Synopsis of Original Research Paper

Elution of Ni ions from materials and enhancement by inflammation

Noriyasu Hirasawa

Laboratory of Pharmacotherapy of Life-style Related Diseases Graduate School of Pharmaceutical Sciences, Tohoku University

Nickel (Ni) is contained in various alloys, which are widely used in accessories and biomaterials, and causes inflammation and allergy. However, little is known about the regulation of Ni release from alloys in *vivo*. In this study, we established a novel *in vivo* model in which the release of Ni from metal wire could be analyzed quantitatively. A Ni wire (99.9 %; ø0.8 mm×5 mm) was implanted subcutaneously in the dorsum of mice. Ni ions in the skin tissue (diameter : 14 mm) on the wire were extracted and quantified by the fluorometry using Newport Green. The content of Ni ion in the tissue was significantly increased from 8 h. When lipopolysaccharide (LPS, 1 μg) was injected into the same site immediately after the implantation of Ni wire, the content of Ni ions in the tissue was significantly increased. These results suggest that the release of Ni from metal wires *in vivo* was enhanced by LPS-induced inflammation. The findings were confirmed by *in vitro* model using a macrophage-like cell line RAW264. RAW 264 cells (1×10^5 cells/mL, 0.2 mL) were seeded on a Ni plate (5 mm square) and incubated for 24 h in the medium containing LPS (0.1, 0.3 and 1.0 μg/mL). LPS enhanced the release of Ni by RAW 264 cells in a concentration-dependent manner. Interestingly, the enhancement was observed only when the cells were attached with Ni plate. The inhibitor of lysosome chloroquine (10 μM) and the V-ATPase inhibitor bafilomycin A_1 (1 nM) but not the Na^+/H^+ exchanger (NHE) inhibitor amiloride inhibited partially the elution of Ni by unstimulated RAW264 cells. In contrast, chloroquine, bafilomycin A_1 and amiloride potently inhibited that induced by the LPS-stimulated RAW264 cells. These results suggested that LPS-stimulated RAW264 cells caused the release of Ni ions via the release of lysosome and via the activation of V-ATPase and NHE. In conclusion, we established the novel models for the release of Ni from metals *in vivo* and *in vitro* and demonstrated that the activation of inflammatory cells apparently enhanced the release of Ni.