

Pathology in RCC: where are we and where are we heading to in 2025?

No conflict of interest

F. Algaba Pathology Department



Fundació Puigvert

UAB

Where are we?

EVOLUTION OF WHO CLASSIFICATIONS OF KIDNEY TUMORS

WHO 2004

Clear cell renal cell carcinoma
Multi-locular clear cell renal cell carcinoma
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Carcinoma of the collecting ducts of Bellini
Renal medullary carcinoma
Xp11 translocation carcinoma
Carcinoma associated with neuroblastoma
Mucinous, tubular, and spindle cell carcinoma
Renal cell carcinoma, unclassified
Papillary adenoma
Oncocytoma

WHO 2016

Clear cell renal cell carcinoma
Multilocular cystic renal neoplasm of LMP
Papillary renal cell carcinoma
Hereditary leiomyomatosis and RCC associated
Chromophobe renal cell carcinoma
Collecting duct carcinoma of the kidney
Renal medullary carcinoma
MiT Family translocation carcinomas
Mucinous tubular and spindle cell carcinoma
Tubulocystic renal cell carcinoma
Acquired cystic disease associated renal cell carcinoma
Clear cell papillary renal cell carcinoma
Succinate dehydrogenase (SDH) deficient renal carcinoma
Renal cell carcinoma, unclassified

WHO 2022

Clear cell
Multilocular cystic renal neoplasm of low m.p
ELOC Mutation
Papillary RCC
Fumarate H deficient
Mucinous tubular spindle RCC
Tubulocystic
Clear cell papillary RC tumor
Chromophobe
Oncocytoma
SDH deficient
Other oncocytic tumours
TFE3- rearranged
TFEB- altered
Collecting duct carcinoma
SMARCB1 deficient renal medullary carcinoma
ALK rearranged renal cell carcinomas
Eosinophilic solid and cystic RCC
Acquired cystic disease associated RCC
RCC NOS

Where are we?

WHO 2022

Clear cell
Multilocular cystic renal neoplasm of low m.p
ELOC Mutation
Papillary RCC low grade, high grade
Fumarate H deficient
Mucinous tubular spindle RCC
Tubulocystic RCC
Clear cell papillary RC tumor
Chromophobe RCC
Oncocytoma
Other oncocytic tumors
SDH deficient
TFE3-rearranged
TFEB-altered
Collecting duct carcinoma
SMARCB1 deficient renal medullary carcinoma
ALK rearranged renal cell carcinoma
Eosinophilic solid and cystic RCC
Acquired cystic disease associated RCC
Unclassified RCC NOS

ESMO 2024

Clear cell RCC

Papillary RCC

Chromophobe RCC

Collecting/Medullary RCC

Sarcomatoid RCC

WHO 2022

Clear cell
Multilocular cystic renal neoplasm of low m.p
ELOC Mutation
Papillary RCC low grade, high grade
Fumarate H deficient
Mucinous tubular spindle RCC
Tubulocystic RCC
Clear cell papillary RC tumor
Chromophobe RCC
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SMARCB1 deficient renal medullary carcinoma
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Eosinophilic solid and cystic RCC
Acquired cystic disease associated RCC
Unclassified RCC NOS

ESMO 2024

Clear cell RCC

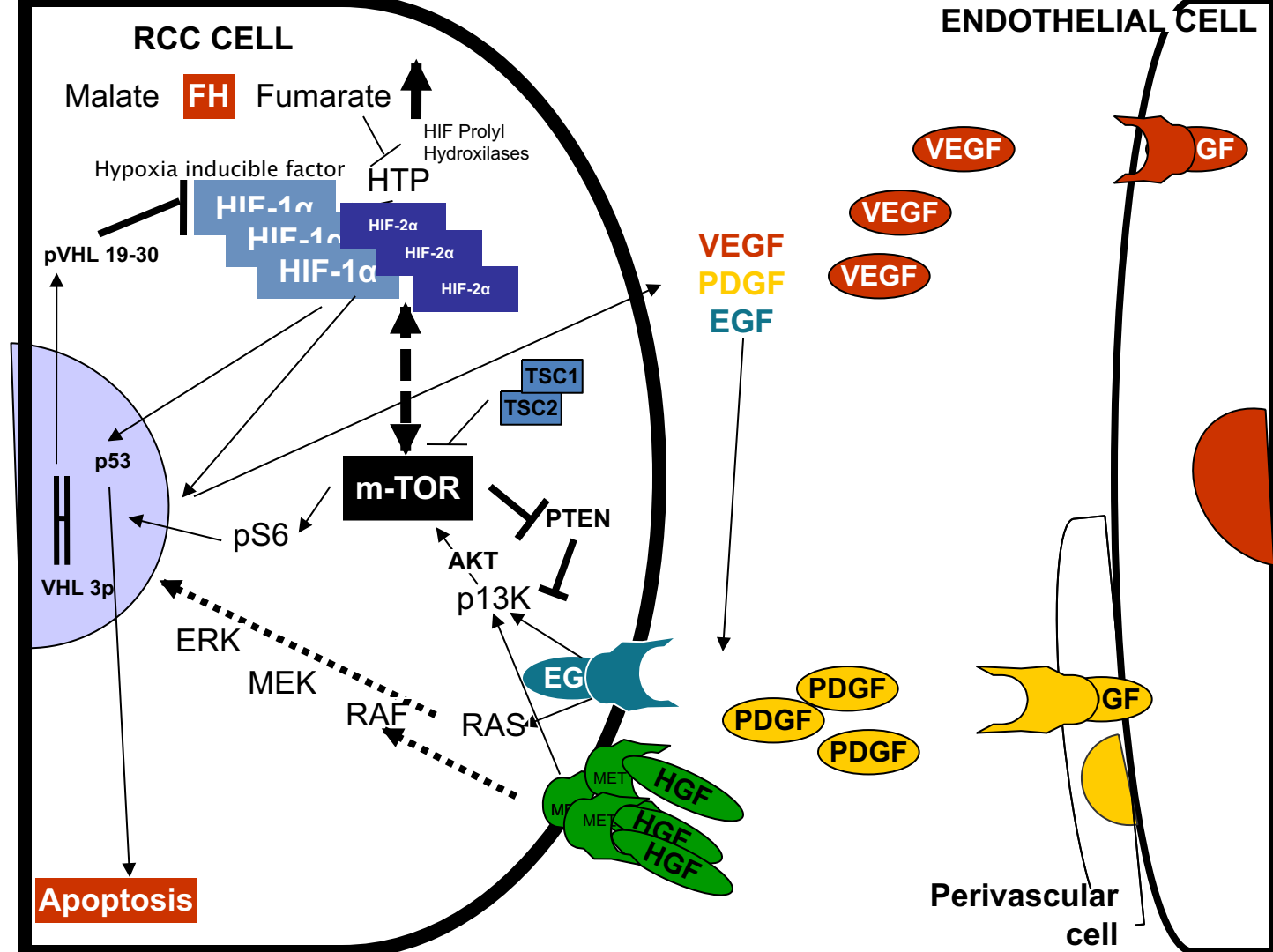
Papillary RCC

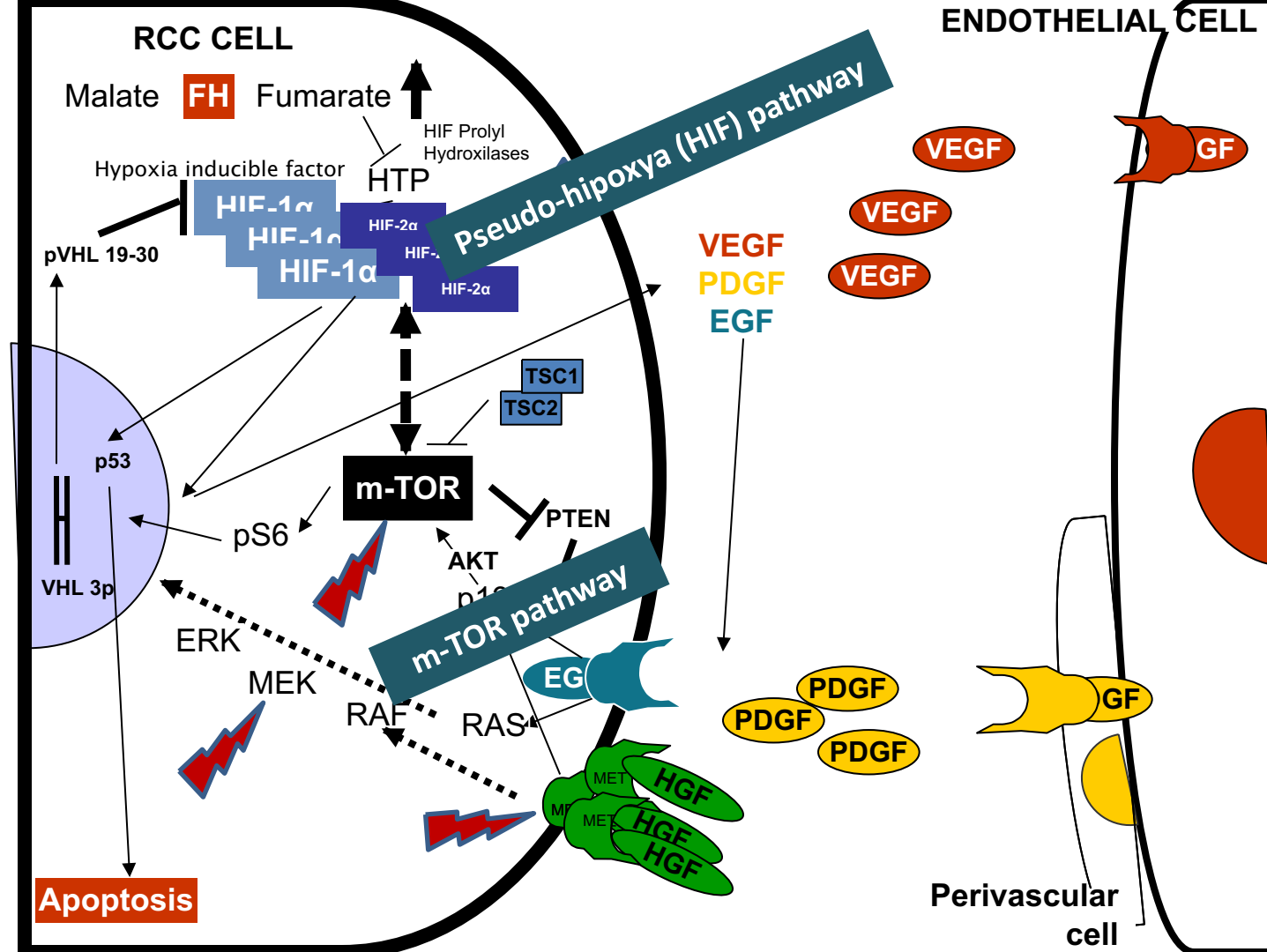
Chromophobe RCC

Collecting/Medullary RCC

Sarcomatoid RCC

NO to these classifications,
let's look for another one
with possible therapeutic
implications

