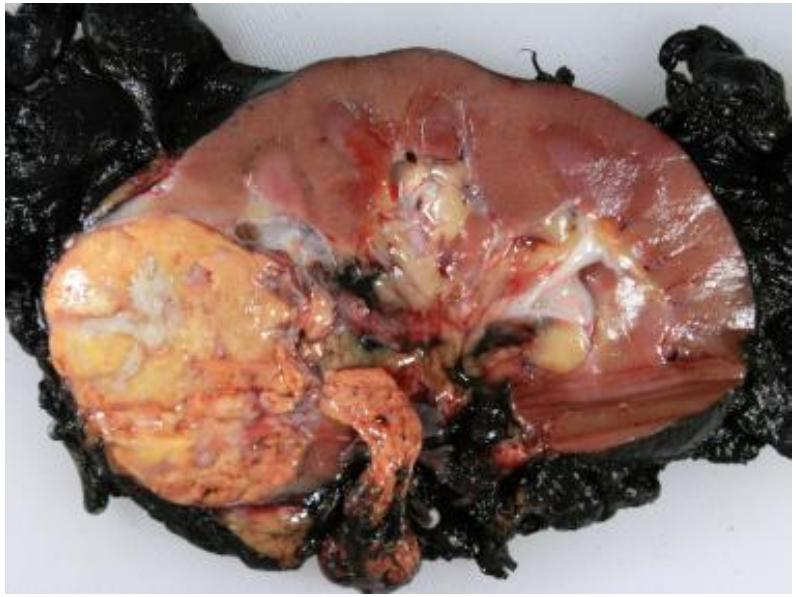
ADAM MICKIEWICZ UNIVERSITY IN POZNAŃ
Faculty of Biology

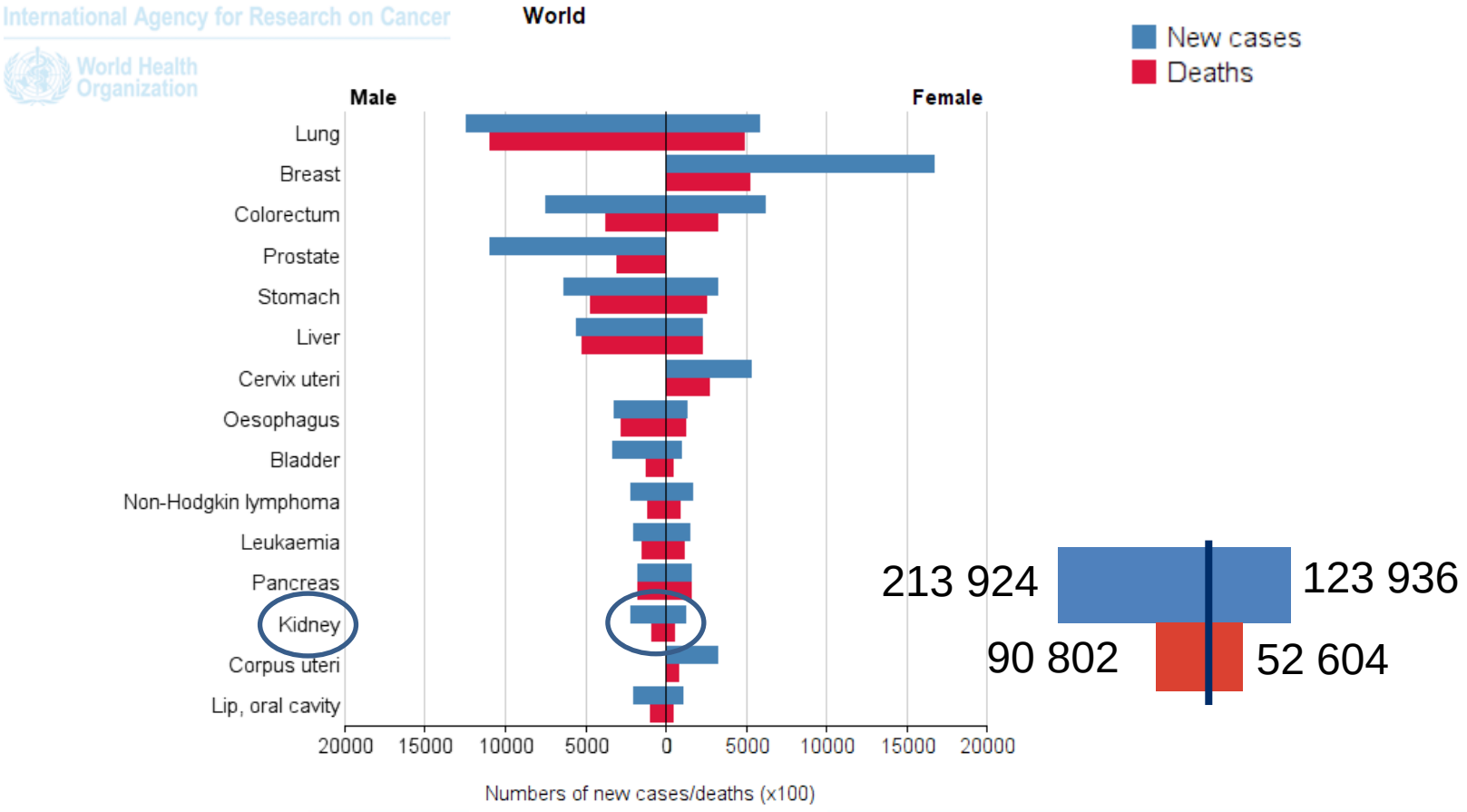
Diagnostics of ccRCC



Hans Bluyssen
26-04-2021

Kidney cancer incidence

2–3% of all adult malignancies diagnosed annually

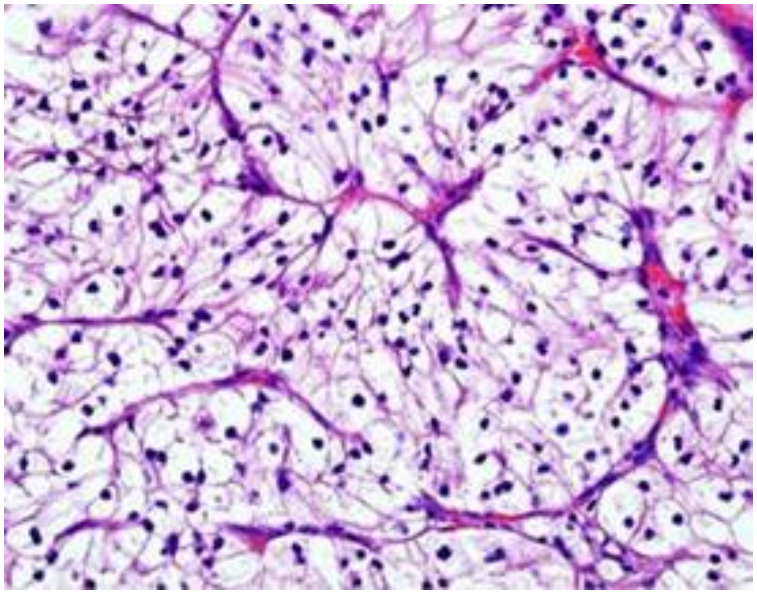


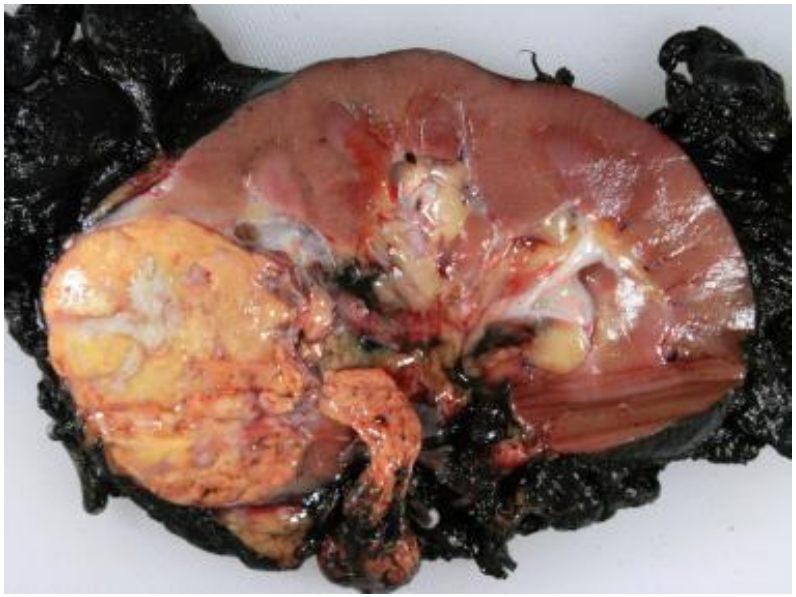
Source: Globocan 2012 (IARC)

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)

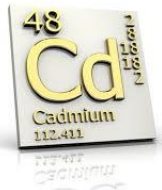
Factors increasing the risk of developing kidney cancer

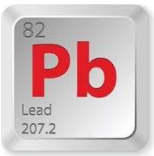
- **Administration of certain medications:**

  diuretics and pain-killers

- **Exposure to toxic compounds:**

  asbestos, cadmium, lead, herbicides or organic solvents

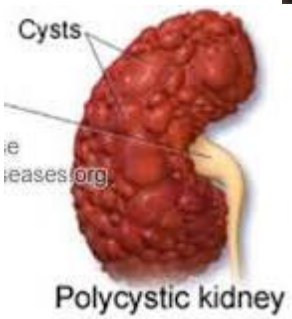




- **Acquired cystic disease of the kidney**

- **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

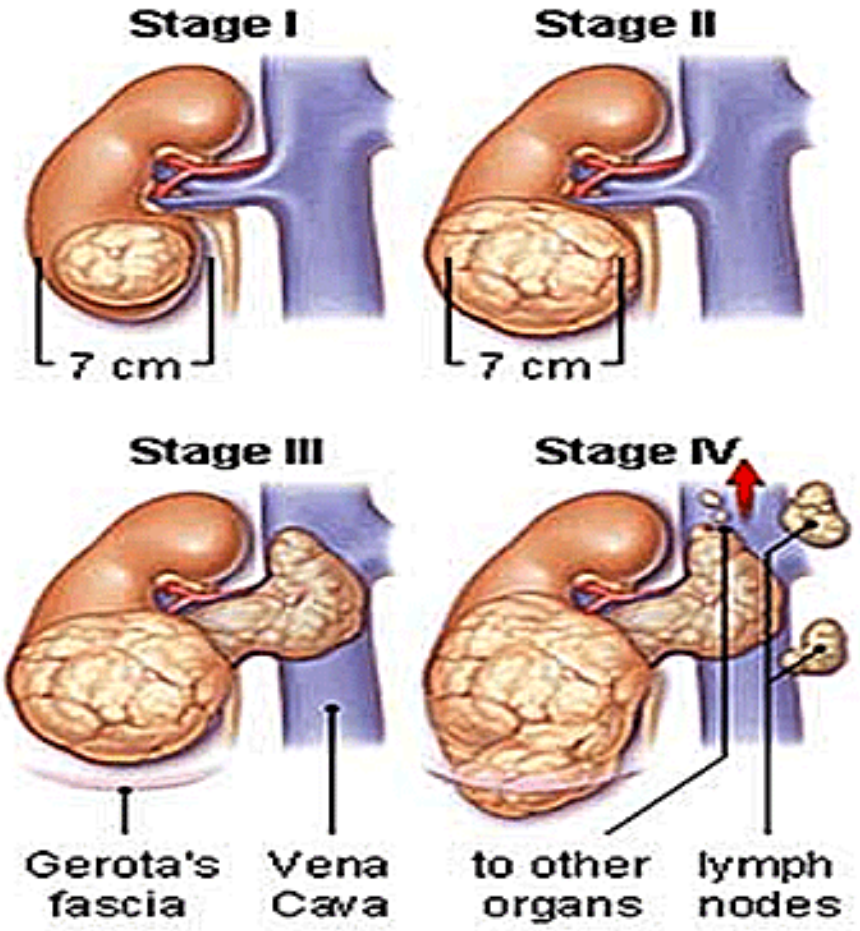
- a mass in the abdomen or flank

weight loss, hypertension, fatigue

Clinical classification: **TNM CANCER STAGE**

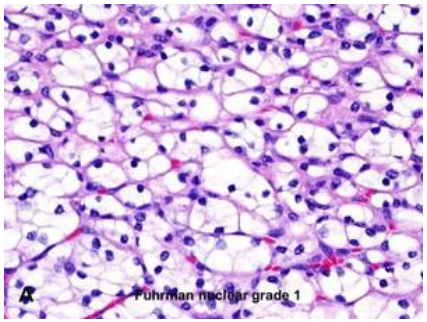
TABLE 3: TNM staging of renal cell carcinoma

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 issues, 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 NUCLER 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



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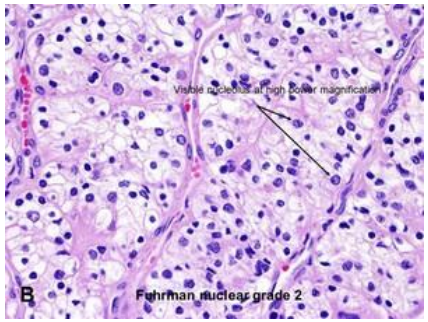
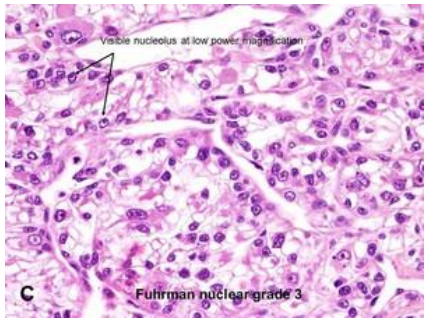
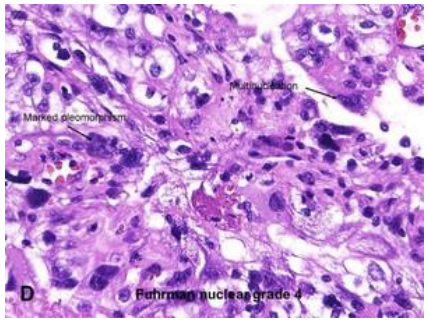


