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Silica nanoparticles reduce fetal weight in mice and induce an inflammatory response in human extravillous trophoblast cells

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ABSTRACT

Advances in nanotechnology make the exposure to nanoparticles inevitable, potentially resulting in unexpected biological effects, particularly in pregnant women and fetuses. In this study, we used silica nanoparticles with a size of 10 nm (nSP10) and evaluated their toxicity during pregnancy in BALB/c mice. To evaluate the effect of nSP10 on the remodeling of uterine spiral arteries by extravillous trophoblast (EVT) cells, we used the human placental cell line HTR-8/SVneo, a model for EVT cells. On gestational day (GD) 10, mice were intravenously injected with a single dose of nSP10. On GD17, placental weight was not changed significantly, but fetal weight was significantly decreased by the treatment. In wound healing assay, nSP10 treatment significantly decreased the relative migration area of HTR-8/SVneo cells in a concentration-dependent manner, suggesting that nSP10 inhibits cell migration. In the cytokine array assay, nSP10-treated cells tended to produce more IL-6 and IL-8 than non-treated cells. In ELISA, nSP10 significantly increased IL-6 and IL-8 production, and JSH-23 (an inhibitor of NF-κB nuclear translocation) significantly suppressed this effect, suggesting that nSP10 increases IL-6 and IL-8 production by inducing nuclear translocation of NF-κB. Our data suggest that nSP10 reduces mouse fetal weight and may inhibit migration and induce inflammatory response of human extravillous trophoblast cells.

1. Introduction

Nanoparticles are artificial particles with at least one dimension of 100 nm or less; their development and use have been expanding with the advancement of nanotechnology [1]. Nanoparticles are widely used in fields ranging from daily necessities and medicines to industrial fields [2,3]; for example, silica nanoparticles are among the most widely used in everyday items, including cosmetics, food additives, and bio-medical applications [4,5]. Thus, we are in an environment where exposure to nanoparticles is unavoidable regardless of age or gender, but there is concern that nanoparticles may induce unexpected biological responses [6,7].

Placenta provides nutrients, exchanges substances with the fetus, and also functions as a barrier, but nanoparticles can pass through the placental barrier [8,9]. Studies on the biological effects of nanoparticles during pregnancy are being conducted worldwide [10–12]. Our group reported that exposure to 70-nm silica nanoparticles during the late stages of pregnancy reduces fetal weight in mice [13,14]. On the other

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hand, the toxicity and kinetics of nanoparticles depend on size [15,16]. Given that synthetic nonporous and typically spherical silica (size range, 5–200 nm) is widely used in food products within the EU [17,18], it is essential to evaluate the biological effects of silica nanoparticles of smaller sizes than 70 nm.

To achieve maternal immune tolerance to fetus and protect against invading pathogens, the immune system is tightly controlled in the maternal-fetal interface [19]. Thus, there is a close relationship between inflammatory control in the placenta and pregnancy maintenance, and inflammation in the placenta can induce premature birth and fetal abnormalities [20,21]. Various nanoparticles, including those of silica, can disrupt immune responses and induce inflammation [22,23]; therefore, silica nanoparticles could restrict fetal growth by inducing an inflammatory response in the placenta.

In this study, we used 10-nm silica nanoparticles (nSP10) and evaluated their toxicity during pregnancy in mice and their effect on placental cell function, focusing on the inflammatory properties of nSP10, in human HTR-8/SVneo cells.

2. Materials and methods

2.1. Silica nanoparticles

An aqueous suspension of nSP10 was purchased from Micromod Partikeltechnologie (Rostock, Warnemünde, Germany). Before use in experiments, the suspension was sonicated for 5 min at 400 W (Ultrasonic Cleaner; AS ONE, Osaka, Japan) and mixed for 1 min with a benchtop vortex mixer (Digital Vortex-Genie 2; Scientific Industries, New York, NY, USA). Previously, we confirmed that the secondary particle size is almost the same as the primary particle size and that the dispersibility is high [16].

