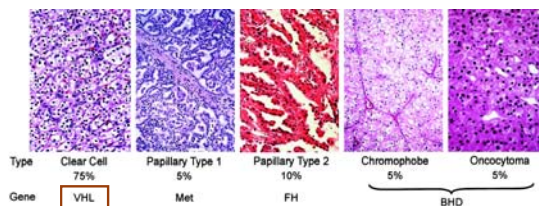




## VHL Regulates Gene Expression and Tumor Growth Through Histone Demethylase JARID1C

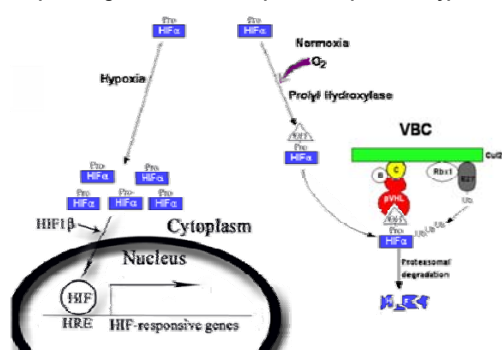
Haifeng Yang, Ph.D.,  
Assistant Staff, Cancer Biology,  
Lerner Research Institute, Cleveland Clinic

**Background:**  
Kidney cancer is made up of a number of different types of cancer

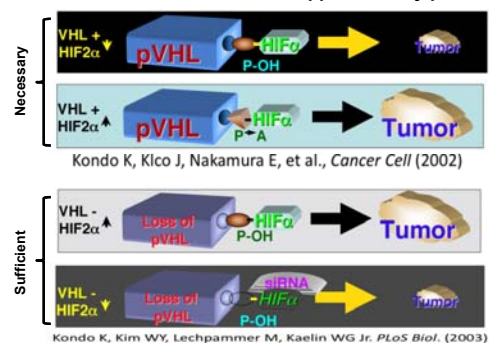


Linehan, W. M. et al. *Clin. Cancer Res.* (2004)

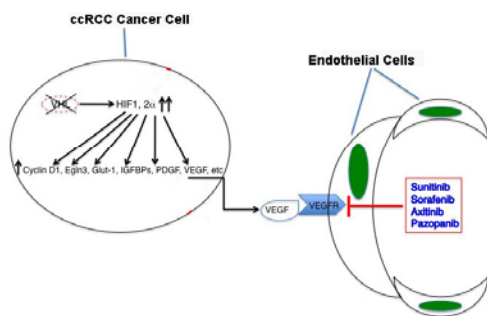
## How pVHL regulates the transcriptional response to hypoxia



## Preclinical models: Inhibition of HIF2α is necessary and sufficient for tumor suppression by pVHL



## Clinically, VEGFR inhibitors have efficacy against RCC



## Activation of HIFα alone is NOT sufficient to cause ccRCC

Hereditary mutations in

Egln1 (P317R, R371H),  
VHL (R200W),  
HIF2α (G537W, G537R, P534L, M535V),  
↑ HIFα levels  
↑ Erythropoietin  
Polycythemia

These patients **DO NOT** have increased incidence of ccRCC.

Conclusion: Other tumor-promoting events collaborate with activated HIF to cause ccRCC.

### Systematic sequencing of renal carcinoma reveals inactivation of histone modifying genes

Dalglish et al., *Nature*, 2010 Jan 21; 463 (7279):360-3.

**Table 2 Mutation summary of highlighted genes in ccRCC**

Gene	Total cancer mutations	Follow-up tissue mutations	Further RCC cell line mutations <sup>a</sup>	Total mutations
HP1A	1 nonsense	1 splice/del, 1 frameshift	ND	3
JARID1C	1 nonsense, 1 missense	5 nonsense, 2 splice/del, 4 frameshift, 1 missense	ND	14
MLL2	2 nonsense, 2 missense	9 missense, 1 nonsense, 4 silent	ND	17
MBD1	1 frameshift	1 frameshift	ND	2
MLL2	3 frameshift, 1 splice	1 frameshift	1 missense, 1 splice/del	7
MLL2	1 frameshift	2 nonsense (spontaneous)	1 frameshift	3
SETD2	4 frameshift, 1 nonsense, 2 missense	4 frameshift, 3 nonsense, 1 missense (spontaneous)	1 frameshift	18
UTX	3 frameshift, 1 splice, 2 missense	1 frameshift, 1 splice/del, 3 missense, 1 nonsense (spontaneous)	ND	12
WDR5	1 nonsense	1 splice/frameshift, 1 missense	ND	3
ZMYND2	3 frameshift, 1 missense, 1 silent	3 frameshift, 4 missense	ND	12

ND, Not done. Deleted mutation annotation can be found in Supplementary Table 8.

