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A hybrid lipid oligonucleotide: a versatile tool for supramolecular chemistry

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Lipid oligonucleotides (LONs) are emerging as promising supramolecular tools for biomedical and technological applications. In this contribution we highlight recent advances in the area of LONs with an emphasis on their supramolecular properties and applications. In the first section we focus on the design, self-assembly and applications of LONs. In the last section, we describe recent biomedical applications thereof.

1. Introduction

Nucleic acids and lipids are central molecules in living organisms. While the former are responsible for the storage and propagation of genetic information, the latter allow for the protection and compartmentalization of the living matter from the external environment. The chemical combination of a lipid with an oligonucleotide, the so-called lipid oligonucleotides (LONs), has been realized with the aim of combining and optimizing the properties of both biomolecules.[1] In fact, the propensity of the lipidic segment of the LONs to aggregate in water brings about new self-assembling opportunities for these bio-inspired amphiphiles. LONs can therefore self-assemble into micelles,[2] liposomes,[3] and nanoparticles. This phenomenon is expected to positively impact the biological effect of the nucleic acid segment of the LON. These different fields have already been covered by us and others in the past.[1,4,5] This contribution will therefore mainly focus on the recent advances with an emphasis on supramolecular and biomedical applications.

2. Lipid–oligonucleotide conjugates, from molecular to supramolecular self-assemblies

Many biomolecules have been covalently attached to nucleic acid sequences to impart new properties to the oligonucleotides, *e.g.* targeting properties (RGD peptides and carbohydrates), higher affinities for their complementary sequence (oligospermine in zip nucleic acids),[6] or cell membrane crossing capabilities with lipid conjugates. Recent developments in the field of oligonucleotide conjugates have been reviewed lately.[7–9] Lipid conjugation to ONs was primarily thought of as a means to anchor the ON to cell membranes, ultimately leading to the internalization of the ON sequence. Many different lipid-antisense ONs have consequently been synthesized in the past. Basically there are three different positions for lipid conjugation to ONs: (i) 3′-terminal, (ii) 5′-terminal and (iii) intra-chain positions. At each location, the lipid conjugates can be incorporated into various sites *i.e.* at the phosphate backbone, at the sugar (at 2′-, 3′-, 5′-positions, *etc.*) and/or at the nucleobase. The specific site(s) of lipid conjugation has/have an impact on the biological and physical properties of the LONs. Therefore, depending on its application, the conjugation site(s) has/have to be carefully chosen so that it facilitates the function of LONs without compromising their binding properties (usually hybridization with the complementary ONs). The synthetic methods that have been used for the preparation of LONs have been thoroughly reviewed and will not be covered here.[1,5,10]

2.1. Supramolecular assemblies

The presence of a lipid in ON sequences improves their solubility in organic solvents. If only one lipid does not seem to be sufficient to provide full solubility, a TG_4T DNA sequence with dodecyl chains at each phosphotriester linkage is soluble in chloroform or THF.[11] Interestingly, this minimal sequence prone to form a G4-quadruplex in water has the ability to form this secondary structure motif and extract alkali metals in chloroform or THF. Wang *et al.* took advantage of the higher tolerance of LONs toward organic co-solvents to play around the solvent composition to trigger the switch between different supramolecular architectures.[12] While micellar aggregates are formed in the presence of THF, their hybrid DNA–dendron LON formed nanofibers after gently evaporating THF followed by slow cooling. The authors hypothesized that the organic co-solvent eliminated π–π stacking interactions important for the integrity of the nanofibers.

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