II



III

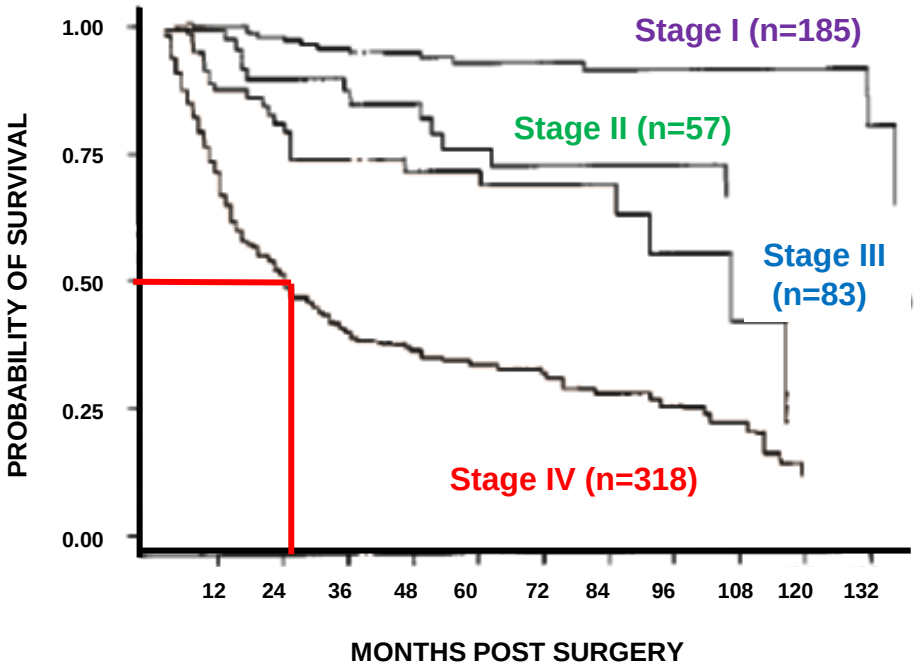


IV

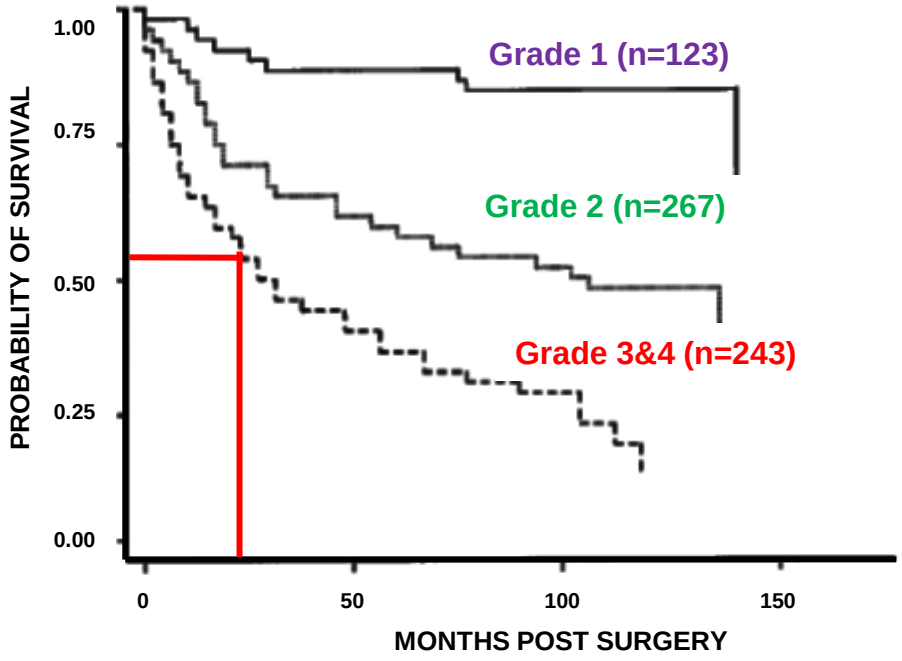
ccRCC - prognosis

Five-year cancer specific survival

tumor TNM stage

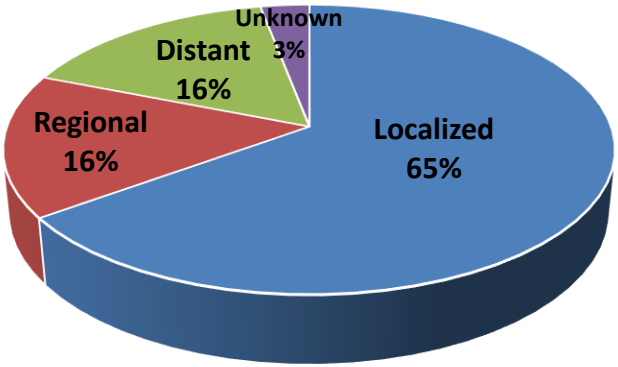


Fuhrman grade



Tsui KH, Vol. 163, 1090–1095, April 2000

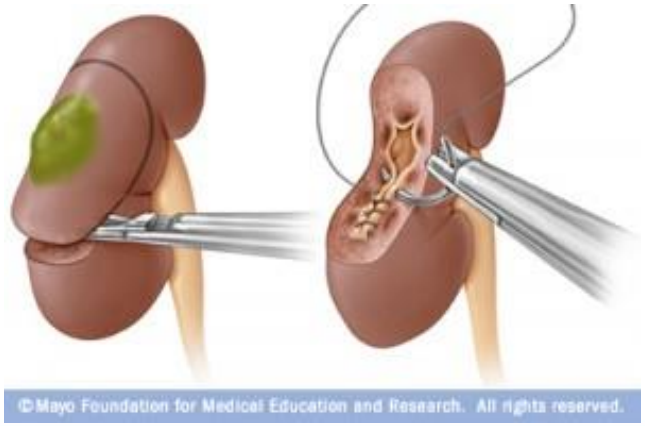
Therapy of ccRCC



TNM stage IV: nephrectomy + systemic therapy
(targeted / immune therapy)

TNM stage I-III: nephrectomy

- Surgery (radical nephrectomy or partial nephrectomy).
- Surgery (nephrectomy), before or after radiation therapy.
- Radiation therapy as palliative therapy to relieve symptoms in patients who cannot have surgery.
- Arterial embolization as palliative therapy.



SEER

National Cancer Institute

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

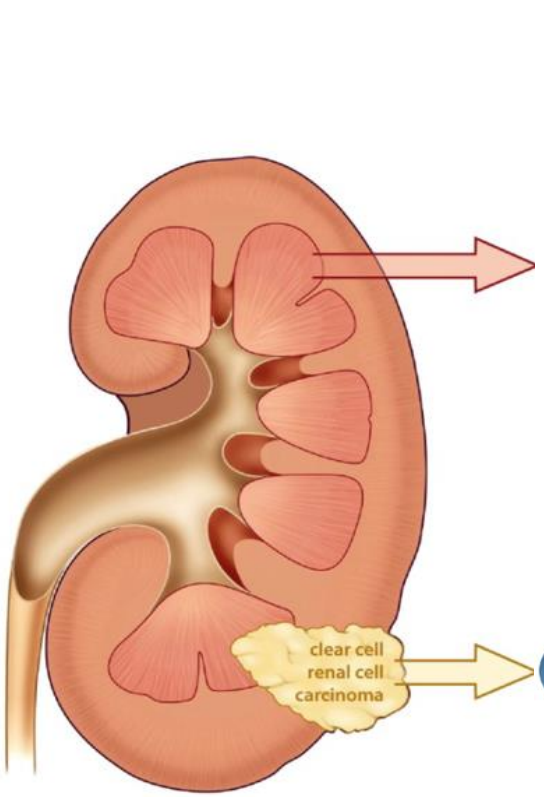
von Hippel-Lindau disease - hereditary

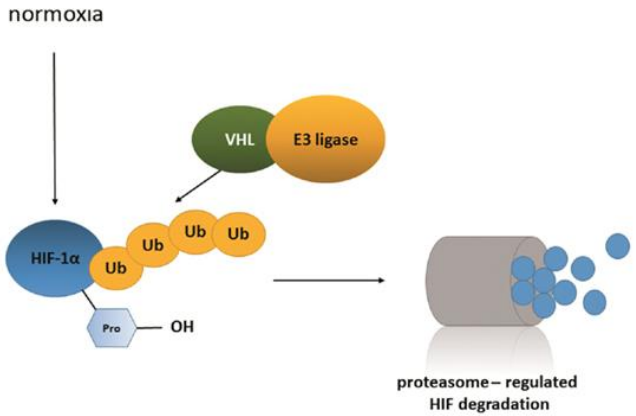
loss of VHL gene
inactivated VHL: mutations,
promoter hypermethylation

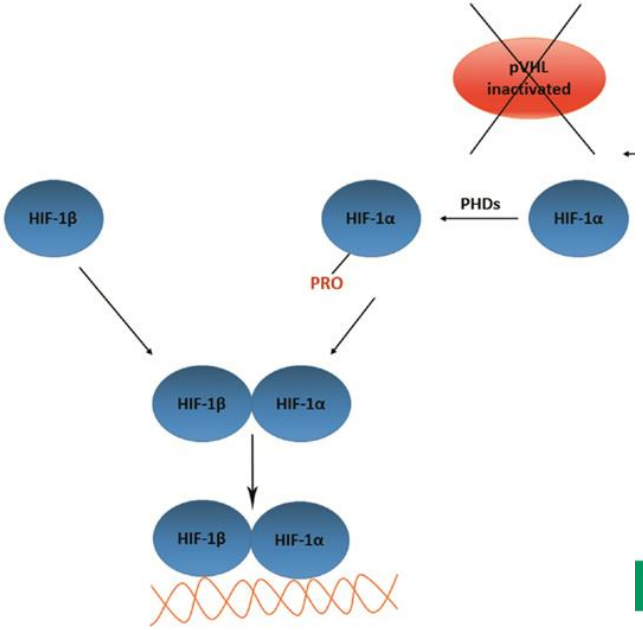
loss of p arm of chromosome 3 harboring VHL gene (70-80%) or
loss of heterozygosity (LOH) at 3p

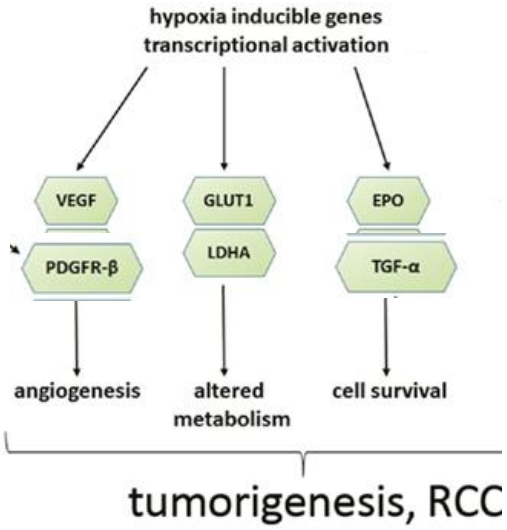
sporadic

VHL function - response to oxygen concentration

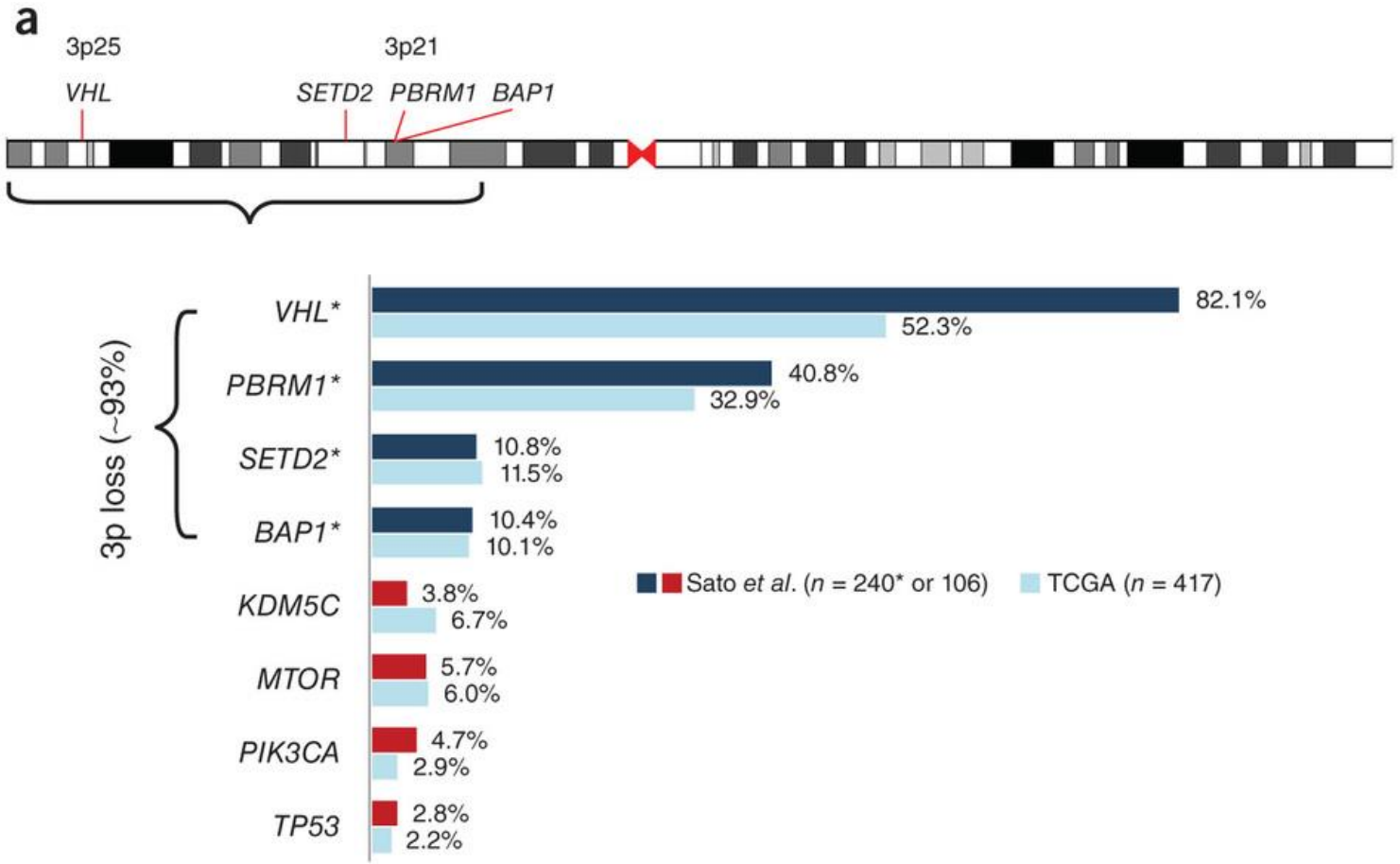






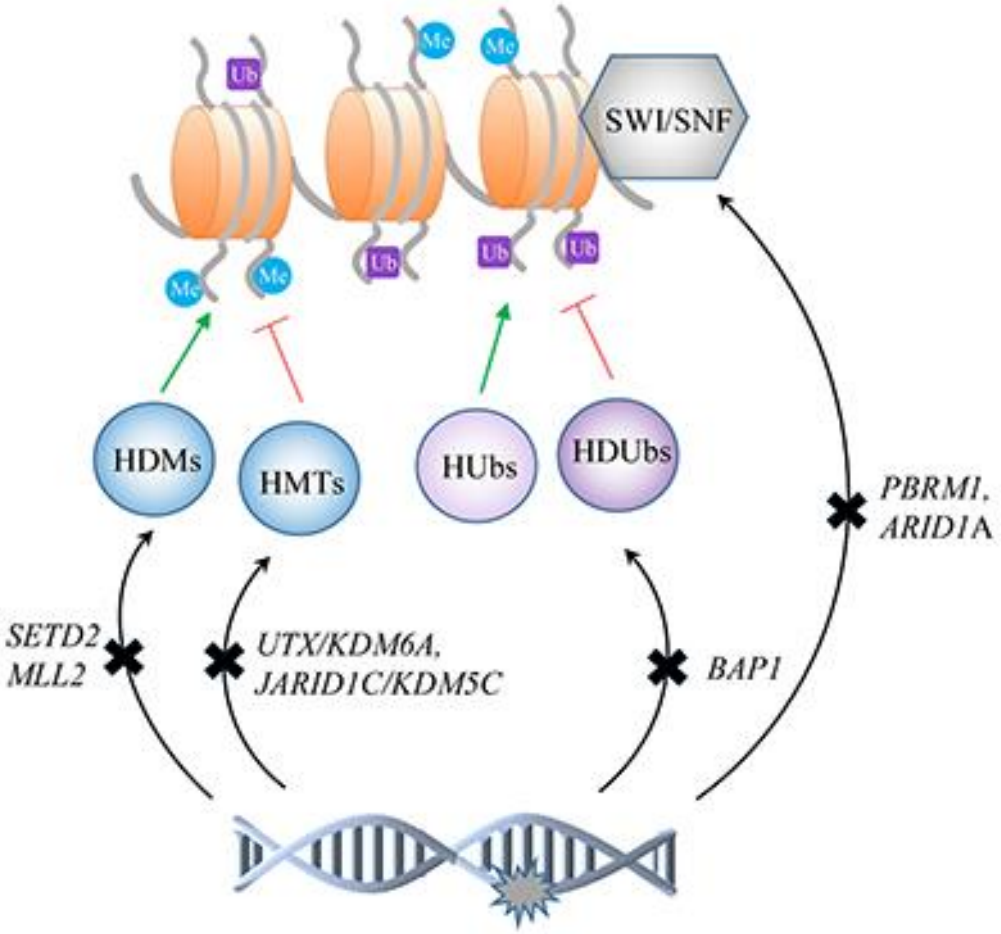


Other genes frequently mutated in ccRCC



Hakimi A, Nature Genetics 45, 849–850 (2013)

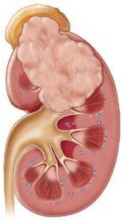
Chromatin remodelling



Histone Modification

Hakimi A, Nature Genetics 45, 849–850 (2013); rewieved by Kluzek et al

Integrative genomic approaches in ccRCC management



Basic research

Chromosomal aberrations | Large scale DNA-Seq | Gene expression analysis | microRNA expression | DNA methylation profiling

Integrated genomic analyses

ccRCC pathology

Normal renal proximal convoluted tubule → Transformation → Primary ccRCC → Transition → Metastatic ccRCC

