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Invitation to review a manuscript for Respiratory Research -RERE-D-15-00051

From: **Massimo Di Maio** (em@editorialmanager.com)
Sent: Thu 3/05/15 5:28 AM
To: Shicheng Guo (shicheng.guo@hotmail.com)

RERE-D-15-00051
Quantitative Analysis of mRNA Expression Levels and DNA Methylation Profiles of Three Neighboring Genes: FUS1, NPRL2/G21 and RASSF1A in Non-small Cell Lung Cancer Patients
Respiratory Research

Dear Dr. Shicheng Guo,

I would like to invite you to review the manuscript above which has been submitted to Respiratory Research. Further details including the full abstract can be found at the end of this email.

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the next three days. If you are unable to review the manuscript, we would be most grateful if you could suggest alternative reviewers.

Thank you for your time, and I look forward to hearing from you.

Best wishes,

Massimo Di Maio
Respiratory Research
http://respiratory-research.com/

RERE-D-15-00051
Research
Quantitative Analysis of mRNA Expression Levels and DNA Methylation Profiles of Three Neighboring Genes: FUS1, NPRL2/G21 and RASSF1A in Non-small Cell Lung Cancer Patients
Respiratory Research

Abstract: Background. Tumor suppressor gene (TSG) inactivation plays a crucial role in carcinogenesis. FUS1, NPRL2/G21 and RASSF1A are TSGs from LUCA region at 3p21.3, a critical chromosomal region in lung cancer development. The aim of the study was to analyze and compare the expression levels of these 3 TSGs in NSCLC, as well as in macroscopically unchanged lung tissue surrounding the primary lesion, and to look for the possible epigenetic mechanism of TSG inactivation via gene promoter methylation. Methods. Expression levels of 3 TSGs and 2 DNA methyltransferases, DNMT1 and DNMT3B, were assessed using real-time PCR method (qPCR) in 59 primary non-small cell lung tumors and the matched macroscopically unchanged lung tissue samples. Promoter methylation status of TSGs was analyzed using methylation-specific PCRs (MSP method) and Methylation Index (MI) value was calculated for each gene.
Results. The expression of all three TSGs were significantly different between NSCLC subtypes: RASSF1A and FUS1 expression levels were significantly lower in squamous cell carcinoma (SCC), and NPRL2/G21 in adenocarcinoma (AC). RASSF1A showed significantly lower expression in tumors vs macroscopically unchanged lung tissues. Methylation frequency was 38-76%, depending on the gene. The highest MI value was found for RASSF1A (52%) and the lowest for NPRL2/G21 (5%). The simultaneous decreased expression and methylation of at least one RASSF1A allele was observed in 71% tumor samples. Inverse correlation between gene expression and promoter methylation was found for FUS1 (rs=-0.41) in SCC subtype. Expression levels of DNMTs were significantly increased in 75-92% NSCLCs and were significantly higher in tumors than in normal lung tissue. However, no correlation between mRNA expression levels of DNMTs and DNA methylation status of the studied TSGs was found.
Conclusions. The results indicate the potential role of the studied TSGs in the differentiation of NSCLC histopathological subtypes. The significant differences in RASSF1A expression levels between NSCLC and macroscopically unchanged lung tissue highlight its possible diagnostic role in lung cancer in situ recognition. High percentage of lung tumor samples with simultaneous RASSF1A decreased expression and gene promoter methylation indicates its epigenetic silencing. However, DNMT overexpression doesn't seem to be a

critical determinate of its promoter hypermethylation.