IN BRIEF

BIOMARKERS

Genetic predictors of oral cancer risk

Predicting whether premalignant lesions will progress to cancer is crucial for making appropriate treatment decisions. Miriam Rosin and colleagues analysed the loss-of-heterozygosity (LOH) status of chromosomes 3p and 9p in 296 patients with low to moderate grade oral dysplasia who had known clinical follow-up. These genetic alterations were predictive of a 22.6-fold increase of progression to oral cancer, thus validating similar results from an earlier cohort. The authors also analysed LOH of additional loci in this cohort, resulting in a new high-risk signature that predicts a 52.1-fold increased risk to progression.

ORIGINAL RESEARCH PAPER Zhang, L. *et al.* Loss of heterozygosity (LOH) profiles — validated risk predictors for progression to oral cancer. *Cancer Prev. Res.* **5**, 1081–1089 (2012)

SIGNALLING

STAT3: friend or foe?

Signal transducer and activator of transcription 3 (STAT3) has well-characterized oncogenic activities in various cancers. However, Jacqueline Bromberg, David Lyden and colleagues found that, in clinical thyroid cancer samples, levels of phosphorylated (active) STAT3 negatively correlated with tumour size and metastasis. Furthermore, loss of STAT3 expression increased thyroid cell tumorigenicity *in vivo* in both xenograft and orthotopic mouse models. This study highlights a possible tumour suppressor role for STAT3 in thyroid cancer, which may involve a STAT3-regulated metabolic switch.

ORIGINAL RESEARCH PAPER Couto, J. P. *et al.* STAT3 negatively regulates thyroid tumorigenesis. *Proc. Natl Acad. Sci. USA* **109**, E2361–E2370 (2012)

METABOLISM

Immature disruption

The heterozygous, neomorphic mutation of isocitrate dehydrogenase 1 (*IDH1*) in glioma results in the generation of D-2-hydroxyglutarate, a proposed oncometabolite. A brain-specific (nestin–Cre) knock-in of one allele of *Idh1* with an R132H mutation results in high levels of neuronal apoptosis, haemorrhage and perinatal lethality. This is associated with the inhibition of collagen prolyl hydroxylases, which leads to the loss of collagen maturation and basement membrane disruption. A few GFAP-Cre mice survive *Idh1* R132H expression but do not develop glioma. This suggests that IDH1 mutation promotes glioma genesis only in the context of other mutations.

ORIGINAL RESEARCH PAPER Sasaki, M. *et al.* D-2-hydroxyglutarate produced by mutant IDH1 perturbs collagen maturation and basement membrane function. *Genes Dev.* 27 Aug 2012 (doi:10.1101/gad.198200.112)

THERAPEUTICS

Dual-pronged proteasomal promise?

The proteasome inhibitor bortezomib is used for multiple myeloma treatment, but drug resistance commonly develops. Dharminder Chauhan, Kenneth Anderson and colleagues reasoned that, rather than broadly inhibiting proteolysis, enhancing the proteolysis of particular oncogenes may be an alternative therapeutic strategy. They identified an inhibitor (P5091) of ubiquitin-specific protease 7 (USP7) that blocked MDM2 deubiquitylation by USP7 and thus stabilized p53. P5091 caused apoptosis and overcame bortezomib resistance in multiple myeloma cells *in vitro* and also slowed the growth of various multiple myeloma xenografts in mice.

ORIGINAL RESEARCH PAPER Chauhan, D. *et al.* A small molecule inhibitor of ubiquitin-specific protease-7 induces apoptosis in multiple myeloma cells and overcomes bortezomib resistance. *Cancer Cell* **22**, 345–358 (2012)