TUMORIGENESIS

FBP1 is suppressed in kidney tumours


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More than 90% of clear cell renal cell carcinomas (ccRCCs) are associated with inactivating mutations in von Hippel–Lindau tumour suppressor (VHL). This leads to stabilization of hypoxia-inducible factor α (HIFα) subunits in normoxia, which is thought to account for the characteristic metabolic alterations that are associated with ccRCC. However, modelling VHL loss in mice does not induce tumorigenesis or ccRCC-specific metabolic changes, indicating that other factors are involved.

To investigate, a group led by Celeste Simon undertook metabolic profiling of 20 primary human ccRCC tumours and integrated these data with metabolic gene set analysis from ccRCC transcriptomic data. They found that gluconeogenesis was uniformly suppressed and carbohydrate storage genes (including fructose-1,6-bisphosphatase 1 (*FBP1*)) constituted the most significantly underexpressed gene set in ccRCC. FBP1 is the rate-limiting enzyme in gluconeogenesis, and they found that FBP1 expression was reduced in almost all of the ccRCC tumour samples analysed. They also found that low FBP1 expression correlates with advanced tumour stage and poor patient prognosis. Other gluconeogenic enzymes were not consistently suppressed in ccRCC. Moreover, HIFα stabilization was not responsible for FBP1 suppression, indicating that FBP1 is specifically suppressed through an as-yet-unknown mechanism.

Li *et al.* turned to the function of FBP1 in ccRCC and showed that ectopic FBP1 expression in several ccRCC cell lines significantly inhibited their growth, whereas FBP1 depletion promoted the growth of kidney proximal tubule cells, which are thought to be the ccRCC cell of origin. Growth suppression by FBP1 was particularly evident when HIFα was stabilized, as shown in a lung cancer cell line cultured under hypoxic conditions, or when glucose levels were limited. They also found that FBP1 suppresses glycolysis, as ectopic FBP1 expression in RCC10 ccRCC cells (in which HIFα is stabilized) reduced glucose uptake, lactate secretion and levels of glucose-derived tricarboxylic acid (TCA) cycle intermediates. Furthermore, the inhibition of glycolysis by FBP1 was diminished when VHL was restored in RCC10 cells (which results in destabilization of HIF), demonstrating that the metabolic effects of FBP1 require HIF in ccRCC cells.

To further investigate the connection between FBP1 and HIF, the authors used two ccRCC cell lines that both express HIF1α and HIF2α. Ectopic expression of FBP1 in these cells suppressed HIF activity and reduced the expression of HIF target genes. The opposite was also true, such that FBP1 loss enhanced HIF activity. Consistently, *FBP1* expression and HIF activity were inversely correlated in ccRCC samples. Further analyses revealed that HIFα and FBP1 colocalized at hypoxia response elements in gene promoters. An FBP1 mutant that is unable to enter the nucleus did not efficiently inhibit HIF target gene expression or suppress glycolysis, whereas a catalytically inactive FBP1 mutant fully mimicked the effects of wild-type FBP1. Together, this indicates that FBP1 inhibits HIF transcriptional activity at target gene loci and this does not require the catalytic activity of FBP1. Indeed, they found that the amino-terminal regulatory domain of FBP1 was sufficient to inhibit HIF activity and FBP1 directly associated with HIF1α and HIF2α through binding to their inhibitory domains.

This paper identifies an additional piece to the puzzle of understanding renal tumorigenesis. This work also indicates that the effects of FBP1 become important when oxygen and glucose levels are limiting, as often occurs in solid tumours. It is important to understand how FBP1 is suppressed in these conditions, as its reactivation may have therapeutic effects.

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> “the effects of FBP1 become important when oxygen and glucose levels are limiting”

ORIGINAL RESEARCH PAPER Li, B. *et al.* Fructose-1,6-bisphosphatase opposes renal carcinoma progression. *Nature* http://dx.doi.org/10.1038/nature13557 (2014)