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CANCER GENETICS

HIF enhances its reputation

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Various genetic lesions, either germline-inherited or somatic, are known to promote renal cell carcinoma (RCC), particularly the loss of the von Hippel–Lindau (*VHL*) tumour suppressor gene. Loss of this ubiquitin ligase is known to stabilize the hypoxia-inducible factor 1α (HIF1α) and HIF2α transcription factors. A new study suggests that HIF2α stabilization in *VHL*-null cells is associated with HIF2α binding to a novel enhancer that regulates cyclin D1 (*CCND1*) expression, and this may explain why a genetic variant at this enhancer locus alters RCC susceptibility.

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Schödel *et al.* noticed that a polymorphic intergenic locus on chromosome 11q13.3 that was associated with the risk of sporadic human RCC coincided with a site of strong HIF2α binding, as shown by chromatin immunoprecipitation followed by high-throughput sequencing (ChIP–seq) studies. This binding specifically occurred in *VHL*-deficient cells. The authors sought to uncover the transcriptional consequences of HIF2α binding, but the large distance to the nearest gene and the lack of islands of CpG dinucleotides suggested that the locus was not a gene promoter. Instead, multiple lines of evidence — such as reduced nucleosome occupancy, characteristic histone modifications and hints of physical interactions with transcriptional machinery from ChIP–seq data — indicated that the locus could be acting as a transcriptional enhancer for genes that are more distal on the chromosome.

The authors then used gene expression microarray analyses on *VHL*-deficient RCC cells with and without knockdown of HIF2α to identify the oncogenic cell cycle regulator *CCND1* as a candidate gene that is regulated by the action of HIF2α at the enhancer. This model was reinforced by the demonstration of physical long-range interactions between the enhancer and the *CCND1* promoter. Although *CCND1* had previously been seen to be HIF2α-regulated, the potential molecular mechanisms for this were unclear.

So, do polymorphisms in this novel enhancer exert their effect on RCC susceptibility through *CCND1* regulation? As preliminary evidence, the authors found that, in a human RCC cell line that is heterozygous for an enhancer variant, the two *CCND1* alleles were expressed differentially. This implies that the enhancer can act in *cis* to regulate *CCND1*, with higher *CCND1* expression likely to increase RCC susceptibility.

It remains to be seen precisely how important *CCND1* expression is for the effect of this RCC susceptibility enhancer variant, relative to other transcriptional targets or any enhancer-independent effects. Manipulations of enhancers and *Ccnd1* in mouse models of RCC may be useful for further interrogation of this model. It will also be interesting to determine whether the susceptibility variant is only relevant after *VHL* loss. Finally, this study serves as a reminder that cancer genome projects will miss important information if only coding regions are analysed.

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ORIGINAL RESEARCH PAPER Schödel, J. *et al.* Common genetic variants at the 11q13.3 renal cancer susceptibility locus influence binding of HIF to an enhancer of cyclin D1 expression. *Nature Genet.* 11 Mar 2012 (doi:10.1038/ng.2204)

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