Targeting Androgen Receptor and TRAIL: A Novel Treatment Paradigm for Breast Cancer

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BACKGROUND & OBJECTIVE: TRAIL (TNF-related apoptosis-inducing ligand) is a promising cancer therapeutic agent due to its minimal toxicity to normal tissues and remarkable apoptotic activity in tumors. However, most breast cancer cells are resistant to TRAIL-induced apoptosis. Our objectives are to investigate the underlying molecular mechanisms and to develop strategies to overcome such resistance. **METHODS:** To identify modulators of TRAIL-induced apoptosis, we carried out a genomewide siRNA screen. To validate the screening result, we either silenced or overexpressed the identified genes in various breast cancer cells and changes in growth and TRAIL-induced cell apoptosis were determined in vitro and in an orthotopic xenograft mouse model. Finally, we investigated whether small molecules targeting the identified genes improve the effectiveness of TRAIL-therapy. **RESULTS:** We unexpectedly identified androgen receptor (AR) to be responsible for TRAIL resistance. While AR is classically viewed as the key factor in prostate cancer progression, we found that AR expression levels were markedly elevated in human invasive breast cancer specimens including triple-negative breast cancers (TNBC) that are highly aggressive with poor prognosis. Importantly, breast cancer cell lines express different levels of AR that correlated with their TRAIL resistance. AR overexpression in MDA-MB-231 and MDA-MB-436 cells suppressed the TRAIL sensitivity whereas knockdown of AR rendered MCF-7 and MDA-MB-453 cells sensitive to TRAIL-induced apoptosis. AR overexpression also induced TRAIL resistance in breast tumors in vivo. Further, we observed an upregulation of the TRAIL receptor, Death Receptor 5 (DR5) in breast cancer cells, following the removal or inhibition of AR by its antagonists Casodex and MDV3100. Treatment with AR antagonists also enhanced TRAIL-induced breast cancer cell apoptosis. **CONCLUSION:** AR signaling suppresses TRAIL-induced breast cancer cell apoptosis, in part, by suppressing DR5 expression, and a combination of AR antagonists together with TRAIL may be a novel and effective therapy for TNBC (The project supported, in part, by the National Institutes of Health Grants R21CA193271 and R01HL116849; the National Natural Science Foundation of China Grants 31100595 and 31300683).