Maansi Solanky
Medical Student
LSUHSC School of Medicine, New Orleans, LA

Mentor: Suresh K. Alahari, PhD, FAAS, FASCB
LSUHSC Department of Biochemistry and Molecular Biology, Stanley S. Scott Cancer Center

"Deciphering the Interplay Between SPDEF Expression and Breast Cancer Subtype Heterogeneity"

Background: Breast cancer remains the most diagnosed non-cutaneous malignancy and second leading cause of cancer-related deaths in women in the United States. Despite advances in targeted therapy, heterogeneity in treatment response and survival persists, particularly among tumors of the Basal PAM-50 subtype. The transcription factor SPDEF has been variably implicated in luminal differentiation and tumor progression across numerous types. We aimed to clarify the prognostic value of SPDEF among breast cancers, characterize demographic and molecular correlates of its expression, and investigate epigenetic mechanisms that may underlie its dysregulation.

Methods: Genomic and clinical data for 1,218 breast cancer tumors were obtained from The Cancer Genome Atlas (TCGA). SPDEF mRNA expression was compared across intrinsic PAM-50 subtypes, age, and race, with prognostic significance evaluated by Kaplan–Meier analysis. Promoter methylation patterns and DNA methyltransferase (DNMT) expression were examined as potential regulatory drivers. Co-expression analysis was performed using gene panels representing luminal differentiation, basal identity, EMT, proliferation, DNA repair, and immune signaling.

Results: Low SPDEF expression was significantly associated with worse overall, relapse-free, and metastasis-free survival across all breast cancers. Expression was lowest in Basal tumors, as well as among younger and Black or African American patients. Promoter methylation at six CpG islands correlated with both reduced SPDEF expression and inferior survival, and DNMT1, DNMT3A, and DNMT3B overexpression also aligned with poor prognosis and Basal enrichment. Co-expression analysis revealed that SPDEF downregulation coincided with loss of luminal markers and increased EMT, proliferation, DNA repair, and immune pathways.

Conclusions: SPDEF functions as a tumor suppressor in breast cancer, with reduced expression linked to poor outcomes, aggressive molecular features, and epigenetic regulation. These findings highlight SPDEF and DNMT-driven methylation as potential prognostic biomarkers for enhanced risk stratification and targets for novel therapies, particularly in Basal breast cancers.