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RESEARCH HIGHLIGHT

Mutagenic replication: target for tumor therapy?

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A study published in *Cell* by Wojtaszek et al. provides a proof of principle that cancer cells can be sensitized to DNA-damaging chemotherapy by the drug-induced inhibition of mutagenic DNA translesion synthesis, a process that endows tolerance of DNA damage. However, the risk/benefit profile of such a combination therapy should be thoroughly evaluated.

Classical genotoxic chemotherapy of cancer is aimed at killing proliferating tumor cells by the introduction of DNA lesions that arrest the replication machinery. The ensuing replication stress triggers the DNA damage response that includes cell cycle arrest, senescence or apoptosis.[1] Although chemotherapeutic drugs are widely used to treat cancer, they not only kill proliferating cancer cells, but also proliferating normal cells. This provokes dose-limiting side effects for the patients, including hair loss, gastrointestinal and hematopoietic attrition and, on the longer term, features of premature aging. Moreover, apart from being cytotoxic, chemotherapeutics are mutagenic, which might accelerate tumor progression and induce secondary tumors (see Fig. 1).

Cytotoxic DNA damage responses to DNA nucleotide lesions are suppressed by so-called DNA damage tolerance mechanisms. Translesion synthesis (TLS) is a dominant damage tolerance mechanism, employing specialized DNA polymerases that are able to replicate across damaged nucleotides, which mitigates replication stress and thereby precludes full deployment of the DNA damage response.[1] However, since TLS polymerases inherently act in an error-prone fashion while replicating damaged nucleotides, they not only provide tolerance of nucleotide lesions but also generate mutations that are associated with tumor initiation and progression. With this in mind, it has been hypothesized that the inhibition of mutagenic TLS might (i) increase the responses of cancer to genotoxic chemotherapeutics and (ii) reduce the mutagenicity and tumorigenicity of chemotherapy (see Fig. 1).

To address the feasibility of such a novel approach in cancer chemotherapy, Wojtaszek et al.[2] have performed a screen for small-molecule inhibitors of REV1, a protein that, in addition to performing TLS at abasic sites and nucleotide lesions at the minor groove of the helix, controls other TLS polymerases including TLS polymerase η and REV7, a subunit of TLS polymerase ζ.[1] Amongst the roughly 10,000 compounds analyzed, Wojtaszek et al. identified a 1,4-dihydroquinolin-4-one derivative, JH-RE-06, that induces the dimerization of REV1 molecules at their C-terminal domains, in an asymmetric fashion. This hides the REV7-binding domain of REV1 and therefore abolishes REV1/REV3/REV7-mediated highly mutagenic TLS while leaving TLS by less mutagenic polymerases intact. Indeed, experiments using *Rev1*-knockout mouse embryonic fibroblasts (MEFs) or REV1-depleted human cells, provided genetic evidence that JH-RE-06 specifically inhibits a REV1-mediated highly mutagenic TLS pathway at severely helix-distorting nucleotide lesions such as those induced by chemotherapeutic drugs. Consistent with this, TLS across a site-specific DNA lesion, introduced by the chemotherapeutic drug cisplatin, was suppressed by treatment of the cells with JH-RE-06. Intriguingly, treatment of MEFs with cisplatin+JH-RE-06 suppressed the mutation frequency even below that of "spontaneous" mutations, i.e., observed in the absence of cisplatin treatment. Although the cause of this phenomenon remains to be investigated, it might suggest that cells, severely damaged by both endogenous and cisplatin-induced DNA lesions, are selectively eliminated by the combined treatment. Finally, JH-RE-06 increased the cytotoxicity of cisplatin and other DNA-damaging agents towards cancer cell lines and immortalized wild-type MEFs but, unexpectedly, not towards primary human fibroblasts.

Wojtaszek et al. then investigated whether JH-RE-06 can be used as an adjuvant to sensitize cancer cells to chemotherapy. To this aim, they injected cisplatin, JH-RE-06 or JH-RE-06+cisplatin, directly into melanomas xenografted in mice. Compared with tumors receiving each compound alone, the combination treatment suppressed tumor growth to a greater extent, and these mice survived 50% longer. In summary, Wojtaszek et al. have demonstrated that a small-molecule inhibitor of REV1 sensitizes cancer cells to cisplatin both in vitro and in vivo, while suppressing induced mutagenesis in vitro. These promising data suggest that REV1 inhibition provides a viable inroad to improve genotoxic chemotherapy, by increasing its efficacy. Importantly, although not addressed in this paper, the suppression of mutagenesis by genotoxic chemotherapy following TLS inhibition might reduce tumor promotion and secondary tumor formation.

