Cancer Research

Clinical Research (Excluding Clinical Trials)

Abstract 4927: Silencing of the RAD50 gene contributes to enhancing the sensitivity of the triple-negative breast cancer cells to carboplatin

Kristina V. Havrysh, Mikhail V. Bogdanov, and Ramziya G. Kiyamova

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Abstract

Triple-negative (TN) breast cancer (BC) is the most aggressive molecular subtype of BC that affected over 250 thousand females worldwide just in 2018. Patients with TNBC have exhibited a higher probability of cancer relapses and poor prognosis of disease outcome which are due to the absence of established and reliable targets for therapy of this subtype of tumors. Only 10% of TN breast tumors have BRCA1/2 mutations associated with high sensitivity of cancer cells to the chemotherapy with platinum salts drugs (e.g., cisplatin, carboplatin (Cb), etc.) and PARP-inhibitors. Recent studies indicated that administration of Cb in neoadjuvant chemotherapy of TNBC increase pCR (pathologic complete response) of patients received Cb in comparison with a control group. Also, Phase II and III of clinical trials have shown that TNBC patients respond differently to adjuvant chemotherapy with Cb. Therefore further studies are required to define subgroups of TNBC patients, which might benefit from carboplatin therapy.

In our previous studies, the RAD50 gene involved in radiation-induced DNA double-strand break repair was identified as a tumor-associated antigen and potential BC marker. We have shown that low expression of RAD50 gene is associated with better TNBC prognosis.

The current study was aimed to evaluate RAD50 as a predictive marker of TNBC cells sensitivity to Cb. The RAD50 gene was silenced in triple negative breast cancer cell lines with wild-type BRCA genes namely MDA-MB-231, MDA-MB-436, and MDA-MB-453 by RNA interference. Then the changes of the cytotoxic sensitivity of these cells to Cb treatment in comparison to the control cells with original RAD50 expression were investigated by using a cell viability assay. Obtained data were analyzed by the Wilcoxon signed-rank test. The statistical analysis was performed using GraphPad Prism 7 software.

Results of this study demonstrated that the knockdown of RAD50 gene expression in human TNBC cells could significantly increase their susceptibility to treatment with Cb (MDA-MB-231: IC50 - 20,65uM (silenced RAD50) and 24,93uM (control), p-value = 0,0098; MDA-MB-436: IC50 - 7,497uM (silenced RAD50) and 10,39uM (control), p-value = 0,0137; MDA-MB-453: IC50 - 7,336uM (silenced RAD50) and 8,711uM (control), p-value = 0,002).

These results strongly indicate that silencing of the RAD50 expression contributes to the sensitization of TNBC cells to treatment with platinum-based drug Cb. Therefore RAD50 could be considered as important TNBC predictive biomarker. Further validation of RAD50 by using the tumors of TNBC patients and animal xenograft models could prove to be essential to use this marker for improving the therapy regimens of TNBC tumors without BRCA1/2 mutations.

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