



Karolinska Institutet

Department of Laboratory Medicine Selenium cytotoxicity in cancer

AKADEMISK AVHANDLING

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Abstract

Selenium is an essential trace element, present in the 21st amino acid selenocysteine, that is specifically incorporated into selenoproteins. Today, there are 25 identified selenoproteins in humans, whereof many comprises redox active functions to uphold the intracellular redox balance. The redox activity is dependent on the location of selenocysteine within their active sites. It is also therefore selenium is recognized as an antioxidant.

There are increasing number of studies with supporting evidences of redox active selenium compounds as anti-tumor metabolites, both in prevention and treatment of cancers, depending on the concentration. At lower doses selenium supplementation supports the synthesis and function of selenoproteins, while at higher concentration, selenium becomes a prooxidant and may cause reactive oxygen speices (ROS) formation, and induces cell death. Still, the selenium induced cytotoxic mechanisms in cancer are not fully characterized. The aim of this thesis was therefore undertaken to study the cytotoxic mechanism induced by some selenium species in tumor cells, and their interaction with the thioredoxin and the glutaredoxin system.

We found selenium compounds to be substrates of the glutaredoxin system, and that elevated Grx1 also increases the cytotoxicity of selenite, selenodiglutathione and seleno-DL-cystine. Moreover, selenite induced a redox shift within cells by increased cysteinylolation and glutathionylation of proteins, which might be an important mechanism in selenium induced cytotoxicity. Methylselenol is considered to be the most reactive selenium metabolite to induce cell death in cancer cells. We showed the occurrence of a spontaneous methylation of selenide by s-adenosylmethionine (SAM) to form methylselenol. Methylselenol was a superior substrate for the thioredoxin and the glutaredoxin systems, compared to selenide. This newly formed selenium metabolite was also more toxic to tumor cells. Furthermore, selenite, selenodiglutathione and seleno-DL-cystine induce different programmed cell death (PCD) in HeLa cells, which was unexpected, since both selenite and selenodiglutathione are reduced to selenide. Selenodiglutathione was found to glutathionylate free protein thiols, which might be the reason to this diverse cell death mechanisms. Selenite induced a necroptosis-like cell death, while seleno-DL-cystine treatment induced two subgroups of cell death. One group was clearly apoptosis while the other displayed a paraptosis-like cell death, with massive cytoplasmic vacuolation and concomitant ER stress and unfolded protein response (UPR).

In a study of selenite to promote all-*trans* retinoic acid (ATRA)-induced differentiation of acute promyelocytic leukemia (APL), we found selenite to potentiate the effect of ATRA induced maturation of NB4 cells. This was determined by increased expression of CD11b, nuclear morphology changes, and decrease of PML-RAR α expression. This differentiation might be redox regulated, since both selenite and ATRA induced changes of redox protein expression both on mRNA and protein level.

In this thesis work, we show that selenium compounds are potent anti-tumoral drugs to induce cell death and to potentiate differentiation in leukemic cells. We conclude that the mechanisms are not only caused by ROS formation, but by multiple mechanisms, depending on molecular structure, which is of benefit to overcome drug resistance in tumors.