Biomimetic nanofibrous scaffolds for neural tissue engineering and drug development

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Neural tissue engineering aims to develop functional substitutes for damaged tissues, creating many promising opportunities in regeneration medicine and drug discovery. Biomaterial scaffolds routinely provide nerve cells with a physical support for cell growth and regeneration, yielding 3D extracellular matrix to mimic the *in vivo* cellular microenvironment. Among the various types of cellular scaffolds for reconstruction, biomimetic nanofibrous scaffolds are recognized as appropriate candidates by precisely controlling morphology and shape. Here, we review the current techniques in fabricating biomimetic nanofibrous scaffolds for neural tissue engineering, and describe the impact of nanofiber components on the properties of scaffolds and their uses in therapeutic models and drug development. We also discuss the current challenges and future directions of applying 3D printing and microfluidic technologies in neural tissue engineering.

Introduction

The ability to reconstruct artificially functional 3D tissues or organs has been recognized as an important technology for animal-alternative drug screening and regenerative medicine [1–3]. Neural tissue engineering offers new therapeutic opportunities for regenerating the damaged nervous tissues in transplantation, and also creates *in vitro* 3D neural models for drug screening [4–6]. In these studies, biomaterial scaffolds are generally required to provide an artificial extracellular matrix (ECM) for the seeding and growth of nerve cells. Rather than simply mixing cells with biomaterials, an effective technique for neural tissue engineering often combines nano- and micro-technological strategies for designing and engineering complex tissues, and tailoring the properties of 3D biological scaffolds; this is crucial for a successful reconstruction to mimic the real cellular microenvironment and reproduce effective tissue functions [7,8]. Therefore, significant efforts have been devoted to promote effective organization and functional integration of the cells into biological scaffolds with closely resembled morphological and physiological features *in vivo* [9–11].

In recent years, many advanced strategies for neural tissue engineering have been developed, especially in fabricating biomimetic nanofibrous scaffolds used to mimic the ECM [12,13]. The current technologies have enabled precise control of the nanoscale morphologies and tune the biochemical properties of nanofiber biomaterials for tissue engineering [14]. In particular, among the materials used for neural tissue engineering, nanofibrous scaffolds have been widely used because of their high surface-area:volume ratio and close imitation of the natural ECMs [15–17]. At the same time, the development of nanofibers greatly extends the scope of fabricating biological scaffolds, and solves the problem of cell loss or neuropathy caused by nonphysiological local stress [13,18]. It is believed that these artificial biomaterials can serve as necessary tissue scaffolds for engineering functional neural tissues [19]. Nowadays, current technological development in biomimetic nanofibrous scaffolds has promoted many biomedical applications of neural tissue

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engineering [20,21]. Typically, it has evolved as an interdisciplinary technology that combines biology, engineering and material science, with the goal of developing neuroregenerative medicine for transplantation and 3D *in vitro* neural models for Q5 drug screening (Fig. 1) [9,22,23]. Besides nanofibrous scaffolds, an alternative choice to recapitulate the 3D aspects of neural connectivity or the microenvironment of the brain is *in vitro* bioengineering of 3D models that mimic native neural tissues. For instance, 3D brain-like cortical tissue formed from primary cortical neurons in modular 3D compartmentalized architec- Q6 tures was reported to be maintained for months *in vitro* [24]. To simplify the operation process, a unique, single-step bioacoustic levitational assembly technology was presented to implement brain bioengineering [25]. These bioengineering approaches accompanied with nanofibrous scaffolds constitute a broad toolbox for the fabrication of 3D architectures that recapitulate the physiological complexity of *in vivo* neural tissues.

In this review, we focus on discussing methods of fabricating nanofibrous scaffolds based on electrospinning and self-assembling, and describe the composites of nanofibrous scaffolds for neural tissue engineering. We start with a brief introduction to the recent development of biomimetic nanofibrous scaffolds in neural tissue engineering. Next, we give a detailed description of the strategies for the fabrication of electrospun and self-assembled nanofibrous scaffolds, classified by natural polymers, synthetic polymers and hybrid composites. Then, we present a discussion in the specific application domains, including drug development and nerve regeneration. The final section highlights the major challenges, emerging opportunities and perspectives for future developments.