<sup>a</sup> The matching normal sequence available, presumptive controls mutation.

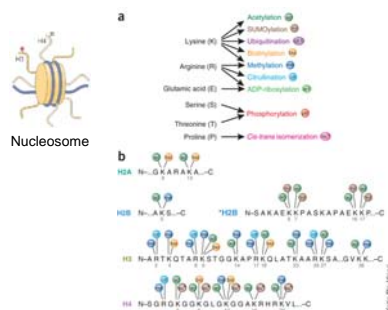
#### JARID1C: Histone H3K4 demethylase (3% mutations)

MLL2: Histone H3K4 methyltransferase (3% mutations)

UTX: Histone H3K27 demethylase, also a component of H3K4 methyltransferase complexes (3% mutations)

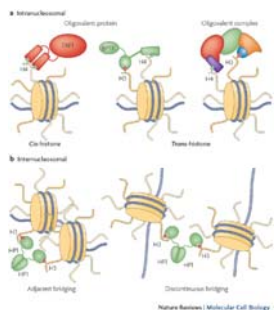
SETD2: Histone H3K36 demethylase (3% mutations)

The histone tails are modified with multiple post-translational modifications (PTMs).



Latham JA, Dent SY. *Nat Struct Mol Biol*. 2007 Nov;14(11):1017-24.

The modified histone tails are "read" by effector proteins.



Ruthenburg AJ, Li H, Patel DJ, Allis CD. *Nat Rev Mol Cell Biol*. 2007 Dec;8(12):983-94.

In *VHL*-defective ccRCC cells, HIF increases the expression of histone demethylases *JMJD1A* and *JMJD2B* that target H3K9Me3

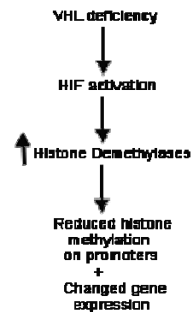
Beyer S, Kristensen MM, Jensen KS, Johansen JV, Staller P. (2008). *J Biol Chem* 283: 36542–36552.

Pollard PJ, Loenarz C, Mole DR, McDonough MA, Gleddie JM, Schofield CJ et al. (2008). *Biochem J* 416: 387–394.

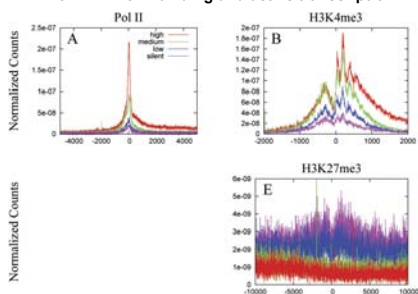
Xia X, Lemieux ME, Li W, Carroll JS, Brown M, Liu XS et al. (2009). *Proc Natl Acad Sci USA* 106: 4260–4265.

Wellmann S, Bettikober M, Zelmer A, Seeger K, Faigle M, Elitzschig HK et al. (2008). *Biochem Biophys Res Commun* 372: 892–897.

Krieg AJ, Rankin EB, Chan D, Razorenova O, Fernandez S, Giaccia AJ. (2010). *Mol Cell Biol* 30: 344–353.

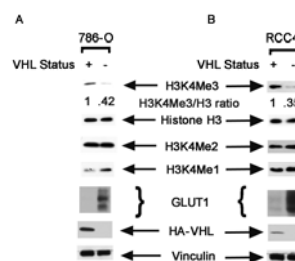


High levels of H3K4Me3 at promoters correlate with RNA Pol II binding and active transcription



