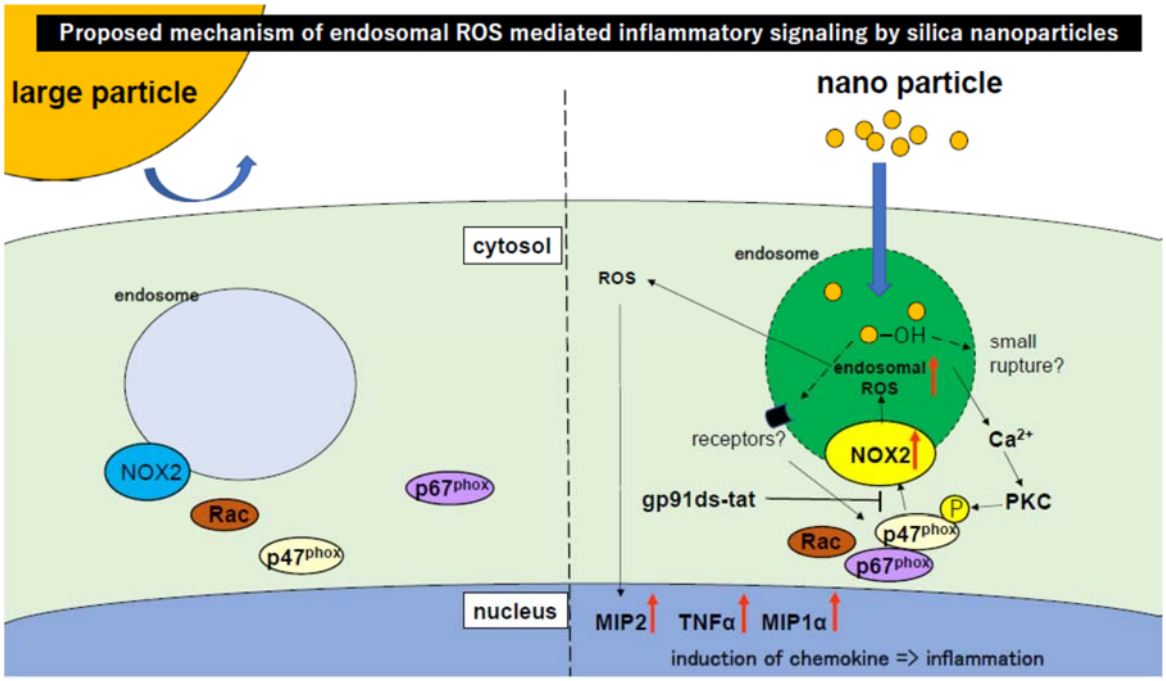
News Release

Title

Discovery of novel mechanism controlling lung inflammation induced by nano materials ~ Focused on the signaling inside small cellular organelles ~

Key Points

- **There is increasing concern about cellular and organ toxicities of "nanomaterials", nanometer- scale artificial materials, which have been widely applied in the area of industry, pharmaceuticals, and foods. Nevertheless, little is known about the precise mechanisms of the toxicity.**
- **A study lead by Nagoya University in collaboration with Osaka Prefectural University investigated the dependence of lung injury induced by silica nanomaterials on their particle properties in mouse model, and found that reactive oxygen species (ROS) in the endosomes, which is generated by the key enzyme "NOX2", can be the determinant of silica nanomaterial induced inflammatory response.**
- **Study suggested a novel target for development of preventive and therapeutic approaches against potential health hazard of nanomaterials.**



Summary

The research team led by Dr. Masahide Inoue (Graduate student), Dr. Koji Sakamoto (Assistant professor), and Naozumi Hashimoto (Associate Professor, Department of Respiratory Medicine) at Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu, MD, PhD) in collaboration with Dr. Makoto Sawada (Professor, Department of Brain Function, Research Institute of Environmental Medicine, Nagoya University) and Dr. Ikuhiko Nakase (Professor, Graduate School of Science, Osaka Prefecture University), investigated the mechanisms of lung inflammation induced by the deposition of nanomaterials in the lungs using mouse models, and found an important role of reactive oxygen species generated in the endosomes of macrophages as a critical regulator of lung inflammation.

