Up-regulation of DDB2 by ERα Confers to Chemoresistance

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Chemotherapy is the most common therapeutic strategy for advanced breast cancer patients. Unfortunately, the development of chemoresistance remains an unsolved clinical problem, and leads to the high cancer recurrence and low survival rate. Both estrogen receptor (ER) expression and p53 mutations have been reported to contribute to chemoresistance through MDR1-dependent drug efflux and anti-apoptotic gene expression, respectively. Interestingly, ER has also been found to regulate DNA repair process through ATM/ATR/p53-induced nucleotide excision repair (NER) pathway, suggesting the existence of cross-talk between these two pathways for the regulation of chemosensitivity. In this study, our results further showed that ER-positive breast cancer cells were insensitive to carboplatin and cisplatin due to the expression of DDB2, a downstream target gene of p53 signaling pathway and an important regulator for damaged DNA recognition and NER process. ERα also can up-regulated DDB2 through transcriptional regulation. Silence of ERα both decrease the activity of acetylation on Lys382 of p53 and the expression of DDB2 protein, and further diminished the binding ability of DDB2 to chromatin for DNA repair in response to platinum drugs. On the other hand, the binding efficacy of DDB2 on chromatin upon DNA damage was attenuated by lincRNA-p21 due to the physically interaction in ER-negative cancer cells, and contribute to chemosensitivity to platinum-drugs. These results indicate that DDB2 mediates the ER-dependent DNA repair and chemoresistance in breast cancer cells.