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Characterizing changes in expression of EMT and metabolic markers during hematogenous dissemination in breast cancer

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Epithelial to Mesenchymal Transition (EMT) and metabolic reprogramming contribute to cancer progression. Here we investigated changes in expression of EMT and metabolic markers during hematogenous dissemination of breast cancer. So, we have performed analysis of EMT (CKs and FOXC1) and metabolic (PGC-1a, COXIV and MCT4) markers in CTCs and tissue samples from naive non-metastatic patients (M0) and metastatic breast cancer patients undergoing therapy (M+). As results, FOXC1 expression was higher in primary tumors than in their correspondent metastases ($p=1.15e^{-4}$). Primary tumors of M+ patients had lower expression of CKs compared to primaries of M0 patients. Both EMT markers were less predominant in CTCs of M+ patients. CTC^{FOXC1+} in M+ patients was associated with HER-2+ primary (p=0.004) and T4 tumors (p=0.036). Positivity for markers of oxidative metabolism, PGC-1a and COXIV, was significantly higher in CTCs from both M0 and M+ groups when compared to MCT4, an aerobic glycolysis marker. M0 patients presenting CTC^{MCT4-} and $CTC^{PGC1a+/COXIV+}$ had shorter progression-free survival (p=0.026). In metastasis, PGC-1a expression was increased while MCT4 was decreased, in comparison to correspondent primary tumors. CTC count and expression of EMT markers changed in CTCs after neoadjuvant therapy while metabolic characteristics were maintained. PGC-1a was the only metabolic marker that presented positivity in CTCs before and after neoadjuvant treatment. This marker also showed increased expression in primary tumor post treatment in one patient. Low or no correlation between CTCs and tumors has been observed for all markers. In this sense, EMT and MET features can be observed in primary tumors and metastasis, respectively and these phenomena can be subjected to alterations by neoadjuvant treatment. The predominance of oxidative metabolism profile in CTCs and metastasis in contrast to aerobic glycolysis in primary tumor suggests that cancer cells reprogram their metabolism from an aerobic glycolysis profile to an oxidative metabolism in order to supply their energetic demand for hematogeneous dissemination. These events can be modulated by neoadjuvant therapy, pointing out metabolic pathways as potential target sites. Furthermore, metastasis is the most common cause *of* mortality in cancer patients. Therefore, characterization of processes that contribute for the dissemination of tumor cells represents an important approach for impairing colonization of new sites. Here we described changes in expression of EMT and metabolic markers using representative samples of different stages of breast cancer progression: CTCs, primary tumors and metastases. Our data point out CTCs and targeting metabolic pathway as additional therapeutic targets in breast cancer as well as the further investigation of HER2 and FOXC1 connections for understanding and modulation of EMT process in breast cancer.

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