Gold coated silver nanoflowers toward SERS-based intracellular pH sensing with low cytotoxicity

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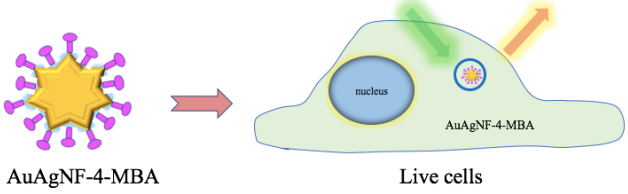
Intracellular pH has been viewed as a crucial factor reflecting the physiological condition of cells. Subtle changes of pH in a cell may lead to diseases. Therefore, the reliable and sensitive local cellular pH sensing is important for understanding many biological processes. Surface-enhanced Raman scattering (SERS) has been widely used in pH sensing because of the attractive advantages including noninvasive and ultrahigh sensitivity.[1] Since chemical enhancement is required for this sensing, use of silver nanoparticles as SERS substrate is ideal. However, the cytotoxicity of silver nanoparticles has been an issue.

We have recently developed a simple method to coat silver nanoparticles with very thin gold layer on a polydimethylsiloxane film.[2] This gold thin layer successfully provides oxidation resistivity while broad spectral range SERS sensitivity of silver nanoparticles, namely at visible light frequency. Here, we applied this coating method to silver nanoparticles in a colloidal solution to realize local pH sensing with low toxicity in a live cell. We successfully obtained silver nanoparticles with flower like morphology (silver nanoflowers: AgNFs) with a good dispersity in aqueous solution. Then coating the AgNFs with thin gold layer (AuAgNFs) was conducted by adding $HAuCl_4$ at pH 11 to suppress galvanic replacement reaction.[2] The obtained AuAgNFs maintain the morphology of nanoflower-like morphology and high enhancement factor for SERS detection. The cytotoxicity of AuAgNFs exclusively decreased compared to the AgNFs thanks to the gold layer coating. The A549 cell viability of AuAgNFs incubated after 24h showed 98.9±3.1 %, while 38.5±3.0 % of AgNFs. Here we used 4-mercaptobenzoic acid (4-MBA) as pH probe molecule. We investigated Raman spectra with different incubation time for pH sensing. pH decreased with the time went by most likely due to the migration of AuAgNFs from endosome to lysosome, indicating that it can be used to monitor the pH of live cells. The designed pH nanoprobe should have great potential for single cell analysis on account of the excellent biocompatibility and strong SERS enhancement capability.

Reference

1. Pallaoro et al. *Small* **2010,** 6, (5), 618-622.
2. Fortuni et al. *Chemical Communications* **2017,** 53, (82), 11298-11301.



Scheme 1 Schematic illustration for the pH sensing