Abstract

Exploring Sensitivity to Replicative Stress in BRCA-Deficient Triple Negative Breast Cancer [†]

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Abstract: In triple negative breast cancer (TNBC), chemotherapy is the only systemic treatment and sustained remissions are rare. We propose to widen therapeutic options. About 30% of TNBC tumors are BRCA1-deficient, presenting defective DNA repair and increased sensitivity to genotoxic drugs. We hypothesized that BRCA-deficient TNBC is highly sensitive to replication stress-inducing drugs, thus, opening new therapeutic perspectives. Our preliminary results showed that BRCA1-deficient TNBC cell lines and a CRISPR/Cas9 BRCA1 KO isogenic model display increased sensitivity to gemcitabine. Cell cycle distribution of gemcitabine-treated BRCA1-deficient cells was characterized by an elevated Sub-G1 fraction caused by increased numbers of cells in replication catastrophe. This was illustrated by 80% of BRCA1-deficient cells showing persistent (48–72 h post treatment) γH2AX staining in the absence of RPA32 co-staining, whereas in the isogenic BRCA1 WT model γH2AX and RPA32 positive cell numbers started decreasing at 24 h. Interestingly, we noted that in addition to replication catastrophe, BRCA-deficient cells treated with gemcitabine underwent aberrant mitosis as shown by a clear increase of micro-nuclei. Interestingly, in vivo experiments appear to reproduce in vitro data. Indeed, a BRCA hypermethylated TNBC PDX showed a higher sensitivity to gemcitabine than the BRCA1 WT. In conclusion, our data suggest that BRCA-deficient tumors are more sensitive to the replication poison gemcitabine. Furthermore, this sensitivity seems to be mediated by an accentuated replicative stress response that is not well managed. Upon gemcitabine treatment, the cells undergo important DNA damage that leads to stalled replication forks, and DNA breakage. In the absence of BRCA1, the HR pathway is compromised, which leads to fork collapse and accumulation of single-stranded DNA, therefore exhausting the pool of RPA within the cell and inducing replicative catastrophe. In addition to deficient replication, gemcitabine treated BRCA-deficient, but not BRCA-proficient cells, are subjected to mitotic catastrophe.

Keywords: triple negative breast cancer; BRCA-deficiency; homologous recombination; replicative stress

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