Original Article Supplemenation of selenium attenuates cisplatin induced podocyte injury via BCL-2/BAX/caspase-3 pathway

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Abstract: Selenium (Se) is an essential trace element and micronutrient primarily discovered in selenoproteins, and involves in the regulation of redox and antioxidant cytoprotection through the glutathione- and the thioredoxindependent redox, and therefore this study aims to elucidate the prevention of Se on the cisplatin induced podocyte damage, and further explores its potential mechanism. To address it, murine podocyte cells-5 was selected and treated with gradient cisplatin, including 7.5 µg/ml, 15 µg/ml and 30 µg/ml, and the cell proliferation activity, the expression level of methane dicarboxylic aldehyde (MDA), glutathione peroxidase (GSH-Px) and glutathione (GSH), the cell apoptosis level was determined to validate the optimal concentration. Based on it, after Se treatment, the cell proliferation activity, the expression level of MDA, GSH-Px and GSH, and the protein expression level of apoptosis associated proteins, including B-cell lymphoma-2 (Bcl-2), Bcl-2 Associated X (Bax) and Caspase-3 was examined. As expected, when different dosages of cisplatin were added, both cell survival rate and GSH expression level were significantly decreased, and the expression level of MDA and GSH-Px and the cell apoptosis level were significantly increased, the results also showed that 15 µg/ml of cisplatin was the optimal concentration. However, after Se treatment, both cell survival rate and GSH expression level were significantly increased when compared to that of cisplatin-treated group, and the expression level of MDA, GSH-Px and the cell apoptosis were significantly decreased when compared to that of cisplatin-treated group. In addition, the level of protein expression of BCL-2 was significantly decreased after cisplatin treatment, but was significantly increased after Se treatment, similarly, that of BAX and Caspase-3 was significantly increased after cisplatin treatment, and was significantly decreased after Se treatment, these indicated that cisplatin had a significant cytotoxicity, and Se could reduce the cytotoxicity of cisplatin via the decrease of oxidative stress and cell apoptosis level, these exhibited a significant application value in clinic.

Keywords: Podocyte, cisplatin, selenium, oxidative stress, cell apoptosis

Introduction

Cisplatin is one of the most important platinumcontaining anti-cancer chemotherapy drugs in clinic, and is widely used for treatment of a broad spectrum of malignancies, including sarcoma, small cell lung cancer, germ cell tumors, lymphoma, ovarian cancer, bladder cancer, and cervical cancer, etc [1-4]. It is an alkylating-like drug that can bind to DNA in the body, and then cause DNA strands to crosslink, and ultimately induce apoptosis or systemic cell death [5-7]. In clinic, cisplatin is often administered intravenously, and is frequently given as part of a combination chemotherapy regimen with other drugs [8-10]. With the wide using of cisplatin in clinic, its side effects have aroused extensive attention, such as nephrotoxicity [5, 11], neurotoxicity [12, 13], nausea [14, 15], vomiting [14, 15], ototoxicity [16, 17], electrolyte disturbance [18, 19] and hemolytic anemia [20, 21], especially nephrotoxicity.

Nephrotoxicity is a major side effect of cisplatin, and recognized since its introduction over 25 years ago [12, 13]. In clinic, approximately 20%-30% of patients treated with cisplatin experience a reversible decline in renal function after the first course of therapy [5, 22, 23]. Despite being the focus of intense investigation in recent years, the underlying mechanism of cisplatin-induced nephrotoxicity is not understood in detail, and may be associated with renal cell apoptosis, inflammation, necrosis,



and oxidative stress etc [5, 24]. Wherein, tubular cell apoptosis is a characteristic feature of cisplatin nephrotoxicity that results in the loss of renal endothelial cells and renal dysfunction [25-27]. After cisplatin administration, p53 is rapidly up-regulated and induces apoptosis in tubular cells [28-30], and however, cell apoptosis level of podocytes of which is a significant type of kidney cells locating in the Bowman's capsule of kidney has no reported so far, and therefore it may be also damaged as wehypothesis, and were selected in this study. So far, although several therapeutic strategies have been proposed to prevent cisplatin-induced nephrotoxicity, such as intensive hydration [31, 32] and cisplatin analogs [33] etc and still no effective strategy and therefore identifying an effective approach to prevent cisplatin-induced nephrotoxicity is a critical issue recently. In this study, sodium selenite (SS) is selected to provide selenium (Se), and expects a preventive measure on the cisplatin-induced damage of podocyte.

