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Drug delivery systems based on nucleic acid nanostructures

Jan Willem de Vries *, Feng Zhang, Andreas Herrmann

Department of Polymer Chemistry, Zernike Institute for Advanced Materials, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

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ABSTRACT

The field of DNA nanotechnology has progressed rapidly in recent years and hence a large variety of 1D-, 2D- and 3D DNA nanostructures with various sizes, geometries and shapes is readily accessible. DNA-based nanoobjects are fabricated by straight forward design and self-assembly processes allowing the exact positioning of functional moieties and the integration of other materials. At the same time some of these nanosystems are characterized by a low toxicity profile. As a consequence, the use of these architectures in a biomedical context has been explored. In this review the progress and possibilities of pristine nucleic acid nanostructures and DNA hybrid materials for drug delivery will be discussed. For the latter class of structures, a distinction is made between carriers with an inorganic core composed of gold or silica and amphiphilic DNA block copolymers that exhibit a soft hydrophobic interior.

1. Introduction

Since the discovery of the DNA double helix in 1953 many researchers have been intrigued not only by its role and the processes involved in storing genetic information but also by its utilization as a building block for nanostructures [1]. This trend has been fuelled by the introduction of automated solid phase synthesis, polymerase chain reaction and molecular cloning techniques allowing to produce oligonucleotides (ODNs) and long nucleic acid strands and make them available for a wide scientific community at an affordable price or effort. The versatile fabrication methods and the notion about the position of each atom within double-stranded (ds) DNA in combination with the unique self-recognition properties of DNA have made nucleic acids one of the most popular construction materials for nano-scale objects [2]. Early models of DNA self-assembly relied on the hybridization of single-stranded (ss) ODNs into double strands to form nucleic acid junctions [3,4]. Each junction is composed of four DNA sequences and contains short ss overhangs called "sticky ends" (Fig. 2A). These units provide a toehold for controlled assembly of multiple junctions, thereby creating a lattice of squares. In a similar way a cube can be formed by catenating six circular DNA strands mediated by hybridization and ligation (Fig. 2B) [5].

However, these assembly processes did not yield rigid junctions with defined angles and hence the geometry of the resulting structures was not well defined. To overcome these shortcomings two methods were developed to obtain well defined and structurally stable DNA nanoobjects. The first one involves DNA tiles that utilize the helical turn of DNA to form crossovers between two or more double strands within its structure (Fig. 3A). This design principle yields more rigid building blocks of high structural integrity that can be used for the construction of larger crystals of DNA [6,7]. Later this method was greatly expanded and generalized to allow the assembly of DNA into any desired shape like squares, triangles, star shapes or even smilies using a single viral DNA strand and many short ones that function as connecting elements, the "staple strands" [8]. An example of a 3D structure is a DNA box that contains a controllable lid (Fig. 1A) [9]. To date these DNA origami structures can be easily designed and synthesized and are applied for detection of biomolecules like proteins or DNA and for performing reactions at the nanometer scale [10–12].

The second method to obtain rigid DNA nanoobjects relies on the tensegrity principle (Fig. 3B) [13,14]. The squares considered earlier were unstable due to flexible junctions. DNA triangles, however, do not face this shortcoming and when the edges are composed of this motif rigid structures are obtained [15]. Therefore, many researchers have used this principle to construct a large number of DNA nanocages resistant to deformation like tetrahedra, octahedra, dodecahedra and icosahedra [16–20].

Aside from using pristine DNA as building block inorganic nanoparticles (NPs) have been used as template for the organization of ODNs. One very appealing template for this purpose is colloidal gold that was first used in 1996 when DNA functionalized gold nanoparticles (DNA-Au NPs) were introduced [21]. Thiol-terminated ODNs readily react with the surface of Au NPs and subsequent hybridization gives access to assemblies of higher order [22,23]. DNA-Au NPs offer some extra features like magnetic properties, plasmonic effects or the ability of fluorescence quenching, which represent a significant extension to the functionality of pristine DNA nanoobjects [24]. These characteristics are important in the field of bio-imaging

* Corresponding author.
E-mail address: a.herrmann@rug.nl (J.W. de Vries).

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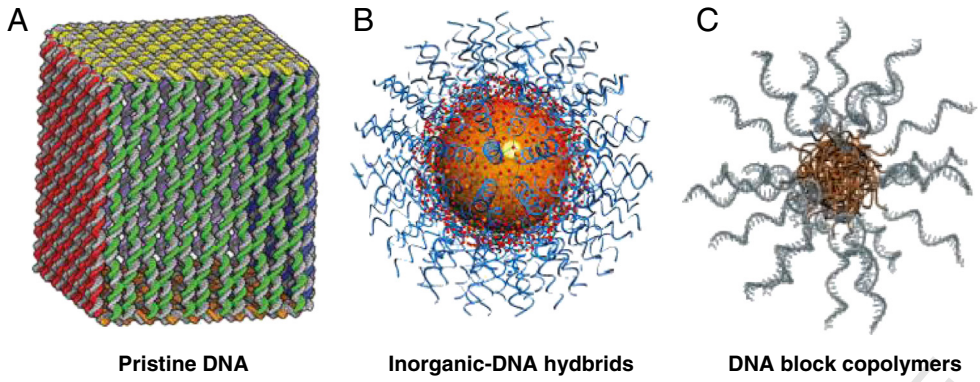

Fig. 1. Different classes of DNA nanostructures including (A) pristine DNA nanoobjects, (B) inorganic-DNA hybrid materials and C) assemblies of amphiphilic DNA block copolymers. Reproduced with permission from [9,24].

and biomedicine; hence DNA-Au NPs have become a very popular template for the assembly of nanoobjects and currently find use in imaging, detection and as transfection agents and gene regulation materials [25–28].