Clinical applications

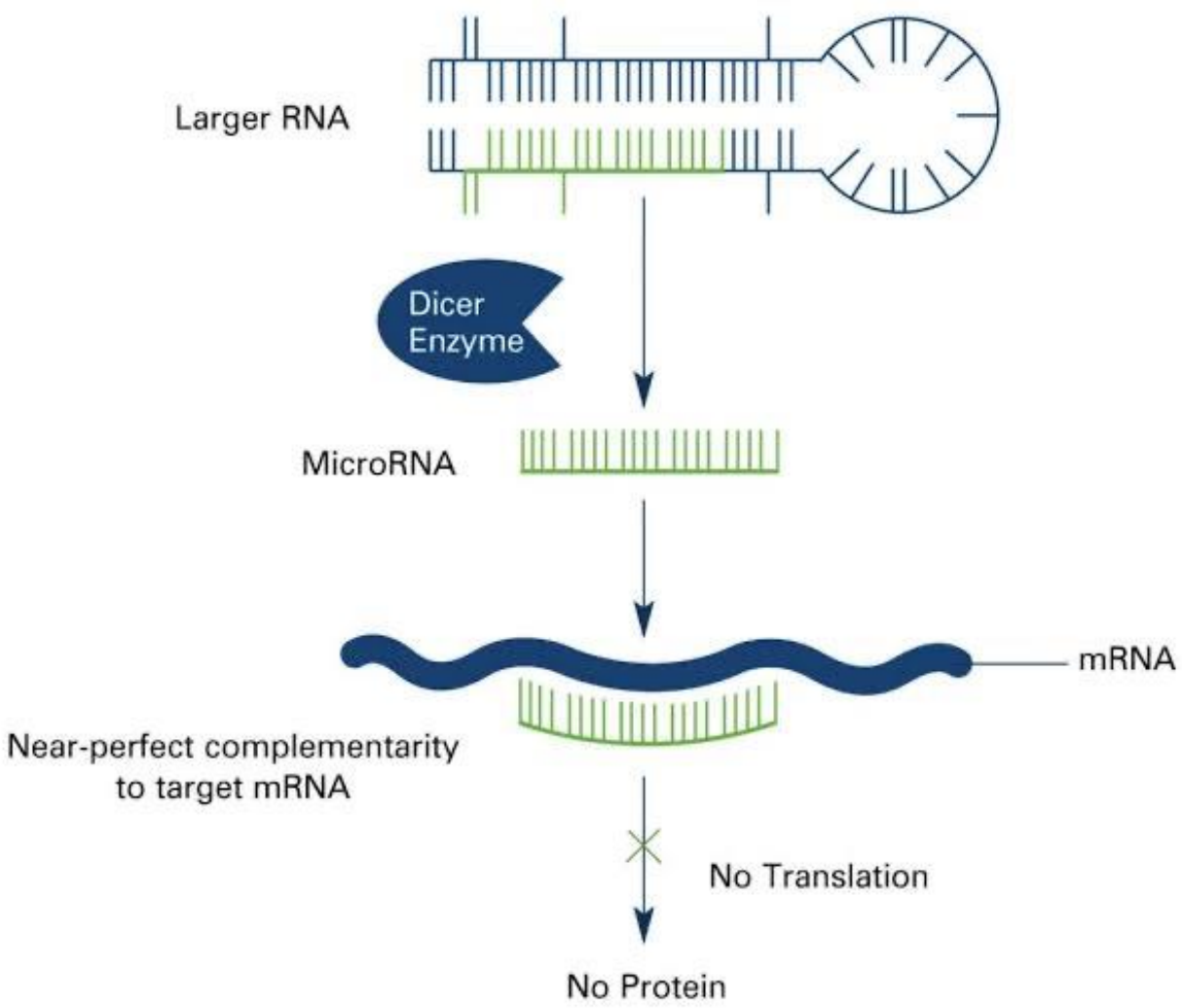
Diagnostic biomarkers | Molecular tumor classification (tumor heterogeneity) | Prognostic biomarkers

Targeted therapies

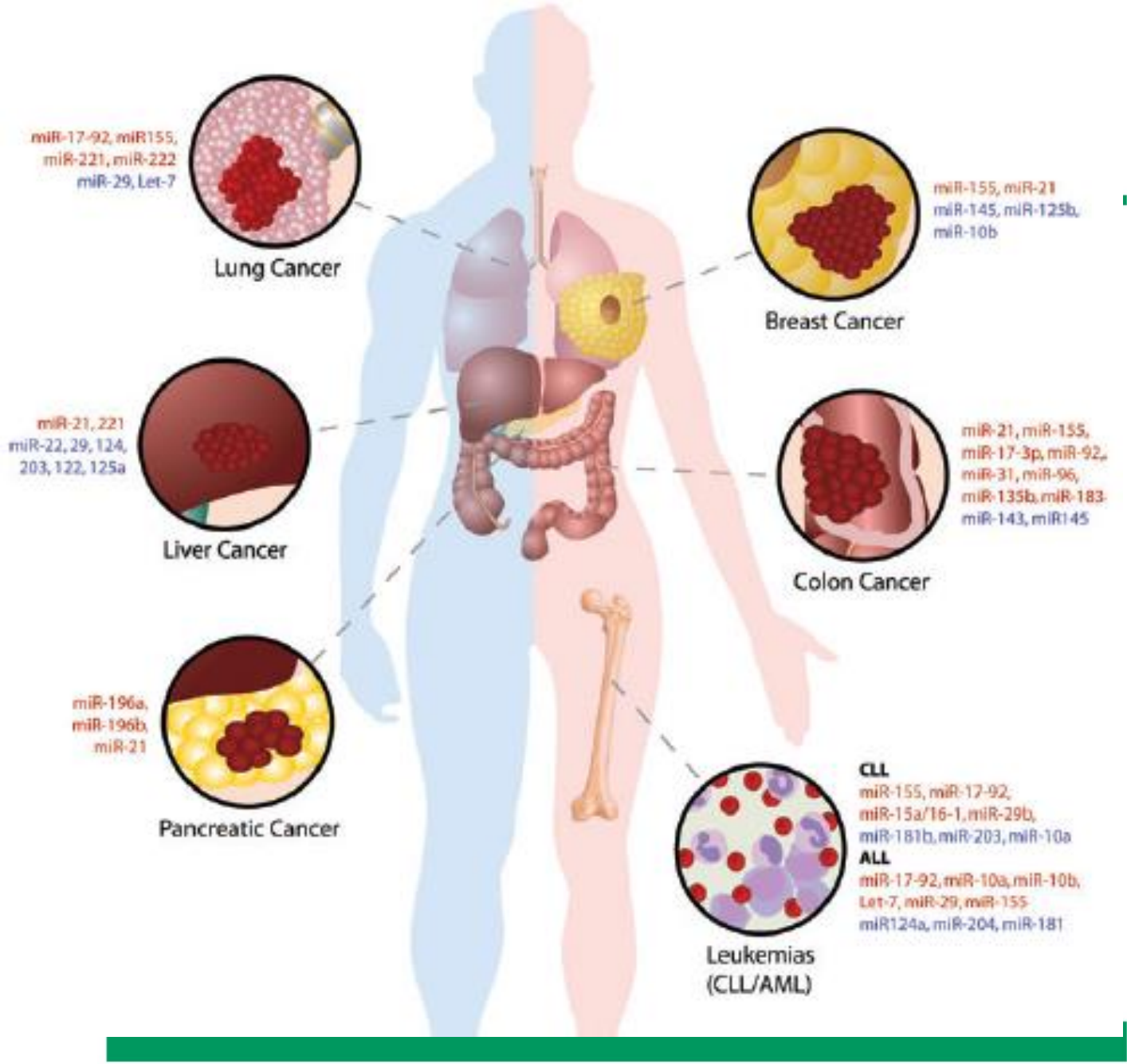
J.Wesoly, Cancer Letters 2013

microRNAs?

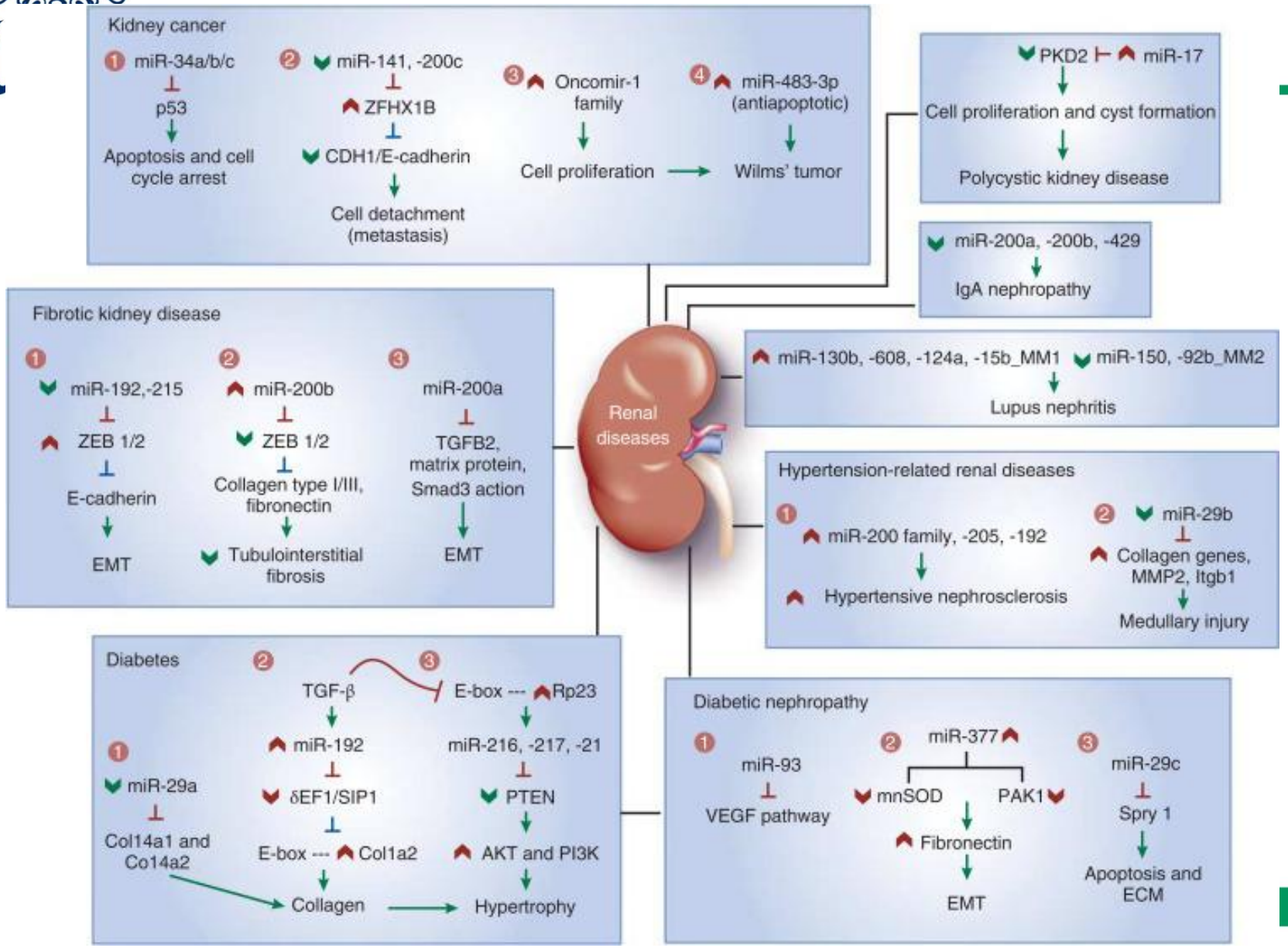
microRNAs


Larger RNA
Dicer
Enzyme
MicroRNA
mRNA
Near-perfect complementarity
to target mRNA
No Translation
No Protein

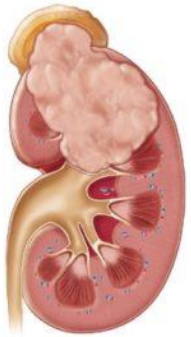
miRNAs in Cancer



miRNAs in ccRCC



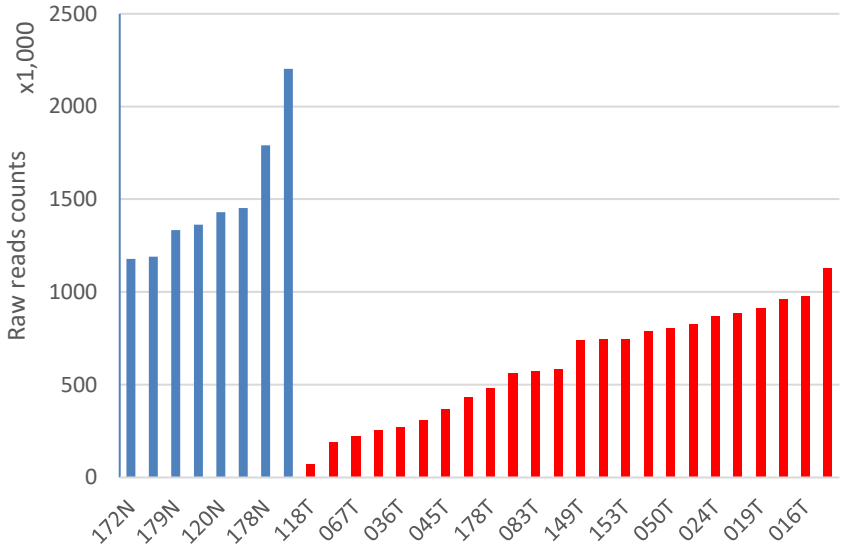
Research questions



Are miRNAs efficient ccRCC biomarkers?

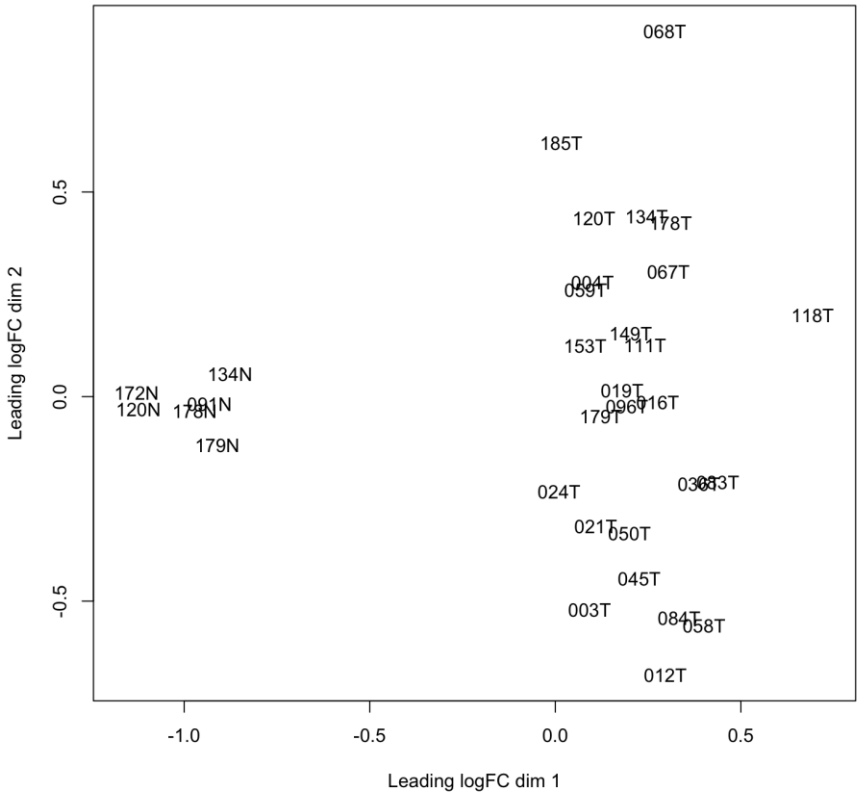
What is the role of miRNAs in ccRCC etiology and/or progression?

