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Review

Challenges facing nanotoxicology and nanomedicine due to cellular diversity

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ABSTRACT

This review examines the interaction of nanomaterials (NMs) with cells from the perspective of major cellular differentiations. The structure and composition of cells reflect their role and function in a particular organ or environment. The normal differentiated-state and diseased cells may respond to NMs very differently. This review progresses with due care on nanotoxicology while emphasizing the potential of NMs in treating stress-associated disorders, including cancer and degeneration. The striking potential of NMs in inducing ROS, scavenging ROS, depleting cellular antioxidants, replenishing antioxidants, mimicking antioxidant enzyme activity, and modulating the immune system all show their considerable potential in treating cancer and other aging-associated disorders. It is now clear that NMs become more active and versatile when they come into contact with biological machinery, surprisingly in some cases, in a manner dependent on cell type. The mechanisms leading to the contrasting bioresponse of NMs ranging from toxicity to anticancer and from cell survival to carcinogenicity followed by their immuno-modulating potential show NMs to be a highly promising agent in biomedical therapy. This first-of-its-kind article seeks the challenges to be addressed that could provide a solid rationale in translating the promises of nanomedicine. A thorough understanding of normal and cancer biology could help to minimize the gap between basic and translational research in nanotechnology-based therapy.

1. Introduction

Cells receive numerous stimuli through a variety of signals, ranging from ligands to mechanical contacts, and produce responses in a manner dependent on cell type. Therefore, understanding the mechanism of nanoparticle cell interactions and consequent cellular responses requires more careful examination and explanation [1]. Different cell types express different cell membrane receptors and molecular signatures that are different in quality and quantity. Moreover, the biochemical composition of cells varies greatly from one another. For example, highly respiring cardiac cells contain a high content of mitochondria [1], and contracting muscle cells contain specialized endoplasmic reticulum called sarcoplasmic reticulum to perform their specialized function better [2,3]. Similarly, secretory cells would contain an elaborate system of endoplasmic reticula and Golgi apparatuses used in the collective synthesis and maturation of proteins to be secreted [4]. The interaction of NMs with cells is a complex event, and it is dependent on not only the size and surface chemistry of NMs but also the sizes and types of cells such as phagocytic versus nonphagocytic and cancer versus normal cells. Macrophages are the major cell population responsible for the clearance of NMs *in vivo* [5]. It is therefore critical to highlight the factors associated with NMs that could affect the recognition and uptake of NMs in a manner dependent on cell type. As NMs have emerged as effective drug carriers to treat complex diseases, it has also become crucial to understand the mechanisms of nanoparticle endocytosis. Our understanding of the role of the physicochemical characteristics of NMs in phagocytic versus nonphagocytic uptake is now slowly emerging. Similarly, as discussed later, due to the perturbations in many biochemical features and the membrane potentials of cancer cells, certain types of NM entry into cancer cells appear to be more favorable than in normal cells. Therefore, it is not surprising if the interaction of a single type of NM with different cell types results in different biological outcomes ranging from anticancer to antioxidative potentials as summarized in Fig. 1. A thorough understanding of cancer biology could help minimize the gap between basic and translational research in nanotechnology-based anticancer approaches [6,7].

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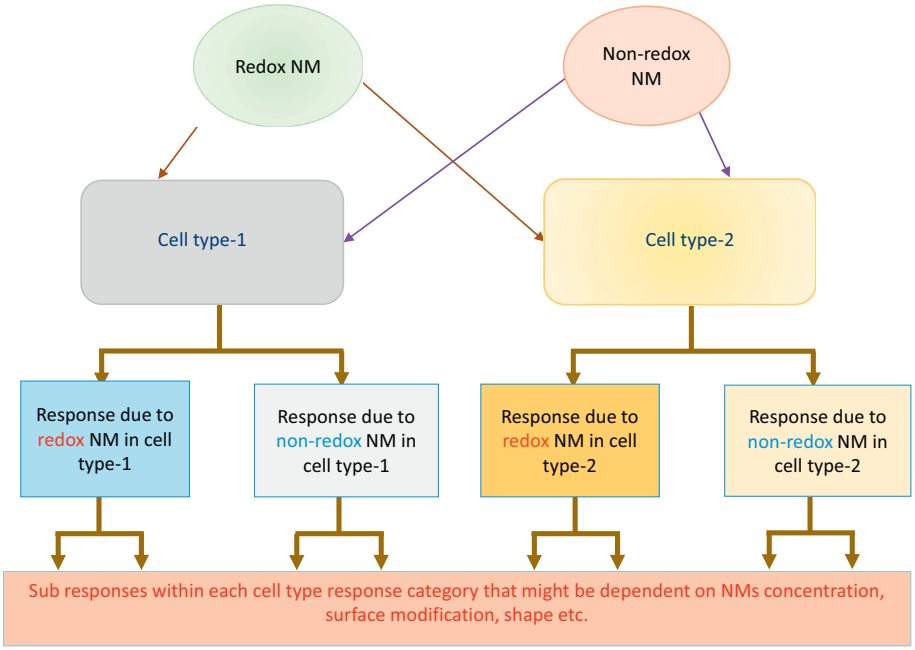

