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Gastrin-releasing peptide receptor as a prognostic biomarker and mediator of doxorubicin resistance in breast cancer

Julia Caroline Marcolin[1], Martina Lichtenfels[2], Matheus Dalmolin[3], Camila Alves da Silva[2], Caroline Brunetto de Farias[2]

[1]Universidade Federal do Rio Grande do Sul, Programa de Pós-Graduação em Farmacologia e Terapêutica – Porto Alegre (RS), Brazil.
[2]Ziel Biosciences – Porto Alegre (RS), Brazil.
[3]Universidade Federal do Rio Grande do Norte, Laboratory of Machine Learning and Intelligent Instrumentation – Natal (RN), Brazil.

Objective: This study aimed to verify the expression and prognostic implications of gastrin-releasing peptide receptor (GRPR) in breast cancer by analyzing multiple cancer-related databases and complementary in vitro assays. **Methods:** GRPR expression and its association with prognosis in breast cancer were assessed using different databases: OncoDB, Gent2, and GEPIA. In vitro experiments were performed using MCF-7 and MDA-MB-231 breast cancer cell lines, both naïve and treated with cytotoxic drugs. GRPR expression and cell viability were assessed to investigate potential roles in drug resistance. **Results:** Bioinformatics analysis revealed overexpression of GRPR in breast cancer compared to healthy tissue. GRPR expression positively correlated with estrogen receptor and low-grade tumors ($p<0.001$). Among molecular subtypes, luminal A exhibited the highest levels of GRPR, followed by luminal B, human epidermal growth factor receptor-type 2-positive (HER2+), triple-negative breast cancer (TNBC), and basal. Prognostic analysis using the Gent2 database indicated that higher GRPR expression was associated with improved overall survival ($p=0.004$). However, GEPIA analysis did not confirm a statistically significant survival difference. In vitro, both cell lines treated with doxorubicin showed decreased viability ($p<0.0001$), along with a significant increase in GRPR expression, with a fold change of 5.7 ($p<0.0001$) for MCF-7 and 2.7 ($p=0.007$) for MDA-MB-231, suggesting that surviving cells express higher levels of GRPR. This pattern was not observed with cyclophosphamide, indicating a potential role of GRPR in acquired resistance to doxorubicin. **Conclusion:** GRPR expression is associated with estrogen receptor positivity and may indicate a favorable prognosis in breast cancer. Nonetheless, its upregulation following doxorubicin exposure suggests a potential role in chemoresistance. The findings support GRPR as a promising biomarker for prognosis and a potential therapeutic target, particularly in the context of resistance to anthracycline-based chemotherapy.

Keywords: breast neoplasm; gastrin-releasing peptide; drug resistance.