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Do Engineered Nanoparticles Penetrate into Cells?

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Understanding the mechanism of engineered nanoparticle (ENP) uptake by cells is important for various biomedical applications including biosensors, imaging, intracellular drug and gene delivery, and toxicity studies [1-3]. This editorial presents a short summary and perspective on the cellular uptake of gold nanoparticles and the mechanisms that govern them. Gold Nanoparticles (GNPs) have been proposed for use in practically all biomedical applications because of the ease in synthesis, chemical stability, and their unique optical and electrical properties [4]. But, spontaneous penetration of functionalized cationic GNPs have shown cell membrane disruption and cytotoxicity, thus limiting their utility [5]. However, recent literature has shown that GNPs (5nm diameter with "special" surface chemistries or arrangements) protected by an amphiphilic monolayer can non-disruptively penetrate the cell membrane to deliver drugs, nutrients or biosensors [6]. Even with endocytosis arrested, this penetration via an energy independent mechanism do not damage or rupture cell membrane [7]. The underlying mechanism of how GNPs can non-disruptively penetrate cell membranes has largely been unknown [8]. Recently, Van Lehn et al. [9] demonstrated that the penetration process consists of multiple steps – (a) first the anionic, striped GNPs will fuse with the cell membrane in a non-disruptive transmembrane configuration, (b) then the GNPs may translocate into the cell interiors. This process is dependent among others on particle size, monolayer composition, and ligand morphology.

GNP size is found to play a critical role in both the rate and extent of cell uptake. Chithrani et al. found that 50 nm transferrin-coated GNPs are taken up by mammalian cells at higher rates and extents compared to other sizes in the range of 10-100 nm [10]. Chithrani et al. [11] suggested "wrapping effect" based on free energy calculations and receptor diffusion kinetics as the basis for how fast and how many NPs are internalized in the cell. Various tools are available to image (using either light or electron microscopy) and quantify (elemental analysis) GNPs concentration inside the cell. Elemental detection techniques such as ICP coupled with Mass Spectroscopy (ICP-MS) is an excellent technique to analyze gold content both inside and outside (growth media) of the cells. In addition, because GNPs are electron-dense, TEM techniques can be used to distinguish gold from other cellular components. Depending on the GNP size, type, cell receptors and cellular signaling cascades, various other pathways such as phagocytosis, micropinocytosis, and receptor-mediated endocytosis (RME) including caveolae-mediated, clathrin-mediated, and caveolae/clathrin independent endocytosis have been proposed [12].

Many researchers have studied how different cells selectively respond to GNPs. For example, in one study, BHK21 and HepG2 cells showed no effect, while A549 cells underwent apoptosis due to accumulation of GNPs in periphery outside cell nucleus [13]. In another work, the mechanisms by which transferrin-coated GNPs entered three cell lines (STO, HeLa, and SNB19) varied [10]. Ultimately, to understand and predict the relationship between NP size and different cell line exocytosis, free energy mathematical models were developed [10].

As stated earlier, microscopic imaging can be used to study GNP internalization and accumulation in different parts inside the cell. It is important to consider cell internalization as a function of size, incubation time, temperature, and surface functional group [14]. Elemental analysis using ICP OES have shown abundant internalization and nuclear localization of gold complexes. This nanoparticle internalization is largely governed by the adsorbed proteins and their relative orientation on the curved nanoscale surface. Depending on chemical faces, receptors can mediate different pathways for cell entry. Negatively charged GNPs are shown to adsorb serum proteins and enter cells via a complex endocytic pathway resulting in higher toxicity and immunological response [15]. GNP internalization can also be manipulated by changing the surface chemistry, polyelectrolytes and surfactants of varying charge. TEM studies have shown GNPs coated with quaternary amines (CTAB and PDAD-MAC) exhibit higher uptake, compared to molecules containing primary amine (PAH) [16]. Cho et al. [17] observed that surface functionalized groups have a stronger influence on cell uptake than its shape. In addition, GNPs have exhibited particle size dependent organ distribution after intravenous administrationin rats. ICP-MS studies indicate that 10nm GNPs are present in blood, liver, spleen, kidney, testis, thymus, heart, lung and brain, while 50-250 nm GNPs are detected only in blood,liver and spleen [18].

Although it seems that GNPs can be taken up by different types of cells, the evidence is disparate and the mechanisms of uptake are either not examined or in their infancy [9]. It also remains unclear whether GNPs taken up by cells exert a cytotoxic effect or not. Accurate and comprehensive physical and chemical characterization data becomes very important to describe both toxicity and the cellular uptake mechanism. Currently, a diverse assortment of nanomaterials and experimental conditions are available, with no reliable and reproducible methods, models and standardized engineered nanomaterials. In future, a more ordered and systematic approach (with computational and experimental methodology) is necessary to both assess the biological responses and to address fundamental mechanistic questions.

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