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KIDNEY TUMOURS

'NRF said

The tumour suppressor gene fumarate hydratase (*FH*) is just one of several genes to be implicated in the development of kidney tumours. Two papers published in *Cancer Cell* have identified a new pathway through which *FH* deficiency might promote tumour development.

Germline *FH* heterozygosity is evident in patients with hereditary leiomyomatosis and renal cell carcinoma (HLRCC), and loss of heterozygosity is evident in the type 2 papillary renal cell carcinomas (PRCC2) that develop in some of these individuals. *FH* loss leads to the accumulation of fumarate, an inhibitor of prolyl hydroxylases (PHDs), which, under conditions of normoxia, hydroxylate hypoxia-inducible factor 1α (HIF1α) thus leading to its ubiquitylation and degradation. Thus, HIF1α stabilization is thought to be important for tumour development in PRCC2. However, recent data indicate that the accumulation of fumarate also readily affects susceptible cysteine residues by converting them to 2-succinyl cysteine (2SC), with functional consequences. Is this relevant to kidney tumour formation?

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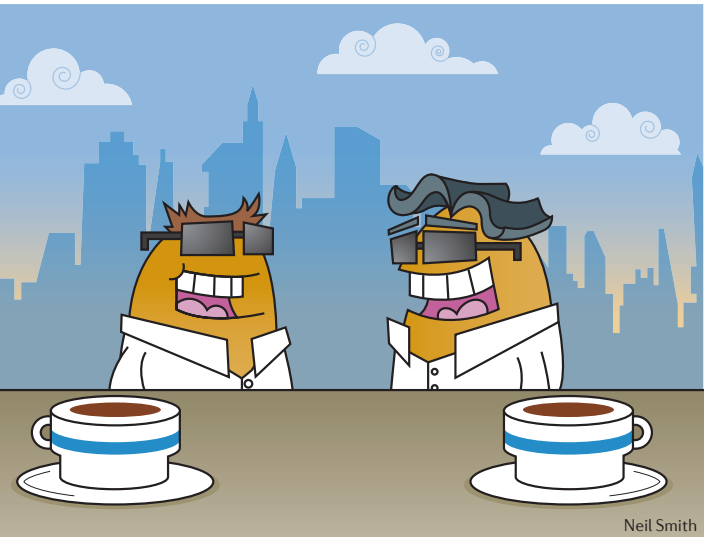

Neil Smith

To address this, Julie Adam and colleagues used conditional mouse models to eliminate *Fh1* from the kidneys, which was combined with deletion of *Hif1a*, *Hif2a* or both. Surprisingly, they found that the loss of HIF1α seemed to accelerate hyperplastic cyst formation and tumour development, whereas the deletion of *Hif2a* had no effect. Comparative genome-wide transcript profiling showed that nuclear factor (erythroid-derived 2)-like 2 (*NRF2*) is highly expressed in $Fh1^{-/-}$ and $Fh1^{-/-}$;$Hif1a^{-/-}$ kidneys. NRF2 is an oncogenic transcription factor that regulates an antioxidant pathway and its activity is controlled by kelch-like ECH-associated protein (KEAP1). Both RT-PCR analysis and immunohistochemistry confirmed that the expression of NRF2-target genes was increased in the absence of both FH and HIF1α, and that, in human tumour samples, this was most evident in PRCC2. Tandem mass spectrometry showed that several cysteines in KEAP1 are succinated as a result of the increased levels of fumarate, two of which (Cys155 and Cys288) are thought to be crucial for the activity of KEAP1. Thus, in the absence of FH, fumarate accumulates, and this inactivates KEAP1 so that it can no longer bind NRF2 and promote its degradation.

Aikseng Ooi and colleagues were also interested in defining tumorigenic pathways in PRCC2. As PRCC2 has several phenotypic differences compared with other kidney tumours that are driven by HIF1α, and because these authors found that the expression of HIF1α-target genes was not abundantly evident in gene expression sets from either HLRCC or PRCC2, they set about finding gene expression signatures that are associated with *FH* loss. Aldo-keto reductase family 1 member B10 (*AKR1B10*) was the most upregulated mRNA in the *FH* gene signature. Computer analyses identified NRF1, NRF2 and JUN as potential factors that regulate *AKR1B10*, all of which bind to antioxidant response elements (AREs). These authors also found that changes in the level of fumarate affect the expression levels of both NRF2 and AKR1B10, and that Cys151 and Cys288 are succinated in the presence of fumarate. These authors showed that this modification is linked to ubiquitylation and the degradation of KEAP1. So, is *AKR1B10* a direct target of NRF1 and NRF2? Chromatin immunoprecipitation showed that both NRF1 and NRF2 can bind to an ARE in the *AKR1B10* enhancer region, and that knockdown of NRF2 substantially reduced the increased expression of *AKR1B10* in response to a membrane-permeable form of fumarate. Immunohistochemistry confirmed that the expression of NRF2 and of NRF2-target genes, including *AKR1B10*, was increased in human samples of HLRCC and PRCC2.

Both of these papers show that the loss of *FH* may lead to HLRCC and PRCC2 through a pathway that is independent of HIF1α and that this requires the activation of NRF2 and its downstream target genes.

Nicola McCarthy

ORIGINAL RESEARCH PAPERS Ooi, A. *et al.* An antioxidant response phenotype shared between hereditary and sporadic type 2 papillary renal cell carcinoma. *Cancer Cell* **20**, 511–523 (2011) | Adam, J. *et al.* Renal cyst formation in Fh1-deficient mice is independent of the Hif/Phd pathway: roles for fumarate in KEAP1 succination and Nrf2 signalling. *Cancer Cell* **20**, 524–537 (2011)