Steroidogenic acute regulatory protein related lipid transfer domain containing-3 n-terminal like(STARD3NL) expression in clinical breast cancerand its connection with metastatic lymph node 64 (MLN64) in breast cancer

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Abstract

Introduction StarD3NL is an ER–endosome tethering protein involved in intracellular cholesterol transport and membrane organisation. Its paralogue MLN64 (StarD3) has known roles in cell adhesion and breast cancer biology, but the clinical significance of StarD3NL remains unclear. This study investigates StarD3NL expression and its association with clinical outcomes in breast cancer. **Methods** Transcript levels of StarD3NL were quantified by qPCR in a Cardiff breast cancer cohort. Associations with clinical–pathological variables and survival were analysed using Mann–Whitney U tests, logistic regression, and Kaplan–Meier survival analyses. **Results** StarD3NL expression was reduced in moderate/poor-prognosis cases and node-positive tumours (p = 0.046). Patients who developed breast cancer–related events had significantly lower StarD3NL levels (p = 0.0086). Low StarD3NL was associated with shorter DFS (p = 0.025, HR = 0.329), with a similar trend for OS. The prognostic link was stronger in HER2-positive, HER3-negative and non-TNBC subgroups. StarD3NL correlated with MLN64 in tumour (r = 0.410) and normal tissues (r = 0.679), with enhanced prognostic impact in MLN64-low tumours (DFS p = 0.009; OS p = 0.043). **Conclusion** StarD3NL is associated with breast cancer outcomes, particularly DFS in specific molecular subtypes, and its prognostic value appears linked to MLN64. Both proteins may serve as promising biomarkers for future prognostic development.

Introduction

StarD3NL (StAR Related Lipid Transfer Domain Containing-3 N-Terminal Like), also known as MENTHO, is an ER–endosome tethering protein that facilitates contact between the endoplasmic reticulum and late endosomes. Through this interaction, StarD3NL contributes to intracellular cholesterol trafficking from the ER to endosomal compartments and the plasma membrane, where cholesterol plays an essential role in organising membrane architecture and the function of integral membrane proteins. A closely related paralogue, MLN64 (also known as StarD3), performs a similar lipid-transport function and has been previously shown by our group to influence cancer cell adhesion and to hold clinical relevance in breast cancer outcomes. However, despite its structural similarity and potential functional overlap with MLN64, very little is known about the biological significance or clinical expression patterns of StarD3NL in breast cancer. This study aims to investigate StarD3NL expression in breast cancer tissues and to evaluate its potential associations with clinical and pathological outcomes.

Methods and Materials

Breast cancer and normal mammary tissue samples (total n = 151) from a Cardiff patient cohort with a 10-year clinical follow-up were analysed. Total RNA was extracted and StarD3NL transcript levels were quantified using quantitative PCR (qPCR) with gene-specific primers. Expression levels were compared across clinical and pathological groups. Statistical analyses were performed to assess associations between StarD3NL expression and clinicopathological factors. Group comparisons were conducted using the Mann–Whitney U test. Logistic regression models were applied to evaluate relationships between StarD3NL expression and clinical outcomes. Disease-free survival (DFS) and overall survival (OS) were assessed using Kaplan–Meier survival analysis with log-rank testing. Correlation between StarD3NL and MLN64 expression was examined using Pearson's correlation coefficient.

Results

StarD3NL expression was found to be lower in patients with moderate or poor prognosis compared with those with good prognosis, and was also reduced in node-positive tumours (p = 0.046). When examined in relation to clinical outcome, patients who later developed breast cancer–related events exhibited significantly lower StarD3NL levels than those who remained disease-free throughout follow-up (p = 0.0086). This was reflected in survival analysis, where reduced StarD3NL expression was associated with significantly shorter disease-free survival (DFS) (p = 0.025, HR = 0.329, 95% CI: 0.116–0.933). A similar trend was observed for overall survival (OS), although statistical significance was not reached. Stratified analyses indicated that the association between low StarD3NL and poorer DFS was more pronounced in HER2-positive, HER3-negative and non-TNBC subgroups, suggesting potential interactions with specific molecular signalling backgrounds. StarD3NL expression also showed a significant positive correlation with MLN64 in both breast cancer tissues (r = 0.410, p < 0.001) and normal mammary tissues (r = 0.679, p < 0.001). Notably, in tumours with low MLN64 expression, the prognostic impact of StarD3NL became more striking, demonstrating a stronger association with both DFS (p = 0.009) and OS (p = 0.043). These findings indicate that the clinical relevance of StarD3NL may be partially modulated by MLN64 expression status.

