

Diagnostics of ccRCC



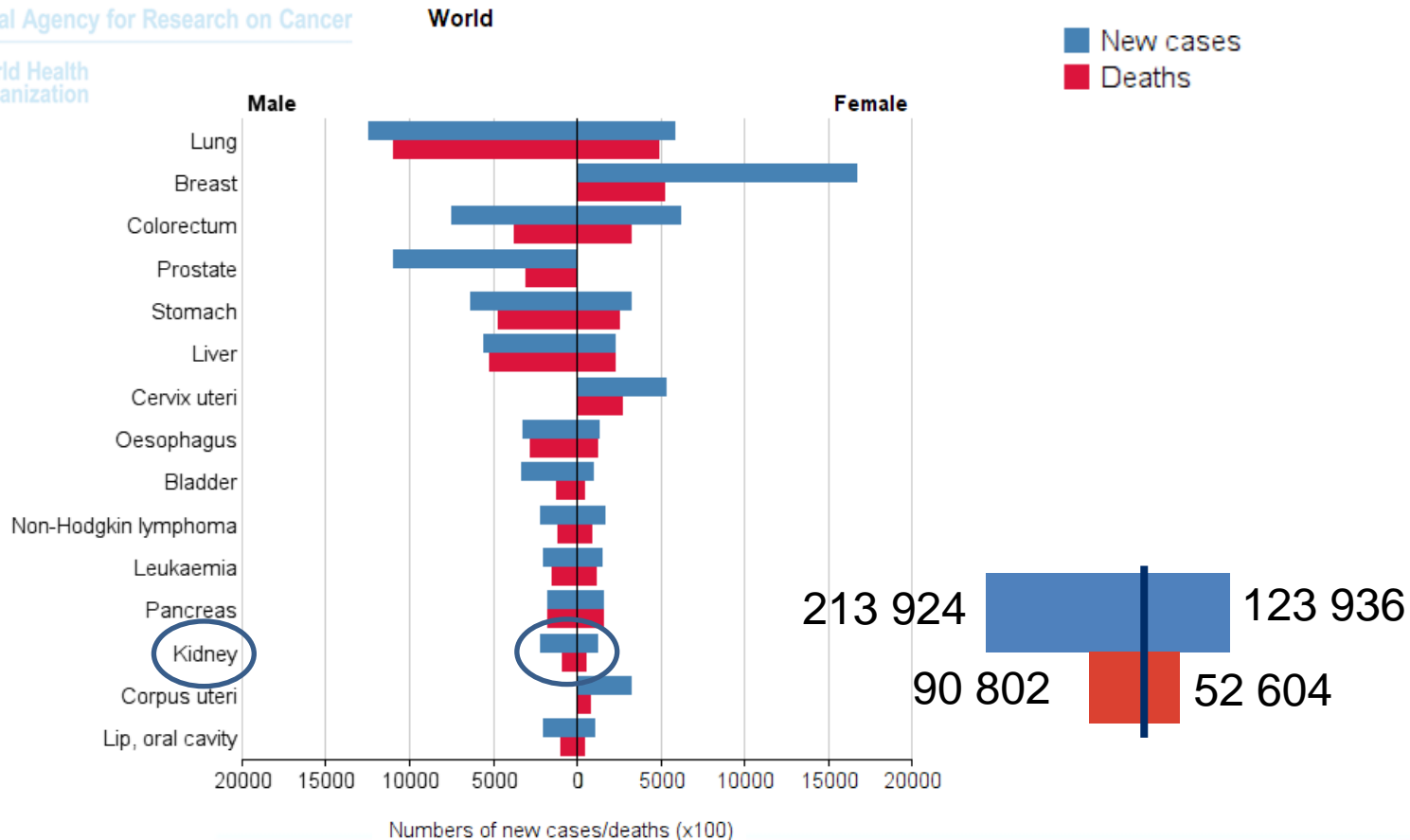
Hans Bluysen
02-12-2020



Kidney cancer incidence

2–3% of all adult malignancies diagnosed annually

International Agency for Research on Cancer

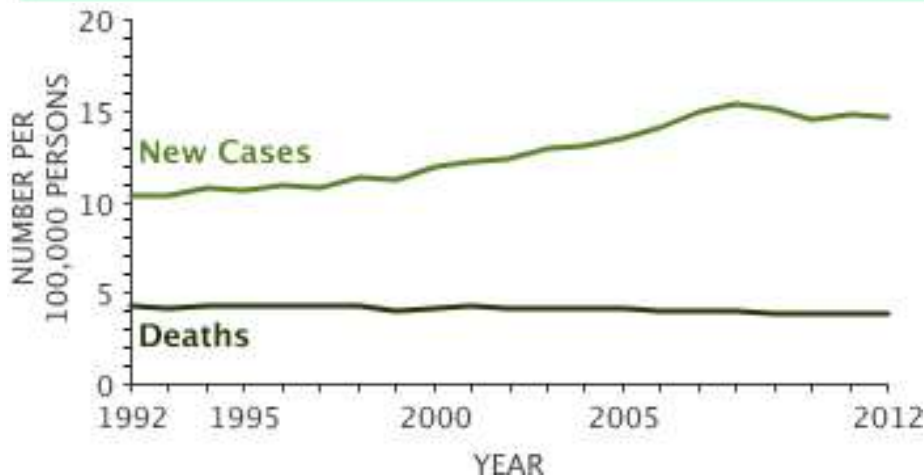


Source: Globocan 2012 (IARC)



Growing number of new cases

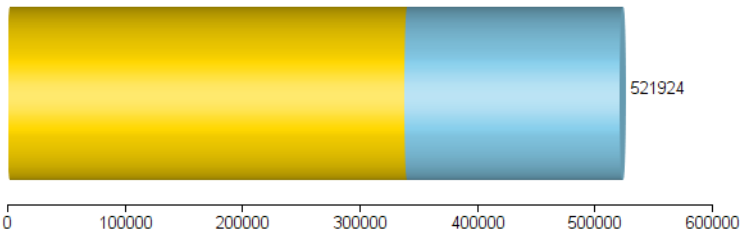
National Cancer Institute



International Agency for Research on Cancer



World Kidney Health
Number of new cancers in 2030 (all ages) - Both sexes



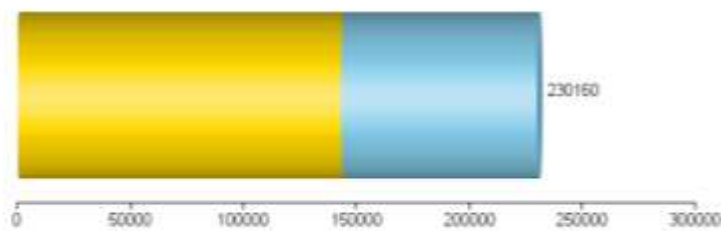
● Incidence in 2012 ● Demographic effect

GLOBOCAN 2012 (IARC) (29.10.2015)

International Agency for Research on Cancer



World Kidney Health
Number of cancer deaths in 2030 (all ages) - Both sexes



● Mortality in 2012 ● Demographic effect

GLOBOCAN 2012 (IARC) (29.10.2015)

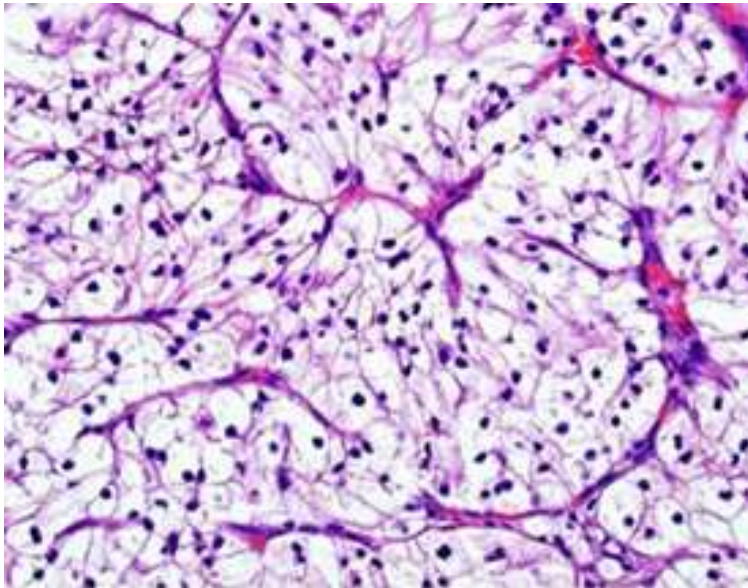
GLOBOCAN 2012 (IARC) (29.10.2015)

Source: Globocan 2012 (IARC); Surveillance, Epidemiology, and End Results Program (SEER)



Clear Cell Renal Cell Carcinoma (ccRCC)

- the most common form of kidney cancer - renal cell carcinoma (RCC)
- ccRCC - 70–80% of RCC cases



Tissue section from a clear cell renal cell carcinoma (ccRCC)



Factors increasing the risk of developing kidney cancer



- **Administration of certain medications:**

diuretics and pain-killers



- **Exposure to toxic compounds:**

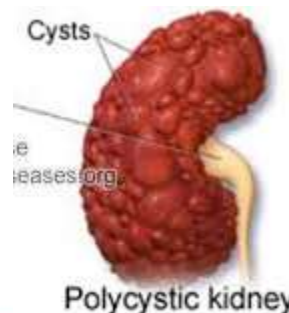
asbestos, cadmium, lead, herbicides or organic solvents



- **Acquired cystic disease of the kidney**

- **Genetic predisposition:**

family members with kidney cancer;
von Hippel-Lindau syndrom



DIAGNOSIS

Only 10% of patients display the classical triad of symptoms:

- hematuria
- flank pain
- a mass in the abdomen or flank



weight loss, hypertension, fatigue



Clinical classification: TNM CANCER STAGE

TABLE 3: TNM staging of renal cell carcinoma

Primary tumor (T)

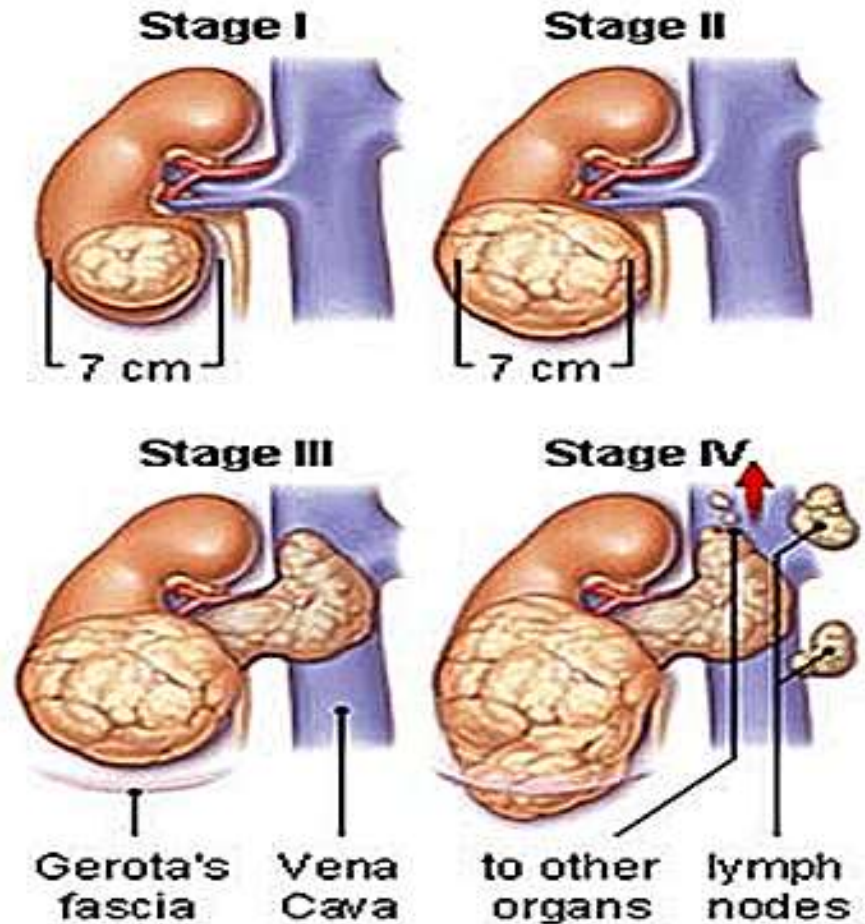
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor in the kidneys
T1	Tumor ≤ 7 cm in greatest dimension, limited to the kidneys
T1a	Tumor ≤ 4 cm in greatest dimension, limited to the kidneys
T1b	Tumor > 4 cm but not > 7 cm in greatest dimension, limited to the kidneys
T2	Tumor > 7 cm in greatest dimension, limited to the kidneys
T2a	Tumor > 7 cm but not > 10 cm in greatest dimension, limited to the kidneys
T2b	Tumor > 10 cm in greatest dimension, limited to the kidneys
T3	Tumor extends into major veins or perinephric tissues, but does not invade the adrenal gland or spread beyond Gerota's fascia
T3a	Tumor spreads into renal vein or its muscles or perirenal and/or renal sinus fat, but not beyond Gerota's fascia
T3b	Tumor grossly extends into vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia and extends into the contiguous adrenal gland

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to regional nodes

Distant metastasis (M)

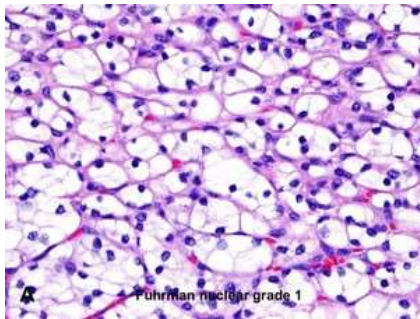
M0	No distant metastasis
M1	Distant metastasis



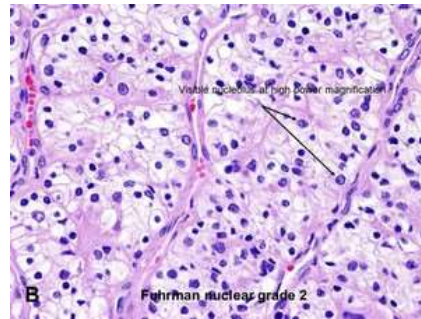


Clinical classification: FUHRMAN NUCLEAR GRADE

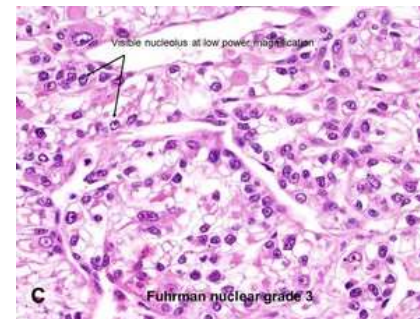
	Nuclear Diameter	Nuclear Shape	Nucleoli
Grade I	Small (10 micrometres)	Round, uniform	Absent, inconspicuous
Grade II	Larger (15 micrometres)	Irregularities in outline	Visible at 400x
Grade III	Even larger (20 micrometres)	Obvious irregular outline	Prominent at 100x
Grade IV	As grade III	As grade III	Bizarre multi-lobed with spindles