2.2. Mice

Pregnant BALB/c mice on gestational day (GD) 9 were purchased from SLC Japan (Shizuoka, Japan). Mice were housed in a ventilated animal room maintained at 25 ± 2 °C with a 12-h light/12-h dark cycle. Mice had free access to water and a standard MF diet (Oriental Yeast, Tokyo, Japan). To ensure ethical treatment of the animals, all experiments were performed in accordance with the institutional guidelines of The University of Osaka (Douyaku R03-8-5).

2.3. Injection of silica nanoparticles

BALB/c mice were intravenously injected on GD10 with a single dose of nSP10 (0.05, 0.1, or 0.2 mg in 200 μL/mouse) or PBS as a control. On GD17, anesthetized with isoflurane inhalation mice were euthanized, and blood was collected through cardiocentesis by using a heparinized syringe. After then uteri, fetuses, and placentae were collected and weighed. Maternal body weight was measured every 3 days and before dissection.

2.4. Cell line and cell culture

The human trophoblast cell line HTR-8/SVneo was purchased from American Type Culture Collection (Manassas, VA, USA) and cultured in RPMI-1640 (Wako, Osaka, Japan) containing 10 % inactivated fetal calf serum (FCS; Biosera, Nuaillé, France) and 1 % (v/v) penicillin–streptomycin–amphotericin B suspension (Fujifilm Wako Pure Chemical, Osaka, Japan). The cells were maintained at 37 °C and >95 % humidity in a 5 % CO_2 atmosphere.

2.5. Cell migration evaluation in wound healing assay

HTR-8/SVneo cells were seeded at 6.0×10^5 cells per well into a 6-well flat plates and treated with nSP10 (25 or 50 μg/mL) for 72 h. Cell confluency was visually confirmed. The center of the well was scratched by a pipette tip, and the medium was replaced with FCS-free RPMI-1640. The scratched area was photographed in bright field under a fluorescence microscope (BZ800, Keyence, Osaka, Japan) at 0, 24, and 48 h after scratching. Images of three fields per well were taken. The area of the photographed images was calculated in ImageJ (ver.1.53q, National Institutes of Health, Bethesda, MD, USA) with the plug-in Wound Healing size tool, and the relative migration area was calculated as follows.

$$\text{Relative migration area} = \frac{\text{wound area after scratch-wound area after incubation}}{\text{wound area after scratch}}$$

2.6. Cytokine array

HTR-8/SVneo cells were seeded at 1.5×10^5 cells per well into a 6-well flat plates, treated with nSP10 (50 μg/mL) for 72 h and centrifuged (3000×*g* for 20 min at 4 °C). The levels of cytokines in supernatants were analyzed using the Proteome Profiler Human Cytokine Array Kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. Luminescence images were captured using an LAS-4000 imager (Fujifilm Wako Pure Chemical). Relative intensity in the captured images was calculated vs. the non-treated group using the MicroArray Profile plug-in in ImageJ.

2.7. Enzyme-linked immunosorbent assay

HTR-8/SVneo cells were seeded at 1.5×10^5 cells per well into 6-well flat plates and treated with different concentrations of nSP10 (12.5, 25, 50, or 100 μg/mL) or nSP10 (50 μg/mL) with or without 5 μM JSH-23 (Sigma Aldrich, St Louis, MO, USA), an inhibitor of nuclear translocation of NF-κB, for 72 h. Cells were centrifuged at 3000×*g* for 20 min at 4 °C. Concentrations of interleukin (IL)-6 and IL-8 were measured in supernatants by using commercial enzyme-linked immunosorbent assay kits (Invitrogen; Carlsbad, CA, USA), according to the manufacturer's instructions.

2.8. Statistical analysis

Statistical analyses were performed using Dunnett's method (Figs. 1 and 2) and Tukey's method (Figs. 3 and 4) in GraphPad Prism Mac version 9.0 (GraphPad Software, San Diego, CA, USA). *P*-values lower than 0.05 were considered to be statistically significant.

