IN BRIEF

EPIGENETICS

Loss of the tumor suppressor Snf5 leads to aberrant activation of the Hedgehog-Gli pathway

Jagani, Z. *et al. Nature Med.* **16**, 1429–1433 (2010)

Jagani and colleagues found that SNF5 — a member of the SWI–SNF chromatin remodelling complex — interacts with GLI1, an effector of the Hedgehog pathway. SNF5 was shown to localize at promoters regulated by GLI1 and to repress GLI1 activity. Loss of SNF5 (which occurs in malignant rhabdoid tumours (MRTs)) activated the Hedgehog pathway, and this was shown to drive the growth of SNF5-deficient MRT cells *in vivo*. Therefore, targeting the Hedgehog pathway might be an effective way to treat patients with SNF5-deficient MRT.

THERAPY

Therapy-induced selective loss of leukemia-initiating activity in murine adult T cell leukemia

El Hajj, H. *et al. J. Exp. Med.* 6 Dec 2010 (doi:10.1084/jem.20101095)

Adult T cell leukaemia/lymphoma (ATL) is thought to be caused by chronic infection with human T cell lymphotropic virus type I (HTLVI), and the viral transactivator Tax has been shown to induce ATL in mice. El Hajj and colleagues showed that treatment of these mice with arsenic trioxide and interferon-α, which induces Tax proteolysis in a proteasome-dependent manner, cured ATL. This combination therapy prevented ATL cell immortality and is reminiscent of the mechanism that makes arsenic trioxide treatment of acute promyelocytic leukaemia so effective.

TUMORIGENESIS

Brca2 heterozygosity promotes Kras(G12D)-driven carcinogenesis in a murine model of familial pancreatic cancer

Skoulidis, F. *et al. Cancer Cell* **18**, 499–509 (2010)

Oncogenic KRas suppresses inflammation-associated senescence of pancreatic ductal cells.

Lee, K. E. & Bar-Sagi, D. *Cancer Cell* **18**, 448–458 (2010)

Mutant *KRAS* is the most frequent driver of pancreatic tumorigenesis. Skoulidis *et al.* used the $Kras^{G12D}$ mouse model of familial pancreatic cancer to show that heterozygosity of the *Brca2* locus can cooperate with $Kras^{G12D}$ to accelerate tumorigenesis. In addition, they found that a functional, wild-type *BRCA2* allele was retained in three of four human pancreatic carcinoma samples that had developed in individuals who have a germline mutation in one allele of *BRCA2*. Cells with a functional *BRCA2* allele were resistant to the PARP inhibitor olaparib, which is lethal to cells lacking BRCA2 function. This suggests that confirmation of *BRCA2* loss by tumour genotyping could inform the clinical use of PARP inhibitors. Lee *et al.* found that senescence of primary pancreatic duct epithelial cells (PDECs) *in vitro* can be bypassed by triggering the expression of an endogenous lox-stop-lox allele of $Kras^{G12D}$ using adenoviral CRE recombinase. $Kras^{G12D}$ activation induces the expression of the transcription factor TWIST1 that inhibits the expression of the cyclin-dependent kinase inhibitor INK4A. These authors also found that inflammation *in vivo* triggers senescence of PDECs, and mutation of KRAS may well be selected for as it can overcome this senescence.