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VHL Alterations and Renal Tumorigenesis

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The *VHL* gene

- The von Hippel-Lindau (*VHL)* disease: A hereditary syndrome with predisposition to various tumors, including renal cell carcinomas, because of *VHL* gene alterations.
- Sporadic clear cell renal carcinomas (the common form of kidney tumors): LOH at 3p25 (>90%), *VHL* mutations (30-60%), and hypermethylation in the *VHL* promoter (up to 19%).

The von Hippel-Lindau disease

Phenotype		Genotype
Type 1	Renal cell carcinomas or cysts (25-60%)	Deletion Frameshift
Type 2A	CNS hemangio-blastomas (44-72%)	Missense
Type 2B	Retinal hemangio-blastomas (25-60%)	Deletion Frameshift Missense
Type 2C	Pancreatic tumors or cysts (35-70%)	Missense
	Pheochromo-cytomas (10-29%)	

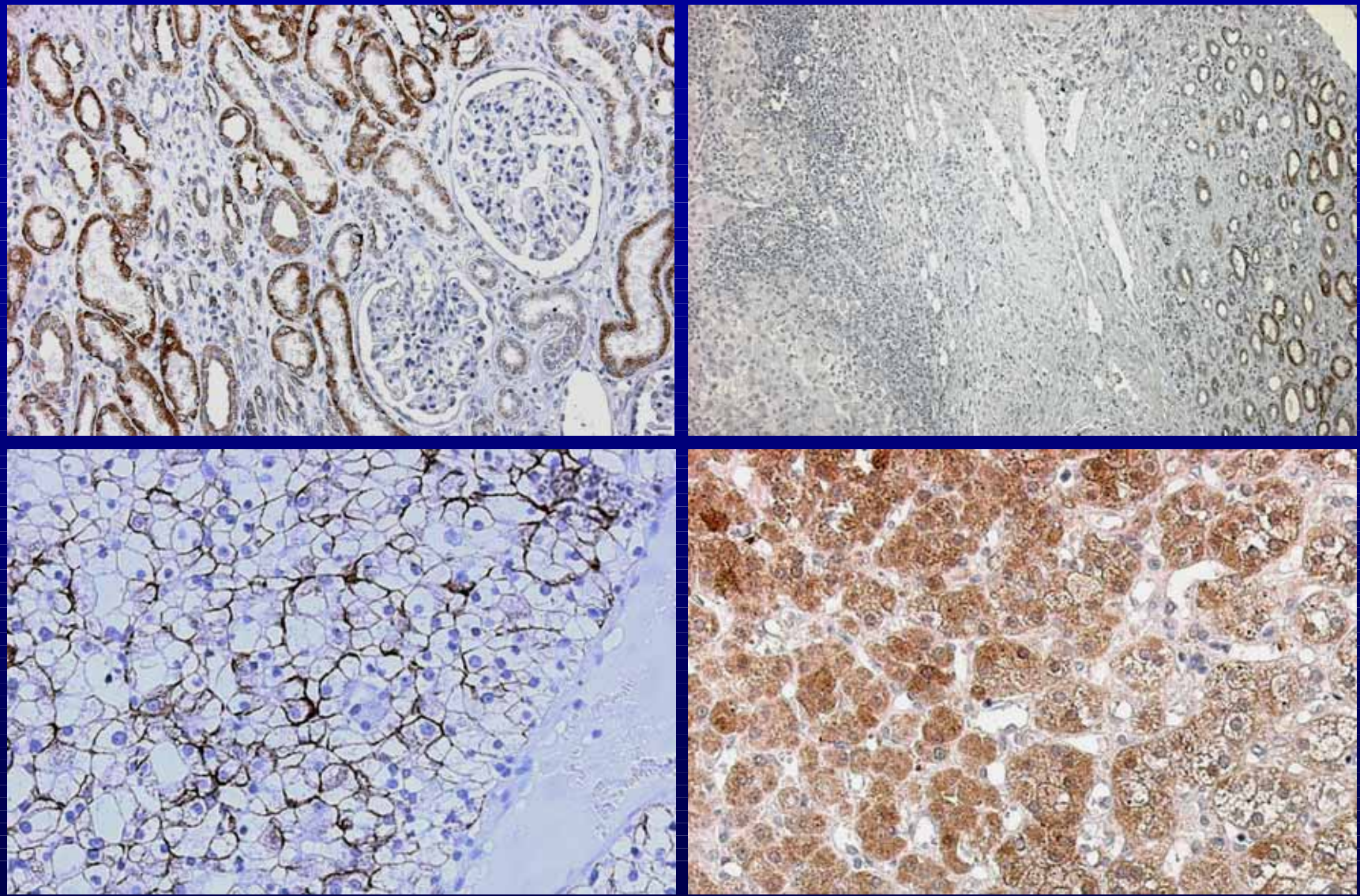
Sporadic renal cell carcinomas

Phenotype	Genotype (*VHL* mutations)
Clear cell (70-80%)	Deletion/frameshift (>50%) Missense (<50%)
Papillary (10-15%)	Rare
Chromophobe (5%)	Rare
Oncocytoma (5%)	Rare

Association of *VHL* gene alteration with renal clinicopathological data

- **Tumor stage: Inconsistent**
- **Nuclear grade: Inconsistent**
- **Metastasis: Inconsistent**
- **Cancer-free or cancer-specific survival: "Better" with *VHL* gene alterations**

VHL protein in renal cell carcinomas



Shiao et al., Kidney Int. 64:1671, 2003

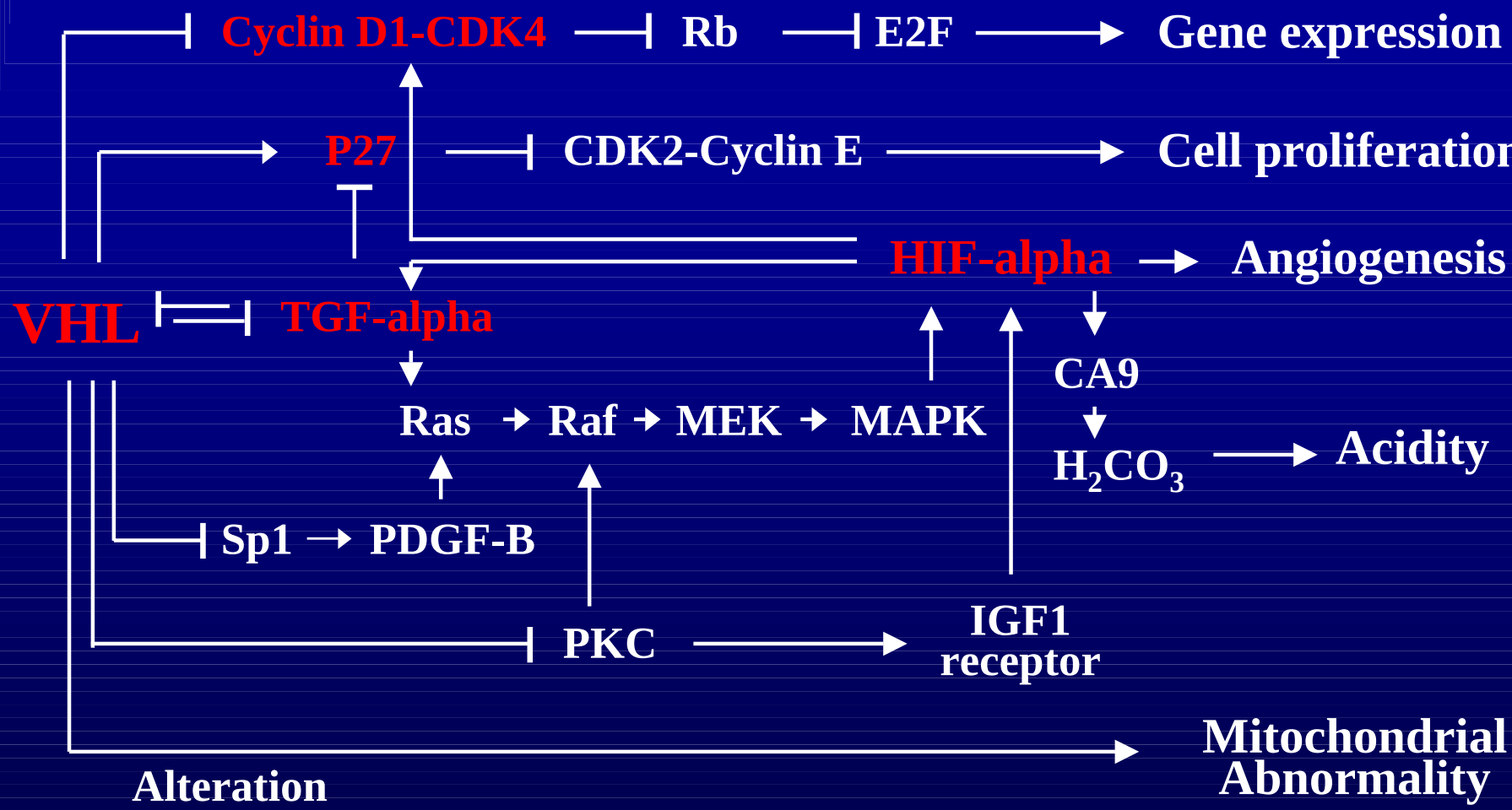
Association of VHL protein expression with renal clinicopathological data

