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"Investigating Tumor Suppressor Function and Regulatory Control of NISCH in Breast Cancer"

Background: Nischarin (NISCH) is a cytosolic protein that participates in a multitude of cellular processes, most notably, interacting with integrin α5β1 and other major regulatory proteins to influence cell adhesion, migration, cytoskeleton, and vesicle trafficking. The NISCH locus is mapped to chromosome 3p21, a region commonly associated with several cancers such as ovarian, breast, lung, and kidney. Evidence currently profiles NISCH as a novel tumor suppressor gene, however, its specific role in breast cancer is still relatively underexplored. This study aimed to investigate patterns between NISCH expression and breast cancer prognosis, and explore potential regulatory mechanisms by integrating NISCH expression, promoter methylation, and copy number alteration data.

Methods: Data was acquired for NISCH from the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) and The Cancer Genome Atlas (TCGA) via UCSC Xena and cBioPortal, including expression levels of NISCH and several DNA methyltransferases (DNMTs), promoter methylation beta values, copy-number values, demographic variables, and clinical data. All retrospective analyses were performed using GraphPad Prism.

Results: High expression of NISCH was significantly associated with improved overall survival in breast cancer, as well as longer distant metastasis-free survival and relapse-free survival. When comparing demographics, a lower expression of NISCH was observed in patients diagnosed at younger ages, within the Basal PAM-50 subtype, and among the Asian race. Certain CpG islands were identified proximal to the promoter region and showed both a negative correlation with NISCH expression, as well as elevated methylation in tumor samples. Co-expression studies revealed inverse correlations between three DNMTs and NISCH, indicating possible involvement in the silencing of the gene. Furthermore, shallow deletions at the NISCH locus correlated with reduced mRNA expression and were linked to poorer survival outcomes.

Conclusions: Together these findings support NISCH's profile as a tumor suppressor in breast cancer, with high mRNA expression consistently linked to better survival outcomes across multiple clinical metrics. Moreover, identifying lower NISCH expression in biologically aggressive subsets of breast cancer—the Basal PAM-50 subtype and younger age at diagnosis—enhances NISCH as a putative marker for poor prognosis. Both promoter methylation and shallow deletions reduced expression of NISCH, indicating that the locus may be regulated through several genomic and epigenetic mechanisms. Inverse expression patterns between NISCH and three DNMTs across similar demographic subsets provides additional evidence that promoter-methylation may drive the silencing process. Collectively, these findings strengthen the rationale for future functional studies to investigate the mechanisms controlling NISCH expression, and to evaluate its potential as a biomarker or therapeutic target in breast cancer.