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TUMORIGENESIS

Some HIFs are more equal than others

Loss of function of the von Hippel–Lindau tumour suppressor VHL, which results in activation of the transcription factors hypoxia-inducible factor 1 (HIF1) and HIF2, is associated with development of highly vascularized tumours in multiple organs. New research from Rankin and colleagues, published in *Oncogene*, suggests that HIF2 and not HIF1 is the dominant factor in the development of these tumours.

The investigators modelled VHL-associated tumorigenesis using mice in which *Vhlh* in hepatocytes is conditionally inactivated by Cre–loxP recombination resulting in the formation of liver haemangiomas. Inactivation of *Hif1a* in these mice has little effect on the development of the haemangiomas, whereas livers lacking both *Hif2a* (also known as *Epas1*) and *Vhlh* were microscopically and macroscopically similar to those of control animals, suggesting that HIF2 is necessary for tumour development in this context. Moreover, the authors showed by real-time PCR that expression of vascular endothelial growth factor (*Vegf*), one of the angiogenic growth factors associated with VHL tumours, was suppressed by inactivation of HIF2 but not inactivation of HIF1.

Rankin and colleagues went on to investigate other HIF-related changes in gene expression by cDNA microarray and gene-ontology analysis, using Albumin–Cre transgenic mice that had *Vhlh* and one or both of the HIF isoforms inactivated. They found 17 other HIF-regulated angiogenic genes, of which 12 were upregulated in livers lacking VHLH or both VHLH and HIF1α, and demonstrated that this upregulation is suppressed more efficiently by inactivation of HIF2α than by inactivation of HIF1α. The presence of HIF2 was associated with increased expression of the angiogenic genes *Bmp4*, *Klf5*, *Nr2f2*, *Angpt13*, *Anxa2* and *Cdh5*, but it is yet unclear whether this is attributable to transcriptional regulation by HIF2 or due to increased angiogenesis. However, the effect of HIF2 on gene expression was shown to be context-dependent, as no changes in expression were observed in liver for HIF2 targets that are associated with VHL tumours in other tissue types.

To what extent can these results be generalized? Different cell types show different HIF isoforms to be dominant in the regulation of angiogenic factors, including VEGF, but in VHL-associated haemangioblastomas in humans, levels of *Vegf* mRNA have a strong correlation with the expression of HIF2 and a poor correlation with that of HIF1. Moreover, HIF2 expression is associated with poor prognosis in other tumour types. Taken together, these results imply that HIF2 might be appropriate as a pharmacological target in VHL-related tumours.

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ORIGINAL RESEARCH PAPER Rankin, E. B. *et al.* Hypoxia-inducible factor-2 regulates vascular tumorigenesis in mice. *Oncogene* 19 May 2008 (doi: 10.1038/onc.2008.160)