VHL Research

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Types of cancer-associated genes

- Oncogenes
  - Normal protein function is to stimulate cell proliferation
  - Mutational ACTIVATION results in uncontrolled cell proliferation
- Tumor Suppressors
  - Normal protein function is to suppress cell proliferation
  - Mutational INACTIVATION results in uncontrolled cell proliferation
- DNA Repair Genes
  - Normal protein function is to repair DNA damage
  - Mutational INACTIVATION results in genome instability

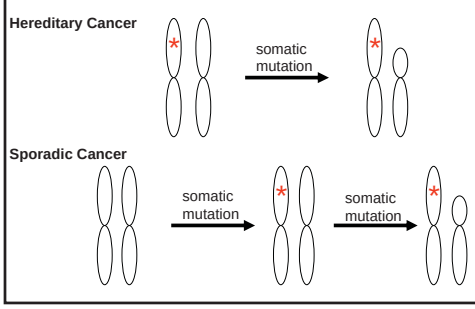
Syndromes associated with inherited renal carcinoma

Syndrome	Histological type	Other neoplasias	Gene
Von Hippel-Lindau Disease (VHL)	Clear cell RCC	Retinal & CNS hemangioblastomas, pheochromocytomas, pancreatic cysts and neuroendocrine tumors	*VHL*, 3p25.5
Hereditary papillary RCC (HPRC)	Type 1 papillary RCC	Papillary thyroid carcinoma (rare)	*MET*, 7q31
Hereditary leiomyomatosis RCC (HLRCC)	Type 2 papillary RCC	Uterine and cutaneous leiomyoma	*FH*, 1q42-43
Birt-Hogg-Dube' syndrome (BHD)	Chromophobe RCC; Oncocytic RCC; Oncocytoma	Fibrofolliculoma, lung cysts, spontaneous pneumothoraces, ?colon polyps	*BHD*, 17p11.2
Tuberous Sclerosis	Chromophobe RCC	Hamartomas, renal cysts & angiomyolipomas	*TSC1* *TSC2*

Significant Findings Related to VHL

1971 Knudson tumor suppressor gene hypothesis

Knudson's 2-Hit Model for Tumorigenesis

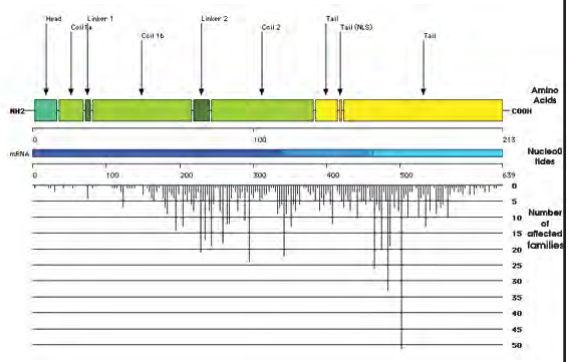


Significant Findings Related to VHL

1971 Knudson tumor suppressor gene hypothesis

1988 VHL gene mapped to chromosome 3p25-26
1993 Identification of the VHL gene
1994 VHL gene mutations in sporadic clear cell RCC
1994 Reliable methods to detect VHL gene mutations
1995 VHL gene mutations correlate with phenotype
1998 Reliable methods to detect VHL gene deletions

VHL germline point mutations

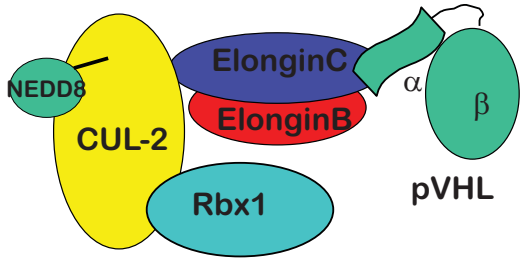


Significant VHL Findings

Biochemistry

1995 VHL protein forms a complex with Elongin and other proteins

The pVHL E3 Ubiquitin Ligase Complex

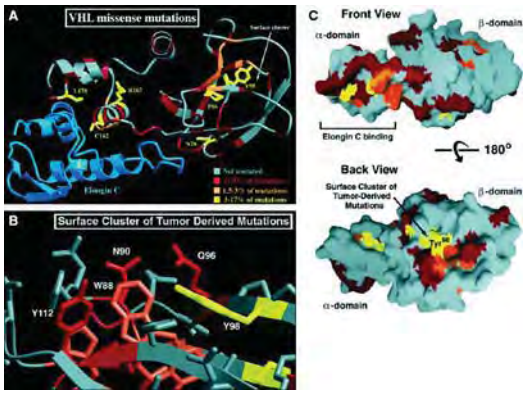


Significant VHL Findings

Biochemistry

1995 VHL protein forms a complex with Elongin and other proteins

1999 Crystal structure VHL-Elongin complex



From Stebbins et al, Science, 284, 455-461, 1999.

