Biomaterials 34 (2013) 1302–1310

Contents lists available at SciVerse ScienceDirect

Biomaterials

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

Induction of rat facial nerve regeneration by functional collagen scaffolds

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ARTICLE INFO

Article history:
Received 17 September 2012
Accepted 10 October 2012
Available online 31 October 2012

Keywords:
Neurotrophic factors
Targeting repair
Laminin
Collagen
Peripheral nerve injury

ABSTRACT

Nerve conduit provides a promising strategy for nerve regeneration, and the proper microenvironment in the lumen could improve the regeneration. Our previous work had demonstrated that linear ordered collagen scaffold (LOCS) could effectively guide the oriented growth of axons. Laminin is known as an important nerve growth promoting factor and can facilitate the growth cone formation. In addition, ciliary neurotrophic factor (CNTF) and brain-derived neurotrophic factor (BDNF) can effectively improve the nerve regeneration after nerve injuries. However, in practice, diffusion caused by the body fluids is the major obstacle in their applications. To retain CNTF or BDNF on the scaffolds, we produced collagen binding CNTF (CBD-CNTF), collagen binding BDNF (CBD-BDNF) and laminin binding CNTF (LBD-CNTF), laminin binding BDNF (LBD-BDNF) respectively. In this work, we developed laminin modified LOCS fibers (L × LOCS) by chemical cross-linking LOCS fibers with laminin. Collagen binding or laminin binding neurotrophic factors were combined with LOCS or L × LOCS, and then filled them into the collagen nerve conduit. They were found to guide the ordered growth of axons, and improve the nerve functional recovery in the rat facial nerve transection model. The combination of CNTF and BDNF greatly enhanced the facial nerve regeneration and functional recovery.

1. Introduction

Facial nerve injuries affect many people and the functional recovery remains clinically challenging. To restore the motor and sensory functions, the transected nerve fibers need to regenerate across and beyond the injury site and form connections with the target tissue. For extensive nerve lesions, a nerve graft is needed for bridging the gap. Autologous nerve graft has been considered as the golden standard [1,2]. However, donor tissue availability, extra incisions, sacrifice of the donor nerve and danger of neuroma forming are still the major concerning factors [3].

Biomaterials provide promising alternative for nerve injury repair [4–6]. An ideal biomaterial should possess the following functionalities: firstly, it should have good tissue compatibility and possess sufficient mechanical strength for sustaining nerve regeneration [7]; secondly, it should give the oriented guidance for the regenerated nerve fibers [7–9]; thirdly, the biomaterial should have bio-activities that can efficiently improve the regeneration [7,10,11].

Nerve conduits are commonly used to bridge the transected nerve stumps and sustain nerve regeneration [12–18]. Collagen has been widely utilized for its favorable biocompatibility, biodegradability and weak immunogenic reactions [19]. In this study, a collagen nerve conduit was produced to provide a "regenerated room" for the injured nerve. Collagen and laminin are two main extracellular matrixes in nerve system [20,21], the linear ordered collagen scaffolds (LOCS) and the laminin modified linear ordered scaffolds (L × LOCS) were both proper guiding materials for nerve regeneration [22–24]. To guide the regeneration of the nerve fibers, LOCS and L × LOCS were applied in the lumen of the tube respectively.

Neurotrophic factors play important roles in nerve regeneration [25–33]. However their clinical applications had been limited by their diffusion in the body. Therefore, it requires periodic injections. To solve these problems, a specific collagen or laminin binding domain was fused to the growth factor [24,34–38]. CNTF and BDNF are two important factors in nerve regeneration. It had been reported that BDNF had strong effects on neuronal survival while CNTF was effective in stimulating neurite outgrowth [39]. After the nerve injury, axons will be destroyed and the neurons will undergo apoptosis. Thus, co-delivery of CNTF and BDNF to the injury site may provide better effect for the regeneration.

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http://dx.doi.org/10.1016/j.biomaterials.2012.10.031