Materials and methods

Cell culture and treatment

Murine podocyte cells-5 (MPC-5) was resurrected from liquid nitrogen using Dulbecco's modified eagle medium (DMEM) with 10% fetal bovine serum, and cultured to the logarithmic phase in a CO_2 -incubator with 5% CO_2 at 37°C. After digestion with 0.25% Trypsin, it was diluted and incubated to a 6-well plate (3×10⁵ cells/

well) followed by culturing in a CO_2 -incubator with 5% CO_2 at 37°C. When the cell confluence was close to 80%-90%, gradient cisplatin, including 0 µg/ml, 7.5 µg/ml, 15 µg/ml, and 30 µg/ml, was added to each well, and incubated in a CO_2 -incubator with 5% CO_2 at 37°C for 48 hrs.

Cell proliferation activity assay by 3-(4, 5-dimethyl-2-thiazolyl)-2, 5-diphenyl-2-Htetrazolium bromide (MTT)

The above-treated MPC-5 cells were transferred to a total of 80 μ L no serum medium with 20 μ L MTT (finally concentration: 5 mg/ml), and cultured

in a CO₂-incubator with 5% CO₂ at 37°C for 4 hrs. Then, a total of 150 μ L dimethyl sulfoxide (DMSO) was added to each well, and incubated for 10 min with shaking. Subsequently, the optical density (OD) at 490 nm was recorded with a microplate reader (Bio-Rad, USA), and the cell survival rate was calculated.

Measurement of the expression level of MDA, GSH-pX, and GSH by enzyme linked immunosorbent assay (ELISA)

The above-collected MPC-5 cells were rapidly frozen by liquid nitrogen, and homogenized with a grinder, and centrifuged at 12,000 rpm at 4°C for 15 min, and the supernatant was collected, and the MDA, GSH-pX, and GSH expression level was detected by mouse MDA ELISA kit (ZKP-1604011, ZEKEBIO, Jiangsu, China), mouse GSH-pX ELISA kit (ZKP-1604013, ZEKEBIO, Jiangsu, China), and mouse GSH ELISA kit (ZKP-1604015, ZEKEBIO, Jiangsu, China) according to the manufacturer's instructions. After detection, data was recorded at 450 nm using a microplate reader during 15 min, and analyzed by SPSS software (version 21.0, http://spss.en.softonic.com/; Chicago, IL, USA), and histogram analysis was performed using Origin 9.5 software (http://www.originlab. com/).

Cell apoptosis assay by flow cytometry

Cell apoptosis was examined using Biouniquer apoptosis kit according to the manufacturer's





Figure 2. The MDA, GSH-pX and GSH expression assay by ELISA. A. The MDA expression level assay by ELISA. B. The GSH-pX expression level assay by ELISA. C. The GSH expression level assay by ELISA. The image indicated that after gradient cisplatin treatment, the MDA and GSH-pX expression level was significantly increased, and that of GSH was significantly decreased (*: P < 0.05, **: P < 0.01).

instructions. After digestion with 0.25% trypsin, MPC-5 cells were washed with PBS for twice times, and centrifuged at 2,000 rpm for 5 min. Added 500 μ l Annexin V Binding Buffer to suspend, and then added 5 μ l Annexin-FITC to mix followed by adding of 5 μ l PI, and reacted at RT for 10 min (keep in dark). Subsequently, the cell apoptosis rate was examined by flow cytometry (Ex=488 nm, Em=530 nm), and analysis by Origin 9.5 software (http://www.originlab. com/).

