IN BRIEF

DNA REPAIR

Double take

Break-induced repair (BIR) is a homologous recombination pathway used to repair damaged replication forks in yeast. This paper examined whether the BIR pathway is active in human cells under conditions of DNA replication stress. Overexpression of cyclin E (a model of DNA replication stress in human cells) showed that POLD3 (the human orthologue of yeast Pol32, which is required for BIR) is needed for cell cycle progression and DNA synthesis during replication stress. Moreover, the DNA duplications that occurred in these cells during replication stress were dependent on POLD3 and BIR-mediated recombination. Thus, BIR might be used to repair collapsed replication forks in human cells and might explain the high levels of genomic duplications that are evident in human cancers.

ORIGINAL RESEARCH PAPER Costantino, L. *et al.* Break-induced replication repair of damaged forks induces genomic duplications in human cells. *Science* http://dx.doi.org/10.1126/science.1243211 (2013)

THERAPEUTICS

Amplifying a response

This paper examines whether it is possible to boost the immune system in patients with glioblastoma, such that the brain tumour-initiating cells (BTICs) are targeted and killed. The authors found that, although immune cells isolated from patients with glioblastoma could recognize BTICs *in vitro*, they were not effective at killing them. However, macrophages and microglia isolated from healthy individuals were more effective at restricting the growth of a population of BTICs in culture. Interestingly, a screen of a library of small molecules identified the antifungal drug amphotericin B as a stimulator of macrophages and microglia. Administration of this drug to mice with human BTIC-induced tumours significantly prolonged their survival. Caution is needed, however, as amphotericin B has substantial and potentially lethal side effects when given at high doses intravenously.

ORIGINAL RESEARCH PAPER Sarkar, S. *et al.* Therapeutic activation of macrophages and microglia to suppress brain tumor-initiating cells. *Nature Neurosci.* http://dx.doi.org/10.1038/nn.3597 (2013)

SIGNALLING

A change of state leads to rewiring

Epithelial tumour cells are known to undergo a form of epithelial to mesenchymal transition (EMT) during the course of tumour progression, and mesenchymal markers are associated with poor prognosis and drug resistance. How molecular signalling pathways are 'rewired' in cells that have undergone EMT is not well characterized. Frank McCormick and colleagues used non-small-cell lung cancer cells expressing regulatable transcription factors that induce EMT to investigate the effects of EMT on signalling pathways downstream of receptor tyrosine kinases. They found that EMT is associated with reduced expression of *ERBB3* and reduced rates of proliferation in serum-free conditions owing to reduced PI3K activation. Re-expression of *ERBB3*, activation of PIK3CA (a catalytic subunit of PI3K) or growth factor stimulation rescued PI3K signalling in the absence of serum. Importantly, examination of mesenchymal-like tumours *in vivo* showed that *PIK3CA* upregulation occurs in tumours with reduced ERBB3 expression.

ORIGINAL RESEARCH PAPER Salt, M. B., Bandyopadhyay, S. & McCormick, F. Epithelial to mesenchymal transition rewires the molecular path to PI3-kinase-dependent proliferation. *Cancer Discov.* http://dx.doi.org/10.1158/2159-8290.CD-13-0520 (2013)