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DUOXA1-mediated ROS production promotes cisplatin resistance by activating ATR-Chk1 pathway in ovarian cancer

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Abstract

The acquisition of resistance is a major obstacle to the clinical use of platinum drugs for ovarian cancer treatment. Increase of DNA damage response is one of major mechanisms contributing to platinum-resistance. However, how DNA damage response is regulated in platinum-resistant ovarian cancer cells remains unclear. Using quantitative high throughput combinational screen (qHTCS) and RNA-sequencing (RNA-seq), we show that dual oxidase maturation factor 1 (DUOXA1) is overexpressed in platinum-resistant ovarian cancer cells, resulting in over production of reactive oxygen species (ROS). Elevated ROS level sustains the activation of ATR-Chk1 pathway, leading to resistance to cisplatin in ovarian cancer cells. Moreover, using qHTCS we identified two Chk1 inhibitors (PF-477736 and AZD7762) that re-sensitize resistant cells to cisplatin. Blocking this novel pathway by inhibiting ROS, DUOXA1, ATR or Chk1 effectively overcomes cisplatin resistance. Significantly, the clinical studies also confirm the activation of ATR and DOUXA1 in ovarian cancer patients, and elevated DOUXA1 or ATR-Chk1 pathway correlates with poor prognosis. Taken together, our findings not only reveal a novel mechanism regulating cisplatin resistance, but also provide multiple combinational strategies to overcome platinum-resistance in ovarian cancer.