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Development of new strategies for non-viral gene delivery: Exploring the microtubule retrograde transport

Adriano R. Azzoni
University of Sao Paulo, Brazil

A major concern in DNA vaccination and gene therapy protocols using non-viral vectors is the low efficiency of gene delivery. This is mainly attributed to the several physical, enzymatic and diffusional barriers that plasmid vectors must overcome during the traffic to the target cells nuclei. Our group has been working on the development of delivery particles formed by the combination of recombinant proteins, specifically designed for plasmid DNA (pDNA) delivery, and lipids. We propose that these particles, also called "artificial viruses", will rely on the high efficiency of cell internalization of the lipids and then, exploit the cell machinery for intracellular trafficking via the recruitment of dynein molecular motors for the transport towards the nucleus. In this work, recombinant dynein light chains (LC8 and RP3) were fused to synthetic DNA binding domains, maintaining the ability to interact with dynein intermediate chain. We confirmed the ability of the proteins to interact and condense pDNA, forming positive particles with size ranging from 100 to 900 nm, depending on the protein construct. Transfection studies indicated that addition of fusion proteins to pDNA (pVAX1Luc) increased the transfection efficiency of mammalian cells (HeLa) up to almost ten thousand times, comparing to naked DNA. Even higher transfection efficiencies are achieved by complexes formed by protein, pDNA and LipofectamineTM, with reduced cytotoxicity. The development of non viral vectors that mimic strategies used by virus to infect mammalian cells may, in the near future, reduce the current advantage of viral vectors, providing new tools for gene therapy studies.

Biography

Adriano R. Azzoni is a professor at the Chemical Engineering Department of the University of São Paulo, Brazil. His research group is focused on the study and development of recombinant proteins specifically designed for non-viral gene delivery. More specifically, he is interested on the development of multi-component transfectant particles formed by pDNA, proteins and lipids that may mimic strategies used by virus to infect mammalian cells.

adriano.azzoni@poli.usp.br