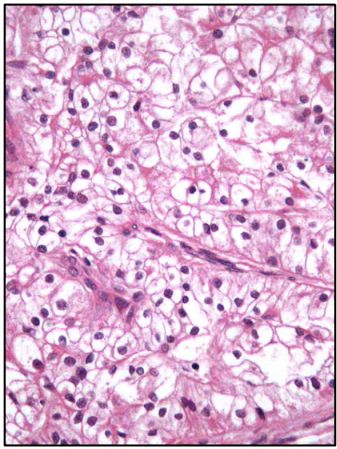




Pseudo-hypoxia (HIF) pathway

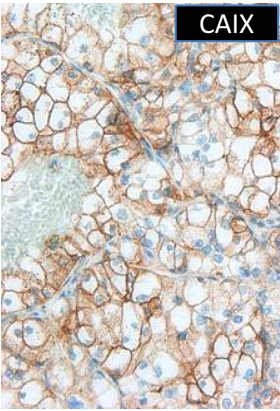
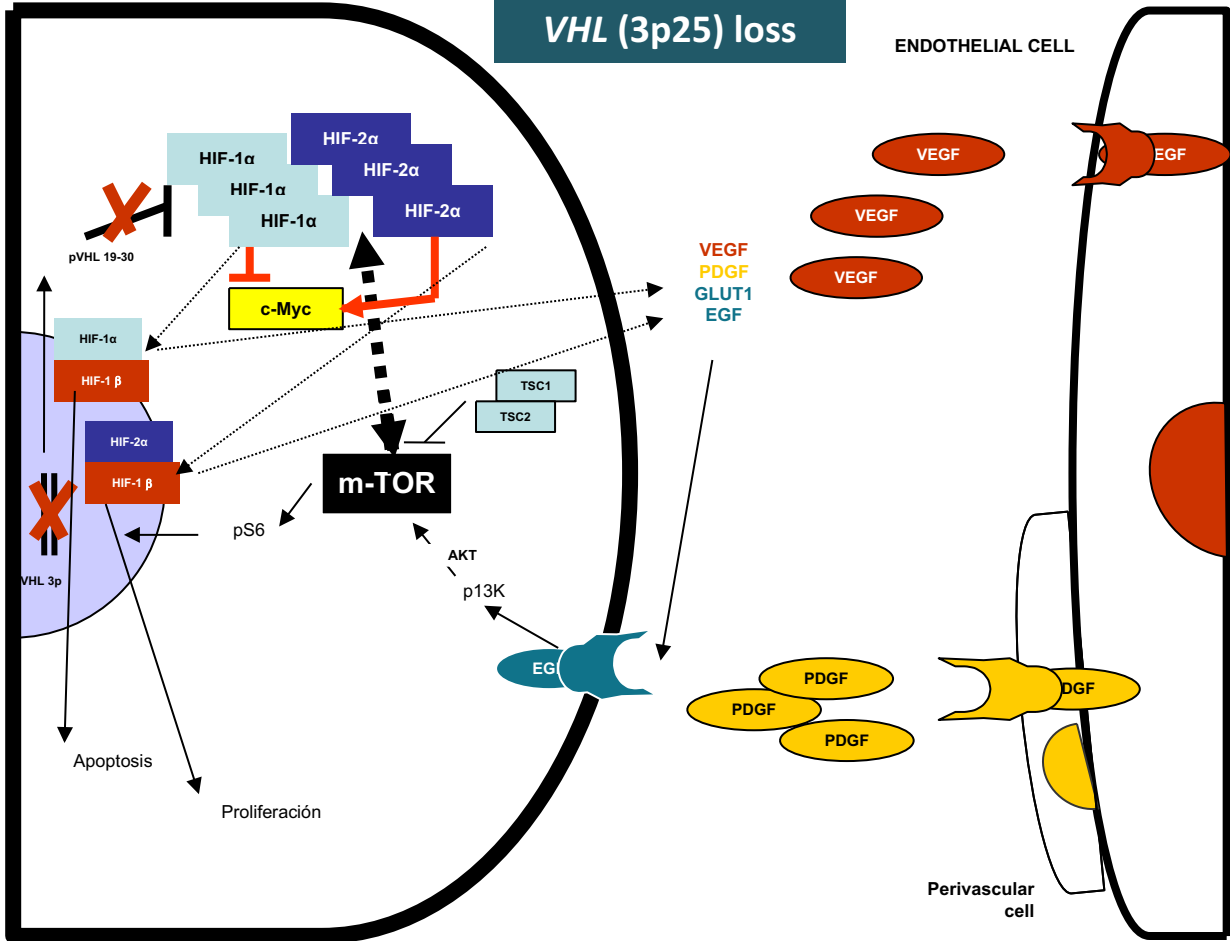
CLEAR CELL RENAL CELL CARCINOMA

60-75%



Pseudo-hipoxya (HIF) pathway

VHL (3p25) loss

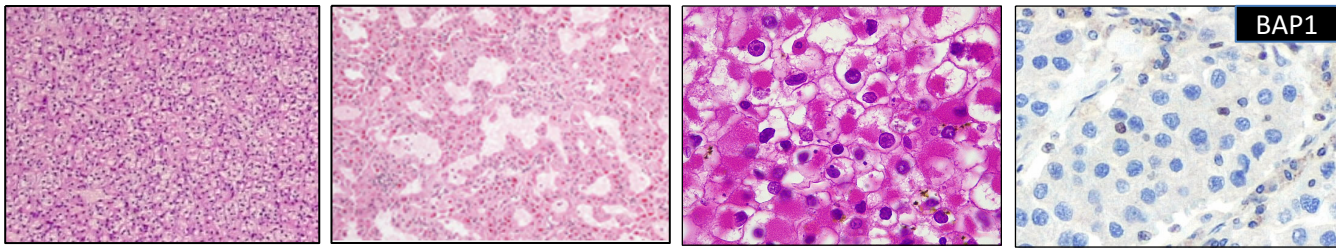
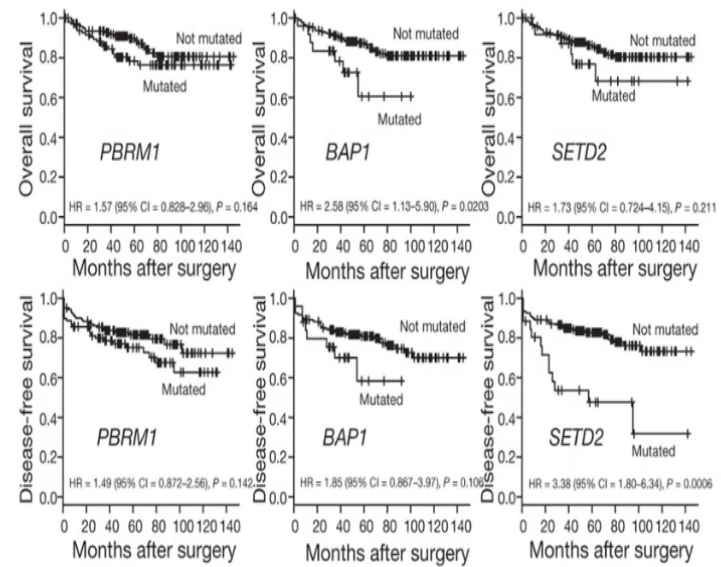
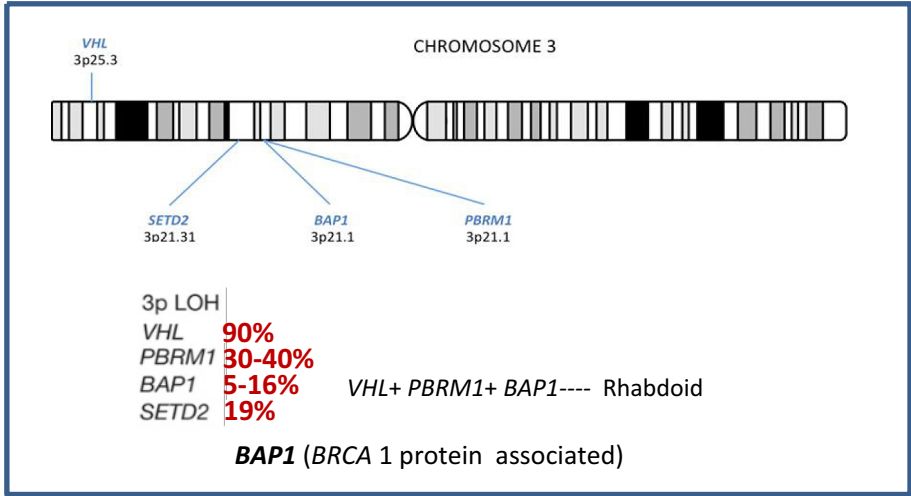


CLEAR CELL RENAL CELL CARCINOMA

60-75%

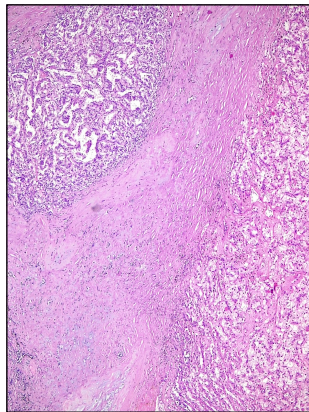
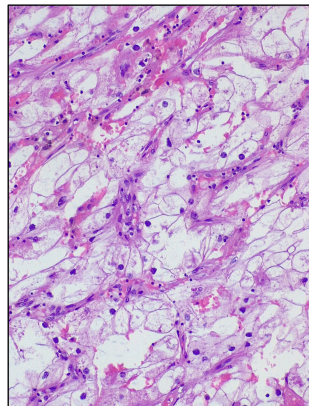
Pseudo-hypoxia (HIF) pathway