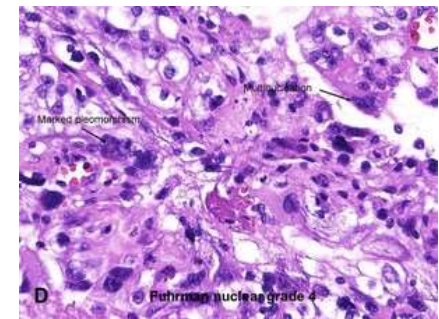
I



II



III



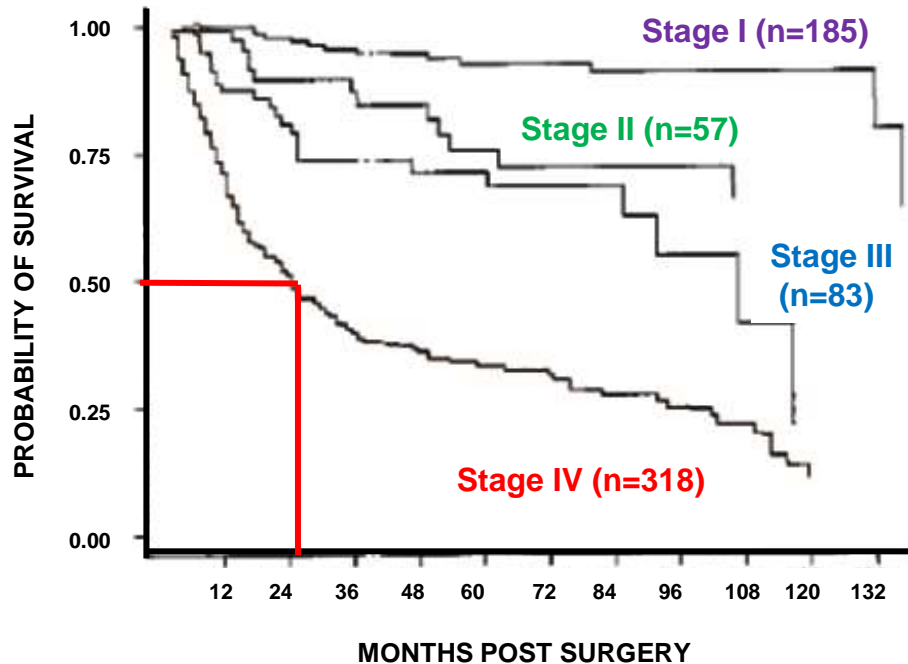
IV



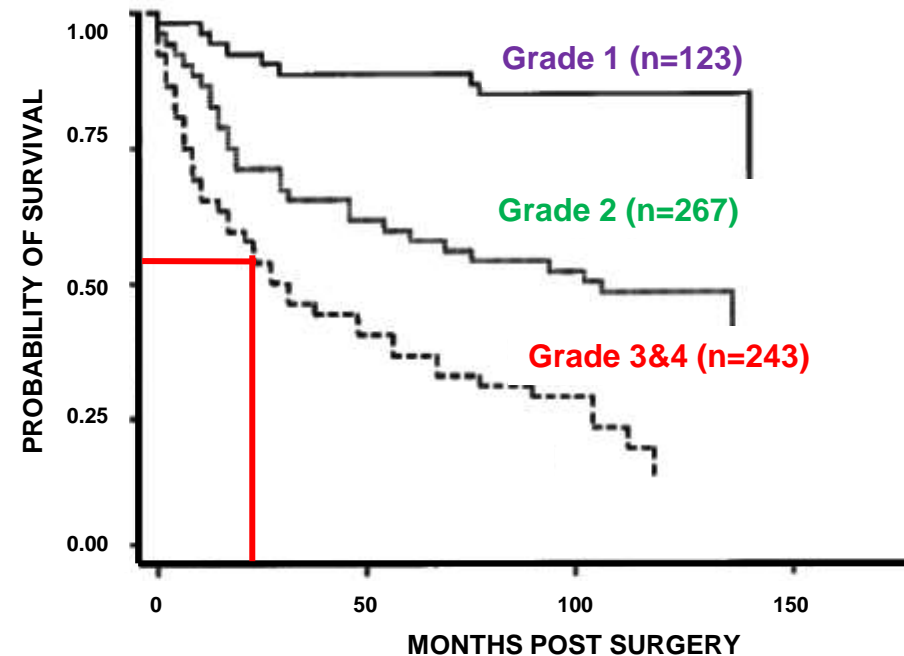
ccRCC - prognosis

Five-year cancer specific survival

tumor TNM stage

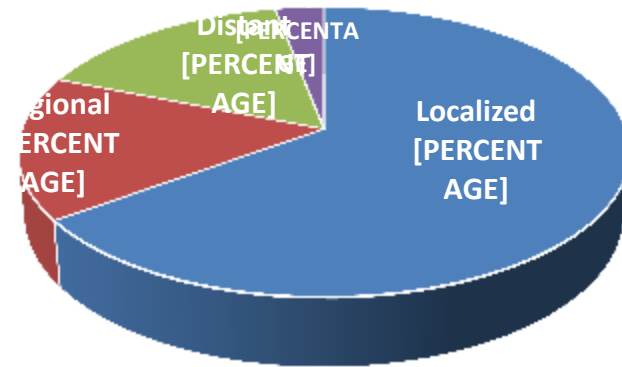


Fuhrman grade



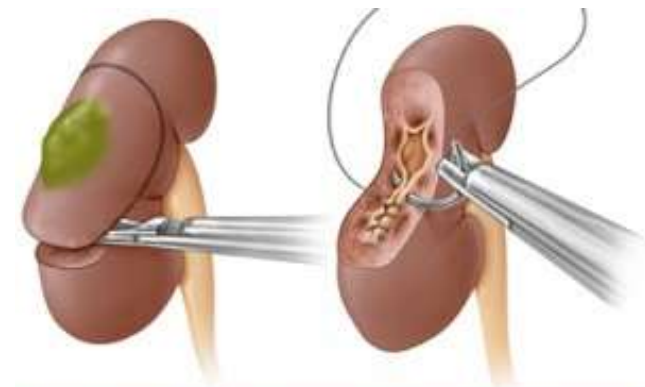


Therapy of ccRCC



TNM stage IV: nephrectomy + systemic therapy

TNM stage I-III: nephrectomy



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Clinical issues

- **DIAGNOSIS** – „classic triad” appears only in 10% of patients
 - **CLASSIFICATION** - remains mostly morphology based, prognostic methods have not changed over the past decade
 - **BIOMARKERS** ????
 - **TREATMENT** - tumor is resistant to conventional therapies; rate of complete response is low
-



ccRCC – genetic background

von Hippel-Lindau disease - hereditary

loss of VHL gene
inactivated VHL: mutations,
promoter hypermethylation

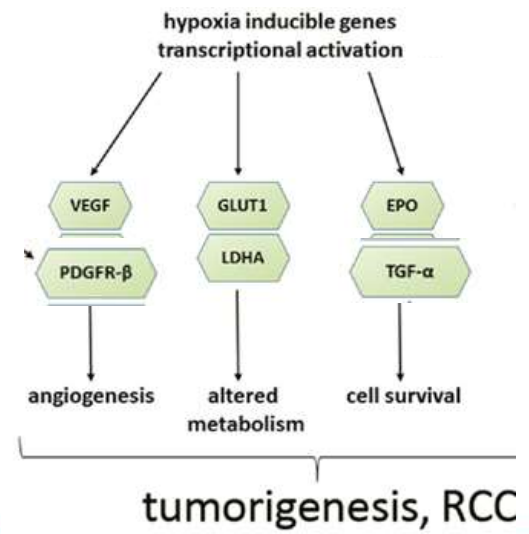
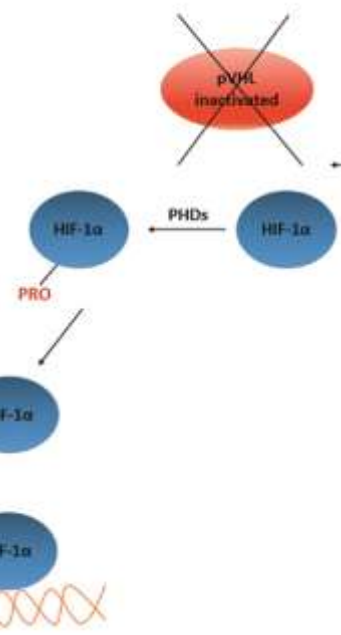
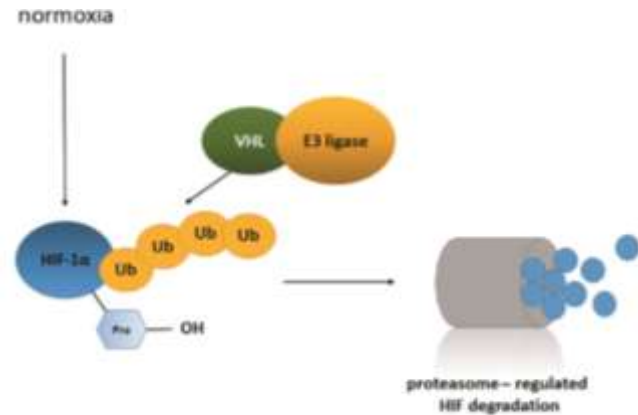
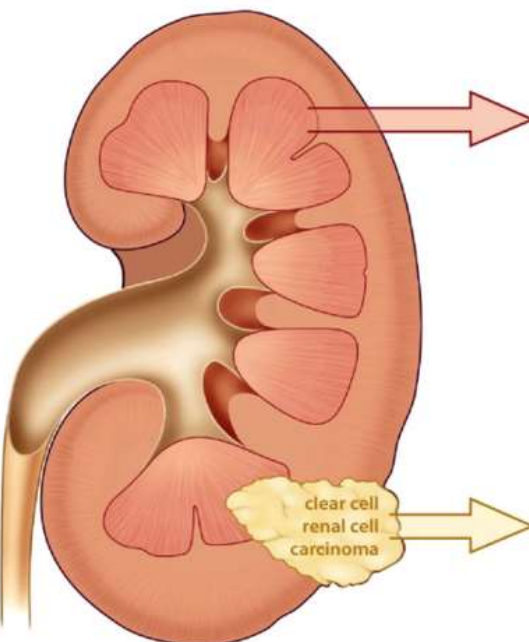
loss of p arm of chromosome 3 harboring
VHL gene (70-80%) or
loss of heterozygosity (LOH) at 3p



