

S011 Gene delivery by cationic lipids: In and out of an endosome

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Non-viral vectors such as cationic lipids are capable of delivering nucleic acids into cells thus potentially resulting in their functional expression. Although an attractive alternative for virus-based delivery systems, the efficiency of cationic lipid-mediated gene delivery, although sufficient for cell biological purposes, runs seriously short from a therapeutics point of view. To develop strategies for improvement, there is not so much a need for novel delivery systems. Rather, better insight is needed into the mechanism of delivery, including lipoplex-cell surface interaction, route of internalization and concomitant escape of DNA/RNA into the cytosol, and transport into the nucleus. The extent to which these steps constitute a critical barrier for entry will be discussed. In addition, possibilities for manipulating the mode of entry of gene delivery complexes will be analyzed. A major obstacle involves the inefficient destabilization of endosomal compartments in which lipoplexes reside after their internalization. Such an activity requires lipoplexes of undergoing polymorphic transitions, like hexagonal phases, a process in which cellular components may aid. Consequently, entry pathways may have to be triggered by specific targeting to select delivery into intracellular compartments which are most susceptible to lipoplex-induced destabilization, thereby allowing the most efficient release of DNA, a minimal requirement for optimizing non-viral vector-mediated transfection.