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TRIM58 inactivates p53/p21 to promote chemoresistance via ubiquitination of DDX3 in breast cancer

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ABSTRACT

Chemotherapy resistance is that the most important reason behind of carcinoma treatment failure but the underlying molecular mechanisms are unclear. Members of the tripartite motif—containing protein (TRIM) family play crucial roles in the carcinogenesis and development of resistance against chemotherapy. Herein, we first confirmed that TRIM58 is highly expressed in triple-negative breast cancer tissues and drug-resistant MCF7/ADR cells. Furthermore, TRIM58 knockdown resulted in increased sensitivity of MCF7/ADR cells toward doxorubicin *in vitro* and *in vivo*. In contrast, TRIM58 overexpression in breast cancer cells increased doxorubicin resistance. TRIM58 was found to interact with DDX3, a protein recently reported to modulate resistance against chemotherapy. We found that TRIM58 negatively regulates DDX3 expression downstream of the P53/P21 pathway, and that DDX3 is degraded by TRIM58-mediated ubiquitination. Knockdown of DDX3 reversed doxorubicin chemotherapy sensitivity induced by TRIM58 knockdown *via* the P53/P21 pathway.Our study reveals that TRIM58 mediates a novel mechanism underlying the development of resistance against chemotherapy in breast cancer and provides potential targets for developing novel therapeutic targets for breast cancer.

1. Introduction

The most common cancer in the world is breast cancer and its incidence is increasing annually, with the highest mortality rate in women with malignant tumors (Sung et al., 2021; Peng et al., 2020). Early diagnosis, the development of surgical methods, chemotherapy, and radiation treatment can significantly reduce mortality and improve survival in patients with breast cancer (Harbeck and Gnant, 2017). Doxorubicin (DOX), an anthracycline DNA implanter, is widely used as a neoadjuvant chemotherapy agent to treat breast cancer (Dai et al., 2019). However, because of the heterogeneity of breast tumors, 30–50% of patients develop drug resistance, resulting in the failure of doxorubicin therapy (Alessandrini et al., 2018). Although the main causes of tumor chemotherapy resistance are known to include high expression of ATP-binding cassette transporters, signaling pathways, drug resistance genes, and tumor microenvironments, the specific mechanism underlying the development of chemotherapy resistance in breast cancer remains unclear (DeMichele et al., 2017). Studies are required to understand the molecular mechanisms underlying the development of drug resistance in breast cancer.

The tripartite motif (TRIM) protein family is a rather large protein family with more than 80 members (Jaworska et al., 2019). TRIMs have similar domain architectures and harbor a RING domain, one or two B-box domains, and a coiled-coil domain. Recent studies indicated that deregulated ubiquitin-mediated degradation of oncoproteins or tumor suppressors is related to the development of chemotherapy resistance in tumors (Di Rienzo et al., 2020). E3 ubiquitin ligase, an important component of the ubiquitin-proteasome system, shows potential to be a diagnostic and therapeutic target for breast cancer (Zhao et al., 2020; Zheng and Shabek, 2017; Pohl and Dikic, 2019). Most TRIMs exhibit E3 ubiquitin ligase activity because of their RING domain (Wang and Hur, 2021). Previous studies revealed that changes in expression may disrupt the balance of TRIM proteins within the cell and alter the ubiquitination of various proteins, resulting in irregular cell signal and development of

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