Correlation between *COL1A1*, *COL1A2* and *ITGA/B*

Correlation between *COL1A1*, *COL1A2* and *ITGA/B* Genes Expression in Tamoxifen Resistant Breast Cancer Cell Lines and their Effect on Migration and Metastasis

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Abstract

Breast cancer is the most widespread type of cancer worldwide and in the Eastern Mediterranean Region (EMR), in addition to being the main reason of cancer mortality among women. Tamoxifen (TAM) has long been considered a primary therapeutic choice for breast cancer patients with estrogen receptor-positive (ER+) tumors. However, drug resistance and metastasis, have posed significant challenges to the effectiveness of TAM in the long term. In this study, the correlation between *COL1A1* and *COL1A2* genes expression and different integrin's *ITGA1*, *ITGA2*, *ITGA10*, and *ITGB1* genes expression in tamoxifen-resistant MCF-7 cell lines, in addition to their role on migration rates, were investigated. The wound healing assay and transwell migration assay were conducted to investigate the cell migration characteristics between tamoxifen-resistant and tamoxifen-sensitive MCF-7 cell lines. As well, gene expression analysis of all genes was

investigated. In addition, correlations between the genes on Breast Cancer Gene-Expression Miner v4.9 database and Kaplan-Meier plotter database were evaluated. *COL1A1* and *COL1A2*, which encode type I collagen, were found to be upregulated in TAM-R MCF-7 cell lines developed at concentrations 35(4) +1 µM , 35(6) µM and 50 µM of tamoxifen. In addition to the upregulation of cell adhesion molecules integrins *ITGA1*, *ITGA2*, *ITGA10*, and *ITGB1*, which encode proteins that bind to collagen type 1, leading to support of cell adhesion, survival, migration, and the development of drug resistance. The migration assay of TAM-R MCF-7 cell lines showed that the cells exhibited aggressive behavior and migrated in clusters, causing them to aggregate on each other and lead to more metastatic behavior. According to breast cancer patients' databases, the data analysis of gene expression of *SDC1*, *CDH1*, *ITGA2*, and *ITGA10* from Breast Cancer Gene-Expression Miner v4.9 database and genes expression of *COL1A1*, *SDC1*, *ITGA2*, *ITGB1*, *CDH1*, and *TGFB1* from Kaplan-Meier plotter of breast cancer patient's databases found that these genes were correlated to DMFS in breast cancer patients, and the overexpression of *COL1A1*, *ITGB1*, *SDC1* and *CDH1* are correlated to poor prognosis and more distant metastasis in breast cancer patients, while overexpression of *ITGA10*, *TGFB1*, *ITGA2* are correlated to better prognosis among DMFS breast cancer patients and lead to less distant metastasis.

Keywords: Breast Cancer, Collagen, Integrins, Metastasis, Tamoxifen Resist