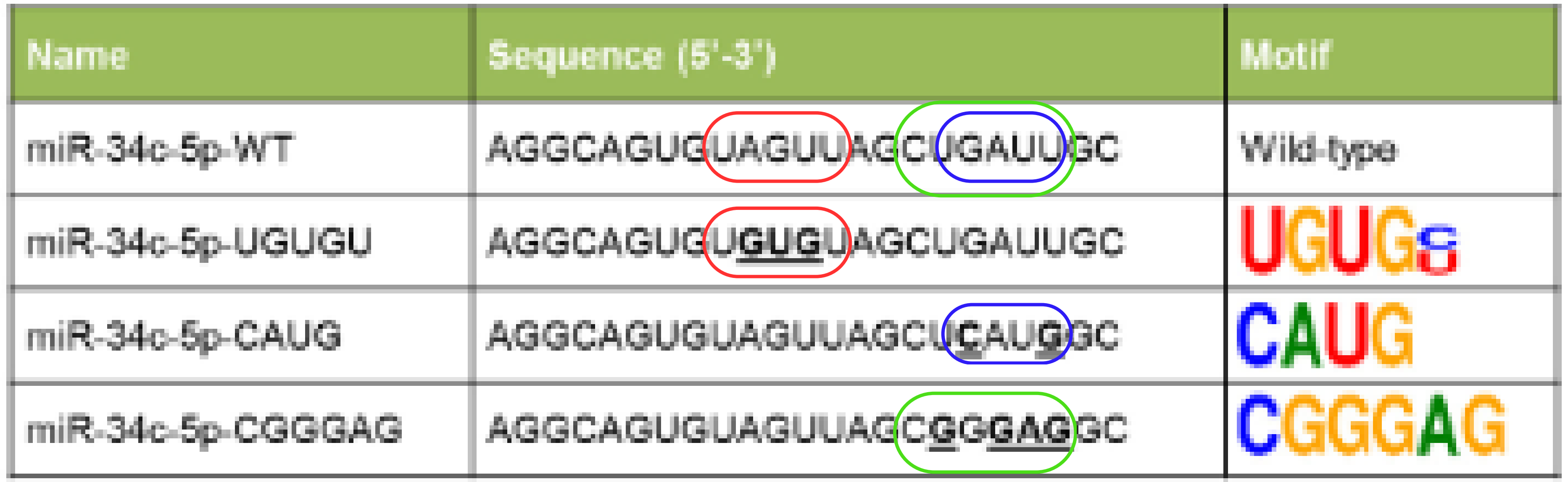
Cell type : Brown fat



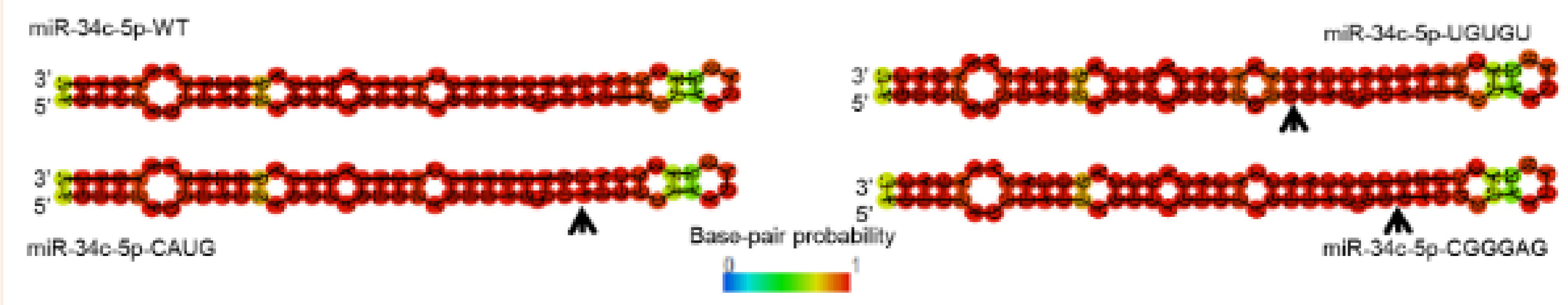
2-What signal induces miRNA fate?

Validation CELL and EXOmotif *in vivo*

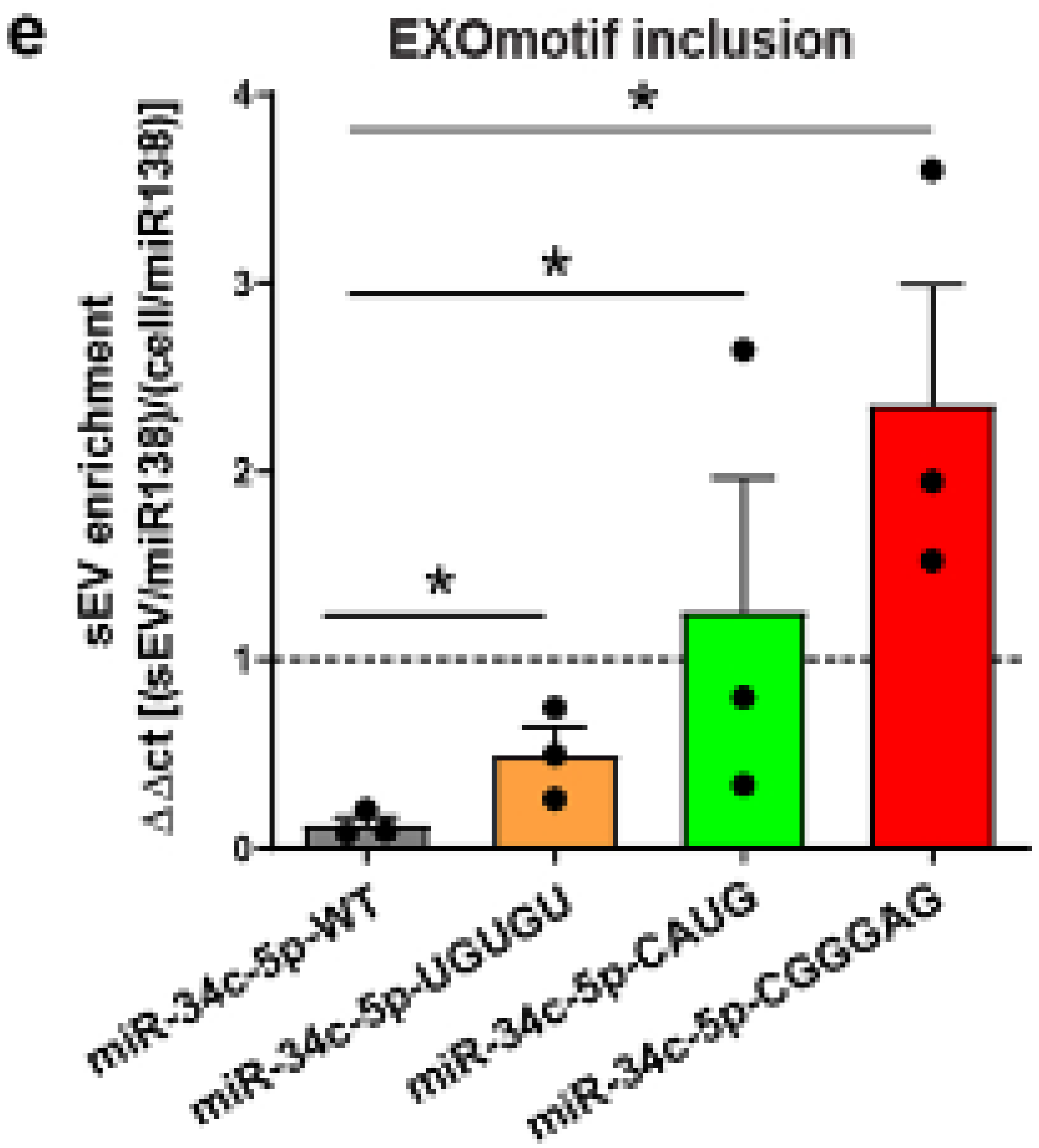
EXOmotif inclusion



Name	Sequence (5'-3')	Motif
miR-34c-5p-WT	AGGCAGUGUAGUUAGCUGAUUGC	Wild-type
miR-34c-5p-UGUGU	AGGCAGUGUGUGUAGCUGAUUGC	UGUGG
miR-34c-5p-CAUG	AGGCAGUGUAGUUAGCUCAUGGC	CAUG
miR-34c-5p-CGGGAG	AGGCAGUGUAGUUAGCGGGAGGC	CGGGAG



Type cell : Brown fat



→ ***Inclusion of different EXOmotifs induce the enrichment of miR-34c into exosomes.***

→ ***The more EXOmotif is enriched in G-C contents, the more miRNA is excreted.***

Take home messages:

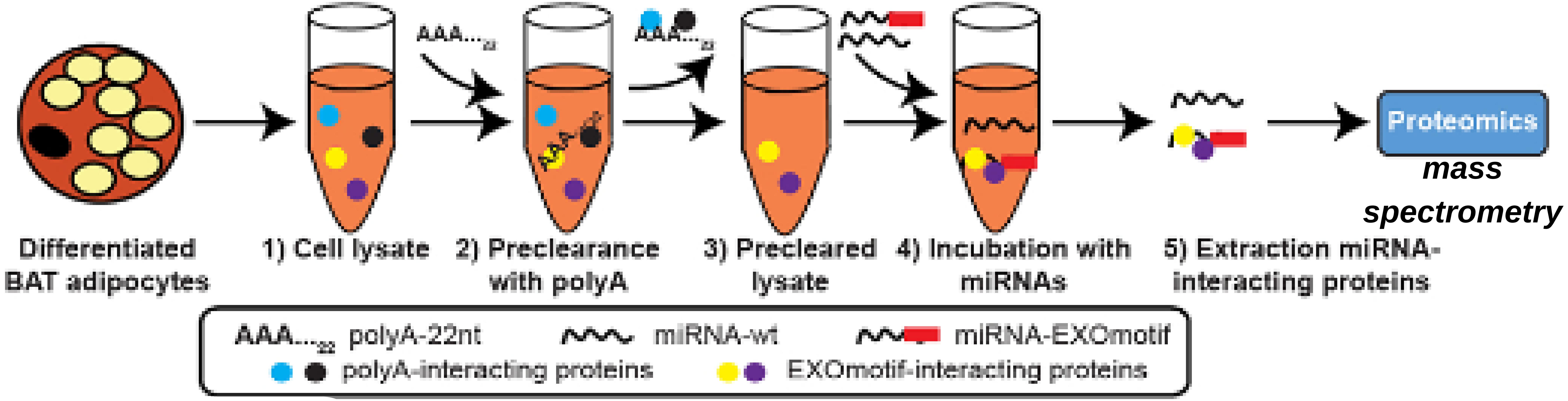
- **Inclusion or removal of EXOmotif changes miRNA addressing**

- **Inclusion or removal of CELLmotif changes miRNA addressing**

→ **Validation *in vivo* of motifs found *in silico***

- **There are stronger and weaker motifs depending on G-C contents**

3-Do these motifs interact with specific miRNA binding proteins ?