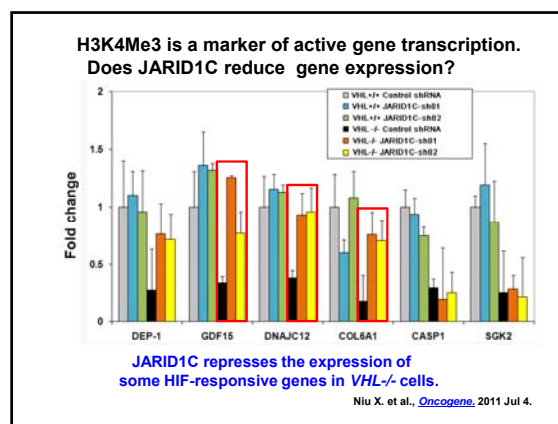
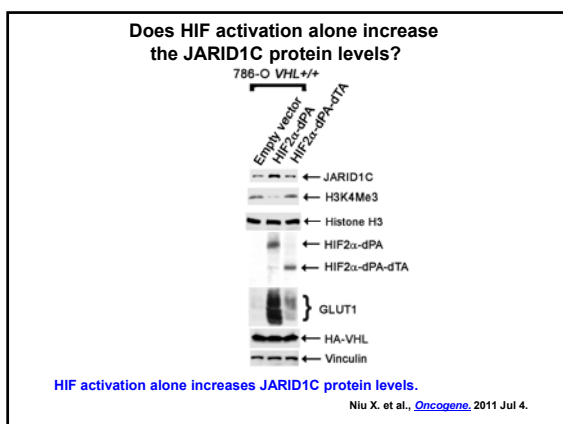
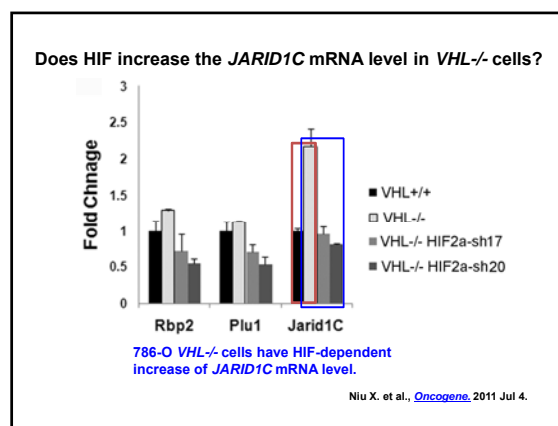
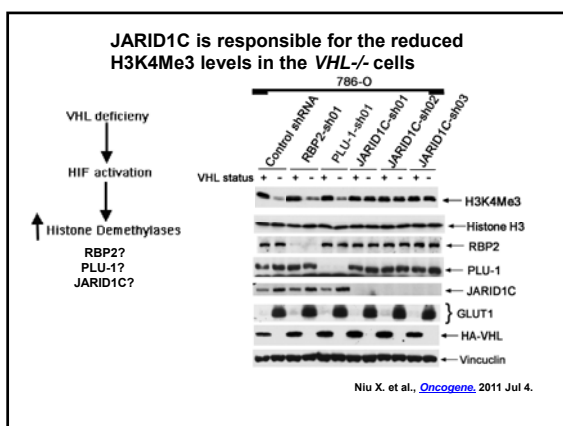
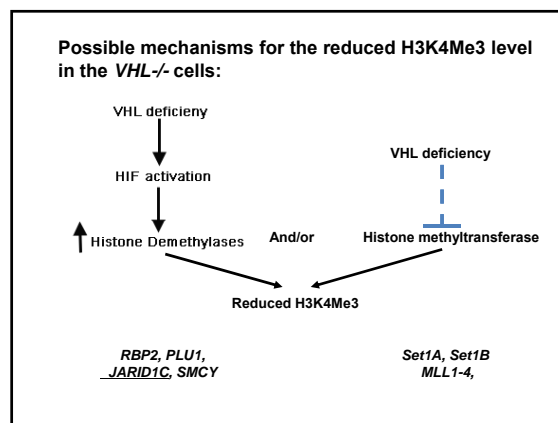
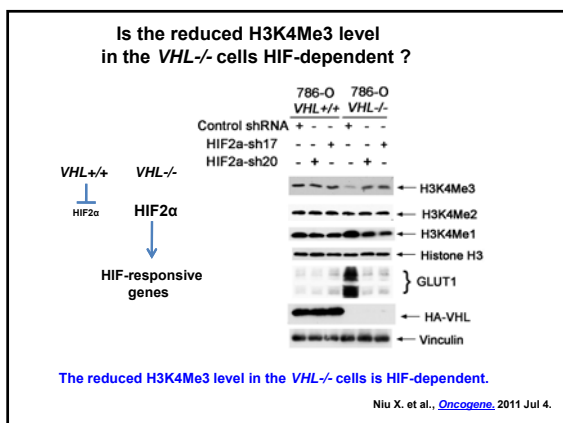
Cell. 2007 May 18;129(4):823-37.  
Barski A, Cuddapah S, Cui K, Roh TY, Schones DE, Wang Z, Wei G, Chepelev I, Zhao K.

H3K4Me3 is one of the most important histone PTMs. Does VHL status affect it?



*VHL*<sup>-/-</sup> ccRCC cells have lower overall H3K4Me3 levels than *VHL*<sup>+/+</sup> cells.

Xiaohua Niu, Ting Zhang, Lili Liao, Liang Zhou, Ming Zhou, Daniel J. Lindner, Brian Rini, Qin Yan, Haifeng Yang. *Oncogene*. 2011 Jul 4.





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