Significant VHL Findings

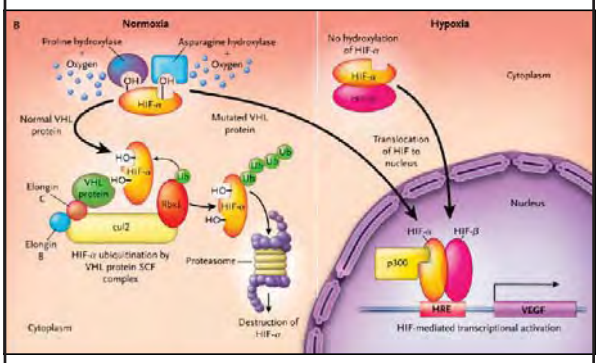
Biochemistry

1995 VHL protein forms a complex with Elongin and other proteins

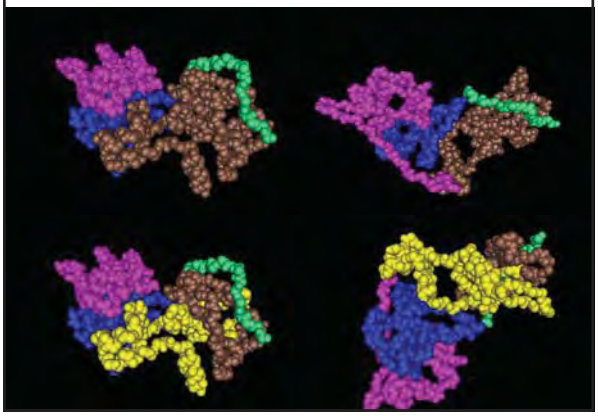
1999 Crystal structure VHL-Elongin complex

1999 VHL is an E3 ubiquitin ligase

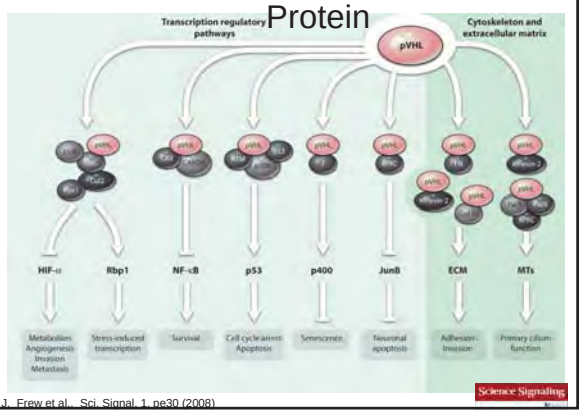
1999 VHL regulates HIF protein levels



Cohen HT, McGovern FJ. *N Engl J Med.* 2005;353:2477-2490



pVHL: A Multipurpose Adaptor Protein

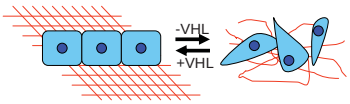


L. J. Frew et al., Sci. Signal. 1, pe30 (2008)

Significant VHL Findings
Cell Biology

1998 VHL associates with fibronectin
1999 VHL controls cell motility and invasion
2001 VHL regulates cell-cell and cell-extracellular matrix interactions
2006 VHL regulates primary cilium formation and cystogenesis
2008 VHL associates with collagen

Cellular phenotypes associated with VHL inactivation in RCC cells



Cell morphology	Epithelial	Mesenchymal
Extracellular matrix	Organized	Disorganized
E-cadherin	Positive	Negative
Cytoskeleton	Stable	Unstable
Adhesion	Increased	Decreased
Motility	Decreased	Increased

Kaelin, W.G., Jr. von Hippel-Lindau Disease, Annu. Rev. Pathol. Mech. Dis. 2007.2:145-173

Significant VHL Findings
Cell Biology

1996 Molecular link between VHL and angiogenesis

Physiologic appearance of the "angiogenic switch"

Images reproduced with permission from Judah Folkman.

