IN BRIEF

METABOLISM

Context-specific metabolism

Many oncogenes are known to modulate metabolic pathways, particularly those involving glucose and glutamine, to promote anaplerosis and tumour cell survival. But, do different oncogenes regulate the same metabolic pathways in the same types of cancer? Yuneva and colleagues found different alterations to glucose and glutamine metabolic pathways in liver tumours in mice depending on whether they were induced by MYC or MET. Moreover, MYC-induced lung tumours in mice had different glucose and glutamine metabolic profiles from MYC-induced liver tumours. Therefore, targeting metabolic pathways for cancer therapy should be preceded by metabolic profiling to account for the apparent context specificity of alterations to metabolism in tumour cells.

ORIGINAL RESEARCH PAPER Yuneva, M. O. *et al.* The metabolic profile of tumors depends on both the responsible genetic lesion and tissue type. *Cell Metabolism* **15**, 157–170 (2012)

ALTERNATIVE SPLICING

Dose-dependent splicing

The pyruvate kinase M (*PKM*) gene can be alternatively spliced to form either PKM1, which is expressed in most adult tissues, or PKM2, which is expressed in embryonic cells and also tumour cells. The splicing of *PKM* is regulated by the expression of three heterogeneous nuclear ribonucleoprotein (hnRNP) splicing repressors, hnRNPA1, hnRNPA2 and polypyrimidine tract-binding protein 1 (PTB). However, the mechanism by which these hnRNPs determine the expression of PKM1 or PKM2 has remained unclear. Chen and colleagues characterized the binding of these hnRNPs to *PKM* and found that the sites bound by these splicing repressors changed according to their expression level. As MYC upregulates the expression of these hnRNPs, which favours the expression of the PKM2 isoform, this paper uncovers how PKM2, rather than PKM1, might be induced in tumour cells.

ORIGINAL RESEARCH PAPER Chen, M. *et al.* Concentration-dependent control of pyruvate kinase M mutually exclusive splicing by hnRNP proteins. *Nature Struct. Mol. Biol.* 5 Feb 2012 (doi: 10.1038/nsmb.2219)

HYPOXIA

Scaffolding the regulation of hypoxia

The expression of a subunit of the hypoxia-inducible factor (HIF) transcription factor, HIF1α, is suppressed in normoxia. This suppression is regulated by prolyl hydroxylases (PHDs), which hydroxylate HIF1α; this hydroxylation in turn recruits the von Hippel–Lindau (VHL) tumour suppressor, which is the recognition subunit of a ubiquitin ligase complex that targets HIF1α for proteasome-mediated degradation. Alterations to this process in tumour cells can cause inappropriate expression of HIF, which promotes tumour cell survival. It has remained unclear whether PHDs and the VHL complex act separately or in a macrocomplex. Foxler and colleagues show that LIM domain-containing (LIMD) proteins bind to both VHL and PHDs to function as a macrocomplex scaffold. Importantly, depletion of LIMD1 increased HIF1α levels in normoxia and hypoxia. Therefore, it will be interesting to investigate LIMD family-mediated regulation of responses to hypoxia in tumours.

ORIGINAL RESEARCH PAPER Foxler, D. E. *et al.* The LIMD1 protein bridges an association between the prolyl hydroxylases and VHL to repress HIF-1 activity. *Nature Cell Biol.* **14**, 201–208 (2012)