IN BRIEF

EPIGENETICS

Targeting histones in metastatic melanoma

Histone variants are important regulatory molecules in cancer. Vardabasso *et al.* have found that histone variant H2A.Z.2 is highly expressed in metastatic melanoma and is associated with poor prognosis. The authors found that H2A.Z.2-regulated genes — which are targets of the transcription factors E2F1 and E2F4 — are highly expressed cell cycle regulatory genes that acquire a unique signature of H2A.Z.2 occupancy in melanoma cells: H2A.Z.2 is enriched at the promoter region and depleted in the gene body. In addition. H2A.Z.2-regulated genes bind the bromodomain and extraterminal domain (BET) protein BRD2 — the levels of which are also elevated in melanoma samples — in a H2A.Z.2-dependent manner. Importantly, the authors reported that knocking down H2A.Z.2 sensitizes melanoma cells to BET and MEK inhibitors, which are potential therapies for melanoma.

ORIGINAL RESEARCH PAPER Vardabasso, C. *et al.* Histone variant H2A.Z.2 mediates proliferation and drug sensitivity of malignant melanoma. *Mol. Cell* **59**, 75–88 (2015)

GENETICS

The importance of mitochondrial tRNA

Although altered mitochondrial function is a feature of tumour cells, not many somatic mutations in the mitochondrial genome have been characterized. Stewart *et al.* used both genomic and transcriptomic sequencing data from 527 tumour samples from 14 different cancer types to reveal imbalances that arise when genetic alleles are differentially transcribed or processed. They have identified 15 somatic mitochondrial DNA (mtDNA) mutations that occur mostly in transfer RNA (tRNA) genes and are associated with strong accumulation of immature tRNA precursors, indicating impaired tRNA maturation in cancer. They also found that tRNA secondary structure is needed for correct maturation. As processing of specific tRNAs by cleaving at tRNA boundaries is a key step to convert mitochondrial large polycistronic RNAs into smaller gene products, the authors found that mutations affecting tRNA folding can impair maturation of not only the affected tRNA but also neighbouring gene transcripts.

ORIGINAL RESEARCH PAPER Stewart, J. B. *et al.* Simultaneous DNA and RNA mapping of somatic mitochondrial mutations across diverse human cancers. *PLoS Genet.* **11**, e1005333 (2015)

BREAST CANCER

A mouse model for metaplastic breast carcinoma

Metaplastic breast carcinoma (MBC) is a rare subset of triple-negative breast cancer characterized by a mesenchymal-like phenotype and poor clinical outcome. As BRCA1 deficiency sensitizes tumours to poly(ADP-ribose) polymerase (PARP) inhibitors and most MBCs harbour mutations in *BRCA1*, Jos Jonkers and colleagues wondered whether MBC could be effectively targeted with PARP inhibitors. The authors generated a genetically engineered mouse model of *Brca1*-deficient MBC by inducing epithelial–mesenchymal transition by overexpressing the *Met* oncogene in a previously established mouse model of *BRCA1*-mutated breast cancer. Mouse MBC showed intrinsic resistance to the PARP inhibitor olaparib owing to overexpression of the drug efflux transporter P-glycoprotein (Pgp). However, using another PARP inhibitor that has low affinity for Pgp (AZD2461) rendered the tumours sensitive to PARP inhibition.

ORIGINAL RESEARCH PAPER Henneman, L. *et al.* Selective resistance to the PARP inhibitor olaparib in a mouse model for BRCA1-deficient metaplastic breast cancer. *Proc. Natl Acad. Sci. USA* **112**, 8409–8414 (2015)