Role of methionine sulfoxide reductase A on cisplatin-induced acute kidney injury (AKI)

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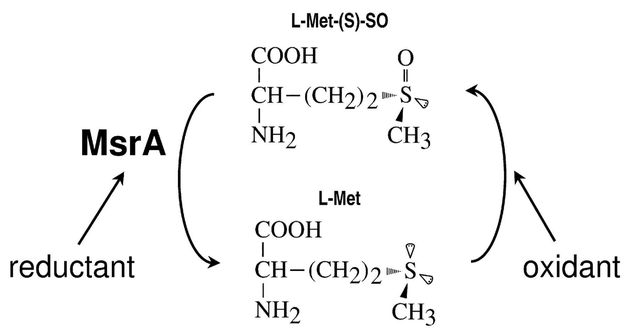
Abstract

Introduction and aims: Methionine sulfoxide reductase A (MsrA) reduces methionine-S-sulfoxide scavenging reactive oxygen species (ROS) and catalyzes the specific reduction of free and protein-based methionine-S-sulfoxide to methionine. This study is aimed to define the role of MsrA in cisplatin-induced acute kidney injury (AKI).
Methods: MsrA gene-deleted (MsrAKO) or wild-type (MsrAWT) mice were intraperitoneally injected with cisplatin or saline. Renal function and morphology were evaluated by the concentration of plasma creatinine and blood urea nitrogen (BUN) and PAS staining. ROS production and oxidative stress were determined in the kidney. Mitochondrial damage was determined by transmission electron microscopy (TEM) and mitochondrial damage markers.
Results: MsrA deficiency in mice exacerbated cisplatin-induced renal functional and morphological injuries. Cisplatin reduced the expression and activity of MsrA in the kidneys, resulting in the increase of ROS production and oxidative stress. These increases in ROS production and oxidative stress were higher in MsrAKO than MsrAWT mice. Mitochondrial fission 1 protein (Fis1) to mitochondrial fusion regulator (Opa1) ratio was greater in MsrAKO mice than MsrAWT mice after cisplatin injection. Indeed, TEM revealed that cisplatin resulted in mitochondrial fragmentation and damage in the proximal tubule cells and this mitochondrial damage was higher in MsrAKO than in MsrAWT mice. As estimated by increases in Bax to Bcl-2 ratio, cleaved caspase-3 level, and TUNEL-positive cell number, cisplatin-induced apoptosis in MsrAKO mice was greater than in that of MsrAWT mice.
Conclusions: These data demonstrate that MsrA deficiency exacerbates cisplatin-induced nephrotoxicity via increased mitochondrial damage, oxidative stress, and apoptosis, suggesting that MsrA represents a useful target protein for the treatment of cisplatin-induced nephrotoxicity.

Background



- **Methionine sulfoxide reductase A (MsrA)** catalyzes the reduction of methionine-S-sulfoxide to methionine.
- MsrA repairs oxidative damaged proteins by reversing the oxidation of methionine residues.
- The cyclic oxidation or reduction of methionine plays an important role for redox balance in the cell.
- **Aim**: to investigate a role of MsrA on the cisplatin-induced acute kidney injury (AKI).