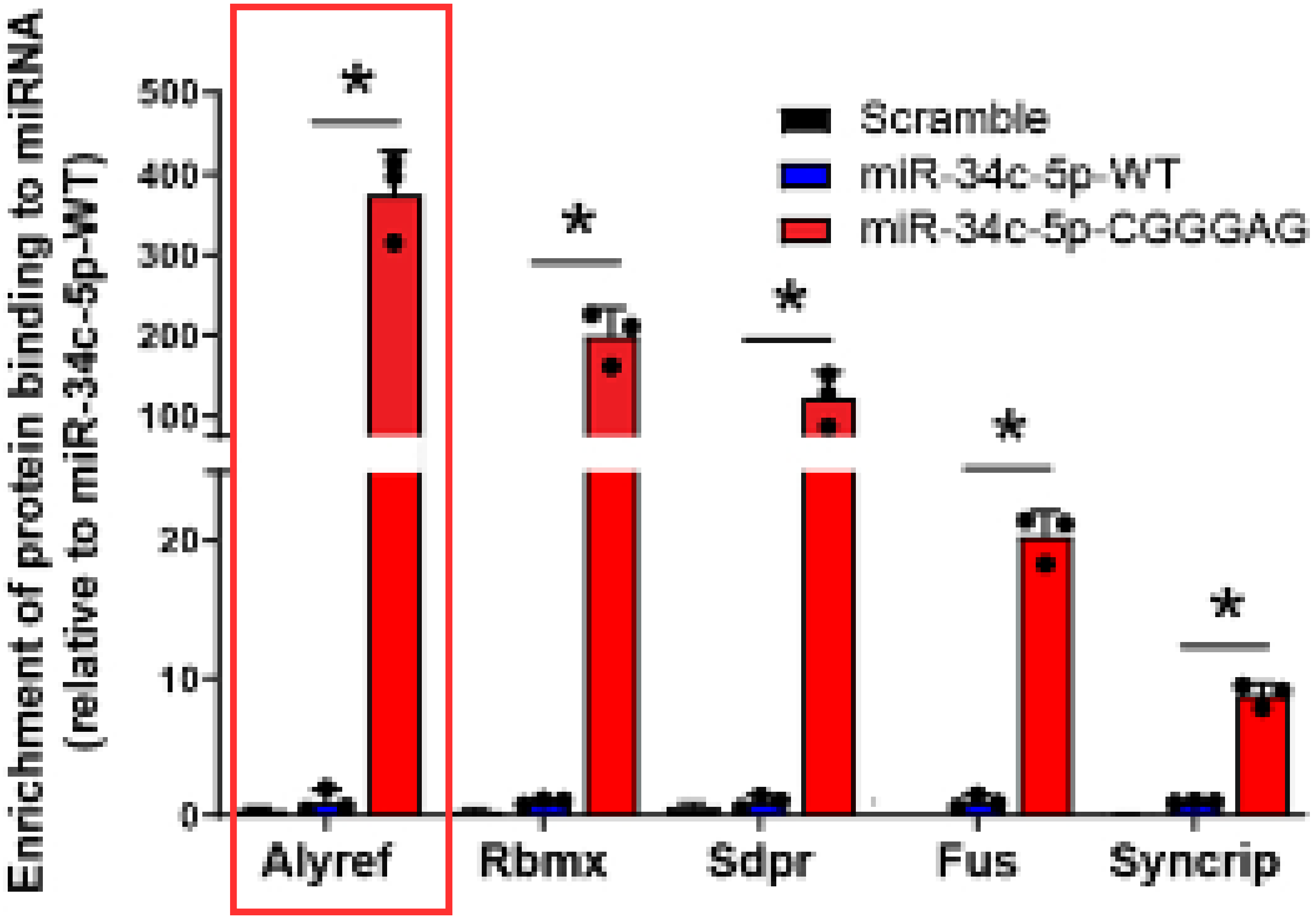


2) Removing all proteins that could interact non specifically to miRNAs

4) Incubation with biotinylated miR-34c OR miR-26a WT or with an EXOmotif

67 proteins found → focus on those proteins which showed at least 8-fold enrichment (EXOmotif compared WT)

3-Do these motifs interact with specific miRNA binding proteins ?

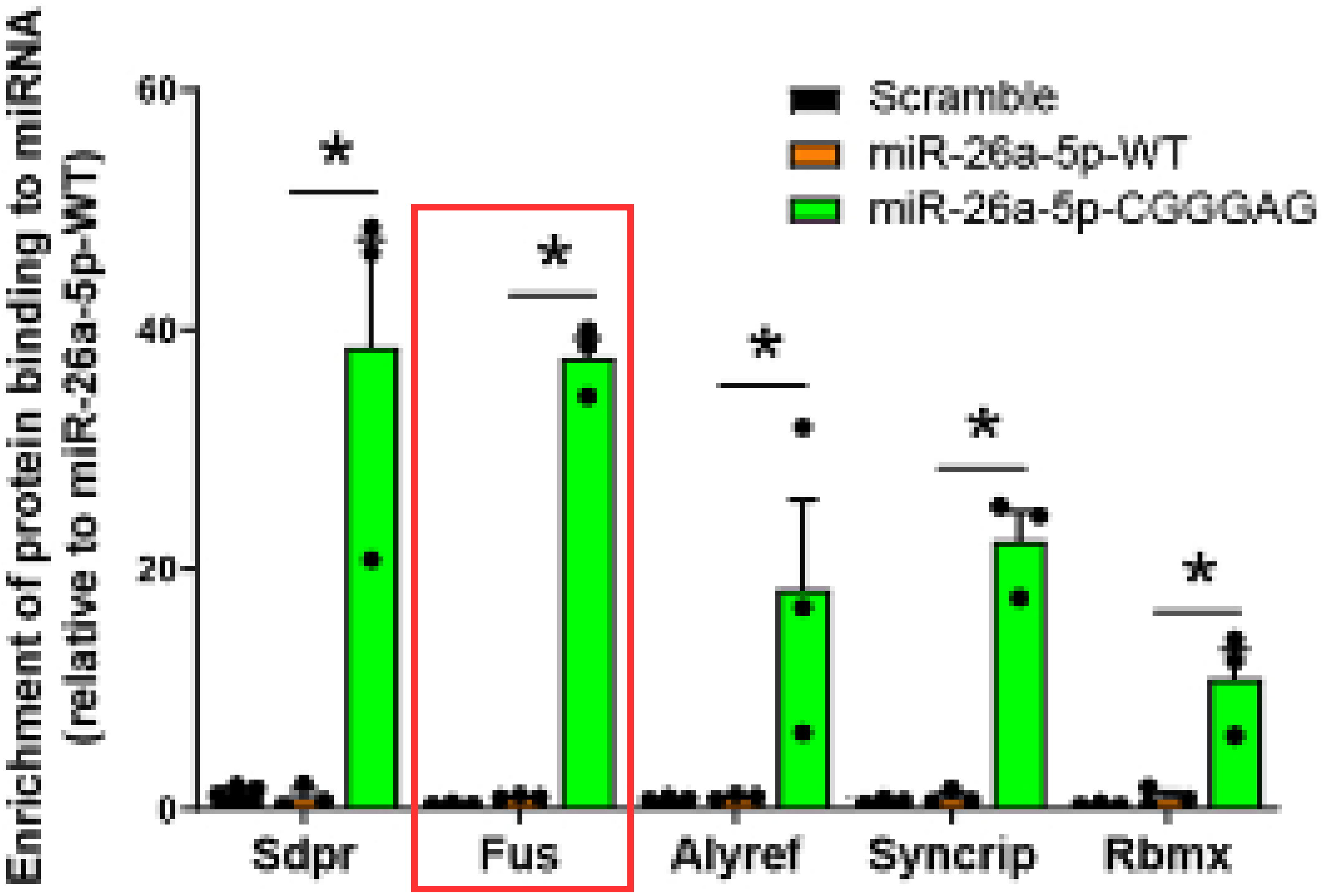


Who‘s Alyref ?

- Molecular chaperone
- Nuclear export of mRNAs
- **Has an RNA recognition motif (RRM)**

Inclusion of an EXOmotif to a preferentially cellular miR-34c significantly increases its interaction with various proteins

3-Do these motifs interact with specific miRNA binding proteins ?