sporadic

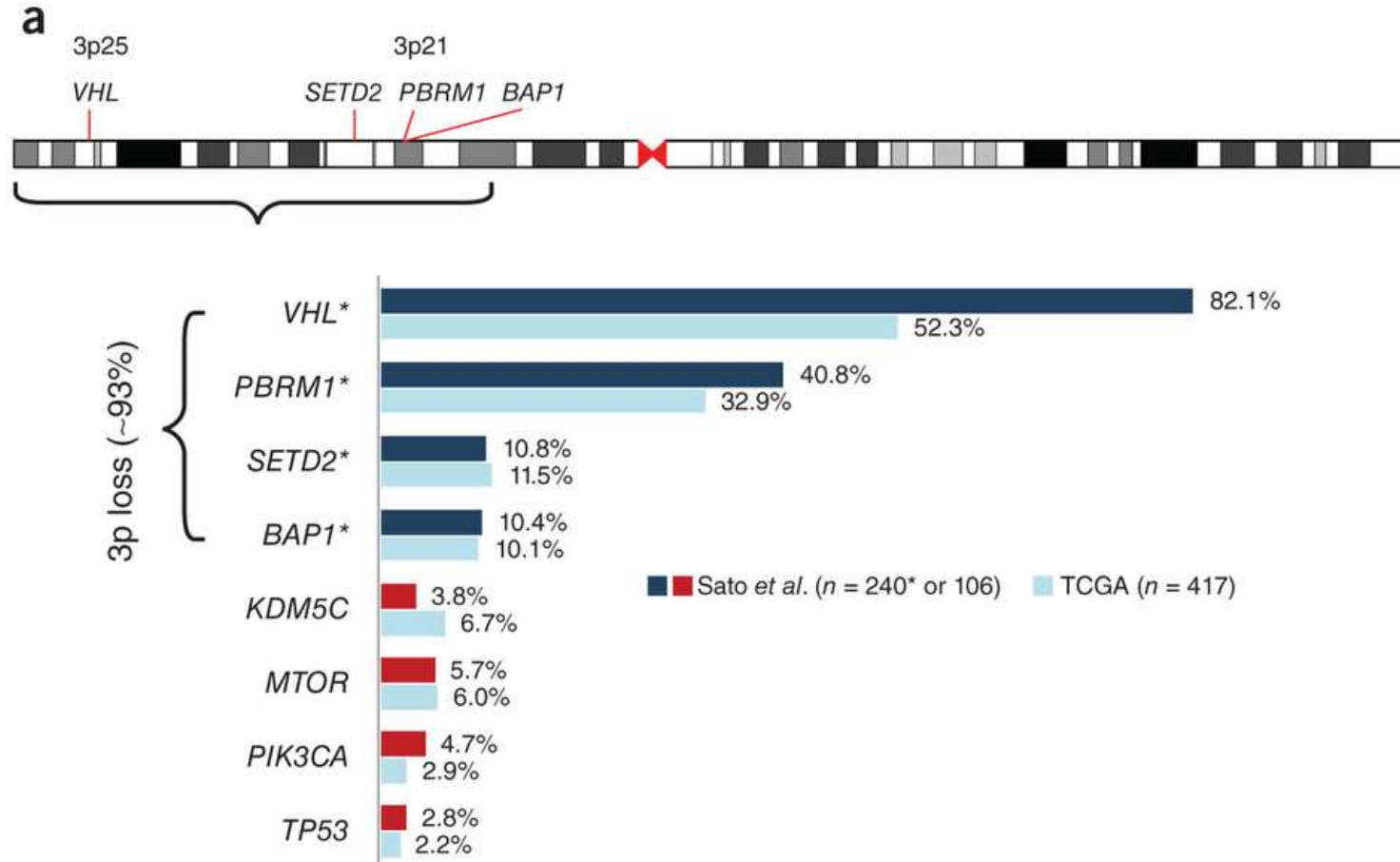


VHL function - response to oxygen concentration

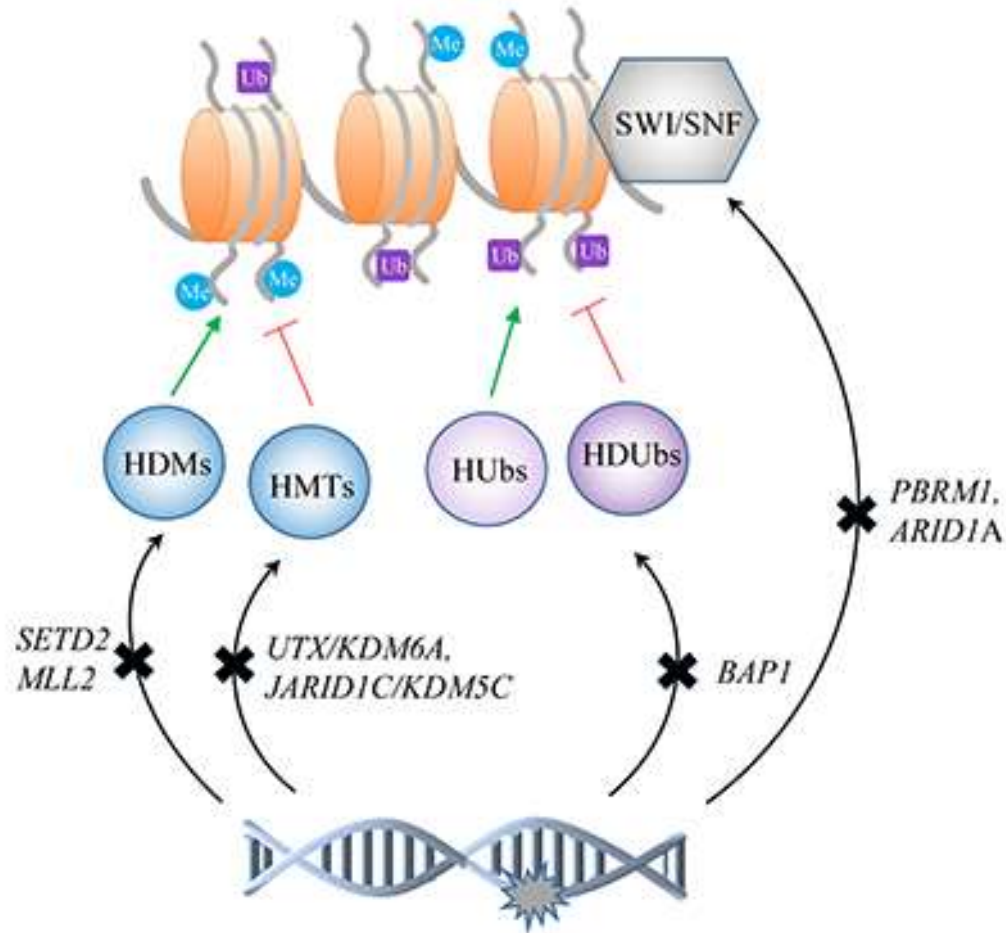




Other genes frequently mutated in ccRCC

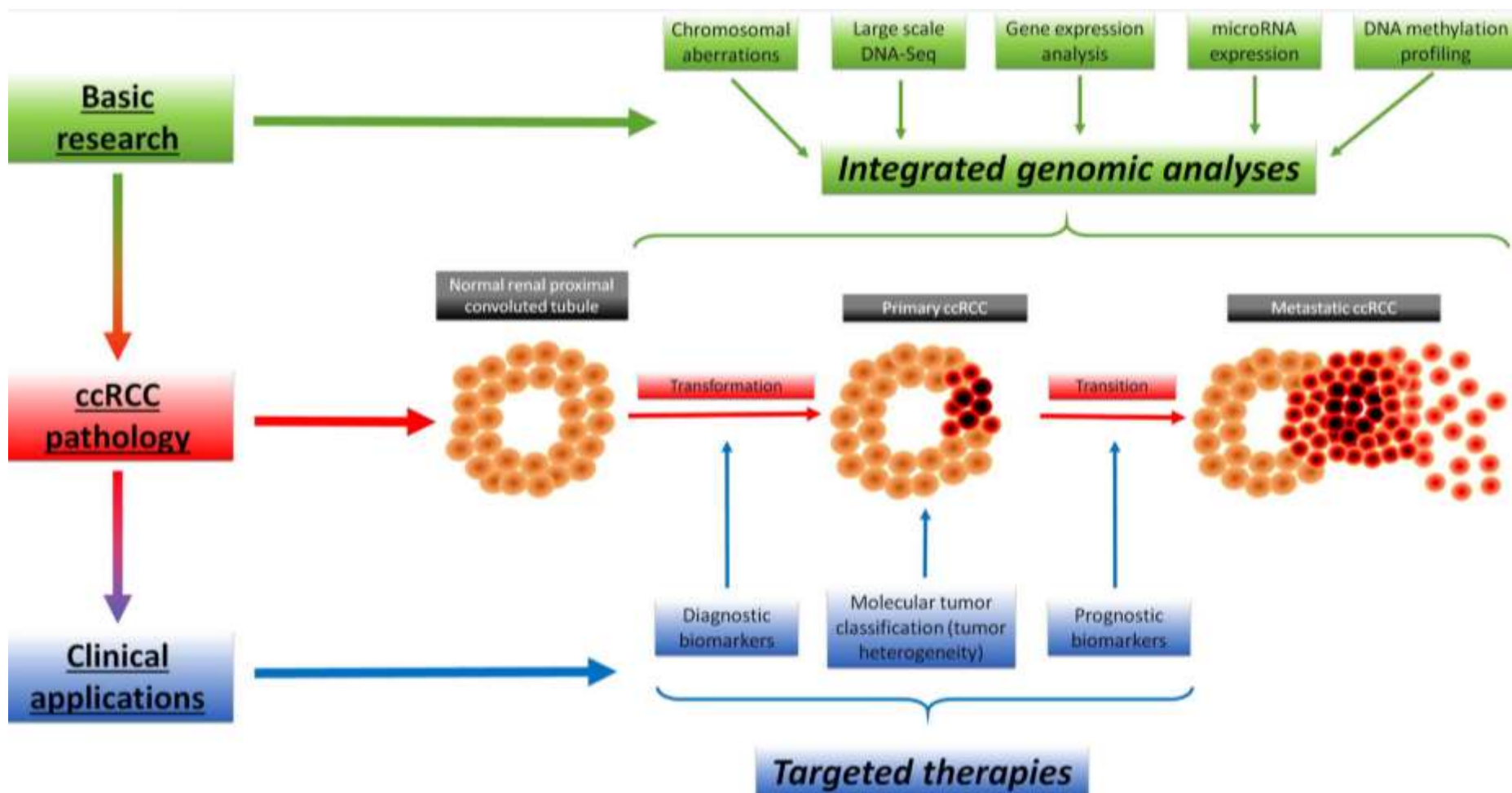


Chromatin remodelling

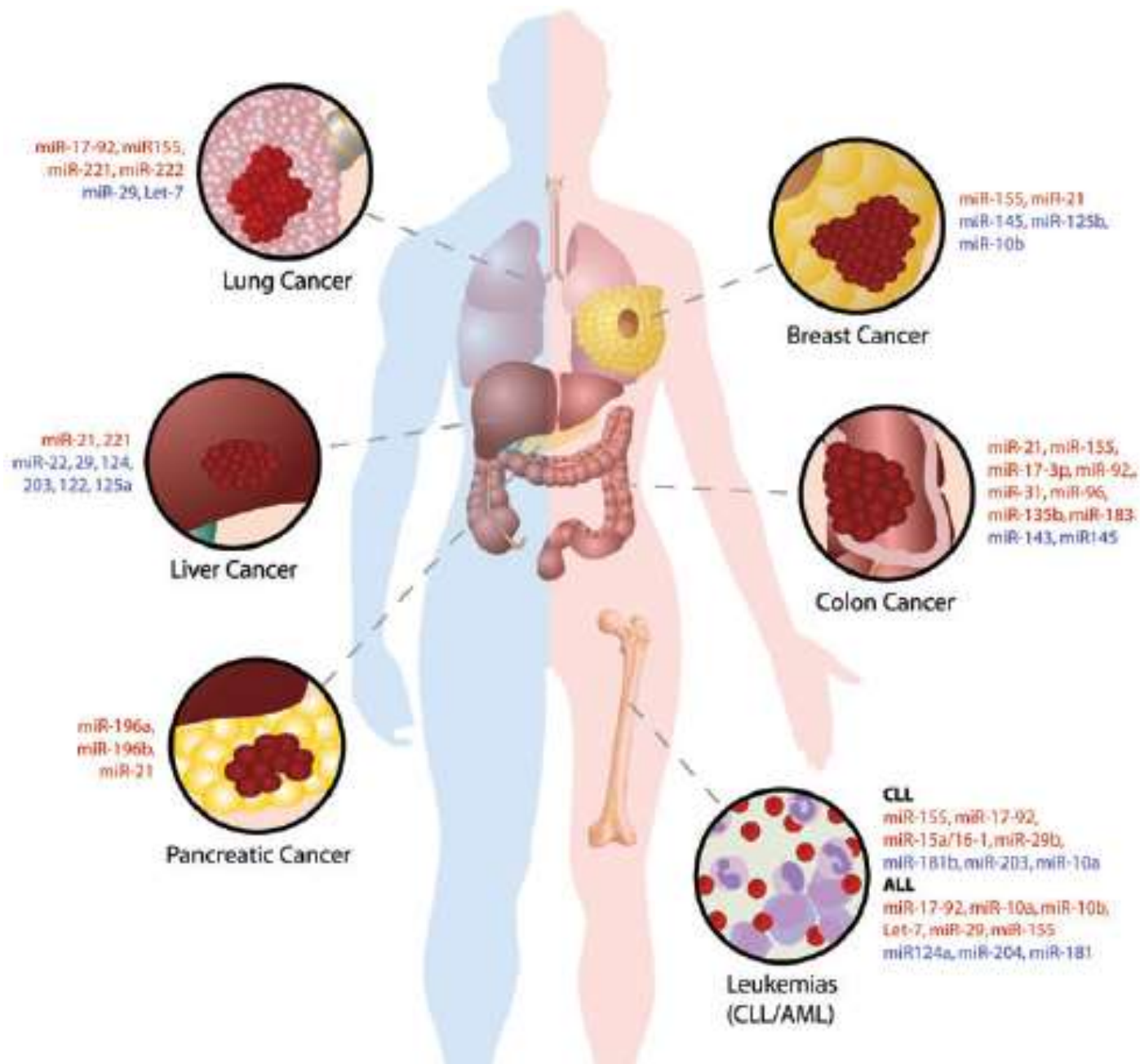




Integrative genomic approaches in ccRCC management



De-regulated miRNAs in Cancer





Research questions

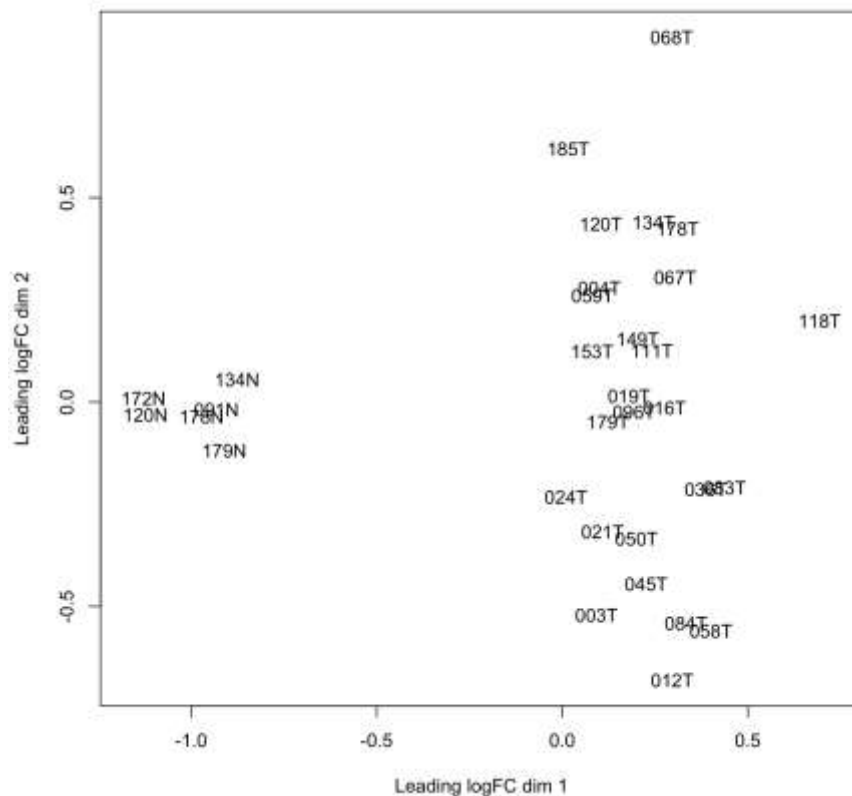
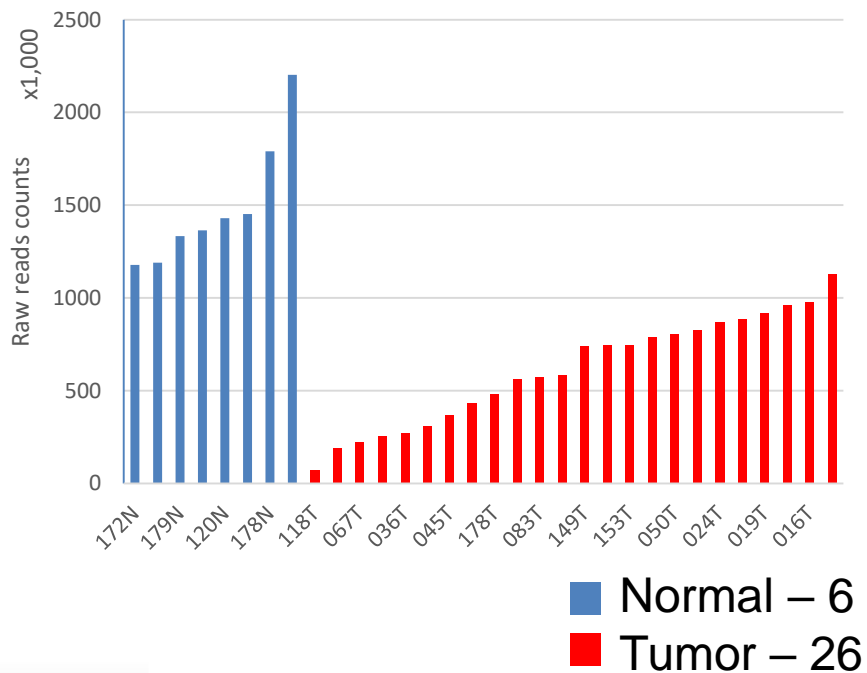


Are miRNAs efficient
ccRCC biomarkers?

What is the role of miRNAs
in ccRCC etiology
and/or progression?



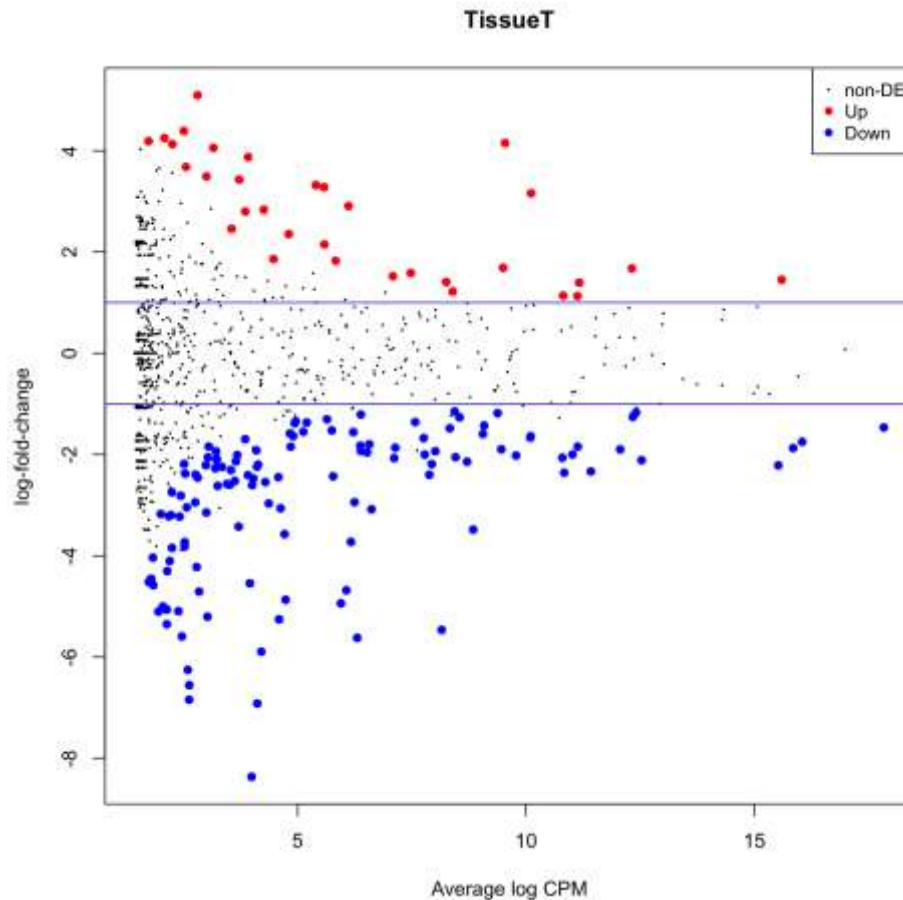
miRNA in polish ccRCC patients



Machine: HiScan SQ
Run: Single Read 50
Reads: 100,000 – 2,200,000



Differential expression of miRNA in ccRCC tumors



Identified miRNAs – 2587

Upregulated – 32

Not changed – 2428

Downregulated – 127

ccRCC

Research question



**Which common miRNAs
are deregulated in ccRCC?**



Commonly deregulated miRNAs in ccRCC–experiments in meta-analysis

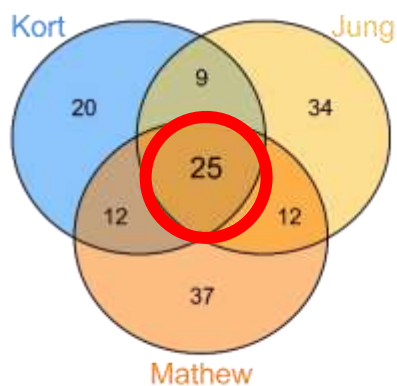
RCC subtype	Deregulated miRNAs		Samples		Experiment	Ref.
	Down	Up	Normal	Tumor		
ccRCC	127	32	6	26	NGS	LHTT, Poznań, Poland
ccRCC	76	30	10	10	NGS	Zhou L, 2010
ccRCC	44	42	11	15	NGS	Osanto S, 2012
ccRCC	243	181	18	18	NGS	Nientiedt M, 2016
ccRCC	165	233	71	512	NGS	TCGA (dbDEMC2)
ccRCC	33	33	8	8	Microarray	Kort EJ, 2008 (dbDEMC2)
ccRCC	32	48	12	12	Microarray	Jung M, 2009 (dbDEMC2)
ccRCC	49	48	13	13	Microarray	Mathew LK, 2014 (dbDEMC2)



Commonly deregulated miRNAs in ccRCC

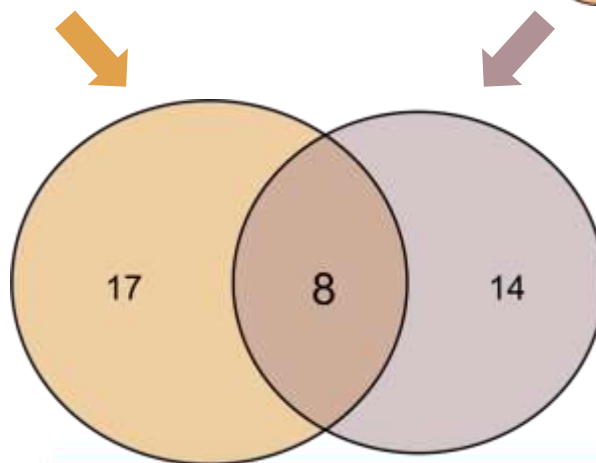
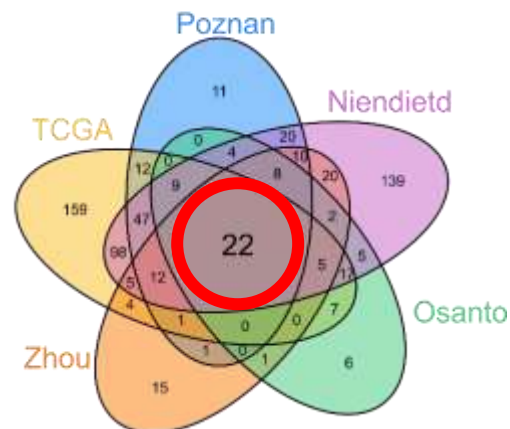
Microarray experiments in ccRCC

(25 commonly deregulated miRNAs)



