IN BRIEF

EPIGENETICS

Histone modification

This paper is one of several recent publications to examine the mechanisms through which mutations of genes that encode histone 3 (H3) variants contribute to glioma development in young children, including in those with diffuse intrinsic pontine glioma (DIPG). A mutation in *H3F3A* that results in a lysine 27 to methionine mutation (K27M) in H3.3, which is found in DIPG, results in reduced levels of trimethylated and dimethylated H3K27 (H3K27me3 and H3K27me2, respectively). However, using two DIPG cell lines that have the H3.3K27M mutation, these authors also found that, at specific cancer-associated loci throughout the genome, H3K27me3 levels and levels of bound EZH2 (the catalytic subunit of polycomb repressive complex 2) were increased, leading to decreased gene expression levels from these loci. These data add more weight to the evidence that epigenetic changes underlie the development of DIPG.

ORIGINAL RESEARCH PAPER Chan, K.-M. *et al.* The histone H3.3K27M mutation in pediatric glioma reprograms H3K27 methylation and gene expression. *Genes Dev.* **27**, 985–990 (2013)

TUMOUR SUPPRESSORS

Restoring function

A high proportion of malignant melanomas express wild-type p53 that is often inactive. Xin Lu and colleagues have found that most malignant melanoma cell lines with wild-type p53 have high levels of phosphorylated iASPP in the nucleus. iASPP interacts with p53 and inhibits apoptosis, and these authors found that iASPP is phosphorylated by cyclin B1–cyclin-dependent kinase 1 (CDK1). This prevents dimerization of iASPP and enables the monomeric phosphorylated form of iASPP to accumulate in the nucleus and to interact with p53. Previous studies have shown that wild-type p53 activity can be increased in cancer cells through the use of inhibitors of MDM2, a ubiquitin ligase that binds and ubiquitylates p53, which can result in its degradation. Inhibition of iASPP phosphorylation and MDM2 activity using small-molecule inhibitors resulted in apoptosis and growth suppression of wild-type p53 melanoma cell lines. Moreover, this approach combined with the BRAF inhibitor vemurafenib substantially reduced the growth of human melanoma xenografts with wild-type p53 and a BRAF-V600E mutation.

ORIGINAL RESEARCH PAPER Lu, M. *et al.* Restoring p53 function in human melanoma cells by inhibiting MDM2 and cyclin B1/CDK1-phosphorylated nuclear iASPP. *Cancer Cell* 25 Apr 2013 (doi:10.1016/j.ccr.2013.03.013)

APOPTOSIS

Direct action

RB1, the gene that encodes the retinoblastoma tumour suppressor protein (RB), is mutated in one-third of human cancers. Although widely appreciated as a transcriptional coregulator, Jacqueline Lees and colleagues have found that RB also functions outside of the nucleus at the mitochondrial membrane. Recombinant RB was able to bind BAX in its active conformation and trigger the permeabilization of mitochondria and liposomes *in vitro*, and to interact directly with BAX *in vivo*. Moreover, a mutant form of RB that was targeted only to the mitochondria promoted apoptosis induced by tumour necrosis factor and other apoptotic stimuli, and was able to block further tumour development when expressed in $Rb1^{-/-}Trp53^{-/-}$ tumours in mice.

ORIGINAL RESEARCH PAPER Hilgendorf, K. I. *et al.* The retinoblastoma protein induces apoptosis directly at the mitochondria. *Genes Dev.* **27**, 1003–1015 (2013)