CANCEROGENESIS

RAD50, A POTENTIAL PREDICTIVE MARKER OF CHEMOTHERAPY RESISTANCE

K. HAVRYSH[1,2], V. FILONENKO[1], R. KIYAMOVA[1,2]

[1]Institute of Molecular Biology and Genetics, NAS of Ukraine, Kyiv;
[2]Institute of Fundamental Medicine and Biology,
Kazan Federal University, Kazan, Tatarstan

Cancer is a morphologically and molecularly heterogeneous disease. Among different cancer types, the breast cancer is the most common one, and it is the leading cause of women death worldwide. Breast tumors belonging to the same intrinsic subtype could have different response to therapy, but reasons of this are still not clear. Moreover poor disease outcome after chemotherapy is often caused by resistance formation to most of commonly used drugs. Effectiveness of anti-neoplastic agents is not fully understood and could be influenced by DNA repair activity. RAD50 protein plays a key role in DNA double strand breaks repair (DSBs), it is crucial to safeguard genome integrity. The aim of this study was to determine whether RAD50 was capable of being a prognostic marker of tumor cells response to chemotherapy.

To directly investigate the association of chemotherapeutic drugs and gene expression or copy number alterations (deletion – log2<-0.3; gain – log2>0.3) of RAD50 in breast cancer, we analyzed the cell line expression and CNA data in 59 breast cancer cell lines; data was taken from Cancer Cell Lines Encyclopedia (https://portals.broadinstitute.org/ccle/home). The response information (IC_{50}) to 12 anti-cancer drugs, namely 5-fluorouracil, carboplatin, doxetaxel, doxorubici, gemicitabine, lapatinib, methotrexate, mitomycin, oxaliplatin, paclitaxel, tamoxifen, vinblastine, were downloaded from Genomics of Drug Sensitivity in Cancer (http://www.cancerrxgene.org) and Cancer Cell Lines Encyclopedia.

We determined the association between mRNA expression of RAD50 and response to drugs as well as between CAN and response to drugs using Pearson correlation and Wilcoxon-Mann-Whitney test. The analysis revealed a significant association between the mRNA expression of RAD50 and sensitivity to vinblastin in breast cancer cell lines (correlation = 0.3625; p-value 0.0215). Correlation directly in cell lines with basal like subtype was stronger and more significant than in not differentiated cohort (correlation = 0.6340; p-value 0.0199). Resistant (mean = 7.787; 25% of available cell lines with highest IC_{50}) to vinblastine cell lines have significantly higher mRNA expression (p-value = 0.0029) than sensitive (mean = 6.989; 25% of available cell lines with lowest IC_{50}). Analysis of cell lines sensitivity to chemotherapeutic compounds taking into account CNA showed a significantly better response to vinblastine in cell lines with deletions (p-value = 0.0143) than in cell lines with diploid RAD50 copy number.

Our data suggests that RAD50 might be a predictive marker in determining the benefit of vinblastin chemotherapy. However, further studies are needed to clarify the outputs using a larger sample group and more in-depth *in vitro*, *in vivo* and *ex vivo* studies.

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