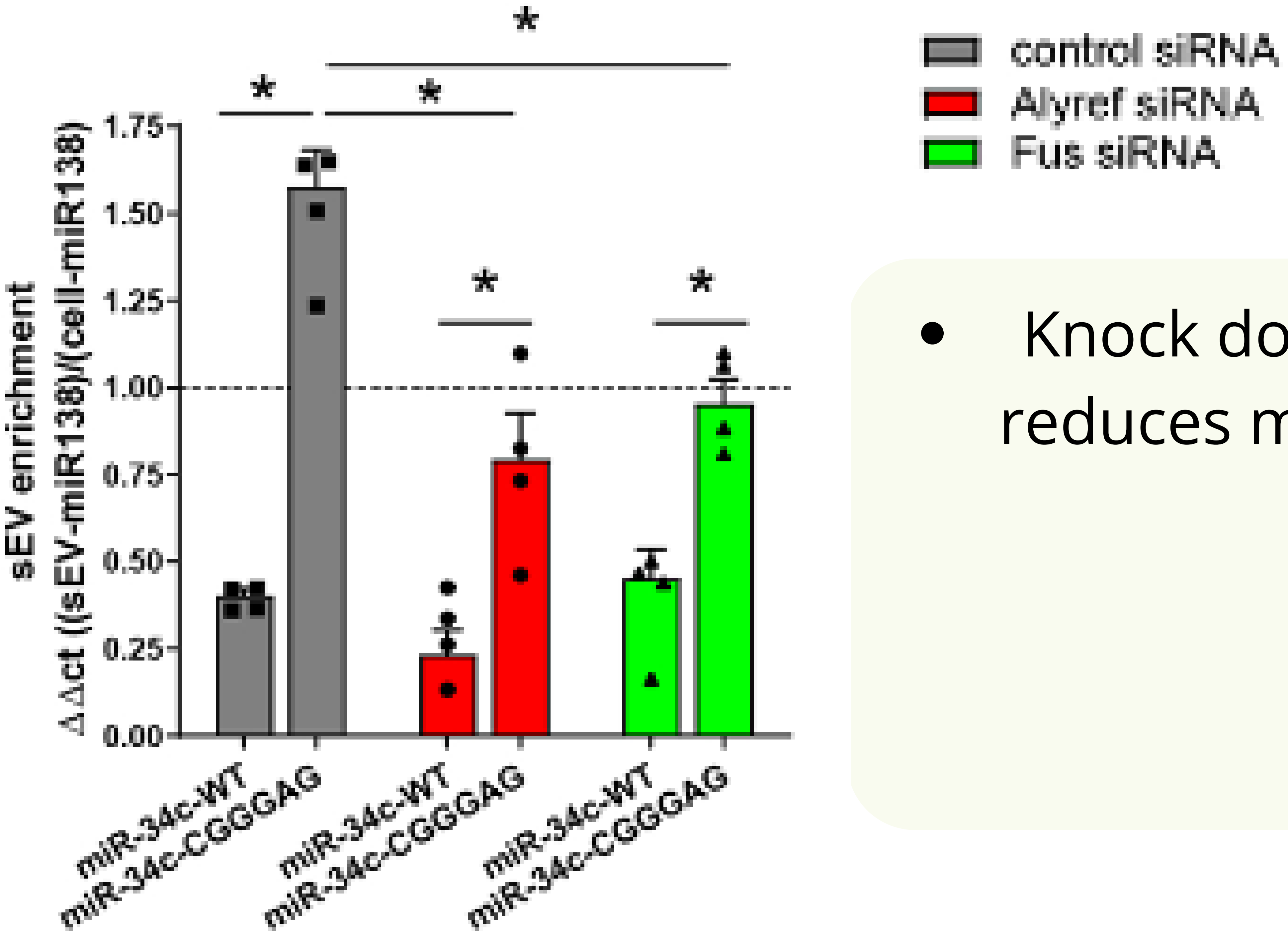
Who's Fus ?

- RNA/DNA binding protein
- Has a role on RNA transports
- **Interacts with AGO2**

→ ***Inclusion of an EXOmotif to a preferentially cellular miR-26a significantly increases its interaction with various proteins***

3-Do these motifs interact with specific miRNA binding proteins ?

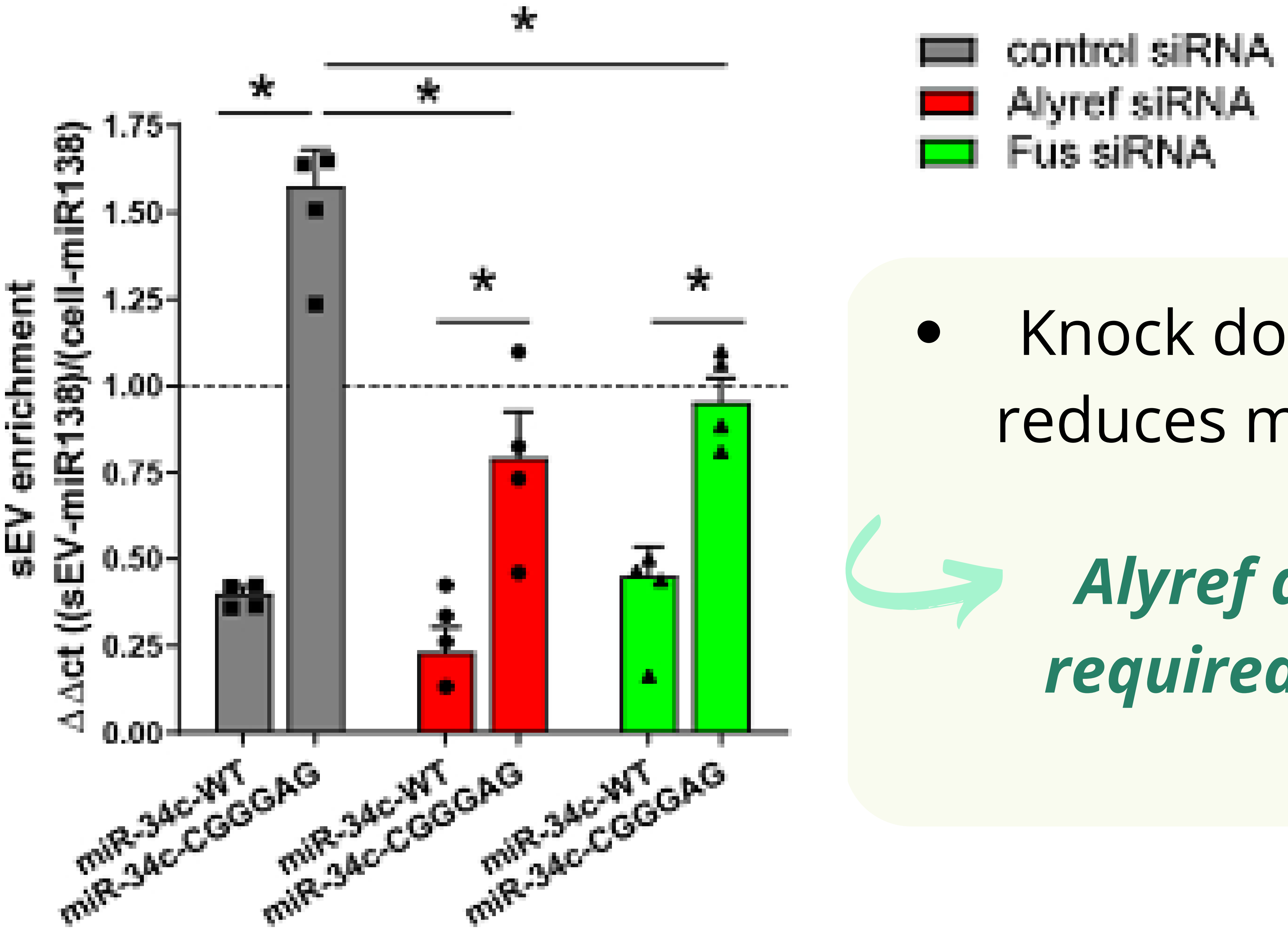
Validation of the preliminary observations



- Knock down of Fus or Alyref significantly reduces miR-34c enrichment in exosomes

3-Do these motifs interact with specific miRNA binding proteins ?

Validation of the preliminary observations

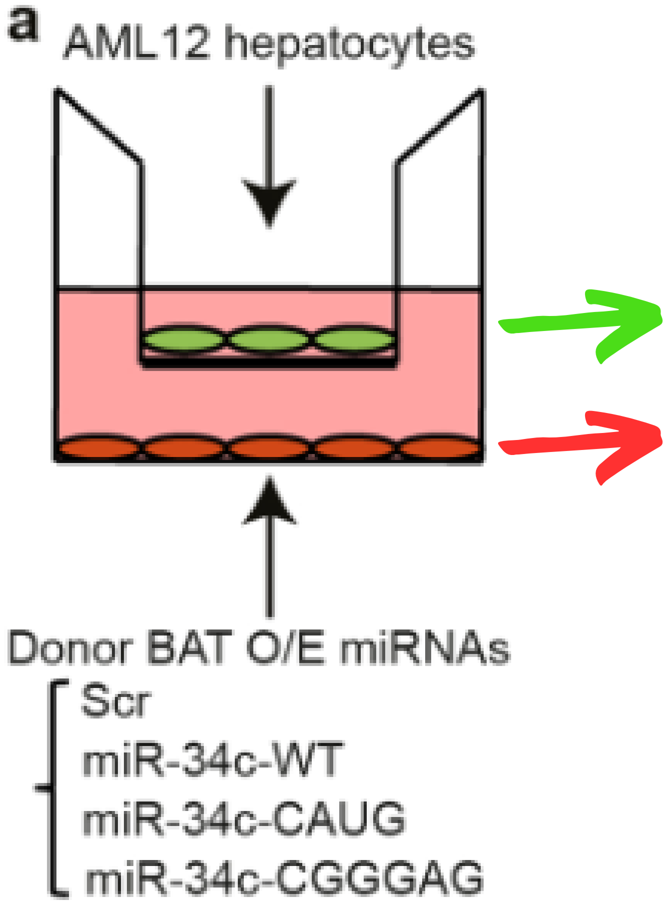


- Knock down of Fus or Alyref significantly reduces miR-34c enrichment in exosomes

Alyref and Fus are at least two proteins required for miRNA motif recognition and export into sEV.

