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Review article

Bio-nano interface: The impact of biological environment on nanomaterials and their delivery properties

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ABSTRACT

The past several decades have witnessed the rapid development of nanomedicine (NM) which integrates the advancement of various interdisciplinary areas of science, engineering, and medicine. While a few clinical successes of NM greatly change the landscape of disease diagnosis and treatment, there are several areas of NM remaining to be explored. One such area is the complicated interactions between the NM and biological environment post administration, and how such interaction affects the biological performance of NM. Here, we review the recent progresses on this topic and discuss the interaction of NM with microscopic biomolecules, cells, and the macroscopic *in vivo* environment. The complete profiling of the bio/nanomaterials interface and interaction should have profound impact on the optimization and *de novo* design of new NM with better *in vivo* performance.

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1. Introduction

Nanomedicines (NMs) have been extensively studied as novel therapeutic and diagnostic agents [1–9] with unprecedented properties *in vitro* and *in vivo* over molecular agents. While several platforms of NM have been investigated including liposomes, polymeric nanoparticles [10–18], carbon materials [19–23], and inorganic particles [24–28], clinical success is limited [29–31]. NM shows prolonged blood circulation and reduced side effect compared to free drugs. Although the biodistribution of NM platforms have been systemically studied by using various imaging techniques including PET/CT [32–34], SPECT [33], optical imaging [35,36], *etc.* [37], limited knowledge is obtained concerning how NM is transported *in vivo* and in which form they are in the tissues, because the imaging techniques can only tell whether the nanomaterials/labeling molecules are present [38]. Nevertheless, understanding how NM interacts with the biological environment *in vivo* is obviously of paramount importance, which will provide guidance to the rational design of drug delivery systems with better therapeutic outcome.

After administration of nanomaterials to live animals, various biological environments will be encountered before therapeutic effect is achieved, such as the complex biological components at the local injection/delivery site [39–41] (subcutaneous tissue, gastrointestinal tract, *etc.*), biological fluid (serum, lymphatic fluid), disease tissues (extracellular proteins, supportive cells, cell membranes), and intracellular compartments (Fig. 1). Local environment of the injection site first interacts with the NM and instantaneously change the biological identity of the nanomaterials because proteins and other biomolecules rapidly adsorb onto the surface of the nanomaterials even though the surface of nanomaterials is modified with stealth coating [42]. After the NM crosses the local administration barrier and reaches the blood circulation, more complicated interactions between NM and the body are involved as the fluid contains a variety of flowing cells and biomolecules. Subsequent processes such as extravasation into local disease tissues, penetration into deep space of tissues far from blood vessels, cellular uptake, and intracellular transport can alter the NM property as well.

Here, we reviewed recent progresses in the understanding of biological effect on nanomaterials, *i.e.* how nanomaterials are affected by biological systems (BSs) under physiological conditions. Three levels of interactions between NM and BSs are discussed, including the interactions of NM with biomolecules, cells, and the *in vivo* environment.

2. Adsorption of biomolecules on nanomaterials

Interaction of NM with biomolecules is the fundamental basis of NM-cell and NM-tissue interactions and is the most widely studied NM-BS interactions. Researchers are able to elucidate different aspects of biomolecule adsorption on NM based on *ex vivo* mimics [43,44]. The intrinsic properties of NMs including size [45–47], shape [48–51], surface property (charge, hydrophobicity, *etc.*) [52], and bulk stiffness [53] can dramatically affect the NM–BS interactions. Since a large number of parameters of NMs can have contradictory effects on biomolecule bindings, comprehensive characterizations of nanomaterials are critical in the study of the NM-biomolecule interface.

A seminal work in 2007 revealed that serum protein coating on carbon nanotubes largely reduced its cytotoxicity [54], which clearly indicated that the surface property of nanomaterials could have tremendous impact on its cellular interactions and the presentation of surface proteins are well recognized in living object. Therefore, surface modification of biological molecules after NM preparation either *ex vivo* or *in situ* can affect the “biological identities” of the synthetic materials [55]. So far, the adsorption of biological molecules on NM *in vivo* has been recognized as a detrimental phenomenon and has negative outcome in most cases since the adsorbed biomolecules such as proteins can be readily recognized by mononuclear phagocyte system (MPS) and inevitably reduce the blood circulation time of NM [56–60].

2.1. Protein corona interaction with nanomaterials

As being widely distributed in biological system, proteins are the most abundant “guests” anchoring onto the NM surface [61]. Protein adsorption can substantially change the “biological identity” of NM since the surface presentation of proteins on NM surface acts as the primary antenna to interact with biological machinery for further cellular interactions [62–64].

The NM-protein interaction can be characterized by a variety of methods. Techniques routinely employed in NM characterization such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM), dynamic light scattering

