GDF15, potential mediator of resistance and disease progression in breast cancer

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Statement of the Problem: Breast cancer-related deaths are due primarily to drug-resistant, metastatic disease. Identification of molecular mechanisms mediating resistance and invasion will allow new targeted therapies to be developed. Growth differentiation factor 15 (GDF15) is an inflammatory cytokine overexpressed in many types of solid tumors, including breast. Past studies have linked high GDF15 levels with HER2 overexpression, drug resistance and cancer stem cell-like characteristics.

Methods: By IHC and informatics, we examined GDF15 in breast tumor tissues and correlated with clinical characteristics or outcomes. Using 2-d and 3-d cellular assays, we examined the role of GDF15 in breast cancer cell proliferation, epithelial mesenchymal transition (EMT), spheroid growth and invasion. Molecular studies, including genetic knockdown and pharmacological inhibition paired with western blotting and PCR, examined the mechanisms through which GDF15 promoted breast cancer cell invasion.

Findings: High GDF15 is associated with high tumor grade, ER-negative status and HER2 overexpression. Stable GDF15 transfection induces EMT and invasion. Upregulation of transcription factor FoxM1 with subsequent induction of target matrix metalloproteinases (MMPs) is required for GDF15-mediated effects, as FoxM1 knockdown and MMP inhibition rescues invasion and EMT. Further, GDF15 knockdown or pharmacological blockade significantly inhibits invasion of HER2-overexpressing and triple-negative breast cancer cells.

Conclusion & Significance: These findings support further preclinical investigation of the role of GDF15 in breast cancer progression and development of GDF15-targeted therapies for breast cancer treatment.

Speaker Biography

Rita Nahta is an expert in breast cancer pharmacology. She has published extensively on mechanisms of resistance to targeted therapies in breast cancer, with a focus on kinase signaling cross talk and novel combination approaches to treating drug-resistant breast cancer.

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