4- Can EXOmotif be used to modify gene expression in neighboring cells ?

The transwell experiment :



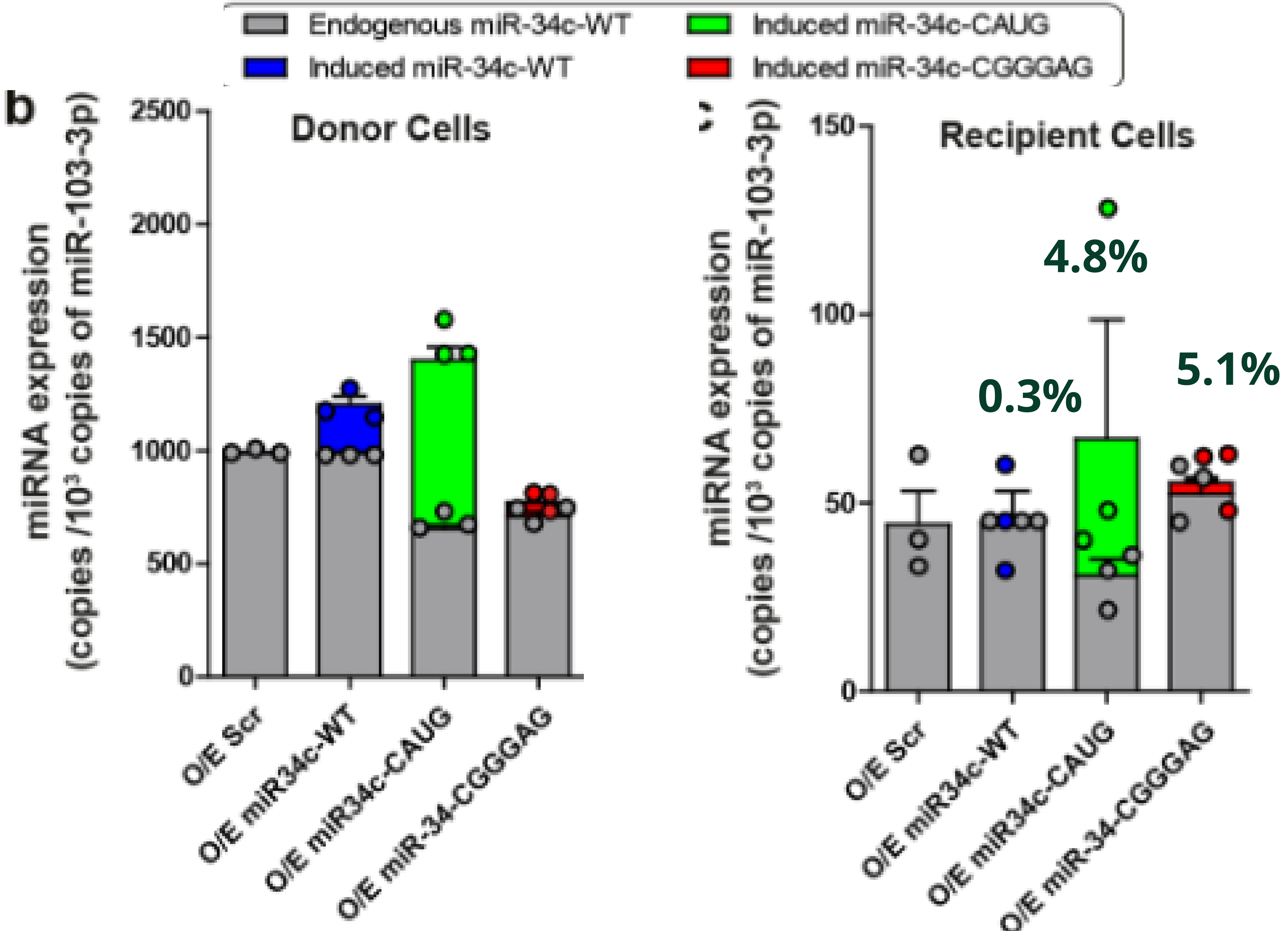
RNA isolation

dropletPCR (ddPCR)

Advantages:

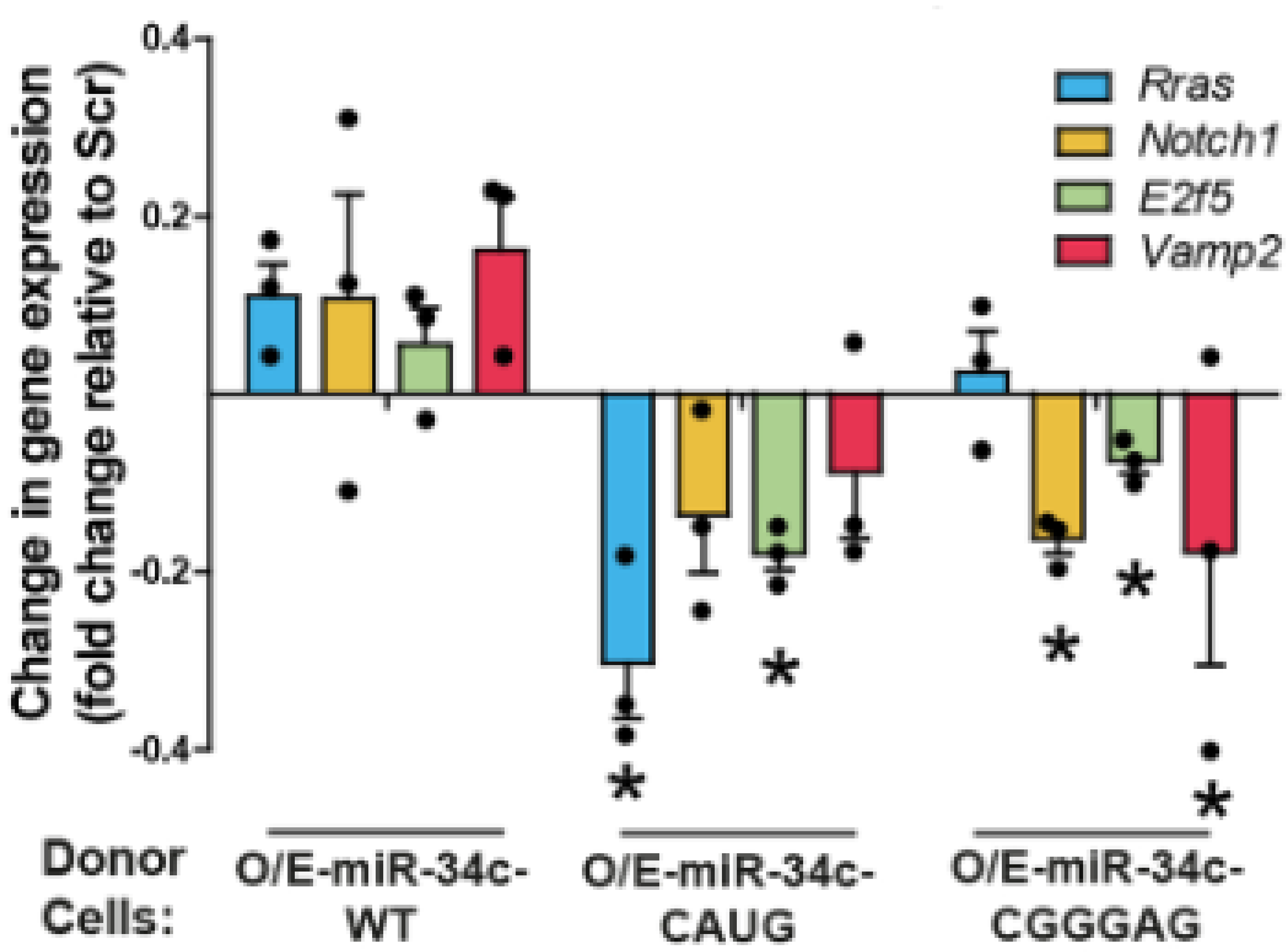
it detects a very small number of molecules, making it much more sensitive than conventional qPCR.

4- Can EXOmotif be used to modify gene expression in neighboring cells ?



Overexpression of miR-34c (WT or modified) increases this miRNA in donor cell and in recipient cells.

4- Can EXOmotif be used to modify gene expression in neighboring cells ?



→ ***miRNAs from donor cell can modify gene expression into recipient cells.***

Take home messages:

- **Overexpression of a miRNA into a cell induces an increase of this miRNA into neighboring cells .**

- **miRNAs from donor cell can modify the expression of target genes into neighboring cells.**

