SULFORAPHANE PROTECTS CARDIAC CELLS FROM DOXORUBICIN-TOXICITY WITHOUT INHIBITING ANTI-CANCER ACTIVITY

Jaz'mon Moore1,2, Mecit Kaplan1, Vetriselvan Manavalan1, Sharda P. Singh1 and Clement G. Yedjou2

1Dept. of Pharmacology and Toxicology at UAMS; 2Natural Chemotherapeutics Research Laboratory, NIH-RCMI Center for Environmental Health College of Science, Engineering and Technology, Jackson State University, 1400 Lynch Street, P.O. Box 18540, Jackson, MS, USA

Abstract: Cardiomyopathy due to oxidative/electrophilic stress often occurs after doxorubicin (DOX) chemotherapy of major malignancies, and may predispose to heart disease. Sulforaphane (SFN), a phytochemical, is known to activate the transcription factor Nrf2 and induce defense mechanisms in normal cells. SFN also inhibits cancer cells seemingly through Nrf2 independent mechanisms. Our studies show that sulforaphane (SFN) protects cardiomyocytes from DOX toxicity by activating Nrf2 without compromising the ability of DOX to kill cancer cells. Therefore, sulforaphane could be a valuable adjuvant in DOX-therapy. To test whether SFN concentrations that protect cardiac cells compromise the ability of DOX to kill cancer cells in vitro, we assayed cell survival and Nrf2 activity in cancer and cardiac cells. H9c2 (cardiac cell line) and 13762 MAT BIII (breast cancer line) were treated for 24h with either DMSO vehicle, 2.5 µM SFN, 5 µg/ml DOX, or DOX + 2.5 µM SFN. Survival was assayed by the Calcein Blue, Acetoxymethyl (AM) assay. Active Nrf2 was measured in cardiac and cancer cells after SFN (2.5 µM), DOX (5 µg/ml) or SFN +DOX treatment for 24h, control cells received DMSO. SFN enhances survival in DOX-treated cardiac H9c2 cells but selectively maintains or enhances DOX-killing of breast cancer cells. SFN enhanced nuclear Nrf2 activity in cardiac H9c2 cells even in the presence of DOX. We detected high basal levels of nuclear Nrf2 activity in the cancer cells compared to cardiac cells and SFN treatment did not alter Nrf2 activity in cancer cells. Our initial results suggest that DOX and SFN act synergistically in cancer cell kill, which may improve therapeutic index of DOX in cancer-therapy. These results imply that Nrf2 activation in cardiac cells, with low Nrf2 activity, is induced by SFN treatment and, unlike in cancer cells, SFN confers cardiac protection from DOX toxicity. Invasive cancer cells are inhibited by DOX chemotherapy but are not protected by SFN treatment, perhaps because Nrf2 is not activated by SFN in those cells. Taken together we demonstrated preclinical proof of principle for SFN/DOX co-therapy for breast cancer.

Keywords: Sulforaphane, doxorubicin, breast cancer, chemotherapy

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