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Role of selenium nanoparticles to dampen the metastatic potential of aggressive cancer cells

Introduction

Selenium (Se) is a trace element that is reported to be efficient in preventing transformation of normal to malignant cells and could be an effective chemopreventive and chemotherapeutic agent(1). Se-bioavailability and toxicity, which are related to its chemical species, limit Se use as a chemotherapeutic agent. Se-nanoparticles (Se-NPs) present interesting characteristics such as a higher bioavailability, low toxicity (towards non-cancerous cells) and anti-proliferative properties(2,3). Chemically synthesized Se-NPs have been studied as a potential cancer therapeutic agent and drug carriers(4,5). Recently, as reviewed by Zheng et al, the chemopreventive capability of Se compounds in vivo is correlated with their abilities to impact the regulation of the cell cycle, to stimulate apoptosis and to inhibit tumor cell migration and invasion in vitro(6). The reasons for these effects of Se-NPs are unknown but it may impact the cellular biomechanical properties of the cancer cells, indeed cancer tissue is commonly much stiffer than normal extracellular matrix and this elevation alters the ECM properties and triggers migration of cancer cells(7). Our objective is to study the impact of physico-chemically characterized Se-NPs on model cancer cell lines representing human prostate cancer (PC3) and ovarian cancer (OVCAR3). The cell viability, genetoxicity through immunofluorescence, cell cycle, cell apoptosis, and migration were studies while quantitative intracellular distribution and speciation of Se-NPs were assessed by synchrotron X-ray fluorescence nanoimaging and synchrotron high energy resolution fluorescence detection X-ray Absorption Spectroscopy respectively.

Materials & Methods

High metastatic human prostate cancer cell lines PC-3 (ECCAC) and high grade serous human ovarian cancer (the most malignant form of ovarian cancer and accounts for up to 70% of all ovarian cancer cases) OVCAR-3 (ATCC) were cultured in ATCC modified RPMI 1640 medium supplemented with 10% of foetal bovine serum and 1% Penicillin- Streptomycin for prostate cancer cell PC-3 and cultured in ATCC modified RPMI 1640 medium supplemented with 20% of foetal bovine serum and 1% Penicillin- Streptomycin and 0.01 mg/mL bovine insulin for ovarian cancer cell OVCAR-3, They are then exposed or not to the IC20 (80% cell viability, in µg/mL) of aqueous solution of monodispersed BSA or chitosan stabilized Se-NPs (NANOCS, USA) for 24h treatment. Sodium selenite (aqueous Se-salt solution) is used as positive control. Cytoxicity (MTT cell viability assay) and genotoxicity (immunofluorescence and repair kinetics) were used to determine the biological impact of SeNP on these cancer cells.

Results & Discussion

BSA- and chitosan-coated SeNPs have been characterized through electron microscopy, X-ray photoelectron spectroscopy and dynamic light scattering. NPs are then well-individualized. BSA-coated Se-NPs (32.6±12.7nm) present a spherical and homogeneous form contrary to chitosan-coated SeNP (28.3±11.1 nm) which are less homogeneously spherical and which tend to form aggregates with increasing concentrations. Spectroscopic analysis confirm a Se(0)-core for both coated NPs.
Chitosan coated SeNPs were more toxic than BSA-ones for a given concentration. The two cell lines were then exposed to low concentration SeNPs or sodium selenite corresponding to 80% of cell viability (below 10 µg/mL for SeNPs and below 10 µM for sodium selenite solution). Genotoxicity experiment was carried out with immunofluorescence against DNA double-strand breaks (DSB) biomarkers like □H2AX that form nuclear foci on the DSB sites. Interestingly, the yields of unrepaired DSB assessed after the different Se treatments were found different in OVCAR and PC-3 and dependent on the nature of the Se treatment, suggesting a molecular response specific on both individual status and on chemical species of Se.
Synchrotron X-ray fluorescence imaging have been performed at a resolution of 50 nm under cryogenic conditions on the X-ray nanoprobe beamline ID16A at the ESRF, Grenoble, France. As seen in Figure 1, Se was present punctually distributed (green dots) within the cells that have been treated with SeNPs. The 2D elemental maps allowed us to suggest that SeNPs, once uptaken, remained mostly in the cytosol with concentration in the range of 0.4 ng/mm2 (for example for PC3). Selenium was not detected in controls. Synchrotron HERFD-XAS have been performed on BM16 (CRG FAME-UHD) at the ESRF, Grenoble, France. XANES spectra in relation to model compounds suggest that after 24h exposure to SeNPs, the intracellular forms of Se were found to be Se(0) (elemental form of Se in the SeNPs) with species including selenocysteine and selenodigluthatione that were not detected in controls.

Conclusion

The impact of the SeNPs on aggressive cancer cells was explored at different levels. We hypothesize that the effect of the SeNPs on the cell migration could rather be induced by the the biotransformation of the SeNP than SeNps per Se. Sub-cytotoxic concentration of synthesized SeNPs could be of interest in cancer treatment.

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