5- Involvement of miRNAs in the disease and therapeutic perspectives

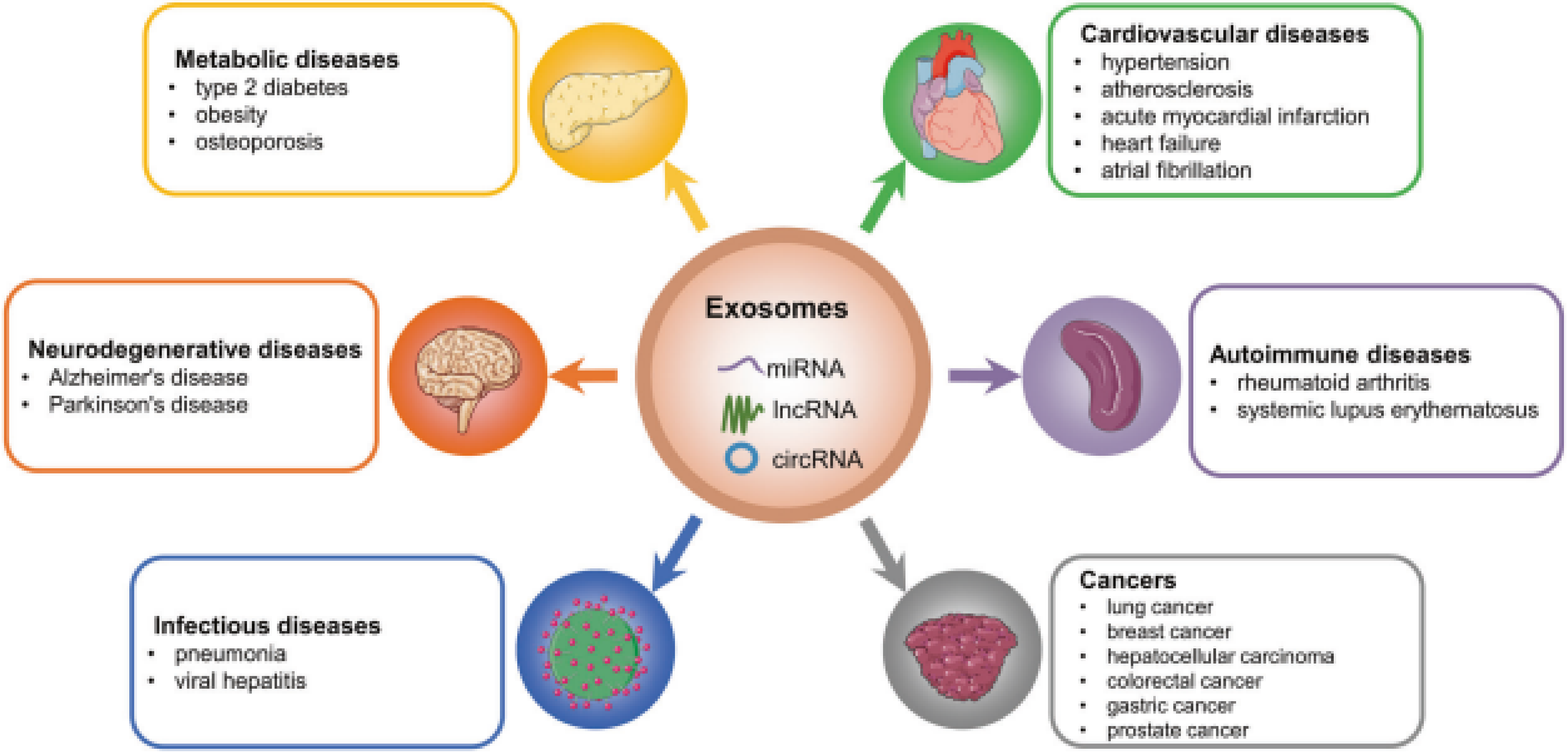
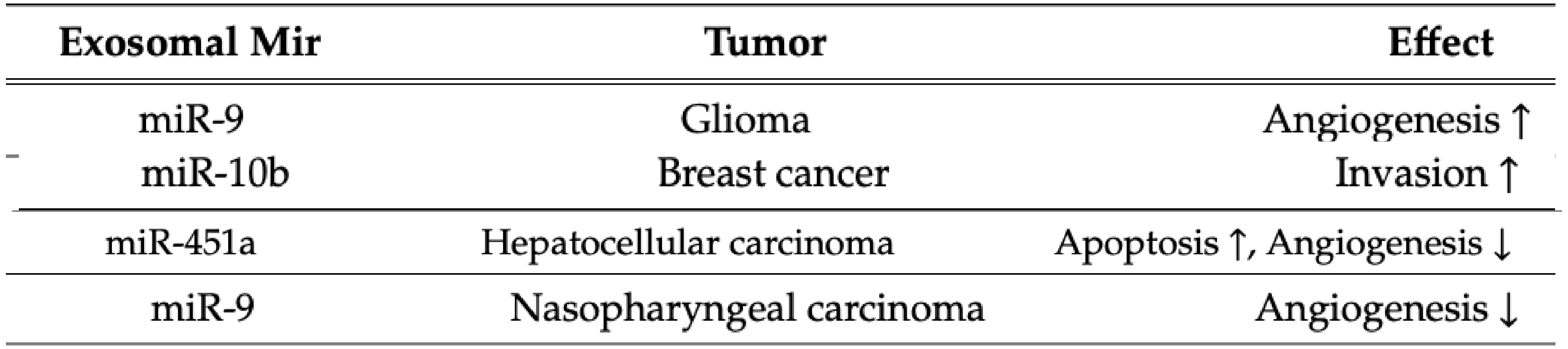


Fig 8 : The roles of exosomal ncRNAs in human diseases. The figure showed examples of human diseases where exosomal ncRNAs exert pivotal function [7]

5- Involvement of miRNAs in the disease and therapeutic perspectives



Exosomal Mir	Tumor	Effect
miR-9	Glioma	Angiogenesis ↑
miR-10b	Breast cancer	Invasion ↑
miR-451a	Hepatocellular carcinoma	Apoptosis ↑, Angiogenesis ↓
miR-9	Nasopharyngeal carcinoma	Angiogenesis ↓

Tab. 1. Examples of miRNA involved in cancer [8] :

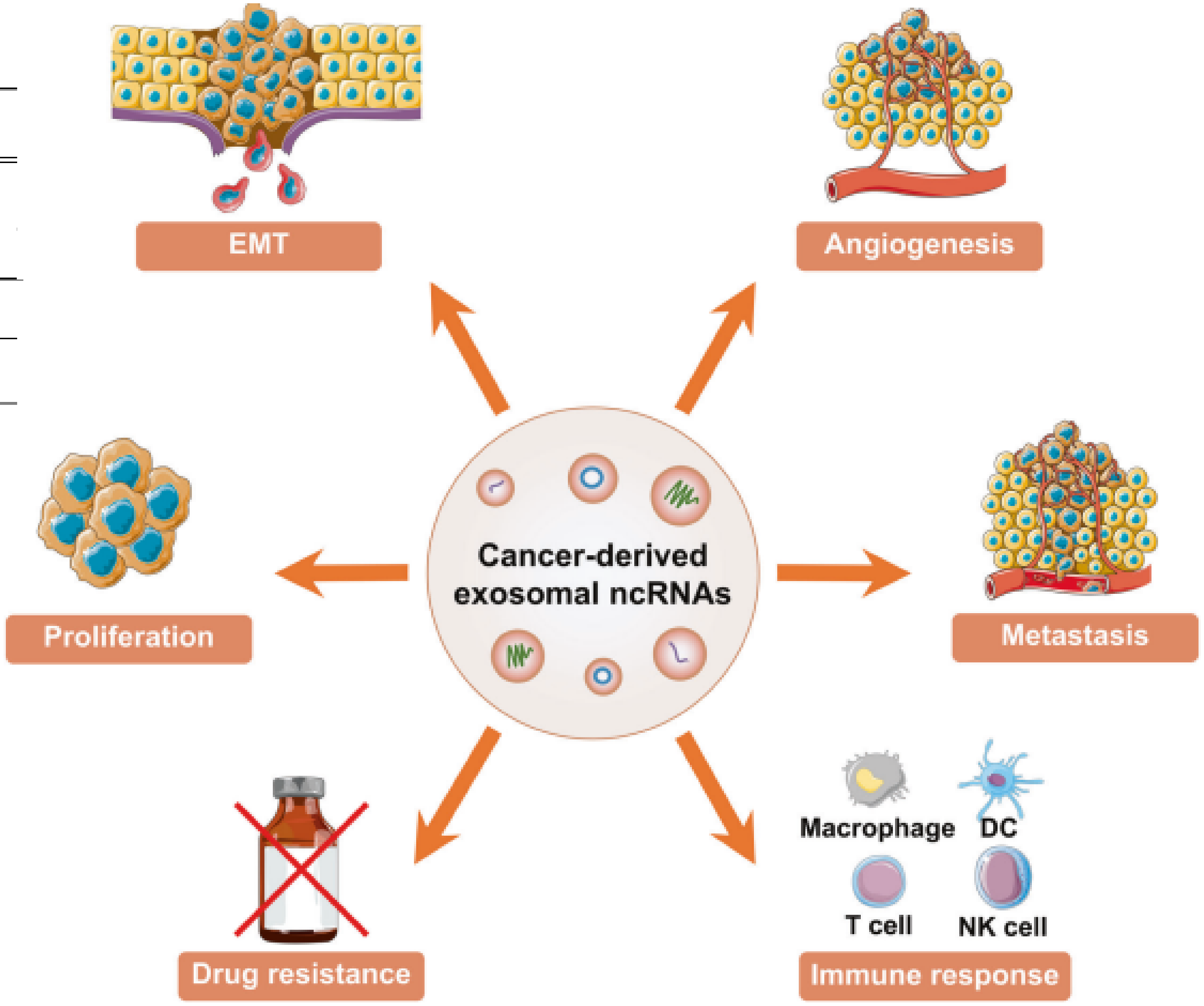


Fig 9 : The roles of exosomal ncRNAs in cancer [7].