Loss of other genes on chromosome 3



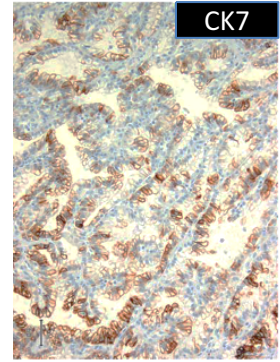
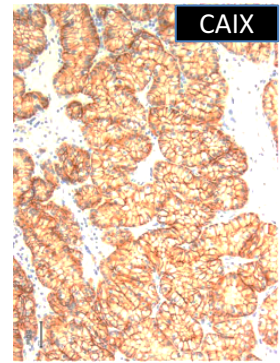
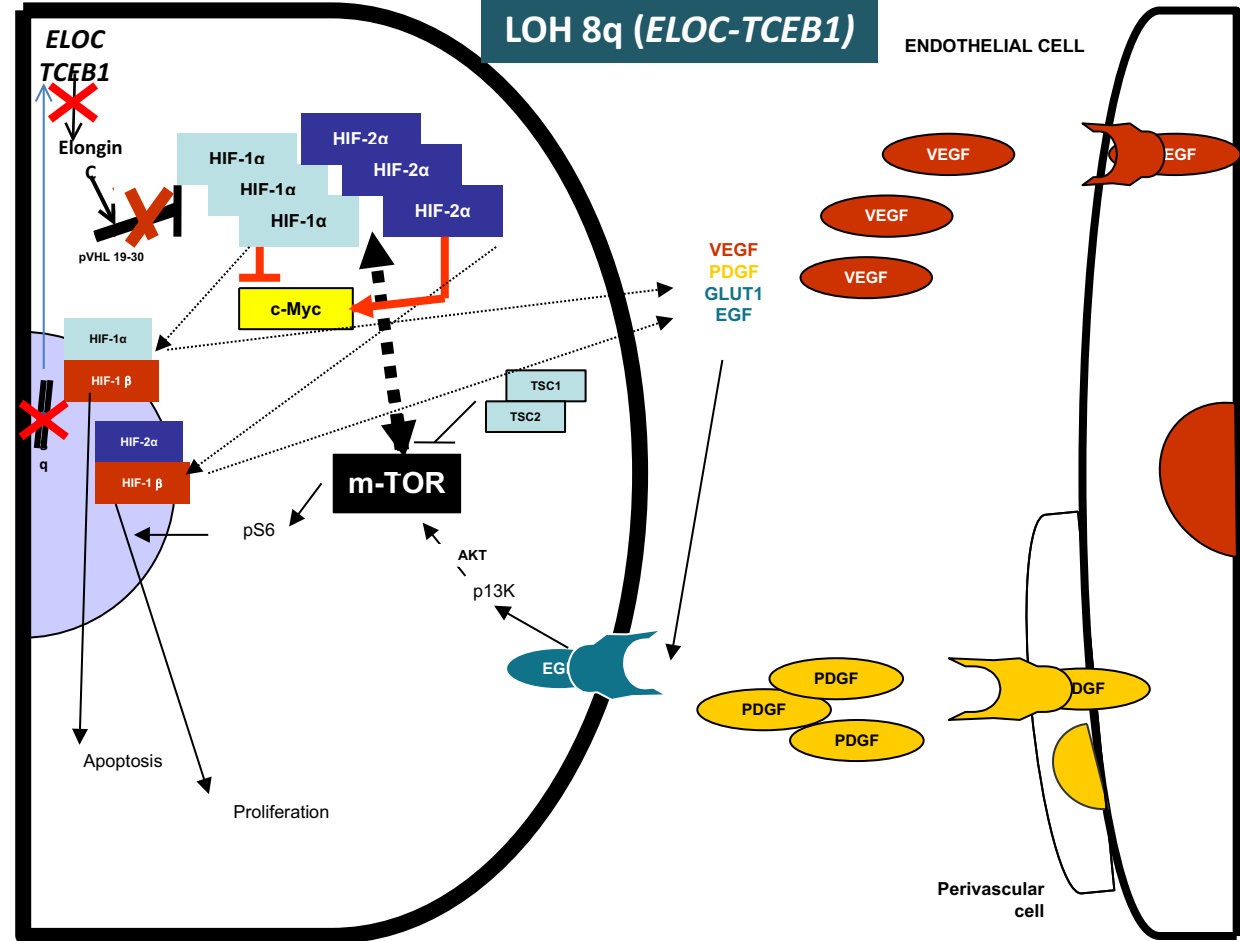
CLEAR CELL RENAL CELL CARCINOMA *ELOC mut*

20 cases



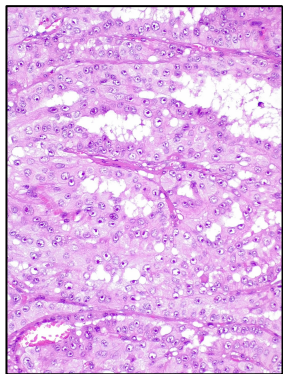
Pseudo-hypoxia (HIF) pathway

LOH 8q (*ELOC-TCEB1*)

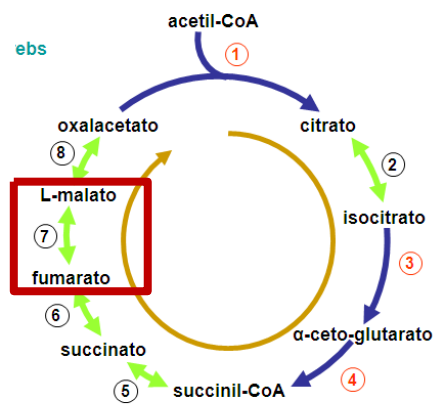


FH DEFICIENT RENAL CELL CARCINOMA

? %

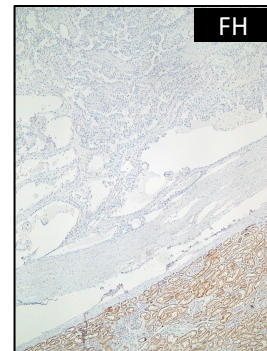
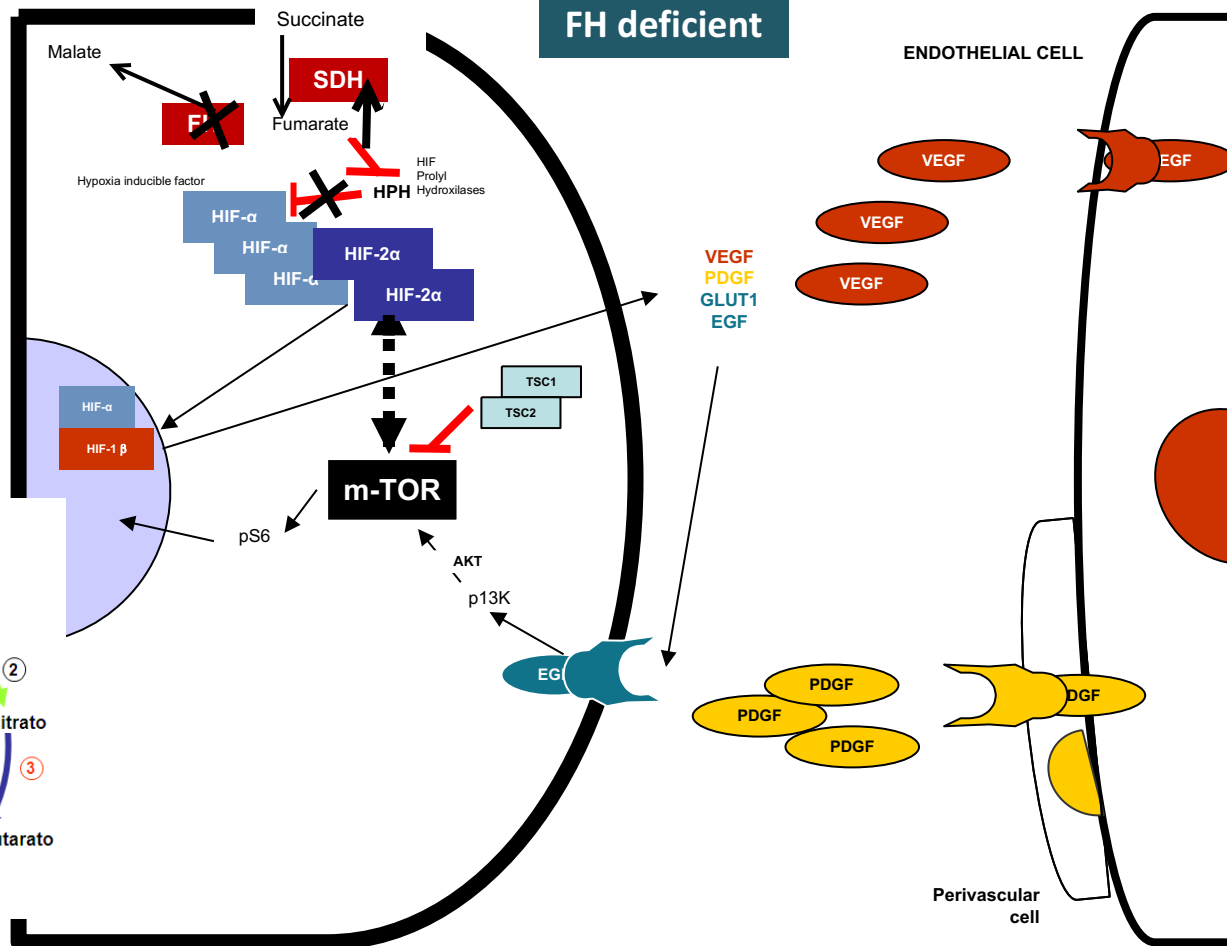