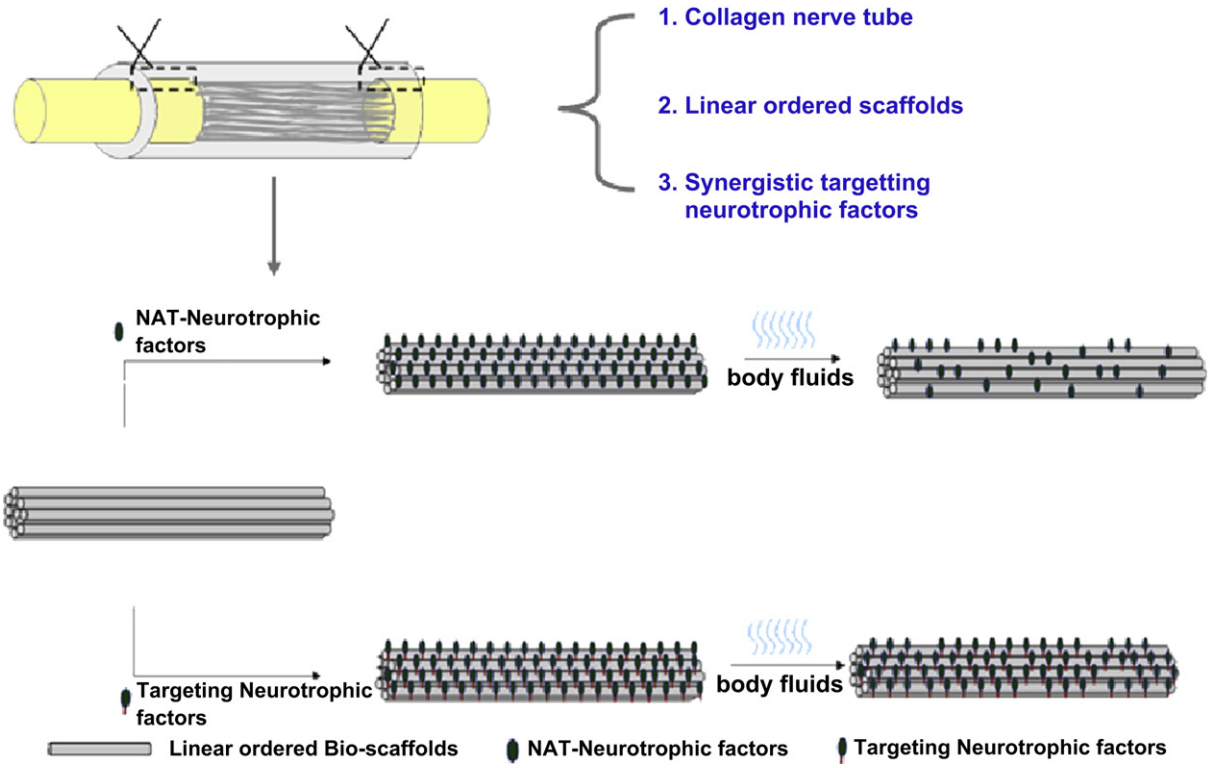

Fig. 1. Functional biomaterials designed for nerve regeneration. The functional biomaterials consisted of the nerve conduit, linear ordered scaffolds, and the collagen or laminin binding neurotrophic factors. The nerve conduit provided an independent chamber for nerve regeneration, linear ordered scaffolds guide axonal growth, and the collagen or laminin binding neurotrophic factors could specifically bind to the scaffolds, promoting nerve regeneration.

In the present study, a nerve repair device was designed: (1) the collagen nerve conduit was used to bridge the transected nerve stumps, providing a "regeneration room" for the injured nerve; (2) the liner ordered biomaterials LOCS or L × LOCS in the conduit lumen would guide the axonal regeneration; (3) the recombinant collagen or laminin binding factors CBD-CNTF, CBD-BDNF, LBD-CNTF and LBD-BDNF can bind to the relative scaffolds. And the synergetic effect of CNTF and BDNF may significantly enhance the

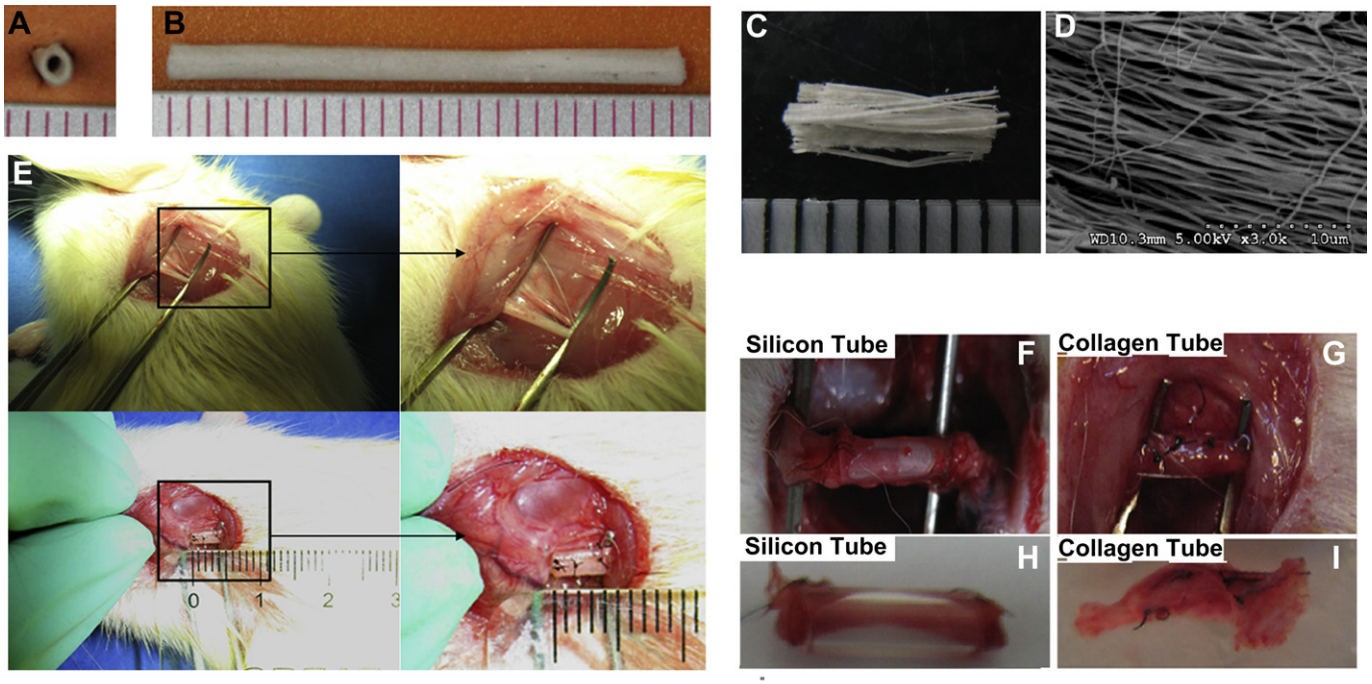

Fig. 2. The biomaterials, facial nerve injury model and the regenerated nerves after different treatment (A, B) The transverse and the longitudinal photo of the collagen nerve tube. (C) Photo of the linear ordered scaffolds. (D) The microstructure of linear ordered scaffolds exhibited by the SEM image.(E)Photos of the surgery procedures. The truck of the facial nerve was exposed. Then the transected nerve was bridged by the functional biomaterials.(F-I) Photos of the nerves regenerated in the collagen tube and the silicon tube.