DNA nanotechnology in neural engineering: A perspective

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Abstract

DNA nanotechnology has great potential as a platform to enhance neural engineering approaches. DNA based nanoparticles are biocompatible and easy to functionalize [1]. Peptides or proteins can be conjugated to DNA nanoparticles to target specific cells and tissues [2], [3], as well as imaging agents to help diagnosis and monitoring purposes [4], [5]. In addition, recent studies have shown the capacity of some DNA based nanoparticles to cross the blood-brain barrier to target brain tumors in rats [4]. Others have shown DNA-peptide nanoparticles that enhanced differentiation of neural stem cell proliferation and neural differentiation [6], as well as new technologies to construct DNA-based molecular circuitry [7]. Besides all of these promising features offered by DNA nanotechnology, DNA has also shown to be a great scaffold for the production of nanoelectronics, giving a realistic perspective of the creation of nano devices that can target a desired tissue or cell and perform as nanochips for diagnosis, sensing or modulatory functions. Therefore, this work reviews some of the characteristics of nanotechnology and DNA-based nanoelectronics that are favorable for the development of nanodevices as neural system probes, as well as some perspectives for this type of technology in the field of neural engineering.

I. INTRODUCTION

Despite the complexity of the central nervous system, the field of neural engineering has brought ingenious solutions to understand, repair, replace, or enhance neural systems [8], [9]. However, most of the techniques used in neural engineering are lacking on specificity of target [10], [11], as well as sensitivity [12]; and some of them are highly invasive [10], [13]. Additionally, one of the biggest problems in neural engineering is the mismatch properties of the incorporation of electronic systems in biological systems [14]. One promising approach is the development of nanosized systems/devices that can achieve neuro sensing and neuro modulation at the cell and organelle level [15]–[17] and that can easily be targeted with high specificity [4], [18]. The integration of electronics and molecular biology into the new field of nanobioelectronics could be the solution to many of the current challenges in current applications of electronics devices in living systems, such as, size, biocompatibility and mechanical properties. However, a very limited amount of materials possess physical properties that would allow them to be used in electronics devices. Some of these are nucleic acids and carbon nanotubes, graphene-based material and some conjugated polymers [19]. Here is the need for discovery and development of biomaterials that allow the creation of nanoelectronics. Fortunately, DNA is a highly versatile biomaterial that can be used not only to build custom objects and devices [7], but also has shown to be a material suitable for the production of nanoelectronics [20], [21]. Some of the advantages of DNA as a scaffold are: DNA is a highly customizable scaffold that can be modified with several strategies for improved biological integration and controlled device-tissue interfaces [22]–[25], DNA follows very specific hybridization rules that makes it possible to predict and control its shape

[26], there are several techniques allow its replication and as already mentioned [27], [25], [28]–[30], it has shown very interesting properties for the development of nanoelectronic components, as well as molecular circuitry [7]. Multiple studies have shown that DNA, and more specifically DNA origami can be used as nanocarrier for targeted treatment [4], [31], [32]. This ability combined with its mechanical properties, biocompatibility and the capacity to create DNA-based nanodevices could be the breakthrough for a new era of targeted nanodevices for the study, diagnosis and treatment of neural systems

II. CHALLENGES IN NEURAL ENGINEERING

Neural engineering concentrates on the design of solutions to tackle neurological problems based on the little is understood about the brain [8], [9]. Some of the areas within the field of neural engineering are neural modulation, neural prosthesis, neuro-therapeutics and neuro-diagnostics. Most of these are using micro and macro scale solutions to problems and dysfunction generated at on neuronal/cellular or even molecular level [9], [33], [34]. For instance, neuromodulation focuses in the development of a wide range of technologies that alter pathological activity within the nervous system to accomplish therapeutic effects[10]. The most widely used of these technologies is deep brain stimulation, which is already FDA approved for the treatment of Parkinson's disease, dystonia, essential tremor and obsessive compulsive disorder [35], [36]. The outcome of neuromodulatory therapies is completely dependent of position of stimulation, which in the case of deep brain stimulation is done by a surgeon that positions the electrodes in the brain [34]. Thus, neuromodulation technologies are lacking on precision of target [35], spatial, temporal, cell-type, and patient-specific stimulation [37]. Most of these interventions are highly invasive and can result in tissues scaring [38], [15], which also can affect the effectiveness of the treatment. Furthermore, there is a need for functional material that allow for more integrated device–tissue interfaces [14]. Additionally, reducing the mismatch in mechanical properties of implanted devices with the biological tissue is fundamental to reduce immune system response and increase the biological integration[38]. In neuroprosthetics, there is a special need for novel device materials that mimic the mechanics of central nervous system tissue, such developments would further the success of this field [14] . Besides technologies to perturb or stimulate, it is important for the field of neural engineering to create tools to assist with observation of the central nervous system phenomena [4]. Indeed, the development of more functional and targeted imaging techniques is key, not only for helping to better understand the brain and for assisting in the diagnosis of pathologies, but also to be integrated with neuromodulation technologies to obtain feedback and improve outcome of these techniques. Overcoming these challenges would make therapies safer, less invasive, and more effective, bringing wellness to patients with a minimized risk [10].

