Editorial

Inhibitors of DNA repair for cancer therapy, ready for prime time?

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Genomic DNA is the central storage place for cellular information in DNA-based life forms. However, its integrity is under constant threat from errors in the replication process and damage from environmental insults. To neutralize these threats, our cells have developed elaborate mechanisms to repair DNA damage. Specialized mechanisms exist to deal with different types of DNA damage. For base damage, which is often caused by reactive oxygen species produced in normal cellular mechanism, the base excision repair system, is mostly in charge. For mis-incorporated nucleotides, the mismatch repair system will take care. For chemically- or UV- induced bulky DNA damage, the nucleotide excision repair is mainly responsible. Finally, for radiation or chemically induced DNA strand breaks, the homologous recombination (HR) or non-homologous end joining (NHEJ) systems will be activated. Each of these DNA repair systems plays a vital role in maintaining the stability of the genome. In the current issue, Hsu *et al*. (1) provided a comprehensive overview of the biological functions of DNA-dependent protein kinase and its potential exploitation as a cancer therapy target.

Despite the existence of sophisticated DNA repair systems in mammalian cells, damage to DNA still occur due to rare mistakes of DNA repair machinery. The consequences of such mistakes can be unnoticeable, as in the case of inconsequential base pair changes that do not alter amino acid sequences. They can also be very severe, such as when DNA strand breaks result in the chromosomal translocation and juxtaposition of bcr and abl genes. Such juxtaposition can result in the development of cancer (2). In rare instances, DNA repair genes themselves can suffer mutations. Under those circumstances the results are often severe. For example, mutations in the ATM gene, which is involved in sensing DNA strand breaks, lead to ataxia telangiectasia, a debilitating disease with multiple developmental defects and cancer development. It also leads to extreme sensitivity of the patients' cells to ionizing radiation. Another example is the DNA-PKcs gene. Mutations in it lead to severe combined immune-deficiency in host and significant radiation sensitivity of the host cells.

Because defects in DNA double strand break repair genes lead to cellular sensitivity to radiation, there have been strong interests in developing therapeutic strategies aimed at attenuating the functions of these genes in cancer cells to make them more sensitive to radiotherapy and chemotherapy. The rationale is that if the DNA repair function of the double strand break repair genes are compromised in cancer cells, they will become susceptible to radiation and chemically induced cell killing. To this end a variety of ATM/ATR and DNA-PKcs kinase inhibitors have been developed. These inhibitors have shown promise in enhancing cancer radiotherapy and chemotherapy in both tissue cultured cancer cells and in mouse cancer models. However, the value of such a strategy has to be evaluated based on clinical trials in human cancer patients.

One caveat of targeting DNA repair genes to enhance cytotoxic cancer therapy is the potential for secondary malignancies that might emerge after successful control of the primary cancer. The risk cannot be ignored because genes such as DNA-PKcs and ATM are believed to be "guardians of genome" whose functions are considered essential to keep pre-cancerous cells at bay. The risks for secondary cancer cannot be ignored especially given recent findings that showed rapid development of squamous cell carcinoma in melanoma patients undergoing B-RAF inhibitor treatment (3). Unexpected toxicity could also

arise because of yet poorly understood functions of DNA strand break repair genes. Indeed, as Hsu *et al*. pointed out, DNA-PKcs activity has been implicated in cell cycle control, mitosis, microtubule dynamics, and chromosomal segregation. As such, small molecule inhibitors of DNA-PKcs may have un-intended toxicities. Only clinical trials will tell if such inhibitors can boost the efficacy of radiation and chemotherapy significantly without causing unacceptable normal tissue toxicities.

In summary, Hsu *et al*. provides a great overview of what we know about DNA-PKcs biology and its exciting promise as cancer therapy target. More insights into the biology of DNA-PKcs and other DNA repair proteins will be gained in the not too distant future. One can also remain relatively optimistic about the prospects of targeting DNA-PKcs or other DNA repair proteins to treat cancer, depending on the results of ongoing and planned clinical trials.

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