Nanomaterials, nanometer-sized artificial materials made from carbon, silica, etc. have been widely applied in various fields such as food, cosmetics, and pharmaceuticals. As their amount of production has been increasing year by year, the concerns of their possible health hazards are also increasing. Especially, lungs are the organ of interest as it contacts to the atmosphere by respiration. Indeed, cases of organ injury induced by inhalation of particular materials have been reported. Therefore, it is warranted to better understand the mechanisms and develop therapeutic/prophylactic approach against nanomaterial induced lung toxicity.

The study team focused on the toxicity of silica nanoparticles, one of the representative nanomaterials in the industry. They created the mouse lung injury models using silica particles with different sizes and surface modifications, and assessed the severity of lung inflammation by them. The results revealed inflammation in the lungs caused by silica nanoparticles were substantially dependent on the size and surface chemical modification of particles. The team further investigated inside the macrophages which internalized silica nanoparticles, and found silica nanoparticles reside in the endosomes and increase reactive oxygen species production inside endosomes. They also revealed that inhibition of the key enzyme “Nox2” by specific peptides reduced the level of endosomal ROS and suppressed the production of proinflammatory mediators.

The research has been conducted under the supported by JST CREST program [Extracellular Fine Particles] (JPMJCR17H3). The present study has been published in the Particle and Fibre Toxicology on June 17, 2021.

Research Background

Nanomaterials are defined as materials having a diameter of less than 100 nm. As the application of nanomaterials continues to expand, increasing chances

of its exposure to the human body and potential harm are anticipated. Lungs are the organ which are continuously exposed to environment by respiration, therefore are at high risk of health hazard by inhalation of microparticles with toxicities. However, little is known about the understanding of the mechanisms and therapeutic approach against lung toxicity possibly induced by nanomaterials.

Research Results

The study team investigated the lung inflammation induced by instillation of 3 types of silica particles with different properties into the lungs. Silica nanoparticles (with 50nm diameters) induced severer lung inflammation compared with particles with larger diameters (3micron) or nanoparticles with surface chemical modification with amino residues. (Figure 1). The severity of lung inflammation correlated with the amount of the expression of chemokines (inflammatory mediators) by macrophages which internalized silica particles.

The researchers focused on the macrophages which take in particles in the lungs and explored the mechanisms which regulate the production of chemokine in macrophages. Tracking of silica nanoparticles revealed that silica accumulated inside endosomes of the macrophages and induced the production of ROS inside the endosomes. (Figure 2) As the levels of endosomal ROS well correlated with the production of chemokines in macrophages, the researchers assumed the endosomal ROS regulates inflammatory response by silica particles. The team confirmed that inhibition of “Nox2”, an enzyme responsible for ROS generation in endosomes, by specific inhibitory peptides efficiently suppressed the induction of chemokines by silica nanoparticles.

Research Summary and Future Perspective

As a summary, the research elucidated the importance of the properties (size and surface chemistry) as determinants of lung toxicity of nanomaterials. The research also suggested that ROS production in the endosomes is critical mechanisms of inflammatory reaction in phagocytes, and the key enzyme NOX2 may be its regulator.

The conclusion of the current research is based on the observation using silica nanoparticles. Now the team is investigating whether endosomal ROS mediated inflammatory regulation would be the common mechanism in toxicities by other nanomaterials and environmental particulate matters such as PM2.5. Also, their

research will aim to modulate endosomal ROS signaling via NOX2 as development of preventive and therapeutic approaches against potential health hazard of nanoparticles.

Figure 1: Extent of lung injury by silica particles are dependent on the properties of particles.

