IN BRIEF

GLIOMA

Targeting a histone mutant

Oncogenic mutation of histone H3.3 occurs frequently in paediatric brainstem gliomas. Funato *et al.* created a model of the aggressive brainstem glioma diffuse intrinsic pontine glioma (DIPG) using human embryonic stem cells (ESCs). Early neural progenitor cells (NPCs) were derived from ESCs and then engineered to express mutant H3.3 (H3.3-K27M), constitutively active platelet-derived growth factor receptor-α (PDGFRA) and a short hairpin RNA against p53, as PDGFRA activation and p53 loss commonly occur with H3.3-K27M mutations. These cells were transformed *in vitro* and formed tumours resembling low-grade DIPGs when injected into the brainstems of immunocompromised mice. Furthermore, the transformed NPCs seemed to undergo epigenetic changes that reverted them to a more primitive state. The authors also used these cells *in vitro* for drug discovery and determined that an inhibitor of menin, which is part of a histone methyltransferase complex and involved in transcriptional regulation, could reduce tumour growth *in vivo*. Hasizume *et al.* showed that brainstem glioma cells with H3.3-K27M mutations have lower levels of dimethylated and trimethylated H3.3-K27. The Jumonji-domain demethylase JMJD3 demethylates lysine 27, and the authors found that an inhibitor of JMJD3, GSKJ4, had antitumour activity against subcutaneous and orthotopic brainstem glioma xenografts. These papers both suggest possible therapeutics for brainstem gliomas.

ORIGINAL RESEARCH PAPERS Funato, K. *et al.* Use of human embryonic stem cells to model pediatric gliomas with H3.3K27M histone mutation. *Science* http://dx.doi.org/10.1126/science.1253799 (2014) | Hasizume, R. *et al.* Pharmacologic inhibition of histone demethylation as a therapy for pediatric brainstem glioma. *Nature Med.* **20**, 1394–1396 (2014)

RESISTANCE

Different means to the same end

Juric and Castel *et al.* examined the development of resistance to the PI3K p110α inhibitor BYL719 in a patient with metastatic breast cancer who had responded initially, but later relapsed and died. The authors collected samples from 14 metastatic sites during rapid autopsy and found that all lesions had loss of one copy of *PTEN*, and those that had developed resistance to BYL719 treatment had heterogeneous genetic alterations that resulted in the complete loss of PTEN expression. This suggests that parallel evolution occurs at metastatic sites, leading to the same phenotypic outcome in all of them.

ORIGINAL RESEARCH PAPER Juric, D. & Castel, P. *et al.* Convergent loss of PTEN leads to clinical resistance to a PI(3)Kα inhibitor. *Nature* http://dx.doi.org/10.1038/nature13948 (2014)

METASTASIS

Home sweet home

Reticker-Flynn and Bhatia have shown that galectin-3 contributes to the formation and establishment of a pro-tumorigenic metastatic niche. The authors analysed the expression of galectin-3 in the liver of a mouse model of metastatic lung adenocarcinoma and found that it was expressed in a population of myeloid cells, which are mobilized in response to soluble factors secreted from cancer cells. Further experiments showed that metastatic cancer cells adhere to galectin-3 through increased presentation of galectin-3 carbohydrate ligand (the Thomsen–Friedenreich antigen), which is mediated by aberrant glycosyltransferase.

ORIGINAL RESEARCH PAPER Reticker-Flynn, N. E. & Bhatia, S. N. Aberrant glycosylation promotes lung cancer metastasis through adhesion to galectins in the metastatic niche. *Cancer Discov.* http://dx.doi.org/10.1158/2159-8290.CD-13-0760 (2014)