

IN BRIEF

GENETICS**Mosaic predisposition mutations**

To identify rare genetic variants that confer moderate risks of breast or ovarian cancer, Ruark *et al.* sequenced 507 genes encoding DNA repair proteins in peripheral blood lymphocytes from 1,150 patients with breast cancer, 69 of whom also had ovarian cancer. They identified protein-truncating variants in the p53-inducible protein phosphatase *PPM1D* that were associated with predisposition to breast and ovarian cancer, and then confirmed this in a case-control analysis of 13,642 individuals. Interestingly, these mutations were mosaic in lymphocyte DNA and were not present in tumour cells. The mutations did not block *PPM1D* function but led to the suppression of p53 following exposure to ionizing radiation.

ORIGINAL RESEARCH PAPER Ruark, E. *et al.* Mosaic *PPM1D* mutations are associated with predisposition to breast and ovarian cancer. *Nature* 16 Dec 2012 (doi:10.1038/nature11725)

THERAPEUTICS**Balancing risks and benefits**

Antagonists of inhibitor of apoptosis (IAP) proteins are being developed as possible apoptosis-inducing cancer therapeutics. However, inhibition of IAPs can also stimulate osteoclasts through stabilization of the kinase NIK (which activates the alternative nuclear factor- κ B (NF- κ B) signalling pathway), indicating that IAP inhibition might increase bone metastasis. Yang *et al.* found that IAP antagonists can indeed enhance the growth of metastatic tumours in bone *in vivo*. They also determined that this could be reduced by co-treating mice with the bisphosphonate zoledronic acid, which inhibits osteoclasts.

ORIGINAL RESEARCH PAPER Yang, C. *et al.* Anti-cancer IAP inhibition increases bone metastasis via unexpected osteoclast activation. *Cancer Discov.* 26 Dec 2012 (doi:10.1158/2159-8290.CD-12-0271)

TUMORIGENESIS**A spiny Hedgehog**

Although primary cilia affect the activity of the Hedgehog (HH) pathway, the response to cilia loss varies among tumour types. Ho *et al.* show that chondrosarcomas (cartilage tumours arising from chondrocytes) have fewer cilia than normal chondrocytes. Transgenic mice with partial cilia loss developed similar cartilage tumours to mice with chondrocyte-specific activation of HH; double-transgenic mice developed more tumours and had further activation of the HH pathway. Disruption of cilia in human chondrosarcoma explants also activated HH signalling, leading to increased proliferation and reduced apoptosis. Therefore, cilia loss may be sufficient to induce these tumours.

ORIGINAL RESEARCH PAPER Ho, L. *et al.* Primary cilia attenuate hedgehog signalling in neoplastic chondrocytes. *Oncogene* 17 Dec 2012 (doi:10.1038/onc.2012.588)

IMAGING**On the edge**

Histopathological analyses and intraoperative magnetic resonance imaging are both used for diagnosis and to define tumour margins during brain tumour surgery, but they have limitations. Eberlin *et al.* developed a strategy using desorption electrospray ionization mass spectrometry (DESI-MS) to analyse lipid profiles, which may improve brain tumour diagnosis and the definition of tumour margins. This was validated using 32 surgical specimens from five patients.

ORIGINAL RESEARCH PAPER Eberlin, L. S. *et al.* Ambient mass spectrometry for the intraoperative molecular diagnosis of human brain tumors. *Proc. Natl Acad. Sci. USA* 8 Jan 2013 (doi:10.1073/pnas.1215687110)