論文の内容の要旨

Quantitative imaging analysis of nanoparticles and ions using laser ablation-single particle ICP-MS

**(レーザーアブレーション-単一粒子誘導結合プラズマ質量分析法による
ナノ粒子・イオンの定量イメージング分析)**

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Nanotechnology is attracting attention as one of the most important technologies to induce a new industrial revolution. Nanoparticles (NPs) are particles that range between 1 to 100 nm in size. NPs possess unique physicochemical properties and high reactivity compared to bulk materials with same chemical compositions due to small size and large surface area to mass ratio. Hence, NPs are widely used for many research fields such as biological, industrial, and medical sciences. Despite the widespread applications of the NPs, there are concerns about the potential risks for the living system. Faced with this, a new sensitive and rapid analytical technique for the NPs is desired.

Single particle inductively coupled plasma-mass spectrometry (spICP-MS) is a new analytical technique, enabling the detection and quantification of inorganic NPs at low concentrations (10^3–10^5 particles mL^{-1}). The spICP-MS is used to measure the elemental/isotopic signals emanating from each NP in solution samples, allowing determination of the particle size and particle number concentrations. The spICP-MS utilises fast data acquisition system (*e.g.*, <100 μs) to measure the NPs, with the analysis throughput of better than 100 particles per second. Despite the success in monitoring the particle sizes and particle number concentrations, the major disadvantage of the technique is that solid samples containing NPs have to be dissolved and suspended for analysis, and thus, the distribution

information on particles in solid samples is lost. In this thesis, the capabilities and modifications of spICP-MS for NPs analysis are discussed as two topics: development of analytical approaches to extend the analytical size range of NPs toward both smaller and larger region, and quantitative imaging analysis of NPs and ions in biological sample.

In the first chapter of this part, the basic principles of spICP-MS are reviewed. Each NP introduced into the plasma produces a burst of ions (one ion cloud per particle) that is measurable as a pulse signal. Since spICP-MS is a mass-based technique, signal intensity depends on the number of ions introduced into the plasma. Hence, particle diameter can be calculated from the determined mass, assuming the density of analyte and shape of a particle are known. Successively, new analytical approaches to extend the analytical size range of NPs toward both smaller and larger region are presented. For size analysis of small NPs (*i.e.*, <10 nm) using spICP-MS, two approaches were employed to improve signal-to-noise ratio of ion signals. The first approach was enhancement of the instrumental sensitivity using desolvation sample introduction system. Second approach was separation of the particle data from background data through deconvolution method. Combination of these approaches enabled us to measure 5 nm Au NPs. As for size analysis of large NPs (*i.e.*, >100 nm), the signal intensity of the analyte-related argide ion was monitored. With the $^{197}Au^{40}Ar^{+}$ signal, the signal intensities emanating from the Au NPs can be reduced to the 10^5 level. The reliability of the approach can be evaluated from the slope of regression line defined by NPs of three sizes (200, 300, and 400 nm). The wider analytical size range achieved in this thesis (*i.e.*, 5–400 nm) demonstrated that these approaches can be used for the various size of NPs.

In this study, spICP-MS coupled with laser ablation sampling technique (LA-spICP-MS) was applied to determine the size of Ag NPs, concentration of ionic Ag, and both the distribution of Ag NPs and ionic Ag on a frozen section of mouse liver (6 hours after intraperitoneal administered 60 nm Ag NPs (0.2 mg per mouse)). For size calibrations, a cellulose filter paper, which mimics the biological sample matrix, containing 60 nm Ag NPs were used. Moreover, for determination of ionic Ag concentration, a custom-made photocurable resin reference material was fabricated. Imaging data demonstrated that accumulation of the ionic Ag in certain regions was observed. The Ag NPs was also accumulated at regions where ionic Ag are. This suggests that there is a possible contribution of dissolution of Ag NPs through cellular activity. This is supported by the detection of many small Ag NPs (8–20 nm). The simultaneous imaging analyses of both NPs and ionic form will provide useful information to understand the mechanism of incorporation or metabolism of the NPs in living things.