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Bioimpacts of nanoparticle size: why it matters?

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Abstract

During the last two decades, applications of nanotechnology are delivered to benefit the human society. The fact is that various nanomaterials are able to be tailor made to achieve desired properties. In biomedical field, nanotechnology has created great excitements to advance both diagnosis and therapy areas – the field so-called nanomedicines in different forms of nanoparticles (NPs) and nanosystems (NSs). It is noteworthy to mention NPs/NSs do not act similarly in the biological milieu, in which their biological behaviors/impacts varies with size, morphology, and physicochemical characteristics. On the other hand, nanomedicines impacts on biological systems seem to be influenced by its possible interaction(s) with different bioelements of cell membrane, in particular the endocytic pathway(s) by which NPs/NSs can be internalized and localized. This latter phenomenon is influenced by membrane viscoelastic property, polymerization/depolymerization of cytoskeletal system, and the particle specification itself. Among all other properties of NPs/NSs, as shown by various researchers, the size is an important parameter in the fate of the particle. Accordingly, in-depth efforts to unravel the size dependent effects of nanomedicins can provide insights to design and develop more efficacious NSs with greater benefits and lower side effects. This editorial aims to highlight some important aspects of size dependent impacts NPs/NSs.

Author Biosketch

Professor Jaleh Barar obtained her PhD degree in Pharmaceutical Cell Biology from Cardiff University, UK, in 2004. Since then, she has worked at the Faculty of Pharmacy, Tabriz University of Medical Sciences (Iran), and the Perelman School of Medicine at the University of Pennsylvania (USA), teaching and conducting researches on various aspects of molecular pharmaceutics. Her main research interest is cancer drug delivery and targeting through exploitation of advanced novel multifunctional nanosystems for simultaneous diagnosis and therapy in different malignancies.

Undeniably the application of nanotechnology in biomedical sciences is rapidly growing, creating a real enthusiasm in the fields of treatment, diagnosis, and prevention. Nanomedicines, in general, deals with the rational delivery of therapeutic or diagnostic compound to the target cell/tissue with the goal of maximized response and minimized side effects. Recent advancement in nanoscience and nanoparticle engineering would result in the expansion of nanomedicine market; hence a detailed knowledge of their impacts on cells, tissues and organisms, the so called nano-bio interaction, is imperative. In this regard, current editorial aims to highlight size dependent cellular internalization, localization and cytotoxicity.

The mechanism(s) by which NPs/NSs enter the cells is extremely imperative, not only for their targeting behavior but also for the final fate and their impacts on biological systems. NPs/NSs may enter the biological system via different routes, where they inevitably encounter and interact with vast variety of biomolecules. Communication with the cell membrane seems to be the hallmarks of NPs' impacts on cellular elements within the biological milieu. This would greatly be influenced by the virtue of the cell membrane ability to selectively direct the outward and/or inward flow of various molecules in a highly controlled manner. Generally, the internalization of NPs can proceed through three main mechanisms, i.e. phagocytosis, pinocytosis, and receptor-mediated endocytosis (RME). All of these mechanisms have been well characterized by the mean of the size of NPs, as follows:

- Phagocytosis, involves cellular engulfment of relatively large (i.e. 0.1-10 μm) and solid particles.
- Pinocytosis, primarily is a mode of endocytosis executed by the formation of invaginations in which the small particles (i.e., within a size range of 50-1000 nm) are to taken up by cell.

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RME can be performed by membranous caveolae and clathrin mediated endocytosis as well as clathrin- and caveolae- independent pathway.1

Rejman et al have systematically investigated the size dependency of the mechanism of the uptake of the NPs. A strong correlation between size and the pathway of entry was observed; where they reported that clathrin-coated pits were involved in the internalization of the particles with a diameter of less than 200 nm, whereas with increasing size, the shift toward caveolae mediated internalization was observed.2 Mathematical modeling of the RME has also shown that an optimal radius of NPs exist for efficient uptake (i.e. 50 nm); where RME function becomes impaired or less efficient below and above this size.3 This model disregards the active dynamics of cytoskeleton during internalization, and only describes the initial steps of receptor mediated internalization of NPs, whilst beside membrane dynamics, the pivotal role of cytoskeleton needs to be considered.

Since identification/utilization of cell specific biomarkers (in particular in the case of malignancies4,5) is a critical component for developing novel drug delivery and targeting systems, the rational engineering of size and selecting the homing or targeting device is highly desired. Targeted uptake of NPs is facilitated by preferential affinity to cell surface biomarkers that can be capitalized on vast and growing knowledge of receptors and ligands undergoing endocytosis. Some insights into dynamic role of molecular drug target for governed internalization of desired cargo has been exemplified by exploitation of folate receptor. Folate decorated NPs are found to increase the cellular uptake substantially.6-10 However, both clathrin and caveolae mediated internalization pathway are found to play striking roles. Yet again, NPs utilize the endocytic pathway in a somewhat size-dependent manner. Langston Suen and Chau have shown that in spite of caveolae and clathrin mediated uptake of folate decorated polymeric NPs in the size range of 50-120 nm, the preferred mechanism for internalization of the larger particles (i.e. 250 nm) is solely caveolae-mediated endocytosis (CME) in retinal pigment epithelium.11 CME were proposed to improve the therapeutic efficacy of acid labile drugs by trafficking to a compartment with neutral pH (the so-called caveosomes) and subsequently to endoplasmic reticulum, instead of subsequent delivery to early/late endosomes with acidified environment.12 This fact is under serious refute,13 but clearly more experiments are required to fully clarify the subject. The impact of size on passive uptake of NPs is also intriguing, and internalization studies in red blood cells, as an interesting model that lack a defined endocytic machinery,14 has demonstrated that NPs with a size greater than 200 nm can enter the cells with a non-phagocytic/endocytic mechanism.15,16 On the other hand, there are evidences that NPs may alter the cellular signaling pathways that are pivotal to vital function and cannot be considered as a simple benign carrier. The interaction of NPs with cell membrane receptors seem to be highly size dependent.

In general, smaller particles have a relatively large surface area as compared to larger ones; this increases the interaction with biological elements and consequently trigger more toxic and adverse effect.1 In a study, the biological impact of colloidal gold nanostructures with a size range of 2-100 nm demonstrated that NPs with the size of 40-50 nm, greatly alter basic cell functions.17 Though the impacts of NPs may be directly influenced by their sizes, to draw a reliable conclusion all other governing factors should be considered. For instance, charge and surface modification are also of critical importance. Cationic NSs have high affinity toward the negatively charged plasma membrane, and may exert more toxic response as shown for cationic non-viral gene delivery systems.18-27 On the other hand, surface modification and chemistry (such as PEGylation) play an equally significant role.10,28-32 Each and every moiety on the surface of NPs designates a novel identity, which may modify the cellular/molecular responses. Therefore, one should meticulously consider all properties in a systematic manner. Despite great achievements in the emerging field of nano-biotechnology, an inclusive understanding of comprehensive cell interaction with NPs is yet to be accomplished. In-depth knowledge of such phenomenon may assist in design of more robust targeted therapeutic systems.

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Ethical issues

There is none to be declared.

Competing interests

There is no competing interests to be announced.

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