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Triple combination therapy for Triple Negative Breast Cancer: A focus on racial disparity

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Mortality from triple negative breast cancer (TNBC) is significantly higher in African American (AA) women compared to White American (WA) women emphasizing ethnicity as a major risk factor; however, the molecular determinants that drive aggressive progression of AA-TNBC remain elusive. Here, we demonstrate for the first time that AA-TNBC cells are inherently aggressive, exhibiting elevated growth, migration, and cancer stem-like phenotype compared to WA-TNBC cells. Meta-analysis of RNA-sequencing data of multiple AA- and WA-TNBC cell lines shows enrichment of GLI1 and Notch1 pathways in AA-TNBC cells. Enrichment of GLI1 and Notch1 pathway genes was observed in AA-TNBC. In line with this observation, analysis of TCGA dataset reveals a positive correlation between GLI1 and Notch1 in AA-TNBC and a negative correlation in WA-TNBC. Increased nuclear localization and interaction between GLI1 and Notch1 is observed in AA-TNBC cells. Of importance, inhibition of GLI1 and Notch1 synergistically improves the efficacy of chemotherapy in AA-TNBC cells. Combined treatment of AA-TNBC-derived tumors with GANT61, DAPT, and doxorubicin/carboplatin results in significant tumor regression, and tumor-dissociated cells show mitigated migration, invasion, mammosphere formation, and CD44+/CD24- population. Indeed, secondary tumors derived from triple-therapy-treated AA-TNBC tumors show diminished stem-like phenotype. Finally, we show that TNBC tumors from AA women express significantly higher level of GLI1 and Notch1 expression in comparison to TNBC tumors from WA women. This work sheds light on the racial disparity in TNBC, implicates the GLI1 and Notch1 axis as its functional mediators, and proposes a triple-combination therapy that can prove beneficial for AA-TNBC.

Biography

Dipali Sharma is a professor of Oncology in Johns Hopkins University, USA. Her research interest includes Oncology, Breast Cancer and Organ Specific Cancers.

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