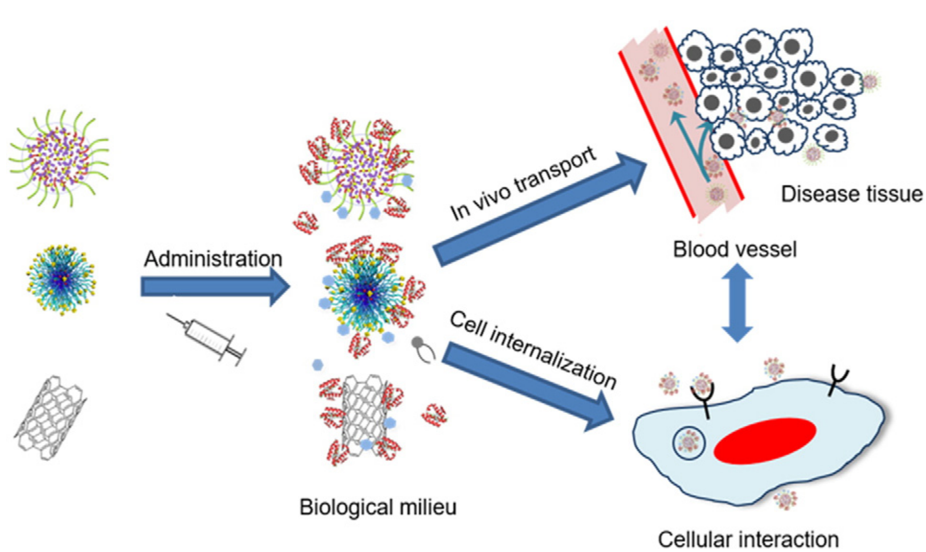

Fig. 1. Schematic illustration of three levels of NM-biological interactions. After administration of nanoparticles (solid particles, polymeric micelles, carbon nanotubes, *etc.*) *in vivo*, the NMs first adsorb various biomolecules including proteins, lipids, and saccharides in the local environment. The biomolecule-modified NMs can be uptaken by circulating cells or extravasate into tissues during circulation. After extravasation, NMs penetrate into deep tissues through interstitial space, interact with disease cells to take effect.

(DLS), ζ-potential measurement, and Raman/IR spectrometry [65,66] can only provide the overall information of the nanomaterials such as size, charge, morphology, and electronic state instead of the adsorbed protein layers. Isothermal titration calorimetry (ITC) and surface enhanced Raman scattering (SERS) were reported to be able to characterize NM interaction with a defined protein of interest [67]. To identify the complex protein composition on NM surface, separation of NM from the biological medium is often needed prior to gel electrophoresis (1D and 2D PAGE) or liquid chromatography-mass spectrometry analysis for proteomic information [42,68–70]. Special cautions should be taken when the proteomic information is assessed after NM separation from the complex medium since some of the dynamic/transient NM-protein interaction information is prone to be missed in the process and the analysis will be biased to thermodynamically favored binding and abundant proteins [71]. In addition to the protein identity on NM surface, protein orientation on NM is also of great interest. A recently contribution by Kelly et al. [72] took advantage of differential centrifugal sedimentation (DCS) and nanoparticle bound antibodies to identify the binding sites of transferrin onto gold nanoparticles. They found that majority of the transferrin on the gold nanoparticles is in a random organization pattern, which is consistent with a stochastic and irreversible adsorption model.

Studies on protein adsorption onto NM have been able to identify a series of proteins that are favorably adsorbed on various nanoparticles [42,68,69,73,74]. Charged [75] and hydrophobic surfaces [76] of NM lead to remarkable adsorption of proteins because both entropy (hydrophobic effect) and enthalpy (charge interaction) favor the adsorption. It is notable that antifouling modification of nanoparticles by poly(ethylene glycol) (PEG), which aims to minimize the opsonization (adsorption of molecules that assist the MPS recognition) [77], demonstrates variable protein adsorption patterns in response to the different PEG density and length [42,78–80]. In addition to the surface chemistry of NM, size [73,81] and shape [82] are also crucial factors. The overall effect of the morphology may be attributed to the surface curvature of NM especially when NM smaller than 200 nm is considered [83]. *In vitro* cell culture environment has also been shown to have significant influence on the protein adsorption on NM. Maiorano et al. [84] revealed that

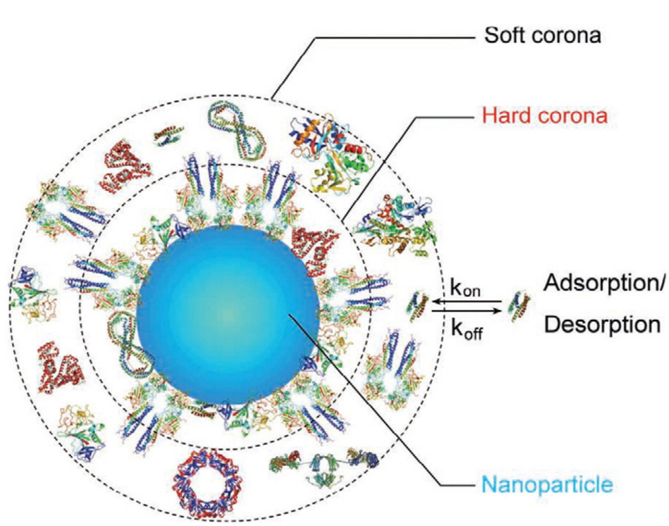

Fig. 2. Illustration of the protein corona on nanoparticles. Note that the protein corona is not spatially homogeneous. The inner protein layer (hard corona) is robust and exchanges slowly with environment while the outer layer (soft corona) quickly binds/unbinds the particle within several seconds to minutes. The analysis of the soft corona is challenging due to the difficulty of separation since the adsorption/desorption is faster or comparable to the typical particle separation time scale.
Adapted from reference [87] with permission. Copyright 2013 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

the culture medium type can affect the protein corona composition on NM and the cellular response accordingly. A summary of protein adsorption type on NMs has been recently reviewed and readers can refer to these publications for more comprehensive information [55,85,86].

