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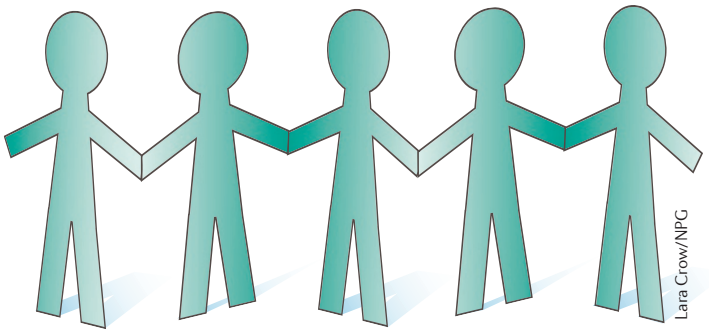
HYPOXIA

New connections



Lara Crow/NPG

Increased expression of the hypoxia-inducible factor (HIF) family of transcription factors, particularly the oxygen-labile HIFα subunits, is associated with increased aggressiveness, resistance to therapy and poor prognosis in many cancer types, including in clear-cell renal cell carcinoma (CCRCC). A similar correlation between CCRCC aggressiveness and increased expression of caveolin 1 (CAV1), the primary structural component of lipid raft membrane microdomains termed caveolae, prompted Michael Ohh and colleagues to examine whether HIF and CAV1 are mechanistically connected.

The analysis of primary CCRCC samples showed a significant correlation between expression of HIF target genes and CAV1, and CCRCC cell lines under hypoxia or lacking expression of the von Hippel–Lindau (VHL) tumour suppressor (which normally functions to degrade HIFα), had increased CAV1 expression. Knockdown of HIF1α or HIF2α suppressed CAV1 expression in several cell lines, and CAV1 was increased by the expression of stable HIFα subunits, indicating that HIF can mediate CAV1 expression. Furthermore, the authors found a hypoxia-responsive element (HRE) in the *CAV1* promoter, which could bind HIF1α and HIF2α *in vitro* and *in vivo*, as shown by chromatin immunoprecipitation.

Does this change in CAV1 expression affect the formation of caveolae? 786-O CCRCC cells are both *VHL*- and *HIF1A*-null, and have high HIF2α levels and high CAV1 levels. 786-O CCRCC cells and 786-O cells that re-expressed VHL but that were maintained under hypoxia had more caveolae, as seen by transmission electron microscopy, than did cells under normoxic conditions or with low HIF2α.

Increased epidermal growth factor receptor (EGFR) signalling is associated with loss of VHL, and CAV1 binds the carboxyl terminus of EGFR, a domain that is required for ligand-independent dimerization and activation of EGFR, which can occur when EGFR concentrations are high (such as in the confined surface area of caveolae). Therefore, the authors investigated whether these phenomena are linked. Knockdown of CAV1 in 786-O cells reduced caveolae formation, as well as dimerization and phosphorylation of EGFR in the absence of ligand. Downstream signalling of EGFR to ERK and cell proliferation were reduced in response to loss of CAV1, and primary CCRCC samples with high CAV1 also had high ERK phosphorylation. These data suggest that, under hypoxic or pseudohypoxic (for example, loss of VHL) conditions, increased caveolae formation leads to a permissive environment for activation of mitogenic EGFR signalling in the absence of ligand.

Xenograft tumours derived from 786-O cells with CAV1 knockdown in immunocompromised mice were smaller and had lower levels of ERK phosphorylation than those derived from cells expressing CAV1, indicating that the HIF–CAV1–EGFR pathway is important for *in vivo* tumorigenesis. These data support the idea that hypoxia or pseudohypoxia allows tumour cells to bypass the requirement for growth factors to activate EGFR-mediated proliferation, and that blocking EGFR in these tumours may be beneficial therapeutically.

Sarah Seton-Rogers

> “hypoxia or pseudohypoxia allows tumour cells to bypass the requirement for growth factors to activate EGFR-mediated proliferation”

ORIGINAL RESEARCH PAPER Wang, Y. *et al.* Hypoxia promotes ligand-independent EGF receptor signaling via hypoxia-inducible factor-mediated upregulation of caveolin-1. *Proc. Natl Acad. Sci. USA* 12 Mar 2012 (doi:10.1073/pnas.1112129109)