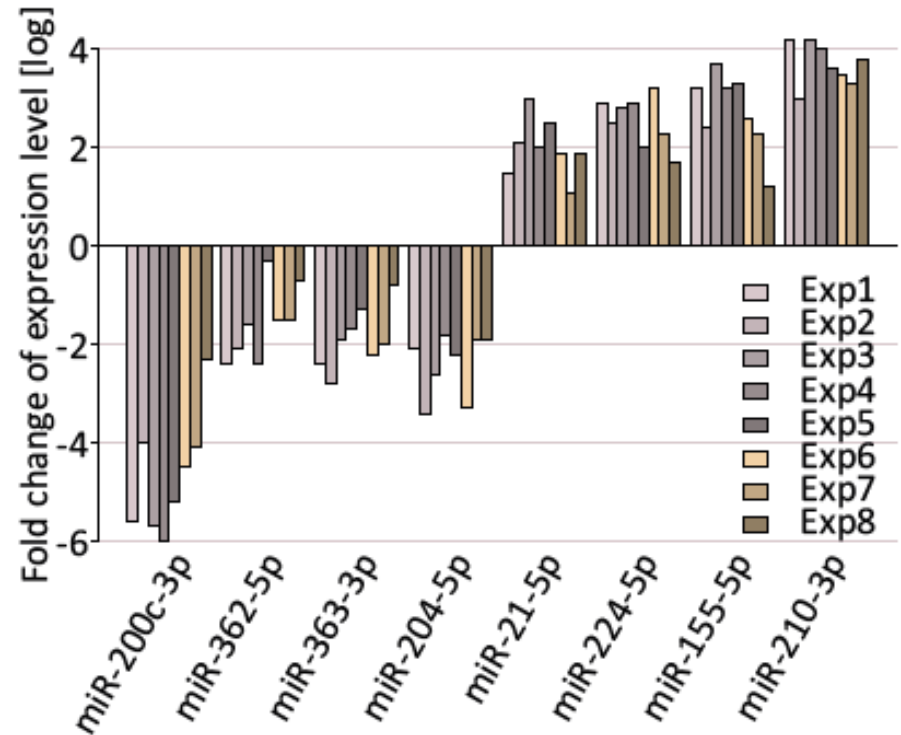
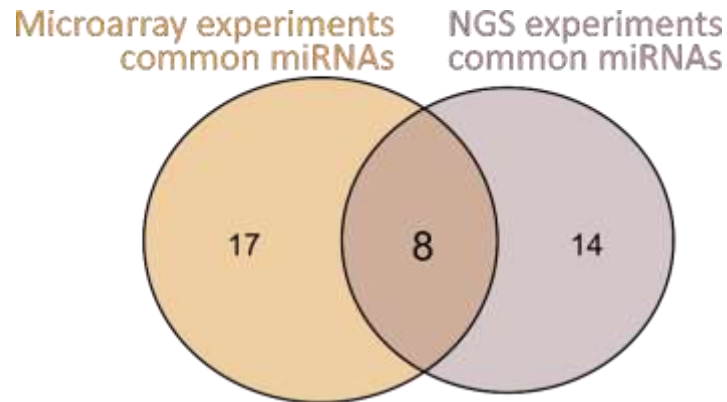
NGS experiments in ccRCC

(22 commonly deregulated miRNAs)





Commonly deregulated miRNAs in ccRCC





Commonly deregulated miRNAs in ccRCC

miRNA ID	Expression status	log ₂ FC LHTT
miR-200c-3p	DOWN	-5.6
miR-362-5p	DOWN	-2.4
miR-363-3p	DOWN	-2.4
miR-204-5p	DOWN	-2.1
miR-21-5p	UP	1.5
miR-224-5p	UP	2.9
miR-155-5p	UP	3.2
miR-210-3p	UP	4.2



Commonly deregulated miRNAs in other RCC subtypes – meta-analysis

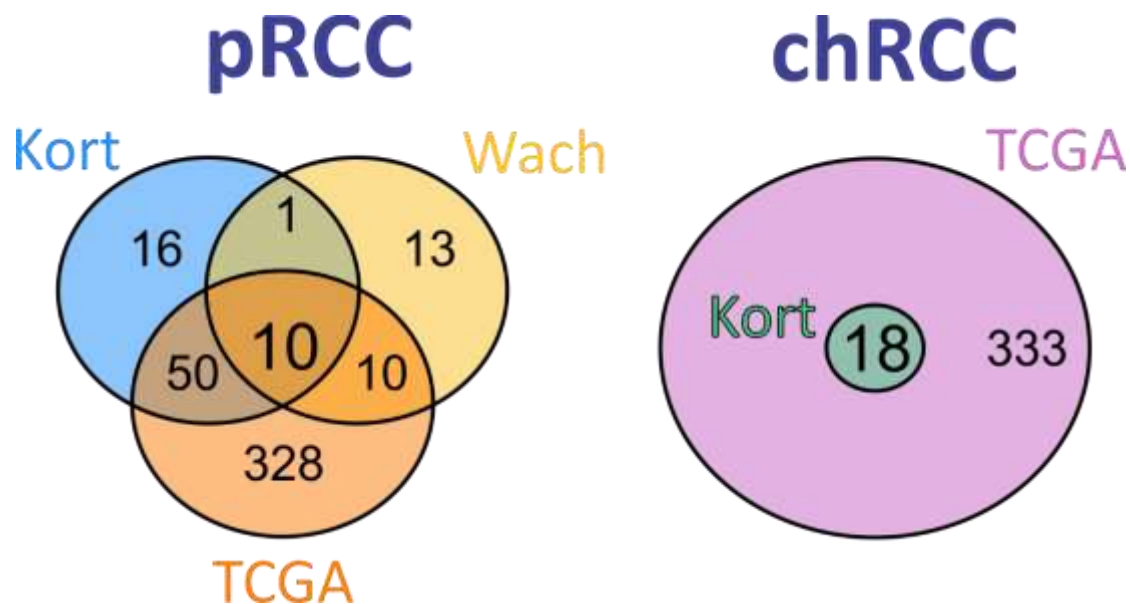
A

No.	RCC subtype	Deregulated miRNAs		Samples		Experiment type	Ref.
		Down	Up	Ctrl	RCC		
Exp1	ccRCC	127	32	6	24	NGS	This work
Exp2	ccRCC	76	30	10	10	NGS	[25]
Exp3	ccRCC	44	42	11	15	NGS	[26]
Exp4	ccRCC	243	181	18	18	NGS	[27]
Exp5	ccRCC	165	233	71	512	NGS	TCGA (dbDEMC2.0)
Exp6	ccRCC	33	33	8	8	Microarray	[35]
Exp7	ccRCC	32	48	12	12	Microarray	[36]
Exp8	ccRCC	49	48	13	13	Microarray	[37]
Exp9	pRCC	153	245	34	290	NGS	TCGA (dbDEMC2.0)
Exp10	pRCC	35	42	4	4	Microarray	[35]
Exp11	pRCC	17	17	18	7	Microarray	[38]
Exp12	chRCC	171	180	25	66	NGS	TCGA (dbDEMC2.0)
Exp13	chRCC	12	6	4	4	Microarray	[35]
Exp14	onco.	14	20	20	14	Microarray	[35]

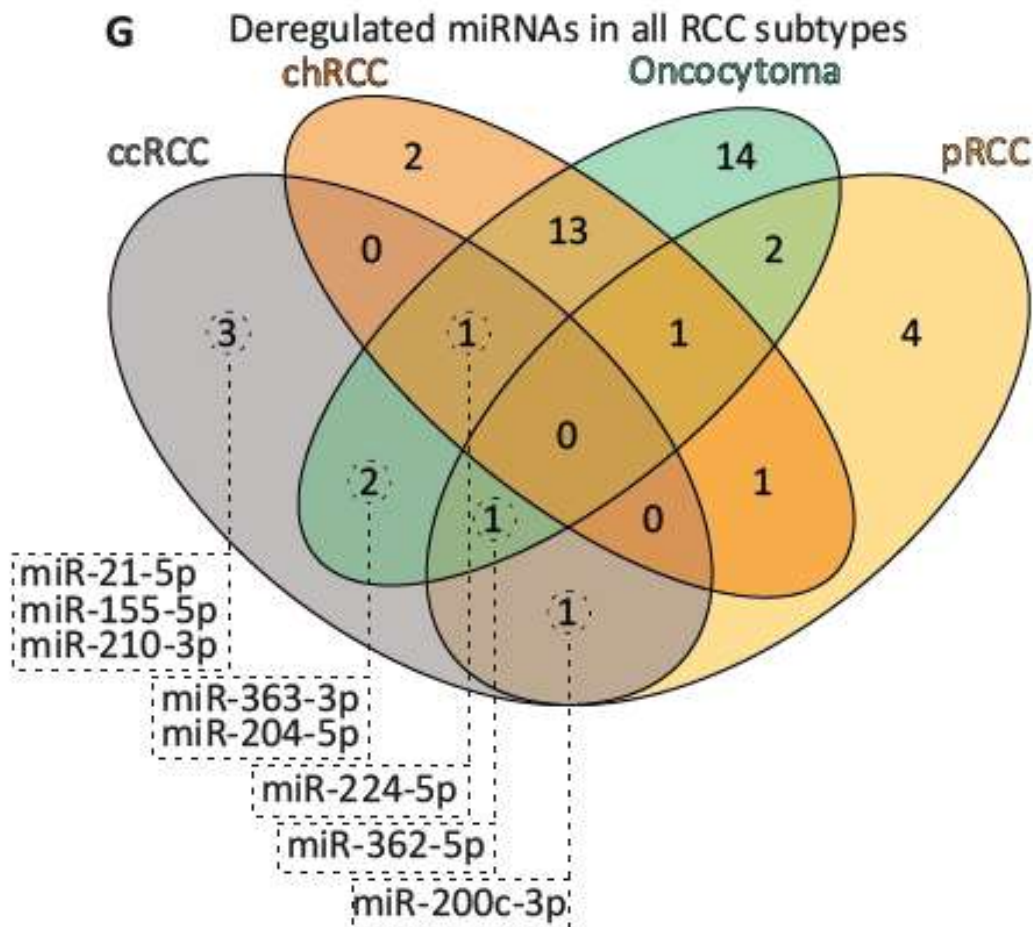
- pRCC – papillary renal cell carcinoma – 15% of RCC
- chRCC – chromophobe renal cell carcinoma – 5% of RCC
- Oncocytoma – 5% of RCC



Commonly deregulated miRNAs in other RCC subtypes



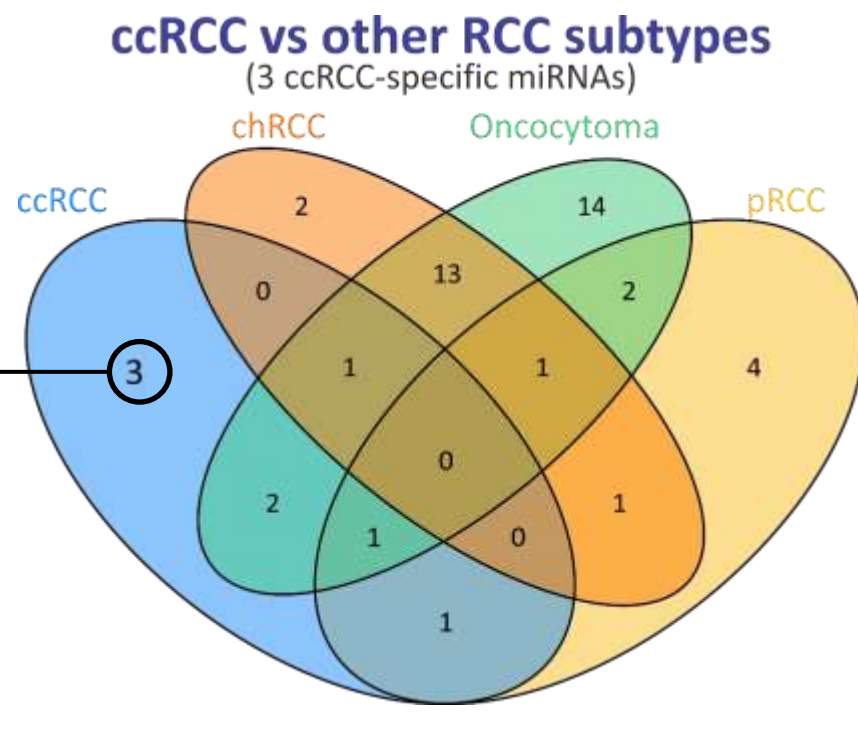
Specifically deregulated miRNAs in different RCC subtypes





Specifically deregulated miRNAs in ccRCC vs. other RCC subtypes

miRNA ID	Expression status	log ₂ FC LHTT
miR-200c-3p	DOWN	-5.6
miR-362-5p	DOWN	-2.4
miR-363-3p	DOWN	-2.4
miR-204-5p	DOWN	-2.1
miR-21-5p	UP	1.5
miR-224-5p	UP	2.9
miR-155-5p	UP	3.2
miR-210-3p	UP	4.2





Research question



Are miRNAs efficient
ccRCC biomarkers?



Validation of miRNA deregulation in ccRCC

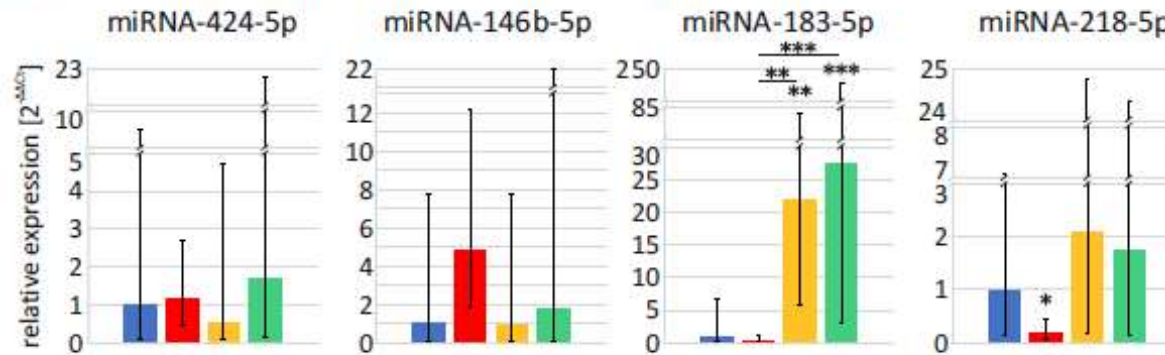
non-ccRCC – 13

ccRCC – 24



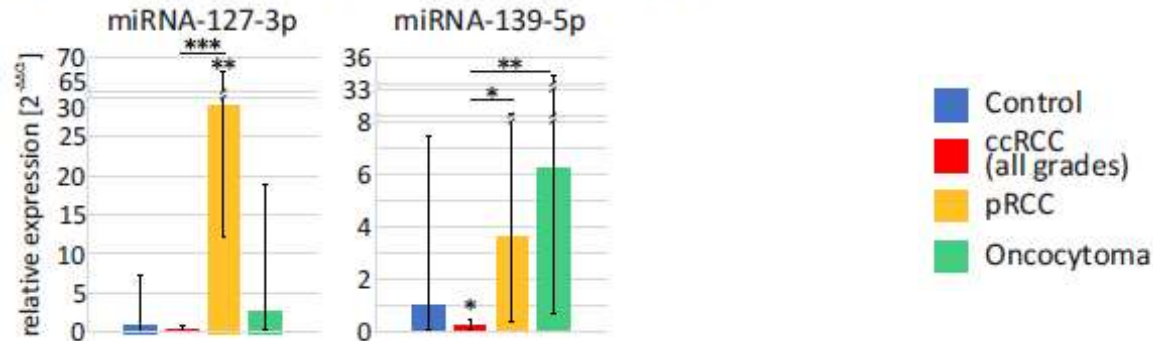
Validation of miRNA deregulation in non-ccRCC tumors

