Clinical impact of pd-l1, junb, and cxcr4 expression in circulating tumor cells and extracellular vesicles derived from triple negative breast cancer patients

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Abstract

Background: Triple-Negative breast cancer (TNBC) accounts for 10-15% of all breast cancer (BC) cases and is the most aggressive subtype. These tumors tend to be more common in younger women, however available treatments are limited and often insufficient. Liquid biopsy is a non-invasive approach for identifying cancer biomarkers in body fluids providing valuable information for prognosis and therapeutic monitoring.

Objective: Our study aimed to evaluate the expression of Programmed Death Ligand 1 (PD-L1), an immune checkpoint molecule, JUNB, a transcription factor of the AP-1 family, and CXCR4, a chemokine receptor, in Circulating Tumor Cells (CTCs) and extracellular vesicles (EVs) from TNBC patients.

Methods: Our research enrolled 35 TNBC patients and 12 healthy donors. CTCs were isolated by ficoll density gradient centrifugation, followed by triple immunofluorescence experiments (CK/PD-L1/CD45 and CK/JUNB/CXCR4) and VyCAP platform analysis. Additionally, EVs were isolated with the Exo-Prep kit and characterized by transmission electron microscopy and Western blot analysis.

Results: CTCs were detected in 54.3% (19 out of 35) of all cases. PD-L1-positive CTCs were present in 47.4% of the CK-positive patients (9 out of 19). Additionally, JUNB-positive CTCs were identified in 63.2% of patients (12 out of 19) and CXCR4 in 47.4% (9 out of 19), with the (CK+JUNB+CXCR4+) being the most frequent phenotype. Analysis of the patients' clinicopathological data revealed that JUNB and CXCR4 expression in either CTCs or EVs was not associated with patients' outcome. However, the presence of (CK+PD-L1+CD45-) phenotype in CTCs was associated with shorter progression-free survival (PFS) (log-rank p=0.002, HR=13.9). Furthermore, PD-L1 overexpression in EVs (above the median observed in healthy donors) was observed in 22.9% of patients and was associated with significantly poorer PFS (log-rank p=0.038, HR=5,4). Interestingly, combined evaluation of the (CK+PD-L1+CD45-) phenotype in CTCs and the PD-L1 overexpression in EVs was also associated with worse clinical outcome (PFS: log-rank p=0.014, HR=6.7).

Conclusions: PD-L1 expression in CTCs and EVs is strongly associated with poorer clinical outcome of the patients. Furthermore, combined analysis of PD-L1 expression in CTCs and exosomes, offers a promising approach to identify TNBC patients at higher risk of relapse, while providing an interesting therapeutic target.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.