miRNA in polish ccRCC patients



Normal – 6
Tumor – 26

Principle component analysis

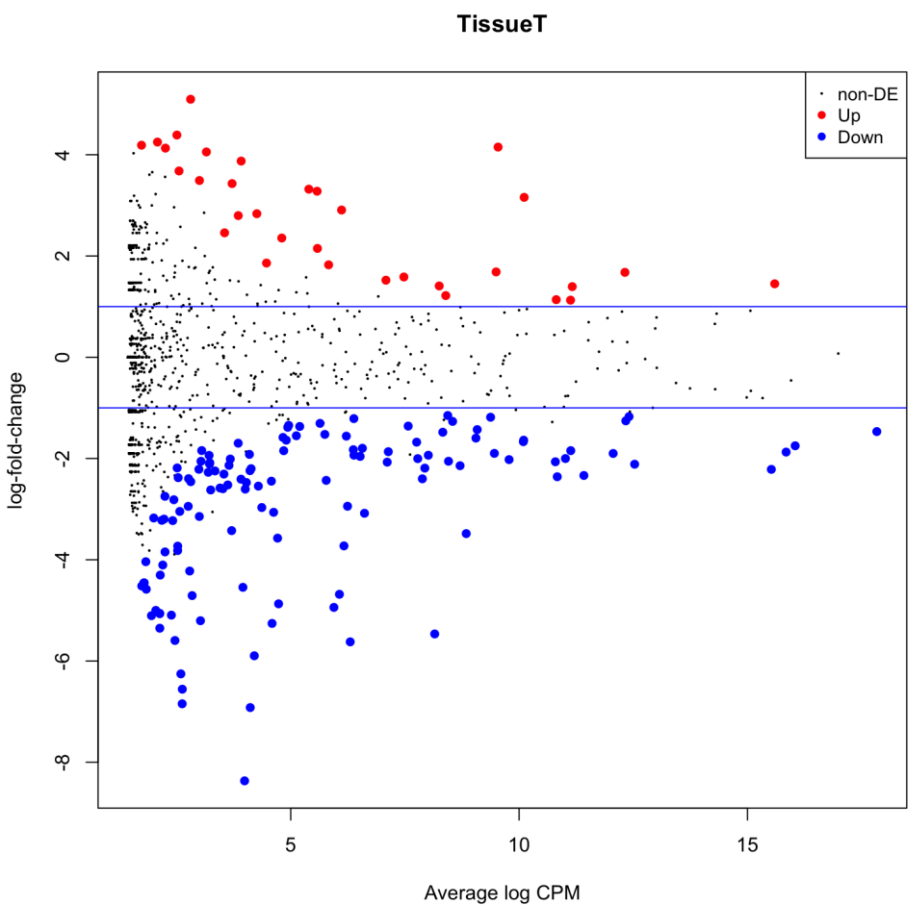


Machine: HiScan SQ
Run: Single Read 50
Reads: 100,000 – 2,200,000

R - edgeR

A. Kajdasz, J.Wesoly, 2020

Differential expression of miRNA in ccRCC tumors



Identified miRNAs – 2587

Upregulated – 32

Not changed – 2428

Downregulated – 127

ccRCC

R - edgeR

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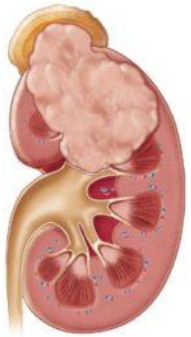
Research question

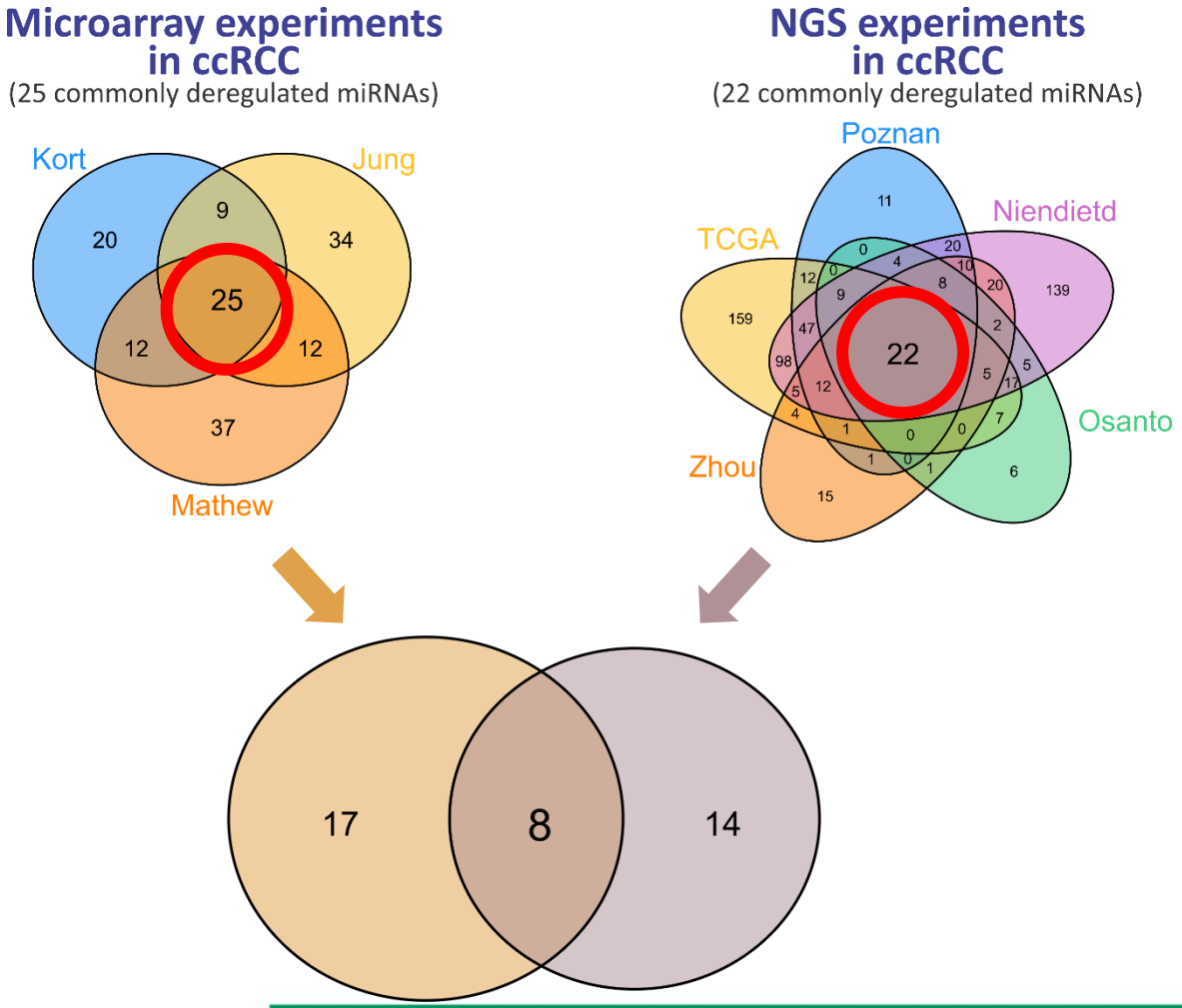


Which common miRNAs are deregulated in ccRCC?

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



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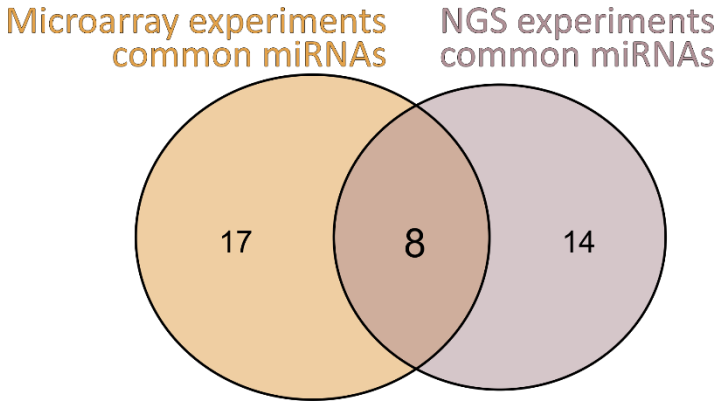
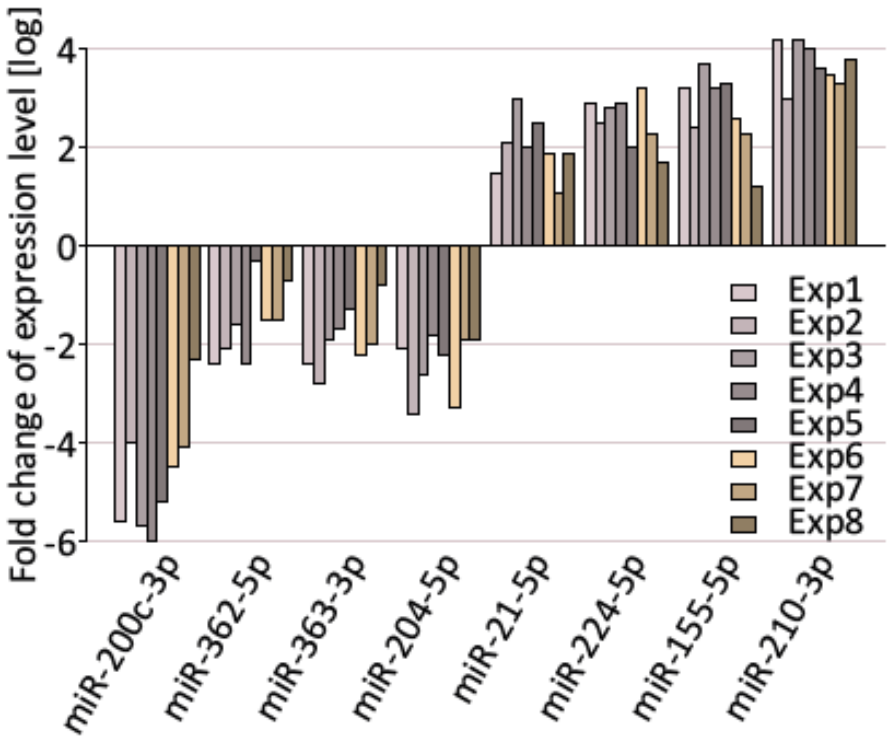
Commonly deregulated miRNAs in ccRCC





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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

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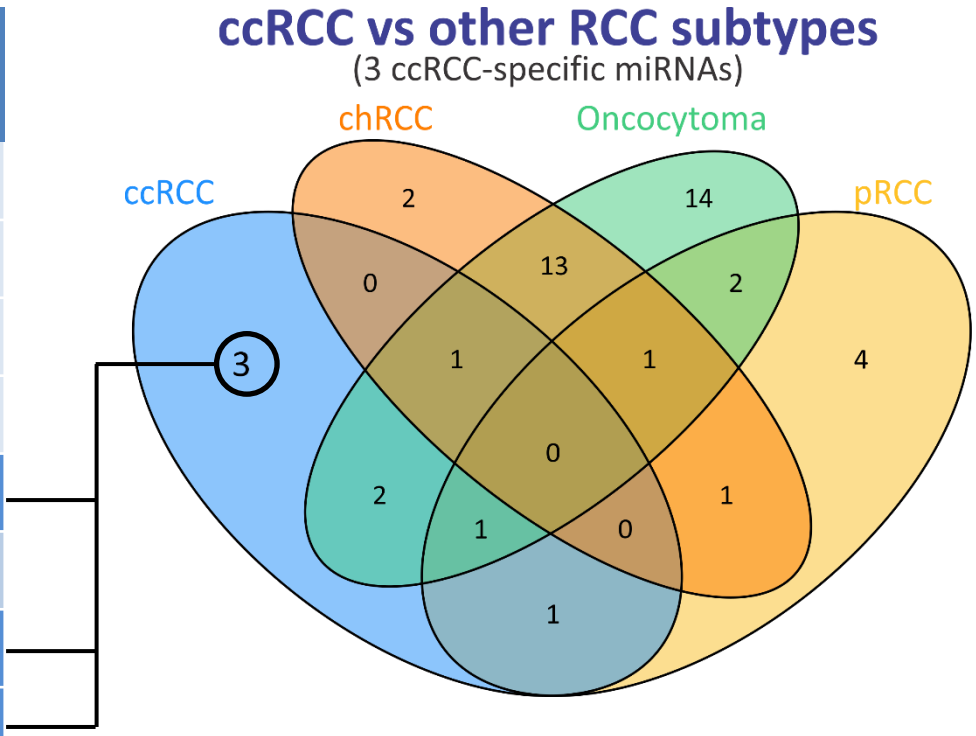
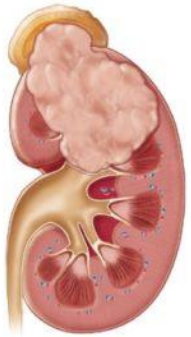
Specifically deregulated miRNAs in ccRCC vs. other RCC subtypes

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



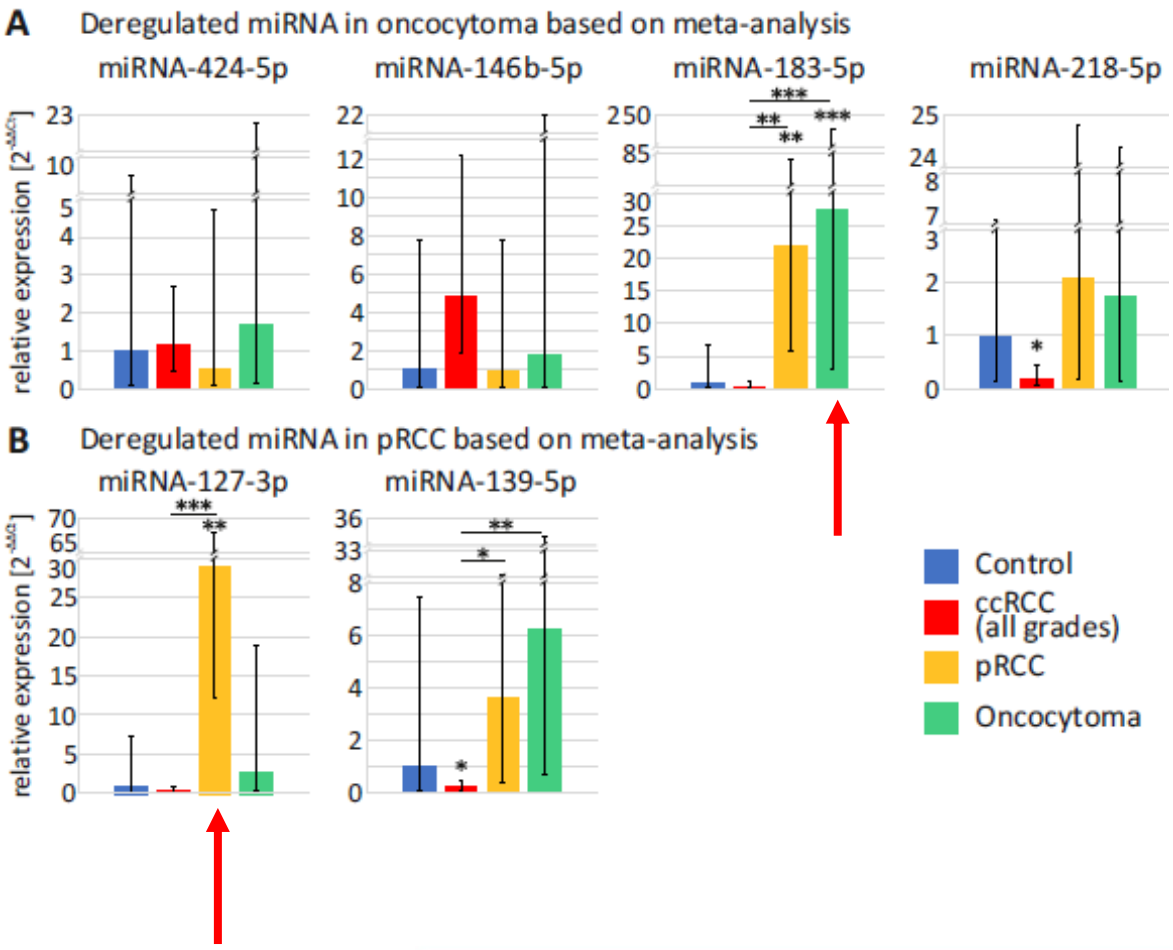
Are miRNAs efficient ccRCC biomarkers?