3. Results

3.1. nSP10 injection during placentation reduces fetal weight in mice

At GD10, mouse placental cells differentiate and acquire their functions, and placental tissue begins to form and grow [24]; at that stage, we intravenously injected mice with three doses of nSP10 and

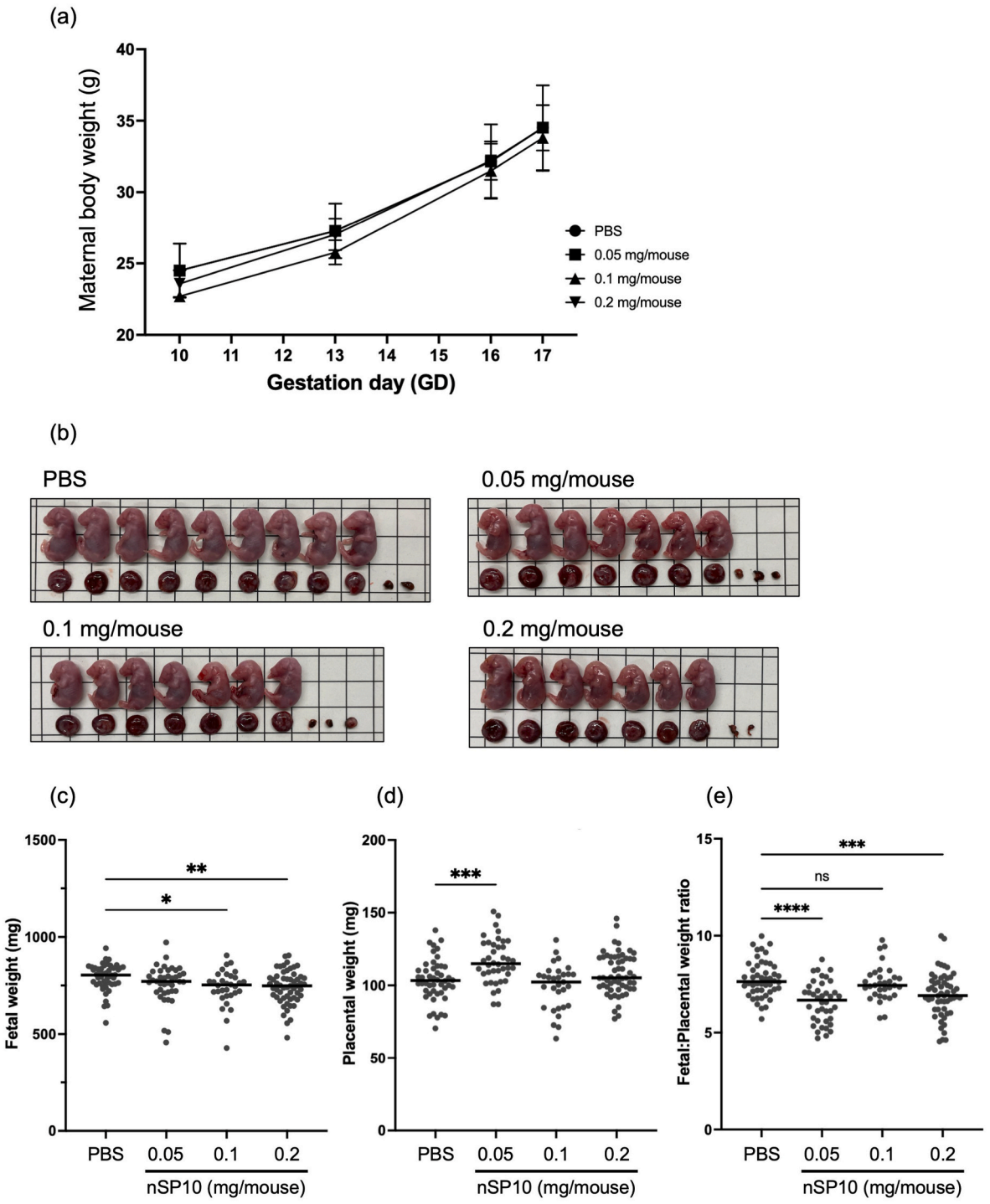


Fig. 1. Treatment of pregnant mice with nSP10 decreases fetal weight.
Pregnant BALB/c mice (n = 4–8 per group) were given a single intravenous injection of PBS or nSP10 at the indicated doses at gestational day (GD) 10 and were euthanized at GD17. (a) Maternal body weight at GD10–GD17. (b) Images of placentae and fetuses at GD17. The grid is 1 cm^2. (c) Fetal weight, (d) placental weight, and (e) fetus/placenta ratio. PBS, n = 48; nSP10: 0.05 mg/mouse, n = 40; 0.1 mg/mouse, n = 32; 0.2 mg/mouse, n = 56. Two independent experiments were performed, and the pooled data are shown. Data are means ± S.E. ns; not significant. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$.

evaluated its effects on the weights of the mother, placenta, and fetus. No significant differences in maternal body weight were observed at any of the four time points examined among nSP10- and PBS-treated groups (Fig. 1a). Fetal body length estimated visually was lower in the nSP10-treated groups than in the PBS-treated group (Fig. 1b). Fetal weight decreased in a concentration-dependent manner (Fig. 1c). Placental weight was significantly increased in the nSP10 (0.05 mg/mouse)-treated group, but the difference was insignificant at the other two doses (Fig. 1d). The fetal/placental weight ratio was significantly decreased in 0.05 and 0.2 mg/mouse nSP10-treated groups, but the difference was insignificant at 0.1 mg/mouse (Fig. 1e). These results suggest that nSP10 treatment during placental formation could restrict fetal growth in a concentration-dependent manner.

