Biomaterials xxx (2014) 1–14

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Leading opinion

Neural tissue engineering options for peripheral nerve regeneration

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ARTICLE INFO

Article history:
Received 1 January 2014
Accepted 16 April 2014
Available online xxx

Keywords:
Neural tissue engineering
Peripheral nerve regeneration
Tissue engineered nerve graft (TENG)
Neural templates
Physicochemical and biological cues

ABSTRACT

Tissue engineered nerve grafts (TENGs) have emerged as a potential alternative to autologous nerve grafts, the gold standard for peripheral nerve repair. Typically, TENGs are composed of a biomaterial-based template that incorporates biochemical cues. A number of TENGs have been used experimentally to bridge long peripheral nerve gaps in various animal models, where the desired outcome is nerve tissue regeneration and functional recovery. So far, the translation of TENGs to the clinic for use in humans has met with a certain degree of success. In order to optimize the TENG design and further approach the matching of TENGs with autologous nerve grafts, many new cues, beyond the traditional ones, will have to be integrated into TENGs. Furthermore, there is a strong requirement for monitoring the real-time dynamic information related to the construction of TENGs. The aim of this opinion paper is to specifically and critically describe the latest advances in the field of neural tissue engineering for peripheral nerve regeneration. Here we delineate new attempts in the design of template (or scaffold) materials, especially in the context of biocompatibility, the choice and handling of support cells, and growth factor release systems. We further discuss the significance of RNAi for peripheral nerve regeneration, anticipate the potential application of RNAi reagents for TENGs, and speculate on the possible contributions of additional elements, including angiogenesis, electrical stimulation, molecular inflammatory mediators, bioactive peptides, antioxidant reagents, and cultured biological constructs, to TENGs. Finally, we consider that a diverse array of physicochemical and biological cues must be orchestrated within a TENG to create a self-consistent coordinated system with a close proximity to the regenerative microenvironment of the peripheral nervous system.

1. Introduction

Peripheral nerve injury is a common global clinical problem, and it significantly affects the patients' quality of life and causes an enormous socioeconomic burden [1–4]. Following traumatic injury to peripheral nerves, a series of pathophysiological events occurs in the injured nerve, leading to Wallerian degeneration in the distal stump and axon degeneration within a small zone distal to the proximal stump. The macrophages and monocytes migrate into the nerve stumps to remove resulting myelin and axon debris, while Schwann cells proliferate to form bands of Bungner, and produce neurotrophic factors and extracellular matrix (ECM) molecules to stimulate axon regeneration, which begins at the proximal stump and continues toward the distal stump. New axonal sprouts emanate from the nodes of Ranvier, and undergo remyelination by Schwann cells. The regenerating axons extend until reaching their synaptic target to achieve functional reinnervation.

Although the peripheral nervous system (PNS) has a greater capacity for axonal regeneration after injury than the central nervous system (CNS), spontaneous peripheral nerve repair is nearly always incomplete with poor functional recovery. Various types of medical therapy have been undertaken for several hundred years with the intention of improving outcomes [5,6].

When peripheral nerve injury results in a substantial nerve gap where tension-free neurorrhaphy (suturing of the nerve stumps) is impossible, interposition of some form of graft between the nerve stumps is required to bridge the gap and support axonal regrowth. Implantation of an autologous nerve graft [7], which is usually a functionally less important nerve segment self-donated from another site of the body, is accepted as the gold standard therapy for peripheral nerve gap repair. However, there are inherent disadvantages of autologous nerve grafting, including the limited supply of donor nerves, the need for a second surgery, donor site morbidity, and a mismatch between the donor nerve and the recipient site [8,9]; collectively these

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http://dx.doi.org/10.1016/j.biomaterials.2014.04.064
0142-9612/

have encouraged the development of alternatives to autologous nerve grafts. With progress in regenerative medicine, and especially in tissue engineering, a subfield of neural tissue engineering has emerged, and various biological and artificial nerve grafts, which are generally placed in the category of tissue engineered nerve grafts (TENGs), have been produced in attempts to supplement, and even substitute for, autologous nerve grafts. As with other tissue engineering constructs, typical TENGs involve both physiochemical and biological cues, which are provided by a biomaterial-based structure, as well as a multitude of cellular and/or molecular components. In recent years many excellent review articles have been published that outline the structure, feature, and nerve regeneration-promoting actions of TENGs, and discuss their clinical applications and future directions [10–20]. Here, we aim to critically discuss the latest advances in neural tissue engineering for peripheral nerve regeneration, focusing on the involvement of new materials, new cues, new techniques, and new concepts.

