Abstract of Doctoral Dissertation

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Precise Control of Thermo-responsive Properties of OEG-alkanethiol Modified Gold Nanoparticles
(OEGを有するアルカンチオールで修飾した金ナノ粒子の温度応答性の精密制御)

Gold nanoparticles have been widely studied due to their optical properties such as localize surface plasmon resonance (LSPR) under incident light irradiation, which accompanies with the absorption of incident light and heat production. Some anisotropic AuNPs like gold nanorod have a strong plasmon absorption in near infrared region and they are expected to be applied for bio-application such as the photothermal treatment of cancer, which kills tumor cells via heat produced by the nanorod under NIR irradiation. But this treatment damage to not only tumor tissues but also normal tissues. It is still a problem. On the other hand, gold nanoparticles have a plasmon absorption of visible light and assemblies of these particles show an absorption in near infrared region due to the interparticle plasmon coupling. As well-known, the body temperature in tumor tissues is slightly higher than that in normal tissues. Thermo-responsive assembly of AuNPs selectively in tumor tissues should be a good method to tumor-targeted photothermal treatment. For thermo-responsive assembly of gold nanoparticles, pNIPAm is a widely used polymer that undergoes phase transition over the LCST. Gold nanoparticles coated with this polymer can assemble in response to temperature. However, there are still some issues in the control this thermo-responsive assembly. First one is the uniformity. Polydisperse in synthetic polymers are supposed to form a variety of conformation on AuNP surface, resulting in broadening surface properties. Secondly, the thickness of surface coating depends on the molecular size. Polymers have large sizes, it leads to the large interparticle gaps on nanoparticle assembly. The large gap will weaken the intensity of plasmon coupling of gold nanoparticles. On the other hand, small molecular alkanethiol can solve these problems. Furthermore, OEG-attached alkanethiols have the thermo-responsive and bio-compatible properties. Our group have reported AuNPs modified with OEG-alkanethiol showed assembly/disassembly due to dehydration/hydration of OEG portion in ligands at a certain temperature (T_A). In addition, both decrease of terminal hydrophobicity in ligand and nanoparticle size caused the drastic increase of T_A, suggesting the controllable thermo-responsiveness. For bio-application, precise control of thermo-responsiveness is required. In this study, I focused on the surface modification to precisely control thermo-responsiveness.

As general introduction, in chapter 1, I introduced the merit of gold nanoparticles, thermo-responsive properties, OEG-alkanethiols and importance of precise control.

In chapter 2, I precisely tuned the T_A by surface modification using mixed ligand based on the relationship between the T_A and the terminal hydrophobicity, core size of AuNPs. According to previous research, T_A changed drastically using different ligands with various hydrophobic terminus. And the difference in T_A is wide. That is expected to tune T_A at between these T_A by mixing these ligands. Therefore, mixed ligands were applied to surface-modify the AuNPs to tune the terminal hydrophobicity, resulting in precise control of thermo-responsiveness. I modified gold nanoparticles with a mixture of two ligands with different hydrophobic at various ratio and determined their T_A. I found all T_A are located at between these two ligands, suggesting T_A can be tune by mixing ligands to control the hydrophobic terminus. Next, I used core size effect to precisely tune the T_A. T_A changed by control of the core size. AuNP size determining the local OEG density which directly relates to T_A is called core size effect. However, precise size control remains challenging. Therefore, in this study, I focused on the local OEG density to tune the T_A instead of changing size. It is expected to tune the local OEG density via surface modification using ligands with different OEG length. For tuning of local OEG density, gold nanoparticles were modified with a mixture of two ligands with different OEG length. T_A are also located at between these ligands, suggesting change of local OEG density have obvious effects on tuning of T_A. Above findings indicated that T_A can be precisely tuned in a wide range by surface modification with mixed ligands to control the hydrophobicity at the terminus and the local density of OEG portion. And these curves plotted with T_A at various mixing ligand ratio are supposed to be the reference of precise control of thermo-responsiveness. Nevertheless, it is worth noting that some curves showed the convex shape, whereas the linear relationship, suggesting the bias surface modification. To approach to bio-application, well control of surface composition is necessary.

In chapter 3, I investigated the factors leading to the bias surface modification and supported the precise control of

thermo-responsiveness by fair surface modification. In this study, I applied the OEG-alkanethiol ligands with similar structure which should equally attach to the AuNPs. However, the real composition of each ligand on surface seemed not to be in accord with the mixing ligand ratio. The bias surface modification suggested there are something influenced the composition on surface even though using the similar alkanethiols. It has been reported that ligand exchange between alkanethiols on AuNP and existing in organic solvent. If ligand exchange occurred on my experiment, the ligands in solution replace immobilized alkanethiols attach on AuNPs. It may result in the change in composition on surface. Therefore, ligand exchange can be one of the reasons of bias surface modification. Firstly, I investigated the ligand exchange by addition of the free ligand to modified AuNPs on heating. I confirmed the ligand exchange by analyses of the changes in thermo-responsiveness. Next, I performed kinetic analyses of ligand exchange by the time course experiment to investigate how ligand exchange give the effect on the surface modification. I found the ligand exchange occurred quickly and the replaced ligand can also return to AuNPs, suggesting unfair ligand exchange. Finally, based on the investigation of ligand exchange, I carefully prepared gold nanoparticle modified with the mixed ligand at 25 ℃, 24h. The fair surface modification can be realized successfully by well-control of reaction condition. In this study, I confirmed the ligand exchange between ligands in highly packed SAMs and existing in water. And the tiny difference in terminal hydrophobicity result in unfairness ligand exchange. Although it remains unclear how much unfairness on ligand exchange contributes to the bias surface modifications, the bias can be restrained by well-control of reaction condition.

In chapter 4, I summarized this thesis. To precisely control the thermo-responsiveness of AuNPs, I applied the mixed OEG-alkanethiol ligands to modify the AuNPs and take advantage of good controllability on terminal hydrophobicity and local OEG density of these mixed ligands to tune the thermo-responsiveness. Then, to restrain the bias on surface modification with mixed ligands, I investigated the possible factors such as ligand exchange influencing the bias surface modification. Based on this investigation, I found the good modification conditions, and performed carefully to approached to the fair surface modification. Although ligand exchange and bias surface modification are complicated and remains unclear, the precise control of thermo-responsiveness by fair surface modification have been realized under well control of reaction condition, which is a positive step to approach to bio-application.