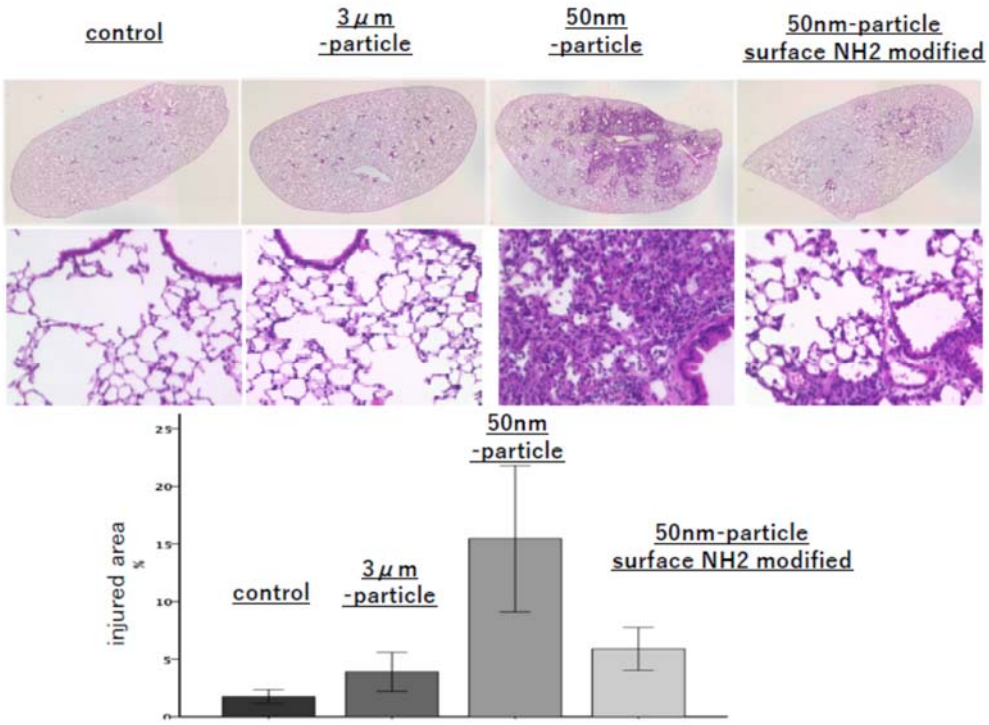


Figure 2: Visualization of intracellular localization of silica nanoparticles and activation of endosomal ROS production in macrophage which endocytosed silica nanomaterials.

