IN BRIEF

SEQUENCING

CpG islands and 5-hydroxymethylcytosine

The mutation of the TET enzymes has been implicated in the development of leukaemia. These convert 5-methylcytosine to 5-hydroxymethylcytosine (5hmC). A new method, oxidative bisulphite sequencing, along with the established method of bisulphite sequencing, can quantitatively map the presence of 5hmC at single nucleotide resolution. High levels of 5hmC were present at CpG islands associated with transcriptional regulators and in LINE1 elements, and this supports the concept that 5hmC is present at DNA sites that are particularly epigenetically plastic.

ORIGINAL RESEARCH PAPER Booth, M. J. *et al.* Quantitative sequencing of 5-methylcytosine and 5-hydroxymethylcytosine at single-base resolution. *Science* 26 Apr 2012 (doi:10.1126/science.1220671)

METABOLISM

In need of a NADPH rush?

A recent paper shows that under conditions of energy stress (the absence of glucose), aside from regulating ATP levels, AMP kinase (AMPK) activation inhibits the acetyl CoA carboxylases ACC1 and ACC2, preventing fatty acid synthesis (which requires NADPH), and promotes fatty acid oxidation (which produces NADPH). Knockdown of ACC enzymes promotes tumour formation *in vivo*, whereas ACC activation suppresses it. The conservation of NADPH levels is required to enable redox reactions that control the levels of reactive oxygen species, which are increased by metabolic stress.

ORIGINAL RESEARCH PAPER Jeon, S.-M., Chandel, N. S. & Hay, N. AMPK regulates NADPH homeostasis to promote tumour cell survival during energy stress. *Nature* 9 May 2012 (doi:10.1038/nature11066)

THERAPEUTICS

Anticancer effect only in diabetics?

A study of 200 non-diabetic women with breast cancer analysed the effect of the anti-diabetic drug metformin or a placebo given ahead of surgical resection. There were no significant differences overall in Ki-67 staining (a surrogate for levels of proliferation) in the resected tumours. However, in women with insulin resistance (but not clinical diabetes), or a high body mass index, metformin reduced levels of Ki-67 staining and reduced systemic concentrations of insulin (a known mitogen). Thus, the potential effect of metformin on breast cancer may depend on the metabolic status of the patients, and this should be considered in clinical trial design.

ORIGINAL RESEARCH PAPER Bonanni, B. *et al.* Dual effect of metformin on breast cancer proliferation in a randomized presurgical trial. *J. Clin. Onc.* 7 May 2012 (doi: 10.1200/JCO.2011.39.3769)

PANCREATIC CANCER

Cooperation

This paper used the *Sleeping Beauty* transposon insertional mutagenesis system to identify genes that accelerate the development of $Kras^{G12D}$-induced pancreatic ductal adenocarcinoma (PDA) in mice. In more than 50% of the tumours the *Usp9x* gene, which encodes a deubiquitylase, was inactivated. Analyses of human PDA samples indicated that low *USP9X* mRNA and protein levels correlate with a poor prognosis. Interestingly, treatment of human PDA cell lines with chromatin-modifying drugs, such as 5-aza-2′-deoxycytidine, increased *USP9X* expression, suggesting that epigenetic therapies might be appropriate for some patients with PDA.

ORIGINAL RESEARCH PAPER Pérez-Mancera, P. A. *et al.* The deubiquitinase USP9X suppresses pancreatic ductal adenocarcinoma. *Nature* 29 Apr 2012 (doi:10.1038/nature11114)