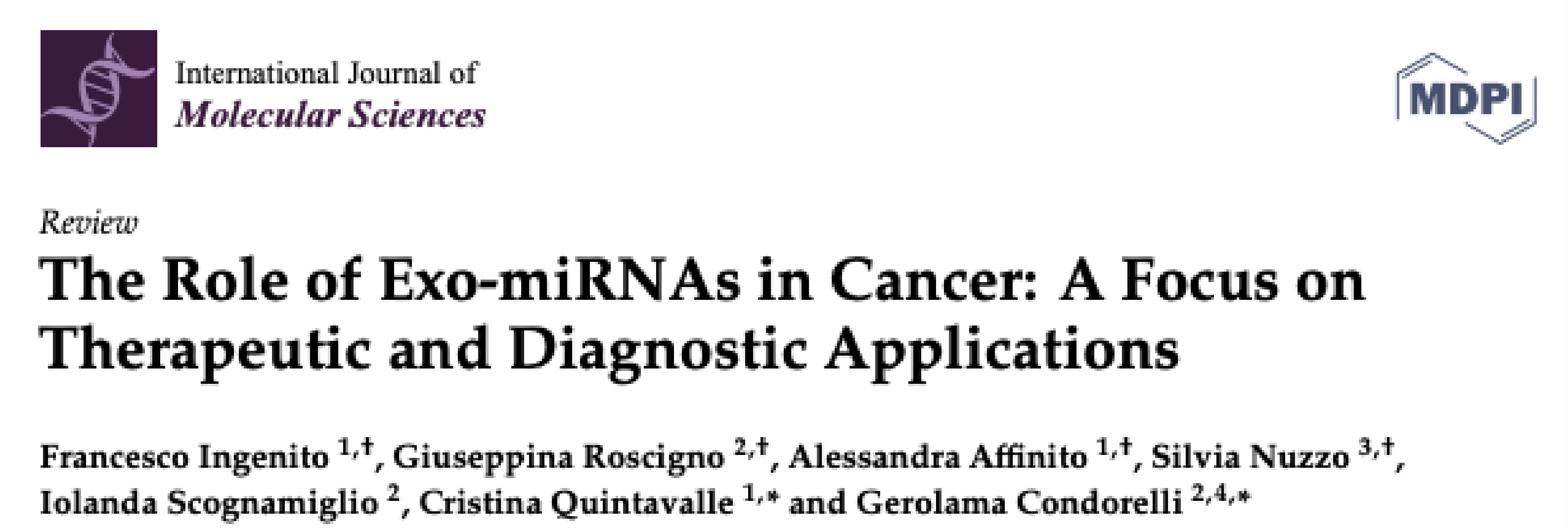
5- Involvement of miRNAs in the disease and therapeutic perspectives

- **Exosomal miRNAs as biomarkers…**

Exosomes can reflect tissue or cell state.

Examples : miR-21, miR-223, and miR-23a, can be used as the diagnostic biomarker of colorectal cancer

… but also as therapeutic weapons



International Journal of *Molecular Sciences*

MDPI

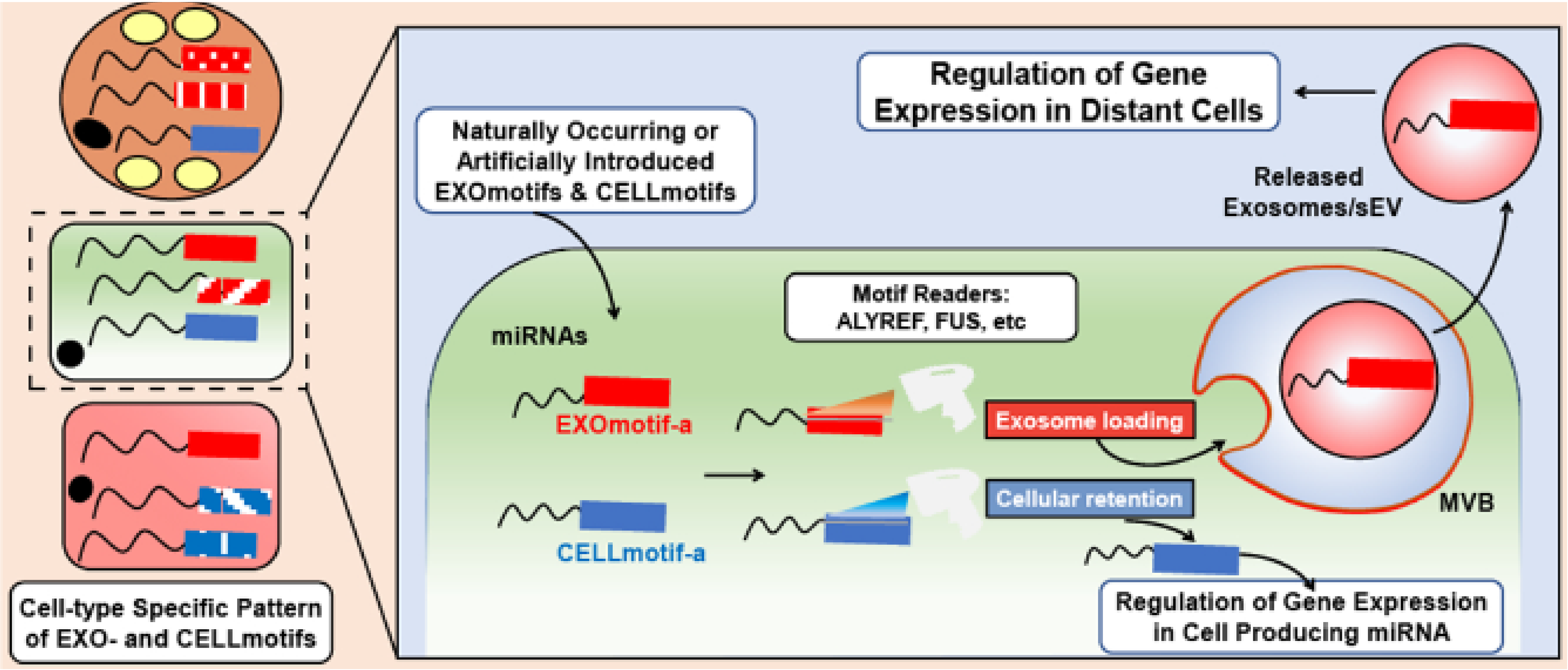
Review

The Role of Exo-miRNAs in Cancer: A Focus on Therapeutic and Diagnostic Applications

Francesco Ingenito [1,†], Giuseppina Roscigno [2,†], Alessandra Affinito [1,†], Silvia Nuzzo [3,†], Iolanda Scognamiglio [2], Cristina Quintavalle [1,*] and Gerolama Condorelli [2,4,*]

"Since exosomes are natural delivery systems between cells, they can be appropriately modified to carry therapeutic miRNAs to specific recipient cells."

Conclusion


Regulation of Gene Expression in Distant Cells
Naturally Occurring or Artificially Introduced EXOmotifs & CELLmotifs
Released Exosomes/sEV
Motif Readers: ALYREF, FUS, etc
miRNAs
EXOmotif-a
Exosome loading
Cellular retention
MVB
CELLmotif-a
Regulation of Gene Expression in Cell Producing miRNA
Cell-type Specific Pattern of EXO- and CELLmotifs

Thank you for your attention

Questions ?

References :

[1] **Non-Coding RNAs: Origin, Biogenesis, Mode of Action and Their Roles in Abiotic Stress**. Waititu, J.K *et al* . Mol. Sci. 2020, 21, 8401

[2] **Strategies to Modulate MicroRNA Functions for the Treatment of Cancer or Organ Injury**.
Tae Jin Lee *et al*. ASSOCIATE EDITOR.Pharmacological Reviews July 2020

[3] **Role of microRNAs in translation regulation and cancer**. Oliveto S *et al* World J Biol Chem. 2017 Feb 26;8

[4] **Exosome Therapeutic Potential in Corneal Diseases.** Tiwari A *et al*. Current Trends and Understanding of . Front Pharmacol. 2021 Aug 19;12:684712

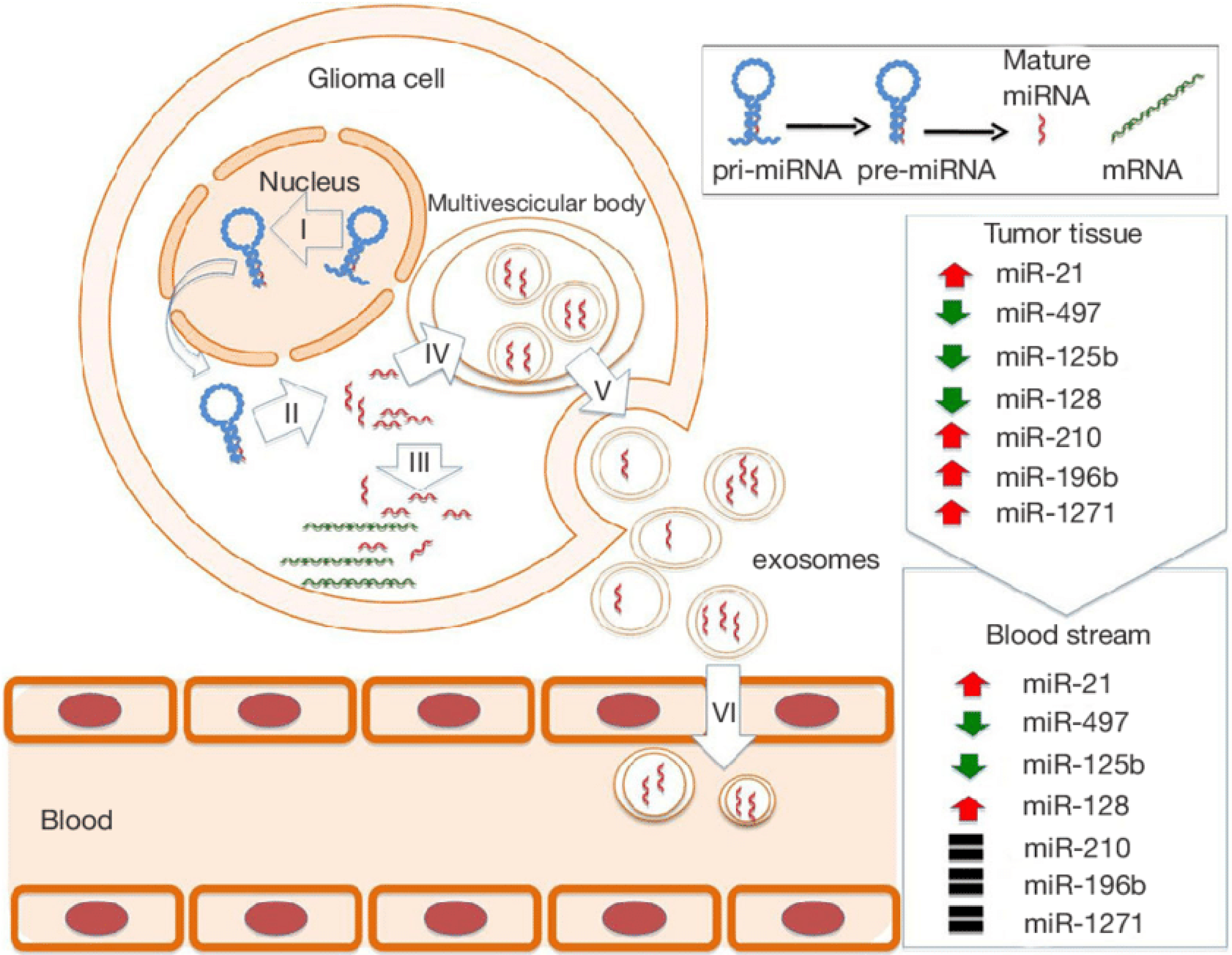
[5] ***Exosome Theranostics: Biology and Translational Medicine*** *[J].He C, Zheng S, Luo Y et al (2018), Theranostics 8(1):237–255*

