

Public Abstract

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Graduation Term:FS 2015

Department:Nursing

Degree:PhD

Title:Characterization of a Novel Regulator and Predictors of Sensitivity to TRAIL-Induced Apoptosis in Breast Cancer Cells

Mesenchymal triple negative breast cancer (TNBC) cells are very sensitive to tumor necrosis factor-related apoptosis inducing ligand (TRAIL) for reasons that are poorly understood. The purpose of this study was to characterize a negative regulator of TRAIL sensitivity in TNBC cells and potentially predictive biomarkers of TRAIL sensitivity in human TNBC. First, gp78, an ubiquitin ligase that facilitates endoplasmic reticulum-associated protein degradation, was found to negatively regulate TRAIL-induced caspases-3/7 activity and loss in viability independently of the unfolded protein response in the TNBC mesenchymal cell line MB231. Second, TNBC cell lines sensitive to drozitumab, a TRAIL pathway agonist, were found to express the mesenchymal markers vimentin and Axl. Vimentin and Axl were determined to be co-expressed in a publically available cDNA microarray dataset and by immunohistochemistry in human TNBC. These findings provide insight into a novel gp78-associated mechanism that governs sensitivity to TRAIL-induced apoptosis in breast cancer cells and demonstrate that the proteins vimentin and Axl may predict sensitivity to a TRAIL pathway agonist in TNBC and are identifiable in human TNBC, which reflects their potential utility in identifying patients who may benefit from a TRAIL pathway agonist. Collectively, these findings may aid in the selection of appropriate combinatorial therapies and the identification of TNBC-affected patients for treatment with a TRAIL pathway agonist.