Krebs cycle



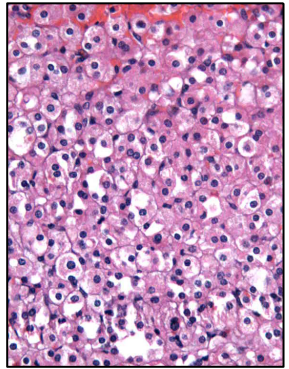
Pseudo-hipoxya (Krebs cycle) pathway

FH deficient

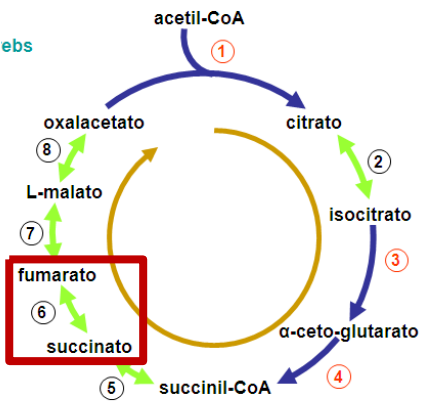


SDH DEFICIENT RENAL CELL CARCINOMA

0.02-05% sporadic

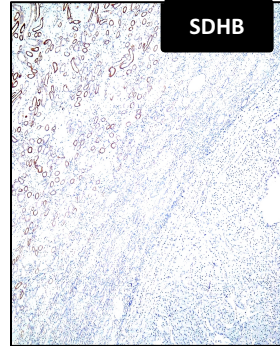
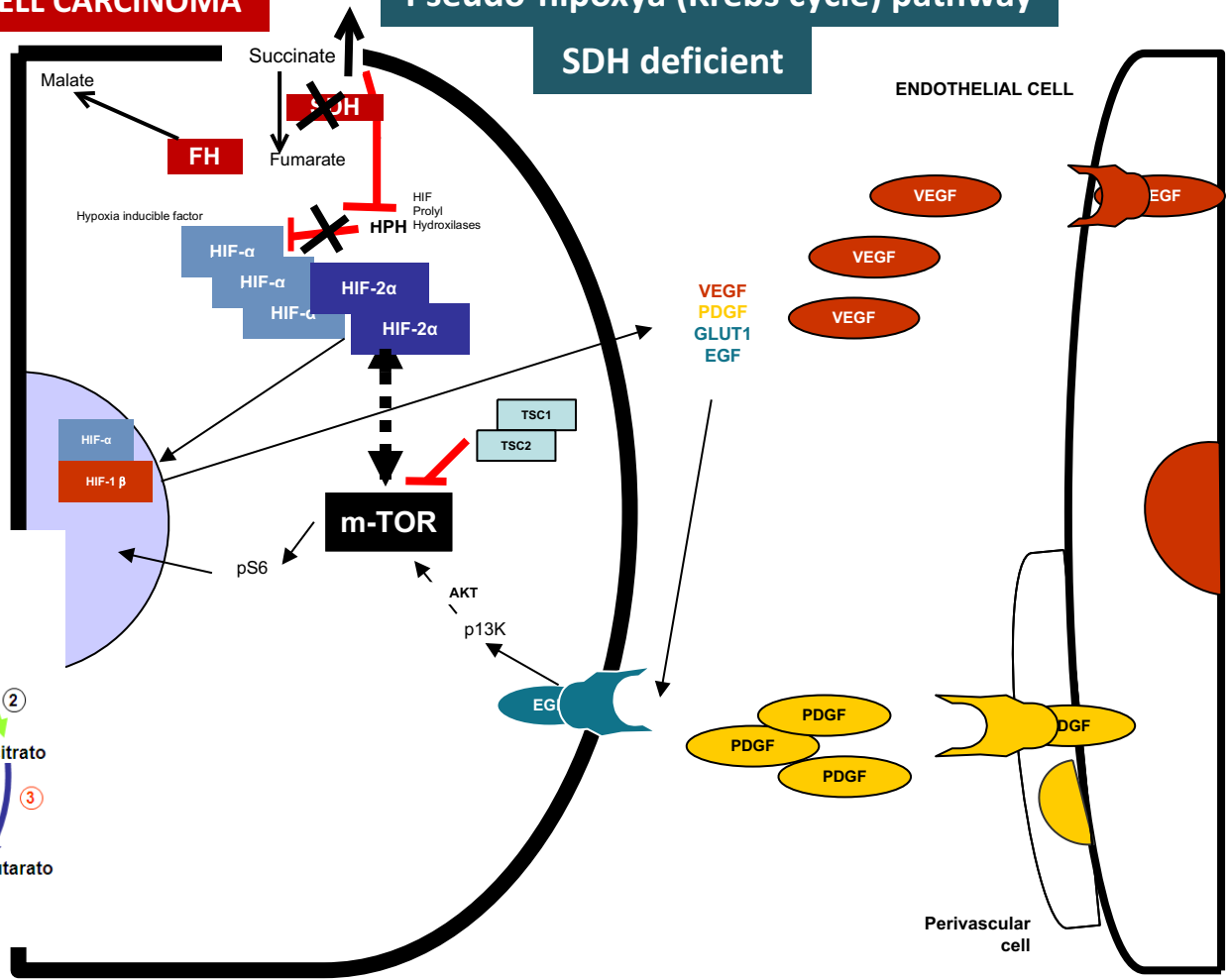