- The "angiogenic switch" leads to neovascularization, as shown in a rat tumor model[1]

Reference: 1. Folkman J. *N Engl J Med.* 1971;285:1182-1186.

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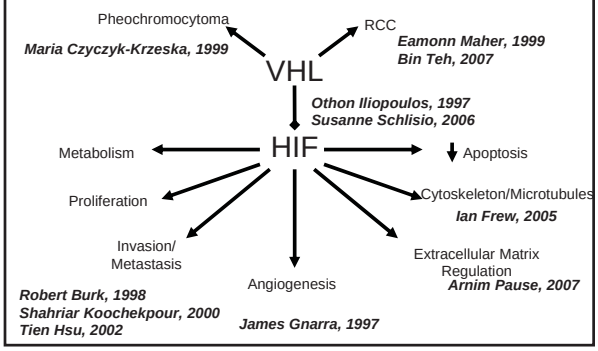
Significant Findings Related to VHL

2005 Sorafenib (VEGF R small molecule inhibitor) approved by FDA for advanced RCC

2006 Sunitinib (VEGF R small molecule inhibitor) approved by FDA for advanced RCC

2007 Temsirolimus (mTOR inhibitor) approved by FDA for advanced RCC

Investigators and their research funded by the Cancer Research Fund of the VHL Family Alliance

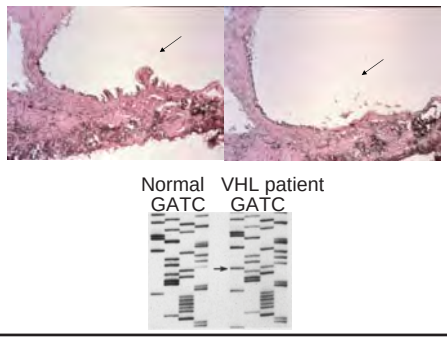


A significant new resource for research

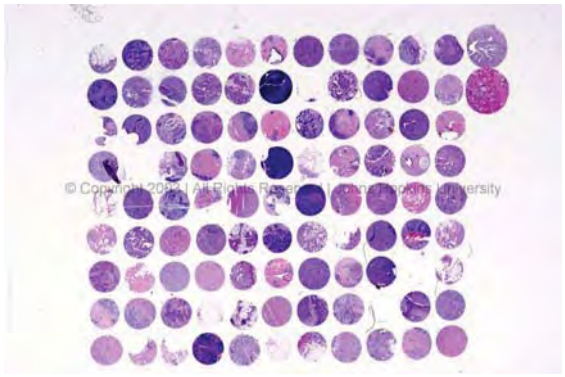
Normal and tumor tissue from the NDRI

Protein expression analysis

Gene mutation analysis



Johns Hopkins University School of Medicine Tissue MicroArray Facility



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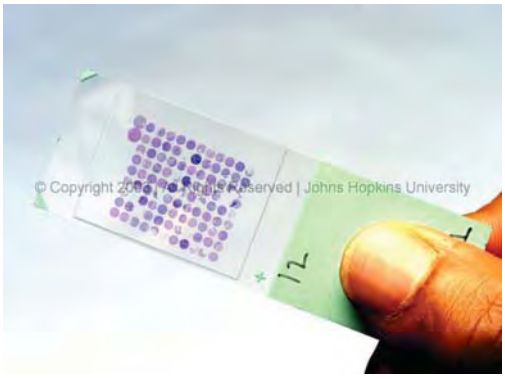

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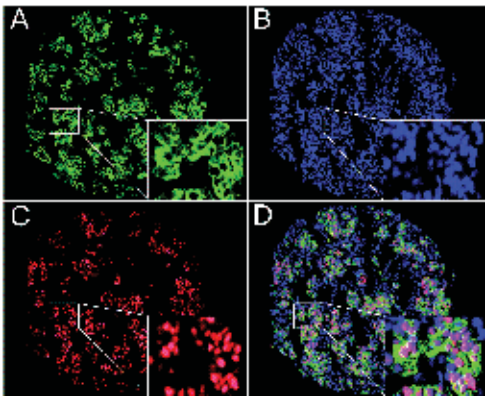

Yale University School of Medicine Tissue MicroArray Facility

Thank You