


**Unravelling the Role of ZCCHC24 in Gastric Cancer**

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Background*:

RNA-binding proteins (RBPs) are critical regulators of Alternative Splicing (AS), controlling pre-mRNA processing by modulating spliceosome activity. Aberrant AS, often caused by dysregulated RBPs, contributes to tumor development and progression. A molecular subtype termed Claudin$^{low}$, characterized by reduced claudin expression, enrichment for epithelial-to-mesenchymal transition (EMT) markers, and tumor-initiating cell features, has been described in breast, bladder, and gastric cancer (STAD). Among dysregulated RBPs, ZCCHC24, containing a zinc finger CCHC-type domain, has emerged as a candidate oncogenic factor. While its molecular role remains poorly defined, ZCCHC24 has been implicated in breast tumorigenicity and correlated with poor survival in STAD patients.

Methods*:
To assess its function, ZCCHC24 was overexpressed in non-Claudin$^{low}$ gastric cancer cell lines and silenced via stable shRNA transfection in Claudin$^{low}$ cells. Cell proliferation, migration and invasion capability were analysed. RNA-Seq was performed to evaluate transcriptional changes, focusing on EMT programs, adhesion molecules, and metabolic pathways.

Results*:
ZCCHC24 overexpression reduced cell cycle proliferation but enhanced migratory ability. RNA-Seq revealed upregulation of EMT-associated genes and downregulation of adhesion molecules and cholesterol biosynthesis pathways, suggesting a trade-off between proliferative activity and invasive potential. Conversely, stable ZCCHC24 silencing impaired invasion and migration while restoring claudin expression. These findings highlight ZCCHC24 as a regulator balancing proliferation with activation of invasive programs in cancer.

Conclusion*:

Our study identifies ZCCHC24 as a crucial modulator of tumor aggressiveness in Claudin$^{low}$ gastric cancer. Its dual role in repressing proliferation while promoting EMT-driven invasiveness suggests potential as a prognostic biomarker. Further investigation into the interplay between ZCCHC24, RNA splicing dysregulation, and EMT-associated pathways may provide novel insights into tumor progression and offer opportunities for targeted therapeutic strategies.