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Construction of tissue engineered nerve grafts and their application in peripheral nerve regeneration

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ABSTRACT

Surgical repair of severe peripheral nerve injuries represents not only a pressing medical need, but also a great clinical challenge. Autologous nerve grafting remains a golden standard for bridging an extended gap in transected nerves. The formidable limitations related to this approach, however, have evoked the development of tissue engineered nerve grafts as a promising alternative to autologous nerve grafts. A tissue engineered nerve graft is typically constructed through a combination of a neural scaffold and a variety of cellular and molecular components. The initial and basic structure of the neural scaffold that serves to provide mechanical guidance and optimal environment for nerve regeneration was a single hollow nerve guidance conduit. Later there have been several improvements to the basic structure, especially introduction of physical fillers into the lumen of a hollow nerve guidance conduit. Up to now, a diverse array of biomaterials, either of natural or of synthetic origin, together with well-defined fabrication techniques, has been employed to prepare neural scaffolds with different structures and properties. Meanwhile different types of support cells and/or growth factors have been incorporated into the neural scaffold, producing unique biochemical effects on nerve regeneration and function restoration. This review attempts to summarize different nerve grafts used for peripheral nerve repair, to highlight various basic components of tissue engineered nerve grafts in terms of their structures, features, and nerve regeneration-promoting actions, and finally to discuss current clinical applications and future perspectives of tissue engineered nerve grafts.

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Abbreviations: BDNF, brain-derived neurotrophic factor; BrdU, bromodeoxyuridine; CNS, central nervous system; CNTF, ciliary neurotrophic factor; CsA, cyclosporin A; ECM, extracellular matrix; ePTFE, expanded polytetrafluoroethylene; ESC, embryonic stem cell; FGFs, fibroblast growth factors; FK506, tacrolimus; GDNF, glial cell line-derived growth factor; GFP, green fluorescence protein; IGF, insulin-like growth factor; lacZ, β-galactosidase; LIF, leukemia inhibitory factor; MSCs, mesenchymal stem cells; NGC, nerve guidance conduit; NGF, nerve growth factor; NT-3, neurotrophin-3; NT-4/5, neurotrophin-4/5; PAN-MA, poly(acrylonitrile-co-methylacrylate); PCL, polycaprolactone; PCLF, poly(ε-caprolactone) fumarate; PDGF, platelet-derived growth factor; PGA, poly(glycolic acid); PHBHHx, poly(3-hydroxybutyrate-co-3-hydroxyhexanoate); PHEMA-MMA, poly(2-hydroxyethyl methacrylate-co-methyl methacrylate); PLA, poly (D,L-lactic acid); PLC, poly(DL-lactide-ε-caprolactone); PLGA, poly(L-lactic-co-glycolic acid); PLLA, poly(L-lactic acid); PNS, peripheral nervous system; PPE, polyphosphoester; Ppy, polypyrrole; PSU, polysulfone; RA, retinoic acid; STX, sialyl-transferase-X; TrK, tyrosine kinase receptor; VEGF, vascular endothelial growth factor.

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1. Introduction

Peripheral nerves are commonly exposed to physical injuries, which are usually caused by transportation and construction accidents, natural disaster and war damage, and other trauma, as well as iatrogenic side effects of surgery. It is estimated that about 2.8% of trauma patients, many of whom acquire life-long disability, are affected by peripheral nerve injuries (Noble et al., 1998). The incidence of these disorders is quite high all over the world. For instance, in the United States approximately 360,000 people suffer from upper extremity paralytic syndromes annually, and 44,000 upper extremity inpatient procedures involved the nervous system during the period of 1989–1991 (Kelsey et al., 1997); in Europe over 300,000 cases of peripheral nerve injury occur annually (Mohanna et al., 2003). Among various types of peripheral nerve injuries, transection injuries where the nerve trunk is completely interrupted, especially those resulting in large neural gaps, may have a devastating impact on patients' quality of life, and in these cases reconstructive surgery is required as a therapeutic management to achieve nerve regeneration and function restoration. In consequence, peripheral nerve repair represents a unique challenge and opportunity to clinical and translational neurosciences. This review first outlines the current therapeutic strategies for treating transection injuries in peripheral nerves, and then elaborates on the development of tissue engineered nerve grafts and their applications in peripheral nerve repair.

Unlike the adult central nervous system (CNS) that fails to spontaneously regenerate after injury, the peripheral nervous system (PNS) has an intrinsic regenerative ability to a certain extent. In response to small injuries, peripheral nerves can regenerate on their own over relatively short distances under appropriate conditions. After peripheral nerves are transected, a series of molecular and cellular events, collectively called Wallerian degeneration, is triggered throughout the distal stump of transected nerves and within a small zone distal to the proximal stump, resulting in the disintegration of axoplasmic microtubules and neurofilaments (Seckel, 1990). Within 24 h most axons along the distal stump of transected nerves are reduced to granular and amorphous debris; by 48 h the myelin sheath has begun to be transformed toward the short segment (Chaudhry et al., 1992). Then macrophages and monocytes migrate into the degenerating nerve stumps to remove myelin and axon debris, while Schwann cells proliferate to form longitudinal cell columns, known as Bands of Bungner (Stoll et al., 1989). Under the influences of neurotrophic