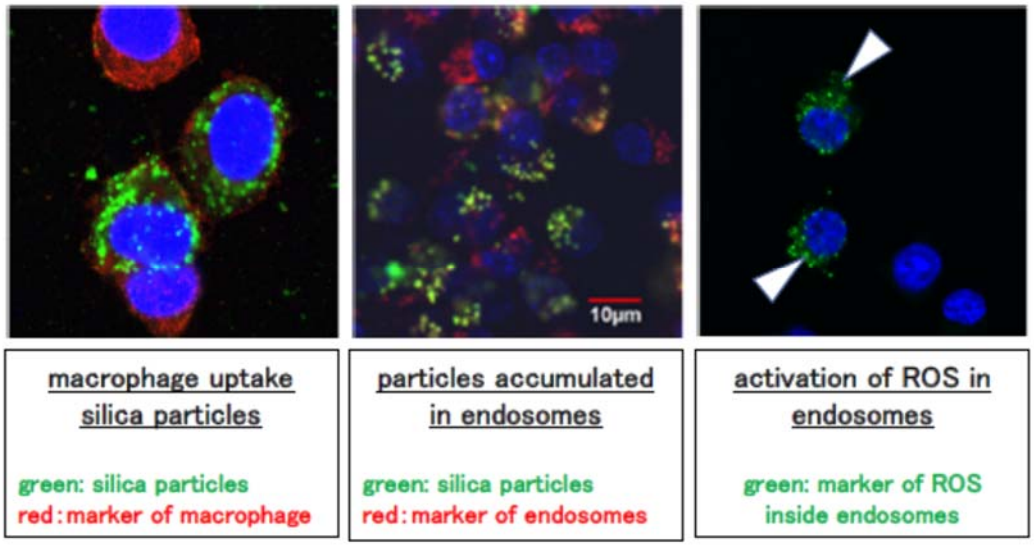
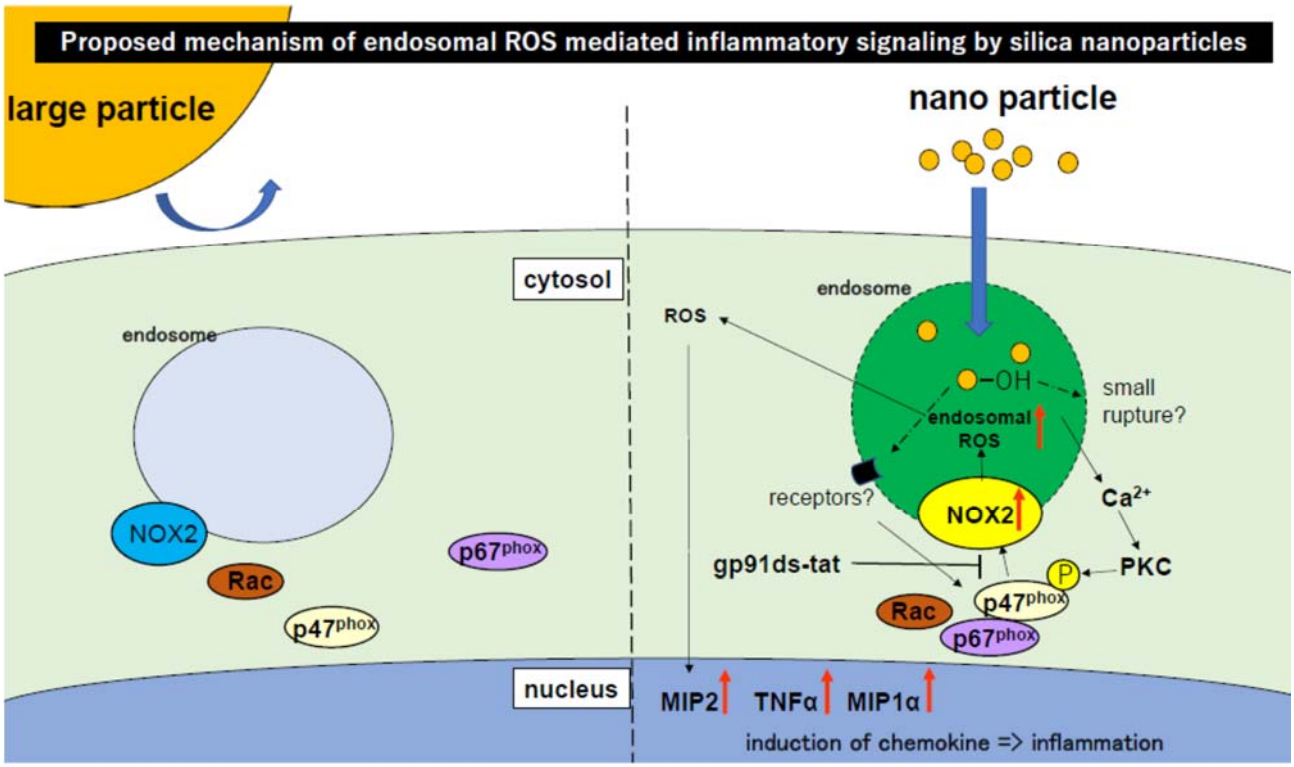


Figure 3: Schematic illustration of proposed mechanism for endosomal ROS-mediated inflammatory signaling in silica endocytosed macrophage



Publication

Size and surface modification of silica nanoparticles affect the severity of lung toxicity by modulating endosomal ROS generation in macrophages

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