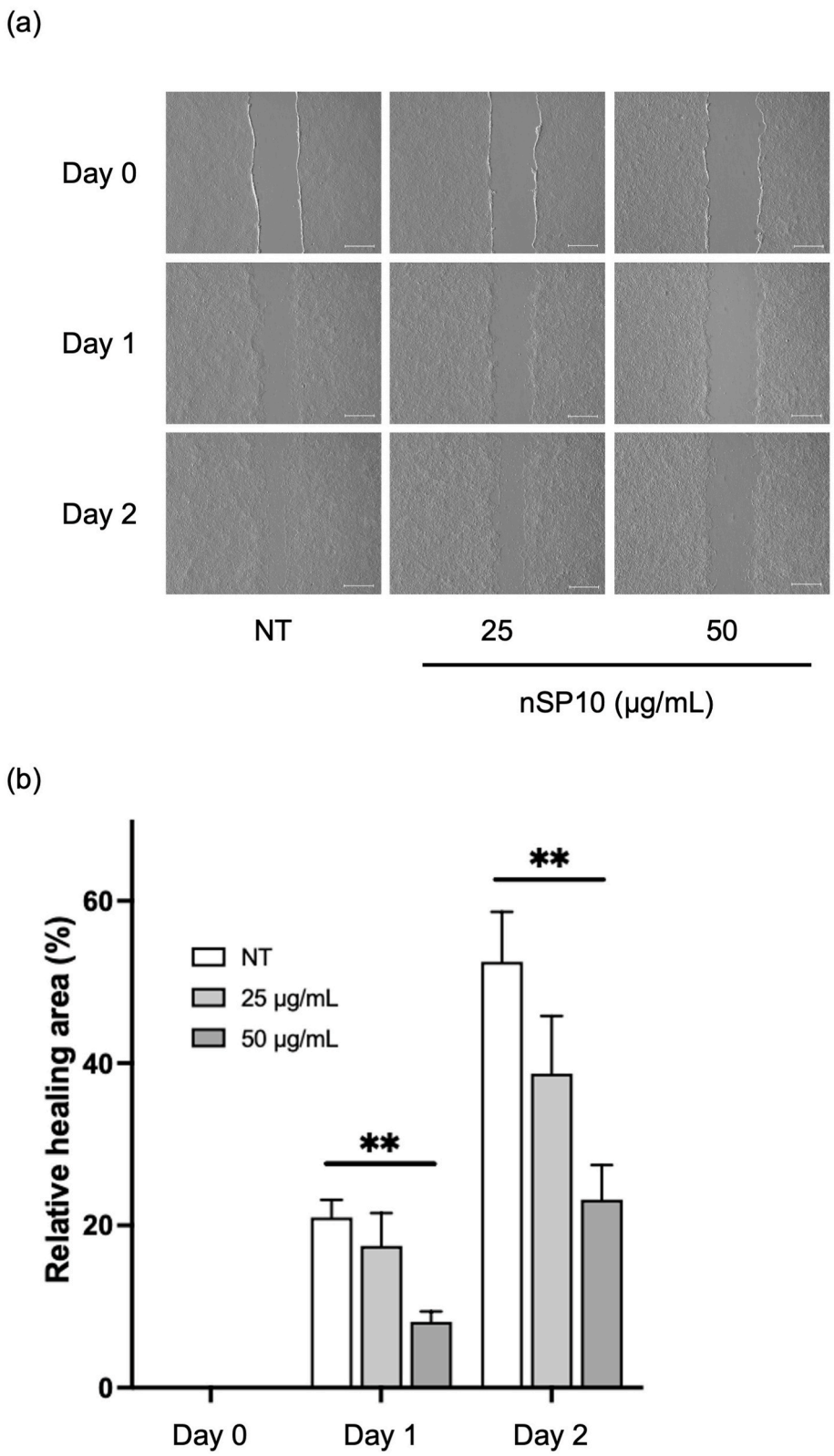
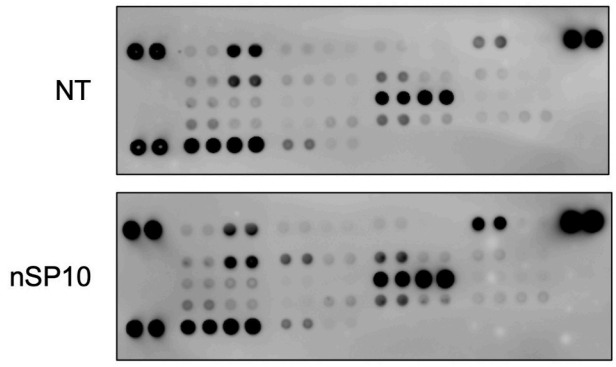


Fig. 2. nSP10 inhibits the migration of HTR-8/SVneo cells.
HTR-8/SVneo cells were treated with nSP10 for 72 h, the confluent cell monolayer was scratched, and the cells were cultured in FCS-free medium. (a) Representative images taken at the indicated time points after scratching. Scale bar = 500 μm. (b) The relative migration area at the indicated time points. Two independent experiments were performed. Data are means ± S.E. NT = not treated. $^{**}P < 0.01$.

(a)

P.S.	CCL1 /I-309	CCL2 /MCP-1	MIP-1α /MIP-1β	CCL5 /RANTES	CD40 Ligand /TNFSF5	Compliment Component C5/C5a	CXCL-1 /GROα	CXCL10 /IP10	P.S.
	CXCL11 /I-TAC	CXCL12 /SDF-1	G-CSF	GM-CSF	ICAM-1 /CD54	IFN-γ	IL-1α /IL-1F1	IL-1β /IL-1F2	
	IL-1ra /IL-1F3	IL-2	IL-4	IL-5	IL-6	IL-8	IL-10	IL-12 p70	
	IL-13	IL-16	IL-17A	IL-17E	IL-18 /IL-1F4	IL-21	IL-27	IL-32α	
P.S.	MIF	SerpinE1 /PAI-1	TNF-α	TREM-1					N.C.