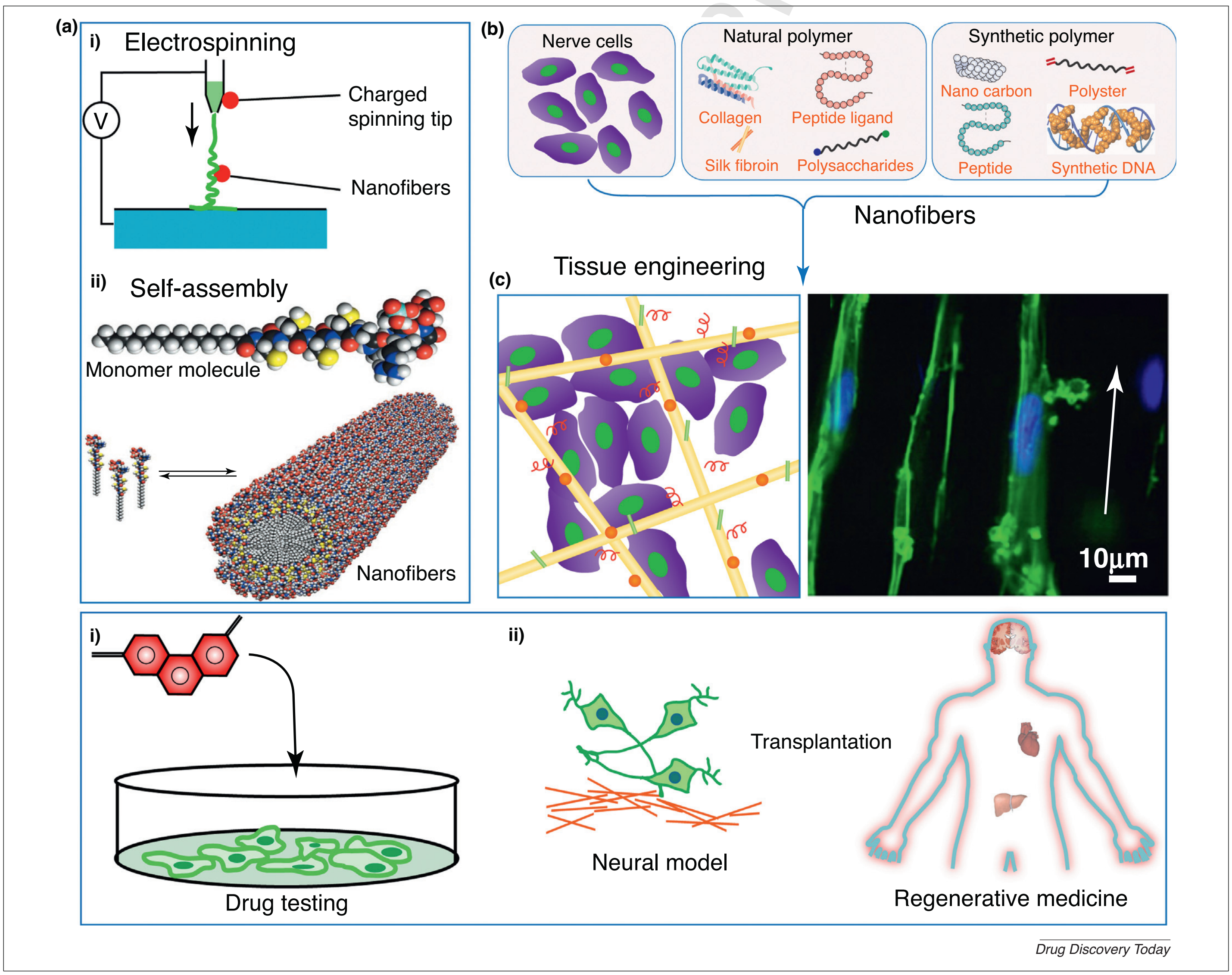

FIGURE 1

Q13 Fabrication of biomimetic nanofibrous scaffolds for neural tissue engineering. (a) Strategies of electrospinning and self-assembly used for nanofiber fabrication. Q14 Reprinted, with permission, from [22]. (b) A general pathway of engineering neural tissues with the use of nerve cells and nanofibers composed of natural polymers and synthetic polymers. **(c)** Schematic illustration and image of neural cells on nanofibrous scaffolds. Reprinted, with permission, from [9,23]. **(d)** Biomedical applications of neural tissue engineering in drug testing and regeneration medicine.

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