Non-covalently adsorbed proteins on NM surface can quickly dissociate and exchange with biomolecules in the surrounding area (Fig. 2). The inner layer of the protein corona, termed as "hard corona", is relatively "robust" and stable [88]. The hard corona can be well characterized by current techniques because the separation and purification of NM from complex medium fall into the similar time scale of the exchange kinetics. It should be noted that the composition of the protein corona is not spatially homogeneous because the first adsorbed layer mainly consists of the most abundant proteins in the biological milieu including serum albumin, apolipoproteins, *etc.*, while the outer layer is composed of thermodynamically favored proteins [89]. Systemic studies on the time-dependent composition of protein corona on silica and polystyrene nanoparticles were recently reported by Tenzer et al. [90]. They mapped the protein adsorption kinetics in plasma and accordingly divided the adsorbed proteins into four categories, including the increasing adsorption, decreasing adsorption, peak adsorption, and U shape adsorption (Fig. 3). It was revealed that currently "detectable" and separable protein corona on NM changes over time even if the biological environment remains the same.

On the other hand, the surface-bound protein layer is more "dynamic" than the inner layer, which exchanges faster with the surrounding environment (on the scale of minutes or less) [85] and tends to be elusive during analysis. Conventional techniques used to analyze NM surface composition *ex situ* are not able to distinguish the soft layer because such information is easily lost during the purification of NM from complex media. An early *in situ* study by Casals et al. [88] confirmed the evolution of protein corona from a loosely bound state to an irreversibly attached state, and they identified serum albumin as the major component adsorbed on gold nanoparticles. A recent *in situ* study using fluorescence correlation spectroscopy by Milani et al. [91] confirmed the existence of a model protein, transferrin, as a "soft" corona on polystyrene nanoparticles. Due to the limited *in situ* characterization method, the identification of the soft protein corona still remains challenging. Proteomic mapping of the soft corona layer is nevertheless of great significance because this dynamic corona is the "apparent" surface layer of NM and may be the direct communicating antenna of NMs with BSs.

Interestingly, the protein corona composition evolves when the NM is transferred into a new environment while the proteome pattern retains a fingerprint of its history [92]. The proteomic mapping of NM corona characterized so far is focused on the static *in vitro* culture of NM with selected fluid mimics such as serum, plasma, urine, *etc.* [69]. The difference between those mimics and real *in vivo* conditions can lead to huge discrepancy on the results. Lesniak et al. [93] discovered that heat inactivation of serum can significantly affect the cellular uptake of gold nanoparticles compared with non-inactivated serum by affecting the adsorbed protein pattern according to the SDS-PAGE analysis. Plasma and serum are the most widely studied biological milieu for the biological interactions of NM because blood is the primary travelling fluid of NM. However, the researches disclosed so far are mostly based on static incubation of those fluids with NM. How NM is affected by proteins in a confined and fast flowing micro-environment remains to be explored.

In summary, NM-protein interactions have been widely studied, and general knowledge about the protein adsorption onto NM surface has been accumulated. Yet, the biological cues of those surface-adsorbed proteins remain elusive with regard to whether the conformation of the adsorbed proteins is completely different from that of its native state [72], and whether the combination of different proteins can promote or inhibit the biological interactions of NM [94,95]. It is also challenging to characterize and predict the protein corona effect for both hard and soft coronas *in vivo*.

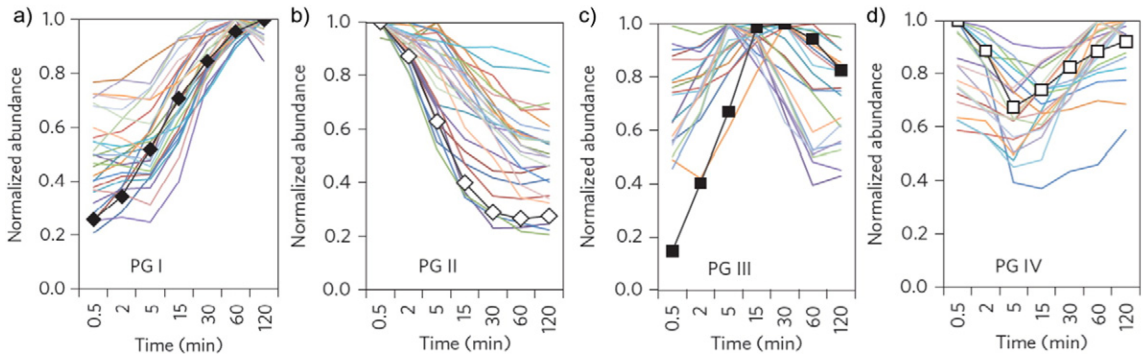

Fig. 3. Time-smoothed normalized protein abundance profiles of 125 nm negatively charges polystyrene nanoparticle coronas after NP exposure to plasma. Four typical plasma protein binding kinetic patterns are shown including increasing (a), decreasing (b), peak (c), and U shape (d).

2.2. Interaction of other biomolecules with nanomaterials

In addition to proteins, phospholipids, nucleic acids, and saccharides constitute a large portion in the biological milieu. Recent studies have suggested that these adsorbed biomolecules other than proteins also have remarkable biological implications. Because lipid, nucleic acid, and saccharides can be used as building blocks of NM, we will confine our discussion in the effect of passively adsorbed biomolecules in complex medium *in situ* instead of artificially designed biomaterials from those biomolecules.

