ANGIOGENESIS

Alternative pathways

The hypoxia-inducible factor 1 (HIF1) is an important transcriptional mediator of the tumour response to hypoxia, as well as an attractive therapeutic target. In the September issue of *Nature Medicine*, Yusuke Mizukami *et al.* report that there are other mechanisms by which cancer cells survive and induce angiogenesis in the absence of oxygen.

HIF1, a heterodimeric protein that consists of α and β subunits, is a transcription factor that becomes activated under conditions of low oxygen to upregulate genes that mediate angiogenesis, such as vascular endothelial growth factor (VEGF). Mizukami *et al.* investigated whether inhibition of HIF1 alone is sufficient to block tumour angiogenesis using HIF1α short interfering RNA knockdown in colon cancer cells. Surprisingly, they observed that when the HIF1 knockdown cells were transplanted into mice, the resulting tumours remained highly vascularized. Furthermore, in these tumours, VEGF expression was only reduced by 50%, compared with tumours that expressed wild-type levels of HIF1α. As VEGF levels were reduced but new blood vessels still formed, could there be other angiogenic factors that are upregulated in a compensatory manner to maintain tumour vascularity in the absence of HIF1?

To answer this question, the authors performed gene-expression analysis on hypoxic colon cancer cells. Strikingly, expression of the pro-angiogenic cytokine interleukin-8 (IL-8) was upregulated 2.5-fold in HIF1α knockdown cells, but not in cells that expressed wild-type levels of HIF1α. Furthermore, knockdown of HIF1α in pancreatic, breast and lung cancer cells resulted in a similar induction of IL-8.

The transcription factor NF-κB (nuclear factor-κB) is a well-known regulator of IL-8 transcription, so the authors investigated its role in this process. They found that in response to hypoxia, reactive oxygen species (ROS) are produced, which activate NF-κB, leading to upregulation of IL-8. This response could be inactivated with ROS inhibitors. Furthermore, the authors observed that the *KRAS* oncogene, which is commonly mutated in colon cancer, can also initiate this pathway — knockdown of KRAS attenuated the hypoxic induction of NF-κB and IL-8 promoter activity.

Since compensatory pathways can be activated to preserve the tumour angiogenic response, strategies that inhibit HIF1α or VEGF might therefore be most effective when IL-8 is simultaneously targeted.

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References and links

ORIGINAL RESEARCH PAPER Mizukami, Y. *et al.* Induction of interleukin-8 preserves the angiogenic response in HIF-1 deficient colon cancer cells. *Nature Med.* 21 Aug 2005 (doi: 10.1038/nm1294)
FURTHER READING Semenza, G. Targeting HIF-1 for cancer therapy. *Nature Rev. Cancer* **3**, 721–732 (2003)
WEB SITE
Daniel Chung's web site: http://www.massgeneral.org/gastro/research_Dchung.htm