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Review

The sciatic nerve injury model in pre-clinical research

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HIGHLIGHTS

- The far most used experimental model for the study of peripheral nerve repair and regeneration is based on the injury of the sciatic nerve.
- The potential application of the sciatic nerve injury model in pre-clinical research is critically reviewed.
- The aim is to help researchers in properly employing this in vivo model and interpreting the results in a clinical translation perspective.

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ABSTRACT

In the pre-clinical view, the study of peripheral nerve repair and regeneration still needs to be carried out in animal models due to the structural complexity of this organ which can be only partly simulated in vitro. The far most used experimental model is based on the injury of the sciatic nerve, the largest nerve trunk in mammals. In this paper, the potential application of the sciatic nerve injury model in pre-clinical research is critically reviewed. This paper is aimed at helping researchers in properly employing this in vivo model for the study of nerve repair and regeneration as well as interpreting the results in a clinical translation perspective.

Contents

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1. Introduction

Because of their spread distribution throughout the body, peripheral nerves are particularly subject to injuries mainly due to traumatic, e.g. work accidents, or iatrogenic, e.g. for tumor excision lesion (Evans, 2001; Siemionow and Brzezicki, 2009; Isaacs et al., 2013). Although usually not threatening the patient's life, nerve injuries represent a heavy social burden in terms of both long term disability and economic costs (Asplund et al., 2009; Rosberg et al., 2013). For this reason, growing efforts are dedicated to the development of effective treatment for peripheral nerve injuries which increase tissue regeneration and functional recovery and might be eventually translated to the patients for improving the clinical outcome (Tos et al., 2013; Griffin et al., 2013).

This body of pre-clinical research is mainly carried out in animal models since, so far, in vitro investigation of nerve regeneration is very limited due to the structural complexity of this organ which can hardly be reproduced in vitro (Geuna et al., 2009). The far most used experimental paradigm for the pre-clinical investigation of peripheral nerve regeneration is represented by the sciatic nerve injury (SNI) model (Siironen et al., 1996; Beer et al., 2001; Varejão et al., 2004a,b; Nichols et al., 2005; Savastano et al., 2014). Among the various reasons that might explain the preponderancy of SNI employment, two are the most important: (i) the large size of the sciatic nerve which facilitates surgery; (ii) the easy surgical access; (iii) the sought for data that can be comparable with previous studies, the very large majority of which have been carried out using the SNI model.

Due to the enormous number of experimental papers reporting data obtained with SNI model, a comprehensive review would be almost impossible and, probably, not so useful for researchers. By contrast, the aim of this paper is to overview a selection of relevant papers with the goal of providing the reader with some useful indications about the potentiality of employment of the SNI model as well as some methodological information that might help researchers in critically interpreting the results in a translational perspective.

2. Compression lesions

Experimental models based on the mechanical compression of the sciatic nerve have been widely used in experimental research in order to investigate the changes occurring to the nerve, proximal and distal to the lesion, as well as to the other central (e.g. neuronal cell bodies) and distal (e.g. muscles) anatomical structures. Sciatic nerve compression can be obtained by either ligation or crush of the epineurium. While ligation, that can be transiently applied and is used for the study of neuropathic pain (Challa, 2015), mainly induces functional changes only and it falls thus outside of the topic of this review, the crush lesion causes permanent anatomical damage and is one of the most used experimental models for the study of nerve repair and regeneration in the pre-clinical perspective (Bridge et al., 1994; Savastano et al., 2014).

Various methods have been devised for producing the crush injury, including various surgical instruments (Chen et al., 1992; Kingery et al., 1994; Savastano et al., 2014) and compression devices (Navarro and Kennedy, 1989; Radevik and Lundborg, 1977; Oliveira et al., 2001; Sarikcioglu et al., 2006). The compression is applied with the goal of interrupting the continuity of all axons (axonotmesis) without interruption of the connective scaffold of the nerve (especially the epineurium) and thus without losing continuity of the nerve trunk. Therefore, the nerve segments proximal and distal to the lesion site remain connected allowing severed axons to regrowth along an optimal regenerating pathway (the distal Wallerian regeneration environment) and reach original innervation targets (Geuna et al., 2009).

In 2001, Beer et al. described a non-serrated clamp aimed at exerting a standardized pressure to the nerve. This device has proven to be reproducible in different animal species (Beer et al., 2001; Varejão et al., 2004a,b) and its use is spreading among peripheral nerve regeneration researchers.

Independently of the procedure, the crush lesion has the main advantage to do not require microsurgical skills. Yet, inter-individual variability in tissue regeneration as well as in functional recovery is limited. These features make the sciatic nerve crush injury model particularly suitable for the study of the biology of peripheral nerve regeneration as well as the treatment strategies to improve it. In fact, its high reproducibility makes easier the identification of the changes occurring not only to the entire tissue but also at the cellular and molecular level (Chen et al., 2008; Toth et al., 2008; Lou et al., 2012; Long et al., 2013; Wright et al., 2014). Yet, high reproducibility of the lesion makes this experimental model also particularly suitable for investigating regeneration-related time course changes (De Leon et al., 1991; Gupta and Channual, 2006; Sta et al., 2014). Finally, changes in the outcome of nerve regeneration after a crush injury of the sciatic nerve might be used as a pre-clinical end-point predictor of the effectiveness of a therapeutic agent and/or tissue engineering strategy on nerve regeneration (Fleming et al., 2007; Amado et al., 2008; Baptista et al., 2008; Gigo-Benato et al., 2010; Dadon-Nachum et al., 2011; Kilic et al., 2013; Wang et al., 2014).

3. Transection lesions

Although the experimental model based on the sciatic nerve crush injury has several advantages in terms of feasibility and reproducibility, its translational potential is limited for two main reasons. First, most surgically relevant nerve lesions in human patients are characterized by at least partial transection/laceration of the nerve. Second, crush lesions in patients have a different clinical history in comparison to experimental crush lesions in laboratory animals, namely spontaneous axon regeneration observed in laboratory animals does not often occur in humans due to frequent extensive fibrosis at the lesion site; thus, in many cases, crush lesions in patients require surgery for removing the damaged tissue and replace it with a conduit (Tos et al., 2012).

For this reason, the translation to the clinics of an innovative nerve repair and regeneration treatment need in most cases to be validated using an adequate nerve transection experimental model that mimics the relevant human clinical condition as outlined in the following paragraphs.

3.1. Chronic denervation

The most severe clinical condition that can be met in a patient is the chronic denervation, i.e. a complete transection of a nerve not followed by reconstruction of the nerve continuity (e.g. because of proximal nerve stump's avulsion or multiple nerve defects with