[6] **Adipose tissue in communication: within and without**. Yu-Hua Tseng *Nat Rev Endocrinol. 2023 Feb;19(2):70-71*

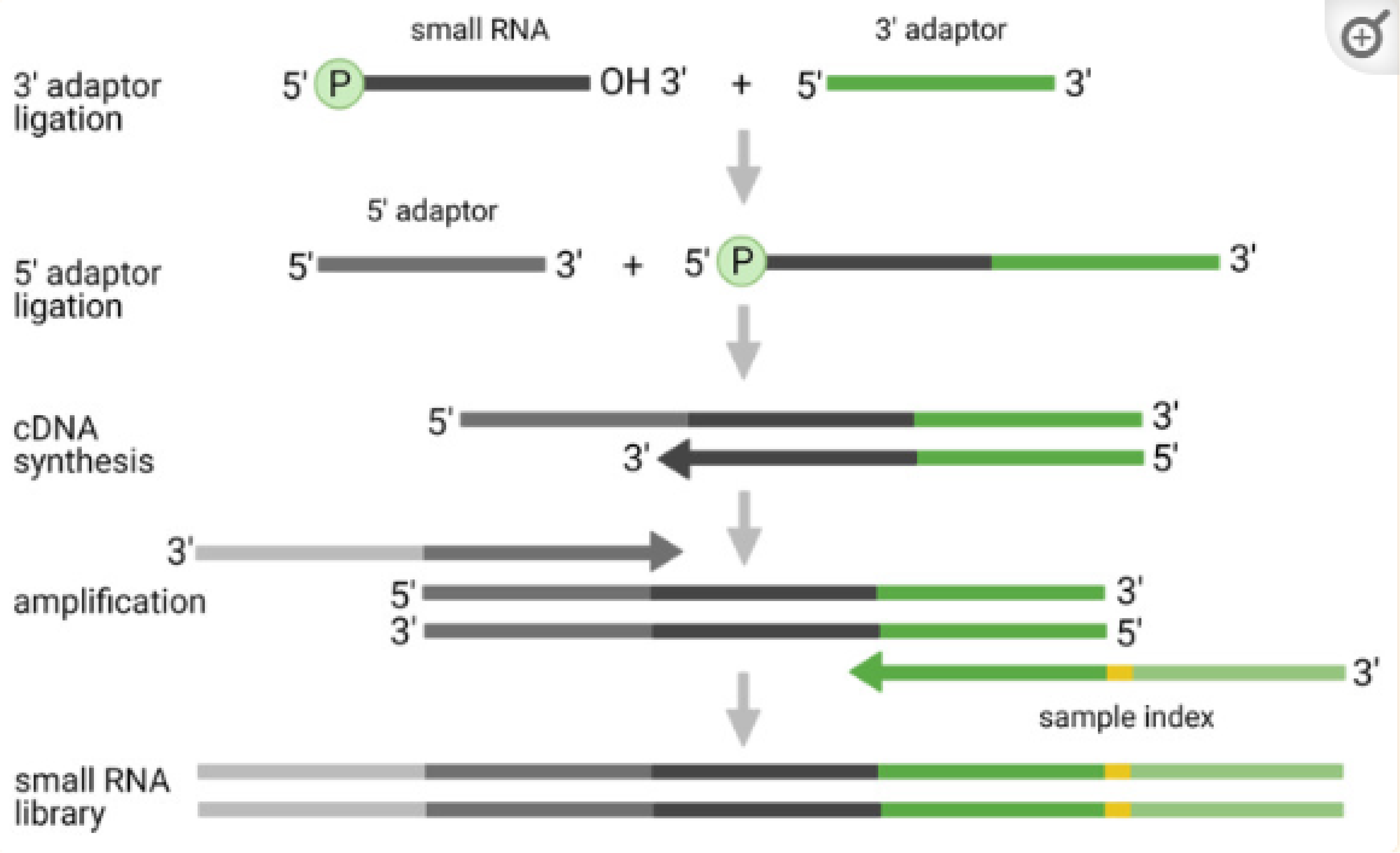
[7] **Roles and mechanisms of exosomal non-coding RNAs in human health and diseases**. *Li C et al . Signal Transduct Target Ther. 2021 Nov 10;6(1):383.*

[8] **The Role of Exo-miRNAs in Cancer: A Focus on Therapeutic and Diagnostic Applications**.Ingenito F et al . Int J Mol Sci. 2019 Sep 21;20(19)

complementary informations

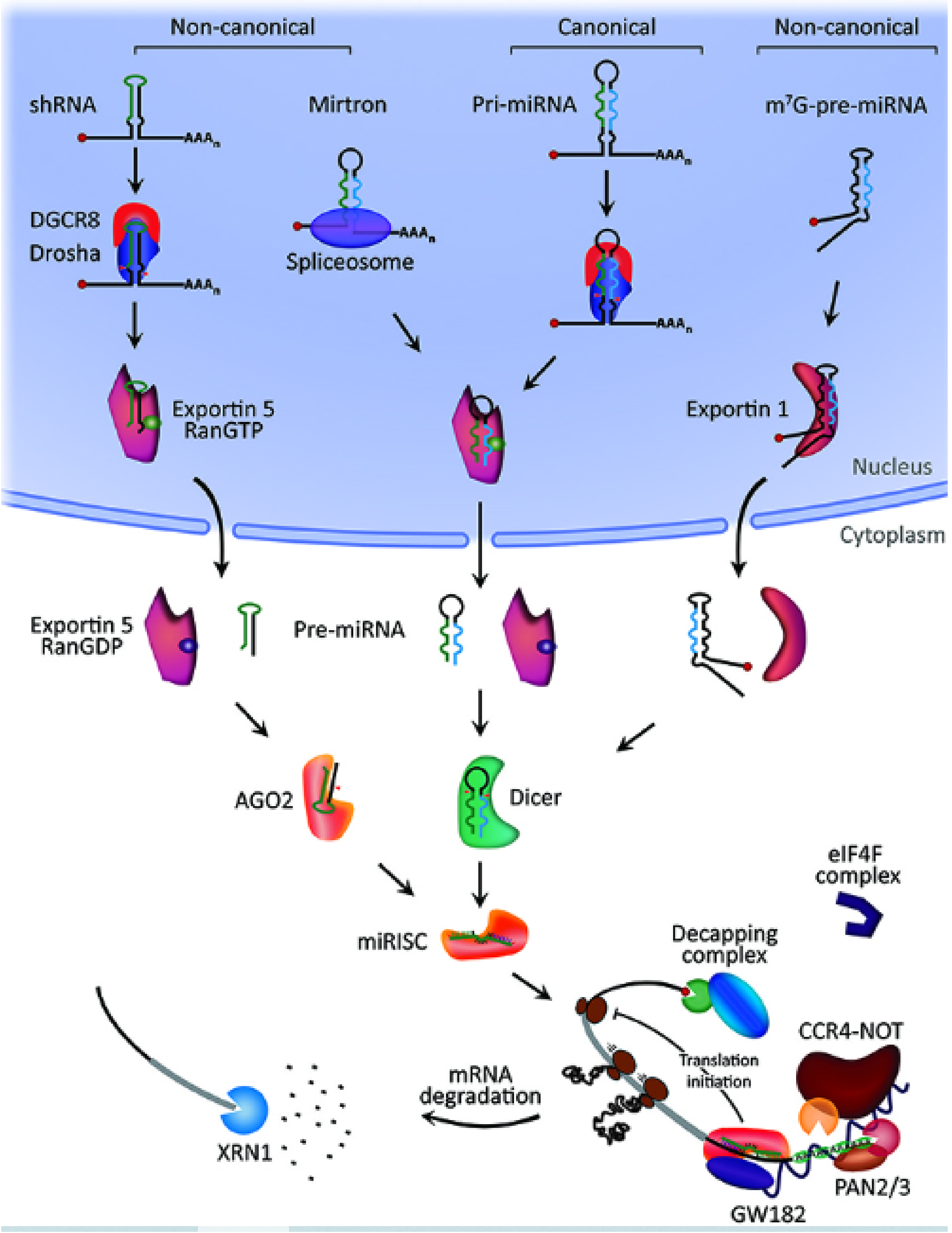

Glioma cell
Nucleus
Multivescicular body
I
II
III
IV
V
VI
exosomes
Blood
pri-miRNA
pre-miRNA
Mature miRNA
mRNA
Tumor tissue
↑ miR-21
↓ miR-497
↓ miR-125b
↓ miR-128
↑ miR-210
↑ miR-196b
↑ miR-1271
Blood stream
↑ miR-21
↓ miR-497
↓ miR-125b
↑ miR-128
▬ miR-210
▬ miR-196b
▬ miR-1271

small RNA sequencing



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8229417/

miRNA non canonical biogenesis :