	Membrane	Cytoplasm /Negative	P[a] value	Nuclei/ Cytoplasm	Negative	P[b] value
Missense	9 (64%)	5 (36%)	0.0025	-	-	-
Others	14 (23%)	47 (77%)				
Grade 1	6 (50%)	6 (50%)	0.2214	40 (87%)	6 (13%)	<0.0001
Grade 2	11 (31%)	25 (69%)		171 (76%)	54 (24%)	
Grade 3/4	6 (22%)	21 (78%)		64 (50%)	63 (50%)	
TI	23 (38%)	37 (62%)	0.0034			
TII/TIII	0 (0%)	15 (100%)				
TI/TII				131 (76%)	42 (24%)	0.0121
TIII				144 (64%)	81 (36%)	
Survival (Cox model)	-	-	-	Better	Poor	0.04

[a]Shiao et al., Kidney Int. 64:1671, 2003; [b]Schraml et al., Am J Pathol. 163:1013, 2003

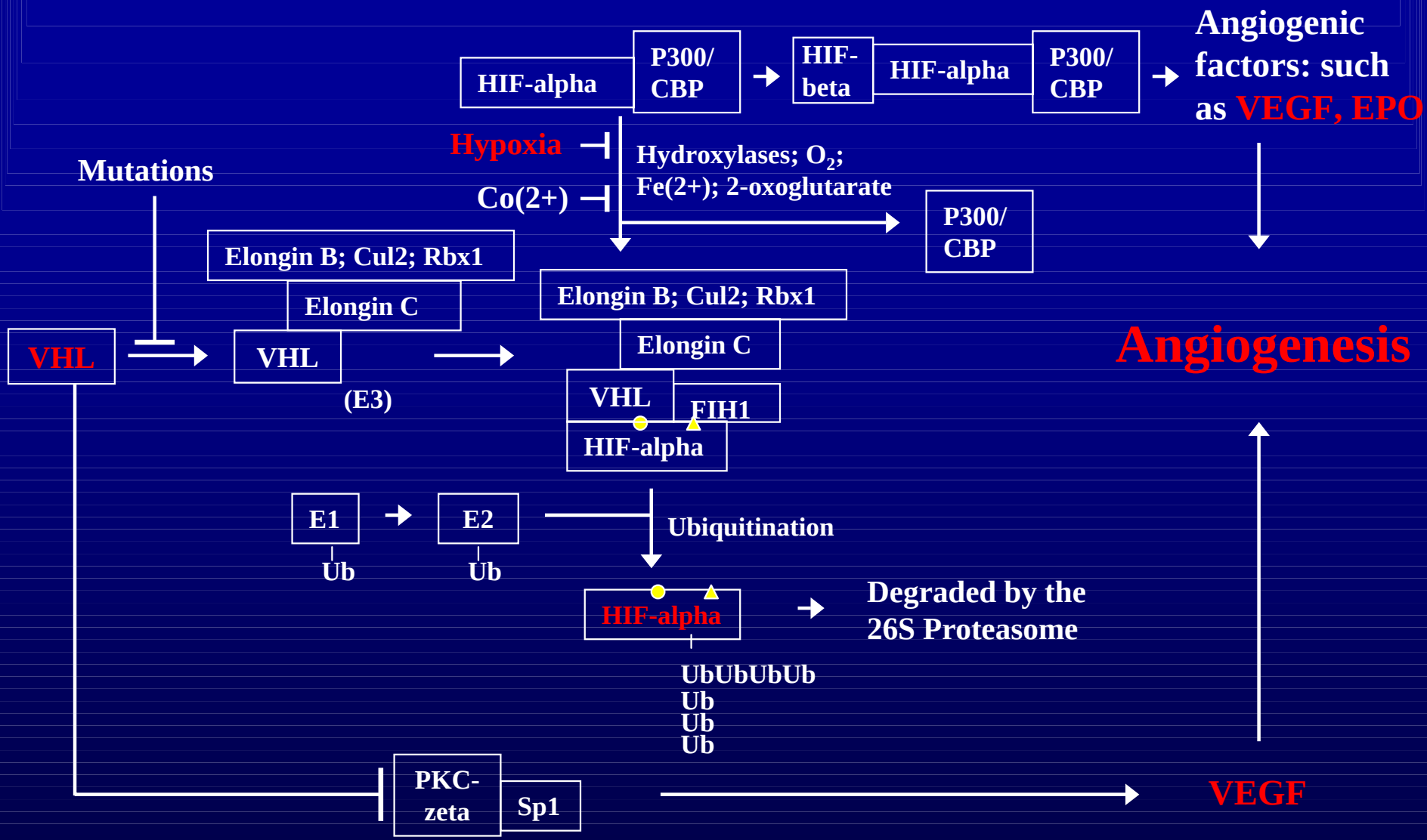
- **Does VHL alteration initiate renal tumorigenesis?**
- **Do different VHL alterations have diverse tumorigenic potentials?**

