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Long-term fate of silica nanoparticles interacting with human dermal fibroblasts

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ABSTRACT

The long-term fate of fluorescent non-porous FITC-SiO_2 nanoparticles of various sizes (10–200 nm) and charge is studied in the presence of human dermal fibroblasts. Particle aggregates are formed in the culture medium and uptaken, at least partially, by macropinocytosis. The smallest particles have a strong impact on cell viability and genotoxic effects can be observed for negatively-charged colloids 10 nm in size. Largest particles do not impact on cellular activity and can be monitored in cellulo via fluorescence and transmission electron microscopy studies over two weeks. These observations reveal a significant decrease in the size of silica particles located in endocytic vesicles. The dissolution process is confirmed by monitoring the cell culture medium that contains both colloidal and soluble silica species. Such dissolution can be explained on the sole basis of silica solubility and has great implication for the use of non-porous silica particles as intra-cellular drug release systems.

1. Introduction

Silica nanoparticles have promising developments in biological fields for bioimaging, diagnosis, controlled drug- or DNA-delivery and phototherapy [1–8]. In addition, the versatility of silica chemistry enables the integration of different functionalities, as for example imaging, targeting and therapy, in a single particle [9–12]. Alongside exploration of their promising properties, better understanding of silica nanoparticles interactions with cells has been gained, especially in relationship with toxicity [13–20], in order to design safe nanomaterials for *in vivo* applications [21–25].

In vitro studies show a rapid internalization of the silica particles and their later localisation in endosomes, cytoplasm, mitochondria or even nucleus [26–29]. Uptake is observed for a wide range of particle size and its kinetic rate is faster for smaller particles. On the contrary, intra-cellular localization depends on the size of the particles, e.g. nucleus entry is limited to a small size-range (40–70 nm). Intra-cellular localization is also highly dependent on the surface charge (such as polyethyleneimine (PEI)) and/or the presence of a protein corona [30–32]) e.g. PEI- coated nanoparticles are more able to escape the endosomal compartment and diffuse in the cytosol. Depending on the physico-chemical characteristics of the particles (size, shape, surface charge,…) [33–39] the cellular response varies in a cell line dependent manner [40–42].

It is well-established that silica particles undergo a dissolution process in biological medium, even if it is slowed down by the presence of proteins [43,44]. Noticeably, no study has so far addressed the possibility for intra-cellular dissolution of internalized particles, except for earlier reports on biopolymer-silica nanoparticles demonstrating that over 48 h the bio-organic component was prone to degradation whereas silica fragments could still be visualized inside the cells [45,46]. If present, such an intra-cellular degradation process may have several important implications: (i) intra-cellular production of silicic acid or silica oligomers that may have an impact on global toxicity, (ii) external release of soluble silicates in addition to particle exocytosis, and more importantly if drug delivery applications are targeted (iii) facilitated release of bioactive molecules initially entrapped within the silica colloids.

To address this point, we hypothesized that the uptake-endosomal fate-exocytosis process must be studied on a long period (*i.e.* up to 2 weeks) and that care must be taken to distinguished between colloidal and soluble silica species. Indeed, it has been shown that longer times of exposure could increase the uptake of silica particles in HepG2 cells [47]. Furthermore, they can also lead to an increase in the local dose, exposure to the product of dissolution of the particles or exocytosis and cell-to-cell transfer of the particles [48,49]. For this purpose, we prepared fluorescent non-porous silica particles in different size (from 10 nm to 200 nm) and surface charge. Based on the fact that silica particles are, among many applications, used in cosmetics and that some recent studies showed their ability to penetrate the skin [23], these particles were put in contact with human dermal fibroblasts. A combination of *in*

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