Validation of miRNA deregulation in ccRCC

non-ccRCC – 13

ccRCC – 24

Validation of miRNA deregulation in non-ccRCC tumors



Oncocytoma

Papillary renal cell carcinoma

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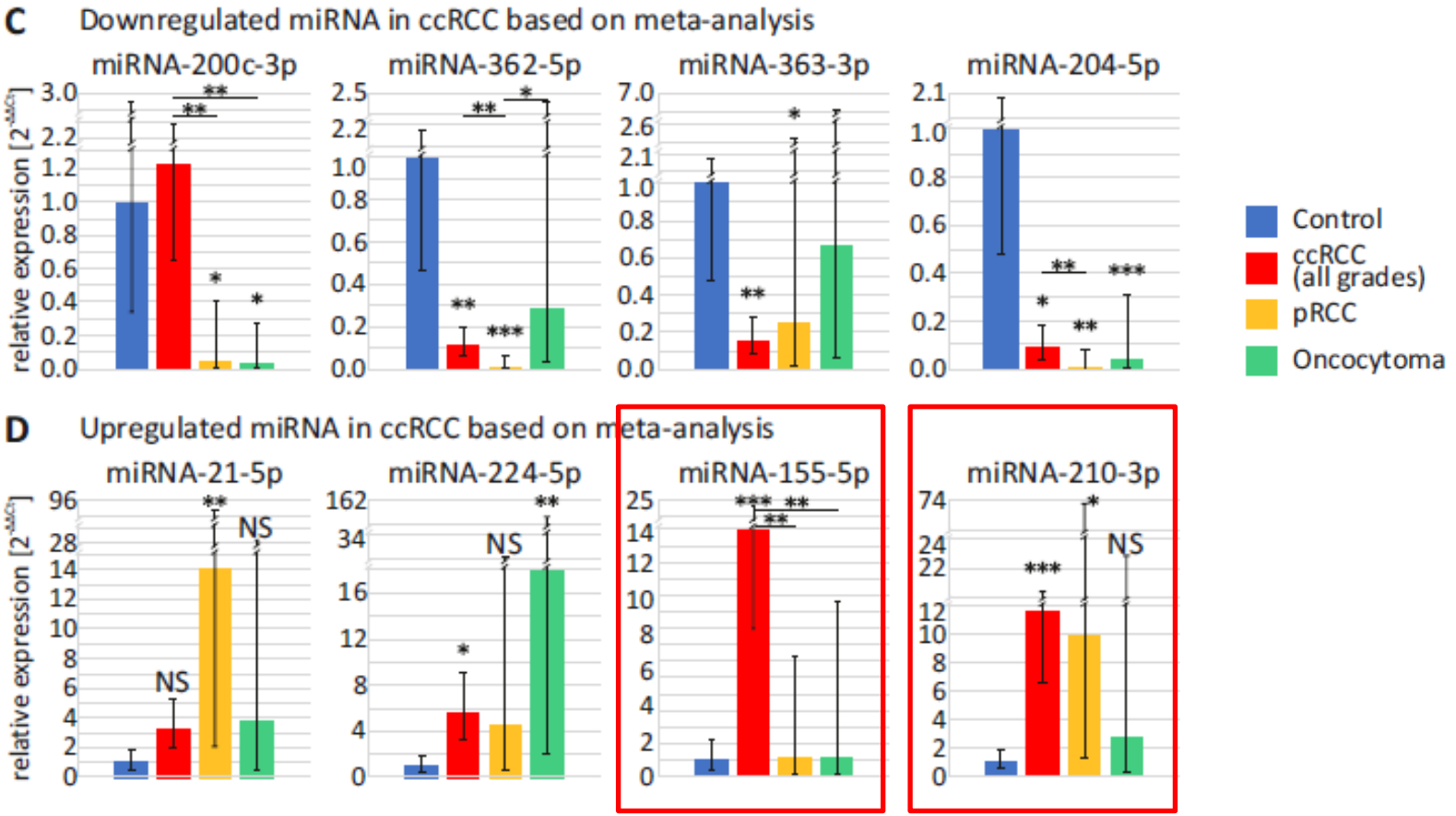
Validation of miRNA deregulation in ccRCC tumors



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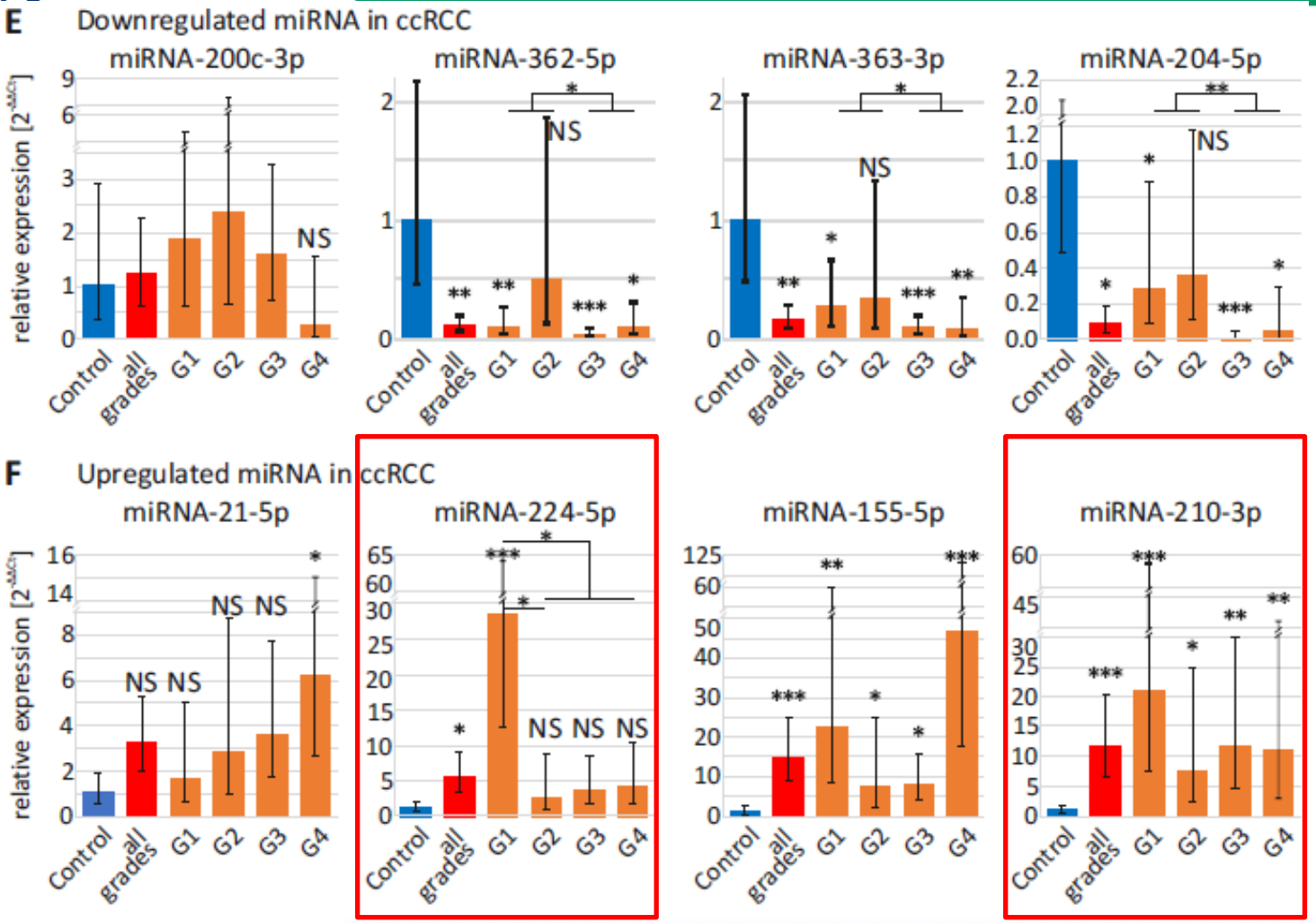
Validation of miRNA deregulation in ccRCC tumors

non-ccRCC – 13

ccRCC – 24

- G1 – 7
- G2 – 6
- G3 – 6
- G4 – 5

Validation of miRNA deregulation in ccRCC: all patients vs grades



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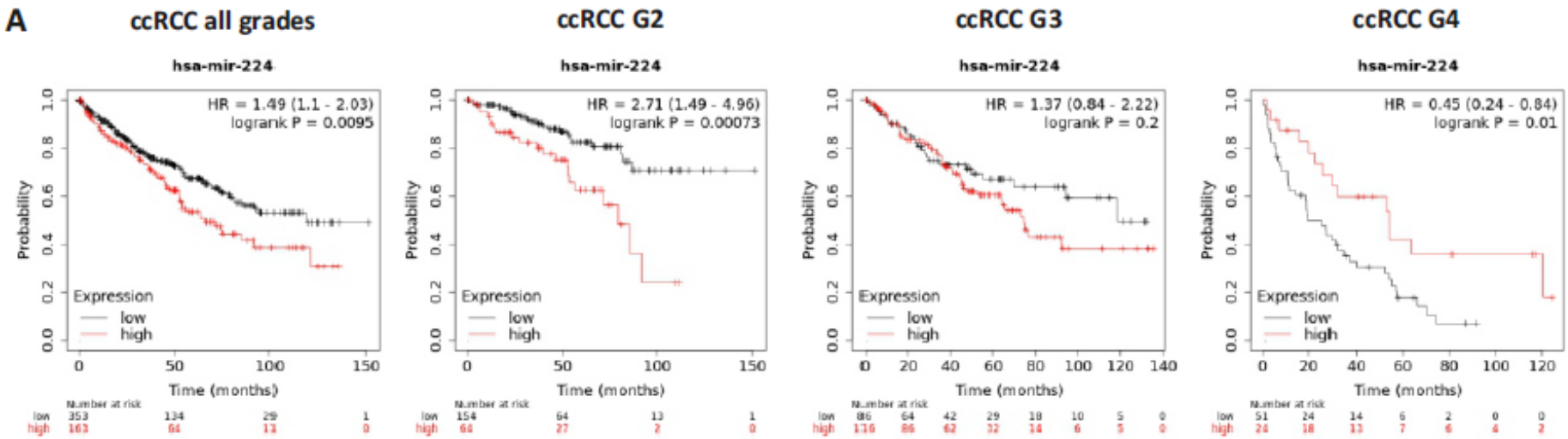
Survival rate analysis of ccRCC patients vs miRNA-224 expression



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

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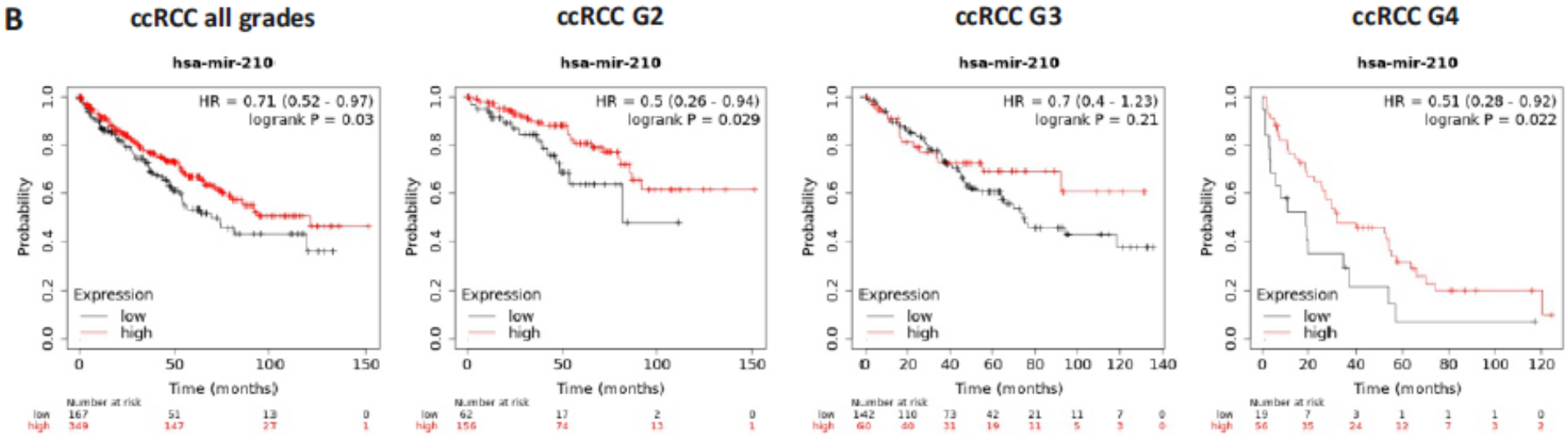
Survival rate analysis of ccRCC patients vs miRNA-210 expression



Patients with high expression (red line) of miRNA-210 in ccRCC tumors have higher survival rate

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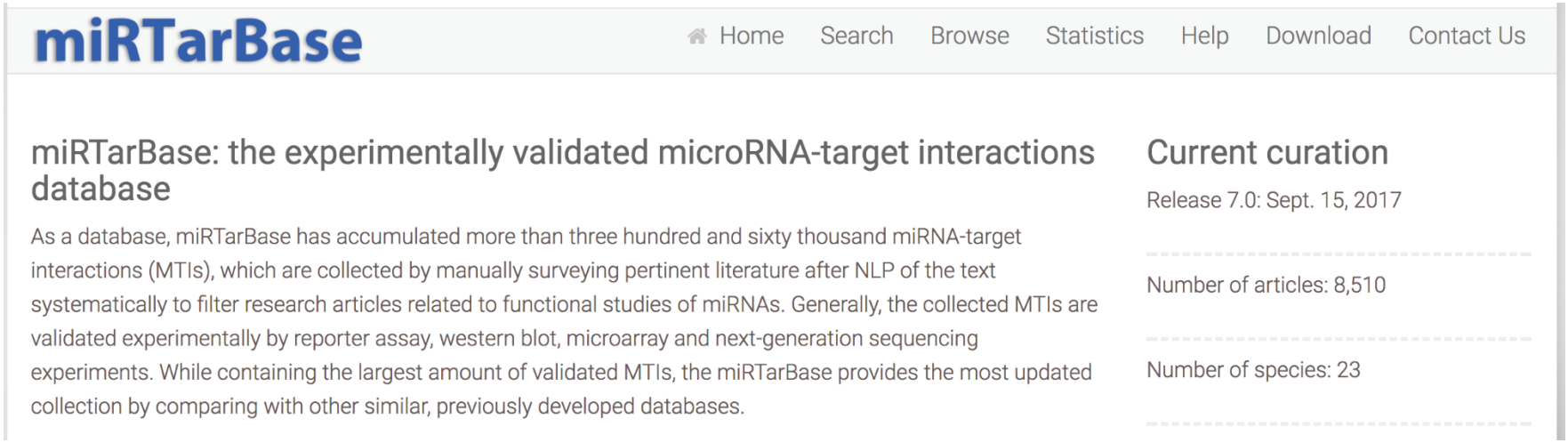
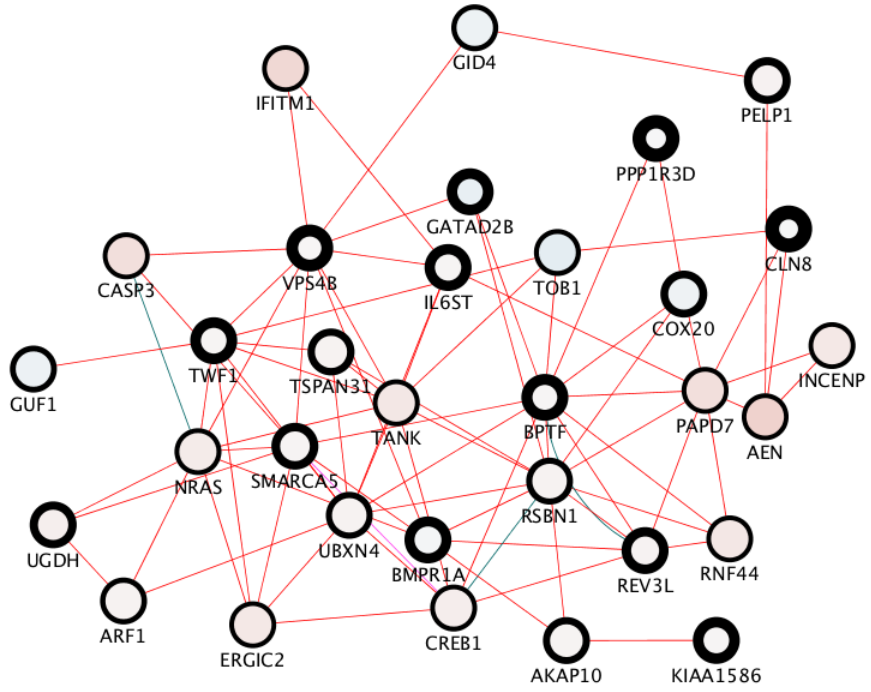
miRTarBase: the experimentally validated microRNA-target interactions database



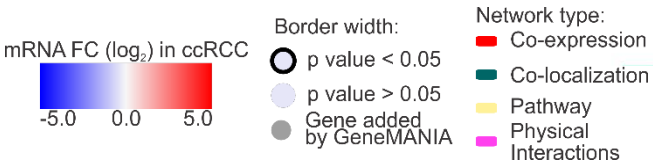
Potential functions of miRNA-363-3p targets

