IN BRIEF

THERAPEUTICS

Passed down to the next generation

Although infertility occurs following chemotherapy or radiotherapy for many patients, some cancer survivors do go on to have children. As such, it is important to understand the hereditary effects of exposure to anticancer therapy. Glen and Dubrova treated male mice with the chemotherapeutic agents cyclophosphamide, mitomycin C or procarbazine at doses similar to those used therapeutically. They had previously found an increased mutation frequency in the germ line of treated males, and in this study they have extended this finding to the germ line and bone marrow of offspring of these mice. Interestingly, an increased mutation rate was also observed in alleles derived from the non-exposed mother, suggesting that genome-wide destabilization can occur in offspring after paternal exposure to chemotherapy.

ORIGINAL RESEARCH PAPER Glen, C. D. & Dubrova, Y. E. Exposure to anticancer drugs can result in transgenerational genomic instability in mice. *Proc. Natl Acad. Sci. USA* 30 Jan 2012 (doi:10.1073/pnas.1119396109)

TUMOUR HETEROGENEITY

All mixed up

Clinical trials of inhibitors against individual receptor tyrosine kinases (RTKs) in glioblastoma have not yielded promising results. By analysing DNA copy number data sets, Szerlip *et al.* determined that 36 of 583 glioblastoma cases had amplification of two or more RTKs in separate cell populations within a tumour. Fluorescence *in situ* hybridization analysis of epidermal growth factor receptor (*EGFR*) and platelet-derived growth factor receptor-α (*PDGFRA*), the most commonly amplified RTKs, showed distinct cells expressing each RTK. Furthermore, DNA sequencing revealed a common clonal origin of these cells. Cell lines derived from these tumours contained cells with either *EGFR* or *PDGFRA* amplification. Inhibition of both RTKs was required to block PI3K signalling in these cells, and this may be required to achieve therapeutic benefit in patients with co-amplified RTKs.

ORIGINAL RESEARCH PAPER Szerlip, N. J. *et al.* Intratumoral heterogeneity of receptor tyrosine kinases EGFR and PDGFRA amplification in glioblastoma defines subpopulations with distinct growth factor response. *Proc. Natl Acad. Sci. USA* 8 Feb 2012 (doi:10.1073/pnas.1114033109)

THERAPEUTIC RESISTANCE

Rational combination

The RAF inhibitor vemurafenib (PLX4032) is effective against melanomas with activated BRAF (BRAF-V600E), but not against colorectal cancers (CRCs) harbouring the same mutation. Two papers now report, using RNA-interference screens and the analysis of signalling pathways in cell lines, that activation of epidermal growth factor receptor (EGFR) occurs following vemurafenib treatment in CRC cells, but not in melanoma cells, leading to vemurafenib resistance. Consequently, both studies found that combination treatment with vemurafenib and an EGFR inhibitor blocked CRC cell growth *in vitro* and CRC tumour growth in xenograft models. This could be a valid therapeutic strategy for patients with BRAF-mutant CRC.

ORIGINAL RESEARCH PAPERS Corcoran, R. B. *et al.* EGFR-mediated re-activation of MAPK signaling contributes to insensitivity of BRAF mutant colorectal cancers to RAF inhibition. *Cancer Discov.* 16 Jan 2012 (doi: 10.1158/2159-8290.CD-11-0341) | Prahallad, A. *et al.* Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. *Nature* 26 Jan 2012 (doi:10.1038/nature10868)