III. NANOTECHNOLOGY

"Nanoscale biomaterials can circumvent the limitations of current technologies, representing a potential imperceptible platform" [33]. Advances in nanotechnology have allowed us to see and control materials at the molecular scale level. Several new technological advancements and areas of research have developed from this concept, nanomaterials , nanomedicine, nanoelectronics, and etcetera. For instance, nanobioelectronic is now a fast growing field that has been assisted by many recent technological advances in biotechnology, nanomedicine and electronics. Nano electronics can help to solve some of the mismatches between elements of the electronic and living biological systems, such as size, biocompatibility and mechanical properties [15], [20], [39]. Some advances have already been made in the area of tissue/nanoelectronic mesh hybrids. Dai et al. achieved seamless Integration of electronics with tissues and successful tracking and modulation of the same

neurons and neural circuits on a year time scale using an injectable mesh nanoelectronic device [40] and three-dimensional macroporous nanoelectronic networks as brain probes [17]. Other examples are, 3D neural tissue, cardiac patches, and vascular constructs, where the nanoelectronic devices have been used to carry out real-time 3D recording of electrophysiological and chemical signals in biological tissue [40]. Importantly, nanobioelectronics gives us the ability to create miniaturized devices that can perform inter and intracellularly, targeting specific organelles and offering more functional specificity [19]. However, to be able to construct technologies at the nanoscale level, it is necessary to utilize or develop materials that allow nanoscale or molecular control.

IV. DNA NANOTECHNOLOGY

DNA, or deoxyribonucleic acid, already plays an essential role in human life. It is a biological molecule that exists mostly within the nucleus of cells in all living organisms and is the carrier of the genetic information [41]. DNA consists of a double helix formed by the hybridization of two antiparallel complementary single-stranded DNA (ssDNA) molecules following the Watson and Crick Base-pairing rules [41]. The high predictability of DNA hybridization, the addressability enabled by sequence specificity, as well as the unique structural feature of the dsDNA molecules have been exploited in the recent years to create nanoobjects that allow new molecularly controlled features. Since Nadrian C. Seeman presented the possibility to form DNA objects, lattices, and crystals [26], DNA has been used to assemble a large spectrum of 1-,2- and 3D lattices and discrete nanostructures with nanoscale predictability [42]. More recently, Paul Rothemund developed the DNA origami technique that enables precise assembly of discrete, monodisperse and pure DNA-NPs in a one-pot reaction paving the way to the broad use of DNA origami in bioengineering and biomedical applications [43]. The unique properties of DNA nanostructures contribute to its importance in the design and development of materials and nanodevices with a wide range of applications [44]. In nanomedicine, for instance, areas such as drug delivery, biosensing and tissue engineering are already incorporating DNA nanotechnology [2], [45]–[47].

V. FEATURES OF DNA NANOTECHNOLOGY

The way DNA strands hybridize follows a set of rules, or Watson and Crick base-pairing rules, making DNA hybridization a very predictable and controlled process. Based on this property exclusive of DNA, it is possible to construct objects and lattices with ssDNA strands designed with sequences that hybridize in very specific places and folds into the desired object. This concept has been further developed with the name of DNA origami and has been facilitated with the introduction of new computer software that assists on the design of the origami objects and the required DNA sequences to fold such objects [48]. DNA origami gives us the opportunity to control arrangements at the molecular level like no other material has done it, making this technology extremely attractive to a wide range of fields. Also, DNA molecules can be functionalized using very straightforward chemical reactions [22], allowing for controlled decoration and functionalization of DNA nanostructures at predetermined sites. Indeed, due to this control in the nanoscale functionalization of DNA origami, it has been highly useful in the study of molecular interactions, such as protein- protein [49, p.], [50], protein-aptamer [46], [51], protein-peptide [22] interactions among others [52], [53]. DNA is a biomolecule and therefore DNA origami is inherently biocompatible [54]. Hence, DNA origami has been largely studied for biomedical applications [23], [55], such as nanocarriers for drug delivery [2], [3], [31], [45] and nanodevices for the study of cell behavior [54]. For instance, DNA nanoparticles have shown ability to cross the blood-brain barrier; they can also be highly conjugated to different moieties for

