Role of cancer stem cells in drug resistance of ER+ breast cancer

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ABSTRACT

Breast cancer (BC) is classified into ER+ and ER− tumors based on Estrogen Receptor (ER) status. ER+ tumors exhibit higher levels of resistance to chemotherapy compared to ER− tumors. It was shown that BCL-2, TP53, BAX and NF-KB are involved in drug resistance in the ER+ tumors. Cancer Stem Cells (CSCs) were shown to be the origin of cancer and play an important role in drug resistance. Here we introduce a commentary on our previously published study entitled (“Estrogen Receptor positive breast tumors resist chemotherapy by the overexpression of P53 in Cancer Stem Cells”) where we tested the hypothesis that CSCs of the ER+ tumors resist drug through the overexpression of BCL-2, TP53, BAX and NF-KB. CSCs (untreated or treated with Doxorubicin (DOX)) were isolated from MCF7 (ER+) and MDA-MB-231 (ER−) cell lines. mRNA expression levels of BCL-2, TP53, BAX and NF-KB were detected by quantitative real time PCR (qPCR) with and without treatment. Interestingly TP53 showed a striking increase in its expression in CSCs of the ER+ MCF7 cells compared to bulk cancer cells. In addition, TP53 showed exceptionally elevated levels of mRNA expression in MCF7-CSCs compared to MDA-MB-231-CSCs. These results suggest that CSCs in the ER+ cells avoid the effect of drug treatment by increasing p53 expression...

Key Words: Breast cancer; ER+ tumors; drug resistance

RESULTS AND DISCUSSION

We found that the expression levels of BCL-2, BAX and NF-KB decreased in MCF7 bulk cancer cells after DOX treatment compared to only BCL-2 and BAX in MDA-MB-231 bulk cancer cells. Also we detected a substantial increase in the mRNA expression of only TP53 in CSCs of the ER+ MCF7 cell line compared to bulk cancer cells. Furthermore, only TP53 displayed high expression level in MCF7-CSCs compared to MDA-MB-231-CSCs suggesting a role for TP53 in CSCs mediated drug resistance and that this role is prominent in ER+ tumors compared to ER− ones.

It is well known that TP53 suppresses tumorigenesis by arresting cell cycle to allow DNA repair [14]. When tumors are treated, if the burden of DNA damage is overwhelming, TP53 pushes cells towards apoptosis. Most cancer drugs target DNA while the cell is dividing. DNA of dividing cells is likely to be un-chromatinized and may be going under-winding to single strand, a state makes it easily to be damaged. CSCs divide slowly, makes its DNA less susceptible to drug mediated DNA damage. One may expect that drug treatment of CSCs induces the expression of TP53 to a level improves their DNA repair machinery.

This suggests that CSCs in ER+ tumors avoid the effect of drug treatment by enhancing their DNA repair machinery through increasing TP53 expression. However, this finding should be mechanistically confirmed by knocking down P53 expression in ER+ breast cancer cells and then investigating cell response to drug treatment. This experiment should then be complemented by the overexpression of TP53 and investigating if this will rescue the phenotype.
In the meantime, to discover more players in this context - we recommend investigating the global gene expression profiles of CSCs isolated from patients with ER+ tumors before and after therapy. This will provide rich information of how CSCs resist therapy in ER+ breast cancer patients. Identification of these genes will help targeting CSCs decreasing the risk of tumor recurrence.

REFERENCES