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Methylation of IGFBP-3 in liquid biopsy is a predictive biomarker of chemotherapy and immunotherapy response in non-small cell lung cancer

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Introduction: Methylation status of IGFBP-3 promoter in tumor tissues was associated with response to chemotherapy. Considering the limitations to obtain tumor tissue of patients, the possibility of analyzing the methylation of this gene in liquid biopsy is of great value.

Objectives: The aim of this work was to assess the clinical value of analyzing IGFBP-3 methylation in liquid biopsy (plasma) to predict response to therapy in advanced non-small cell lung cancer (NSCLC) patients.

Methods: The methylation of IGFBP-3 was analyzed in 21 plasma samples collected prior to chemotherapy or immunological treatment based on anti-PD-1/anti-PD-L1. The response to therapy was evaluated by computed tomography (CT). After plasma DNA conversion by bisulfite, methylation was analyzed by quantitative methylation-specific PCR (qMSP).

Results: Plasma methylation levels of IGFBP-3 (% methylation) before starting chemotherapy treatment were significantly higher (p=0.02) in patients with disease progression after the treatment (N=8; mean±SD: 37.00%±23.80%) than those with disease stabilization (N=6; mean±SD: 13.22%±9.11%). Receiver operating characteristic (ROC) curve analysis showed that methylation of IGFBP-3 in plasma before chemotherapy has a high diagnostic accuracy to identify the patients whose disease will progress after chemotherapy treatment (AUC=0.88; 95%CI: 0.68-1.00; p=0.02). Considering a methylation cut-off for IGFBP-3 of 20.01% the highest combination of sensitivity and specificity to identify the progression of patients was 88% and 83%, respectively. With this cut-off, we obtained a positive predictive value (PPV) of 88% and a negative predictive value (NPV) of 83% to predict the response to chemotherapy. In addition, patients who responded to immunotherapy treatment showed a tendency to present higher levels of methylation (P=0.05) before starting treatment (N=4; mean±SD: 23.85%±12.19) than patients with stabilization or progression of the disease (N=3; mean±SD: 12.35%±1.49%)

Conclusions: The methylation status of IGFBP-3 in liquid biopsy before treatment allows to predict the response to chemotherapy and immunotherapy in patients with advanced non-small cell lung cancer (NSCLC). The results obtained in this work indicate that the methylation of IGFBP-3 promoter in liquid biopsy could be a biomarker with clinical value for precision oncology in lung cancer.

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