A Deregulated miRNA in oncocytoma based on meta-analysis



Oncocytoma

B Deregulated miRNA in pRCC based on meta-analysis

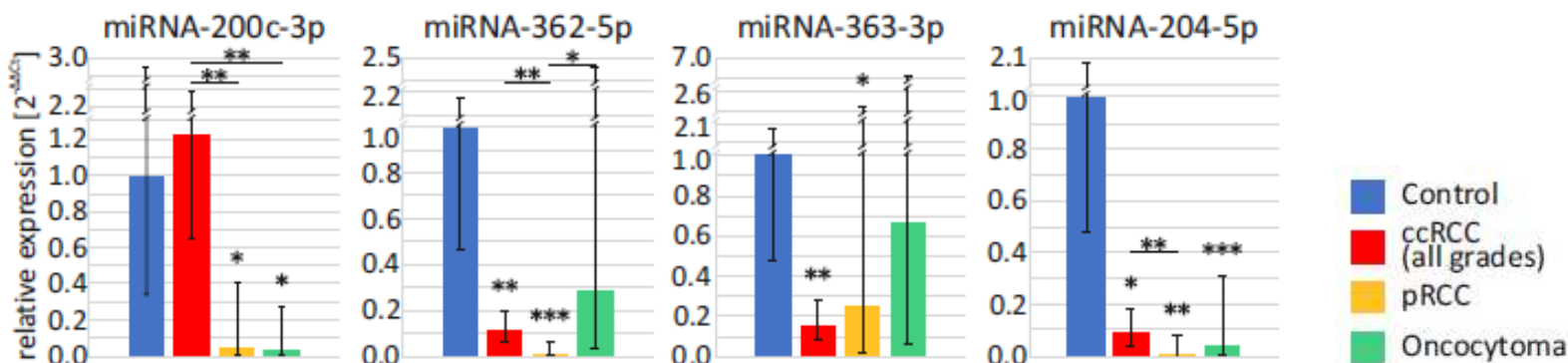


Papillary renal cell carcinoma

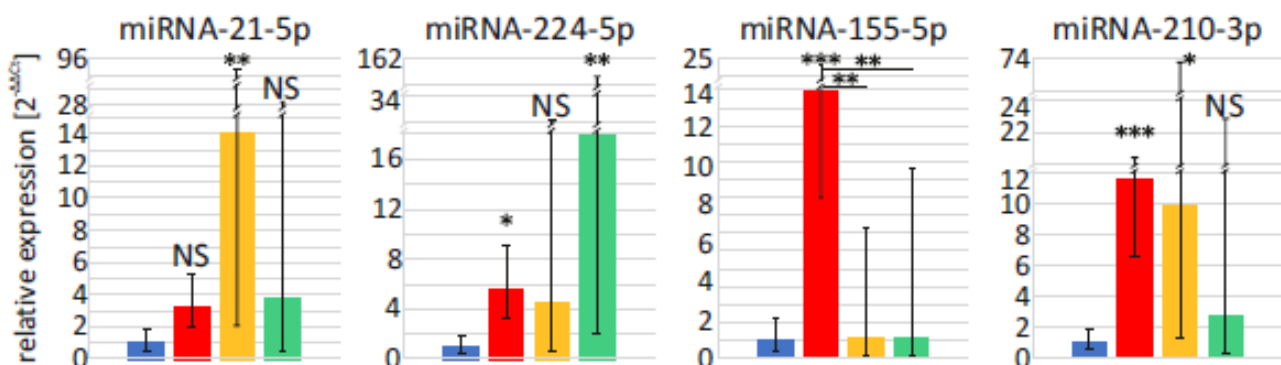


Validation of miRNA deregulation in ccRCC tumors

C Downregulated miRNA in ccRCC based on meta-analysis



D Upregulated miRNA in ccRCC based on meta-analysis





Validation of miRNA deregulation in ccRCC tumors

non-ccRCC – 13

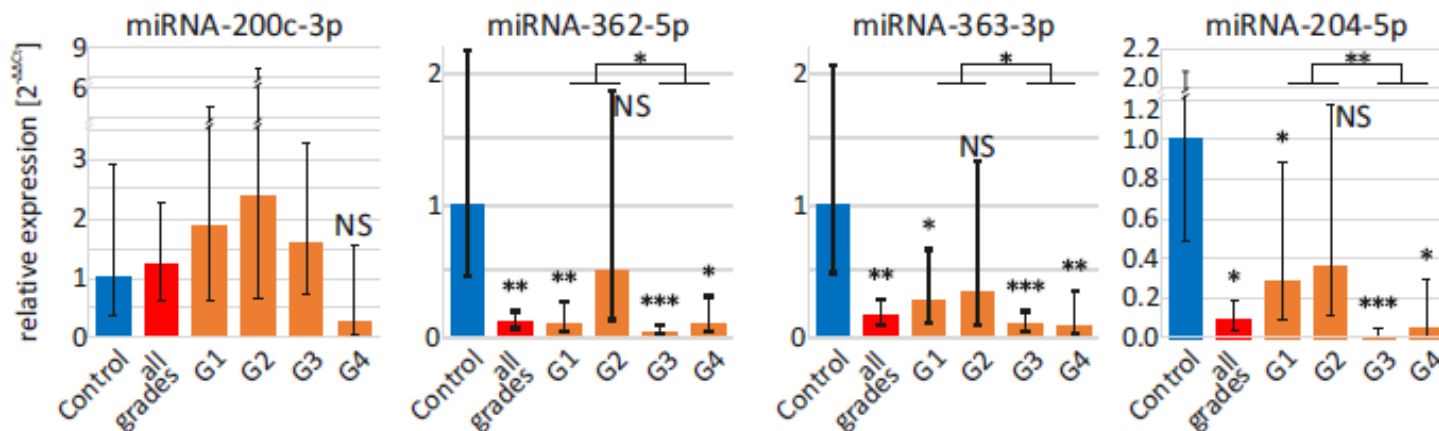
ccRCC – 24

- G1 – 7
- G2 – 6
- G3 – 6
- G4 – 5

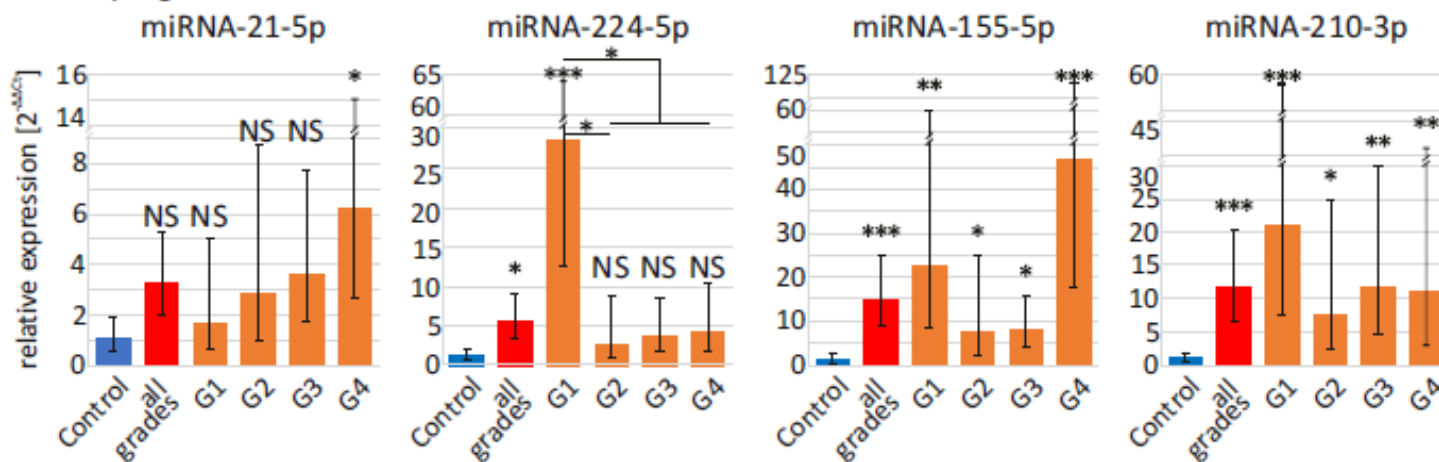


Validation of miRNA deregulation in ccRCC: all patients vs grades

E Downregulated miRNA in ccRCC



F Upregulated miRNA in ccRCC



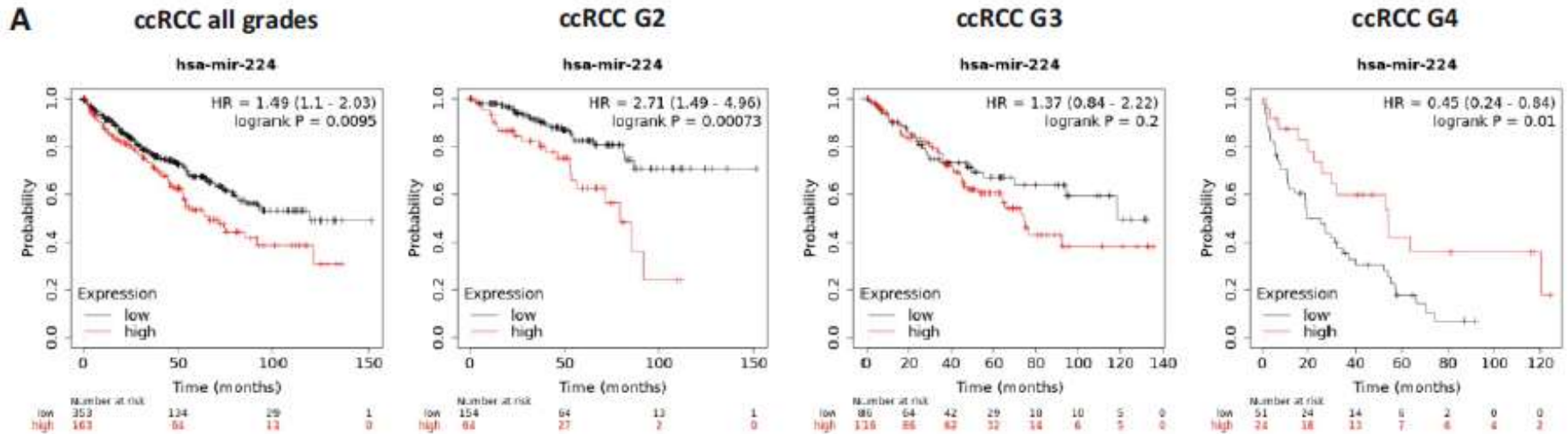


Validation of miRNA deregulation in ccRCC – summary

	all	G1	G2	G3	G4
miR-21-5p	UP			UP	
miR-210-3p	UP	UP			
miR-224-5p	UP	UP			
miR-155-5p	Needs optimization				
miR-362-5p	DOWN			DOWN	DOWN
miR-363-3p				DOWN	DOWN
miR-200-3p				DOWN	DOWN
miR-204-5p	Needs optimization				



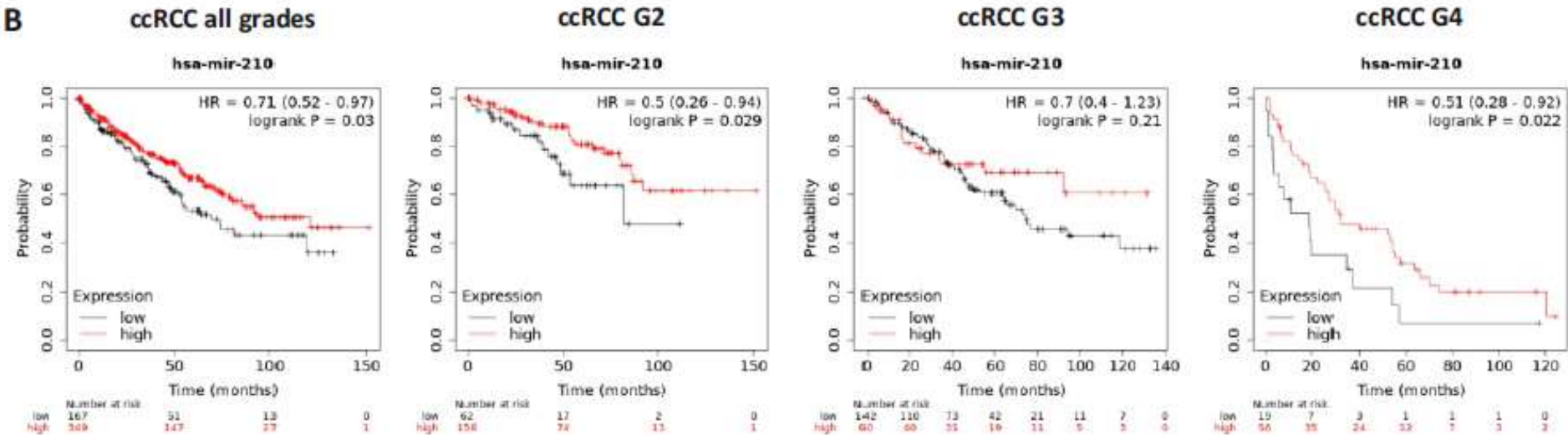
Survival rate analysis of ccRCC patients vs miRNA-224 expression



Patients with high expression (red line) of miRNA-224 have worst hazard ratio (HR) in ccRCC G2 than in G4.



Survival rate analysis of ccRCC patients vs miRNA-210 expression



Patients with high expression (red line) of miRNA-210 have higher survival rate although its massive upregulation in ccRCC tumors.



Research question



**What is the role of miRNAs
in ccRCC etiology
and/or progression?**

What is the effect of miRNA deregulation in ccRCC?

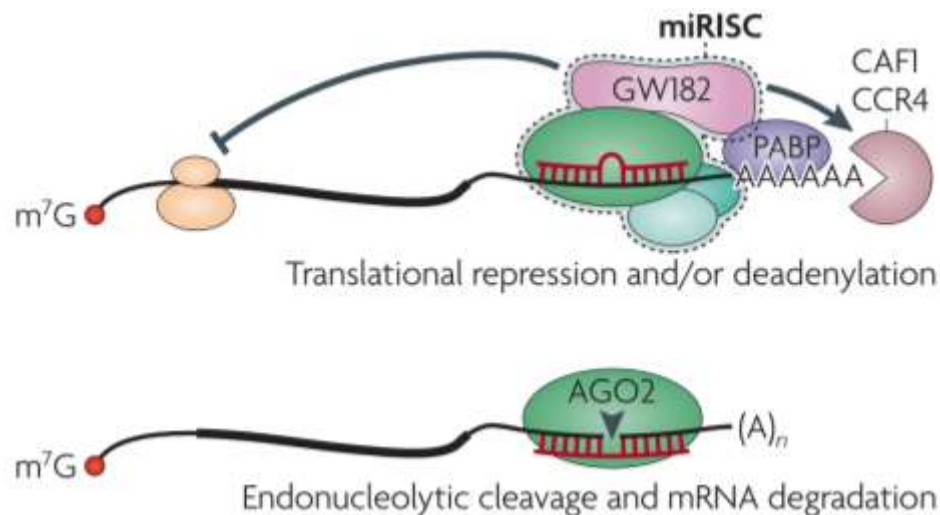
Hypothesis:

↓ miRNA

↑ targets

↑ miRNA

↓ targets





miRTarBase: the experimentally validated microRNA-target interactions database

miRTarBase

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miRTarBase: the experimentally validated microRNA-target interactions database

As a database, miRTarBase has accumulated more than three hundred and sixty thousand miRNA-target interactions (MTIs), which are collected by manually surveying pertinent literature after NLP of the text systematically to filter research articles related to functional studies of miRNAs. Generally, the collected MTIs are validated experimentally by reporter assay, western blot, microarray and next-generation sequencing experiments. While containing the largest amount of validated MTIs, the miRTarBase provides the most updated collection by comparing with other similar, previously developed databases.

Current curation

Release 7.0: Sept. 15, 2017

Number of articles: 8,510

Number of species: 23



Targetosome analysis methodology

Genes (with FC)
from RNA-Seq
in ccRCC tumors

Gene name	log2 FC
5S_rRNA	2
7SK	-0,7
A1BG	1,2
A1BG-AS1	0,4
A1CF	-1
A2M	0,6
A2M-AS1	0,9
A2ML1-AS1	1,1
A2MP1	1,3
A4GALT	0,3
A4GNT	1
AAAS	0,3
AACS	-0,5
AACSP1	0,7
AADAC	3,2
AADACP1	1,7
AADAT	-1,1
AAED1	0,9
AAGAB	-0,8
AAK1	-0,7
AAMDC	-0,4
AAMP	-0,4
AANAT	0,8
AAR2	-0,1
AARD	-2
AARS	-0,4
AARS2	0,2
AARSD1	0,1
AASDH	-0,3
AASDHPT	-0,4

RNA-Seq
Normal – 18
Tumor – 69



Targetosome analysis methodology

Genes (with FC)
from RNA-Seq
in ccRCC tumors

Gene name	log2 FC
5S_rRNA	2
7SK	-0,7
A1BG	1,2
A1BG-AS1	0,4
A1CF	-1
A2M	0,6
A2M-AS1	0,9
A2ML1-AS1	1,1
A2MP1	1,3
A4GALT	0,3
A4GNT	1
AAAS	0,3
AACS	-0,5
AACSP1	0,7
AADAC	3,2
AADACP1	1,7
AADAT	-1,1
AAED1	0,9
AAGAB	-0,8
AAK1	-0,7
AAMDC	-0,4
AAMP	-0,4
AANAT	0,8
AAR2	-0,1
AARD	-2
AARS	-0,4
AARS2	0,2
AARSD1	0,1
AASDH	-0,3
AASDHPPT	-0,4
AASS	-1,8
AATF	0,4
AATK	0,8

miRNA targets
from miRTarBase

Gene name
BDNF
NOTCH1
NOTCH1
GNAI2
GNAI2
GNAI2
UBE2I
BECN1
BECN1
BECN1
BECN1
MUC17
MUC17
TNRC6A
TNRC6A
UBE2I
HNRNPM
ELMOD2
TNFRSF10B
TNFRSF10B
ITGA2
TMEM87A
IDH1
SEC62
CHD1
CHD1
JUN
SLC4A10
NT5E
NT5E
LMNB2
SLC4A7
SLC4A7
TMEM41B
CFTR

RNA-Seq
Normal – 18
Tumor – 69



Targetosome analysis methodology

Genes (with FC)
from RNA-Seq
in ccRCC tumors

Gene name	log2 FC
5S_rRNA	2
7SK	-0,7
A1BG	1,2
A1BG-AS1	0,4
A1CF	-1
A2M	0,6
A2M-AS1	0,9
A2ML1-AS1	1,1
A2MP1	1,3
A4GALT	0,3
A4GNT	1
AAAS	0,3
AACS	-0,5
AACSP1	0,7
AADAC	3,2
AADACP1	1,7
AADAT	-1,1
AAED1	0,9
AAGAB	-0,8
AAK1	-0,7
AAMDC	-0,4
AAMP	-0,4
AANAT	0,8
AAR2	-0,1
AARD	-2
AARS	-0,4
AARS2	0,2
AARSD1	0,1
AASDH	-0,3
AASDHPPT	-0,4
AASS	-1,8
AATF	0,4
AATK	0,8
ABAT	-4,7

miRNA targets
from miRTarBase

Gene name
BDNF
NOTCH1
NOTCH1
GNAI2
GNAI2
GNAI2
UBE2I
BECN1
BECN1
BECN1
BECN1
BECN1
MUC17
MUC17
TNRC6A
TNRC6A
UBE2I
HNRNP1M
ELMOD2
TNFRSF10B
TNFRSF10B
ITGA2
TMEM87A
IDH1
SEC62
CHD1
CHD1
JUN
SLC4A10
NT5E
NT5E
LMNB2
SLC6A7
SLC6A7
TMEM111
TMEM111

