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Arch Can Res 2017, 5:4
DOI: 10.21767/2254-6081-C1-003

Metformin prevents cisplatin resistance by suppressing *RAD51* expression in triple-negative breast cancer cells

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Triple-negative breast cancer (TNBC) is characterized by tumors that do not express the estrogen receptor (ER), progesterone receptor (PR), or *HER2* genes. Since TNBC does not respond to endocrine therapy, this type of cancer presents an important clinical challenge. Although cisplatin is effective against TNBC, its use is limited due to the development of drug resistance. We found that metformin suppressed cisplatin resistance by down-regulating *RAD51*, a DNA homologous recombinase. Metformin suppressed cisplatin-mediated *RAD51* up-regulation via regulating the protein stability and ubiquitination of *RAD51*. In addition, cisplatin increased phosphorylation of extracellular signal-regulated kinases 1/2 (ERK1/2). Inhibition of ERK1/2 blocked cisplatin-mediated expression of *RAD51*. Metformin suppressed cisplatin-mediated ERK phosphorylation, indicating that metformin regulates *RAD51* by suppressing cisplatin-mediated ERK activation. Moreover, metformin increased cisplatin-induced phosphorylation of γ-H2AX, a hallmark of DNA double-stranded breaks, suggesting that metformin enhances sensitivity to cisplatin by inducing DNA double-stranded breaks. Overexpression of *RAD51* blocked the inhibition of metformin-mediated cell invasiveness, while *RAD51* knockdown enhanced cisplatin-induced invasion and migration of breast cancer cells. Collectively, these results suggest that metformin prevents cisplatin resistance by regulating *RAD51* expression.

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