【P-60】

Critical Involvement of Jun N-Terminal Kinase in G2/M Arrest And Caspase-Mediated Apoptosis Induced by Sulforaphane in DU145 Prostate Cancer Cells And Lack of Potentiation Effect of Selenium

Sung Dae Cho[1], Ji Won Jung[1], Junxuan Lu[2], Yong Soon Lee[1] and Kyung Sun Kang[1]

[1]College of Veterinary Medicine, Seoul National University, Seoul, Korea, [2]Hormel Institute, University of Minnesota, 801 16th Ave NE, Austin, MN 55912

Sulforaphane (SFN) is a major isothiocyanate compound in cruciferous vegetables such as broccoli, cauliflower, and Brussels sprouts. Preclinical work has recently indicated that SFN and other isothiocyanates may be useful for prostate cancer chemoprevention. The trace element selenium has documented activity for prostate cancer prevention. Selenium-enrichment through cultivation of broccoli has recently been shown to significantly enhance the anti-cancer activity. In this study we used DU145 human prostate cancer cell culture model to investigate the protein kinase signaling pathway(s) through which SFN induces cell cycle arrest and apoptosis and whether selenium might impact the apoptotic activity of SFN. The results showed that SFN exposure for 24 h or longer significantly decreased the number of viable DU145 cells in a dose-dependent manner with an IC50 of ~ 10 mM. The decreased cell number was associated with a strong G2/M phase arrest and apoptotic cell death, with the latter being evidenced by the caspase-mediated cleavage of poly(ADP-ribose) polymerase and increased release of histone-associated DNA fragments. A peptide inhibitor of caspase-8 completely blocked SFN-induced apoptosis and that for caspase-9 exerted a major protection, however, neither inhibitor attenuated SFN-induced G2/M cell cycle arrest. Regarding the protein kinase signaling pathways, SFN treatment induced the activation of JNK within 1 h, but did not have anydetectable effect on the phosphorylation of p38MAPK or ERK1/2 at 6, 12 and 24 h. Inhibiting the JNK activity with a pharmacologic inhibitor SP600125 completely abolished the induction of G2/M arrest and apoptosis by SFN, whereas chemical inhibitors for p38MAPK and MEK1/2 did not have any modulating effect on SFN-induced apoptosis.

Taken together, the data indicate that SFN decreased viable DU145 cell number through JNK-mediated mechanisms that led to G2/M arrest and caspase-dependent apoptosis. However, when cells were treated simultaneously with SFN and selenite or methylseleninic acid, there was no synergistic enhancement effect of either form of selenium on the induction of apoptosis by SFN. In light of the extensive metabolism of selenium and isothiocyanates in vivo, animal models may be necessary to evaluate the merits of combining these agents for prostate cancer chemoprevention or therapy.

Keyword : prostate cancer, sulforaphane, selenium, G2/M arrest, apoptosis, c-Jun N-terminal kinase