

Research Paper

USP37 downregulation elevates the Chemical Sensitivity of Human Breast Cancer Cells to Adriamycin

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Abstract

Background: The evolution of adriamycin (ADR) resistance in the treatment of breast cancer often leads to a poor prognosis in patients. Ubiquitin-specific peptidase 37 (USP37) has been recently identified as a modulator in regulating the stemness of breast cancer cells, but its underlying mechanism remains unclear. In this study, we investigated whether USP37 knockdown could hamper the chemical resistance of MCF-7 and MCF-7/ADR cells to adriamycin and elucidated the potential mechanism.

Methods: Immunohistochemistry, western blotting, and RT-qPCR assays were performed to detect the USP37 expression in MCF-7 and MCF-7/ADR cells. The efficiency of USP37 knockdown in breast cancer cells was confirmed by western blotting and RT-qPCR assays. We also performed CCK-8 assay, flow cytometry, western blotting, and TUNEL assays to evaluate cell viability and apoptosis in breast cancer cells. *In vivo* study was performed to detect the tumorigenicity of MCF-7/ADR cells transfected with shScramble or shUSP37#1 under adriamycin treatment.

Results: Bioinformatic analysis indicated that USP37 overexpression was positively correlated with adriamycin resistance. The expression levels of USP37 in both MCF-7 and MCF-7/ADR cells increased significantly with the exposure to adriamycin in a dose-dependent manner. It was verified by the observation that USP37 downregulation elevated the inhibitory effects of adriamycin on breast cancer cells, suppressed cell proliferation caused by cell cycle arrest in G1/S transition, as well as induced apoptosis. Furthermore, *in vivo* study showed that knockdown of USP37 expression also decreased tumorigenicity of MCF-7/ADR cells in mice. TUNEL assay and observation of cell morphology magnified USP37 knockdown synergized with Adriamycin could elevate the apoptosis of MCF-7 and MCF-7/ADR cells. Western blotting assay illustrated that the combination of USP37 knockdown with adriamycin treatment significantly upregulated the expression levels of cleaved caspase 3 and Bax, whereas the expression level of Bcl-2 was inhibited.

Conclusion: Knockdown of USP37 gene expression can reverse the resistance of breast cancer cells to adriamycin, and down-regulating USP37 might be a valuable strategy against ADR resistance in breast cancer therapy.

Key words: USP37; Adriamycin; Breast cancer; Bcl-2; Bax.

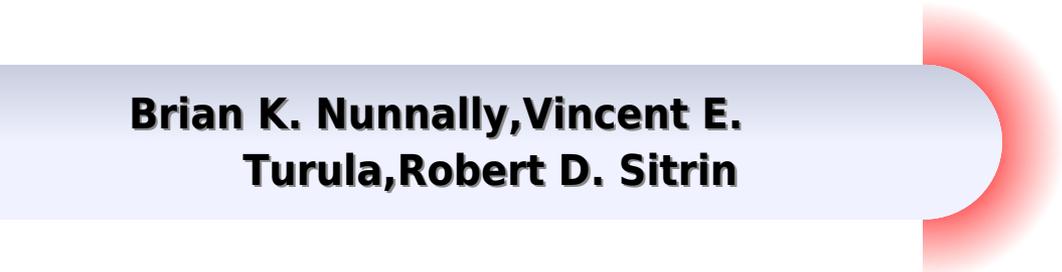
Introduction

Breast cancer is one of the most prevalent malignancies and is the second leading cause of

cancer-related deaths, exerting severe threat on females' health [1]. According to GLOBOCAN2018

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