Krebs cycle



Pseudo-hipoxya (Krebs cycle) pathway

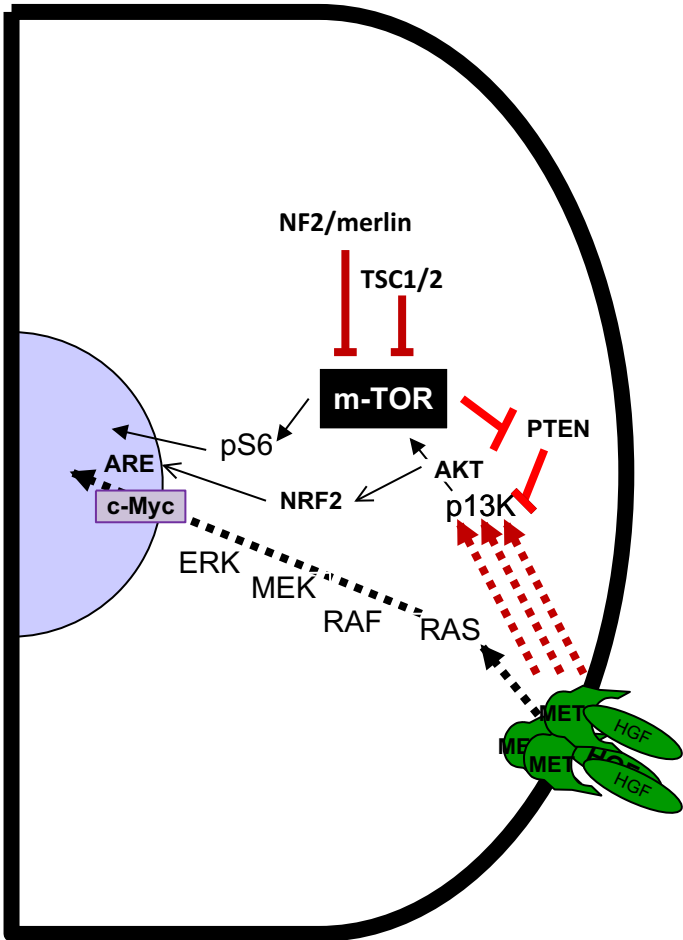
SDH deficient



SDHB

m-TOR pathway

LOW GRADE PAPILLARY RENAL CELL CARCINOMA

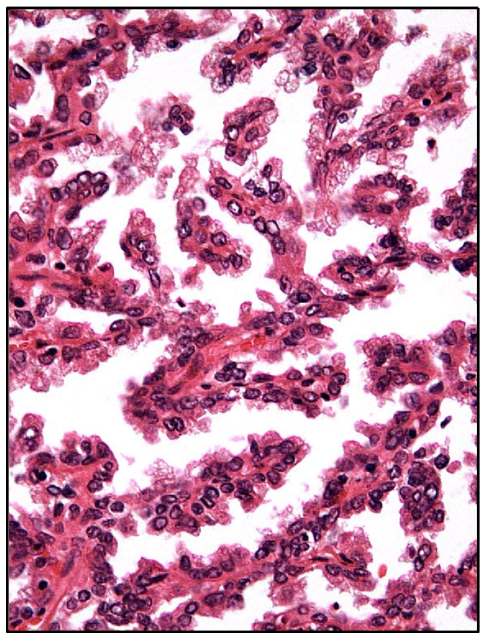


13-20%

m-TOR pathway

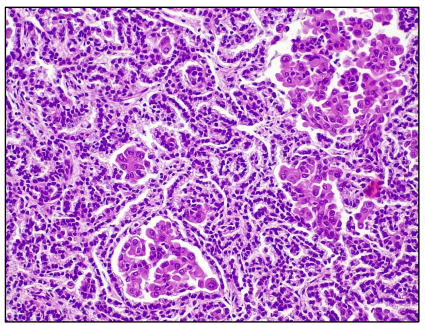
c-MET

CLASSICAL



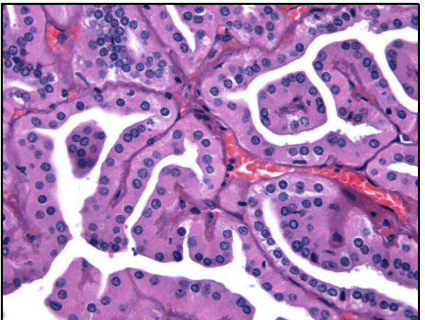
***c-MET* 33%**

BIPHASIC SQUAMOID



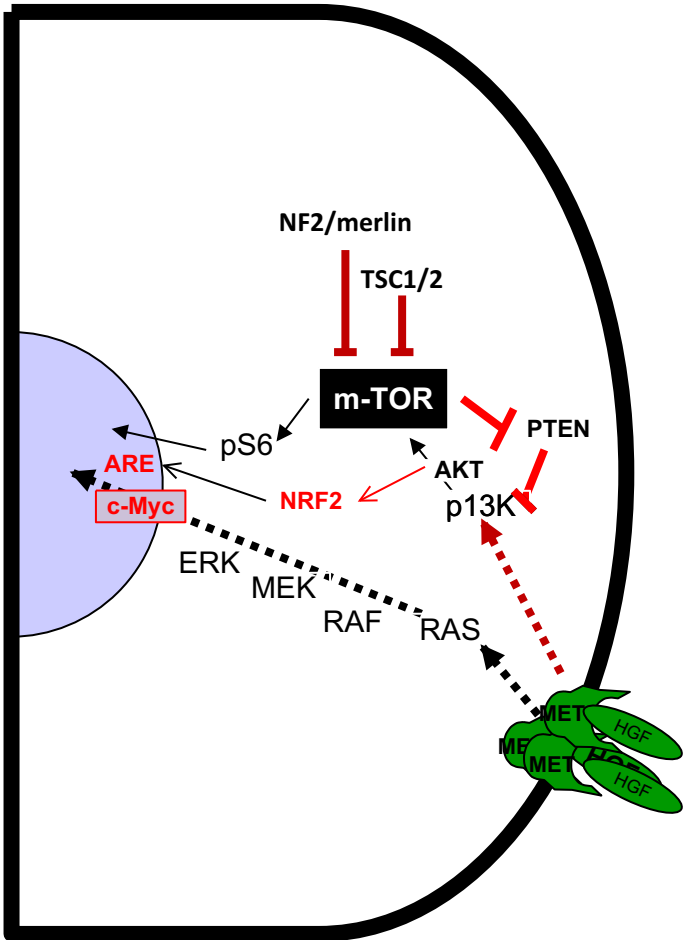
***c-MET* 60%**

REVERSE POLARITY



***KRAS* 80%**

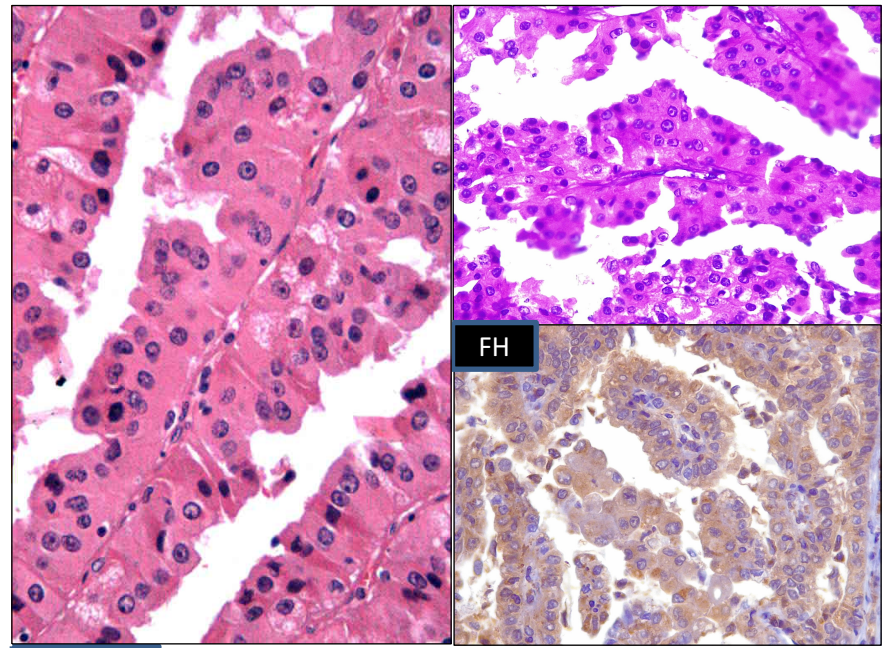
HIGH GRADE PAPILLARY RENAL CELL CARCINOMA



m-TOR pathway

NRF2/c-Myc

NF2



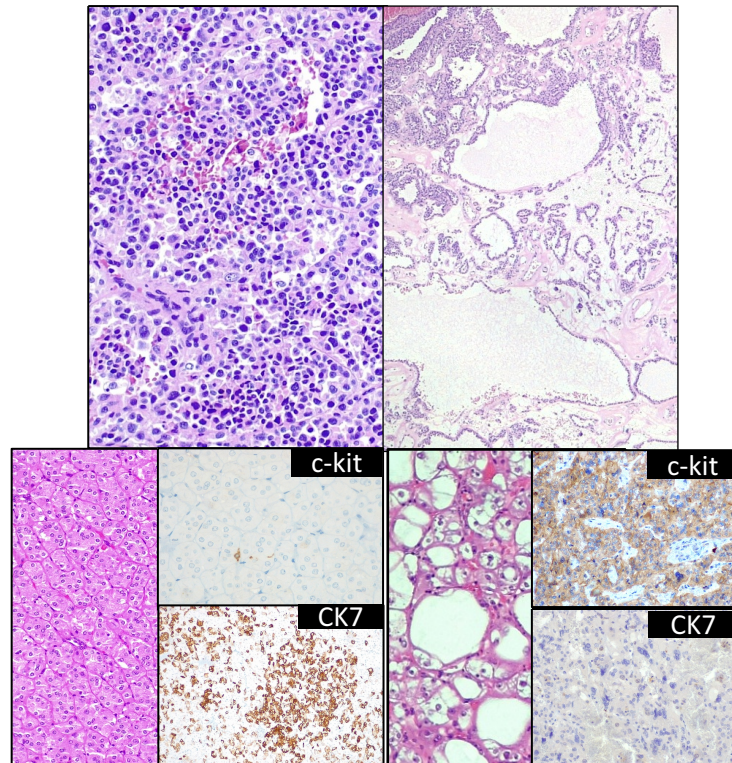
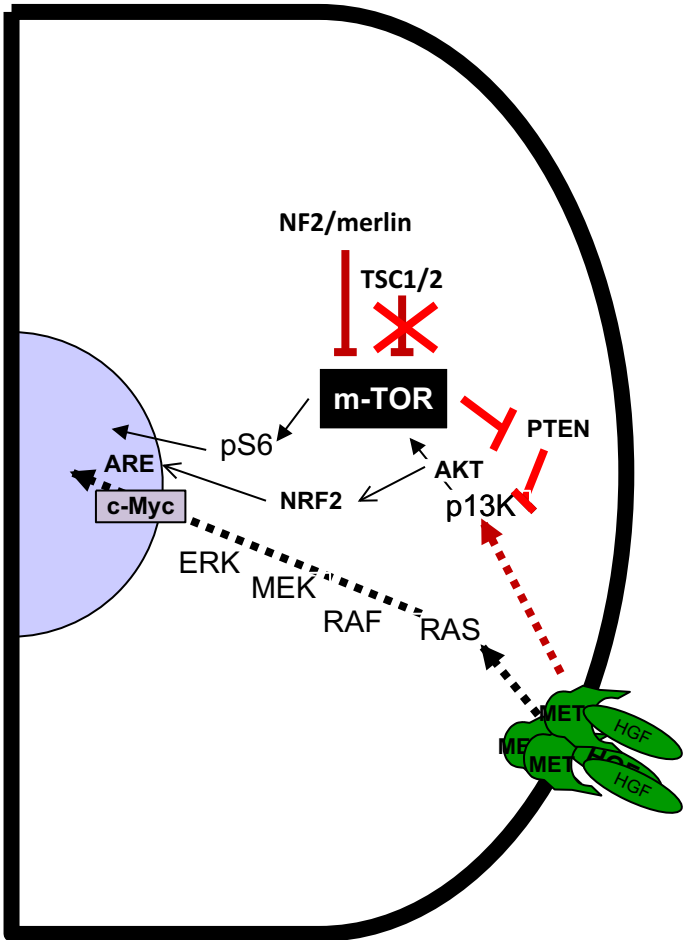
ABCC2

c-MET 7%

EOSINOPHILIC SOLID AND CYSTIC RCC

m-TOR pathway
TSC1/2

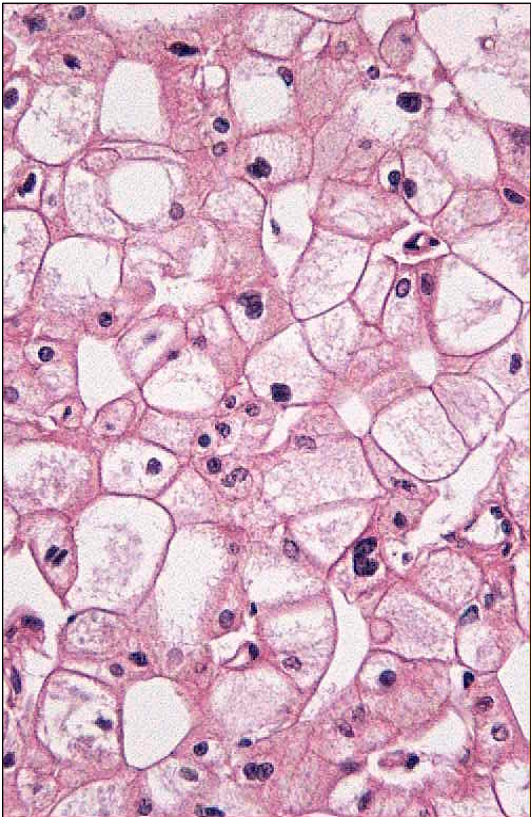
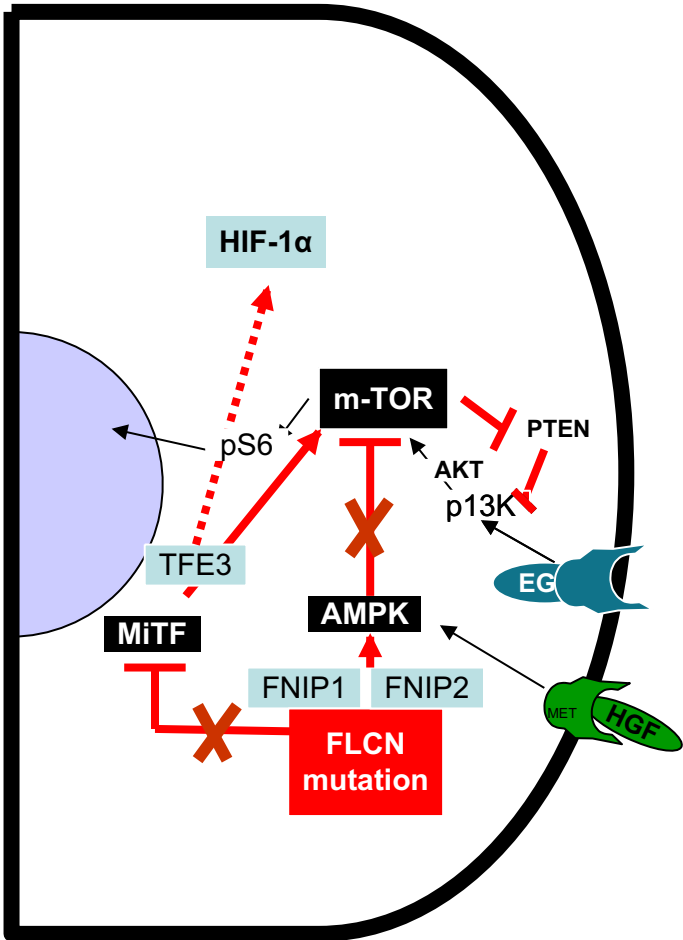
OTHER ONCOCYTIC TUMORS
(LOT/EVT)



SPRADIC CHROMOPHOBE RCC ?

m-TOR pathway
FLCN?