Phospholipids have more defined and simpler chemical structures than proteins – affording a hydrophilic charged head and two hydrophobic tails. Phospholipids can easily adsorb on NM surface through hydrophobic and electrostatic interactions. In 2009, Hellstrand et al. [96] reported that phosphatidylcholine, an important type of phospholipid, can adsorb onto poly(*N*-isopropylacrylamide-co-*N*-*t*-butylacrylamide) (pNIPAM-BAM) nanoparticles in human plasma, indicating that even in the presence of competing proteins in physiological fluid, lipid adsorption on NM is still quite significant. A more recently study by Kapralov et al. [97] for the first time demonstrated adsorption of phospholipids on unmodified single wall carbon nanotube (SWCNT) *in vivo*. SWCNT recovered from bronchoalveolar lavage fluid was shown to have significant adsorption of phospholipids and proteins when being administered through pharyngeal aspiration in mice. Assembled phospholipids, *i.e.*, lipid membrane, is the basic building unit of cell membrane. Therefore, the study of NM-lipid membrane interactions provides fundamental understandings to the NM-cell interactions, including NM adhesion, cellular uptake, *etc.* Computational methods have been used to study the NM interactions with model lipid membrane [98]. Similar to that of protein-NM interactions, NM-membrane interactions are affected by the size [99], shape [98], and surface chemistry [99] of NMs. NM interactions with lipid and lipid membranes have been discussed in recent reviews [100–103] and readers can refer to those publications for more comprehensive information of the NM-lipid interactions.

The interactions of NM with polysaccharides, an important category of biomolecules, have recently been studied. A common polysaccharide, hyaluronic acid (HA), was shown to bind citrate capped gold nanoparticles and was able to replace serum proteins such as IgG on the gold nanoparticles [104]. Since HA concentration is elevated in the tumor extracellular matrix, the discovery suggested that polysaccharide interaction with NM should be seriously considered in cancer therapeutics. In addition to polysaccharides, various sugar molecules exist in glycoproteins and proteoglycans, which partially constitute the protein corona on NM surface. Recently, Wan et al. [105] used a glycosidase mixture to remove the surface glycan of the protein corona on silica nanoparticles and showed that the deglycosylation of protein corona increased the cellular uptake of NM in macrophages. Apart from the surface modification of NM, saccharides can also be utilized as a disease specific trigger for NM-assisted therapeutic delivery. One of the major monosaccharides, glucose, has been rationally designed to trigger insulin release from NM-based hydrogels for diabetes treatment [106,107]. The artificially designed glucose-insulin feedback loop helps to alleviate the hyperglycemic condition in mice models.

The direct influence of nucleic acid on NM has rarely been explored presumably due to their relatively low concentration in the extracellular compartment and low activity compared to other components. Rational design of nucleic acid-responsive NM for targeted delivery has been realized recently by the DNA gating strategy on nanoparticle surface [108, 109]. The release of encapsulated drug could be intracellularly triggered by the designed miRNA target that "opened" the DNA gate on the mesoporous silica-coated quantum dot surface. Nucleic acids targeted therapy, *i.e.* gene therapy, has also been widely studied based on the delivery of DNA or RNA sequence with NM. Nucleic acids are often condensed in NMs through charge interaction with [110–119] or covalently linked to the vehicle [120–122] and their interactions with biological environment are similar to those conventional NMs.

3. Cellular impact on nanoparticles

As a mutual interplay, NM and cells exert their impacts on each other. The intracellular delivery of NM can affect cellular functions while cellular environment can also change the integrity and identity of NM. Since the influence of NM on cellular functions has been extensively reviewed in recent publications [43,74,102], we herein mainly focus on the cellular uptake and intracellular transport of NM, two major processes that are affected by the biological corona discussed above.

The major cellular uptake pathways include phagocytosis, pinocytosis, receptor-mediated endocytosis, and passive diffusion (Fig. 4). Phagocytic cells including neutrophils, monocytes, and macrophage are mainly responsible for phagocytosis of NM *in vivo* [123]. This process is also in conjunction with protein opsonization, which is defined as the adsorption of protein on antigens (*e.g.* NM) that can be subsequently recognized by MPS. The *in vivo* clearance of NM is largely due to the phagocytosis of NM by MPS-mediated phagocytosis [57]. Approaches to reduce the phagocytosis by macrophages have been shown to effectively prolong the blood circulation of NM [124]. Pinocytosis is a size-dependent pathway that leads to the non-specific uptake of NM in non-phagocytic cells. Particularly, it includes a variety of pathways such as macropinocytosis, clathrin-mediated endocytosis, caveolae-mediated endocytosis, and clathrin- and caveolae-independent endocytosis, which generally tend to take up NM with size > 500 nm, ~100 nm, ~80 nm, and ~50 nm, respectively [125,126]. Clathrin- and caveolae-mediated endocytosis of NM has been shown to be highly size-dependent [127]. Receptor-mediated endocytosis is also an important

