Peripheral Blood DNA Methylation as Potential Biomarker of Malignant Pleural Mesothelioma in Asbestos-Exposed Subjects


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Abstract

INTRODUCTION:
Malignant pleural mesothelioma (MPM) is an aggressive tumor strongly associated with asbestos exposure. Patients are usually diagnosed when current treatments have limited benefits, highlighting the need for noninvasive early diagnostic tests to monitor asbestos-exposed people.

METHODS:
We used a genome-wide methylation array to identify, in asbestos-exposed subjects, novel blood DNA methylation markers of MPM in 163 MPM cases and 137 cancer-free controls (82 MPM cases and 68 controls, training set; replication in 81 MPM cases and 69 controls, test set) sampled from the same areas.

RESULTS:
Evidence of differential methylation between MPM cases and controls was found (more than 800 cytosine-guanine dinucleotide sites, false discovery rate p value (pfdr) < 0.05), mainly in immune system-related genes. Considering the top differentially methylated signals, seven single-cytosine-guanine dinucleotides and five genomic regions of coordinated methylation replicated with similar effect size in the test set (pfdr < 0.05). The top hypomethylated single-CpG (cases versus controls effect size less than -0.15, pfdr < 0.05 in both the training and test sets) was detected in FOXK1 (Forkhead-box K1) gene, an interactor of BAP1 which was found mutated in MPM tissue and as germline mutation in familial MPM. In the test set, comparison of receiver operating characteristic curves and the area under the curve (AUC) of two models, including or excluding methylation, showed a significant increase in case/control discrimination when considering DNA methylation together with asbestos exposure (AUC = 0.81 versus AUC = 0.89, DeLong's test p = 0.0013).

CONCLUSIONS:
We identified signatures of differential methylation in DNA from whole blood between asbestos exposed MPM cases and controls. Our results provide the rationale to further investigate, in prospective studies, the potential use of blood DNA methylation profiles for the identification of early changes related to the MPM carcinogenic process.

KEYWORDS:
Asbestos exposure; Case-control discrimination; DNA-methylation; Early biomarker; Malignant pleural mesothelioma