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Molecules in focus

Metal nanoclusters: Protein corona formation and implications for biological applications

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ABSTRACT

Metal nanoclusters (NCs) are a new type of nanoprobe with great potential in various biological applications. For biocompatible and efficient utilization of NCs, a thorough understanding of their interactions with biological systems is highly important. Herein, we focus on recent studies addressing interactions between metal NCs and proteins as well as implications for their further biological application. These findings show that protein adsorption not only affects the photophysical properties of NCs, but also influences their subsequent biological behavior, i.e., cellular uptake and cytotoxicity. Moreover, specific protein–NC interactions have also been harnessed to develop novel protein discrimination strategies.
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1. Introduction

Metal nanoclusters (NCs), composed of a few to roughly a hundred atoms, are a new type of nanomaterial that are being investigated intensively at present (Shang et al., 2011; Zhang and Wang, 2014). Metal NCs typically possess diameters below 2 nm and physicochemical properties that place them in-between isolated atoms and larger nanoparticles (NPs). For NC dimensions approaching the Fermi wavelength of electrons, the continuous density of states breaks up into discrete energy levels, leading to optical, electronic and chemical properties that are markedly different from those of bulk metals (Zheng et al., 2007). Most importantly, these ultrasmall metal NCs can exhibit strong photoluminescence (PL). Combined with other distinct advantages, including ultrasmall size, attractive photophysical properties and facile synthesis, metal NCs show great promise for biological applications such as cellular imaging (Yin et al., 2015; Zhang et al., 2014a) and cancer therapy (Hembury et al., 2015; Zhang et al., 2014b).

In order to ensure reliable and safe use of NCs in biological applications, their interactions with the biological environment need to be thoroughly explored. Upon entering a biological milieu, nanoparticles (NPs) will inevitably come into contact with a huge variety of biomolecules including proteins, sugars and lipids. Recent studies have shown that these biomolecules immediately coat the NP surfaces and form a so-called 'protein corona' (Treuel and Nienhaus, 2012), an adsorption layer of proteins that determines the biological identity of the NPs (Lynch et al., 2009) and influences their subsequent biological behavior (Akesson et al., 2012; Serpooshan et al., 2015; Tenzer et al., 2013). Moreover, considering the large surface-to-volume ratio of ultrasmall NCs, surface changes are likely to alter their photophysical properties, which in turn affect their performance as luminescent labels. Consequently, understanding NC–protein interactions is of great value to further advance the development of metal NCs for bionanotechnology applications (Shang and Nienhaus, 2013). Until recently, there have only been a few attempts to address this important issue. Here we will summarize some recent work in this area.

2. Structure and properties

Bare NCs are unstable in solution, so they need to be protected by ligands, e.g., thiolates, phosphines or polymers. In general, determination of the atomic structure of nanostructured materials is challenging because their typically heterogeneous structures preclude crystallographic structure analysis (Billinge and Levin, 2007). Recent advances in X-ray crystallography and computation

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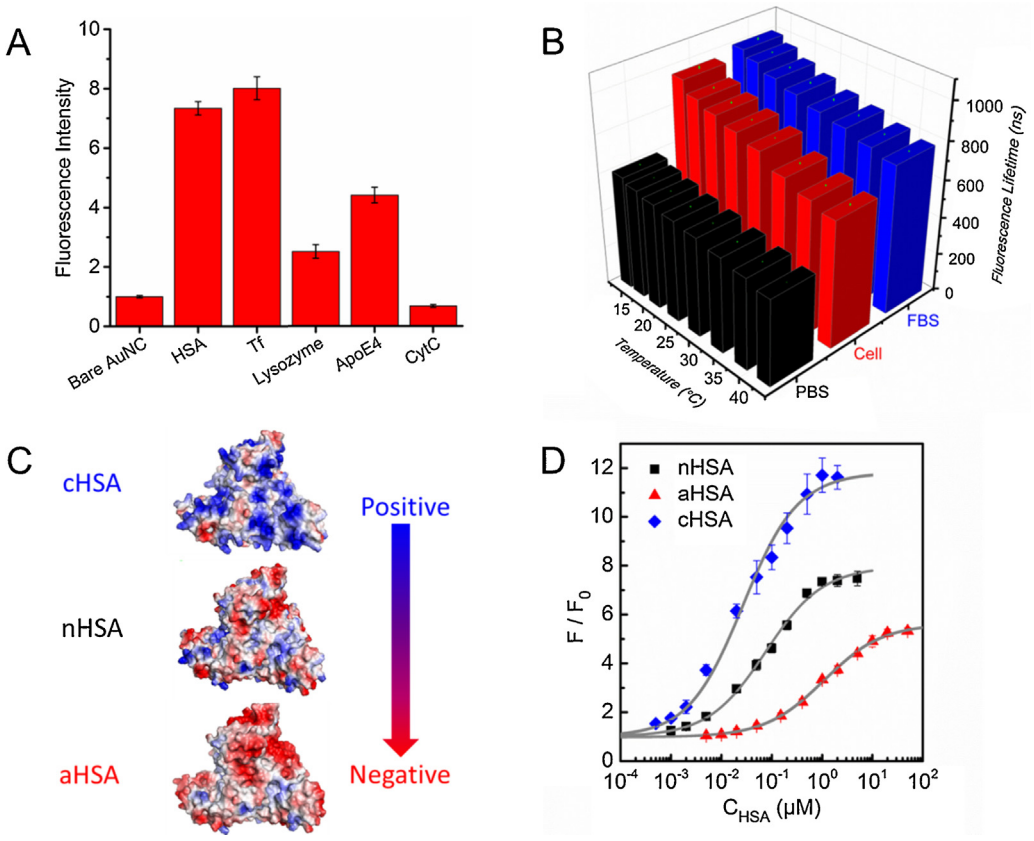

