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ZEB1 confers chemotherapeutic resistance to breast cancer by activating ATM

Shuang Yang
Nankai University, China

Statement of the Problem: Although zinc finger E-box binding homeobox 1 (ZEB1) has been identified as a key factor in the regulation of breast cancer differentiation and metastasis, its potential role in modulating tumor chemoresistance has not been fully understood.

Methodology & Theoretical Orientation: The expression of ZEB1 and its correlation with breast cancer chemoresistance was investigated through the study of specimens from a large cohort of human breast cancer subjects. The effect of ZEB1 on DNA damage response was studied using the HR reporter DR-GFP system.

Findings: Our results demonstrated that patients with tumors that expressed high levels of ZEB1 responded poorly to chemotherapy. Moreover, ZEB1 expression was positively correlated with the expression of B cell lymphoma–extra-large (Bcl-xL) and Cyclin D1, which are key components of tumor chemoresistant mechanisms. Mechanistically, ectopic ZEB1 impairs the responsiveness of breast cancer cells to genotoxic drug treatment. During this process, ZEB1 transcriptionally activates the expression of ataxia-telangiectasia mutation (ATM) kinase by forming a ZEB1/p300/PCAF complex on its promoter, leading to increased homologous recombination (HR)-mediated DNA damage repair and the clearance of DNA breaks. Thus, inhibition of ATM activity attenuated the effect of ZEB1 on cell growth inhibition and restored cell sensitivity to genotoxic drug treatment. We further confirmed ZEB1-induced resistance of breast cancer to genotoxic drug using a nude mouse xenograft. Notably, specific downregulation of ZEB1 by a natural compound, Biochanin A, demonstrated chemosensitizing potency in vitro and in vivo.

Conclusion & Significance: Our findings suggest that ZEB1 is a crucial determinant of chemotherapeutic resistance in breast cancer. Thus, ZEB1-targeting agents, such as Biochanin A, have the potential to be used as tumor chemosensitizers. Moreover, various ATM inhibitors are being tested in anticancer treatment, which warrant investigation as candidate chemosensitizing agents for breast cancer with high levels of ZEB1.

Biography

Shuang Yang has her expertise in the research area of tumor pathologic mechanism and epigenetic regulation. In recent years, she has been working on elucidating the potential role of ZEB1, a key regulator of epithelial-to-mesenchymal transition, in breast cancer growth, metastasis, recurrence, and therapeutic resistance. Through the studies of specimens from large cohort of human breast cancer subjects and ZEB1 transgenic/knockout mouse models, etc., her work has demonstrated that ZEB1 plays important roles in the acquisition of malignant properties of cancer cells via a combination of genetic, epigenetic, and transcriptional controls. The research (as Principle Investigator) has been supported by grants from the National Natural Science Foundation of China, the International S&T Cooperation Program of China, Ministry of Science and Technology of China, and the Program for New Century Excellent Talents in University, Ministry of Education of China, etc.

yangshuang@nankai.edu.cn

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