VS

miRNA targets
in ccRCC

=

Gene name	log2 FC
ABCB10	0,3
ABCE1	0,2
ABI2	-0,1
ABL1	-0,1
ACER3	0,2
ACP2	-0,2
ACSL4	-0,8
ACTC1	-1,8
ACTH10	-0,4
ADAM9	0,7
ADAP2	1,7
ADO	0
ADPGK	1
ADPRHL1	-0,7
AFF4	0,1
AGO1	0
AGO2	0,9
AGPAT5	0,2
AIFM1	-2
AK2	-0,6
AKRIN1	-0,7
ALDH5A1	-1,6
ALG9	0,2
ANAPC5	0,2
ANKRA2	0,7
ANKRD26	0,3
ANPEP	-1,7
ANXA1	1,7



Targetosome analysis methodology

Genes (with FC)
from RNA-Seq
in ccRCC tumors

Gene name	log2 FC
5S_rRNA	2
7SK	-0,7
A1BG	1,2
A1BG-AS1	0,4
A1CF	-1
A2M	0,6
A2M-AS1	0,9
A2ML1-AS1	1,1
A2MP1	1,3
AAGALT	0,3
AAGNT	1
AAAS	0,3
AAAS	-0,5
AAACSP1	0,7
AADAC	3,2
AADACP1	1,7
AADAT	-1,1
AAED1	0,9
AAGAB	-0,8
AAK1	-0,7
AAMDC	-0,4
AAAMP	-0,4
AANAT	0,8
AAR2	-0,1
AARD	-2
AARS	-0,4
AARS2	0,2
AARS01	0,1
AASDH	-0,3
AASDHPP1	-0,4
AASS	-1,8
AATF	0,4
AATF	0,3
AATF	-

miRNA targets
in ccRCC

Gene name	log2 FC
ABCB10	0,3
ABCE1	0,2
ABI2	-0,1
ABL1	-0,1
ACER3	0,2
ACP2	-0,2
ACSL4	-0,8
ACTC1	-1,8
ACTR10	-0,4
ADAM9	0,7
ADAP2	1,7
ADO	0
ADPGK	1
ADPRHL1	-0,7
AFF4	0,1
AGO1	0
AGO2	0,9
AGPAT5	0,2
AIFM1	-2
AK2	-0,6
AKR1N1	-0,7
ALDH5A1	-1,6
ALG9	0,2
ANAPCS	0,2
ANKRA2	0,7
ANKRD26	0,3
ANPEP	-1,7
ANXA1	1,7

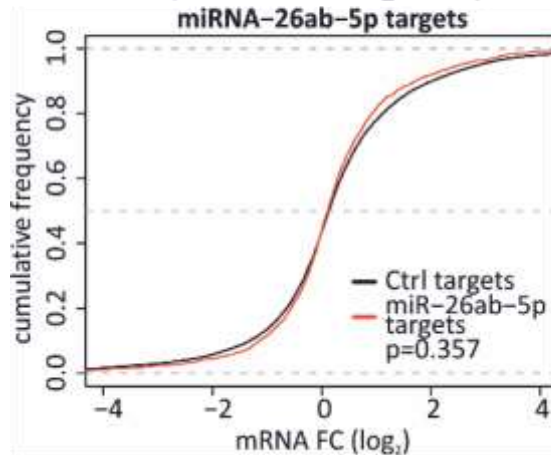
Expression status of all genes from RNA-Seq in ccRCC
compared with expression status of miRNA targets

RNA-Seq
Normal – 18
Tumor – 69



Potentially deregulated miRNA targets in ccRCC

Control miR-26ab-5p (1869 targets)



miRNA ↔

targets ↔

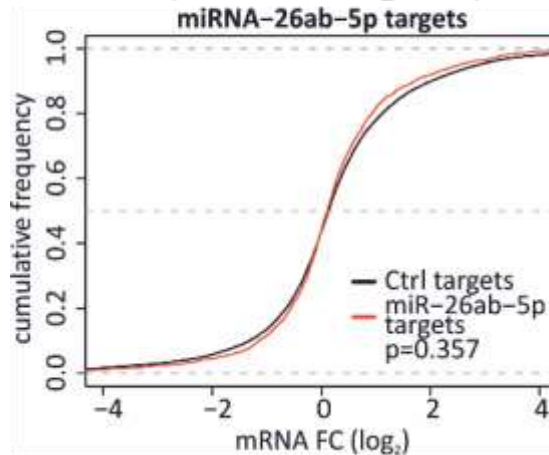
Mann-Whitney test, * $p < 0.05$

A. Kajdasz, J. Wesoly, 2020

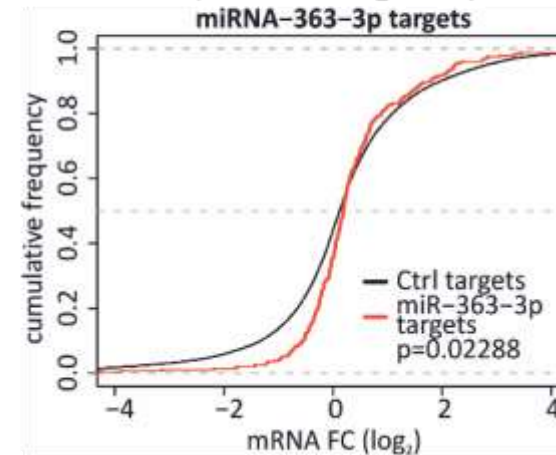


Potentially deregulated miRNA targets in ccRCC

Control miR-26ab-5p (1869 targets)



miR-363-3p (327 targets)



miRNA ↔

targets ↔

↓ miRNA

↑ targets

Mann-Whitney test, * p<0.05

A. Kajdasz, J.Wesoly, 2020



Potentially deregulated miRNA targets in ccRCC

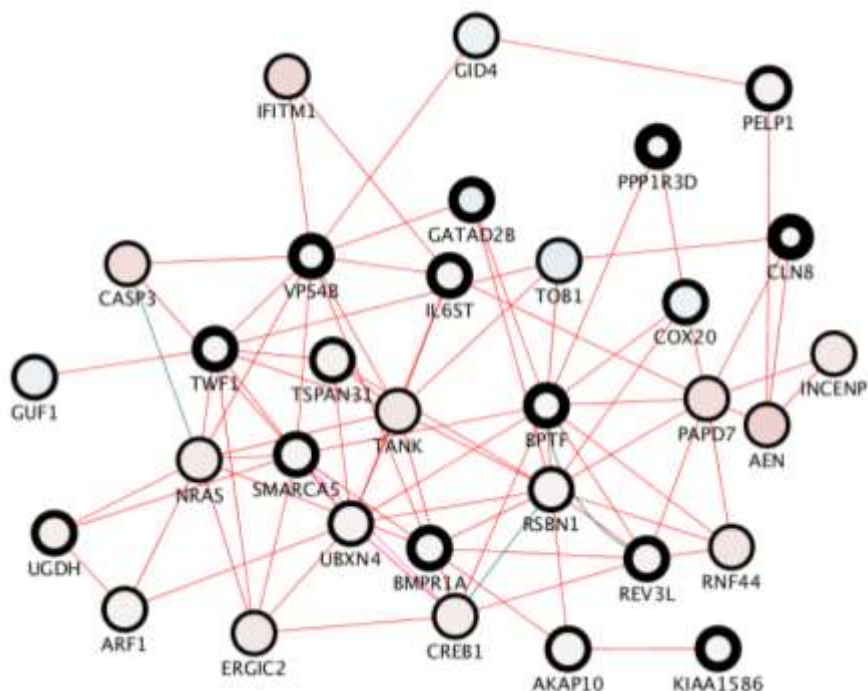
miRNA ID	Expression status	Targets
miR-200c-3p	DOWN	UP
miR-362-5p	DOWN	N.S.
miR-363-3p	DOWN	UP
miR-204-5p	DOWN	N.S.
miR-21-5p	UP	N.S.
miR-224-5p	UP	N.S.
miR-155-5p	UP	N.S.
miR-210-3p	UP	N.S.



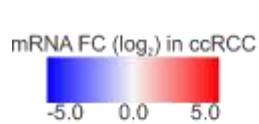
Potential functions of miRNA-363-3p targets

↓ miRNA

↑ targets



GO id	Description	q-value	in Sample	in Genome
GO:0000289	nuclear-transcribed mRNA poly(A) tail shortening	1.6E-06	10	31
GO:0000288	nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay	4.2E-04	10	58
GO:0031124	mRNA 3'-end processing	4.2E-04	12	88
GO:0030014	CCR4-NOT complex	6.2E-04	6	15
GO:0031123	RNA 3'-end processing	8.7E-04	12	101
GO:0000956	nuclear-transcribed mRNA catabolic process	1.1E-02	14	179
GO:0006397	mRNA processing	1.1E-02	18	287
GO:0010608	posttranscriptional regulation of gene expression	1.6E-02	18	298
GO:0006402	mRNA catabolic process	1.7E-02	14	190
GO:0006417	regulation of translation	3.3E-02	12	152
GO:0006401	RNA catabolic process	4.3E-02	14	215
GO:0060211	regulation of nuclear-transcribed mRNA poly(A) tail shortening	4.3E-02	4	11
GO:0060213	positive regulation of nuclear-transcribed mRNA poly(A) tail shortening	4.3E-02	4	11



Border width:
 ○ p value < 0.05
 ○ p value > 0.05
 ● Gene added by GeneMANIA

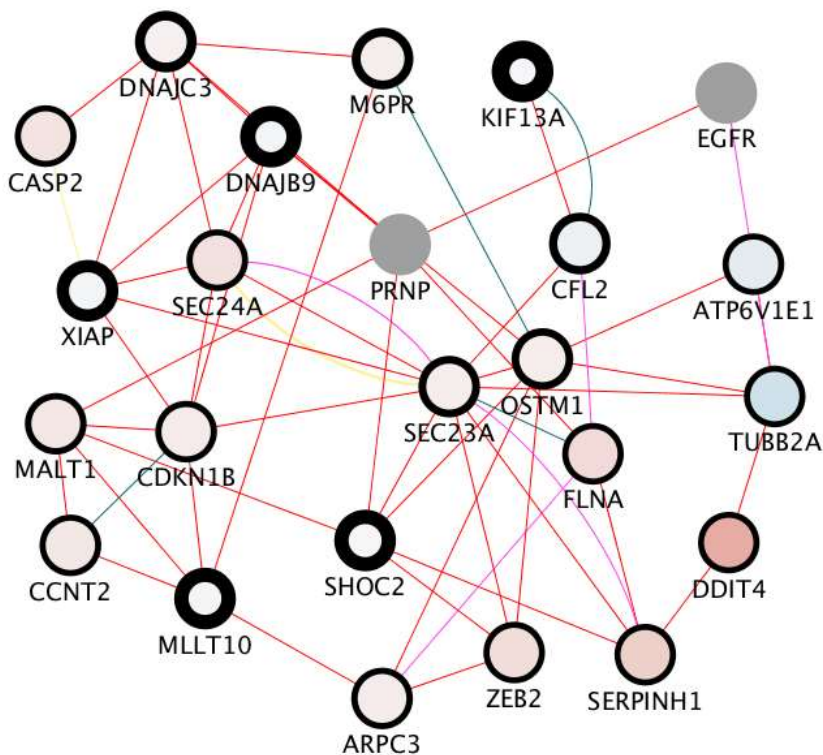
Network type:
 — Co-expression
 — Co-localization
 — Pathway
 — Physical Interactions



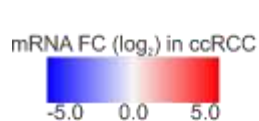
Potential functions of miRNA-200c-3p targets

↓ miRNA

↑ targets



GO id	Description	q-value	in Sample	in Genome
GO:0038093	Fc receptor signaling pathway	9.35E-12	23	219
GO:0002768	immune response-regulating cell surface receptor signaling pathway	9.35E-12	26	296
GO:0048011	neurotrophin TRK receptor signaling pathway	8.39E-11	24	274
GO:0038179	neurotrophin signaling pathway	8.39E-11	24	277
GO:0038095	Fc-epsilon receptor signaling pathway	2.68E-10	19	166
GO:0008543	fibroblast growth factor receptor signaling pathway	3.46E-10	19	170
GO:0044344	cellular response to fibroblast growth factor stimulus	9.97E-10	19	183
GO:0071774	response to fibroblast growth factor	9.97E-10	19	183
GO:0048015	phosphatidylinositol-mediated signaling	3.26E-09	18	173
GO:0048017	inositol lipid-mediated signaling	3.26E-09	18	173
GO:0007173	epidermal growth factor receptor signaling pathway	9.96E-08	18	213
GO:0038127	ERBB signaling pathway	1.15E-07	18	216

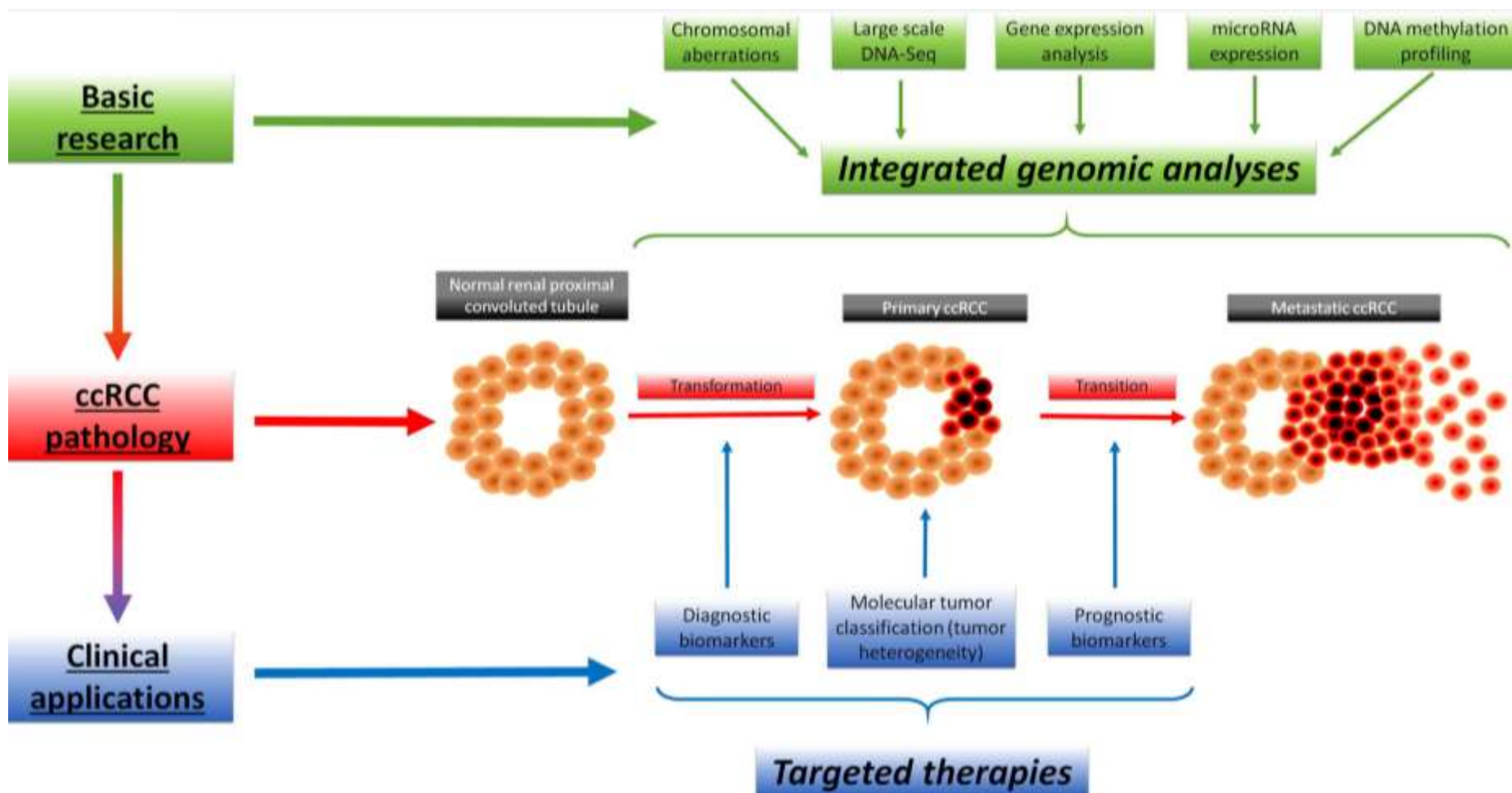


Border width:
 ○ p value < 0.05
 ○ p value > 0.05
 ● Gene added by GeneMANIA

Network type:
 — Co-expression
 — Co-localization
 — Pathway
 — Physical Interactions



