ERβ sensitizes NSCLC cells to chemotherapeutic agents by regulating DNA damage response

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The expression of wild-type estrogen receptor β (ERβ1) correlates with increased survival in patients with Non-Small Cell Lung Cancer (NSCLC). However, the molecular mechanism that accounts for this association is unknown. ERβ1 was previously shown to sensitize breast cancer cells to chemotherapeutic agents. The role of the receptor in regulating sensitivity of NSCLC cells to chemotherapy, a common treatment option for advanced disease, has not been studied. Here we show that upregulation of ERβ1 decreases the survival of NSCLC cells in response to treatment with doxorubicin. This effect was observed in p53-defective but not wild-type p53-expressing cells. ERβ1 enhanced G2/M cell cycle arrest in NSCLC cells by activating the checkpoint kinase 1 (Chk1) and altering downstream signaling. The expression of p63 target genes including cyclin G2 that regulate the G2/M checkpoint was induced by ERβ1 proposing an ERβ1-p63 transcriptional cooperation. Our findings suggest the involvement of ERβ1 in the regulation of DNA damage response in NSCLC cells and support the potential predictive value of the receptor in clinical management of the disease.