Mechanisms of Nanoparticle Internalization and Transport Across an Intestinal Epithelial Cell Model: Effect of Size and Surface Charge

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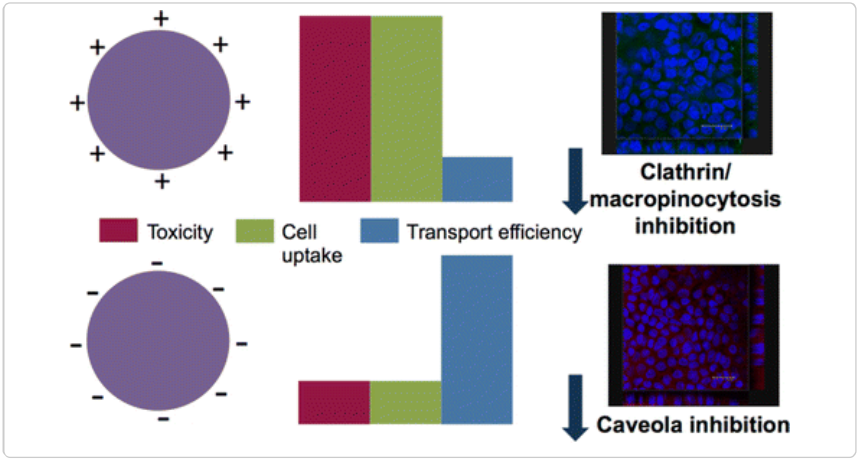

This study investigated the effect of nanoparticle size (50 and 100 nm) and surface charge on their interaction with Caco-2 monolayers as a model of the intestinal epithelium, including cell internalization pathways and the level of transepithelial transport. Initially, toxicity assays showed that cell viability and cell membrane integrity were dependent on the surface charge and applied mass, number, and total surface area of nanoparticles, as tested in two epithelial cell lines, colon carcinoma Caco-2 and airway Calu-3. This also identified suitable nanoparticle concentrations for subsequent cell uptake experiments. Nanoparticle application at doses below half maximal effective concentration (EC_{50}) revealed that the transport efficiency (ratio of transport to cell uptake) across Caco-2 cell monolayers is significantly higher for negatively charged nanoparticles compared to their positively charged counterparts (of similar size), despite the higher level of internalization of positively charged systems. Cell internalization pathways were hence probed using a panel of pharmacological inhibitors aiming to establish whether the discrepancy in transport efficiency is due to different uptake and transport pathways. Vesicular trans-monolayer transport for both positively and negatively charged nanoparticles was confirmed via inhibition of dynamin (by dynasore) and

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microtubule network (via nocodazole), which significantly reduced the transport of both nanoparticle systems. For positively charged nanoparticles a significant decrease in internalization and transport (46% and 37%, respectively) occurred in the presence of a clathrin pathway inhibitor (chlorpromazine), macropinocytosis inhibition (42%; achieved by 5-(*N*-ethyl-*N*-isopropyi)-amiloride), and under cholesterol depletion (38%; via methyl-β-cyclodextrin), but remained unaffected by the inhibition of lipid raft associated uptake (caveolae) by genistein. On the contrary, the most prominent reduction in internalization and transport of negatively charged nanoparticles (51% and 48%, respectively) followed the inhibition of lipid raft-associated pathway (caveolae inhibition by genistein) but was not significantly affected by the inhibition of clathrin pathway.

Keywords: **Cell uptake**; **Caco-2**; **endocytosis**; **epithelial cells**; **nanoparticles**; **nanoparticle transport**; **nanotoxicity**

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