5-7%



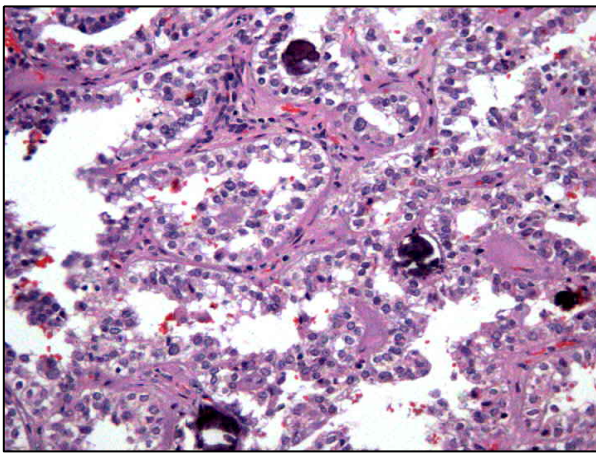
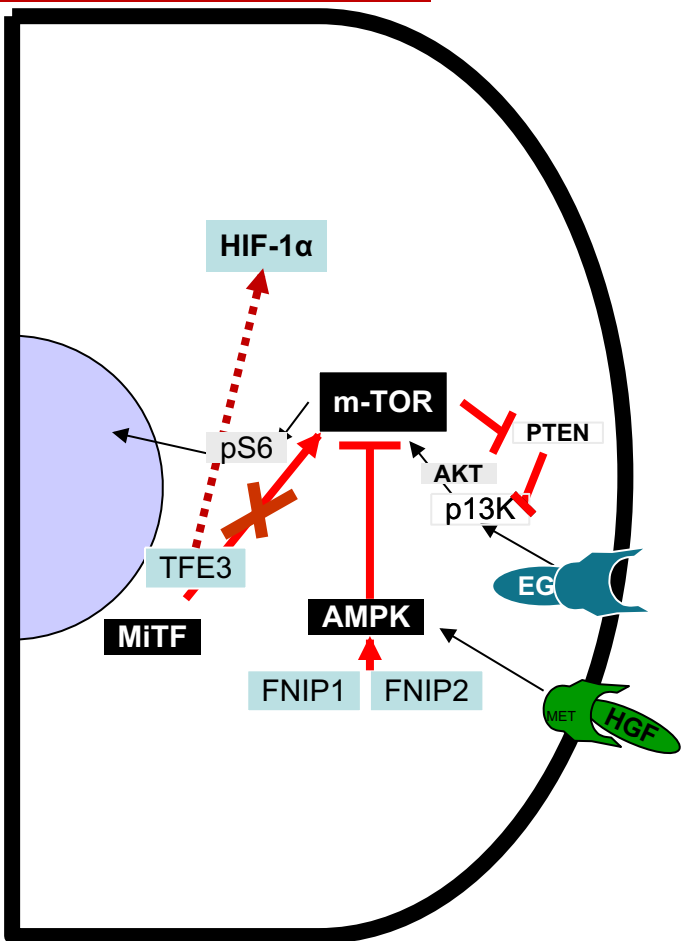
TP53 (32-64%), PTEN (9-45%), TERT (12%)

TFE3- rearranged, TFEB-altered RCC

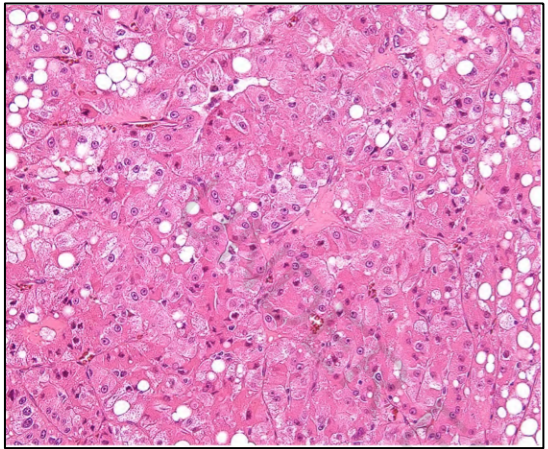
m-TOR pathway

Translocations

2-4% adults



TFE3

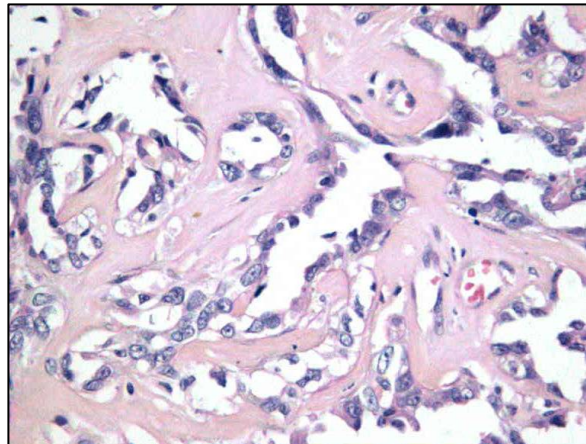
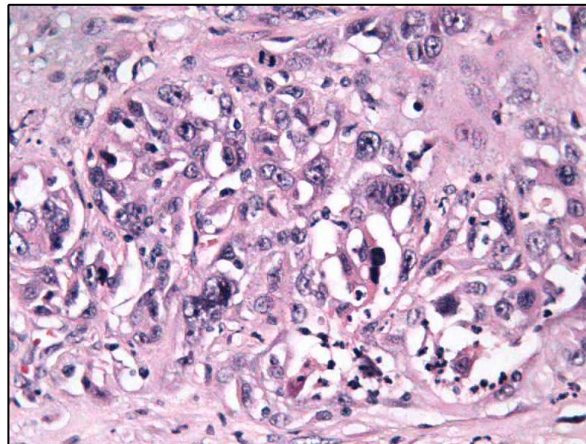
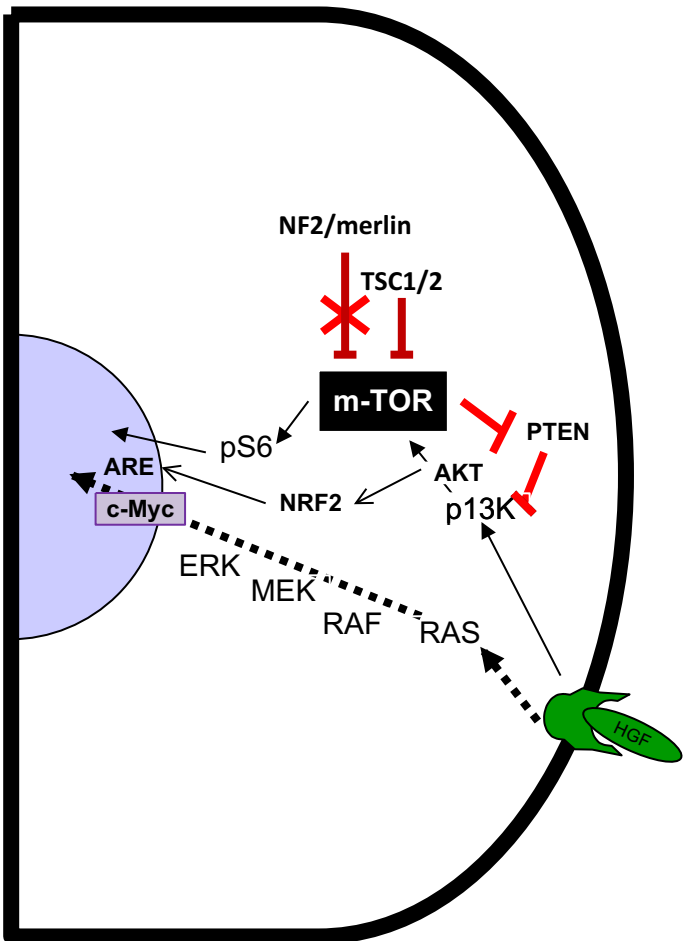


TFEB

COLLECTING DUCT RENAL CELL CARCINOMA

m-TOR pathway

NF2

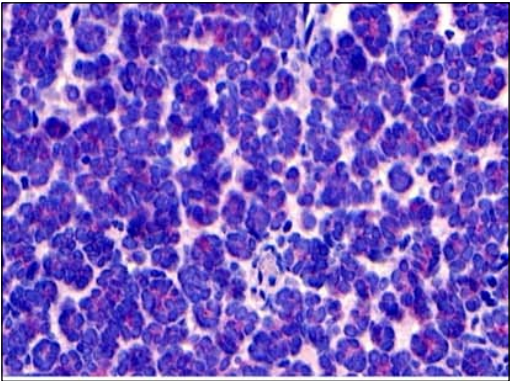
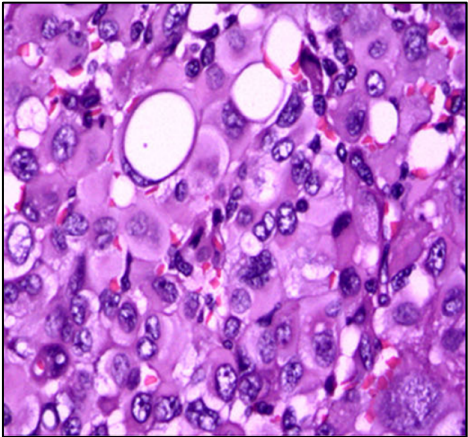
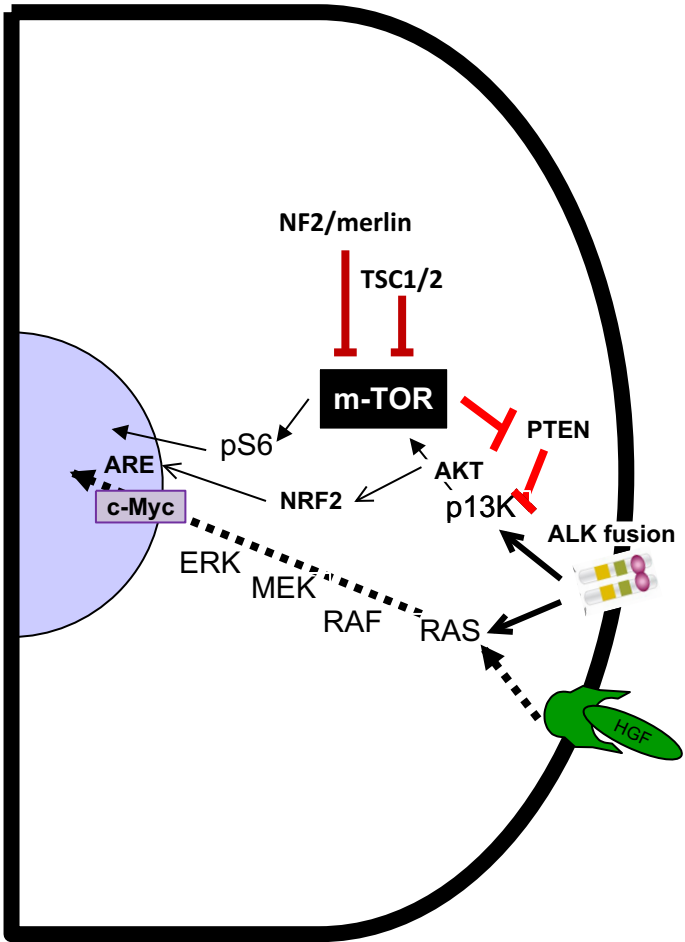