different purposes, such as imaging and active targeting[4]. For instance, Tian et al. designed DNA origami-based imaging probes that can cross the blood-brain barrier and actively target brain tumors in vivo studies[4]. Langecker et al. constructed transmembrane channels for single molecule cellular sensing using DNA nanotechnology, this type of advances carry great potential for the development of nanosize sensing and neuron signaling probes [5]. Li et al. very well summarize the current abilities of DNA/RNA nanotechnology to construct nucleic acid nanostructure-based molecular circuitry to realize applications in live cells. The construction of nucleic acid based molecular circuitry could be repurposed for applications including diagnosis, cancer therapy, optogenetics, biomanufacturing and robotics [7].

Additionally, the interest for this biological scaffold material has spread to other fields, such as the electric, mechanic and computational fields. As a result, much research has been done to determine the physical properties of DNA. Although, there is some discrepancy in the findings, particularly on the electrical properties of DNA, this is potentially caused by the different conditions and settings used in each study. Furthermore, as it has been stated recently by Wang, "consensus has been reached that a short DNA molecule is a one-dimensional conductor and can be used as molecular wires" [21]. Additionally, other studies suggest that, when coupled with some particular small molecules, intercalating molecules or covalently attached molecules, DNA has the potential to mimic the electronic behavior of standard materials used in electronic components such as transistors and diodes [56]. As a result, DNA nanotechnology promises a great future for the development of molecular chips and devices.

VI. DNA-BASED NANOELECTRONICS

DNA electrical behavior have been explored and it has been found that DNA can be modified in a great number of ways to change and control its electric properties. Some DNA- based electronic components like, DNA nanowires, diodes and switches have been created. Research has shown that at certain conditions DNA behaves as an insulator, but at other conditions the charge transport can significantly increase [57], [58]. Although the conductive properties of pure DNA could be limited by its length, sequence and chemical proper of its environment [57] DNA can be easily modified to increase and facilitate its conductivity. In 1998, Braun et al. were able to assemble DNA-templated silver nanowires connected to two gold electrodes. In this study, each electrode was functionalized with a DNA strand complementary to each other, then the strands were allowed to hybridize, and the silver was chemically deposited on the double-stranded DNA forming the silver nanowire [59]. Since multiple approaches have been explored towards the construction of DNA conductive nanowires, most of them are based on the use of DNA as the frame to grow metal nanowires [60]–[62]. Additionally, achieving the development of nanoelectronics requires the use of molecules with properties similar to those of conventional electronic components, such as molecular switches and rectifiers. Luckily, DNA is a very versatile molecule that has shown very promising results for the production of this type of electronic components as well. For instance, Guo et al. designed a DNA-based molecular rectifier with strong diode-like rectification behavior using coralyne, a long molecule with high content of aromatic rings, as an intercalator in a DNA duplex [63]. In 2017, Xiang et al. demonstrated conductance switching in DNA between to levels using an electrochemical (EC) gate. With the substitution of a DNA base with a redox group, the EC gate causes the switching of the redox group between two states, oxidized and reduced, producing the reversible switching of the DNA conductance between two discrete levels [64]

VII. DISCUSSION

DNA is a flexible tool that combines its biocompatibility with its outstanding customization properties. In the light of the challenges of present neural engineering technologies, DNA nanotechnology is a powerful tool for the design of future nano-enabled devices and neural interfaces that can overcome the current limitations of neural engineering technologies [33]. DNA nanoelectronics offer the possibility to probe the coupling of electric and physiological phenomena from the scale of tissues and organs to the scale of cells and even organelles. With the integration of DNA origami with DNA-based nanocircuits, very complex nanodevices can be built for purposes of neuron stimulation and inhibition. DNA nanotechnology can also be used to incorporate nanosensors that can provide with feedback from the stimulation [5], [46]. Additionally, DNA nanodevices could be specifically targeted to a type of cells, such as a neuron, by functionalization with targeting moieties [4]. With the incorporation of chemical modifications on the surface of the DNA nanodevices, this type of technology would allow for controlled creation of device- tissues interface. Nonetheless, invasiveness and mechanical mismatch is not an issue at the nanoscale level and especially for a biomolecule such as DNA. All of the outstanding characteristics of DNA nanotechnology could be the breakthrough for a new era of targeted nanodevices that would help us better understand, repair, replace, or enhance neural systems [7], [17], [19], [33], [37], [42].

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