Targeting DNA repair as cancer therapy: TLS comes into focus

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DNA repair plays critical roles in maintaining genome stability. There are six major DNA repair pathways that handle different types of DNA damages, namely base excision repair (BER), nucleotide excision repair (NER), mis-match repair (MMR), homologous recombination repair (HR), non-homologous end joining (NHEJ), and translesion synthesis (TLS) (1). Numerous studies have shown that alteration in DNA repair genes, including deletions, mutations, and copy number alterations, and altered gene expression, is one of the major causes of mutagenesis and cancer. In fact, cancer cells are often defective in one of their six major DNA repair pathways. For example, approximately half of the epithelial ovarian cancers have alterations in genes that regulate HR, which accounts for their genomic instability and thus aggressiveness (2). The cancer risk dramatically increases in the population who carry mutations in HR genes, including the well-known breast cancer susceptibility genes (*BRCA1* and *BRCA2*) (3).

Counterintuitively, targeting DNA repair pathways has emerged to be a promising strategy for cancer therapy. The rationale is that the cancer cells defective in one repair pathway are hyper-dependent on an alternative repair mechanism. Therefore, inhibition of the alternative pathway leads to a synthetic lethality in cancer cells but not normal cells (4, 5). The recent approved PARP inhibitors (PARPi) may be the most successful examples along this theory. HR-deficient cells (*e.g. BRCA1/2* deficient cells) are hypersensitive to PARPi, since PARP inactivation prevents the repair of DNA single-strand breaks (SSBs), which are subsequently converted to double-strand breaks (DSBs) (6-8).

In this issue (11), the review by Cynthia Harris and Nimrat Chatterjee summarized the molecular mechanisms of translesion synthesis (TLS) and the status of developing TLS inhibitors for cancer treatment. The authors illustrated why TLS is critical for cell survival, and explained the current models of TLS in action: the polymerase switch model and the gap-filling model. The review also summarized recent findings of targeting TLS to reduce intrinsic and acquired mutations during chemotherapy. The review has a specific focus on studies from Dr. Graham Walker's laboratory at MIT, who have done tremendous amount of work on TLS and mutagenesis over the last few decades (9).

The review highlights targeting TLS as cancer treatment, and the authors discussed two avenues that we can pursue. While the avenue of inhibition the catalytic activity of TLS appears to be murky, inhibiting TLS by targeting the protein-protein interactions seemed a promising strategy. Two recently discovered inhibitors were discussed in detail; one targets to Rev1 and the other targets to Rev7. Particularly, the new inhibitors that targets the RIR interface of Rev1 appears to be a very interesting and promising, shining some lights on the relatively new strategy of targeting TLS (10). It makes good sense that these inhibitors will sensitize cells to chemotherapy and potentially inhibitors of another DNA repair pathway (*i.e.* PARPi). Although there is a long way to go for the TLS inhibitors to advance from bench-side to bedside, the current findings are promising.

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