ALK RERARRANGED RCC

m-TOR pathway

ALK

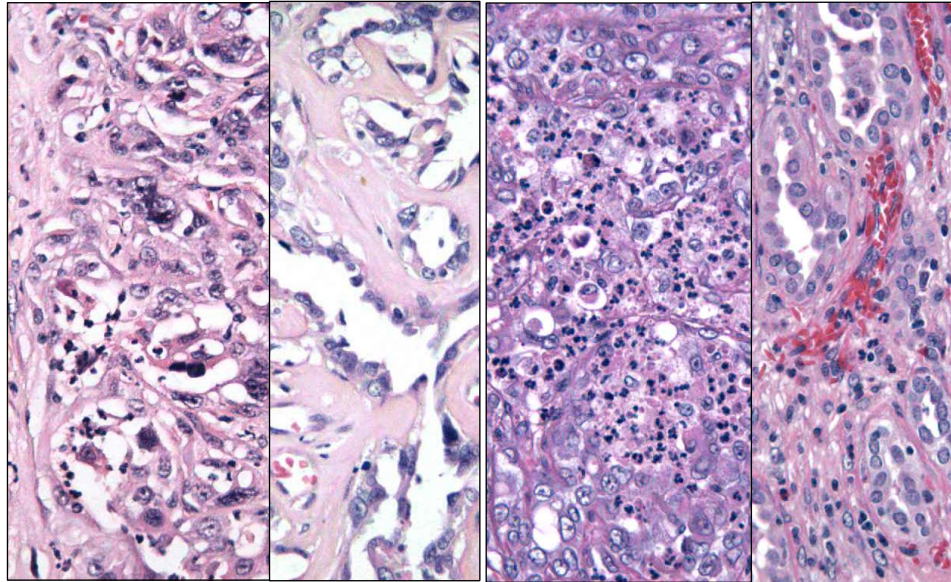
0.3% ?



Another pathway

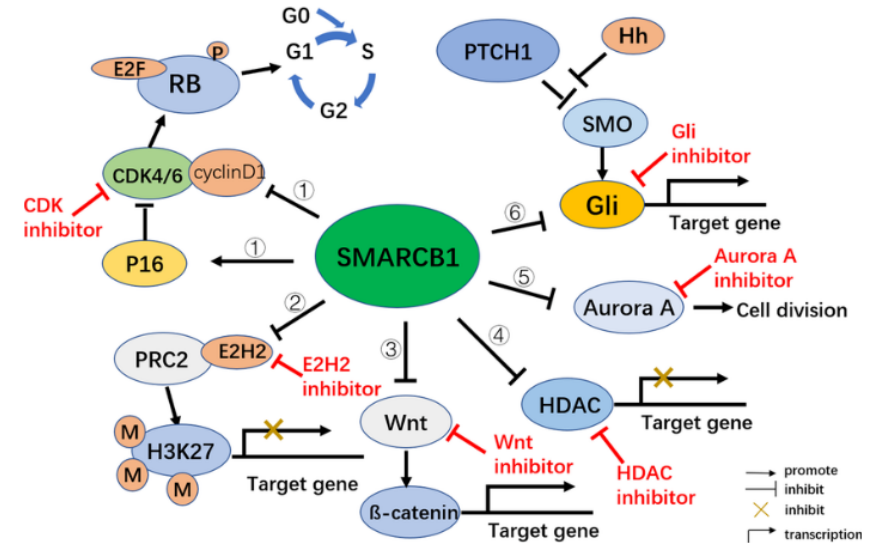
Mutation that unifies several histological subtypes?

(SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily B, Member 1)



COLLECTING DUTS 0.6%

MEDULLARY 0.5%



Renal medullary carcinoma (primary loss of *SMARCB1*)

Renal carcinoma due to *SMARCB1* deficiency

with variable histological forms

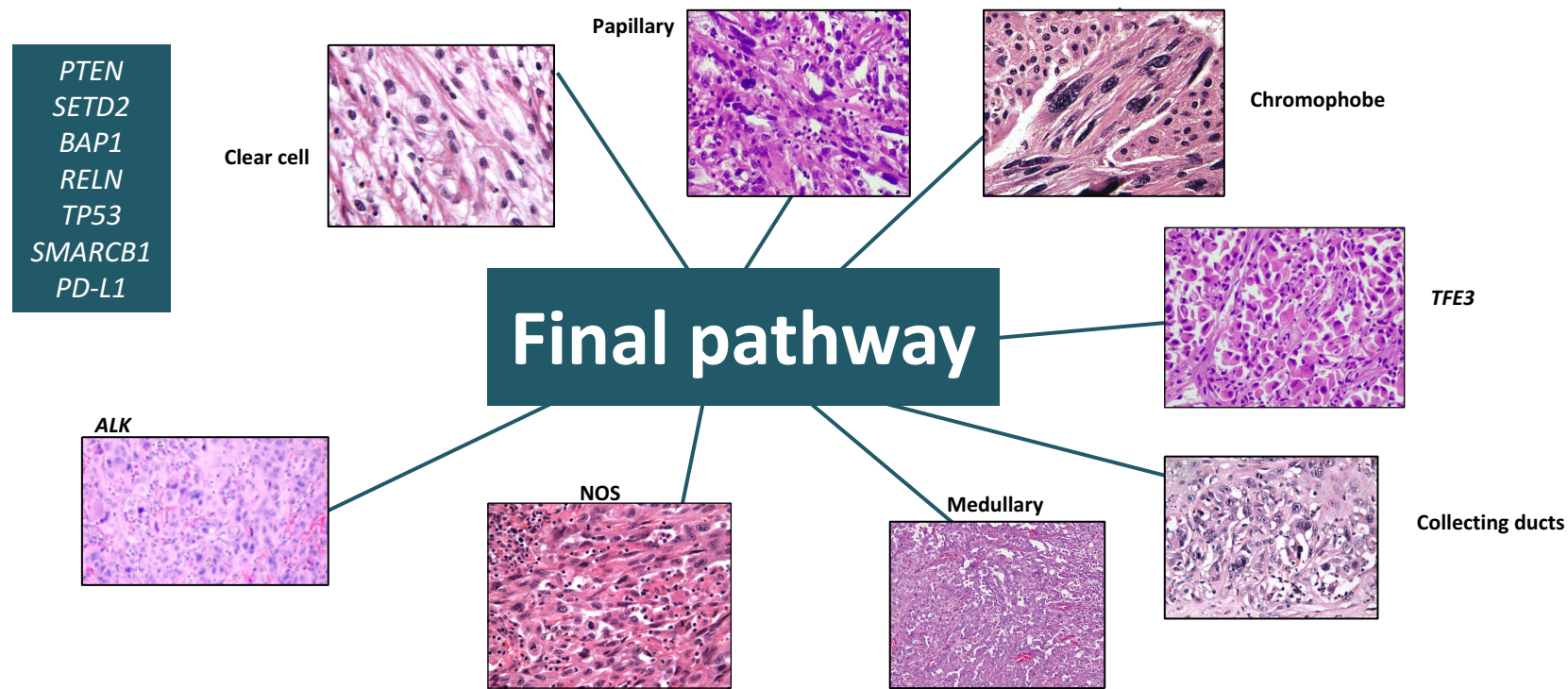
Collecting ducts RCC

High grade papillary RCC

Medullary-like (without sickle cell disease)

Renal carcinoma with secondary *SMARCB1* loss

SARCOMATOID RENAL CELL CARCINOMA



Where are we heading to?

Clear cell
 Multilocular cystic renal neoplasm of low m.p
 ELOC Mutation
 Papillary RCC
 Fumarate H deficient
 Mucinous tubular spindle RCC
 Tubulocystic
 Clear cell papillary RC tumor
 Chromophobe
 Oncocytoma
 SDH deficient
 Other oncocytic tumours
 TFE3- rearranged
 TFEB- altered
 Collecting duct carcinoma
 SMARCB1 deficient renal medullary carcinoma
 ALK rearranged renal cell carcinomas
 Eosinophilic solid and cystic RCC
 Acquired cystic disease associated RCC
 RCC NOS

PSEUDOHIPOXIA



m-TOR

SMARCB1

UNKNOWN

VHL..... Clear cell
 Multilocular cystic renal neoplasm of low m.p
ELOC..... ELOC Mutation
FH..... Fumarate H deficient
SDH..... SDHB deficient
YAP/PAZ.... Mucinous tubular spindle RCC

c-MET..... Low grade papillary RCC
KRAS..... Inverted polarity RCC
NRF2..... High grade papillary RCC ★
FLCN..... Chromophobe
TSC1/2..... Eosinophilic solid and cystic RCC
 Other oncocytic tumours (LOT, EVT)
ALK..... ALK rearranged RCC
NF2..... Collecting duct RCC ★
TFE3/TFEB.... TFE3 rearranged, TFEB altered

