

ERCC1 and personalized medicine in lung cancer

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Abstract: Excision repair cross-complementing group 1 (ERCC1) is known to be a key player in nucleotide excision repair (NER) pathway. Its prognostic or predictive relevance has been extensively investigated in cancer patients including non-small-cell lung cancer. However, several questions should be addressed before its clinical application as biomarker for patient classification or guiding platinum treatment.

Keywords: Biomarker; excision repair cross-complementing group 1 (ERCC1); non-small-cell lung cancer; personalized medicine

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Introduction

Recently, great advances in molecular classification and development of new target drugs have occurred in diagnosis and treatment of lung cancer. However, benefit from these progresses is limited to a small number of lung cancer patients. Platinum is known to kill tumor cells through intra- or inter-strand cross links. For decades, it has been in the mainstay of treatment of lung cancer. Many proteins involved in DNA damage-response (DDR) machinery have a role in repairing the cross links by platinum (1). However, exact mechanism of DDR machinery is still elusive and needs to be further elucidated. Excision repair cross-complementing group 1 (ERCC1) has a crucial role in nucleotide excision repair (NER) pathway which is one of DDR machinery. So far, many studies have suggested that ERCC1 at levels of protein, messenger RNA or germline DNA could be a prognostic or predictive biomarker in non-small-cell lung cancer patients treated with platinum doublets, whereas contradictory results have been concurrently reported (2-7).

A recent report in *The New England Journal of Medicine* by Friboulet and colleagues addressed elegant validation of ERCC1 protein expression as a biomarker for adjuvant platinum-based chemotherapy and provided insights into methodological issue on its measurement (2).

For validation of the predictive or prognostic effect, 494 samples were obtained from two phase III adjuvant clinical trials as an independent set: National Cancer Institute of Canada Clinical Trials Group JBR.10 and Cancer and Leukemia Group B 9633 (8,9). These trials compared adjuvant platinum-based chemotherapy to surgery alone. Their study cohort and design were similar to those of testing set: International Adjuvant Lung Cancer Trial study (10). The ERCC1 protein expression was measured by 8F1 antibody. However, authors failed to validate prognostic or predictive relevance of ERCC1 protein expression in the independent set (P=0.62 for ERCC1 negative tumors; P=0.09 for ERCC1 positive tumors). They postulated possible explanations for the failure. First, discordance of ERCC1 H score between old and new batches of the 8F1 antibody was observed in 36% of the patients and could cause false classification of the patients. Therefore, the authors suggested that precise information on antibody including batch number was needed for publication of future studies of immunohistochemical biomarker. Second, four ERCC1 protein isoforms were heterogeneously expressed by alternative splicing in tumor samples. These isoforms had different functions in repairing platinum-DNA adduct. Therefore, this also could cause the misclassification of the tumors in testing

and validation sets where the isoforms were not examined. Future development of specific antibody for functional isoform (ERCC1-202) is required to predict the benefit from platinum more accurately.

Although this study provided insightful information on ERCC1 protein isoforms as potential biomarker, several questions have to be resolved before clinical application for patient classification or guiding platinum treatment. ERCC1 is just one player among many proteins involved in the NER pathway. Moreover, the cross links can be repaired by other pathways involved in DDR machinery rather than NER pathway. Thus, it might be less reasonable to extrapolate the repair capacity from the single ERCC1 protein expression, even its isoforms. Furthermore, recent advances in high throughput technology and system biology can facilitate the identification of other players and their meaningful interactions. In addition, it is required to develop clinically applicable tool that measures the repair capacity as a whole. Finally, well-known, but hard problems still exist in clinical application of immunohistochemical biomarker in terms of reproducibility, specificity and accuracy.

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