Nevertheless, the relationship between TLS and cancer may be more complex than anticipated. Thus, paradoxically, perturbation of TLS may accelerate, rather than reduce, carcinogenesis.[3–6] Furthermore, mutagenic TLS is essential for the maintenance of normal tissues[7,8] by providing tolerance not only of genotoxic drugs but also of endogenous nucleotide lesions or of difficult-to-replicate genomic sequences (such as centromeric DNA, fragile sites or G-quadruplex structures).[1] Finally, TLS plays an important role in the diversification of the immune system.[9] Thus, systemic exposure to REV1 inhibitors might enhance endogenous or chemotherapy-induced toxicity towards proliferating normal tissues.

In conclusion, the work of Wojtaszek et al. provides an important proof of principle that the inhibition of REV1 might provide benefits for cancer chemotherapy. However, thorough study of the possible short- and long-term consequences of systemic REV1 inhibition is required before bringing this novel therapeutic option to the clinic.

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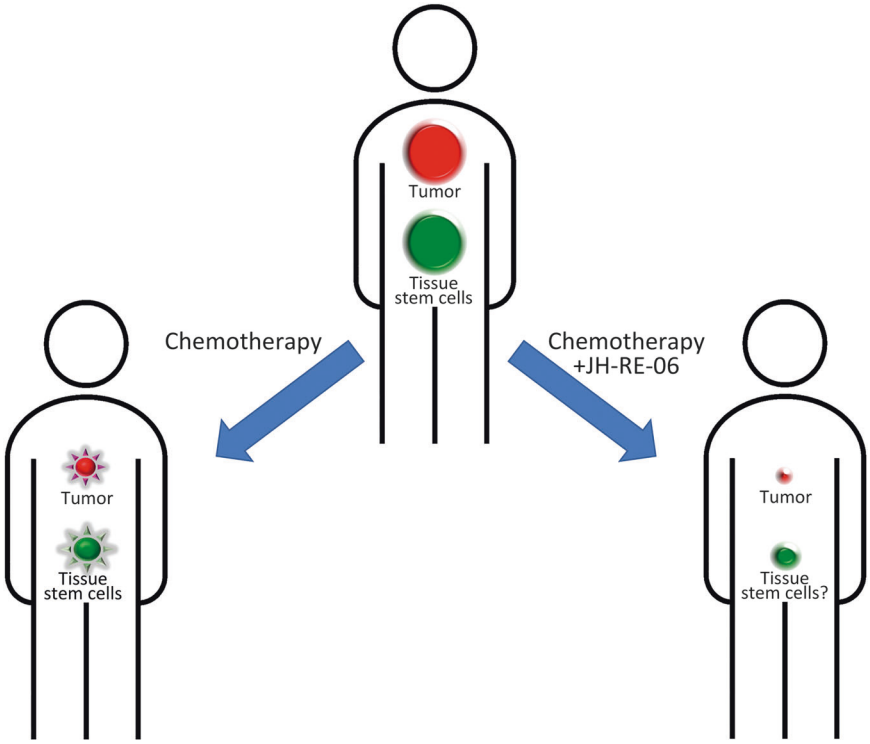

Fig. 1 Genotoxic chemotherapy exerts toxicity towards proliferating cells, including tumor cells and stem cells in tissues (left). The toxicity of chemotherapy-induced DNA damage is counteracted by TLS, at the expense of mutations that might contribute to tumor progression (red star) or to secondary tumorigenesis (green star). JH-RE-06 inhibits REV1-mediated mutagenic TLS. This results in sensitization of proliferating tumor cells (and, possibly, also of normal stem cells) to the toxic effects of chemotherapy, while avoiding the mutagenic consequences of TLS. Nevertheless, it cannot be excluded that systemic REV1 inactivation provokes undesired phenotypes (see the text)

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