Letters to the Editor

Genetic Effect of ERCC1 Codon 118 Polymorphism and Confounding Factors

To the Editor: Viguié et al. (1) reported that the ERCC1 codon 118 polymorphism has a predictive value in colorectal cancer patients treated with platinum combination chemotherapy. However, there are contradictory reports on the effects of this polymorphism on the survival of cancer patients. Although Viguié et al. suggested that cancer patients carrying a variant genotype survived for a longer period, we found that the wild genotype favored a better survival (2). On the other hand, there are some reports showing no association between the ERCC1 codon 118 polymorphism and survival (3, 4). These inconsistencies make the prognostic or predictive relevance of this marker unsuitable for clinical practice. Similar observations were also reported for other polymorphisms of the MDR1 gene, such as C3435T and G2877T, where contradictory genetic effects were also noted.

There is increasing evidence suggesting that environmental factors modulate the genetic effect of these polymorphisms. For example, a case-control study showed the presence of a gene-smoking interaction with the ERCC1 polymorphism (5). This interaction was also observed in our recent study (6). Prognostic significance was observed only in those patients with non–small cell lung cancer who were heavy smokers (≥50 pack-years; P = 0.03, using the log-rank test).

The apparent conflicting information regarding the ERCC1 codon 118 polymorphism might be explained by the coexistence of major confounding factors, such as ethnicity, environmental factors (smoking or diet), the number of patients enrolled, or some linkage to other polymorphisms, which might mask the relatively minor gene effect associated with a single genetic polymorphism. Moreover, there was no direct or clear evidence for the functional significance of the ERCC1 codon 118 polymorphism.

In addition to a functional study, further research will be needed to verify which confounding factors have the most significant results.

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References

In Response: Please find below our reply to the points that were raised by Dr. Ryu. We agree with Dr. Ryu’s statements as far as lung cancer is concerned, but do not find them relevant to colorectal cancer for the following reasons:

1. Non–small-cell lung cancer patients were treated with cisplatin, not by oxaliplatin. Indeed, a number of cellular processes discriminate between the DNA adducts formed by each of these compounds (reviewed in ref. 1). Nucleotide excision repair is required for the repair of both platinum intrastrand adducts, whereas DNA mismatch repair system is specifically involved in the repair of cisplatin-induced adducts, being unable to recognize oxaliplatin-induced adducts (2). Yet, recognition of cisplatin-GG adducts by the MSH2/MSH6 complex plays a critical role in the toxicity of cisplatin, either by activating apoptosis or by causing futile cycles of translesion synthesis (3). Further, defects in mismatch repair are associated with resistance to cisplatin, but have no effect on the cytotoxicity of oxaliplatin. Altogether, these observations provide mechanistic explanations for the inability of ERCC1 polymorphisms to predict clinical outcome of patients with lung cancer receiving cisplatin.

2. The possible effect of smoking as a confounding factor may be relevant as far as lung cancer is concerned, but its involvement in colorectal cancer is much less likely.

It should be noted that we agree with Dr. Ryu on some of the raised matters, although we would like to provide our additional comments to his statements.

3. It is difficult to disagree on the statement that the larger the study, the stronger the conclusions. Indeed, we have encouraged other groups to perform independent investigations on large series of patients with colorectal cancer receiving oxaliplatin. Our article concludes with the proposal that the ERCC1 codon 118 polymorphism may be useful as a marker “provided that our results were confirmed on larger prospective studies” (4).

4. Lastly, we agree that ERCC1 codon 118 polymorphism may not be directly involved. Yet, this possibility has largely been explained in the discussion of our article: “The possibility that the ERCC1 codon 118 polymorphism is in linkage disequilibrium with another ERCC1
mutation or polymorphism that directly affects its expression, or with another gene, cannot be ruled out. However, although genetic testing for the ERCC1 codon 118 polymorphism would be in this case an indirect predictor, it may still represent a valuable molecular marker to predict the response of metastatic cancer to oxaliplatin treatment” (4).

Throughout our article, we have been very cautious when discussing our data. Notably, we have never suggested that our results could directly be extrapolated to any other type of cancer, including lung cancer, or other platinum-based therapeutic agents, such as cisplatin.

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References
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