Fig. 1. Inorganic NMs can be divided into two broad classes based on their ability and inability of donating or accepting electrons. NMs that possess key elements that enable them to oscillate between multioxidation states can potentially participate in and modulate cellular redox reactions, and they are known as redox-active NMs. NM that have no electron-transferring potential are known as redox-inactive NMs. Redox-active and -inactive NMs can thus differ from each other substantially in modulating the cellular components sensitive to redox-active materials. Moreover, cells having different sets of redox components can give different responses to the same type of NMs. Similarly, a single type of cell response would be different for redox-active NMs from that of redox-inactive NMs. Our notion of response-1 and response-2 is purely arbitrary and used just for highlighting the complexity in the ongoing response due to engineered NMs.

2. Cell membrane recycling limits the rate of NM endocytosis

To enter cells via endocytosis (clathrin-dependent or independent), NMs must contact and attach to the cell surface, which forms a vesicle around the NM to be endocytosed. In each incident of endocytosis, a certain fraction of the membrane bilayer is consumed [8]. A time would come when the membrane surface tension allows no further endocytosis to occur without the efficient recycling of vesicles to the plasma membrane [8,9]. Moreover, a larger cell membrane surface area would be required for the endocytosis of bigger NMs and vice versa. It is therefore not surprising that professional phagocytes are significantly bigger in size than nonphagocytes [8]. It is safe to conclude that microparticles would be internalized in a particular cell in fewer numbers than their nanosized counterparts, a reason partly explaining why micron-sized particles are lesser toxic than their nanosized counterparts. It is estimated that cells internalize the equivalent of their cell surface one to five times per hour [9]. For every particle that is capable of cellular entry, a threshold radius (r_{th}) exists below which cellular uptake is reduced; a larger optimal particle radius (r_{opt}) accelerates wrapping. Whereas values of r_{opt} of approximately 15 and 30 nm have been deduced for cylindrical and spherical particles, respectively, the optimal wrapping of transferrin-coated gold NMs occurs at approximately 50 nm [10,11]. However, there are dramatic differences between normal metabolically driven endocytosis and the endocytosis induced by NMs at high concentrations during *in vitro* studies [12,13].

Mathematical modeling has demonstrated that receptor-mediated endocytosis is optimal when there is no ligand shortage on the NP and no localized receptor shortage on the cell surface [14]. Thermodynamically, a 50-60 nm NP is capable of recruiting sufficient receptors in triggering the successful internalization of NMs [15]. The nature of the protein corona on the NP surface therefore significantly affects the nanobio interface and hence the nanoresponse [15]. Incomplete internalization gives rise to the phenomenon of “frustrated phagocytosis” and can produce intense inflammation as in the cases of the microparticles of silica and asbestos exposed to phagocytes [16]. Phagocytic cells can therefore endocytose small particles, whereas bigger crystals or fibers can induce incomplete phagocytosis [17,18]. The size factor vividly explains how the nanosize-facilitated ‘internalization process’ is actively accountable for a robust bioresponse (for NMs) rather than the simple ‘particle contact’ with cells that could occur for larger microparticles. Therefore, short fibers induce a minor role in the inflammatory response due to particle contact compared with the longer fibers because of the greater particle contact surface area [19]. Length-dependent frustrated phagocytosis, cytotoxicity and pro-inflammatory conditions in macrophages are induced by MWCNTs [20].

3. Major cell diversity-dependent interaction with NMs

Cells vary greatly in their size, lipid bilayer composition, surface receptors and mechanism of communicating with other cells and the extracellular environment. The structure and composition of cells reflect their role and function in a particular organ or environment. The normal differentiation program and sometimes diseases enable cells to respond to foreign particles differently. We have chosen the states of cell differentiation and types that are most relevant in (nano) particulate-cell-specific interactions during their internalization, systemic circulation and clearance. Similar to cells, NMs can impart greater diversity in addition to their primary chemical nature. Cellular diversity, when combined with diversity in NMs, could result in responses that can be manifold as depicted in Fig. 2.

3.1. Phagocytic versus non-phagocytic interaction with NMs

Phagocytes are key cellular participants determining important aspects of host exposure to NMs, initiating clearance, bio distribution balancing between host tolerance and nanotoxicity [5]. Because mammals have successfully lived with the deleterious effect of a wide variety of NMs without significant toxicity, human must have developed systems to tolerate and eliminate the hazardous effects of particulates [21]. Naturally, the materials necessary for cellular life, such as ions and nanosized proteins, can pass through the lipid bilayer using specialized membrane-transport protein channels [22]. The NM internalization process would depend on not only the NM size, shape, and surface chemistry but also the cell type [23]. Phagocytes such as macrophages and monocytes react more strongly to silica microparticles than to silica NMs [24]. Compared with non-phagocytic cells, human monocytes (THP-1 cells) were found to be much more resistant to silica NMs (30-70 nm) than silica microparticles (1 μm) [25]. Macrophages were also more resistant to NMs of Ag (20–200 nm) and TiO_2 (21 nm) [26]. Direct Ag NMs-macrophage interactions dominate at