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A novel chemopreventive mechanism of selenomethionine: enhancement of APE1 enzyme activity via a Gadd45a, PCNA and APE1 protein complex that regulates p53-mediated base excision repair.

Jung HJ[1], Kim HL, Kim YJ, Weon JI, Seo YR.

Author information

Abstract

Organic selenium compounds have been documented to play a role in cancer prevention. Our previous study showed that selenomethionine (SeMet) induces p53 activation without genotoxic effects including apoptosis and cell cycle arrest. In this study, we investigated the mechanism by which organic selenium compounds promote p53-mediated base excision repair (BER) activity. Our data demonstrated for the first time that the interaction between growth arrest and DNA damage-inducible protein 45A (Gadd45a), which is a p53-activated downstream gene, and two BER-mediated repair proteins, proliferating cell nuclear antigen (PCNA) and apurinic/apyrimidinic endonuclease (APE1/Ref-1), was significantly increased in a p53-dependent manner following treatment with organic selenium compounds. Furthermore, we observed that the activity of APE1 was significantly increased in a p53-dependent manner in response to the organic selenium compounds. These results suggest that BER activity is dependent on wild-type p53 activity and is mediated by the modulation of protein interactions between Gadd45a and repair proteins in response to organic selenium compounds. We propose that p53-dependent BER activity is a distinct chemopreventive mechanism mediated by organic selenium compounds, and that this may provide insight into the development of effective chemopreventive strategies against various oxidative stresses that contribute to a variety of human diseases, particularly cancer.