(b)



(c)

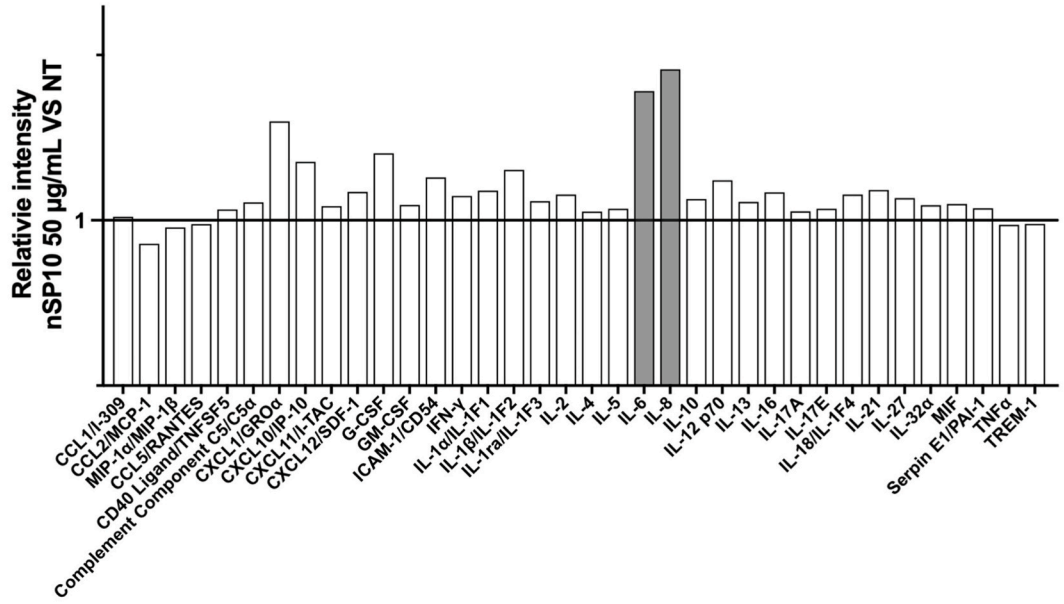


Fig. 3. Cytokine array assay of the supernatant of HTR-8/SVneo cells treated with nSP10. (a) Cytokine array layout. P.S., positive signal; N·C., negative control. (b) Luminescence images of cytokine array assay. Cells were treated with nSP10 (50 μg/mL) for 72 h, and the supernatant was analyzed. (c) Ratios of cytokine levels in supernatants from non-treated culture (NT) to those in the nSP10 supernatant.