2. Biomaterials, scaffolds and templates

2.1. Some new principles

We must preface this section with a brief discussion of the development of biomaterials for tissue engineering applications, especially on the basis of biocompatibility considerations. As recently discussed by one of the present authors [21], success in tissue engineering in general has been limited through a lack of understanding of the mechanisms of biocompatibility within a regenerative environment and the consequent difficulty in establishing practical specifications for so-called tissue engineering scaffolds. Tissue engineering is the creation of new tissue for the therapeutic reconstruction of the human body, by the deliberate and controlled stimulation of selected target cells through a systematic combination of molecular and mechanical signals [22]. The delivery of those molecular and mechanical signals does not take place in a vacuum and there will usually have to be a vehicle that controls, with spatiotemporal accuracy, these processes. Such vehicles have usually been described as scaffolds, but this conveys an old fashioned meaning of an inert structure that is temporarily used to assist in the construction of inanimate objects, taking no part in the characteristics of the finished product. A preferred term is ‘template’ which incorporates the sense of an active structure. In this paper we have to discuss the present cohort of TENGs in the context of traditional concepts of these biomaterials and existing scaffolds, but should bear in mind that future developments will have to be based on new paradigms. As discussed in detail elsewhere [23,24], these paradigms move away from the search for biomaterials and structures that passively allow cells to express new extracellular matrix; instead these materials have to be actively involved in the delivery of cues to cells. Indeed, it should be borne in mind that a tissue engineering template should replicate, as far as possible, the niche of those target cells. We shall return to this matter later in this Opinion Paper.

2.2. Traditional biomaterials selection

As the basic component of TENGs, the neural scaffold guides and protects axonal regrowth in the injured nerve; it should also act as a carrier for the delivery of biochemical cues [25–27]. A wide range of synthetic or natural biomaterials has been used to prepare neural scaffolds. The principal material used in early nerve guides was the non-degradable, biologically inert silicone elastomer. More recently, different classes of biodegradable synthetic polymers, including aliphatic polyesters, poly(phosphoesters), polyurethanes, piezoelectric polymers, and some electrically conducting polymers have served as scaffold biomaterials in neural tissue engineering. Among the US Food and Drug Administration (FDA), or European (CE) regulated commercially available products used for peripheral nerve repair, Neurotube® and Neurolac® are made of polyglycolic acid (PGA) and poly(D,L-lactide-co-ε-caprolactone) (PLC), respectively [28,29].

Natural biomaterials for neural scaffolds may fall into two categories: (1) autologous non-neural tissues and allogeneic or xenogeneic neural/non-neural tissues that have been subjected to decellularization [10], and (2) naturally-derived polymers, including extracellular matrix (ECM) molecules (collagen, laminin, fibrin, fibronectin, and hyaluronan), and other polysaccharides (chitosan, alginate, agarose) and proteins (silk fibroin, keratin) [30]. Importantly, many USA/European approved commercially available products are made of Type I collagen, e.g. Neurotube® NeuroGen®, NeuroFlex™, NeuroMax™, NeuroWrap™, and NeuroMend™ [28,29]. Also in China, chitosan-based nerve grafts have been approved by the China’s State Food and Drug Administration (CFDA) for clinical trials [31].

Table 1 [32–57] summarizes currently approved, commercially available neural scaffold products for peripheral nerve repair.

It should also be noted that, in order to meet the requirements of preparing optimal neural scaffolds, biomaterials are usually modified or blended with each other.

In addition to natural and synthetic polymers, some ceramic, carbon, and metallic-based materials, have been investigated for use as neural scaffold materials. For example, a biodegradable glass fabric was used to repair the facial or median nerve in the sheep [58,59]; an active piezoelectric nanostructured ZnO ceramic was fabricated into a neural scaffold to support PNS regeneration [60]; carbon nanostructures, including nanotubes, nanofibers and graphene, have been incorporated in some experimental neural prostheses and guides [61,62]; Al/Al_2O_3 nanostructures have been investigated for their biocompatibility with peripheral neural cells [63]; biodegradable magnesium and magnesium alloys have been processed into implants for nerve repair [64,65].

Any biomaterial used to prepare neural scaffolds should possess appropriate physicochemical, biomechanical and biological properties. In the first category are the characteristics of porosity and permeability, while the second involves a balance between flexibility and rigidity. The biological properties, obviously, incorporate biocompatibility and biodegradability as well as the desired surface properties. As noted earlier, these characteristics are poorly understood. Although many biomaterials are essentially non-toxic, non-allergic, non-mutagenic and non-carcinogenic, they are likely to trigger a wide variety of unwanted responses in the human body [66,67]. Moreover, the avoidance of unwanted responses is only part of the story; if the biomaterial is unable to positively influence the performance of the target cell, then functional recovery will be significantly compromised.

The inflammation-inducing property of biomaterials cannot be ignored because the inflammatory response to peripheral nerve injury may induce both positive and negative effects on normal regeneration in the PNS [68]. The inflammatory potential needs to be reflected in the specifications for biomaterials suitable for neural scaffolds [69], and the implanted neural scaffold biomaterial must be elaborately monitored for this inflammatory potential. This was exemplified in a recent study that evaluated the long-term safety of using support cells-containing TENGs to repair a 50 mm long median nerve gap in monkeys in terms of the data from blood test, immunological and tumor marker detection, and histopathological examination of organs and glands [70].

Please cite this article in press as: Gu X, et al., Neural tissue engineering options for peripheral nerve regeneration, Biomaterials (2014), http://dx.doi.org/10.1016/j.biomaterials.2014.04.064