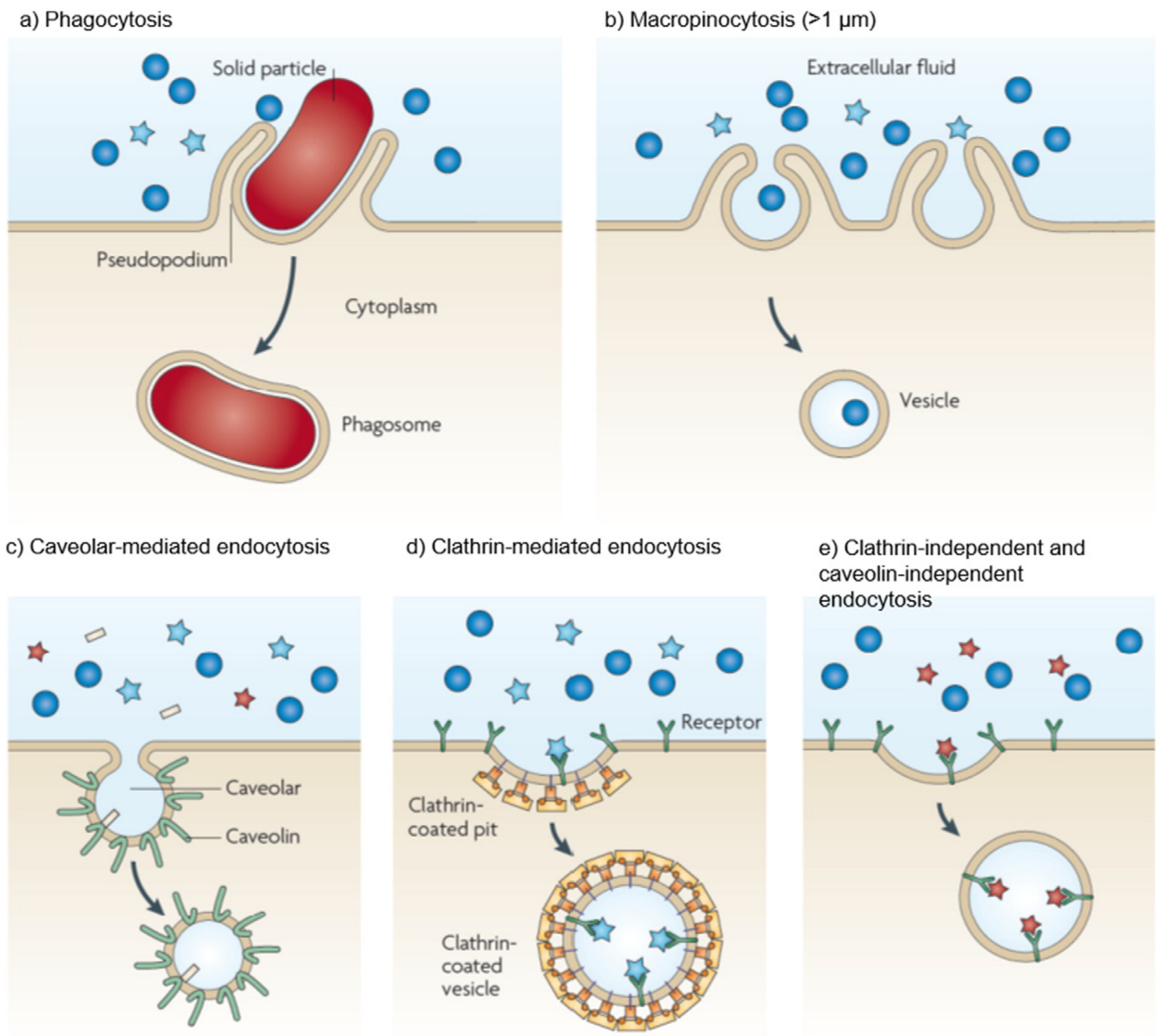

Fig. 4. Illustration of cellular uptake pathways including phagocytosis (a), micropinocytosis (b), and receptor-mediated endocytosis (c–e). The relative size discrepancy is depicted. Adapted from reference [1] with permission. Copyright 2010 Nature Publishing Group.

class of cell uptake. The over-expression of certain receptors on disease cells offers a selective target for ligand-modified NM while minimizing side effects in non-targeted cells [128].

The intracellular fate of NM is closely related to the degradation and toxicity of NM [129]. Various approaches have been applied to study the subcellular localization and degradation of NM after endocytosis [130–134]. It is also critical to understand how the therapeutic cargo in NM is released over the course of delivery in response to the cellular environment since drugs often target specific biomolecules in specific organelles. A FRET (Förster resonance energy transfer) study using polymeric nanoparticles prepared from poly(ethylene glycol)-b-poly(D,L-lactic acid) revealed that the polymeric micelles were not taken up by cells as a whole through endocytosis [135]. Instead, the therapeutic cargo was separated from the micelle and released into the cell membrane during cell internalization. The observed phenomenon indicated the difficulty in achieving a subcellular precision delivery of drugs by polymeric micelles [126].

Surface modification of NM with defined biomolecules or construction of NM with biomolecules themselves has been extensively studied as a unique strategy for targeted therapy. Serum albumin [136–140], transferrin [141], hyaluronic acid [142], nucleic acid [143–145], *etc.*, have been shown to have desired cancer targeting effect. The complex biomolecular corona effect on the cellular uptake of NM has also been investigated recently. As discussed above, the protein corona is affected by a number of NM parameters. It is therefore not surprising that the corona effect is contradictory in various targeting systems considering that different cell types may favor the uptake of different proteins [146,147]. It should also be noted that static *in vitro* cell culture condition is not a perfect mimic for studying the NM-cellular interactions because the nutrients are generally abundant in the culture medium and cellular receptors are interacting constantly with both NM and free biomolecules including saccharides, serum proteins, *etc.* The quasi-saturated cell surface receptors can potentially change the uptake pattern of NMs that have surface coatings of biological origins.