Fig. 1. (A) Luminescence intensity enhancement of DHLA-AuNCs in the presence of different proteins (1 μM) in phosphate buffered saline (PBS) solution (the intensity in bare PBS was set to one). (B) Average luminescence lifetime of AuNCs versus temperature in PBS (black), HeLa cells (red) and Dulbecco's modified eagle medium (DMEM) with 10% fetal bovine serum (FBS). (C) Chemical modification of HSA to vary its surface charge. Red and blue colors in the protein structure correspond to negatively and positively charged patches, respectively, calculated by using the PyMOL software. (D) Dependence of the luminescence enhancement on protein concentration. The gray lines represent fits to the data using the Hill equation (Röcker et al., 2009). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Images reproduced with permission from Wiley (Shang et al., 2014).

have allowed the structures of atomically precise metal NCs to be resolved (Qian et al., 2012). NC structure analysis with atomic resolution provides detailed structural information about the metal core and thiolated ligands, also known as staple motifs, around the core, which greatly aids in understanding their unique physicochemical properties and, specifically, the structure-luminescence relationships of thiolated AuNCs. For example, single-crystal X-ray crystallography on phenyl-ethanethiol-coated Au_{25} NCs revealed a central icosahedral Au_{13} core and an exterior shell made of 6 S–Au–S–Au–S staples (Zhu et al., 2008). Later, ultrafast spectroscopy revealed that the emission of Au_{25} NCs at 500 nm fundamentally arises from electron-hole recombination within the Au_{13} core with little perturbation by surface ligands, whereas near-infrared emission at 700 nm is dependent on a passivating monolayer and involves a relaxation of the core excited states to S–Au–S–Au–S semi-ring states (Devadas et al., 2010). Recently, the important role of ligands in modulating the luminescence of metal NCs has been addressed. Specifically, surface ligands can modulate the luminescence of metal NCs in two different ways: (i) charge transfer from the ligands to the metal core via the Au—S bonds, and (ii) direct donation of delocalized electrons from electron-rich groups of the ligands to the metal core (Wu and Jin, 2010). Although significant progress has been made in elucidating the physicochemical properties of NCs, further studies are needed to obtain a profound understanding of the relation between the detailed NC structure and the luminescence properties.

3. Interactions with proteins

Recently, we investigated the interactions of proteins with ultrasmall AuNCs coated with dihydrolipoic acid (DHLA-AuNCs, diameter 3.2 nm) by using steady-state and time-resolved fluorescence and X-ray photoelectron spectroscopy (XPS) (Shang et al., 2012a). Employing human serum albumin (HSA) as a model protein, we noticed that its presence in phosphate buffered saline (PBS) solution markedly enhanced the luminescence emission from the colloidal AuNCs. Concomitantly, the average luminescence lifetime was significantly prolonged. Similar luminescence variations were observed with apotransferrin (Tf), lysozyme, apolipoprotein E4 (ApoE4) and cytochrome C (CytC) (Fig. 1A). The extent of luminescence variation was strongly dependent on the particular type of protein, which likely originates from their different capabilities to screen the AuNCs against the aqueous solvent. For CytC adsorption, we note that quenching by the heme cofactor may be responsible for the weak photoluminescence. A quantitative analysis of the multiexponential luminescence decay showed that HSA binding mainly affected the slowest decay component, which is associated with luminescence from Au(I)-thiol complexes on the AuNC surface (Forward et al., 1995). In agreement with this finding, XPS measurements revealed an essential contribution from NC surface states to the luminescence enhancement. Similar changes in the emission upon protein adsorption have also been reported for other NCs, such as AgNCs (Shang et al., 2012b) and Au/Ag alloy NCs (Le Guevel et al., 2012). These results clearly show that the photophysical

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