DNA REPAIR

A single-edged sword?

Deficiencies in DNA repair processes modulate both tumorigenesis and chemotherapy response. Therapeutic inhibition of DNA repair can sensitize cancer cells to chemotherapy or can function as a synthetic lethal strategy for the treatment of cancers with certain DNA repair defects. However, DNA repair inhibition is typically accompanied by the threat of accelerated mutagenesis. Two recent papers suggest that targeting DNA repair mechanisms is not always a double-edged sword: repression of translesion synthesis (TLS) can not only sensitize chemoresistant tumours to therapy but can also keep mutagenesis in check.

TLS is a DNA damage tolerance mechanism whereby alternative DNA polymerases use error-prone DNA synthesis to bypass bulky DNA lesions, such as those caused by chemotherapeutics. Components of TLS include REV3L (a subunit of DNA polymerase-ζ) and REV1 (a TLS scaffold protein). To investigate the role of TLS in therapy response and mutagenesis, both groups combined tractable mouse models of cancer with short hairpin RNA (shRNA)-mediated depletion of TLS components.

Graham Walker and colleagues used a chemosensitive *Eμ-Myc* lymphoma model and showed that knock down of REV3L or REV1 further sensitized lymphomas to the crosslinking agent cisplatin. To investigate whether TLS repression could also increase the therapeutic response of chemorefractory tumours, Mike Hemann and colleagues knocked down REV3L in a $Kras^{G12D}$;$Trp53^{-/-}$ mouse model of non-small-cell lung cancer (NSCLC). REV3L knockdown markedly sensitized NSCLC cells to cisplatin *in vitro*, accompanied by a persistence of unrepaired DNA damage. shRNA-transduced NSCLC cells injected into the tail vein colonized the lung and allowed assessment of the *in vivo* therapeutic response — REV3L knockdown slowed NSCLC tumour progression and prolonged the survival of the mice.

To investigate the mutagenic role of TLS following chemotherapy treatment, both groups used a cellular mutagenesis assay, in which mutations at the mouse hypoxanthine guanine phosphoribosyl transferase (*Hprt*) locus, acquired during chemotherapy treatment, result in resistance to 6-thioguanine (6-TG). A reduction in mutagenesis on TLS suppression was evident in REV3L-downregulated NSCLC cells treated with cisplatin. REV1-downregulated lymphomas were not immediately sensitized to an alkylating agent, cyclophosphamide, either *in vitro* or *in vivo*. However, following successive rounds of treatment, REV1 knockdown delayed the emergence of therapeutic resistance, possibly owing to fewer mutations. Therefore, the mutagenic effect of TLS could be a crucial determinant of therapeutic response. However, other studies have shown that, in cells that can tolerate the loss of TLS, *Rev3l* deletion causes the collapse of replication forks, leading to chromosomal instability and thus promoting mutagenesis.

It will be interesting to see whether the effects of cancer cell-specific TLS gene knockdown can be replicated using systemic delivery of TLS-targeted therapeutics. The potential toxicity of a TLS-targeted agent towards normal cells would need to be considered and carefully balanced, as knock out of *Rev3l* in mice is embryonic lethal, in contrast to the absence of obvious viability defects in REV3L-knockdown cells. Finally, it remains to be seen whether TLS inhibition can be selectively lethal to cancer cells with particular types of DNA repair deficiencies.

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ORIGINAL RESEARCH PAPERS Xie, K., *et al.* Error-prone translesion synthesis mediates acquired chemoresistance. *Proc. Natl Acad. Sci. USA* **107**, 20792–20797 (2010) | Doles, J., *et al.* Suppression of Rev3, the catalytic subunit of Polζ, sensitizes drug-resistant lung tumors to chemotherapy. *Proc. Natl Acad. Sci. USA* **107**, 20786–20791 (2010)