Evidence for tumorigenesis *in vitro*



Shiao YH, Curr Med Chem. 10:2461, 2003

Evidence for angiogenesis *in vitro*



Shiao YH, Curr Med Chem. 10:2461, 2003

Evidence from *VHL*-knockout animals

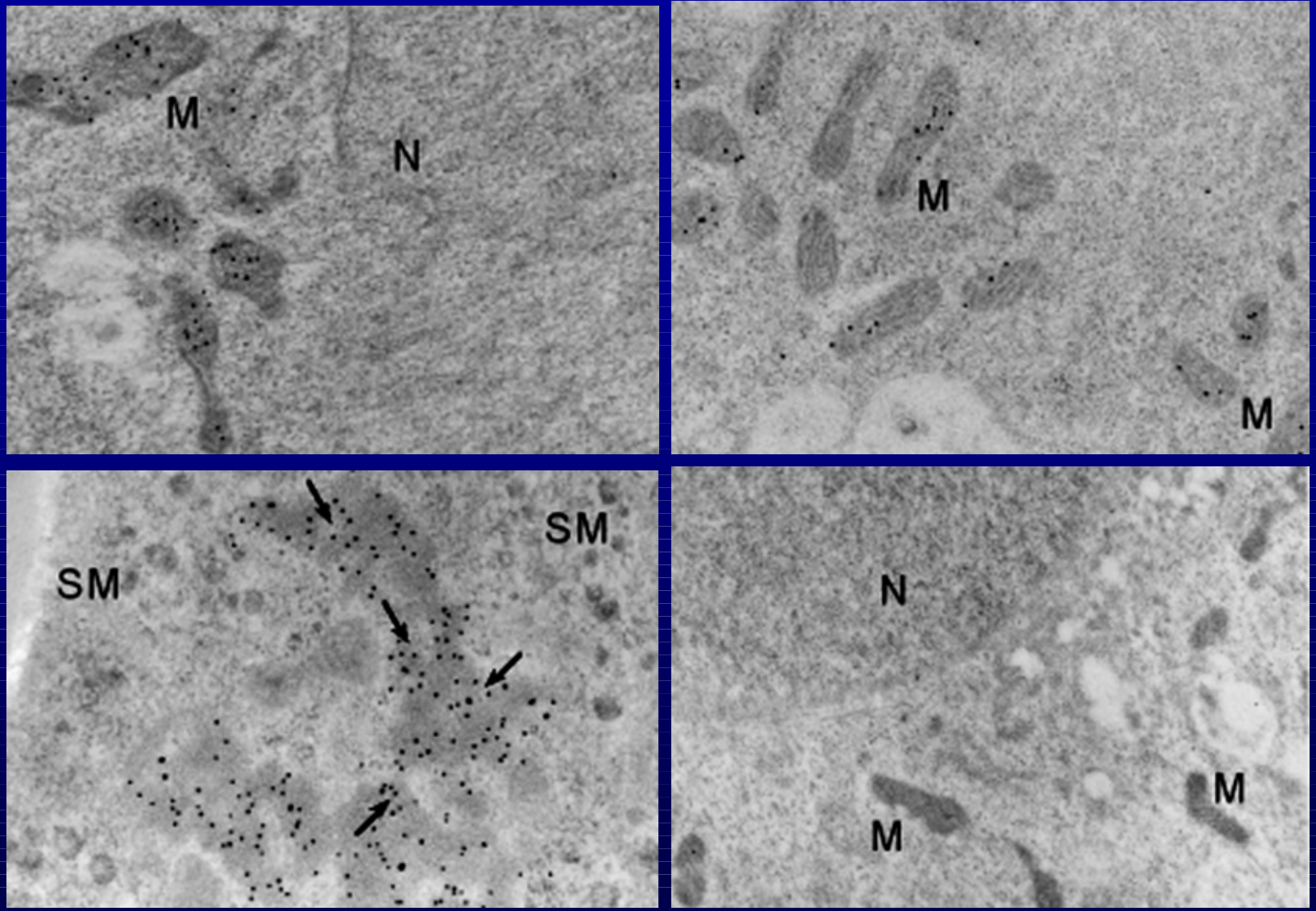
- ***VHL*$^{-/-}$ mice: Embryonic lethality**
- ***VHL*$^{+/-}$ mice: Susceptible to vascular lesions in the liver (21%)**
- **Mice with conditional *VHL*$^{lox/-}$ and *Cre* alleles: Vascular lesions in the liver (>90% over 12 months of age), heart, kidney, and pancreas**

Tumor initiation

vs

Tumor progression

VHL immunogold electron microscopy



Shiao et al., Cancer Res. 60:2816, 2000.

Mutation spectra indicative of exposures

Missense	Possible causes
Transitions	
GC to AT	Deamination of 5-methyl-C (CpG sites) or C Alkylation of G at O^6 position
AT to GC	Deamination of A; alkylation of T at O^2 or O^4 position
Transversions	
GC to TA	Mispairing of A with 8-OH-G or with apurinic G
AT to TA	Mispairing of A with apurinic A site
AT to CG	Misincorporation of 8-OH-G; error-prone repair of O^2- or O^4-alkyl T
GC to CG	Mispairing of G with oxidatively-damaged G

