Abstract

Triple Negative Breast Cancer (TNBC) being devoid of the hormonal receptors manifests a difficult challenge for different therapeutic approaches. As TRAIL (TNF Related Apoptosis Inducing Ligand) is known for its ability to cause damage specifically to the tumor cells. Whole transcriptome analysis of MDA-MB-231 cell line treated with rhTRAIL showed upregulation of more than 1.5fold in nine genes from the complement pathway. Kaplan-Meiers plotter showed Complement component 4B (CFB) to be positively corelated with relapse free survival in breast cancer patients. CFB was also observed to be co-related and co-expressed with TRAIL in TNBC patients. Because of the heterogenicity of breast tumor population, some cells are inherently resistant to TRAIL induced apoptosis. Via microarray analysis of the selected resistant cells, we observed CDH1 to be downregulated in the resistant cell population in comparison to the sensitive cells. Upregulation of CDH1 sensitized the resistant cells towards rhTRAIL mediated cell death. Another commonly used approach to increase the effectiveness of the TRAIL treatment is through combination therapy. Theophylline has a cytotoxic effect on the MDA-MB-231 cell line. It increased ROS production causing DNA damage and lipid peroxidation. We further observed theophylline to increase the level of TNFR1, thereby activating the caspase mediated apoptotic pathway. Moreover, rhTRAIL in combination with theophylline caused increased cell death in comparison to rhTRAIL or theophylline alone. Combination treatment increased the levels of DR5 in the rhTRAIL and theophylline treated cells. Therefore, we can conclude that CFB and CDH1 can be used as biomarkers for TRAIL therapy in breast cancer. Furthermore, rhTRAIL in combination with theophylline could be a possible alternative for breast cancer therapy.

Keywords: rhTRAIL, CFB, CDH1, DR4, DR5 and theophylline