The biomolecule corona on NM has multiple impacts on the cellular uptake of NM. 1) For bare NM (*i.e.* surface without antifouling coating), protein adsorption on the hydrophobic surface usually facilitates cellular uptake because the NM-cell recognition is improved [148]; 2) for antifouling NM that does not have targeting ligands, cellular uptake is mainly mediated through clathrin- and caveolae-mediated endocytosis and the corona has non-unified effect [149,150]; 3) for NM that are designed for "active" targeting, a series of studies have reported that protein corona adsorption would reduce or even abolish the targeting effect, presumably due to the partial or complete shielding of the targeting ligand from the environment. Salvati et al. [151] showed that serum protein corona formed on transferrin (Tf)-modified silica nanoparticles eliminated the Tf-mediated targeting effect toward cancer cells. Further modification of the nanoparticles with antifouling PEG (MW up to 20 kDa) either as a linker between the Tf and silica nanoparticles or directly on Tf did not rescue the targeting property of NM in serum containing medium. This study evidently demonstrated that protein corona formed *in situ* can undermine the active targeting properties. Similar results were also reported by Dai et al. [152] who modified NM with Herceptin to target ErbB2 receptors on breast cancer cells. They found that for Herceptin with a 5 kDa PEG spacer on 50 nm gold nanoparticles, the optimized antifouling PEG coating is 1 kDa rather than 5 kDa or 10 kDa in the presence of serum.

The packing pattern of simple molecules on nanoparticles can significantly affect the uptake pathway of NM (Fig. 5). Striated anionic/hydrophobic coating on 6-nm gold nanoparticles facilitated energy-independent cell uptake while randomly modified gold nanoparticles were endocytosed and largely trapped in endosomes [153]. Although the ultrasmall size of the gold nanoparticles is distinct from commonly used NM, the implication of the observed phenomenon is instructive to the rational design and understanding of NM with optimized cellular uptake. All the current surface modification strategies of NM with proteins lack spatial control of the protein orientation on the surface, which is clearly opposite to the molecular patterns on cell surfaces where the functional components (proteins, saccharides, receptors, *etc.*) are well organized on the lipid membrane in spatial distribution as well as functional orientation. Because the molecular recognition is largely dependent on the three-dimensional topology/orientation, the controlled surface modification of NM in three-dimensions is challenging yet promising.

4. Complex *in vivo* interactions with nanoparticles

The *in vivo* machinery is much more complicated than the *in vitro* conditions of free biomolecule solutions or cultured cell. The biodistribution of NM is the result of multi-dimensional factors including NM-biomolecules interaction, NM-cell (*e.g.* phagocytes) recognition, NM-tissue interaction, *etc.* It is easier to characterize the interactions between NM and blood biomolecules as discussed in Section 2.1, while NM-blood cell interactions have not been fully disclosed. On the other hand, disease tissues (*e.g.* tumors) differ greatly from *in vitro* cultured cells considering the presence of complex extracellular matrix, stroma, and three-dimensional organization of various cell types.

4.1. NM interaction with circulating cells

It has received increasing attention to utilize circulating cells to deliver NM [154,155] by *ex vivo* modification of live cells through cell encapsulation and surface binding of NM. *Ex vivo* encapsulation of NM in live cells can be realized by electroporation, Osmosis–based method, and phagocytosis [156]. *Surface binding* of NM on live cells including red blood cells [157,158], monocytes [159], lymphocytes [160], and macrophages [161] have been implemented *via* both covalent conjugation, non-covalent electrostatic interaction, van der Waals and hydrophobic interactions [162]. Several key features of circulating cells have been employed for NM delivery including long circulation in blood, selective tissue targeting, and barrier crossing [162]. Exogenous nanomaterials administered *in vivo* are mainly cleared by MPS and renal filtration [31,62,163] while blood cells can evade the process to achieve long blood circulation. NM delivered by circulating cells features longer circulation half-life than NM themselves [157,164–166]. Targeted NM delivery by live cells have also been demonstrated to improve the NM accumulation in MPS [167,168], tumors [169–171], inflammation site, *etc.* Notably, cell-mediated delivery can facilitate the transport of NM to otherwise forbidden areas, such as the brain. The presence of blood brain barrier (BBB) prevents the central nerve system from most circulating NM [172] while monocytes and macrophages have the intrinsic properties to trespass the BBB [173], and thus have been used to deliver NM to treat brain disease [161,174–176].

Modification of NM with cell-derived membranes is an alternative strategy to cell-based NM delivery. As a bio-inspired strategy, Zhang's group [177–182] has developed cell membrane coated polymeric NM as a new modality of therapeutics (Fig. 6). Shape and mechanical mimics of red blood cells have also been explored recently as drug delivery carriers [183,184]. All these cell mimics showed much longer circulation half-life than conventional PEGylated NM even if some of the particles are larger than 1 μm [183,185–187].

Both the cell modification and cell mimicking approaches require tedious modification of NM with complex components during the formulation process, and thus it will be ideal if rationally designed NM can recruit/hitchhike circulating cells *in vivo* to mediate the transport of