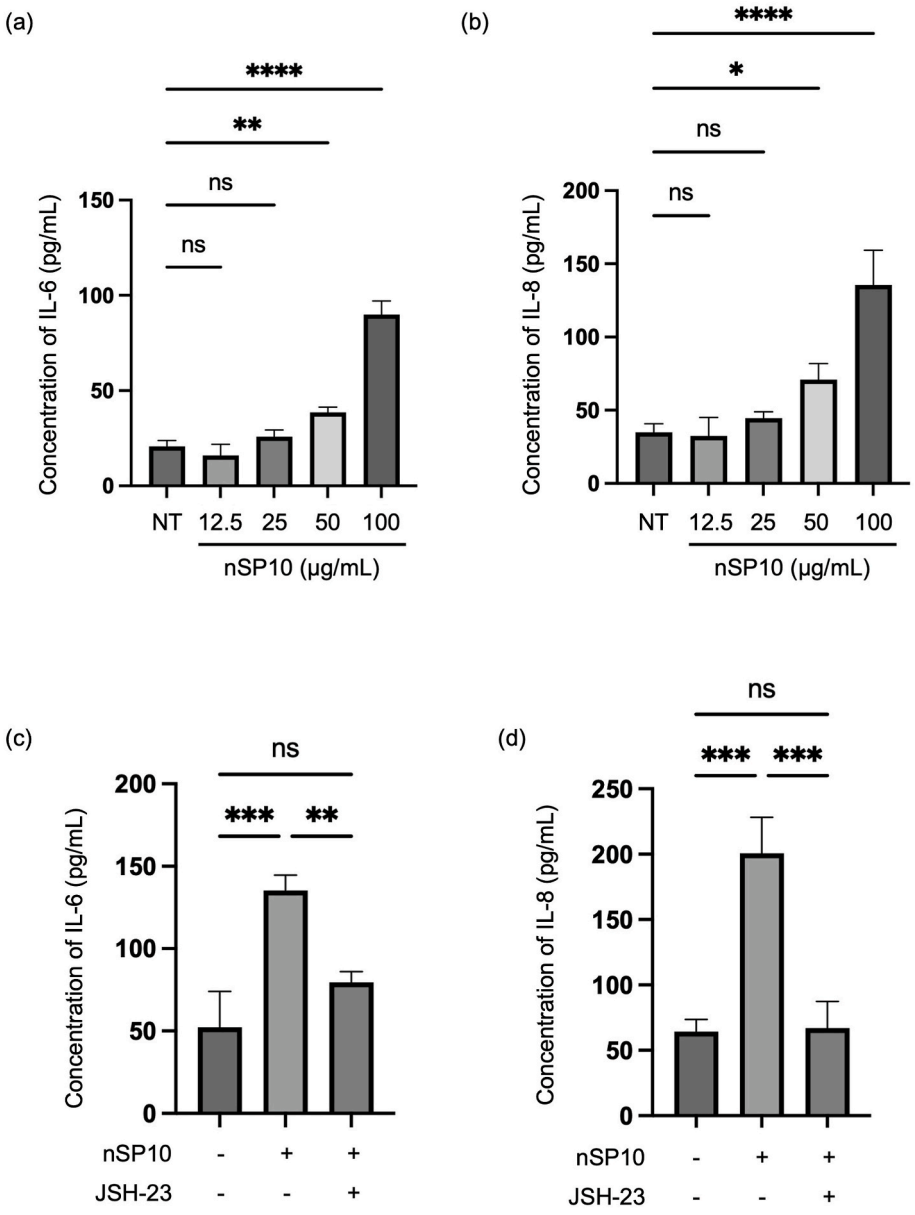


Fig. 4. Effect of nSP10 on cytokine concentration in the culture supernatant of HTR-8/Svneo cells.
Cells were treated with nSP10 at the indicated concentrations or nSP10 (50 μg/mL) with or without 5 μM JSH-23 for 72 h. Concentrations of (a, c) IL-6 and (b, d) IL-8 were measured by ELISA. Two independent experiments were performed. Data are means ± S.E (n = 3). NT = not treated. ns = not significant. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$.

3.2. *nSP10 suppresses migration of human HTR-8/SVneo cells*

During placentation, extravillous trophoblast (EVT) cells migrate from the placenta, invade the endometrium, replace vascular smooth muscle cells, and remodel the uterine spiral arteries to form vascular walls to supply sufficient oxygen and nutrients to the fetus [25]. Defective remodeling can affect the supply of nutrients to the placenta and restrict fetal growth [26]. To elucidate the mechanism of nanoparticle-induced fetal toxicity, we focused on the remodeling and evaluate the effect of nSP10 on migration ability of EVT cells. HTR-8/SVneo is a model cell line for EVT cells [27]. MTT assay revealed that 100 μg/mL nSP10 was cytotoxic, as it significantly suppressed cell proliferation in FCS-free culture medium (Supplementary Fig. 1); therefore, we used lower concentrations. Bright-field images of the scratched areas at 0, 24, and 48 h after scratching are shown in Fig. 2a. The relative migration area significantly decreased in a concentration-dependent manner in the nSP10-treated group (Fig. 2b), suggesting that nSP10 inhibits migration of HTR-8/SVneo cells.