nature COMMUNICATIONS

ARTICLE

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DOI: 10.1038/ncomms3980

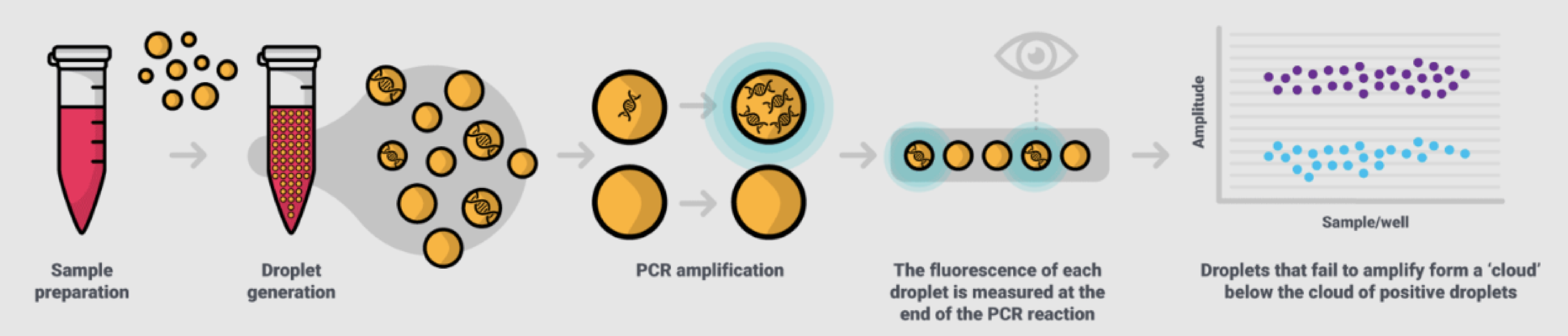
OPEN

Sumoylated hnRNPA2B1 controls the sorting of miRNAs into exosomes through binding to specific motifs

Carolina Villarroya-Beltri[1,2], Cristina Gutiérrez-Vázquez[1], Fátima Sánchez-Cabo[1], Daniel Pérez-Hernández[1], Jesús Vázquez[1], Noa Martin-Cofreces[2], Dannys Jorge Martinez-Herrera[3], Alberto Pascual-Montano[3], María Mittelbrunn[1,*] & Francisco Sánchez-Madrid[1,2,*]

- Primary T lymphoblasts
- EXOmotif seems to be present in the 3' extremity

DropletPCR (ddPCR) :



https://sampled.com/services/analyze/droplet-digital-pcr-ddpcr-services/

Nanoparticle tracking analysis :

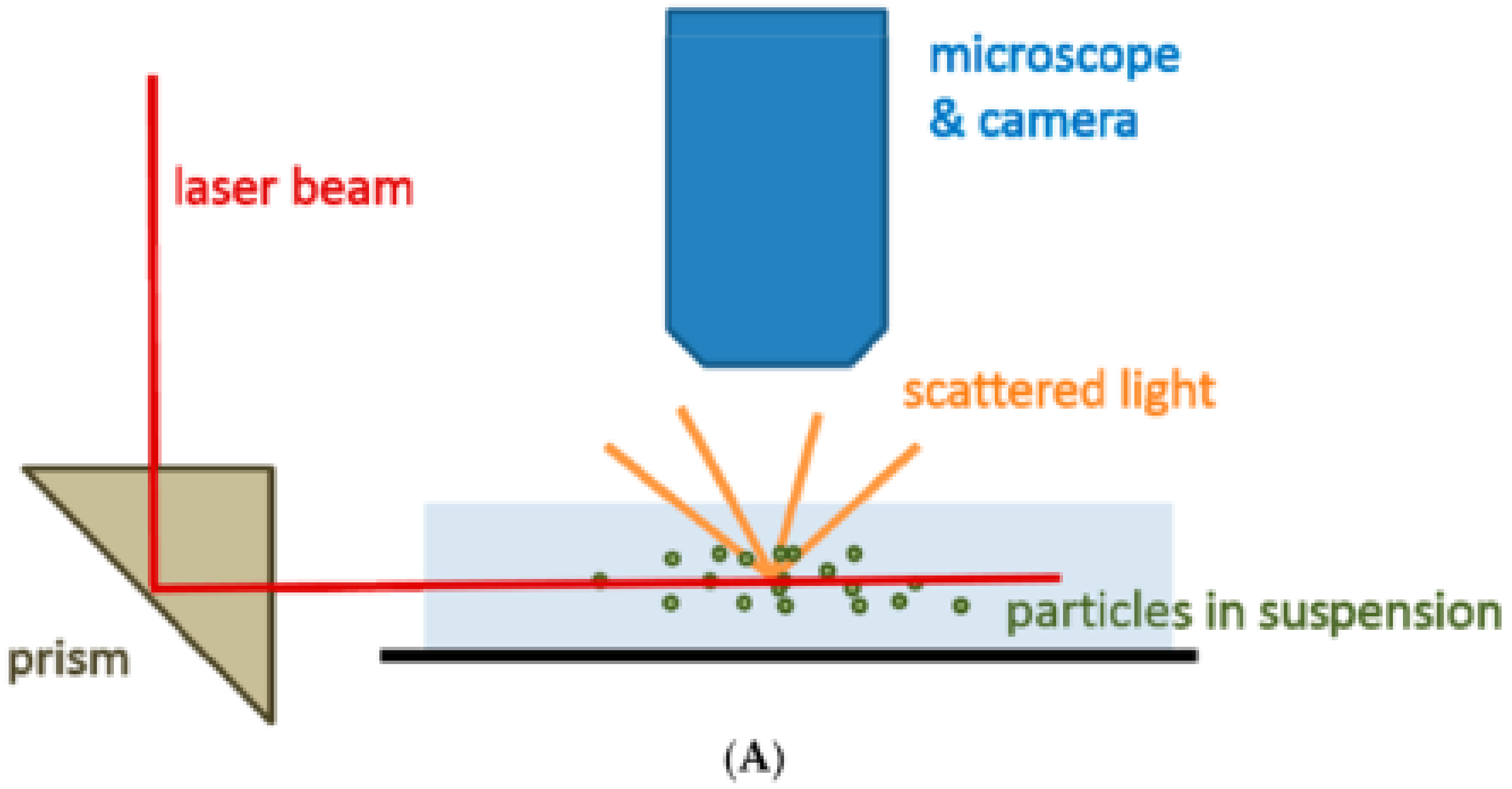
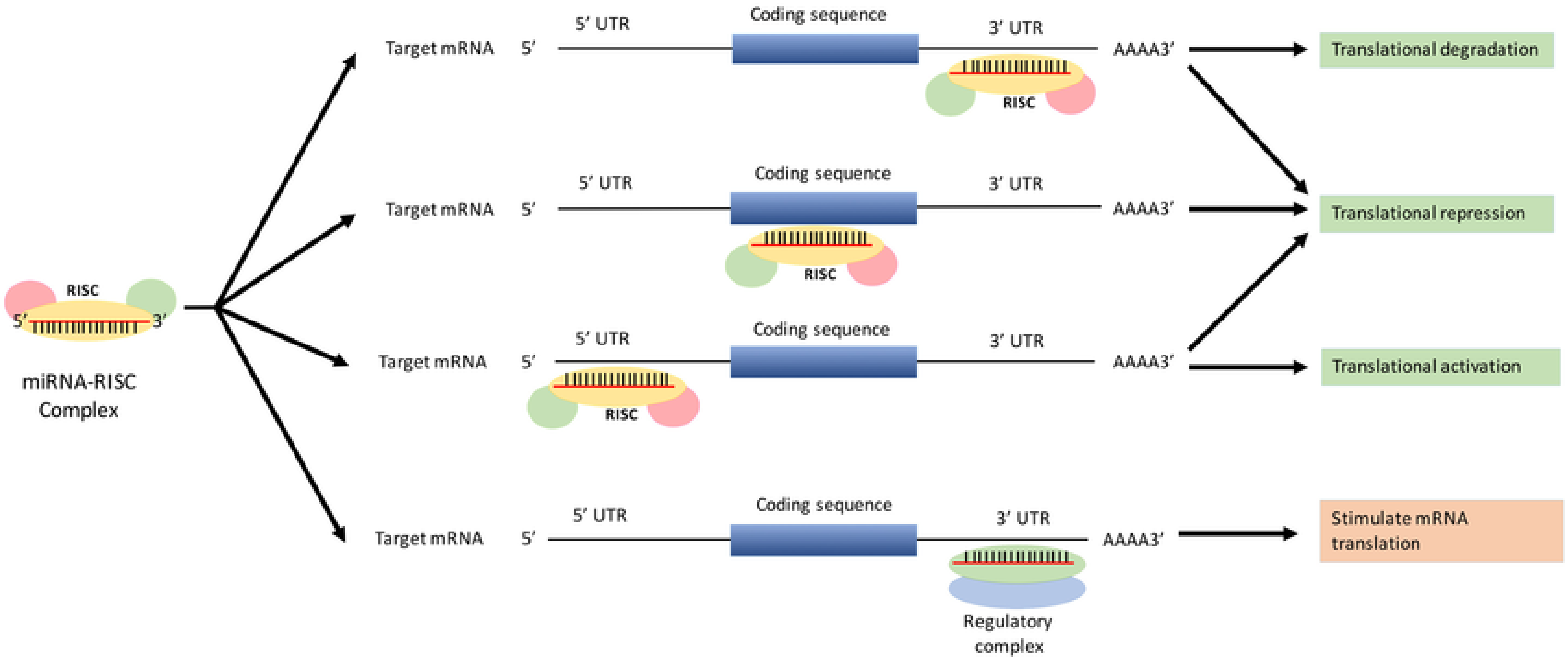


Fig.1 A graphic representation of the nanoparticle tracking analysis (NTA) principle. (Szatanek, 2017)

Nanoparticle tracking analysis (NTA) is a method for visualizing and analyzing particles in liquids that relates the rate of Brownian motion to particle size. NTA allows the determination of a size distribution profile of small particles with a diameter of approximately 10-1000 nanometers (nm) in liquid suspension.

miRNA functions :



miRNA 34C :

the gene coding for this mir is found on chromosome 11 in humans

Overexpression of miR-34c Caused Memory Impairment (mice)

Mass spectometry :