Gemini-like peptide-based amphiphiles for application in gene transfection

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There is continued interest in the development of non-viral vectors. Cationic gemini lipids consisting of 2 cationic head groups and 2 hydrophobic tails linked by an alkyl spacer, have lower critical aggregation concentrations than conventional single-chain, single-head group lipids. We have shown that lysine-based cationic gemini surfactants, when combined with the helper lipid dioleoylphosphatidylethanolamine (DOPE), transflect DNA in vitro with efficiencies comparable to those of commercially available cationic amphiphiles. A possible explanation for the efficiency of cationic gemini lipids in transfection is that the lipid aggregates have 2 pKₐ values, one above, one below physiological pH; as a result the lipoplex undergoes pH-induced morphological changes that allow escape from the endosome.

To enlarge the scope of possible vectors we have now designed and synthesized gemini-like peptide-based amphiphiles in which the alkyl spacer is replaced by a peptide. Two types of alkylated peptides that resemble the early lysine based gemini surfactants can be distinguished. The first type is formed by peptides that are alkylated by forming amide bonds between their C and N termini with alkyl amine and alkyl carboxylic acid, respectively. The second type is formed by peptides that are alkylated on two or more amide bonds. Using bio-inspired peptide sequences such as those found in histones and cell-penetrating peptides, we hope to be able to make surfactants with special properties, and interesting results with in vitro transfection have been obtained. One bio-inspired alkylated peptide has shown very interesting properties without helper lipid and has been tested successfully in various cell lines.

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