The Biology Behind

Nucleotide Excision Repair, Oxidative Damage, DNA Sequence Polymorphisms, and Cancer Treatment

Commentary on Gu et al., p. 1408

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INTRODUCTION

Can a single polymorphic site help tailor a cancer patient’s chemotherapy regimen? The study by Zhao et al. (1) presented in this issue of Clinical Cancer Research suggests that in fact polymorphic sites in noncoding gene regions may determine how a patient will react to a given chemotherapy and the likelihood of cancer recurrence after treatment. The group focused their investigation on a common polymorphism termed xeroderma pigmentosum group A (−4) [XPA (−4)], whereby the fourth nucleotide before the ATG start codon is A in about half the population and G in about the other half (2, 3). The polymorphism is in the Kozak sequence and thus the A form of the allele may affect the translation efficiency of XPA resulting in reduced XPA level and reduced excision repair capacity. Indeed, this group previously reported that the A allele (XPA A variant in the authors’ terminology) is associated with reduced excision repair capacity (4). In the current study, the authors report that the XPA G variant in which both alleles contain G at the fourth position before the initiation codon is associated with a higher rate of recurrence of superficial bladder cancer after Bacillus Calmette-Guerin (BCG) treatment. The authors report that during the follow-up period of 27.6 months from diagnosis, tumor recurred in 44% of patients with the AA genotype, 62% in those with the AG genotype, and 27.6 months from diagnosis, tumor recurred in 44% of patients with the GG genotype. To explain these findings, the authors suggest that the XPA G variant exhibits increased DNA repair capacity (4). This increase in DNA repair capacity may be responsible for removing a greater percentage of oxidative damage from DNA, preventing the apoptotic pathway, and its response to oxidative damage, to explain why the XPA G variant is less responsive to BCG treatment. The suggestion is that BCG therapy provokes an inflammatory cellular response, which subsequently results in the production of oxygen radicals and extensive oxidative damage to DNA followed by apoptosis. Reactive oxygen species are by-products of oxidative metabolism and are also produced in great quantities during inflammatory reactions. They induce numerous DNA adducts, reactive oxygen species by-products of oxidative metabolism and are also produced in great quantities during inflammatory reactions. They induce numerous DNA lesions including thymine glycols, 8-oxoguanine, and cyclo-oxygenase. Nucleotide excision repair is capable of removing all of these DNA lesions induced by reactive oxygen species (13, 14).

In the study by Zhao et al. (1), the authors propose a mechanism that involves the nucleotide excision repair pathway and its response to oxidative damage, to explain why the XPA G variant is less responsive to BCG treatment. The suggestion is that BCG therapy provokes an inflammatory cellular response, which subsequently results in the production of oxygen radicals and extensive oxidative damage to DNA followed by apoptosis. The XPA G variant was reported to have increased DNA repair capacity (4). This increase in DNA repair capacity may be responsible for removing a greater percentage of oxidative damage from DNA, preventing the apoptotic pathway, and permitting tumor cell survival, rendering BCG ineffective for patients homozygous for the XPA G variant.

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This is a reasonable speculation. However, there are certain caveats to this interpretation. The report that the XPA G variant allele shows increased DNA repair capacity requires verification by more than just the reporter gene assays reported previously (4). Currently, there is no evidence that the level of XPA protein is increased constitutively or in response to damage in XPA G variant patients. Furthermore, there is no evidence by independent repair assays that there is increased excision repair activity in cells with the XPA G variant. In addition, although it has been shown that human nucleotide excision repair excises 8-oxoguanine, thymine glycol, and perhaps other oxidative stress base lesions from DNA as efficiently as the light-induced cyclobutane thymine dimer (13), 8-oxoguanine and other oxidative stress lesions are repaired very efficiently by 8-oxoguanine DNA glycosylase and other glycosylases (15). Therefore, the magnitude of contribution of nucleotide excision repair in the removal of oxidative damage to nucleotide bases remains to be determined. As a final caveat, previous studies (4, 16) have shown that the XPA G variant allele has a protective effect against the onset of lung cancer. Those reports predict that individuals with XPA G variant would have lower incidence of bladder cancer as well. Zhao et al. (1) did not study an unaffected sample of the population to determine if the XPA G variant allele shows a similar protective effect against superficial bladder cancer. If it does, this study reveals an interesting issue in the genetic consideration in carcinogenesis and cancer treatment: a mutation makes the carriers more resistant to cancer, but once they develop cancer, the same mutation may make them less responsive to treatment by agents that directly or indirectly damage DNA.

This is an interesting study, and in conclusion, the connection between the XPA G variant polymorphism and lack of response to BCG treatment could have significant clinical implications.
applications. However, whether or not this polymorphism is relevant to nucleotide excision repair activity needs further investigation.

REFERENCES

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