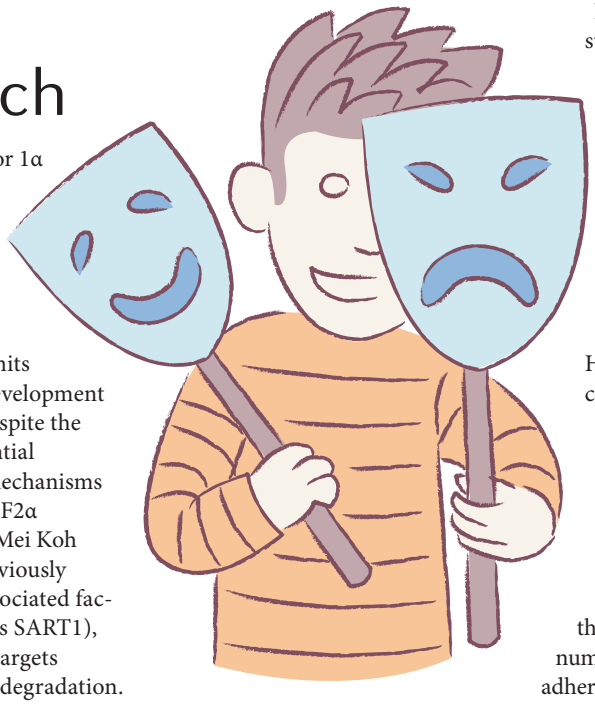
HYPOXIA

HIF switch



Hypoxia-inducible factor 1α (HIF1α) and HIF2α are crucial mediators of the hypoxic response, regulating the transcription of both common and unique genes. Both HIFα subunits have roles in tumour development and progression, but despite the interest in their differential effects, the molecular mechanisms behind the HIF1α to HIF2α switch remain unclear. Mei Koh and colleagues have previously shown that hypoxia-associated factor (HAF; also known as SART1), an E3 ubiquitin ligase, targets HIF1α for proteasomal degradation. They have now provided evidence that HAF can also promote HIF2α activity, thus switching the hypoxic response from HIF1α-dependent to HIF2α-dependent.

Using a panel of cancer cell lines, the authors confirmed that HAF overexpression decreased HIF1α levels. HAF did not affect HIF2α levels in normoxic or hypoxic conditions, but instead increased the transcriptional activity of HIF2α independently of its E3 ligase activity. Immunoprecipitation analyses showed that HAF binds both HIF1α and HIF2α, but at different sites. Blockade of the HAF–HIF2α interaction reduced HIF2α-dependent transcription in both normoxia and hypoxia without affecting HIF2α protein levels, indicating that binding is necessary for HIF2α activation.

What are the physiological consequences of overexpressing HAF? In three-dimensional neurosphere cultures that were grown in hypoxic conditions, colonies of U87 glioblastoma cells expressing HAF were diffuse, rather than spheroid, suggesting increased cell motility or invasion. *HIF1A* small interfering RNA (siRNA) induced a similar morphology, but this morphological change was inhibited by *HIF2A* siRNA. This indicates that HAF expression can both increase HIF2α-dependent spreading and reduce HIF1α-dependent spheroid formation.

HIF2α may also promote stem cell maintenance in glioblastoma. Indeed, HAF overexpression in U87 cells increased the levels of stem cell markers, particularly in the subpopulation of floating (rather than adherent) cells. Stimulation of tumour stem cell proliferation in wild-type U87 cells in neurosphere cultures also induced HAF expression, and the stem cell population was reduced by expression of *HAF* siRNA.

How does HAF affect tumour growth *in vivo*? Intracranial injection of adherent HAF-overexpressing U87 cells in nude mice did not affect survival. By contrast, the injection of high and low numbers of pooled floating and adherent cells that expressed HAF enhanced tumour progression and initiation, respectively, indicating that HAF promotes tumour stem cell-like behaviour.

Although there is still much to work out about the HIF1α to HIF2α switch and its ultimate role in cancer, Koh and colleagues have identified HAF (which is overexpressed in many human tumours) as an important component of this pathway that may enhance tumour initiation and progression.

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> “HAF can also promote HIF2α activity, thus switching the hypoxic response from HIF1α-dependent to HIF2α-dependent”

ORIGINAL RESEARCH PAPER Koh, M. Y. *et al.* The hypoxia associated factor (HAF) switches cells from HIF-1α to HIF-2α dependent signaling promoting stem cell characteristics, aggressive tumor growth and invasion. *Cancer Res.* 21 Apr 2011 (doi:10.1158/0008-5472.CAN-10-4142)