Chemosensitization of Triple-Negative Breast Cancer by Targeting Mutant p53

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Triple Negative Breast Cancer (TNBC) refers to a subtype of particularly aggressive breast cancer that lack hormone receptor expression and HER2 overexpression. This subtype accounts for approximately 15% of all types of breast cancer and is much more prevalent among African-American women who are premenopausal. Due to lack of sufficient targets, patients with TNBC are not candidates for endocrine therapy or targeted therapy against HER2. TNBC is managed with standard treatments and chemotherapy is the primary choice of systemic therapy for this disease. TNBCs are often accompanied with higher frequency of p53 gene mutation comparing with other type of breast cancer. Failure of p53 signaling is increasingly recognized to be importantly involved in chemo-resistance, which is considered as a predictor of survival and recurrence rate. Rational design of combination therapies directed restoring p53 function or signaling should offer substantial benefit in improving the outcome of chemotherapy for TNBC.

In the present study, we show that MethylSeleninic Acid (MSA), a low-toxicity, small molecule anticancer agent, behaves in a similar fashion as the mutant-p53-rescue drug PRIMA-1 in enhancing chemosensitivity of TNBC cells. Both MSA and PRIMA-1 could synergistically increase the efficacy of DNA-damage reagent doxorubicin in several TNBC cell lines in which the p53 gene is mutant. The growth inhibition and apoptosis induction by the combination between these two drugs and doxorubicin are mutant p53 protein dependent. These combinations could lead to transcription of p53 target genes, such as p21/\textit{cip1}, \textit{PUMA} and \textit{BAX} than each single treatment alone. This elevation of p53 target genes is important for the combinatory efficacy.

Our findings indicate the potential of MSA to re-activate mutant p53. Considering the high p53 mutation prevalence among TNBC patients, bypass p53 mutation and/or restore p53 function should offer substantial benefit in improving the outcome of chemotherapy for TNBC.