Treatment of MPC-5 cells with sodium selenite (SS)

After treatment of MPC-5 cells with the optimal cisplatin for 48 hrs, 5 mM SS was added, and incubated at in a CO_2 -incubator with 5% CO_2 at 37°C for 48 hrs, and cells were collected to examine the cell proliferation activity, the expression level of MDA, GSH-Px and GSH, and the cell apoptosis level as the above-mentioned methods.

Western blot assay

The above-collected MPC-5 cells were prepared, and about 35 μg of total proteins was

fractionated by electrophoresis through 12% polyacrylamide gels, and transferred to a polyvinylidene difluoride membrane following the manufacturers' instructions. The membrane was probed with the first antibody, Rabbitderived anti-BCL-2 antibody (BA0412, 1:200; Wuhan Boster Biological Engineering Co., LTD, Wuhan, China), Rabbit-derived anti-BAX (BA03-15, 1:200; Wuhan Boster Biological Engineering Co., LTD, Wuhan, China), and Rabbit-derived anti-Caspase-3 antibody (BA3968, 1:200; Wuhan Boster Biological Engineering Co., LTD, Wuhan, China) for 1.5 hrs at room temperature. Afterward, the membrane was incubated with horseradish peroxidase-conjugated goat antimouse secondary antibody (1:5,000 in TBST; Beijing Golden Bridge Biotechnology Company Ltd, China) at room temperature for 1 hrs. The chemiluminescence luminol reagent (ZKP-C150044-1, Suzhou Zeke biotech Co., LTD, Jiangsu, China) were used to develop the immune-labeled bands on X-ray film, and the optical density of the bands was quantified using the ImageJ 1.46 software (http://rsb.info. nih.gov/ij/download.html), and a histogram was generated using the Origin 9.5 software (http://www.originlab.com/).

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Figure 3. The apoptosis assay of podocyte after gradient cisplatin treatment by flow cytometry and histogram analysis. A. The apoptosis level assay of podocyte after gradient cisplatin treatment by flow cytometry. B. Histogram analysis of the cell apoptosis level of podocyte after gradient cisplatin treatment. The images indicated that after gradient cisplatin treatment, MPC-5 cell apoptosis level was significantly increased (*: P < 0.05, **: P < 0.01).



Figure 4. Cell proliferation assay of podocyte after sodium selenite treatment by MTT. The images indicated that after sodium selenite treatment, the cell proliferation activity was significantly increased when compared to cisplatin treatment group (**: P < 0.01).

Statistical analysis

All data expressed as the mean \pm standard deviation (SD). Statistical analysis was performed with one-way ANOVA using SPSS software (version 21.0, http://spss.en.softonic. com/; Chicago, IL, USA), and Student's t-tests were performed in a group of two sample, and P < 0.05 and P < 0.01 were considered to indicate significant differences and highly significant differences, respectively.

Results

Cell proliferation activity was significantly decreased with the concentration increasing of cisplatin

When compared to control, MPC-5 cells proliferation activity was decreased with the concentration increasing of cisplatin, and had a significant difference when cisplatin was increased to 7.5 μ g/ml (*: P < 0.05, **: P < 0.01), and around 50% cells was survival after 15 μ g/ml of cisplatin treatment (**Figure 1**).

MDA and GSH-pX expression level was significantly increased after cisplatin treatment, and GSH was significantly decreased

With the concentration increasing of cisplatin in **Figure 2**, the MDA expression level was sig-

nificantly increased when cisplatin was added to 7.5 µg/ml (*: P < 0.05, **: P < 0.01), similarly, the GSH-pX expression level was also significantly increased in the group with cisplatin of 7.5 µg/ml (*: P < 0.05, **: P < 0.01), and synchronously the expression level of GSH was significantly decreased (*: P < 0.05, **: P < 0.01).

