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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.

Contents

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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

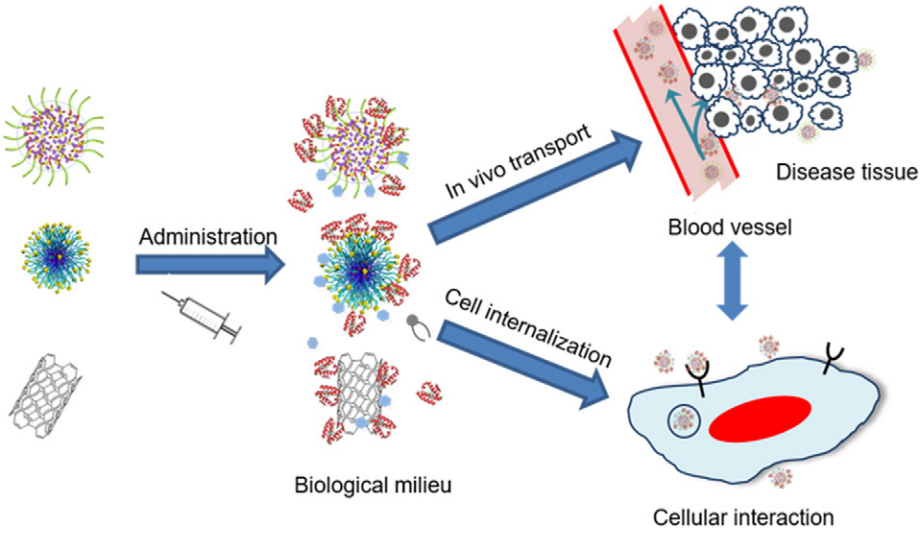

Fig. 1. Schematic illustration of three levels of NM-biological interactions. After administration of nanoparticles (solid particles, polymeric micelles, carbon nanotubes, *etc.*) *in vivo*, the NMs first adsorb various biomolecules including proteins, lipids, and saccharides in the local environment. 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.