DNA nanotechnology 2.5

For DNA nanodevices to be deployed in living cells and higher organisms, they need to be biocompatible and inexpensive enough to be produced in large quantities.

Deoxyribonucleic acid (DNA) — the molecule that carries the genetic information of a living organism — is diverse in structure and function. The components that make up DNA (the nucleobases) snap together in very specific ways through hydrogen bonding. In nature, this complementary base-pairing contributes to DNA's helical structure and the way genetic information is stored and retrieved. Biologists have long used the circularized form of DNA (known as plasmids) to carry genes into bacterial cells for cloning and amplification. Because of its programmability, DNA has also earned itself a reputation as a versatile engineering material. In the last 30 years, the DNA nanotechnology community has gone from an initial wave of making static structures of different shapes and sizes, to a second wave of creating increasingly sophisticated and dynamic structures capable of carrying drugs, interacting with cell surface proteins and performing certain functions inside cells[1,2]. At the same time though, significant developments in the design of static DNA nanostructures continue to be made, as illustrated, for example, by Hao Yan and colleagues in this issue[3]. In the near future, as researchers look to move DNA nanodevices from cells and into higher organisms, there is plenty to consider.

DNA nanodevices are constructed by either tiling together the sticky ends of different DNA motifs (a method called DNA tiling), or by folding a long single-stranded DNA scaffold into a desired structure with the help of short staple strands (which is known as DNA origami). In the case of dynamic structures, such as those that can move or perform computational tasks, strand displacement is used, whereby the nanodevice is programed to respond to an incoming DNA strand that displaces an existing one on the nanodevice.

The ability to program these structures to fold a certain way, carry information and reconfigure themselves means that DNA nanodevices can be designed to do many things. They can, for example, carry drugs and deliver them to targets in clever ways, or can be designed to have movable parts that can sense and/or amplify signals, or even perform logic functions like a computer. Furthermore, it is expected that the programmability of DNA could resolve the long-standing issue of selectivity in drug targeting and delivery. Ultimately, these devices would be able to interact with the cell, and/or emulate the missing components of a complex biological system. In a Review article in this issue, Georg Seelig and colleagues examine some of these applications and outline the key issues that need to be resolved before DNA nanostructures can emerge as a competitive alternative drug delivery technology, and a unique therapeutic and/or diagnostic material[4].

> Organisms have sophisticated mechanisms to detect and eliminate foreign DNA to protect their own DNA.

The first step in making the leap from well-controlled cell-free settings to complex cellular environments, and then on to higher organisms, is to resolve issues surrounding the stability of these DNA nanostructures. The inside of a cell is complex and crowded — DNA nanodevices will struggle to diffuse through the complex cytoplasmic mixture, and will need to fend off DNA-binding proteins and enzymes that break them down. Furthermore, most DNA nanostructures (with the exception of the DNA icosahedron and tetrahedron) require high concentrations of divalent cations, such as magnesium ions, to assemble. Because physiological concentrations of magnesium ions are considerably lower, the nanostructures fall apart; stability can be achieved through the addition of salt, the protein actin, or magnesium ions. Importantly, more studies are needed to understand how stability can be programmed into the DNA nanostructures, rather than attained through manipulating environmental conditions.

As more DNA nanostructures are injected through different routes into higher organisms for various applications, it is becoming increasingly important to better understand how these structures distribute and move around the body, and how the body's immune system reacts to their presence. Although DNA is a natural biopolymer, organisms have very sophisticated mechanisms to detect and eliminate foreign or unnatural DNA in order to protect their own DNA. It is much like a response to a viral infection: in the presence of foreign DNA, cells upregulate certain genes and stimulate the release of cytokines that have antimicrobial or inflammatory properties. For DNA-based vaccines, this feature is useful for boosting the immune system. However, in other cases, chronic expression of these genes and inflammatory responses can be very damaging. In a Perspective article in this issue, Yamuna Krishnan and co-workers outline the anticipated molecular, cellular and organismal pathways that DNA nanodevices will encounter when they are introduced into higher organisms[5]. The choice is designing DNA nanostructures to either evade or interact with the body's surveillance system.

Although it is believed that DNA nanodevices have considerable potential as drug delivery vehicles, the community should carefully consider exactly how the programmability of DNA can be exploited to create a conceptually new type of drug delivery device. Recent advances in DNA nanotechnology have provided a rich toolbox for engineering living organisms and building molecular logic circuits. With the help of such capabilities, drug delivery vehicles or approaches can be envisaged to offer something more sophisticated than the injection of a static container, as practiced today. For this to become a reality, the cost of producing high-quality DNA, which has decreased in recent years, will first have to become competitive with that of producing antibodies and polymers[6]. ❐

References

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