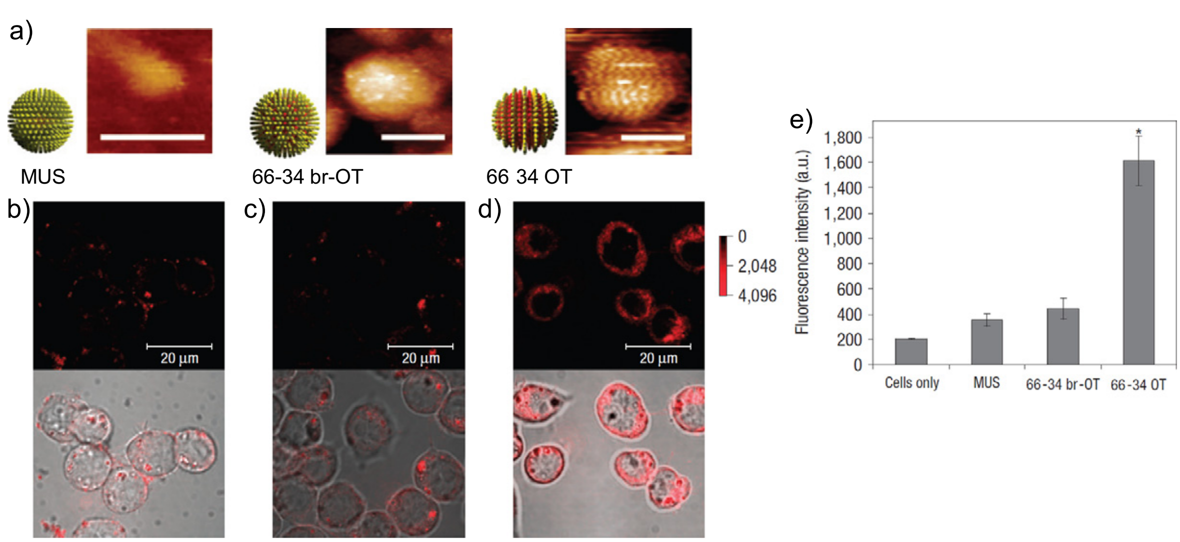

Fig. 5. 6-nm gold nanoparticles with various surface modification patterns have different energy independent uptake levels. The striated negatively charged particles (denoted as "66-34 OT": 67% 11-mercapto-1-undecanesulphonate and 33% 1-octanethiol coating) have much higher dendritic cell uptake than randomly and fully negatively charged particles. a) Schematic representation of the three types of Au NPs, homogeneous anionic coating (MUS), random anionic/hydrophobic coating (66-34 br-OT), and striated anionic/hydrophobic coating (66-34 OT), and STM images (scale bars = 5 nm). b–d) brightfield/fluorescence overlay of cells incubated with corresponding Au NPs labeled with BODIPY at 4 °C. e) Mean fluorescence intensities of the nanoparticles quantified from the images.
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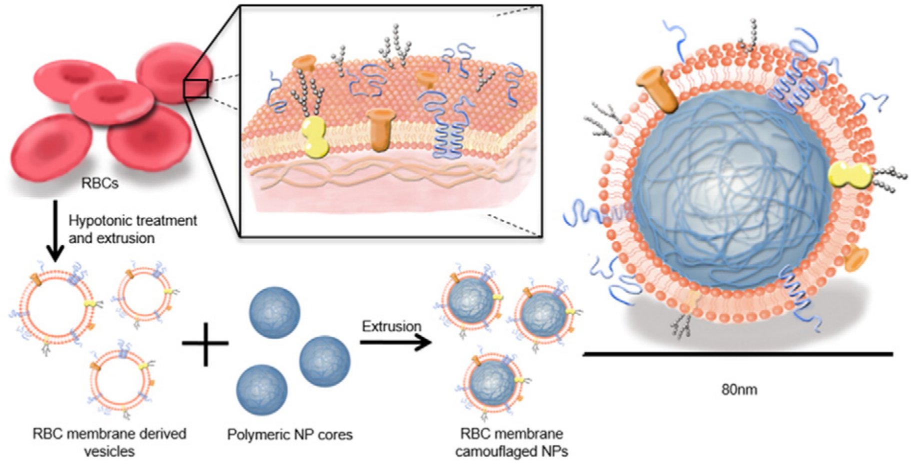

Fig. 6. Schematic preparation of polymeric nanoparticles coated with red blood cell membrane.
Adapted from reference [180] with permission.

NM. An early study by Kontos et al. [188] designed an antigen to target red blood cell for T cell depletion. Although NM is not involved, the underlying mechanism validated the strategy of targeting *in vivo* circulating cells for therapeutic purposes. More recently, a study by Smith et al. [36] showed that PEG-modified carbon nanotubes were exclusively transported by a type of monocyte (Ly-6C^{hi} monocytes) to tumor tissues. Although it is still unknown whether this is a universal phenomenon for nanomaterials, the unprecedented findings clearly highlight a previously ignored pathway for NM delivery – *in vivo* transportation of administered NM may be mediated by circulating cells instead of free NM itself.

4.2. NM interaction with tissues

During biodistribution of NM, NM will interact with complex disease tissues before reaching the targeted cells. The endothelium of blood vessels against extravasation [189,190] and the tissue stroma against penetration are the two major local barriers that prevent NM from reaching the terminal cells. The poor vascularization of tumor tissues, for example, restricts the NM delivery into malignant cells, especially for those poorly permeable tumors [191]. Vessel normalization has thus been a novel strategy to improve NM availability in tumors in contrast to anti-angiogenesis therapy [191–193].

The complex tissue (tumor) microenvironment strongly supports the cancer progression and metastasis [194] and is largely disparate from normal tissues. The components of the stroma layer including the basement membrane, fibroblast, immune cells, pericytes and extracellular matrix, can dramatically affect the local penetration and accumulation of NM [195,196]. The accumulation of NM in tumor tissues have been shown to be size-dependent for PEGylated polymeric micelles [197,198] and silica nanoparticles [46]. Nanoparticles larger than 100 nm generally have minimal tumor penetration especially in poorly permeable tumors [197]. On the other hand, smaller particles (~20 nm) can penetrate deeply into tumor tissues, but can hardly retain locally due to the ease of diffusion outward (Fig. 7) [46]. A middle-sized nanomedicine (20–100 nm) is therefore desired to achieve good therapeutic efficacy. While the effect of NM size on the tumor penetration capacity has been well characterized, it should be noted that size is not an isolated factor. *In vivo* protein adsorption and MPS clearance should be both dependent on NM size as discussed above. Therefore, the synthetic