Integrative genomic approaches in ccRCC management





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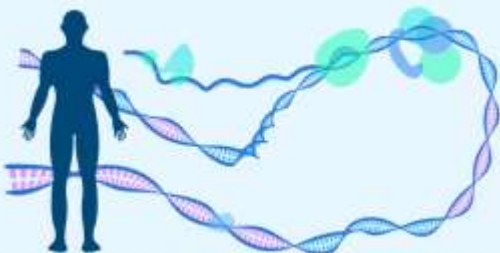


Lab of HTT

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Dr Natalia Derebecka

Dr Arkadiusz Kajdasz



Department of Human Molecular Genetics

Laboratory of High Throughput Technologies

<http://dhmg.amu.edu.pl>



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RNA

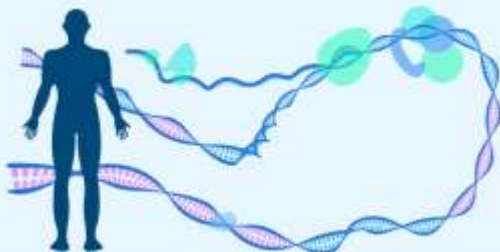


nanofun

UNIA EUROPEJSKA
EUROPEJSKI FUNDUSZ
ROZWOJU REGIONALNEGO



INNOWACYJNA
GOSPODARKA
NARODOWA STRATEGIA SPÓJNOŚCI



Department of Human Molecular Genetics
Laboratory of High Throughput Technologies

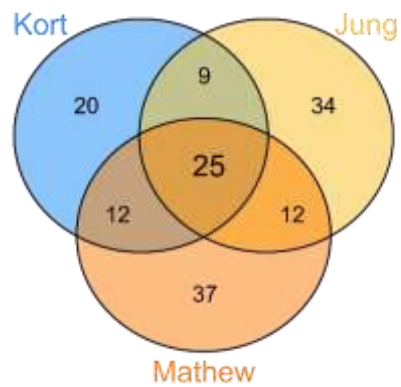
<http://dhmg.amu.edu.pl>



Common miRNAs deregulated in ccRCC

Microarray experiments in ccRCC

(25 commonly deregulated miRNAs)

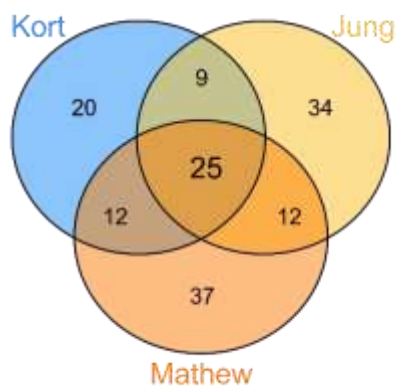




Common miRNAs deregulated in ccRCC

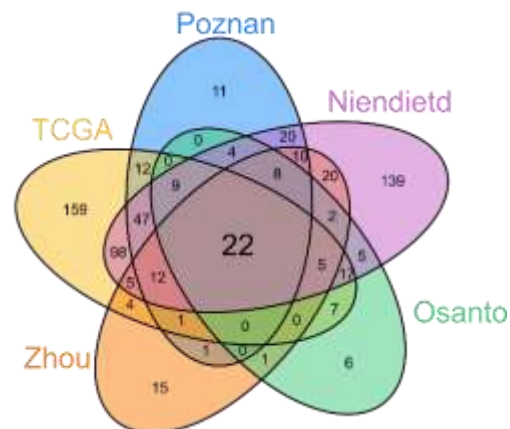
Microarray experiments in ccRCC

(25 commonly deregulated miRNAs)



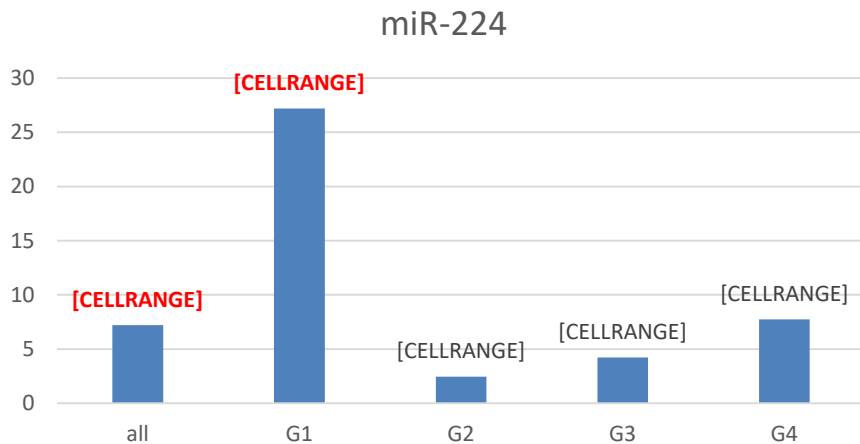
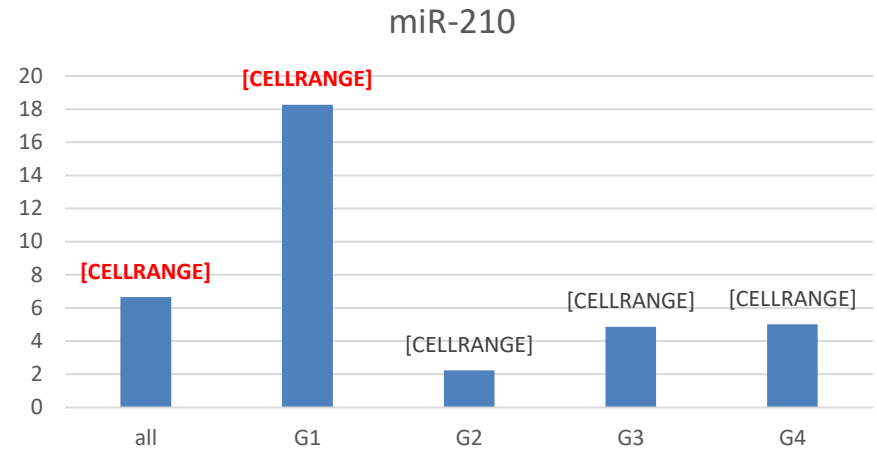
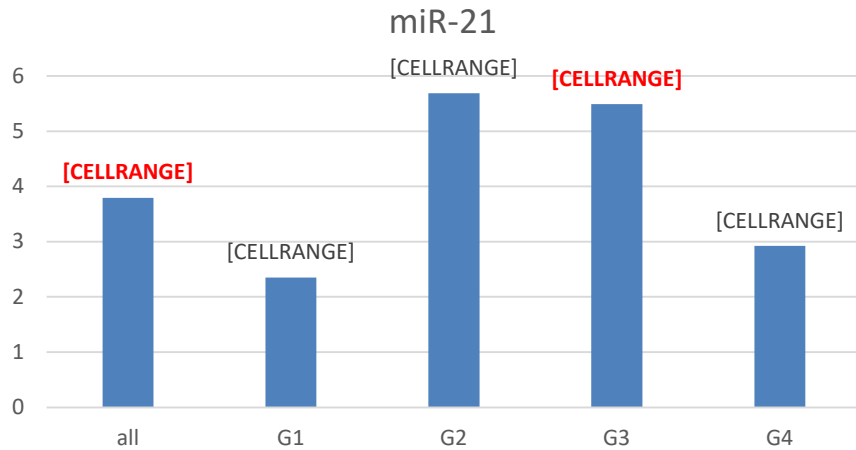
NGS experiments in ccRCC

(22 commonly deregulated miRNAs)





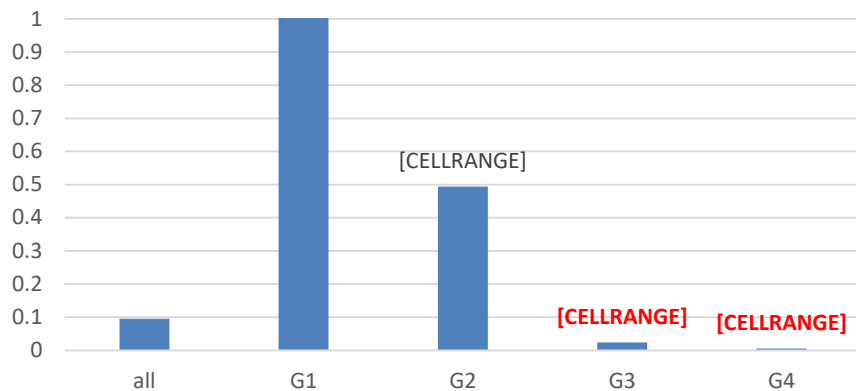
Validation of miRNA deregulation in ccRCC tumor



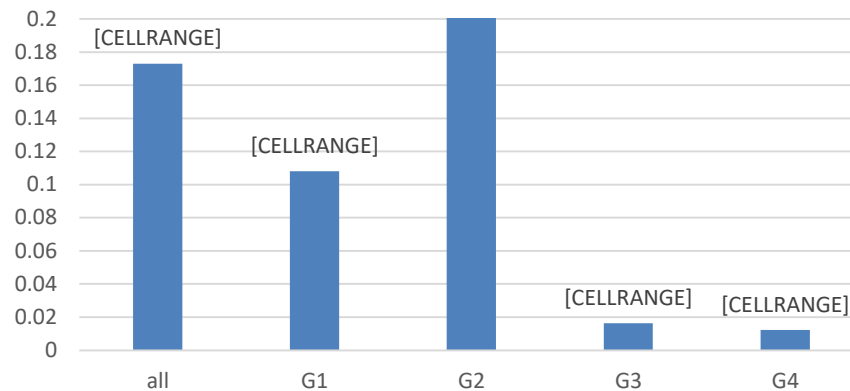


Validation of miRNA deregulation in ccRCC

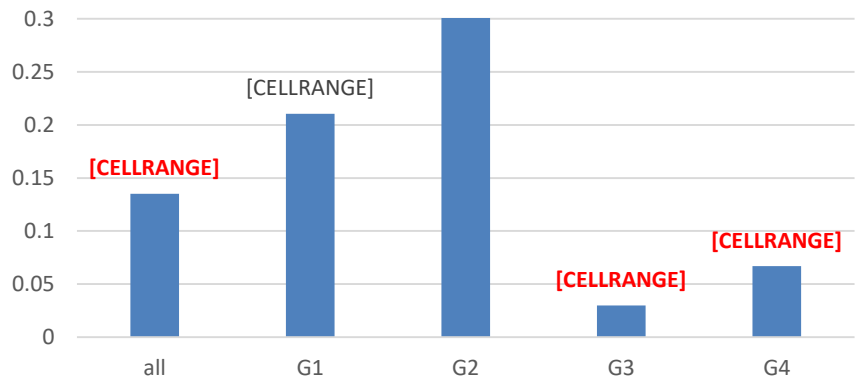
miR-200



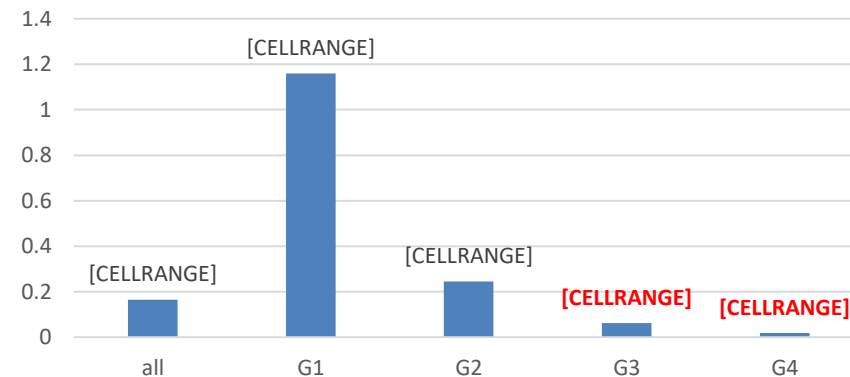
miR-204



miR-362

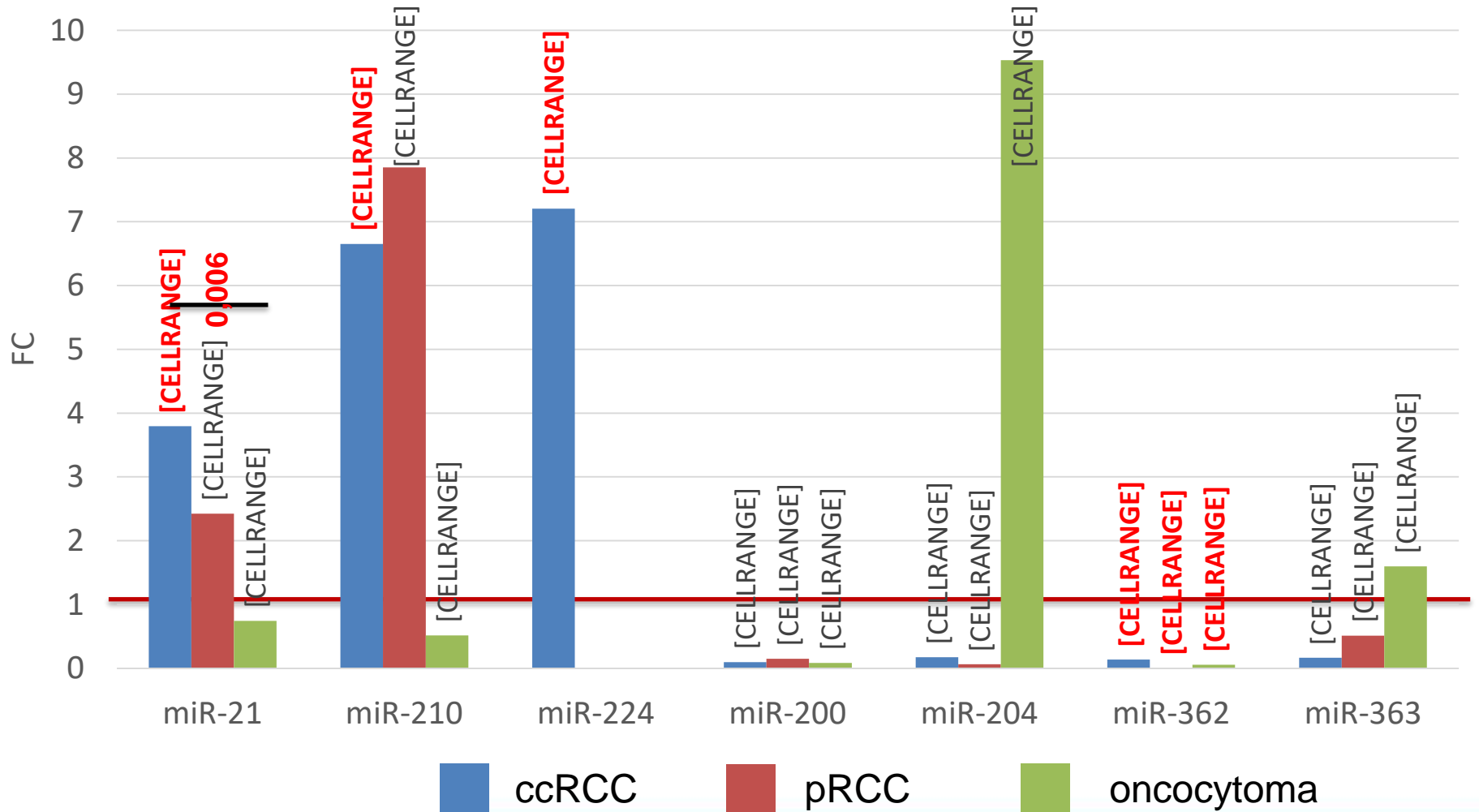


miR-363





miRNA deregulation in RCC subtypes





pRCC – papillary renal cell carcinoma – 15% of RCC
chRCC – chromophobe renal cell carcinoma – 5% of RCC
Oncocytoma



