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TUMOR BIOLOGY AND HUMAN GENETICS

Differential expression of DNA repair machinery genes in normal bronchial tissue and non-small cell lung cancer (NSCLC)

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Abstract

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Background: Genes involved in DNA repair and/or replication have been recently investigated as predictive markers of response to chemotherapy in NSCLC. However, few data on the expression of these genes in NSCLC tumor samples versus corresponding normal lung are currently available. Aim of this study was to evaluate differential mRNA levels of 22 DNA repair genes belonging to 5 different DNA

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repair pathways: direct (DR), base excision (BER), nucleotide excision (NER), double strand break (DSBR) and post-replicative (PRR) repair. In addition, 6 genes involved in DNA replication (REP) and 2 telomere maintenance (TM) genes were also investigated. **Methods:** Total RNA was extracted from fresh snap-frozen tumors and corresponding normal tissues from 50 consecutive chemo-naive resected NSCLC patients. Transcript levels were quantified by Real-Time PCR (TaqMan), fold changes were calculated with the 2- $\Delta\Delta C_t$ method and statistical significance assessed by Wilcoxon's test. POLR2A and 18SrRNA were used as reference genes and normal specimens as calibrators. **Results:** A significant overexpression in 13 out of 22 (60%) DNA repair and in 7 out of 8 (88%) REP and TM genes was detected (all $p < 0.0001$). Three out of 22 (14%) DNA repair genes were instead significantly down-expressed. Interestingly, among DNA repair pathway, DSB genes were those with the highest overexpression rate, and high transcript levels were significantly associated with tumor grade and male gender. BRCA1, BRCA2, XRCC3, XRCC5, uracil-DNA glycosylase, thymidylate synthase and topoisomerase DNA III β (TOPIII β) genes were correlated with poor prognosis at univariate, while at multivariate analysis only TOPIII β ($p = 0.02$) and tumor grade ($p = 0.04$) were retained as independent prognostic markers adjusting for major clinico-pathological parameters. **Conclusion:** This pivotal study shows that the overexpression of DNA repair genes in lung tumors are correlated with a more aggressive phenotype. Moreover, DNA repair genes (TOPIII β especially) should be further investigated as candidate prognostic markers in NSCLC.

Author Disclosure

Employment or Leadership	Consultant or Advisory Role	Stock Ownership	Honoraria
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