IN BRIEF

SIGNALLING

An original SIN1

Mammalian target of rapamycin complex 2 (mTORC2) kinase controls both cell proliferation and survival, but how mTORC2 is regulated is not well understood. This paper shows that phosphorylation of SIN1, an mTORC2 component, results in mTORC2 inactivity. SIN1 phosphorylation by either S6 kinase or AKT leads to its dissociation from mTORC2 and inhibition of growth factor-mediated activation of mTORC2. Cancer-associated mutations in SIN1 that impair its phosphorylation result in hyperactivity of mTORC2 and activation of AKT.

ORIGINAL RESEARCH PAPER Liu, P. *et al.* Sin1 phosphorylation impairs mTORC2 complex integrity and inhibits downstream Akt signalling to suppress tumorigenesis. *Nature Cell Biol.* http://dx.doi.org/10.1038/ncb2860 **(2013)**

GENETICS

Bespoke mutations

Specific mutations in *H3F3A* and *H3F3B*, the two genes that encode histone 3.3 (H3.3) proteins, have been identified in two rare tumour types: 73 of 77 cases of chondroblastoma had a Lys36Met amino acid change predominantly in H3F3B, and 49 of 53 cases of giant cell tumour of bone had a Gly34 to Trp or Leu change in H3F3A. Importantly, these mutations occurred in the stromal cells and not in osteoclasts or their precursors. Moreover, these mutations are different from those identified in *H3F3A* in childhood brain cancers in which Lys27 is mutated to Met and Gly34 is changed to Arg or Val, suggesting that H3.3 driver mutations are specific for each tumour type.

ORIGINAL RESEARCH PAPER Behjati, S. *et al.* Distinct *H3F3A* and *H3F3B* driver mutations define chondroblastoma and giant cell tumor of bone. *Nature Genet.* http://dx.doi.org/10.1038/ng.2814 (2013)

IMMUNOTHERAPY

Improved efficacy

SS1P is an immunotoxin comprised of the variable fragment of a mesothelin-targeted antibody linked to a bacterial toxin. Although SS1P induces apoptosis in mesothelioma cell lines, which express mesothelin, only minor antitumour activity was observed in Phase I trials in patients with mesothelioma, primarily because patients developed neutralizing antibodies to SS1P. To circumvent this, Hassan *et al.* treated patients with pentostatin and cyclophosphamide to deplete B cells and T cells prior to SS1P treatment. This regimen resulted in major tumour regression in three of ten patients with chemotherapy-refractory mesothelioma.

ORIGINAL RESEARCH PAPER Hassan, R. *et al.* Major cancer regressions in mesothelioma after treatment with an anti-mesothelin immunotoxin and immune suppression. *Sci. Transl Med.* **5**, 208ra147 (2013)

GENOMICS

X marks the spot

Jäger *et al.* examined whole cancer genomes of 402 samples of diverse cancer types and discovered that the inactive X chromosome (Xi) in the tumours of female cancer patients has a high rate of somatic mutation. Hypermutation of Xi seemed to be cancer-specific, and hypermutation was not observed on the active X chromosome. Furthermore, Xi had a higher mutation rate than autosomes, and various analyses showed that hypermutation of Xi occurs early in tumorigenesis and by the same mutational processes that lead to autosomal mutations.

ORIGINAL RESEARCH PAPER Jäger, N. *et al.* Hypermutation of the inactive X chromosome is a frequent event in cancer. *Cell* **155**, 567–581 (2013)