MPC-5 cells apoptosis level was significantly increased after gradient cisplatin treatment

With the concentration increasing of cisplatin, MPC-5 cell apoptosis level was significantly increased after gradient cisplatin treatment when compared to that of non-cispl-

atin treatment (**Figure 3**, *: P < 0.05, **: P < 0.01).

Sodium selenite was significantly increased the cell proliferation activity and GSH expression level, and was significantly decreased the MDA and GSH-pX expression level

When compared to control, the cell proliferation activity was significantly decreased after cisplatin treatment (**Figure 4A**, **4B**, **: P < 0.01), and was significantly increased after sodium selenite treatment (**Figure 4A**, **4B**, **: P < 0.01). Similarly, after cisplatin treatment, both MDA and GSH-pX expression level was significantly increased when compared to control (**Figure 5A**, **5B**, **: P < 0.01), and significantly decreased after sodium selenite treatment (**Figure 5A**, **5B**, **: P < 0.01), and synchronously the GSH expression level was significantly decreased after sodium selenite treatment (**Figure 5C**, **: P < 0.01), and increased after sodium selenite treatment (**Figure 5C**, **: P < 0.01).

Sodium selenite significantly decreased the cell apoptosis level

As exhibiting of **Figure 6A**, the cell apoptosis level was significantly increased after cisplatin treatment (**: P < 0.01), and then significantly decreased after sodium selenite treatment (**:



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P < 0.01), and the histogram exhibited the trend which was examined by Flow Cytometry (**Figure 6**, **: P < 0.01).

Sodium selenite considerably increased the expression level of BCL-2, and significantly decreased the expression level of BAX and caspase-3

After cisplatin treatment, the protein expression level of BCL-2 was significantly decreased (**: P < 0.01), but increased after sodium selenite treatment (**: P < 0.01), and similarly the protein expression level of BAX was significantly increased (**Figure 7C**, **: P < 0.01), and significantly decreased after sodium selenite treatment (**Figure 7C**, **: P < 0.01). In addition, the protein expression level of Caspase-3 was significantly increased after 15 µg/ml cisplatin treatment, and largely decreased after sodium selenite treatment (**Figure 7D**, **: P < 0.01).

Discussion

In this study, cisplatin of gradient concentration was selected, and exhibited an obvious dam-



Figure 5. The MDA, GSH-pX and GSH expression assay after sodium selenite treatment by ELISA. A. The MDA expression assay by ELISA. B. The GSH-pX expression assay by ELISA. C. The GSH expression assay by ELISA. The images indicated that after sodium selenite treatment, GSH expression level was significantly increased when compared to cisplatin treatment group, and that of MDA and GSH-pX was significantly decreased (*: P < 0.05, **: P < 0.01).

age on podocyte, and manifested as the decreasing of cell proliferation activity and GSH level, and the increasing of MDA and GSH-pX level, and cell apoptosis level, and 15 µg/ml cisplatin was selected as an optimal concentration. After treatment of SS, cell proliferation activity and GSH level was significantly increased, and MDA and GSH-pX level, and cell apoptosis level was significantly decreased, and the BCL-2 protein expression level was significantly increased, and that of BAX and Caspase-3 was decreased, and these indicated that SS had a significant preventive role on cisplatin-induced podocyte damage via the decreasing of cell apoptosis level, and exhibited a promising treatment on the cisplatininduced nephrotoxicity.

Cisplatin, as one of the most important platinum-containing anti-cancer chemotherapy drugs has been widely used in clinic recently [7, 34], and also its side effects have been drew much more attention, especially nephrotoxicity [5, 11]. Here, to elucidate the optimal concentration of cisplatin on podocyte, the gradient



concentration cisplatin was selected, including 7.5 μ g/ml, 15 μ g/ml, and 30 μ g/ml. After 48 hrs treatment of cisplatin, the cell proliferation activity of podocyte was significantly decreased with the concentration increasing of cisplatin, and indicated that cisplatin could inhibit the regeneration of podocytes. In addition, the oxidative stress indexes, including MDA, GSH-pX and GSH, changed significantly, manifested as the significant increasing of MDA and GSH-pX,

and the significantly decreasing of GSH, and also cell apoptosis level of podocyte was significantly increased with the concentration increasing of cisplatin, and these indicated that cisplatin could increase the oxidative stress indexes and further induced podocyte apoptosis.

