MarvelD1 expression in breast cancer and the impact on the aggressive nature of breast cancer cells

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Abstract

Introduction MarvelD1 is a membrane-associated protein localizing at tight junction regions and potentially interacting with microtubules. Its functional role in cancer remains unclear and context-dependent. The role of MarvelD1 in human breast cancer has not been previously characterized. **Methods** MarvelD1 expression in breast cancer tissues was examined at transcript levels and correlated with clinicopathological variables and patient outcomes. Lentiviral shRNA was used to generate MarvelD1 knockdown breast cancer cell models. Effects on proliferation, migration, adhesion, and paracellular barrier function were assessed. **Results** MarvelD1 expression was significantly higher in breast tumors than in normal mammary tissues (p=0.023) and was elevated in HER2-positive tumors (p=0.0129). Triple-negative tumors showed the lowest expression. High MarvelD1 expression was associated with reduced overall survival (p=0.019, HR=0.304). This association was stronger in PR-negative, HER3-positive, and HER4-positive subgroups. MarvelD1 knockdown suppressed cell growth, weakened adhesion, and reduced migration. **Conclusions** MarvelD1 is clinically relevant in breast cancer, correlating with tumor subtype and patient survival. Functional studies support its role in promoting aggressive cancer cell phenotypes, indicating MarvelD1 and its signaling partners as potential therapeutic targets.

Introduction

MarvelD1 (MARVEL (MAL and related proteins for vesicle trafficking and membrane link) domain containing-1) is a four-pass transmembrane MARVEL-domain protein localized primarily at epithelial tight junctions, where it contributes to junctional stability, barrier integrity, and cell polarity. It interacts with scaffold proteins such as ZO-1/ZO-2 and can also translocate to the nucleus, suggesting both structural and regulatory functions, including potential roles in microtubule dynamics and cell cycle control. Dysregulation of MarvelD1 has been reported in various solid tumors, but its biological role appears context-dependent: it acts as a tumor suppressor in hepatocellular and colorectal cancers, yet shows oncogenic behavior in pancreatic and glioma models. Despite these observations, the functional significance and clinical impact of MarvelD1 in human breast cancer remain unknown. This study addresses this gap by examining MarvelD1 expression patterns in breast tumors and evaluating its influence on breast cancer cell behavior.

Methods and Materials

The expression of the MarvelD1 gene transcript in breast cancer patient cohort were investigated by quantitative gene transcript analysis. MarvelD1 expression was analysed against clinical outcome, pathological factors, hormone receptor status and molecular subtypes of the patients. We created breast cancer cell models by knockdown the MarvelD1 with anti-MarvelD1 shRNA delivered by lentiviral approach. The biological responses following MarvelD1 knockdown were assessed including the rate of cell growth, cellular migration, cell adhesiveness, drug resistance and potential paracellular barrier functions of the breast cancer cells.

Results

Breast tumour tissues exhibited significantly higher levels of MarvelD1 compared with normal mammary tissues (p = 0.023). ERBB2/HER2-positive tumours expressed higher MarvelD1 levels than HER2-negative tumours (p = 0.0129), while no significant differences were observed across hormonal receptor subtypes (ER and PGR status). Among the major molecular subtypes, triple-negative breast cancers demonstrated the lowest MarvelD1 expression. Clinically, patients with high MarvelD1 expression had significantly shorter overall survival (OS) than those with low expression (p = 0.019, hazard ratio (HR) 3.040, 95% confidence interval 1.113–8.18). Notably, the association between high MarvelD1 levels and poorer OS was more prominent in PGR-negative (p = 0.006), ERBB3/HER3-positive (p = 0.007) and ERBB4/HER4-negative (p = 0.026) tumours.

We successfully established lentiviral shRNA-mediated MarvelD1 knockdown breast cancer cell models and confirmed efficient knockdown at both the RNA and protein levels using qPCR and Western blotting. ECIS real-time impedance analysis showed that MarvelD1 depletion markedly reduced cell adhesion and impaired wound-healing dynamics in MDA-MB-231 cells, indicating compromised epithelial integrity and motility coordination. MTT-based proliferation assays further demonstrated that MarvelD1-deficient cells exhibited substantially slower growth compared with control cells. In addition, MarvelD1 knockdown increased the chemosensitivity of MDA-MB-231 cells to multiple therapeutic agents, including docetaxel, paclitaxel, epirubicin and carboplatin.