pRCC – papillary renal cell carcinoma – 15% of RCC

n = 4

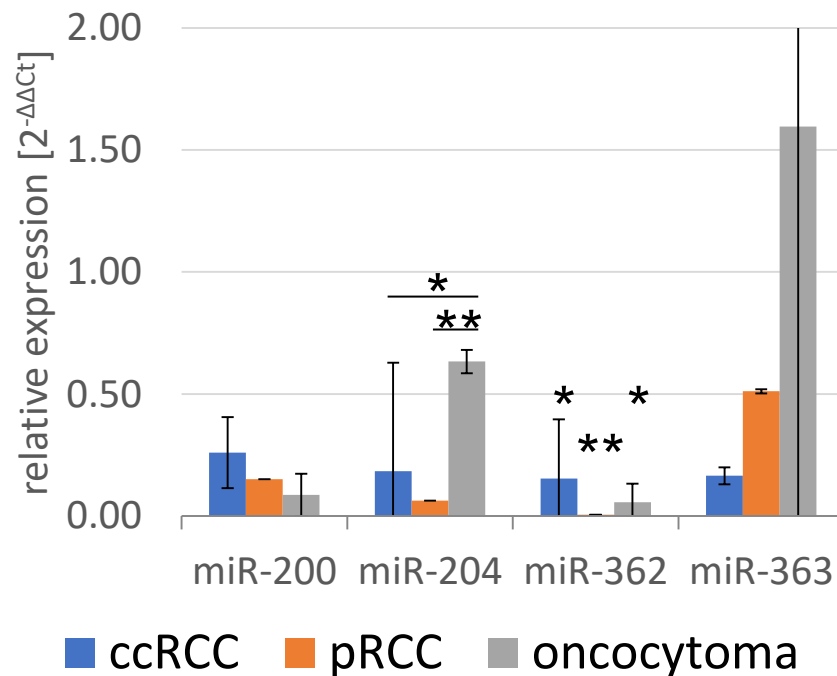
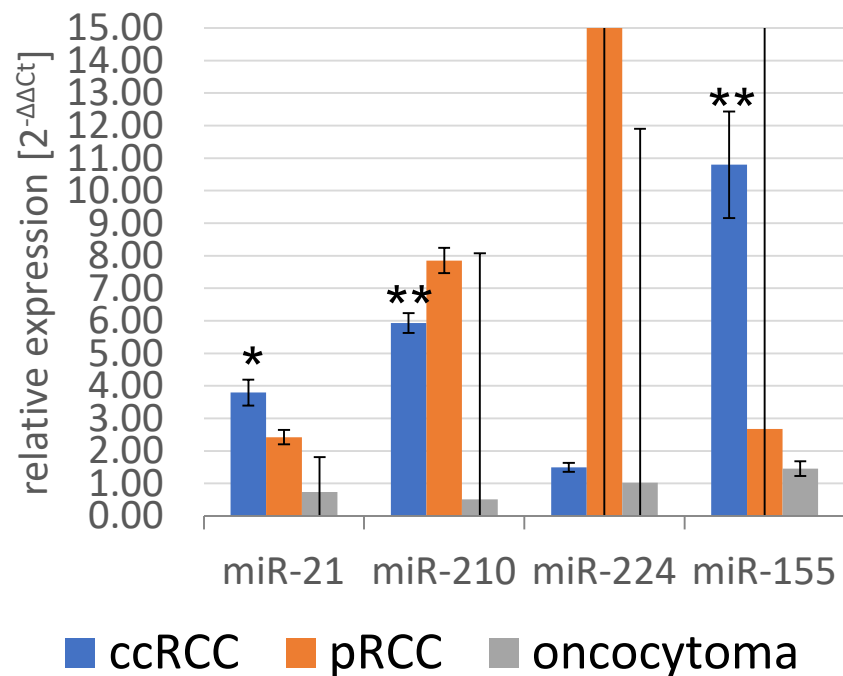
chRCC – chromophobe renal cell carcinoma – 5% of RCC

Oncocytoma

n = 3



miRNA deregulation in RCC subtypes



t-test

* p<0.05

** p<0.01

*** p<0.001



miRNA deregulation in RCC subtypes – summary

ccRCC and pRCC have similar miRNA expression pattern

Oncocytoma has different miRNA expression pattern than ccRCC or pRCC

miR-362 could be RCC marker or play role in RCC progression?



Commonly deregulated miRNAs in other RCC subtypes – experiments in meta-analysis

RCC subtype	Deregulated miRNAs		Samples		Experiment	Ref.
	Down	Up	Normal	Tumor		
pRCC	153	245	34	290	NGS	TCGA (dbDEMC2)
pRCC	35	42	4	4	Microarray	Kort EJ, 2008 (dbDEMC2)
pRCC	17	17	18	7	Microarray	Wach S, 2013 (dbDEMC2)
chRCC	171	180	25	66	NGS	TCGA (dbDEMC2)
chRCC	12	6	4	4	Microarray	Kort EJ, 2008 (dbDEMC2)
Oncocytoma	14	20	20	14	Microarray	Kort EJ, 2008 (dbDEMC2)

pRCC – papillary renal cell carcinoma – 15% of RCC

chRCC – chromophobe renal cell carcinoma – 5% of RCC

Oncocytoma



Validation of miRNA deregulation in ccRCC: all patients

non-ccRCC – 13

ccRCC – 24

Y axis

>1 – upregulation

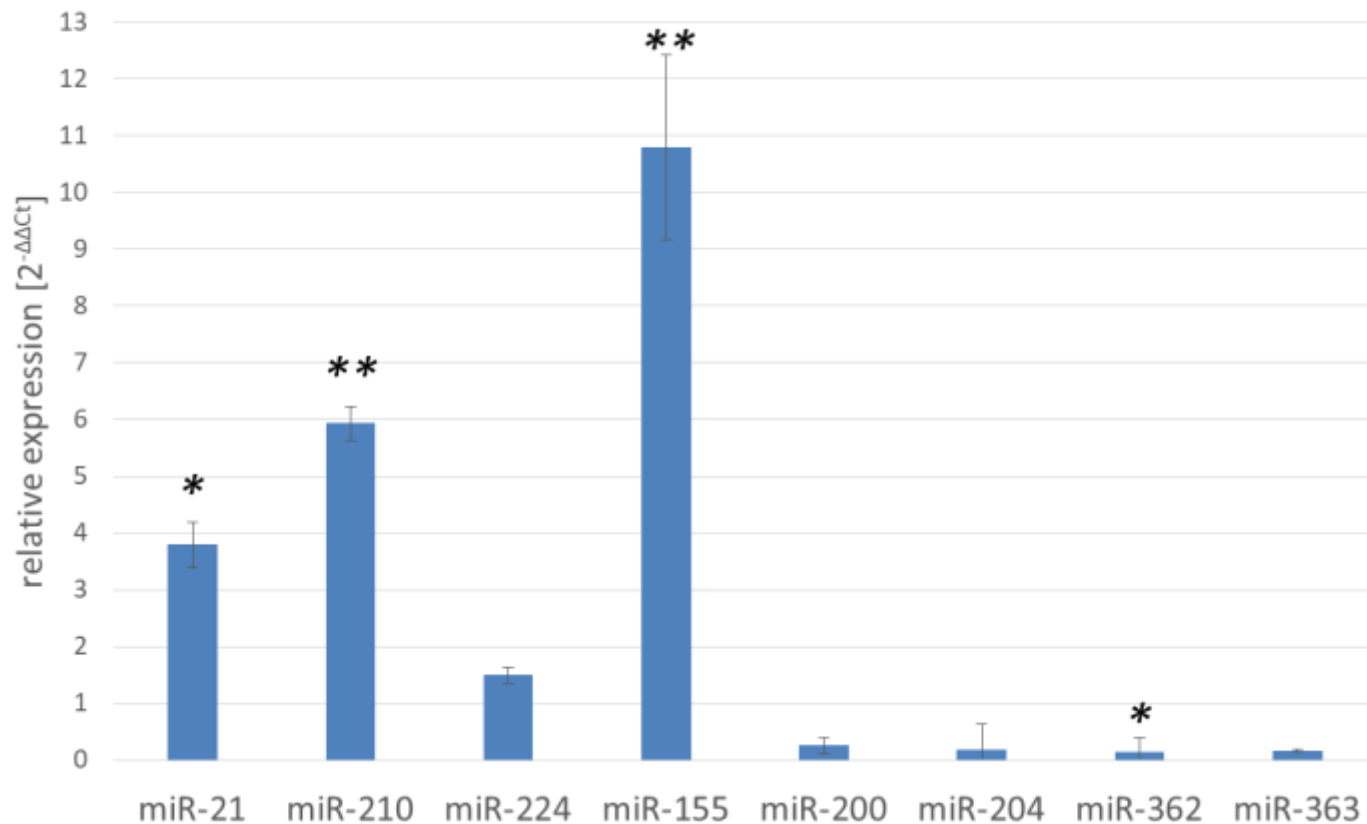
<1 - downregulation

t-test

* p<0.05

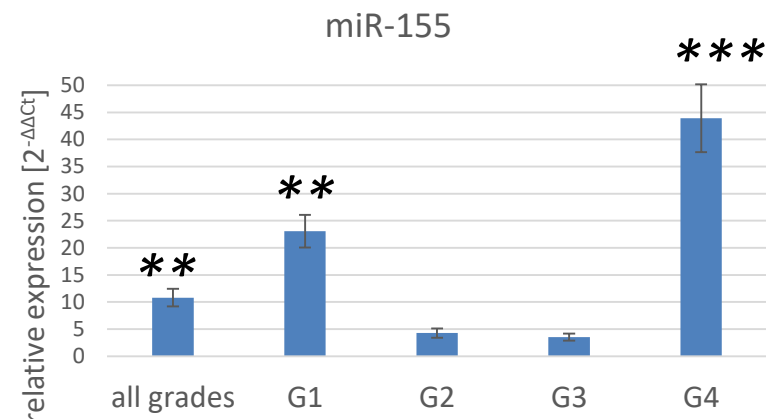
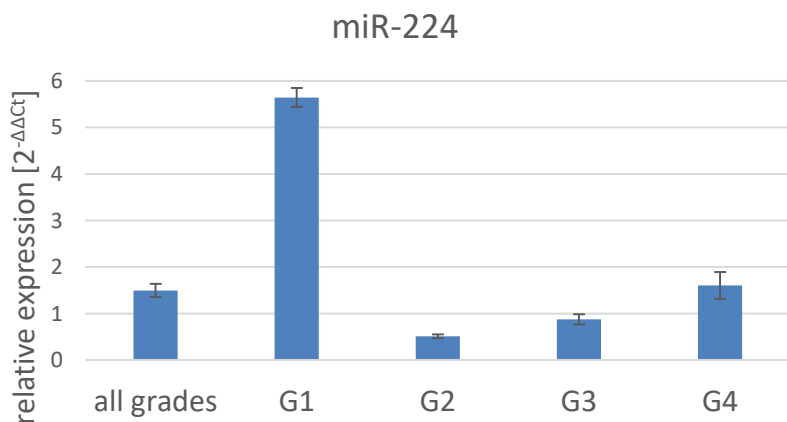
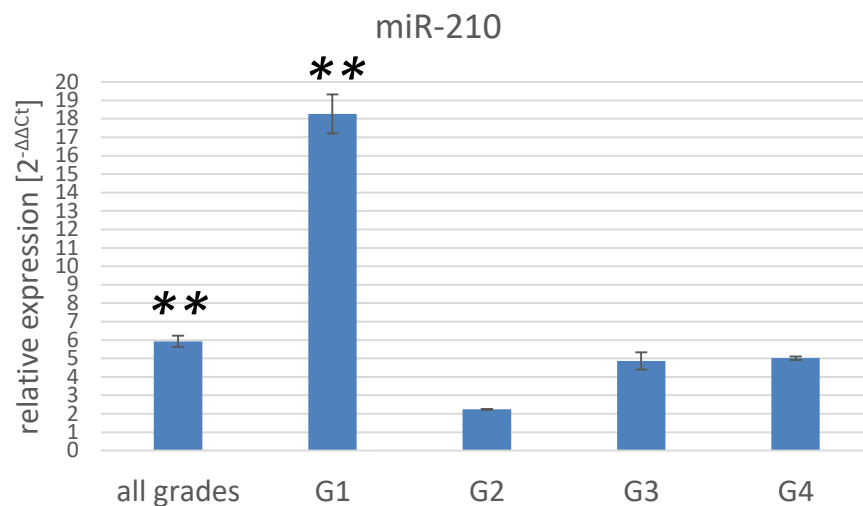
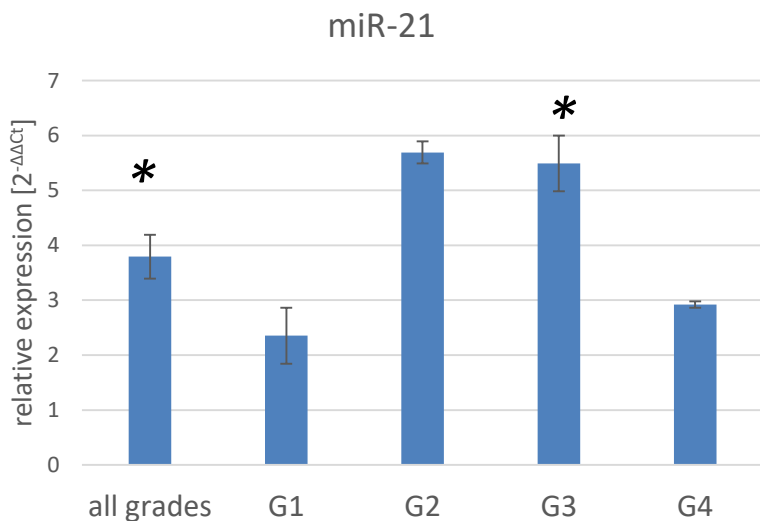
** p<0.01

*** p<0.001





Validation of miRNA deregulation in ccRCC: all patients vs grades

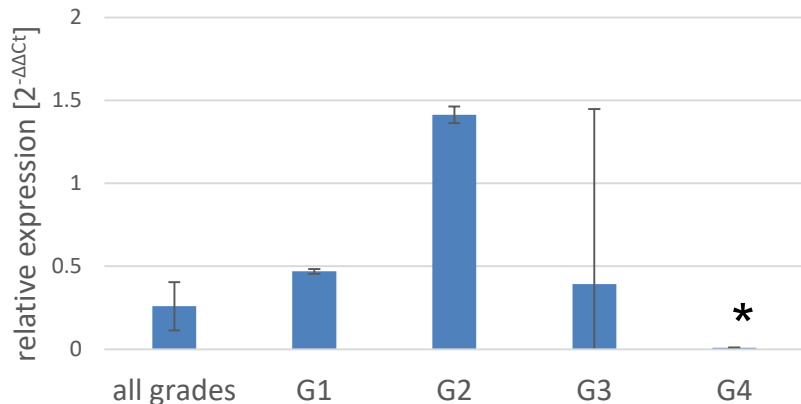


t-test
* p<0.05
** p<0.01
*** p<0.001

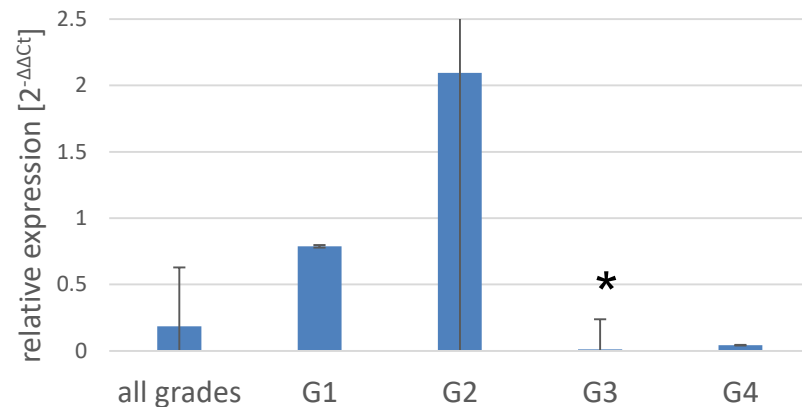


Validation of miRNA deregulation in ccRCC: all patients vs grades

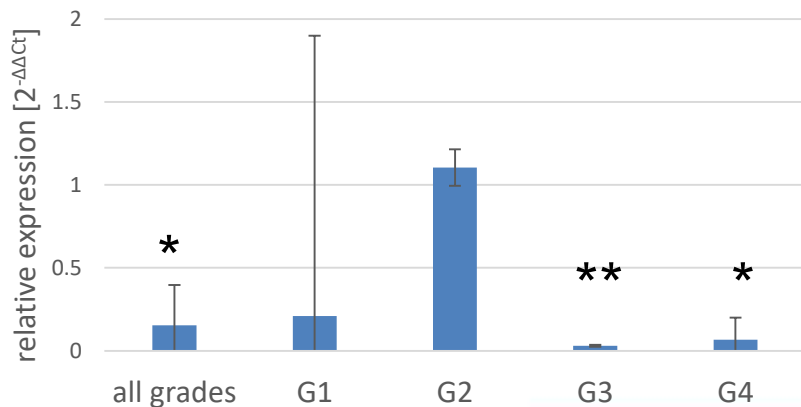
miR-200



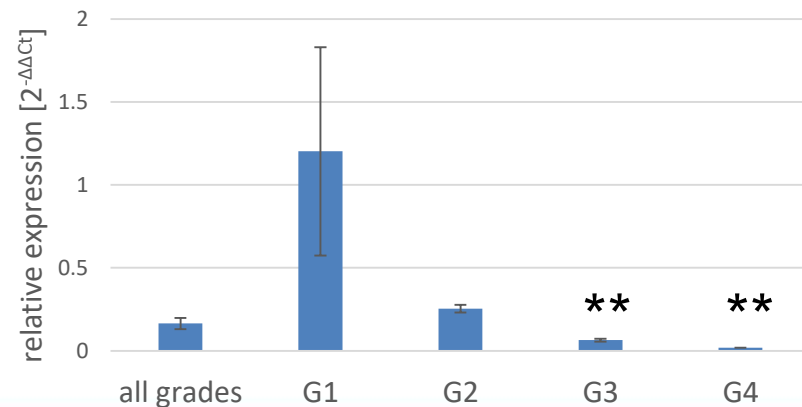
miR-204



miR-362



miR-363



t-test
* p<0.05
** p<0.01
*** p<0.001