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REVIEW

Using the power of organic synthesis for engineering the interactions of nanoparticles with biological systems

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Summary The surface properties of nanoparticles (NPs) dictate their interaction with the outside world. The use of precisely designed molecular ligands to control NP surface properties provides an important toolkit for modulating their interaction with biological systems, facilitating their use in biomedicine. In this review we will discuss the application of the atom-by-atom control provided by organic synthesis to the generation of engineered nanoparticles, with emphasis on how the functionalization of NPs with these ''small'' organic molecules (Mw <1000) can be used to engineer NPs for a wide range of applications.

Introduction

Fabricating nanoparticles (NPs) with unique biological properties is a challenging but rewarding task [1—3]. The combination of multiple NP features such as core size [4—7], shape [8—10], and surface chemistry [11,12] allows the regulation of the biological behavior. The NP surface is the interface with the outside world, and plays a prominent role in the interaction with biomolecules. The relatively large surface area of NPs facilitate the attachment of a wide range of biomacromolecules such as peptides [13,14], proteins [15,16], nucleic acids [17,18], and viruses [19] to dictate NP-protein or NP-cell interactions. Likewise, polymers have been widely employed as NP coverages [20]. The structural complexity and/or potential biodegradability of these macromolecular systems, however, introduce complexity to the interactions between NPs and biomolecules.

The use of non-polymeric ''small'' organic molecules provides a robust and scalable methodology to tailor the nano-bio interface. The wide variety of moieties available through organic chemistry provides a rich toolkit to provide atom-by-atom control of the NP-biomolecule interactions [21—23]. In this review we will present research focusing on controlling the interactions of NPs with proteins and cells by using these ''small'' molecule (Mw <1000) ligands.

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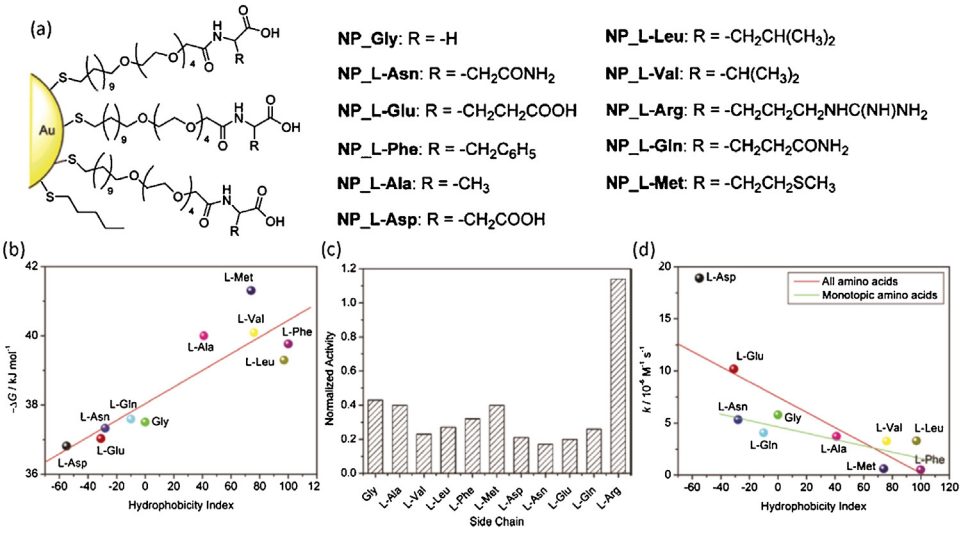

Figure 1 (a) Structures of amino acid functionalized AuNPs. (b) Correlation between Gibbs free energy changes and hydrophobicity index of amino acid side chains. (c) Normalized activity of ChT (3.2 μM) with nanoparticles (0.8 μM) bearing various amino acid side chains. (d) Correlation between the denaturation rate constants (*k*) of ChT and the hydrophobicity index of amino acid side chains in nanoparticles.
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Modulating the Interaction between NPs and biological systems

The interaction modes of NPs with proteins and cells can be modified by designing the surface monolayer, concomitantly modulating biological functions [24]. This fine-tuned control provides a finely honed tool for a wide array of biological interactions.

Modulating enzyme-nanoparticle interactions

Engineered interactions between NPs and enzymes provide tools for both enhancing enzyme stability and regulating activity. Decorating NPs with engineered ligands facilitates the 'dialing in' of specific modes of interaction including electrostatic, hydrogen bonding, and van der Waals forces [25]. This capability has been demonstrated using anionic gold nanoparticles (AuNPs) and chymotrypsin (ChT), utilizing the positive ''patch'' around the ChT active site [26,27]. The studies demonstrated that the anionic surface of NPs can selectively recognize this cationic patch, thus inhibiting ChT activity [28,26,29]. Similarly, a variety of amino acid-terminated ligands bearing tunable charge and hydrophobicity (Fig. 1(a)) provided detailed information about NP-ChT interfacial recognition. A thorough examination of the binding constants revealed that AuNPs bearing hydrophobic groups bind more strongly to ChT than AuNPs with hydrophilic groups, indicating the importance of hydrophobic interactions at the interface (Fig. 1(b)) [30]. In addition to hydrophobicity, the chirality of the amino acids is also an important factor for the affinity of NPs and proteins [31]. These results demonstrate that very specific chemical features can be employed to modulate protein recognition. Furthermore, these studies also evidenced that unlike small molecule enzyme regulators, the binding affinity of NPs to enzymes is not the only factor that modifies the catalytic activity. The work from Rotello et al. showed that the reduction of enzymatic activity mediated by NPs was also observed when NPs were functionalized with hydrophilic ligands because of the denaturation of ChT caused by these functional groups (Fig. 1(c) and (d)). Likewise, Hamad-Schifferli et al. reported that irreversible denaturation of Glucose Oxidase (GOx) caused by the interaction with NPs had a negative effect on its enzymatic activity [32]. Recently, Das et al. reported that NPs can also improve enzymatic activity [33]. Their investigation on the activity of mitochondrial membrane Cytochrome c (Cyt c) bound with cationic NPs demonstrated the enhanced peroxidase activity by increasing hydrophobicity of NPs. Structural reorganization caused by hydrophobic NPs exposed the heme group of the enzyme, facilitating substrate access to the catalytic site.

In stark contrast to their ability to denature protein, functionalized NPs have been used as synthetic chaperones that assist in the refolding of denatured enzymatic proteins. For instance, fully recovery of enzymatic activity of thermally denatured cationic proteins such as ChT and papain has been observed using malonic acid-functionalized anionic AuNPs followed by disruption of the protein-NP complex with aqueous sodium chloride [34].

Enzymatic activity can also be modified by using the NPs functionalized with specific small molecule enzyme inhibitors or activators. Supuran and co-workers coated AuNPs with an inhibitor of carbonic anhydrase (CA), and the NP displayed higher selectivity toward tumor associated isoform IX over the cytosolic isozymes I and IIIX [35]. Likewise, CA showed increased enzymatic activity when mixed with NPs bearing a CA activator [36]. These studies show functionalization on NP surface can modulate the activity of small molecule enzyme regulators, providing a new platform for the enzyme regulation.