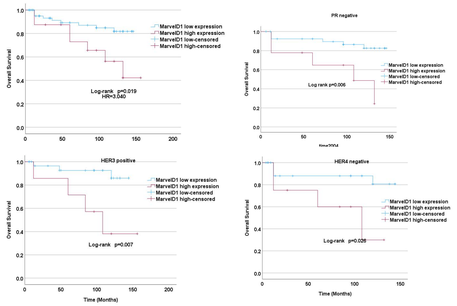


Figure 1. Overall survival (OS) analysis based on MarvelD1 expression in breast cancer. (A) Kaplan–Meier survival curve showing that high MarvelD1 expression is associated with significantly poorer OS. (B) In PR-negative tumours, high MarvelD1 expression is linked to reduced OS. (C) In HER3-positive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

Discussion

Our findings demonstrate that MarvelD1 is clinically important in breast cancer and may exert multifaceted influences on tumour biology. MarvelD1 expression is markedly elevated in breast tumour tissues and shows clear associations with HER2 status and molecular subtype patterns. Its relatively low expression in triple-negative breast cancers suggests subtype-specific regulatory mechanisms and potential functional divergence across tumour groups. Clinically, high MarvelD1 levels are linked to significantly poorer overall survival, with particularly strong prognostic value in PGR-negative, HER3-positive and HER4- negative tumours. These associations imply that MarvelD1 may interface with hormonal and HER/ERBB signalling pathways in shaping patient outcomes. Functional analyses further support a tumour-promoting role for MarvelD1. Knockdown of MarvelD1 impaired cell adhesion, migration and proliferation, indicating a disruption of epithelial integrity and reduced tumour cell fitness. These cellular effects align with the aggressive clinical phenotype observed in MarvelD1-high tumours. Moreover, MarvelD1 depletion increased sensitivity to multiple key chemotherapeutic agents, including docetaxel, paclitaxel, epirubicin and carboplatin, suggesting that MarvelD1 contributes to drug-response regulation, potentially through adhesion- or cytoskeleton-associated mechanisms.

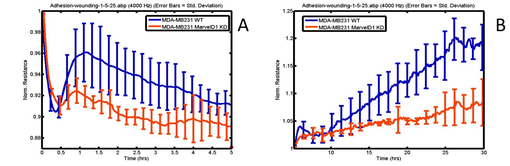


Figure 2. ECIS analysis of adhesion and wound recovery in MDA-MB-231 WT and MarvelD1-KD cells. (A) Early adhesion phase: MarvelD1-KD cells show markedly reduced normalized resistance compared with WT cells. (B) Post-wounding recovery: MarvelD1-KD cells display significantly slower recovery of monolayer integrity.

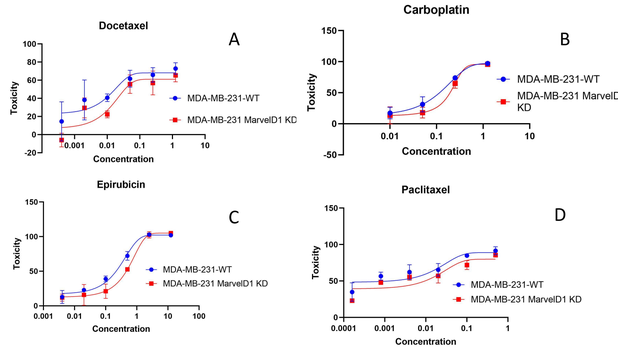


Figure 3. Chemosensitivity of MDA-MB-231 wild-type and MarvelD1-knockdown cells to four chemotherapeutic agents. Dose–response toxicity curves were generated for docetaxel (A), carboplatin (B), epirubicin (C) and paclitaxel (D) in MDA-MB-231 wild-type (WT) and MarvelD1-knockdown (KD) cells. Across all 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

MarvelD1, a membrane- and microtubule-associated protein, shows clinical relevance in breast cancer, with its expression linked to patient survival in a receptor-dependent manner. Functional studies indicate that MarvelD1 promotes malignant behaviours and decreases chemosensitivity. Together, these findings support MarvelD1 as both a prognostic marker and a contributor to breast cancer aggressiveness, highlighting its potential as a therapeutic target.

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