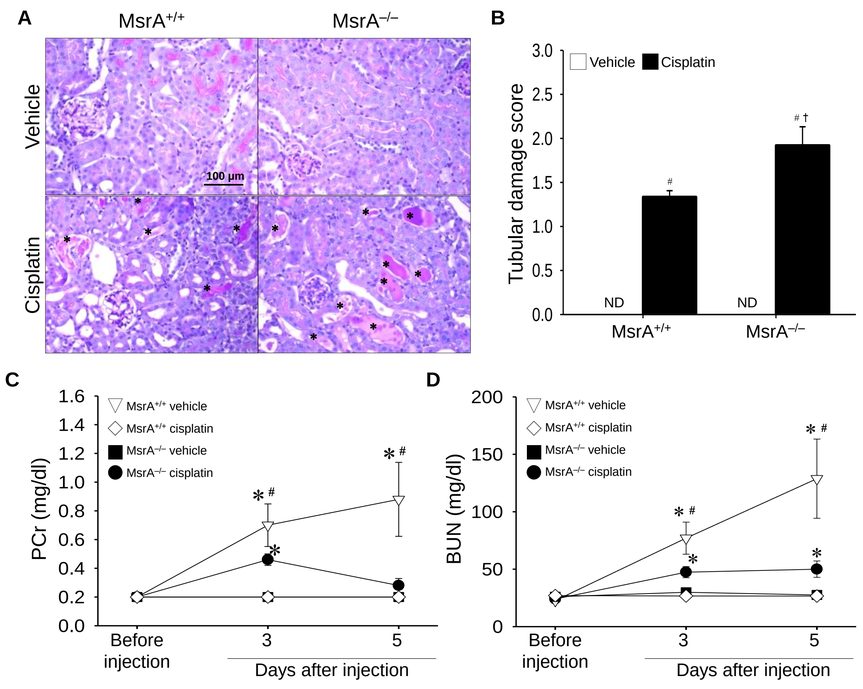
Materials & methods

Animal preparation

MsrA gene-deficient ($MsrA^{-/-}$) and wild-type ($MsrA^{+/+}$) C57BL/6 male mice