Medullary and Medullary-like
 Collecting ducts RCC ★
 High grade papillary RCC ★

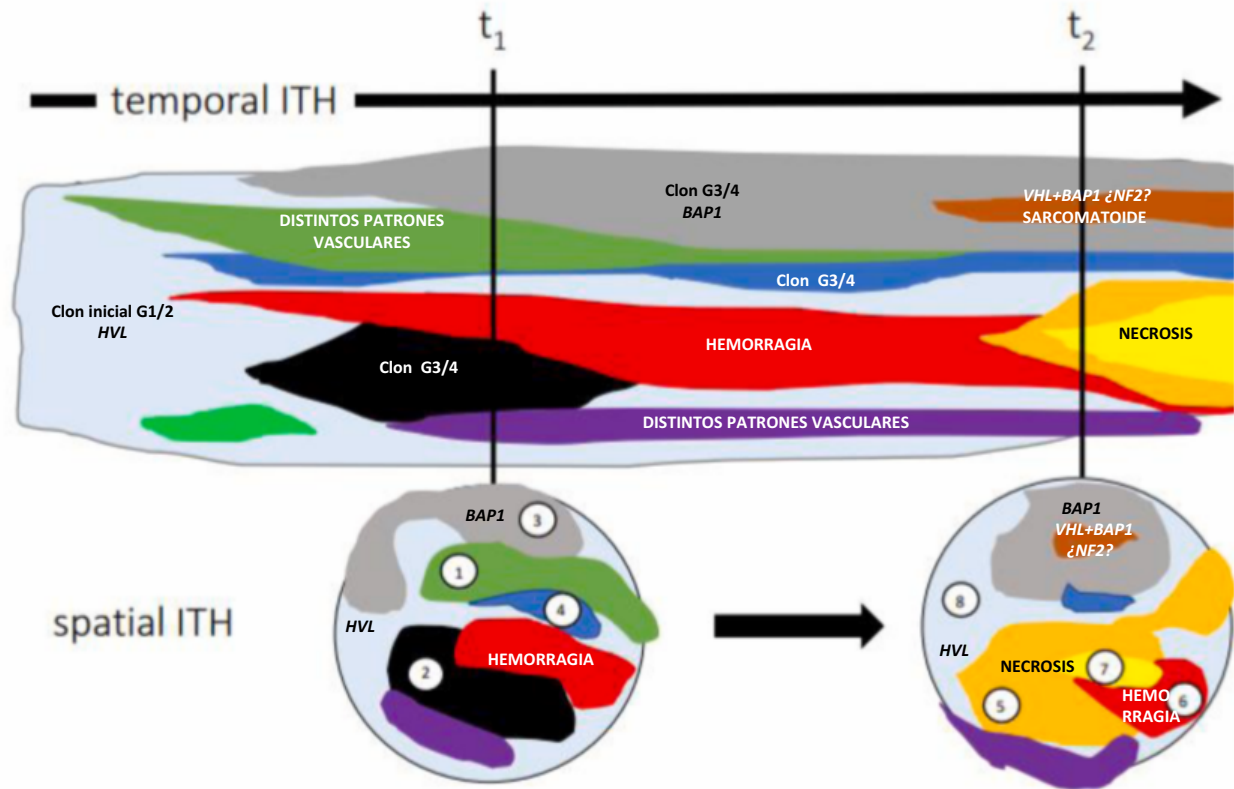
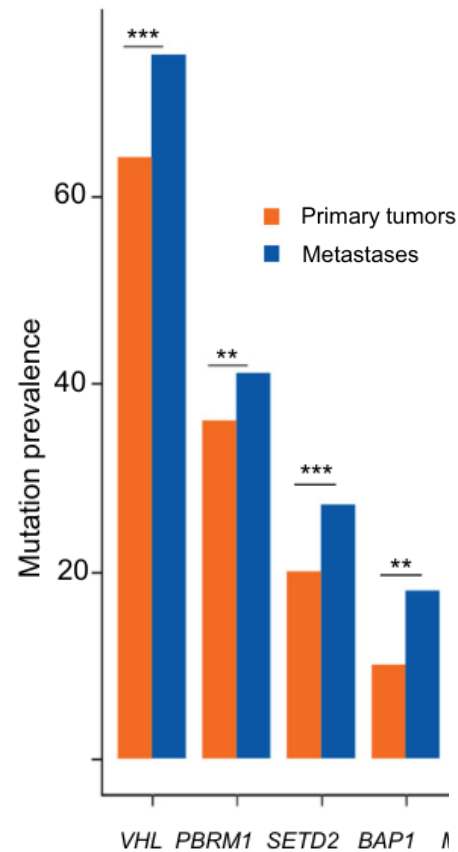
Tubulocystic
 Clear cell papillary RC tumor

SARCOMATOID

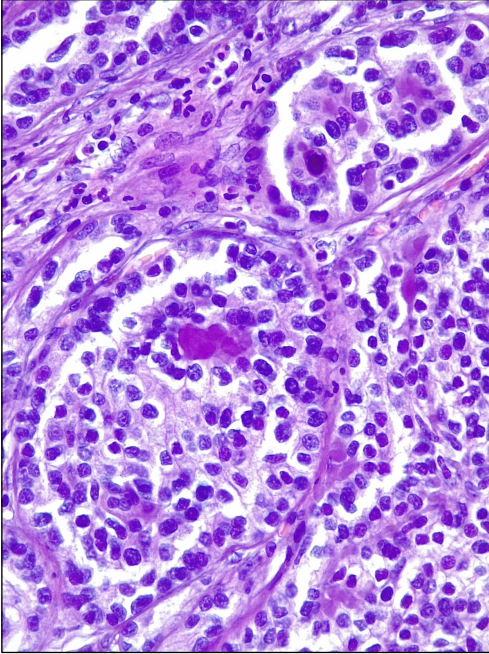
Table 1 Gene mutations and SCNAs in renal cancer

Entity	Gene mutations (%) [*]	SCNAs
ccRCC	VHL (25.5–79.5%), PBRM1 (29.2–54.3%), SETD2 (4.1–42.9%), BAP1 (7.1–24.4%), BRAF (2.9%), CDKN2A (1.1%), FH (2.9%), KRAS (0.2%), MET (1.3–5.7%), PTEN (1.9–10.3%), SDHA (0.4–2.9%), SDHB (0.2–0.9%), SMARCB1 (0.9–11.3%), TP53 (2.8–6.4%), TSC1 (0.4–3.1%), TSC2 (0.9–6.4%), ELOC (0.7–4.7%)	Losses of 3p, 1p36; gains of 5q, 8p, 9p, and 14 [9]
chrRCC	TP53 (33%), PBRM1 (1.5%), PTEN (9.1%), SDHA (7.6%), SETD2 (3%), SMARCB1 (1.5%), TSC1 (3%), TSC2 (4.5%), VHL (1.5%)	Losses of 1, 2, 6, 10, 13, 17, 21, and Y [9, 10]
ELOC-mutated RCC	ELOC (100%), BAP1 (9.1%)	
ESC-RCC	TSC2 (71.4%), TSC1 (28.6%), TP53 (14.3%)	
FH-dRCC	FH (96–100%), NF2 (12–16.7%), CDKN2A (1.8%), KRAS (3.5%), MET (5.3%), PBRM1 (8%), PTEN (7%), TP53 (8.8%), TSC1 (3.5%), TSC2 (3.5%), VHL (1.8%)	22q loss [11]
LOT	TSC1 (10%)	
Pediatric Rhabdoid Tumor	SMARCB1 (9.7%)	
papRCC	BAP1 (5%), BRAF (1.4%), CDKN2A (0.7%), FH (0.7%), KRAS (1.8%), MET (7.4%), PBRM1 (3.9%), PTEN (2.5%), SDHA (0.4%), SETD2 (5.7%), SMARCB1 (3.5%), TP53 (2.5%), TSC1 (0.7%), TSC2 (2.1%), VHL (1.1%), ELOC (0.4%)	Gains of chromosomes 7 and 17 [9]
PRNRP	KRAS (44.1%)	
Rhabdoid Cancer	SMARCB1 (2.5%)	
RMC	MET (3.2%), SDHA (6.5%), SETD2 (6.5%), SMARCB1 (6.5%)	Gain of chromosome 8q; loss of chromosome 22 [12]
TC-RCC	MET (23%), TP53 (16%), VHL (17%)	Gain of chromosome 9 and 17 [3, 13]
TFE3-tRCC	FH (1.9%)	
CDC	NF2 (29%), SETD2(24%), SMARCB1 (18%), CDKN2A (12%)	Losses of 1p, 6, 8, 9, 14, and 22 [14, 15]

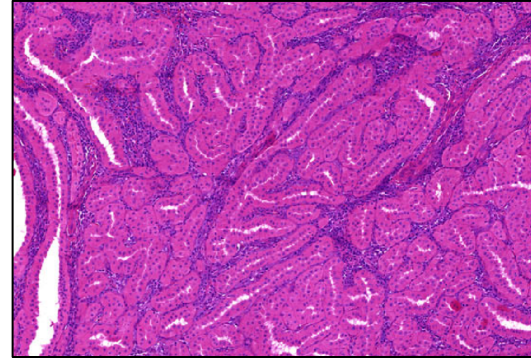
Clear Cell RCC MORPHO-MOLECULAR EVOLUTION



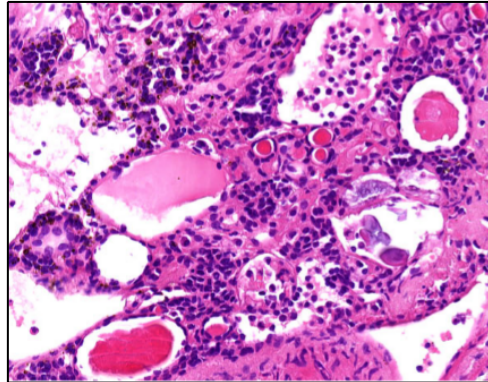
but... THERE ARE EVEN MORE POSSIBLE RCC SUBTYPES



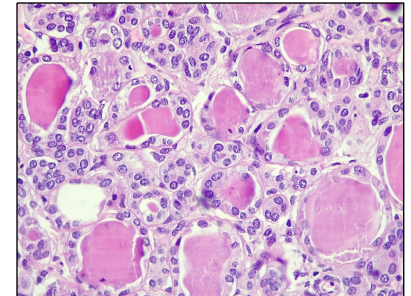
Biphasic hyalinizing psammomatous RCC
NF2



Warthin-like RCC



Pseudo-atrophic RCC



Follicular RCC



*The truth is rarely pure and
never simple.*