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Original Contribution

Selenite induces apoptosis in sarcomatoid malignant mesothelioma cells through oxidative stress

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Abstract

Malignant mesothelioma cells differentiate into sarcomatoid or epithelioid phenotypes. The sarcomatoid cell type is more resistant to chemotherapy and gives a worse prognosis. We have investigated whether selenite alone and in combination with doxorubicin induced apoptosis in variously differentiated mesothelioma cells. Selenite in concentrations that could potentially be administered to patients strongly inhibited the growth of the sarcomatoid mesothelioma cells (IC_{50} = 7.5 μM), whereas epithelioid cells were more sensitive to doxorubicin. Benign mesothelial cells remained largely unaffected. Selenite potentiated doxorubicin treatment. Apoptosis was the dominating mode of cell death. The toxicity of selenite was mediated by oxidative stress. Furthermore the activity of the thioredoxin system was directly dependent on the concentration of selenite. This offers a possible mechanism of action of selenite treatment. Our findings suggest that selenite is a promising new drug for the treatment of malignant mesothelioma.

Keywords: Mesothelioma; Phenotype; Drug resistance; Apoptosis; Selenium; Thioredoxin reductase; Free radicals

Malignant mesothelioma is a tumor arising from mesothelial cells after asbestos exposure. The tumor is aggressive and highly resistant to chemotherapy. Mesothelioma cells may differentiate into an epithelioid or a sarcomatoid phenotype. The presence of sarcomatoid cells in the tumor correlates with a poor prognosis. Furthermore, a survival advantage for patients receiving surgery and adjuvant chemotherapy has been confirmed only in patients with epithelioid morphology, and such therapy had no impact on survival in patients with sarcomatoid mesothelioma [1]. The ability of mesothelioma cells to differentiate into these two phenotypes has been retained in the cell lines STAV-AB (epithelioid) and STAV-FCS (sarcomatoid). Both sublines are derived from the same tumor, and their growth patterns depend on serum composition [2].

A detailed and systematic molecular screening approach, based on suppression subtractive hybridization and RNA microarray analyses, has uncovered important differences in the molecular basis of mesothelioma differentiation [3,4]. Some of these differences may be further explored for therapeutical purposes. In particular, the thioredoxin system is highly upregulated in both STAV cell lines, with the epithelioid STAV-AB cells having the highest amounts of thioredoxin reductase 1 (TrxR1) reported so far [3]. Overexpression of thioredoxin-1 (Trx1) in malignant mesothelioma has also been reported using cDNA and mRNA microarrays [5–7], and malignant mesothelioma tissue biopsies show immunoreactivity to both these proteins [8].

The thioredoxin system comprises Trx1, TrxR1, and NADPH. This system has the capacity to reduce protein disulfides in general. It plays an important role in the regulation of the redox balance in the cell. TrxR1 is a selenoprotein and

Abbreviations: AB, human AB serum; ASK-1, apoptosis signal regulating kinase-1; DCF, 2′,7′-dichlorodihydrofluorescein diacetate; DCFH-DA, 5(6)-carboxy-2′,7′-dichlorodihydrofluorescein diacetate; DMSO, dimethyl sulfoxide; DTNB, 5,5′-dithiobis(nitrobenzoic acid); EDTA, ethylenediaminetetraacetic acid; FACS, fluorescence-activated cell sorting; FCS, fetal calf serum; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione (reduced); GSSG, glutathione (oxidized); Hepes, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; PI, propidium iodide; ROS, reactive oxygen species; SEP15, selenoprotein-15; Trx1, thioredoxin-1; TrxR1, thioredoxin reductase 1.

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