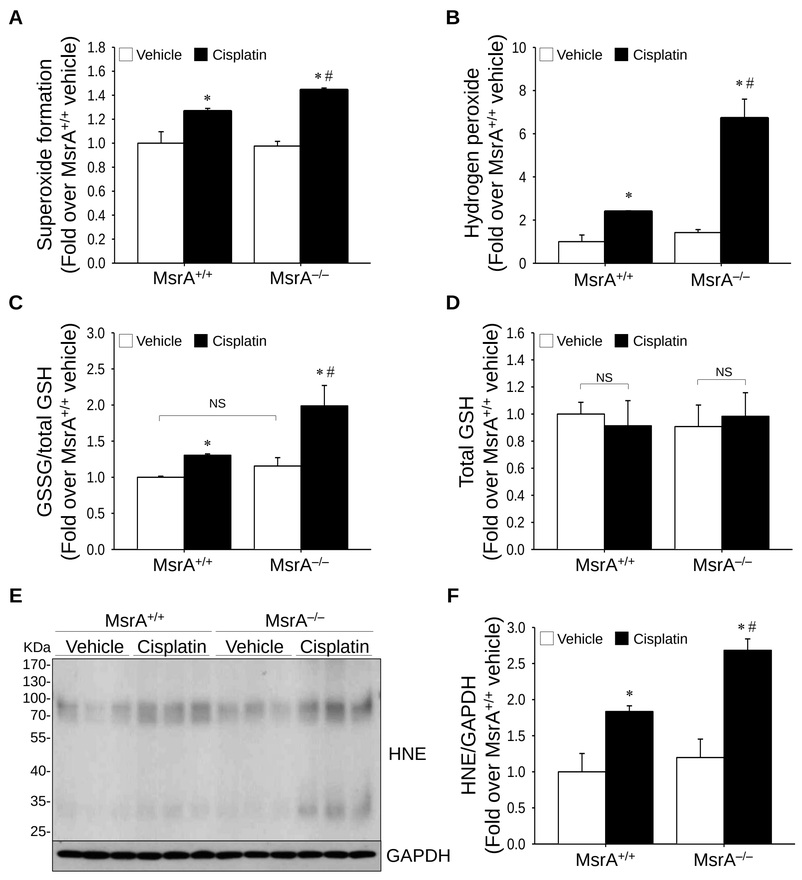
Results

1. Effect of MsrA gene-deletion cisplatin-induced nephrotoxicity.



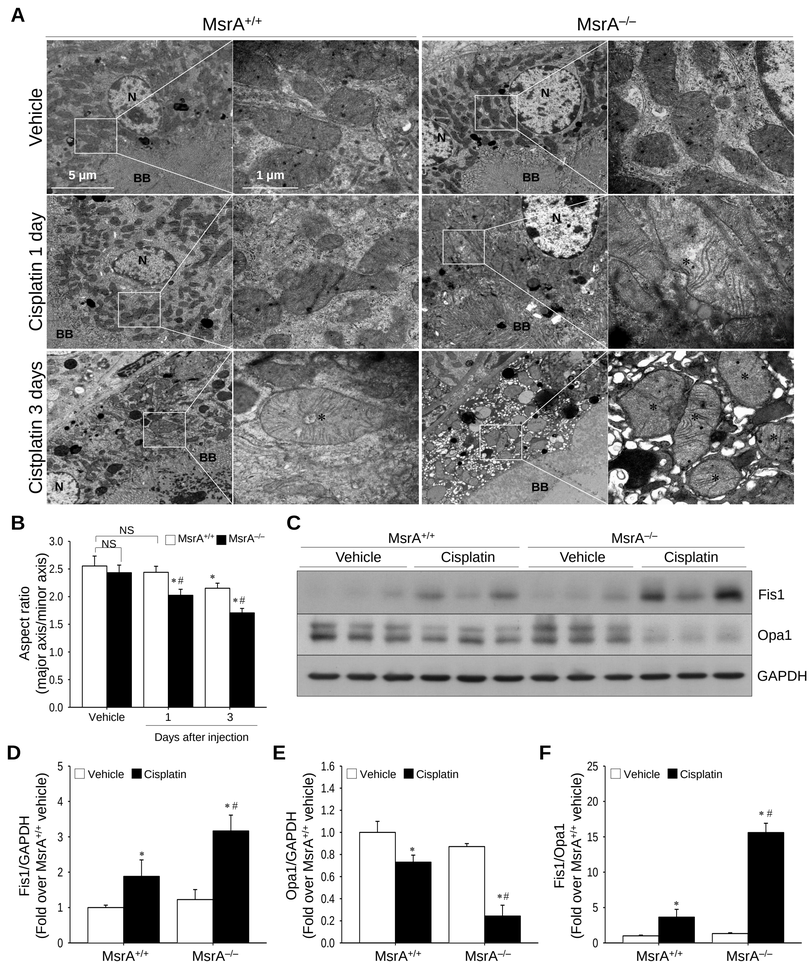
MsrA gene-deletion worsens cisplatin-induced functional and morphological damage.

2. Effect of MsrA gene-deletion on cisplatin-induced ROS production and oxidative stress.



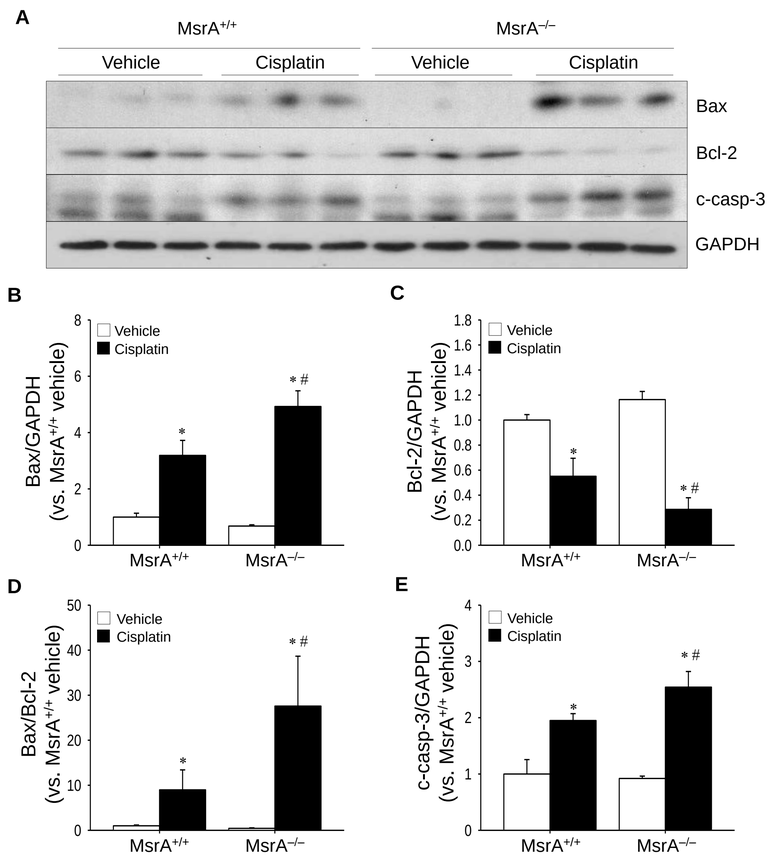
MsrA gene-deletion augments cisplatin-induced increases of ROS production, methionine oxidation, and oxidative stress.