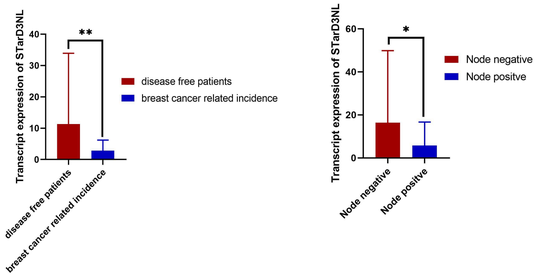
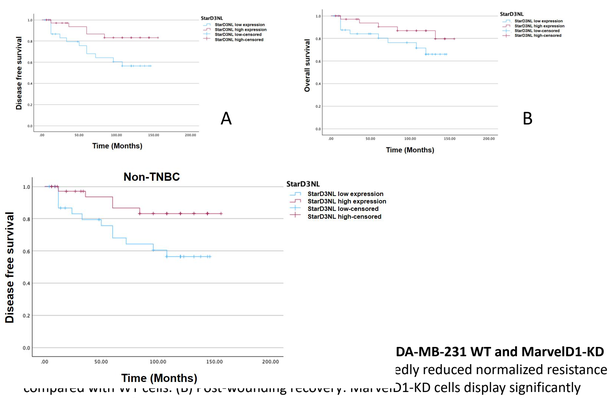


Figure 1. Overall survival (OS) analysis based on MarvelD1 expression in breast cancer. (A) Kaplan–Meier survival curve showing that high MarvelD1 expression is associated with significantly poorer OS. (B) In PR-negative tumours, high MarvelD1 expression is linked to reduced OS. (C) In HER3-positive tumours, high MarvelD1 expression predicts significantly worse survival. (D) In HER4-negative tumours, high MarvelD1 expression is similarly associated with poorer survival.

Discussion

This study provides new evidence that StarD3NL may hold clinical relevance in breast cancer. StarD3NL expression was consistently lower in patients with adverse prognostic features, including node-positive disease and those who later developed breast cancer–related events. Its reduced expression was also associated with significantly shorter disease-free survival, suggesting a potential tumour-suppressive or protective role. The stronger prognostic effect observed in specific molecular contexts—particularly HER2-positive, HER3-negative and non-TNBC tumours—indicates that the biological function of StarD3NL may depend on the underlying receptor-signalling environment.

The strong correlation between StarD3NL and its paralogue MLN64 further suggests coordinated regulation within cholesterol-transport or membrane-organisation pathways. Notably, the prognostic impact of StarD3NL became more pronounced in tumours with low MLN64 expression, raising the possibility that reduced activity of both proteins may synergistically contribute to impaired membrane function, altered cellular signalling, or more aggressive disease behaviour. These findings align with the known roles of MLN64 in cancer adhesion and progression and extend the concept to include StarD3NL as an additional contributor. Together, our results suggest that StarD3NL may have functional and prognostic relevance in breast cancer and that its interplay with MLN64 warrants further mechanistic investigation. Future studies exploring their combined roles in membrane dynamics, lipid transport, and tumour progression may provide new opportunities for biomarker development.



DA-MB-231 WT and MarvelD1-KD
edly reduced normalized resistance
compared with WT cells. (B) Post-wounding recovery. MarvelD1-KD cells display significantly slower recovery of monolayer integrity.

Figure 3. Chemosensitivity of MDA-MB-231 wild-type and MarvelD1-knockdown cells to four chemotherapeutic agents. Dose–response toxicity curves were generated for docetaxel (A), carboplatin (B), epirubicin (C) and paclitaxel (D) in MDA-MB-231 wild-type (WT) and MarvelD1-knockdown (KD) cells. Across all four agents, MarvelD1-KD cells exhibited a modest but consistent increase in drug sensitivity, shown by reduced viability and a downward shift of the response curves compared with WT cells.

Conclusions

StarD3NL appears to be significantly related to breast cancerpatient disease free survival, which was pronounced in HER2 positive and HER3 negative tumour types; moreover, this change was linked to MLN64expression. These data suggest that these two proteins could be an interesting target for future prognostic development.

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