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Quercetin and INT3 Inhibits Endocrine Therapy Resistance and Epithelial to Mesenchymal Transition in MCF7 Breast Cancer Cells

Authors : S. Pradhan, D. Pradhan, G. Tripathy

Abstract : Anti-estrogen treatment resistant is a noteworthy reason for disease relapse and mortality in estrogen receptor alpha (ERα)- positive breast cancers. Tamoxifen or estrogen withdrawal increases the dependance of breast malignancy cells on INT3 signaling. Here, we researched the contribution of Quercetin and INT3 signaling in endocrine resistant breast cancer cells. Methods: We utilized two models of endocrine therapies resistant (ETR-) breast cancer: tamoxifen-resistant (TamR) and long term estrogen-deprived (LTED) MCF7 cells. We assessed the migratory and invasive limit of these cells by Transwell assay. Expression of epithelial to mesenchymal transition (EMT) controllers and in addition INT3 receptors and targets were assessed by real-time PCR and western blot analysis. Besides, we tried in vitro anti-Quercetin monoclonal antibodies (mAbs) and gamma secretase inhibitors (GSIs) as potential EMT reversal therapeutic agents. At last, we created stable Quercetin over expessing MCF7 cells and assessed their EMT features and response to tamoxifen. Results:We found that ETR cells acquired an epithelial to mesenchymal transition (EMT) phenotype and showed expanded levels of Quercetin and INT3 targets. Interestingly, we detected higher level of INT3 however lower levels of INT31 and INT32 proposing a switch to targeting through distinctive INT3 receptors after obtaining of resistance. Anti-Quercetin monoclonal antibodies and the GSI PF03084014 were effective in obstructing the Quercetin/INT3 axis and in part inhibiting the EMT process. As a consequence of this, cell migration and invasion were weakened and the stem cell like population was considerably decreased. Genetic hushing of Quercetin and INT3 prompted proportionate impacts. Finally, stable overexpression of Quercetin was adequate to make MCF7 lethargic to tamoxifen by INT3 activation. Conclusions: ETR cells express abnormal amounts of Quercetin and INT3, whose actuation eventually drives invasive conduct. Anti-Quercetin mAbs and GSI PF03084014 lessen expression of EMT molecules decreasing cellular invasiveness. Quercetin overexpression instigates tamoxifen resistance connected to obtaining of EMT phenotype. Our discovering propose that focusing on Quercetin and/or INT3 warrants further clinical assessment as substantial therapeutic methodologies in endocrine-resistant breast cancer.

Keywords : quercetin, INT3, mesenchymal transition, MCF7 breast cancer cells
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