VHL mutations and TCE exposure

TCE[a] exposure	Base # 454	Mutation(s) No	1	⩾2	GC to AT	Missense
High	7/17 (41%)	2 (11%)	4 (24%)	11 (65%)	21/27 (78%)	27/50 (54%)
Medium	6/24 (25%)	6 (25%)	15 (63%)	3 (13%)		
Low	0/3 (0%)	3 (100%)	0 (0%)	0 (0%)		
No	0/107 (0%)	31/73 (42%)	42/73 (58%)	0/73 (0%)	~25%[b]	~30%[b]
P value	<0.0001	<0.0001			-	-

[a]Patients working in metal-processing plant

[b]Beroud et al., Human Mut. 15:86, 2000.

Brauch et al., JNCI. 91:854, 1999

Conclusion

- There is still lack of direct evidence that VHL alterations initiate renal tumorigenesis, although they may be involved in tumor progression.

- Different VHL alterations have distinct tumorigenic potential: Higher tumorigenicity tends to associate with frameshift mutations and protein down-regulation.

- Comparison of mutation spectra in renal cell carcinomas may be able to identify specific base changes associated with TCE exposure but more population-based studies are needed to have sufficient statistical power.

- Co-exposures, such as metals, smoking, hypertension, obesity, and chronic renal disease, need to be examined.