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Mannosyl-coated nanocomplexes from amphiphilic cyclodextrins and pDNA for site-specific gene delivery

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ABSTRACT

Fully homogeneous facial amphiphiles consisting in a cyclodextrin (CD) platform onto which a polycationic cluster and a multi-tail hydrophobic moiety have been installed (polycationic amphiphilic CDs; paCDs) self-organized in the presence of plasmid DNA to form nanometric complexes (CDplexes) which exhibit broad-range transfection capabilities. We hypothesized that biorecognizable moieties located at the hydrophilic rim in the CD scaffold would be exposed at the surface of the corresponding nanoparticles after DNA-promoted aggregation, endowing the system with molecular recognition abilities towards cell receptors. This concept has been demonstrated by developing an efficient synthetic strategy for the preparation of multivalent polycationic glyco-amphiphilic CDs (pGaCDs). Self-assembled nanoparticles obtained from mannosylated pGaCDs and pDNA (average hydrodynamic diameter 80 nm) have been shown to be specifically recognized by mannose-specific lectins, including concanavalin A (Con A) and the human macrophage mannose receptor (MMR). Further macrophage adhesion studies indicated that unspecific binding, probably due to electrostatic interactions with negatively charged cell membrane components, can also operate. The relative specific *versus* non-specific internalization is dependent on the pGaCD:pDNA proportion, being optimal at a protonable nitrogen/phosphate (N/P) ratio of 5. The resulting GlycoCDplexes were shown to specifically mediate transfection in Raw 264.7 (murine macrophage) cells expressing the mannose-fucose receptor in vitro. FACS experiments confirmed that transfection using these nanoparticles is mannose-dependent, supporting the potential of the approach towards vectorized gene delivery.

1. Introduction

Gene therapy, which implies introduction of genes into cells to prevent or cure a wide range of genetic or acquired diseases, represents nowadays an extremely active domain of research. Successful delivery of genetic materials is dependent on the design of efficient technologies allowing compaction, protection, cell internalization and final release of the nucleic acid payload. Viral vectors have proved very effective in achieving highly efficient gene delivery and expression in vitro; however, this approach early met with severe limitations in terms of immunogenicity and toxicity issues in clinical trials [1]. Research on synthetic gene delivery systems has subsequently gained an increasing relevance due to advantages with regard to non-immunogenicity, scaling-up production and potential for delivery of large DNA fragments into target cells [2]. Among nonviral vectors, cationic polymers and lipids hold a prominent position, both capable of complexing DNA into nanocondensates (polyplexes and lipoplexes, respectively) featuring improved pharmacokinetics and pharmacodynamics [3,4]. The overall positive surface electrostatic potential of those

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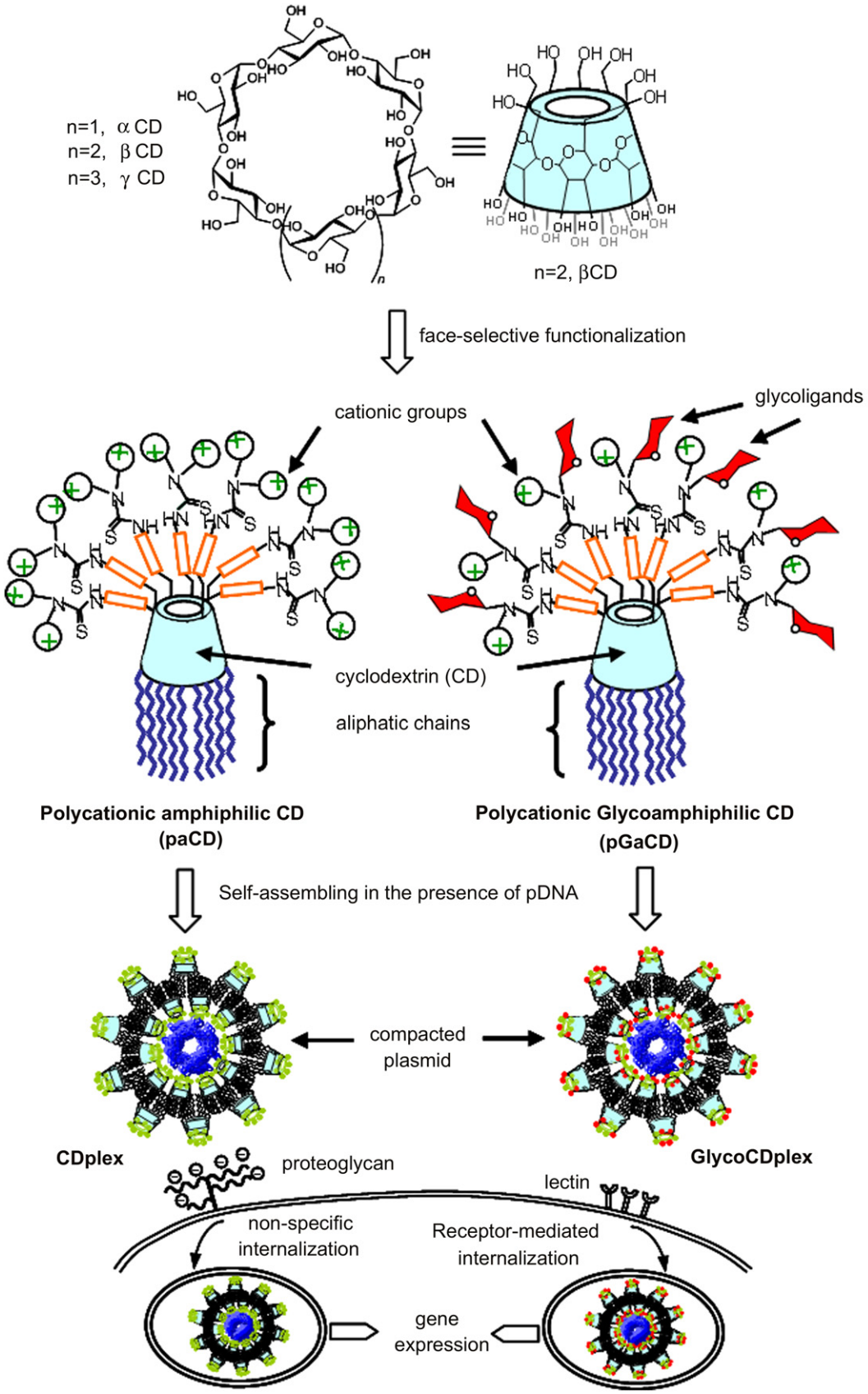

Fig. 1. Schematic representation of cyclodextrins (CDs), polycationic amphiphilic CDs (paCDs; left), polycationic glyco-amphiphilic CDs (pGaCDs; right), the corresponding nanocomplexes with pDNA (CDplexes and GlycoCDplexes, respectively) and their presumed internalization routes.