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



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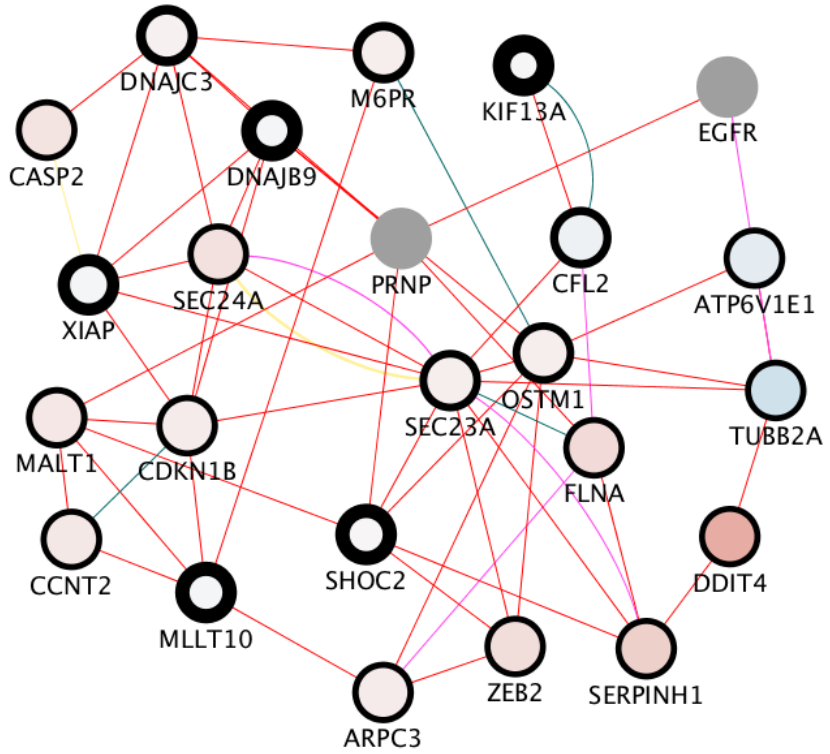
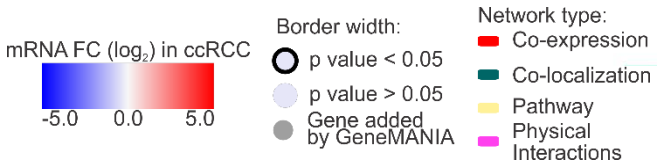
Potential functions of miRNA-200c-3p targets

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

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miRNAs as Biomarkers in ccRCC

SYSTEMATIC REVIEW ARTICLE

Front. Oncol., 04 December 2020 | https://doi.org/10.3389/fonc.2020.543817

Check for updates

Systematic Analysis of microRNA Biomarkers for Diagnosis, Prognosis, and Therapy in Patients With Clear Cell Renal Cell Carcinoma

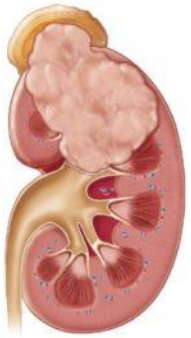
Guiyun Cheng†, Mengru Li†, Xiaoyu Ma†, Fangmei Nan, Lu Zhang, Zhongyi Yan, Huimin Li, Guosen Zhang, Yali Han, Longxiang Xie* and Xiangqian Guo*

Cell Signal Transduction Laboratory, Bioinformatics Center, Henan Provincial Engineering Center for Tumor Molecular Medicine, Department of Preventive Medicine, School of Basic Medical Sciences, Institute of Biomedical Informatics, Henan University, Kaifeng, China

miRNAs as Biomarkers in ccRCC

Performed a systematic analysis for ccRCC-related miRNAs as biomarkers by searching keywords in the NCBI PubMed database and found 118 miRNAs as diagnostic biomarkers, 28 miRNAs as prognostic biomarkers, and 80 miRNAs as therapeutic biomarkers in ccRCC.

In this paper, we identified highly specific miRNAs in the pathogenesis of ccRCC and explored their potential applications for diagnosis, prognosis, and treatment of ccRCC.



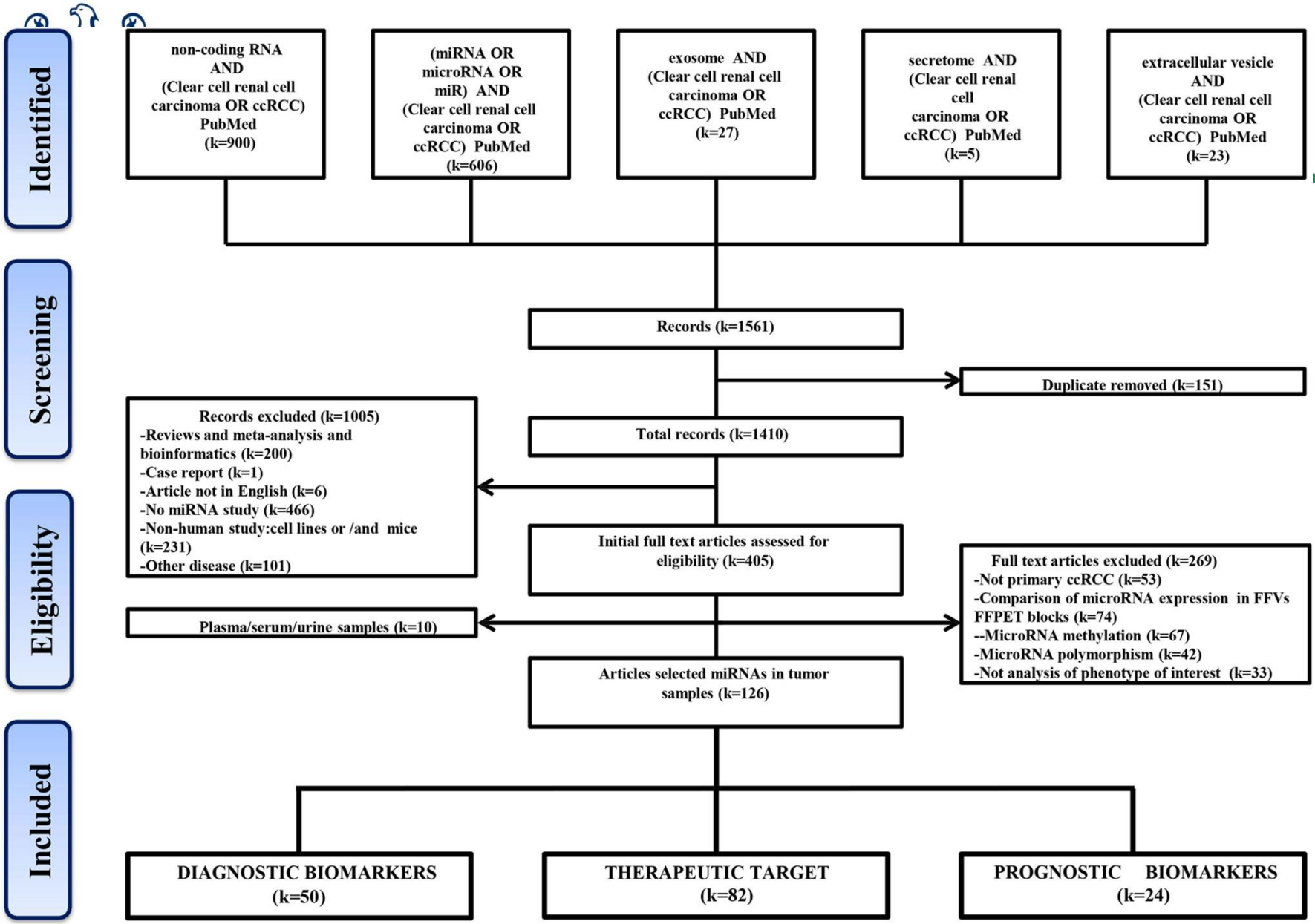
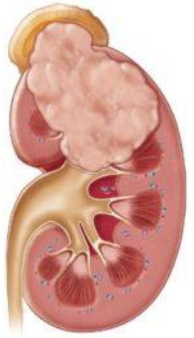

Identified
Screening
Eligibility
Included
non-coding RNA AND (Clear cell renal cell carcinoma OR ccRCC) PubMed (k=900)
(miRNA OR microRNA OR miR) AND (Clear cell renal cell carcinoma OR ccRCC) PubMed (k=606)
exosome AND (Clear cell renal cell carcinoma OR ccRCC) PubMed (k=27)
secretome AND (Clear cell renal cell carcinoma OR ccRCC) PubMed (k=5)
extracellular vesicle AND (Clear cell renal cell carcinoma OR ccRCC) PubMed (k=23)
Records (k=1561)
Duplicate removed (k=151)
Total records (k=1410)
Records excluded (k=1005)
-Reviews and meta-analysis and bioinformatics (k=200)
-Case report (k=1)
-Article not in English (k=6)
-No miRNA study (k=466)
-Non-human study:cell lines or /and mice (k=231)
-Other disease (k=101)
Initial full text articles assessed for eligibility (k=405)
Full text articles excluded (k=269)
-Not primary ccRCC (k=53)
-Comparison of microRNA expression in FFVs FFPET blocks (k=74)
--MicroRNA methylation (k=67)
-MicroRNA polymorphism (k=42)
-Not analysis of phenotype of interest (k=33)
Plasma/serum/urine samples (k=10)
Articles selected miRNAs in tumor samples (k=126)
DIAGNOSTIC BIOMARKERS (k=50)
THERAPEUTIC TARGET (k=82)
PROGNOSTIC BIOMARKERS (k=24)

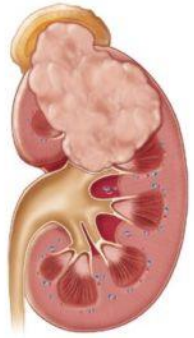
TABLE 1 | miRNAs as diagnostic biomarkers for ccRCC in more than two studies.



Name	Expression Level[§]	n (ccRCC)	n (Control)	Detection Method	Target	Sample source	PubMed ID
miR-21	**Up**	104	104	qPT-PCR	TIMP3	Tissue	29131259
	Down	30	10	qPT-PCR	ND	Fresh frozen	24129247
miR-155	**Down**	30	10	qRT-PCR	ND	Fresh frozen	24129247
	Up	137	77	qRT-PCR	ND	Tissue	23050614
	Up	78	78	qRT-PCR	ND	Fresh frozen	24647573
	Up	30	10	qRT-PCR	ND	Fresh frozen	24129247
	Up	32	132	qRT-PCR	ND	Fresh frozen	25381221
miR-141	**Down**	30	10	qRT-PCR	ND	FF Fresh frozen	24129247
	Down	78	78	qRT-PCR	EphA2	Fresh frozen	24647573
miR-221	**Up**	28	28	qRT-PCR	TIMP2	Tissue	26191221
	Up	24	24	qRT-PCR	ND	Tissue	27427222
miR-122	**Up**	32	32	qRT-PCR	ND	Fresh frozen	25381221
	Up	148	60	qRT-PCR	Dicer	Fresh frozen	28921581

[§]*Down, significantly downregulated miRNAs in human ccRCC tissues; Up, significantly upregulated miRNAs in human ccRCC tissues; qRT-PCR, quantitative real-time PCR; ND, not determined; CASC2, cancer susceptibility 2; EphA2, erythropoietin-producing hepatocellularA2; TIMP2, TIMP metallopeptidase inhibitor 2.*

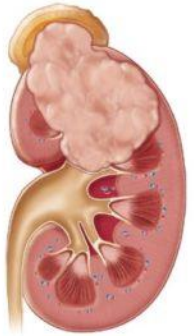
TABLE 2 | miRNAs as prognostic biomarkers for ccRCC in more than two studies.



Name	Expression Level	n (ccRCC)	Sample source	Detection Method	Prognosis[§]	Survival	PubMed ID
miR-21	**Up**	37	Formalin-fixed paraffin-embedded	qRT-PCR	Unfavorable	CSS	25279769
	Up	71	Tissue	qRT-PCR	Unfavorable	OS and DFS	22580180
miR-126	**Down**	264	Tissue and Formalin-fixed paraffin-embedded	qRT-PCR	Favorable	OS and DFS	25572155
	Down	37	Formalin fixed paraffin embedded	qRT-PCR	Favorable	CSS	25279769
	Down	116	Formalin fixed paraffin embedded	qRT-PCR	Favorable	DSS and RFS	30988818
miR-122	**Up**	46	Tissue	qRT-PCR	Unfavorable	MFS	30483771
	Up	80	Fresh frozen	qRT-PCR	Unfavorable	PFS	28534944

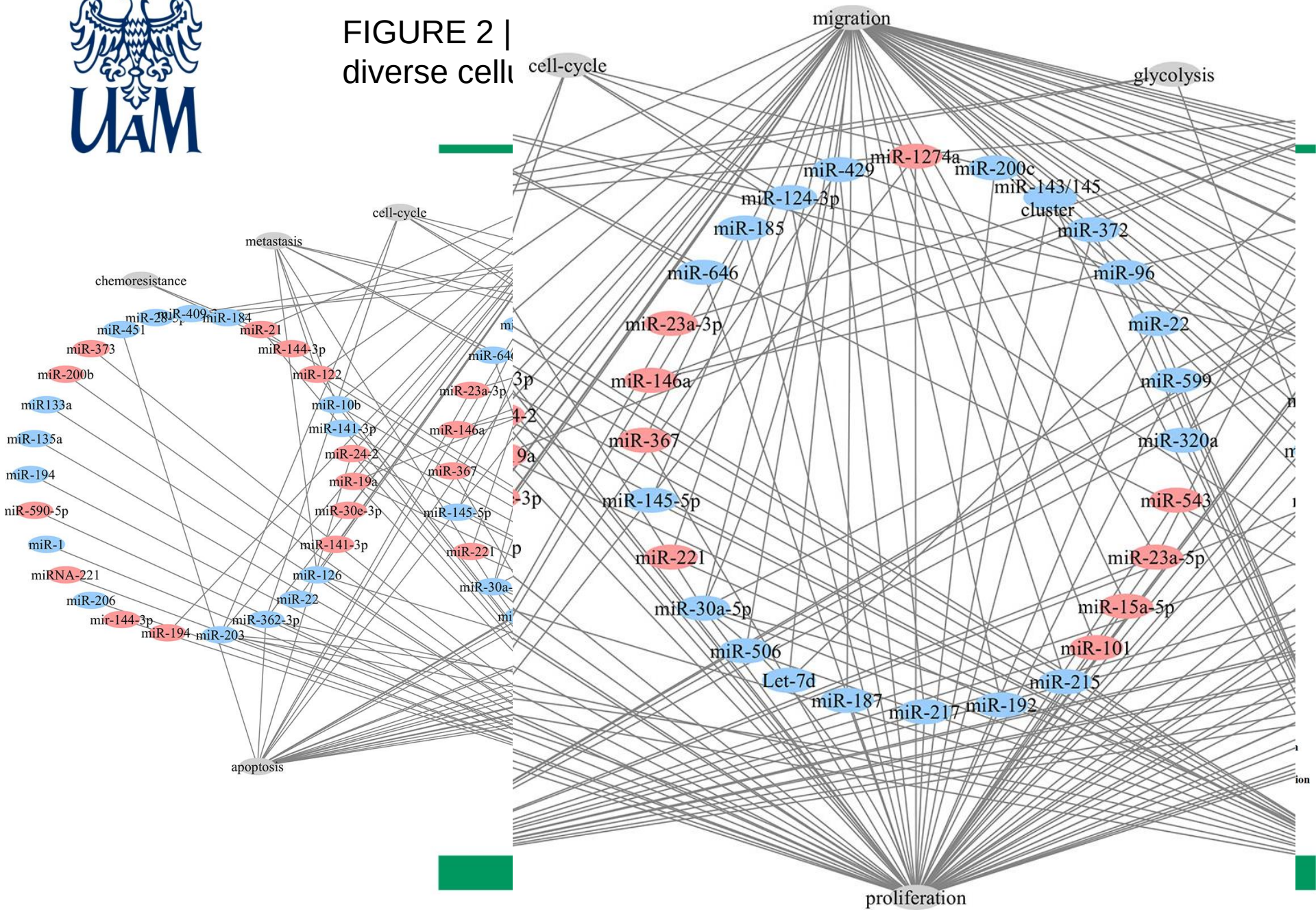
[§]CSS, cancer specific survival; OS, overall survival; DFS, disease free survival; DSS, disease specific survival; RFS, recurrence free survival; MFS, metastasis free survival; PFS, progression free survival.