Selenium (Se) is an essential trace element and micronutrient primarily discovered in sele-



Figure 7. The BCL-2, BAX and Caspase-3 protein expression assay by Western blot and histogram analysis. A. Western blot assay of the BCL-2, BAX and Caspase-3 protein expression level. B. Histogram analysis of the BCL-2 protein expression level. C. Histogram analysis of the BAX protein expression level. D. Histogram analysis of the Caspase-3 protein expression level. D. Histogram analysis of the Caspase-3 protein expression level. Analysis of the Caspase-3 protein expression level. D. Histogram analysis of the Caspase-3 protein expression level. D. Histogram analysis of the Caspase-3 protein expression level. Analysis of the Caspase-3 protein expression level. D. Histogram analysis of the Caspase-3 protein expression level, and then significantly increased after sodium selenite treatment, and synchronously the BAX and Caspase-3 protein expression level was significantly increased after cisplatin treatment, and significantly decreased after sodium selenite treatment (**: P < 0.01).

noproteins, and involves in the regulation of redox and antioxidant cytoprotection through the glutathione- and the thioredoxin-dependent redox [35-37], and therefore sodium selenite (SS) was selected to provide Se in this study. As expected, after SS treatment, the decreased cell proliferation activity of cisplatin-induced could be significantly increased close to normal, and exhibited a significant prevention on cisplatin-induced cytotoxicity. Furthermore, when compared to control, after cisplatin treatment, the MDA and GSH-pX expression level was significantly increased, and GSH expression level was significantly decreased, and manifested as the significant decreasing of MDA and GSH-pX, and the significant increasing of GSH after SS treatment. Similarly, when

compared to control, after cisplatin treatment, the cell apoptosis level was significantly increased, and then significantly decreased with the treatment of SS. Randjelovic et al, showed that selenium attenuates oxidativestress-associated kidney injury by reducing oxygen free radicals and lipid peroxidation in gentamicin-treated rats [38]. In the study of adriamycin-induced kidney damage in rats, Taskin et al, showed that selenium is protective in vivo against adriamycin-induced renal toxicity through the restoration of total antioxidant- oxidant status [39, 40]. But in the above studies. the mechanisms in which selenium protected the kidney from injury still remain unknown. This study demonstrated that the cell apoptosis-associated protein of BCL-2 expression

level was significantly decreased with the treatment of cisplatin, and then significantly increased after SS treatment, and synchronously the protein expression level of both BAX and Caspase-3 was significantly decreased after cisplatin treatment, but significantly increased after SS treatment, and these indicated that SS had a significant preventive role on cisplatin-induced podocyte damage via the decreasing of cell apoptosis. Bcl-2, Bax, and Caspase-3 are three important factors that involve in proapoptotic signaling of P53 MAPK in podocyte [41-43]. It has been demonstrated that the activation of P38 can regulate Bcl-2 and Bax expression and induce dysfunction of mitochondria [43]. The dysfunction of mitochondria subsequently releases apoptogenic proteins and activates caspase-3, which finally result in cell apoptosis [41, 42].

Certainly, this study is a pilot study to explore the prevention of Se on cisplatin-induced podocyte damage in vitro and future studies of investigating preventive roles of podocyte in vivo need to be further explored.

In summary, this study demonstrated that cisplatin exerts injuries in podocytes through the inhibiting of cell proliferation, the increasing of oxidative stress indexes and cell apoptosis level, and supplementation of Se exhibited a significant preventive role on cisplatin-nephrotoxicity via the increasing of cell proliferation, the decrease of oxidative stress index and cell apoptosis level, thus these exhibited a promising therapeutic strategy on cisplatin-induced nephrotoxicity.

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Disclosure of conflict of interest

None.

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