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EFFECT OF SELENIUM COMPOUNDS ON CHEMOPREVENTION AND TUMOR INVASION

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Selenium is known to have both chemopreventive and therapeutic benefits of cancer. Recent studies have implicated that apoptosis is one of the most plausible mechanism of chemopreventive effects of selenium compounds and tumor invasion is a new factor involved in chemotherapy. In the present study, we demonstrate that Se-methylselenocysteine (MSC), one of the most effective selenium compounds at chemoprevention, induces apoptosis in HL-60 cells and that ROS plays a crucial role in MSC-induced apoptosis. MSC uptake occurred quite early reaching the maximum within 1 hour. The dose-dependent decrease in cell viability was observed by MSC treatment, which was coincident with increased DNA fragmentation. Flow cytometric analysis showed that apoptotic sub-G1 population was increased by MSC. 50 μM of MSC was able to induce apoptosis in 48% of cell population at a 24 hours time point. MSC induced release of cytochrome c from mitochondria and activated caspase-3 and caspase-9. The measurement of ROS by dichlorofluorescein fluorescence revealed that dose- and time-dependent increase in ROS was induced by MSC. *N*-Acetylcysteine, glutathione, and deferoxamine blocked cell death, DNA fragmentation, and ROS generation induced by MSC. Moreover, *N*-acetylcysteine effectively blocked caspase-3 activation and the increase of the sub-G1 population induced by MSC. These results imply that ROS is a critical mediator of the MSC-induced apoptosis in HL-60 cells. Further study demonstrates that low level of selenite (less than 3 μM) inhibits the invasion of tumor cells and also adhesion of HT1080 cells to the collagen matrix. Moreover, selenite reduced expression of matrix metalloproteinase-2,-9 and urokinase type plasminogen activator, which are involved in matrix degradation, but increased a tissue inhibitor of

metalloproteinase-1. This inhibitory effect of selenite on the proteases expressions was mediated by the suppression of transcription factors, NF-κB and AP-1. These results suggest that selenium compounds are used for both chemoprevention at the high level and tumor invasion at the low level.