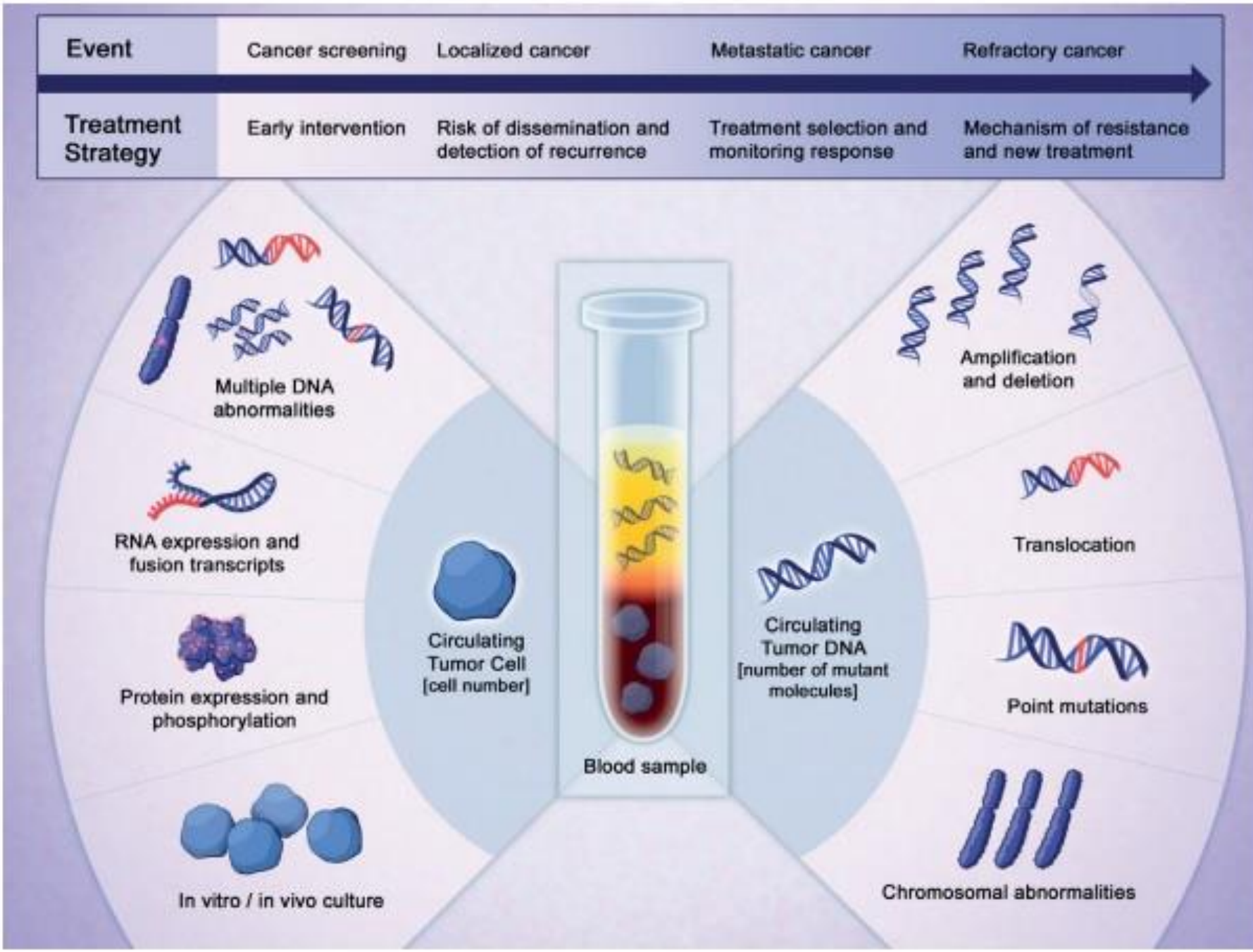
TABLE 5 | Metastasis-related miRNAs as prognostic biomarkers for ccRCC.



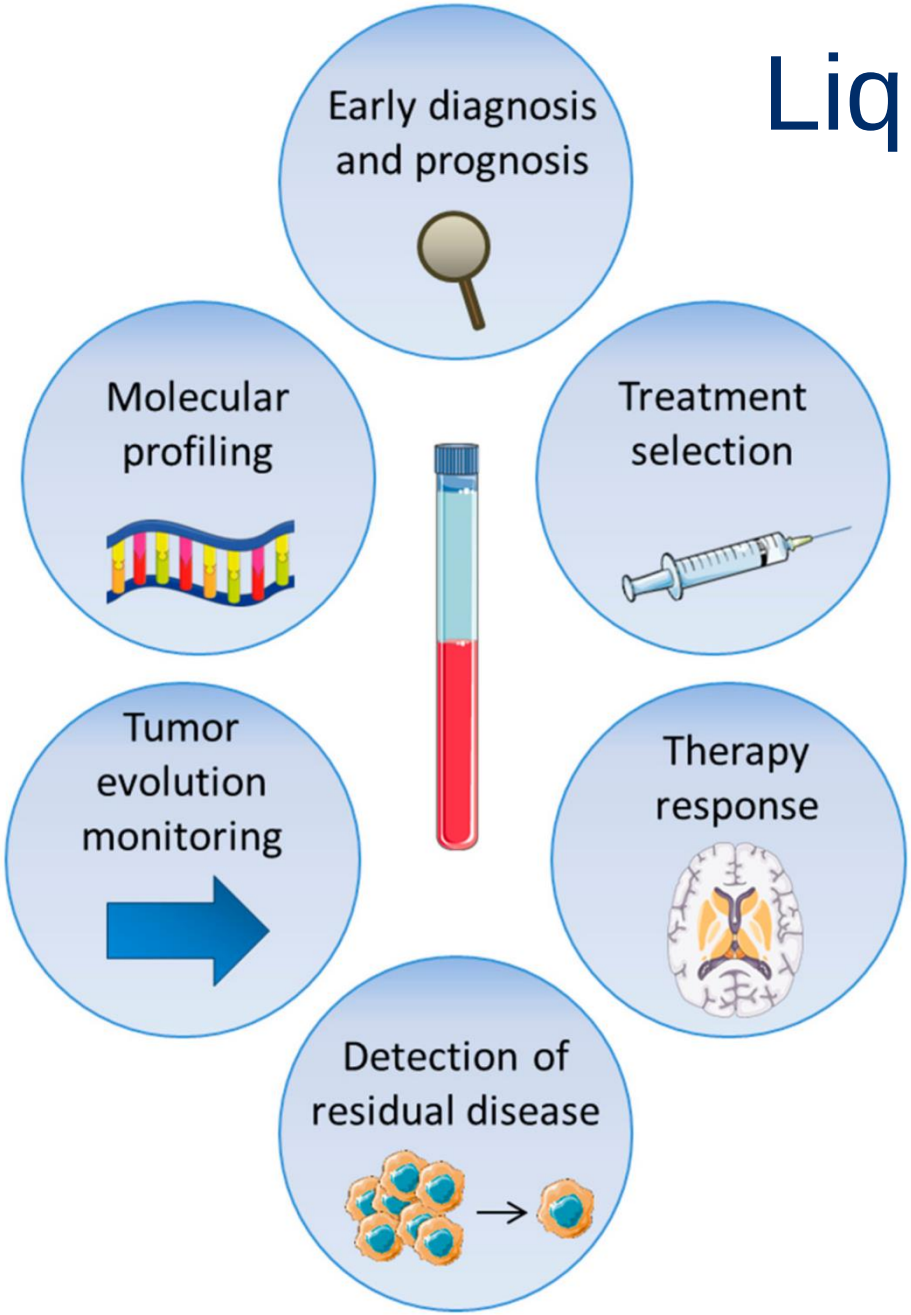
Name	Expression Level	n (ccRCC)	Target	Sample source	PubMed ID
miR-122	**UP**	148	Dicer	Fresh frozen	28921581
	UP	46	FOXO3	Tissue	30483771
miR-30a	**Down**	90	DLL	Tissue	23826258

FIGURE 2 |
diverse cellu




Event
Cancer screening
Localized cancer
Metastatic cancer
Refractory cancer
Treatment Strategy
Early intervention
Risk of dissemination and detection of recurrence
Treatment selection and monitoring response
Mechanism of resistance and new treatment
Multiple DNA abnormalities
RNA expression and fusion transcripts
Protein expression and phosphorylation
In vitro / in vivo culture
Circulating Tumor Cell [cell number]
Blood sample
Circulating Tumor DNA [number of mutant molecules]
Amplification and deletion
Translocation
Point mutations
Chromosomal abnormalities

Liquid Biopsies



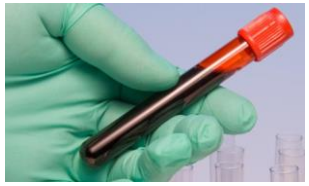
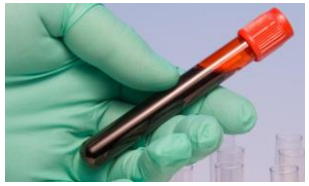


TABLE 3 | Circulating miRNAs as diagnostic biomarkers for ccRCC.

Name	Expression Level	n(ccRCC)	n(control)	Sample source	PubMed ID
miR-210	**Up**	82	80	Serum exosomes	28753793
	Up	34	23	Serum	24212760
miR-1233	**Up**	82	80	Serum exosomes	28753793
	Up	30	15	Serum	28336290
miR-508-3p	**Down**	85	10	Serum	31661117
miR-885-5p	**Up**	85	10	Serum	31661117
miR-34a	**Down**	30	15	Serum	28336290
miR-141	**Down**	30	15	Serum	28336290
miR-144-3p	**Up**	106	123	Plasma	27633984
miR-625-3p	**Down**	50	74	Serum	31737199
miR-210-3p	**Up**	38	10	Urine	29050224

TABLE 4 | Circulating miRNAs as prognostic biomarkers for ccRCC.



Name	Expression Level	n (ccRCC)	Prognostic value	Survival event	Sample source	PubMed ID
miR-122-5p	**Down**	68	Unfavorable	PFS, CSS, and OS	Serum	29410711
miR-206	**Down**	68	Unfavorable	PFS, CSS, and OS	Serum	29410711
miR-150	**Down**	94	Favorable	RCC-specific survival	Plasma	28639257
miR-224	**Up**	108	Unfavorable	PFS	Serum exosomes	29299115

[§]CSS, cancer specific survival; OS, overall survival; DFS, disease free survival; DSS, disease specific survival; RFS, recurrence free survival; MFS, metastasis free survival; PFS, progression free survival.

FIGURE 3 | Verified downstream target genes and involved signaling pathways associated with miR-21 in the tumorigenesis of ccRCC.

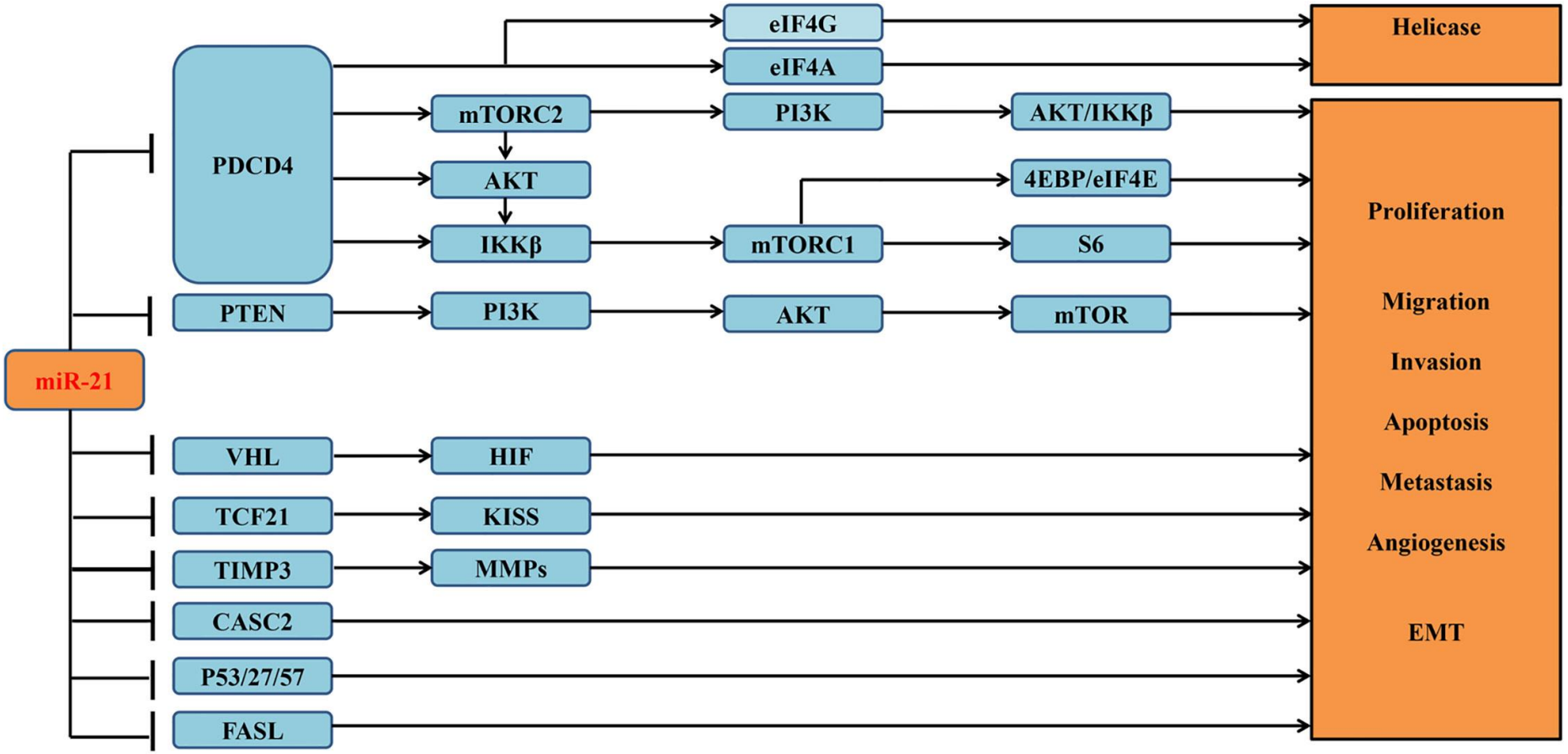


FIGURE 4 | Venn diagrams of potential target genes for five miRNAs including mir-21, miR-221, miR-141, miR-155, and miR-126 from three predicting tools.

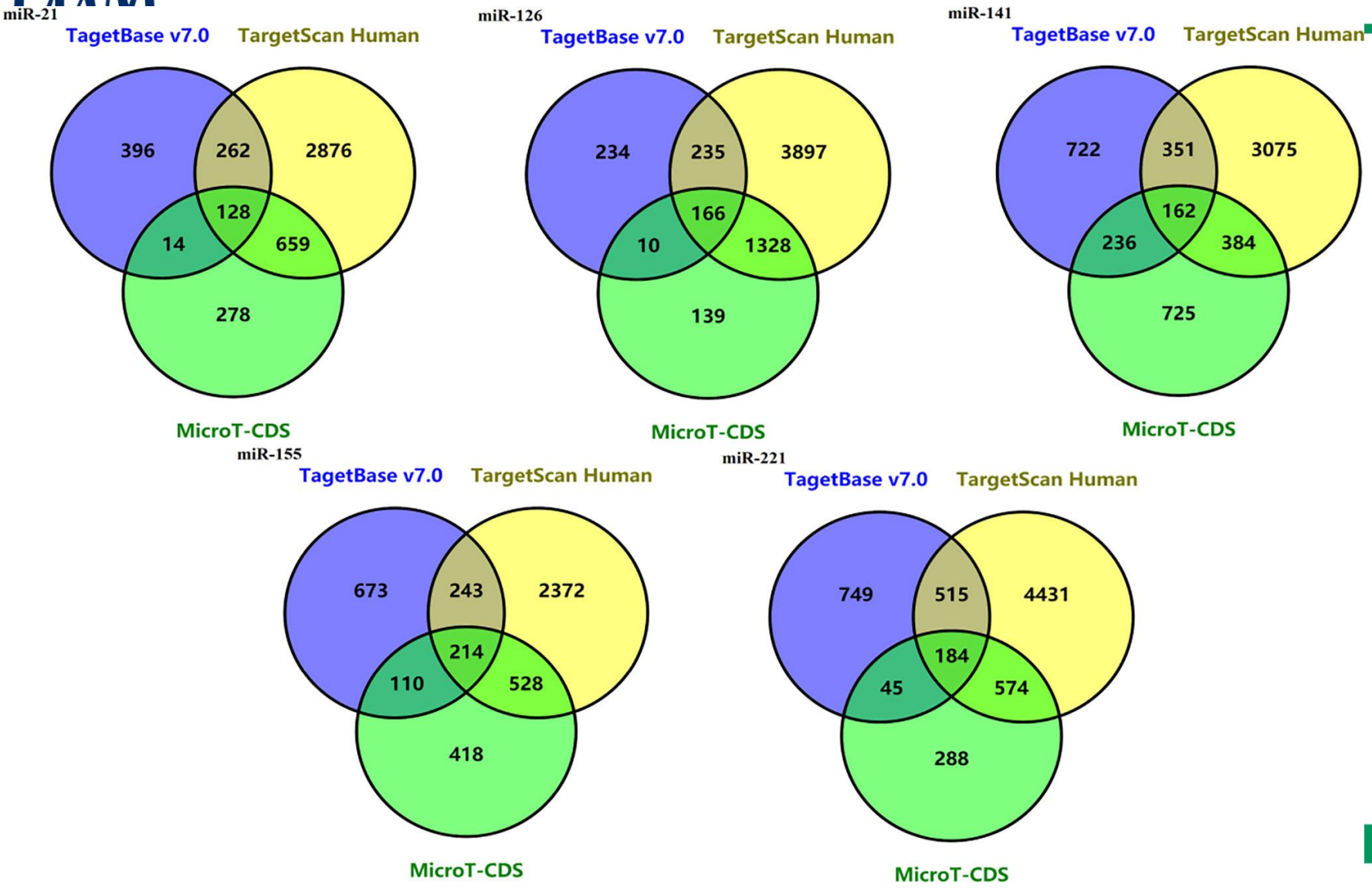


FIGURE 5 | Functional enrichment analysis of the potential target genes of miRNA-21 (A). Chart of the GO and KEGG enriched pathways (B); Network of GO and KEGG enriched terms colored by clusters.