3. Effect of MsrA gene-deletion cisplatin-induced mitochondrial injury.



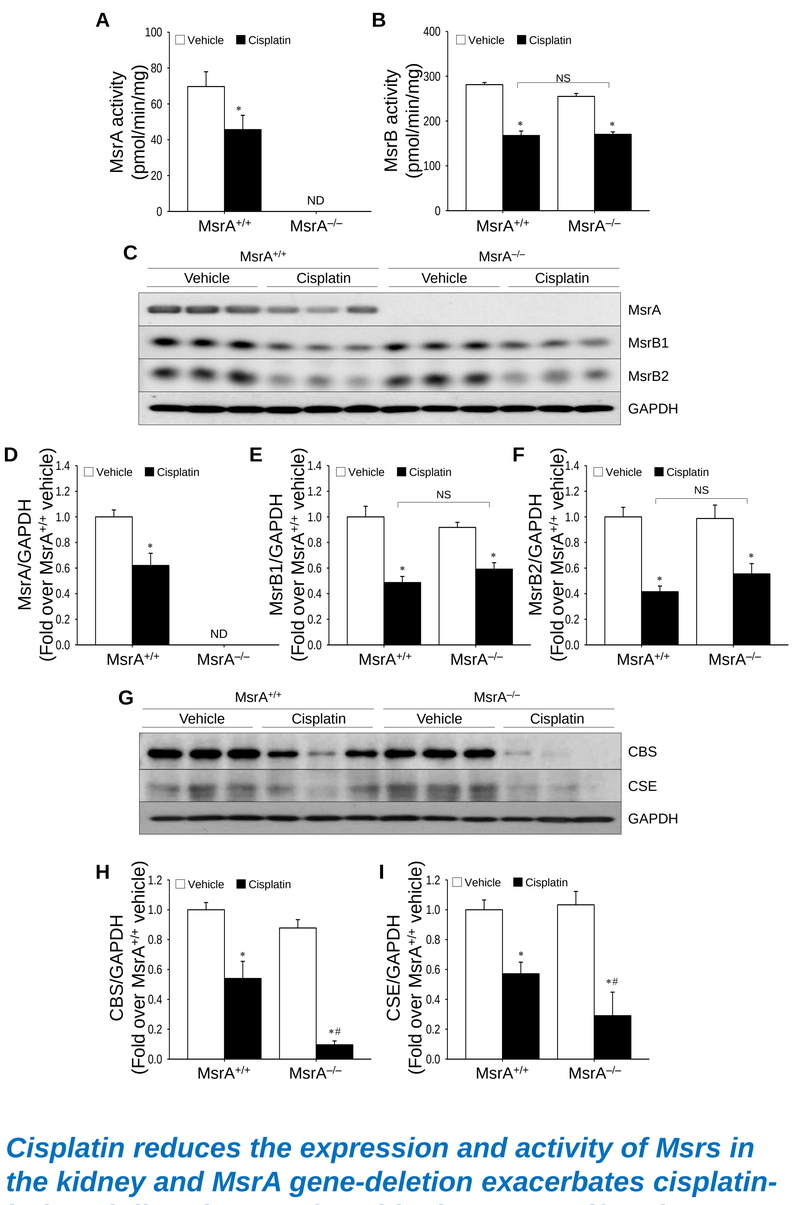
MsrA gene-deletion aggravates cisplatin-induced impairments of mitochondrial dynamics and mitochondrial damage.

4. Effects of MsrA gene-deletion on cisplatin-induced apoptosis.



MsrA gene-deletion augments the cisplatin-induced apoptosis in kidneys.

5. Effect of cisplatin on transsulfuration pathway



Cisplatin reduces the expression and activity of Msrs in the kidney and MsrA gene-deletion exacerbates cisplatin-induced disturbance of methionine transsulfuration pathway.

Conclusion

Cisplatin disrupts MsrA activity and transsulfuration pathway and MsrA gene-deletion worsens cisplatin-induced mitochondrial oxidative stress and apoptosis, suggesting that MsrA protects kidney against AKI.

54 ERA
173--SP
Experimental AKI I
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DOI: 10.3252/pso.eu.54ERA.2017
ePosters supported by F. Hoffmann- La Roche Ltd.
54th ERA-EDTA CONGRESS Madrid, Spain June 3rd-6th 2017
PosterSessionOnline.com