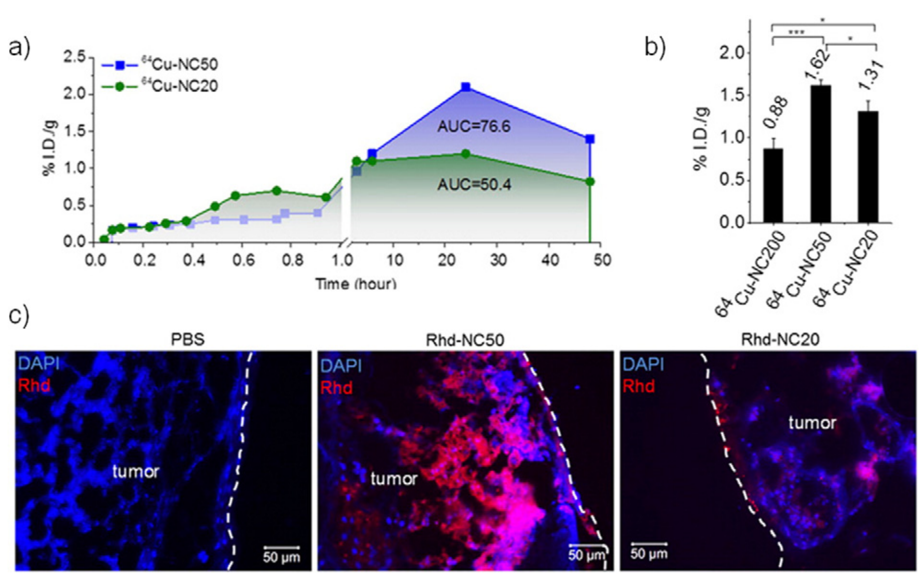

Fig. 7. Size-dependent accumulation and penetration of PEG modified silica nanoparticles in MCF-7 tumors. a) Tumor accumulation kinetics of ^{64}Cu labeled 50-nm (^{64}Cu-NC50) and 20-nm (^{64}Cu-NC20) silica nanoparticles within 48 h post injection. b) *Ex vivo* quantification of tumor accumulation of 200 (^{64}Cu-NC200), 50, and 20 nm silica nanoparticles 24 h post injection. c) *Ex vivo* clearance of 50 and 20 nm silica nanoparticles in MCF-7 tumors. Tumors were first incubated with rhodamine labeled silica nanoparticles in medium for 24 h and then let the penetrated nanoparticles cleared in fresh medium for 48 h. 50-nm silica particles showed significantly higher accumulation in tumors than 20-nm particles after the clearance.
Adapted from reference [46].

property of NM is an indirect measurement of the real biological identity encountered by the tumor environment. The observed size dependency *in vivo* should be taken as a superposition of intrinsic NM property and *in vivo* interaction with biological molecules and cells.

5. Conclusion and future perspectives

Due to the high cost and long time span for animal studies, researchers have endeavored to develop various *ex vivo* mimics of *in vivo* conditions to more effectively study the efficacy and biological interactions of NM. Tumor spheroids/cylindroids, as a mimic of three-dimensional organization of tumor cells with extracellular matrix, have been widely used in NM research [52,199,200]. Microfluidics capable of mimicking the interstitial fluids have been reported to be able to identify NM with optimized properties for tumor penetration [201]. Yet, more *in vitro* models are needed to better simulate the real situations *in vivo*. For example, NM-biomolecule interactions have rarely been systemically studied under dynamic fluidic conditions which are closer to the real situation where the fluid flow rate, pressure, and composition of serum proteins change during NM circulation.

The inevitable event of protein adsorption that reduces the stability of NM and facilitates the fast *in vivo* clearance, has long been a challenge to NM design. It will be a smart forward step to take advantage of the *in situ* biomolecule adsorption to achieve uncompromised or even improved therapeutic effect [202,203] rather than avoid the adsorption *via* NM design [204,205]. On the other hand, there are many unresolved questions about the protein corona on NM. The 3D conformation of various proteins on NM are presumably different from their native states, but how this uncharacterized discrepancy for either a single protein or a combination of protein libraries affect the NM-cell and NM-body interactions remains to be explored.

The surface properties of nanomaterials have been considered as the primary factors that affect the biological fate of NM in addition to morphologies (size, shape), while the properties of the bulk material of NM have received less attention. Inorganic nanoparticles (gold, silver, silica, *etc.*) have been widely used in fundamental studies due to the reproducible synthesis of NM with controllable size, shape, and defined surface properties [24,206–210]. In comparison, polymeric materials have been studied much less in this field due to the lack of effective method to control the uniformity, despite their broad applications in NM [53, 183,197,198]. Preparation of size-controlled polymeric NM with uniform size (ranging from 10 nm to hundred nanometers), shape [211], and surface functionalities is thus highly demanded [212].

The rising applications of nanotherapeutics in the clinics have witnessed the burgeoning development of NM. However, many fundamental questions in the area remain to be answered by virtue of elegant design and comprehensive experimental and theoretical studies. Rational design of materials with desired therapeutic outcomes and marginal side effect is still a challenge. Although substantial progresses have been made in the past few decades, the *in vivo* systems remain a dark box to researchers where NM is administered at the start and the outcome is observed as a combined consequence of "mysterious" systemic interactions. The inefficient accumulation of NM in disease tissues also needs to be improved as the current "targeted" therapeutics generally have much less than 10% accumulation in disease tissues [213]. Despite the fact that the *in vivo* bio-fluid and cellular environments greatly complicate our understanding of NM-body interactions, the advancement of the area will be sure to shine light to the NM research.

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