3.3. *nSP10 increases IL-6 and IL-8 cytokine production via NF-κB nuclear translocation in HTR-8/SVneo cells*

The layout of the cytokine array is shown in Fig. 3a. Changes in cytokine production in HTR-8/SVneo cells treated with 50 μg/mL nSP10 for 72 h are shown in Fig. 3b. IL-6 and IL-8 tended to be increased by the treatment (Fig. 3c). Quantitation of IL-6 (Fig. 4a) and IL-8 (Fig. 4b) by ELISA in the supernatant of HTR-8/SVneo cells treated with nSP10 at 12.5, 25, 50, or 100 μg/mL revealed that IL-6 and IL-8 concentrations were increased in an nSP10-concentration–dependent manner. Transcription factor NF-κB plays a central role in immune responses and is an inflammatory mediator [28]; NF-κB nuclear translocation can be inhibited by JSH-23 [29]. HTR-8/SVneo cells were cultured for 72 h

with no treatment or with nSP10 alone (50 μg/mL) or in the presence of JSH-23 (5 μg/mL). The concentrations of IL-6 (Fig. 4c) and IL-8 (Fig. 4d) were significantly increased by nSP10 alone, and these increases were significantly suppressed by JSH-23. These results suggest that nuclear translocation of NF-κB is required for the increase in IL-6 and IL-8 production induced by nSP10.

4. Discussion

Concentrations of nSP10 used in this study were much higher than exposure in daily life. The estimated daily human intake of silica nanoparticles as a food additive is about 2 mg/kg body weight [30]. Silica nanoparticles are used not only as food additives in the food market, so other exposure routes are possible [4,5]. Further studies are needed to consider the intake amount, intake route, and intake period for risk analysis of silica nanoparticles.

The mechanism of fetal toxicity caused by nanoparticle exposure is important, but progress in its elucidation has been slow. We consider that understanding the signs of toxicity not only in the fetus but also in the placenta will help to elucidate the mechanism of nanoparticle-induced fetal toxicity. Cytokines IL-6 and IL-8 are involved in the control of uterine spiral artery remodeling by EVT cells [31]. They promote EVT cell migration and uterine artery remodeling [32], but IL-6 has also been reported to inhibit EVT cell migration and infiltration by excessively activating macrophages [33]. IL-6 and IL-8 may affect hormone production in villous trophoblast cells and uterine decidua: IL-8 stimulates progesterone secretion from villous trophoblast cells [34] and IL-6 stimulates prostaglandin secretion from endometrial stromal cells [35]. The increase in IL-6 and IL-8 production in placental cells induced by hSP10 may affect the function of surrounding villous trophoblast cells and uterine decidua.

In this study, we showed that nSP10 inhibits migration and increases the production of IL-6 and IL-8 in HTR-8/SVneo cells, but the limitation is that these phenomena were not verified *in vivo*. Since nSP10 did not affect mouse maternal body weight or placental weight, it likely decreased nutrient supply from mother to fetus because of EVT cell dysfunction rather than because of excessive maternal toxicity or failure of placental formation. Further studies are required to evaluate the effect of nSP10 on placental remodeling in pregnant mice and to elucidate its mechanism.

CRediT authorship contribution statement

Rena Yamamoto: Data curation, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. **Kazuma Higashisaka:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Risa Sakai:** Investigation, Validation, Visualization, Writing – review & editing. **Yurina Nakamoto:** Investigation, Writing – review & editing. **Momoe Serizawa:** Investigation, Writing – review & editing. **Yuya Haga:** Supervision, Writing – review & editing. **Yasuo Tsutsumi:** Funding acquisition, Project administration, Supervision, Writing – review & editing.

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Declaration of competing interest

All authors have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrc.2025.152803.

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