学 位 論 文 内 容 の 要 旨
Abstract of Doctoral Dissertation

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Development of envelope-type lipid-coated gold nanorods for anti-cancer photothermal therapy

（癌の光熱療法を目指した脂質エンベロープ型金ナノロッドの創製）

Photothermal therapy (PTT) is currently an auspicious approach in treating cancer. This is exemplified by the use of gold nanorods (AuNRs) that produce heat in response to near infrared (NIR) irradiation. AuNRs are commonly prepared by using a highly toxic surfactant, cetyltrimethylammonium bromide (CTAB). Because of this, it is necessary to remove traces of CTAB while stabilizing the AuNR surface. In this study, the encapsulation of AuNRs in liposomes is reported. To develop this AuNR-multifunctional envelope-type nano device (AuNR-MEND), an SS-cleavable and pH-activated lipid-like material was employed as a component of the lipid envelope. Several methods were attempted in the process of encapsulation. Here, AuNRs were stabilized with bovine serum albumin (AuNR-BSA), and then further encapsulated in the lipid envelope by the ethanol dilution method. Change in the ζ-potential of the nanoparticles verified the modifications in coating. Encapsulation was confirmed by transmission electron microscopy (TEM) images. More importantly, the intrinsic properties of AuNRs in terms of heat production in response to NIR irradiation was retained after AuNR-MEND preparation.

The *in vitro* photothermal cytotoxicity of the AuNR-MEND was further demonstrated in 4T1 mouse breast cancer cells. After NIR radiation (750-900 nm) at 1 W/cm^2 for six minutes, the temperature of the medium was increased to approximately 60^{o}C, and cell viability was drastically decreased to approximately 11%. However, this cytotoxic effect cannot be explained simply from the point of view of temperature increase of the medium, since incubation of cells in medium that had been pre-warmed at 60^{o}C resulted in a slight decrease in viability (to approximately 70%). Intracellular delivery of the AuNRs therefore is a key factor for the high photothermal cytotoxicity. At a low dose, the photothermal cytotoxicity of AuNR-BSA was higher than that of AuNR-MEND. In contrast, a higher dose of AuNR-MEND resulted in the complete destruction of the cells when subjected to NIR irradiation, while the cell survival rate reached a plateau at 30% in the case of AuNR-BSA. Cellular uptake of AuNR-MEND has been shown to be dose-dependent and efficient.

Moreover, the increase in caspase-3 production suggests that apoptosis was induced after treatment with the nanoparticles.

As for the *in vivo* study, it has also been demonstrated that AuNR-MEND is long circulating, tumor-accumulating, and non-hepatotoxic in BALB/c mice. Thus, delivering AuNR by means of functionalized lipid nanoparticles represents a promising approach to induce NIR-triggered apoptosis without non-specific cytotoxicity. This doctoral work offers an innovative concept of AuNR-encapsulation into the lipid particle for applications of future tumor photothermal therapy.