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Biological Function of Selenium and Selenoproteins in Human Disease

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Selenium is an essential trace element for mammalian cells that at low concentrations (nM) stimulates cell growth and at higher concentrations (mM) suppresses cell growth. Although selenium compounds do in fact inhibit cell proliferation at high concentrations, the precise mechanism of this inhibitory effect has not yet been elucidated. Selenite is a rather strong oxidizing agent and is reduced by an excess of thiols. It has been reported that a number of biological effects of selenium compounds are influenced by SH compounds.

Selenocysteine is recognized as the 21st amino acid in ribosome-mediated protein synthesis and its specific incorporation is directed by the UGA codon. In *Escherichia coli*, it has been established that the products of four genes, *selA*, *selB*, *selC*, and *selD*, are required for synthesis and specific insertion of selenocysteine into proteins as directed by the UGA codon. Selenocysteine esterified to a unique $tRNA^{sec}$, *selC* gene product, is formed in situ from a serine residue initially ligated to the tRNA. Selenocysteine synthase, *selA* gene product, reacts with the seryl-$tRNA^{sec}$ forming 2,3-aminoacrylyl-$tRNA^{sec}$. Generation of selenocysteinyl-$tRNA^{sec}$ from 3-aminoacrylyl-$tRNA^{sec}$ requires a diffusible selenium donor compound. The reactive selenium donor compound, monoselenophosphate, is a reaction product of selenophosphate synthetase, the *selD* gene product. A new GTP-dependent translation factor that specifically interacts with the selenocysteinyl-$tRNA^{sec}$ transports the tRNA to the ribosome. This translation factor is the product of *selB* gene. The mechanism of distinguishing between selenocysteine insertion into a polypeptide and termination of polypeptide synthesis by release factors in response to the presence of a UGA codon in the open reading frame of an mRNA has been investigated with prokaryotic and eukaryotic genes. Several proteins from bacteria and animals contain selenocysteine in their primary structure. Each of the cDNA clones of these selenoproteins contains one TGA codon, which corresponds to UGA in mRNA, in the open reading frame.

NF-kB is a major transcription factor consisting of 50- and 65-kDa proteins

that controls the expression of various genes, among which are those encoding cytokines, cell adhesion molecules, and inducible NO synthase (iNOS). Activation of NF-kB in human T cells and lung adenocarcinoma cells was induced by recombinant human tumor necrosis factor alpha or bacterial lipopolysaccharide. After lipopolysaccharide activation, nuclear extracts were treated with increasing concentrations of selenite, and the effects on DNA-binding activity of NF-kB were examined. Binding of NF-kB to nuclear responsive elements was decreased progressively by increasing selenite levels. Selenite inhibition was reversed by addition of DTT. Proportional inhibition of iNOS activity as measured by decreased NO products in the medium (NO_2^- and NO_3^-) resulted from selenite addition to cell suspensions. This loss of iNOS activity was due to decreased synthesis of NO synthase protein.

Selenite protects HEK293 cells from cell death induced by ultraviolet B radiation (UVB). Exposure of HEK293 cells to UVB radiation resulted in the activation of caspase-3-like protease activity, and pretreatment of the cells with a caspase-3 inhibitor, prevented UVB-induced cell death. Interestingly, enzymatic activity of caspase-3-like protease in cell lysates of UVB-exposed cells was repressed in vitro by the presence of selenite. Selenite also inhibited the in vitro activity of purified recombinant caspase-3 in cleaving Ac-DEVD-pNA or ICADL and in the induction of DNA fragmentation. The inhibitory action of selenite on a recombinant active caspase-3 could be reversed by sulfhydryl reducing agents, such as dithiothreitol and β-mercaptoethanol. Furthermore, pretreatment of cells with selenite suppressed the stimulation of the caspase-3-like protease activity in UVB-exposed cells, whereas dithiothreitol and β-mercaptoethanol reversed this suppression of the enzymatic activity. Taken together, our data suggest that selenite inhibits caspase-3-like protease activity through a redox mechanism and that inhibition of caspase-3-like protease activity may be the mechanism by which selenite exerts its protective effect against UVB-induced cell death. And it was also observed that selenite suppresses both the c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) and the p38 mitogen-activated protein kinase pathway in 293T cells. In contrast, selenite had little effect on the extracellular signal-regulated kinase pathway. Furthermore, selenite directly inhibited JNK/SAPK activity in vitro but not the p38 activity. And human cytosolic glycerol-3-phosphate dehydrogenase is also regulated by selenite through a redox mechanism.

Selenoprotein W is a *selW* gene product and mainly cytoplasmic protein containing a selenocysteine that is encoded by UGA codon in the open reading

frame of the mRNA. The function of selenoprotein W is unknown so far, although some results suggest that selenoprotein W should be connected to white muscle disease and redox control in intracellular compartment. In order to elucidate the function of selenoprotein W, the *sel W* gene was cloned from a mouse brain cDNA library and stably transfected the cDNA in mammalian cells, such as human lung cancer cell H1299 and CHO cell. Whereas the viability of control cells was decreased by treatment of H_2O_2, the Se W transfected cells showed very stable viability in the same condition. However, resistance of the transfected cells to H_2O_2 was abolished in the presence of L-buthionine- [S, R]-sulfoxide (BSO) which is an inhibitor of glutathione synthesis. This result indicates that the antioxidant activity of selenoprotein W is GSH-dependent. Comparing with control cells, intracellular level of ROS of the transfected cells was not changed by treatment of H_2O_2. In addition, we found that selenoprotein W over-expressed cells could be retard cell cycle arrest in G2 phase against H_2O_2.