Keynote

CARBON NANOTUBE CELLULAR INTERACTION, BINDING & INTERNALIZATION: A CASE OF 'NANOSYRINGE'?

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The interaction between cells and carbon nanotubes (CNT) is a critical issue that will determine any future biological application of such structures. In this communication we will show that various types of functionalized carbon nanotubes (*f*-CNT) exhibit a capacity to be uptaken by a wide range of cells (prokaryotic and eukaryotic) and can intracellularly traffick through different cellular barriers. The mechanism by which *f*-CNT are able to cross cell membranes and deliver their cargo will also be discussed. Energy-independent mechanisms are explained based on the cylindrical shape and high aspect ratio of *f*-CNT that can allow their penetration through the plasma membrane, similar to a 'nanosyringe'.

One of the most important parameters in *in vitro* and *in vivo* studies with CNT is the type of nanotube used, which is determined by the process by which they are made biocompatible. Interactions with cells and tissues have to be performed using biocompatible CNT, achieved by either covalent or non-covalent surface functionalisation that results in water-dispersible CNT. A variety of different functionalisation strategies for CNT have been reported by different groups. In our laboratories, CNT were made compatible with physiological environments after functionalization by the 1,3-dipolar cycloaddition reaction (Fig.1).

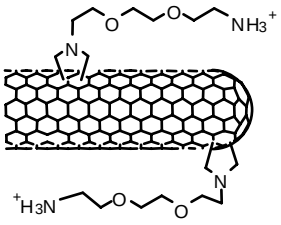

Figure 1. Molecular structure of CNT-NH_3^+.

In Figure 2, a high resolution transmission electron microscopy (TEM) image of MWNT-NH_3^+ is showing the initial interaction of the nanotubes with mammalian cells. We have observed that the nanotubes adopt a perpendicular orientation towards the plasma membrane of the cells during the process of cellular internalization.

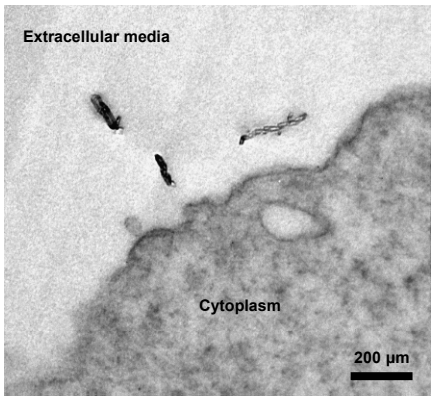

Figure 2. Transmission Electron Microscopy image of A459 cells incubated with MWNT-NH_3^+ for 1 h at 37 °C (5% CO_2).

The spontaneous transmembrane penetration via flipping of membrane lipid molecules is, contrary to endocytosis, an energy-independent process, not dependent on receptor, coat or lipid raft interactions, therefore potentially relevant to all cell types. Furthermore, the hypothesis of *f*-CNT acting as 'nanoneedles' on plasma membrane, has recently been observed also by others using different CNT to those of our original observations: a) non-covalently functionalized block copolymer-coated MWNT; and b) oxidized, water-dispersible CNT. In summary, the work accumulating gradually by different groups is confirming that novel, very interesting mechanisms other than 'classical' endocytosis are contributing to the cellular internalization of CNT.

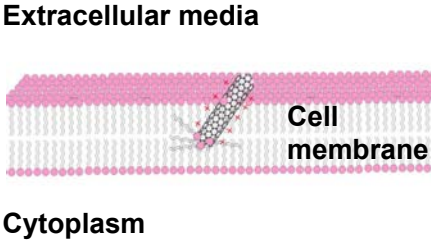

Figure 3. Schematic representation of "nanoneedle" mechanism for *f*-CNT cross cellular membranes.

So far water-dispersible, individualized CNT have shown interesting properties that can be utilized in biomedical applications. Currently CNT are being considered and explored as novel carrier systems of therapeutics and diagnostics because: a) CNT can be internalized by a wide range of cell types; and b) their high surface area can potentially act as a template of cargo molecules such as peptides, proteins, nucleic acids and drugs. CNT have been described as delivery systems in mainly proof-of-principle studies for a variety of different biomedical applications. In our laboratories we have observed that *f*-CNT are able to facilitate the intracellular transport of plasmid DNA, peptides and drugs. Water-dispersible CNT are now considered vectors for gene delivery and novel tools for effective delivery of imaging and therapeutic proposes in cancer.

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