In addition to DNA nanoparticles with an inorganic core such structures can be produced with a soft interior. The realization of these structures implies the use of synthetic organic polymers. The first DNA polymer conjugates date back to the late 1980s, where poly(L-lysine)-*block*-DNA was used as anti-viral agent [29,30]. Nowadays, nucleic acid-polymer hybrid materials are already in clinical use [31]. Thereby, a hydrophilic synthetic macromolecule component was connected to an aptamer for increasing the in-vivo stability of the nucleic acid. For the realization of DNA polymer nanoobjects hydrophobic polymers need to be attached to the DNA units to achieve self-assembly into larger aggregates. The first example of such an amphiphilic biodegradable DNA block copolymer (DBC) contained poly(D,L-lactic-*co*-glycolic acid) as a hydrophobic polymer block [32]. These compounds form micellar structures that exhibit a hydrophobic core and a hydrophilic corona of ss DNA. More recently, several groups realized such micellar morphologies and in addition showed that the overall structure can be altered from spherical to cylindrical assemblies by stimuli like changes in pH, addition of endonucleases or through hybridization with complementary DNA [33,34]. Due to these unique properties, DBCs are currently applied in purification of biomaterials [35,36], DNA detection [37], templated synthesis [38] and in nanoelectronics [39].

All classes of DNA nanomaterials described above have in common that the size and shape are very well defined, probably better than in any other bottom-up fabricated material. This feature has dramatic consequences for applications in the field of biomedicine where multifunctional nanoparticles start to play an increasingly important role, especially in the areas of drug delivery and bioimaging. The DNA nanoobjects act as a shape persistent scaffold allowing precise positioning of various moieties like targeting units or drug payloads. On the other hand all the different types of DNA assemblies exhibit distinctive properties. While the functionality of a pristine DNA scaffold is relatively limited, in the case of DNA hybrid materials extra functions are implemented via the non-nucleic acid components. All these different features will be highlighted in this review article.

Although the use of DNA nanoobjects in biomedicine is still in its early stages, promising examples have been provided that demonstrate the applicability and benefits of using DNA-based nanomaterials over other systems like liposomes, polymeric micelles and polymersomes [40–43]. The most obvious use of oligonucleotide nanostructures in the medical field is the delivery of siRNA, antisense RNA or genes. However, several excellent reviews on this topic have been published recently [44–47]. The same holds true for DNA nanoobjects employed in the context of cellular and in-vivo bioimaging [48,49]. Therefore, both topics will not be covered in this manuscript. Here we will summarize the use of pristine DNA nanoobjects and DNA hybrid materials as carriers in the field of therapeutic delivery and vaccination. For the different classes of DNA nanomaterials we start with describing the preparation methods followed by the stability in biological environments and cell uptake behavior. Finally, we discuss controlled release or performance of the nanostructures in-vitro and in-vivo.

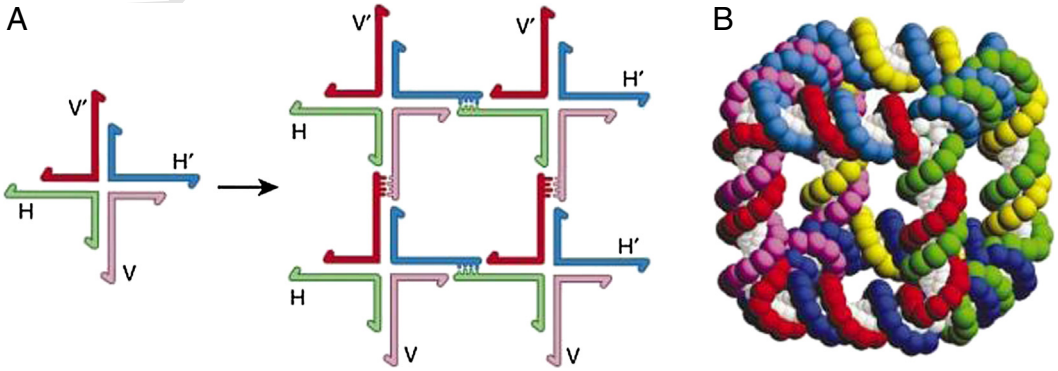

Fig. 2. (A) On the left a representation of a nucleic acid junction formed from four ss DNA sequences is shown and on the right the corresponding lattice formed by hybridization of the sticky ends is depicted. (B) DNA cube formed by catenated circular DNA strands.
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