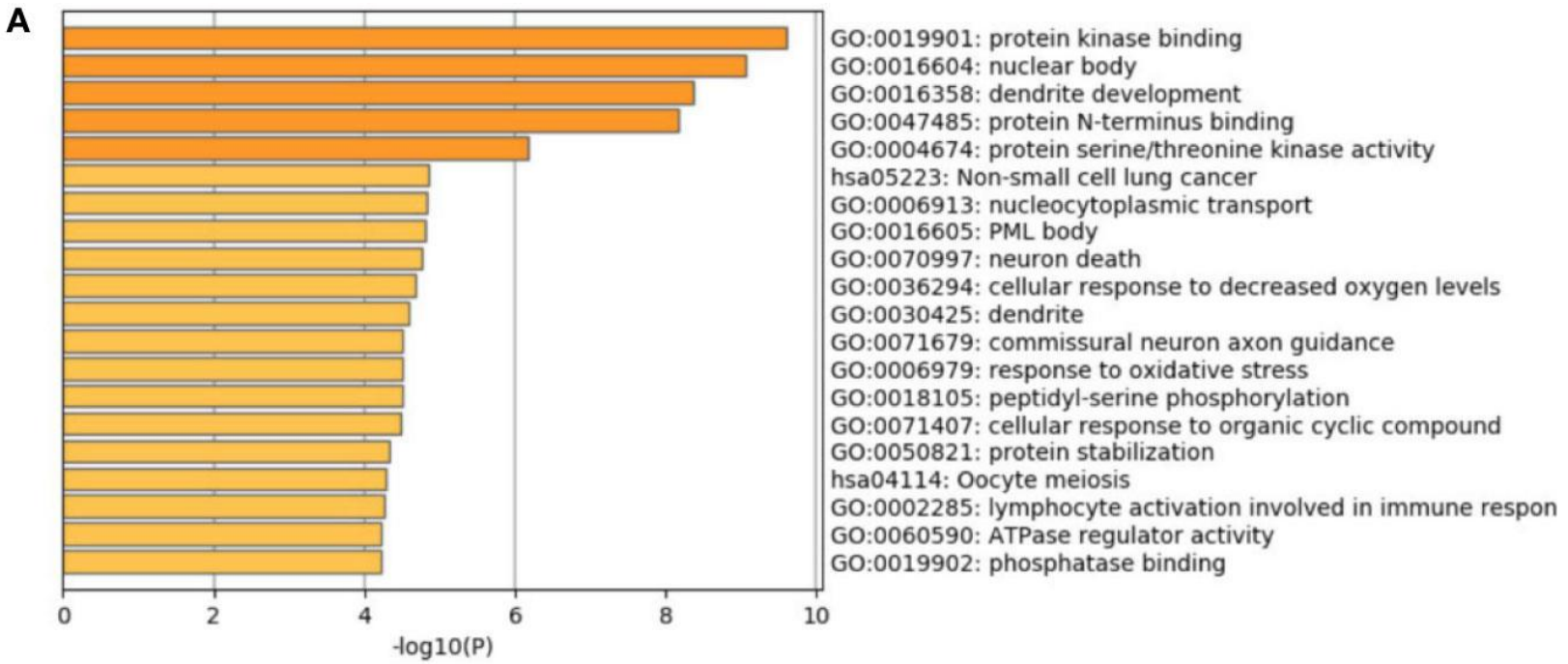
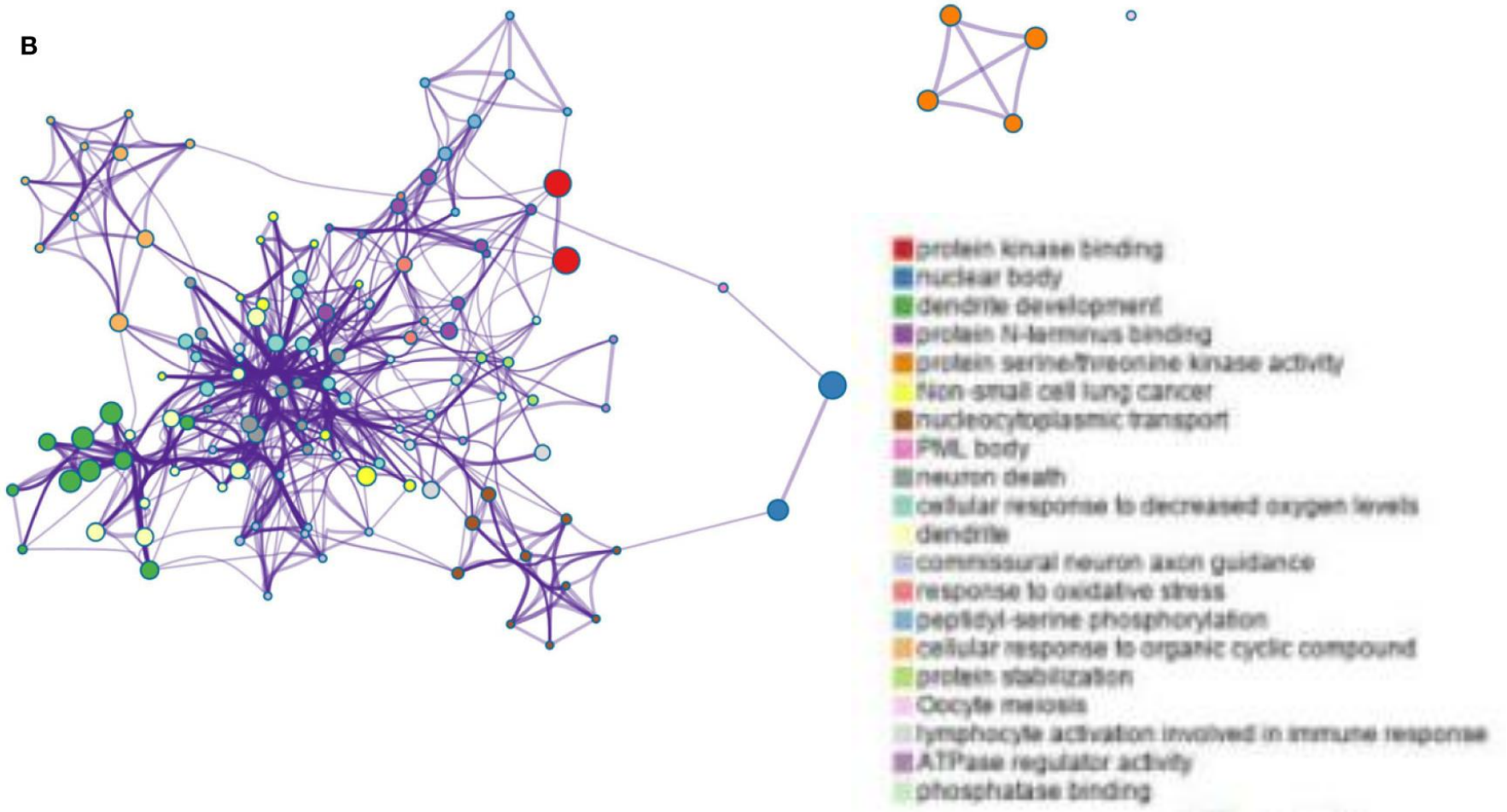
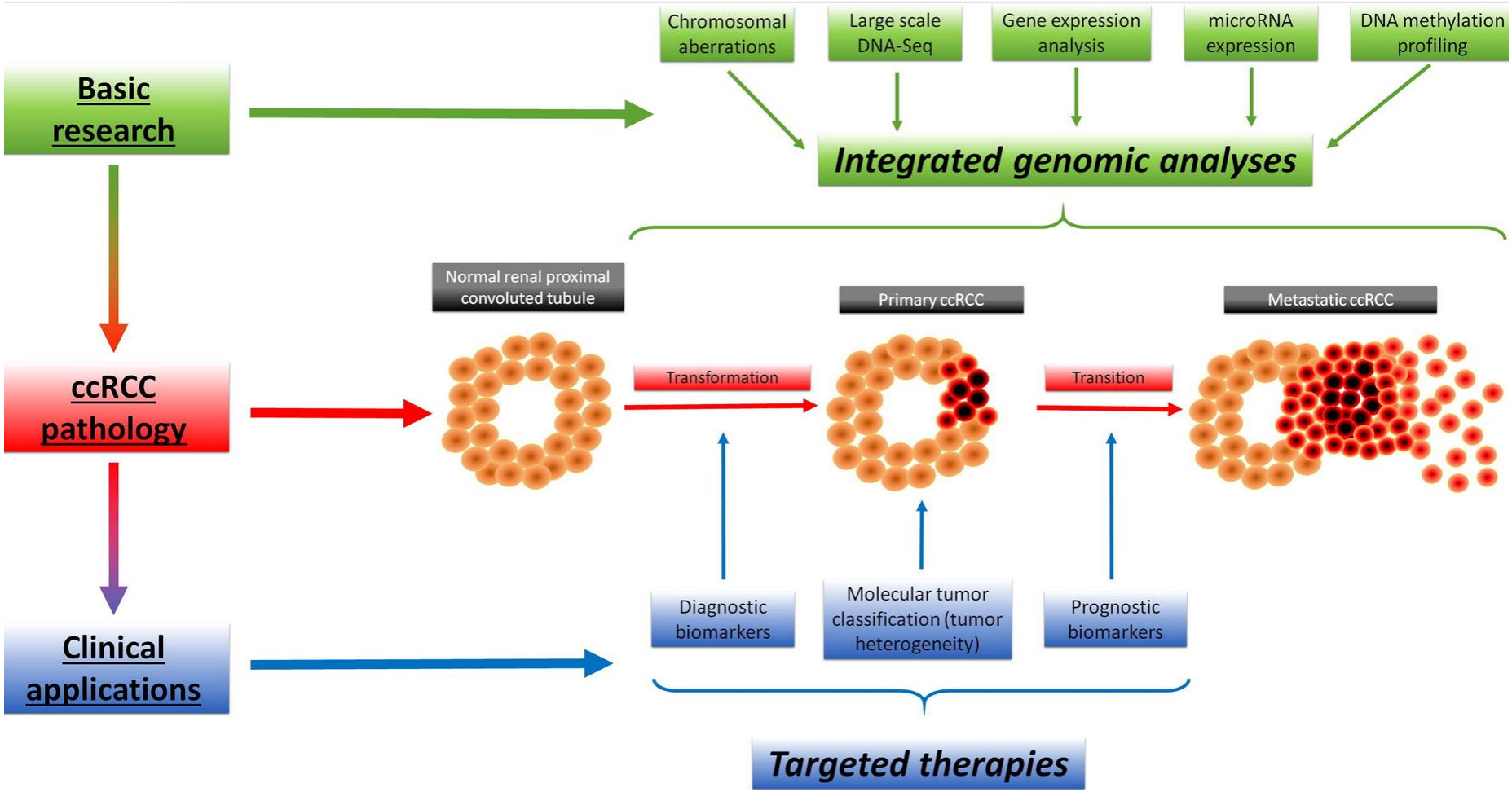


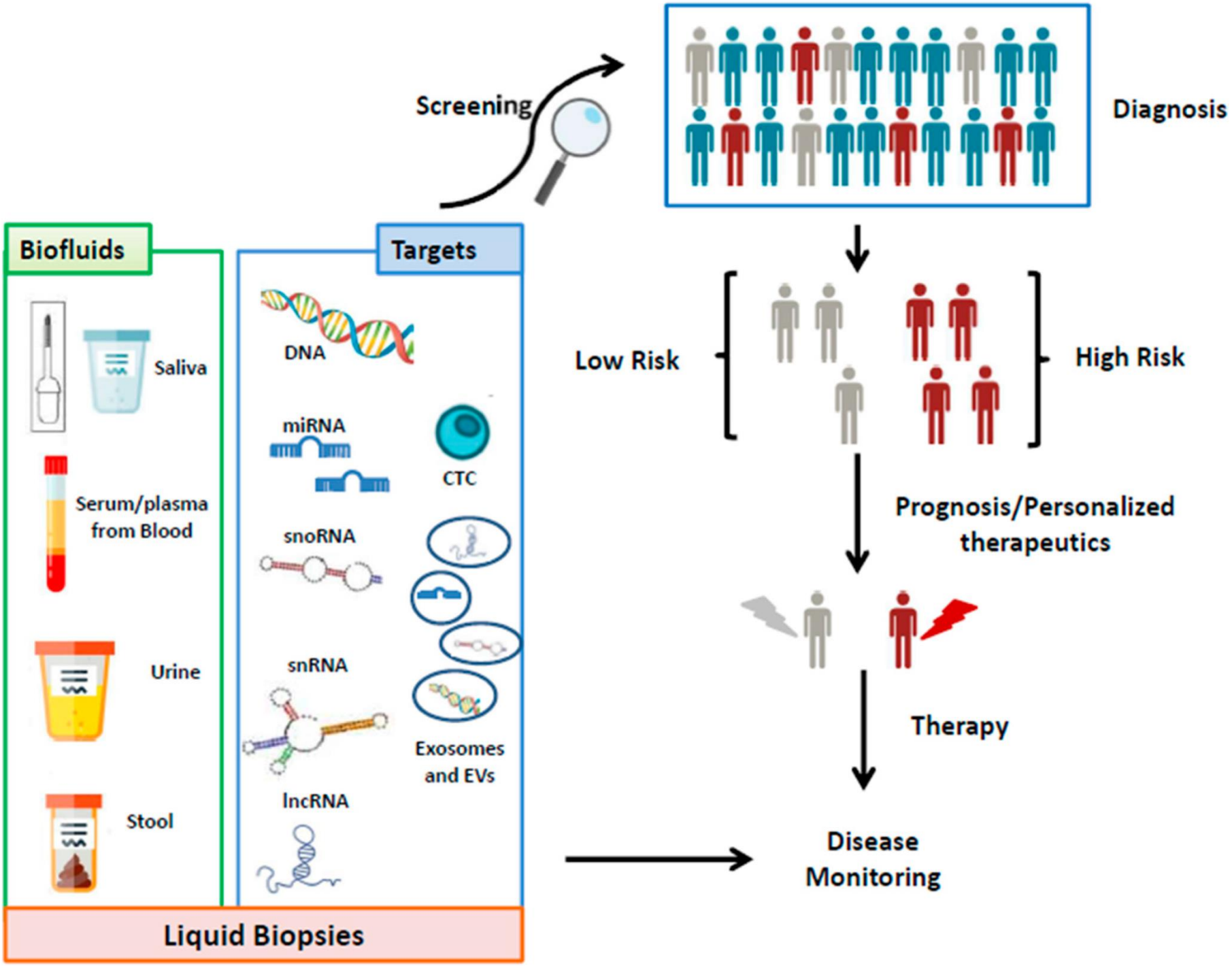
FIGURE 5 | Functional enrichment analysis of the potential target genes of miRNA-21 (A). Chart of the GO and KEGG enriched pathways (B); Network of GO and KEGG enriched terms colored by clusters.



Integrative genomic approaches in ccRCC management



J.Wesoly, Cancer Letters 2013


Screening
Diagnosis
Biofluids
Saliva
Serum/plasma from Blood
Urine
Stool
Targets
DNA
miRNA
CTC
snoRNA
snRNA
Exosomes and EVs
lncRNA
Liquid Biopsies
Low Risk
High Risk
Prognosis/Personalized therapeutics
Therapy
Disease Monitoring

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Anna Piaszyk-Borychowska
Agata Michalska
Martyna Plens Gałąska
Aleksandra Antonczyk
Sanaz Hassani
Katarzyna Blaszczyk

Lab of HTT

Prof J. Wesoly
Dr Natalia Derebecka
Dr Arkadiusz Kajdasz

Department of Human Molecular Genetics
Laboratory of High Throughput Technologies

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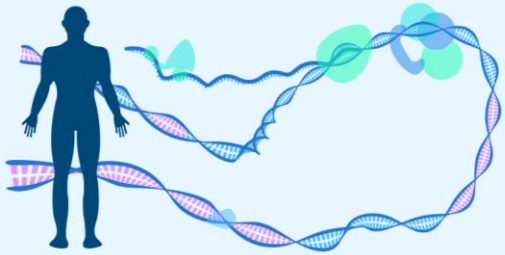
ROZWOJU REGIONALNEGO

INNOWACYJNA
GOSPODARKA
NARODOWA STRATEGIA SPÓJNOŚCI



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