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Review

Mouse models of spinal cord injury and stem cell transplantation

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ABSTRACT

Spinal cord injury is one of the most devastating neurologic conditions that mostly affects young, and otherwise healthy, patients. Following the primary phase of injury, deleterious secondary inflammation and vascular disruption lead to a more sustained and permanent damage. Over the years, various animal models of spinal cord injury have been developed to help understand the mechanism and the pathophysiology of injury, and to develop reliable treatment strategies. These animal models, especially for the mouse, have also become the target of stem cell therapy, which aims to replace the lost cellular element at the site of injury. In this review, we will discuss the different types of mouse models of spinal cord injury, and elaborate on the therapeutic use of stem cells transplantation.
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1. Introduction

Spinal cord injury (SCI) is a devastating condition that may result in a permanent neurological damage ranging from minor deficit, to hemiplegia, quadriplegia, and death. Despite the extensive and rapid advancement in medicine, there is still no effective therapy. Over the last two decades, stem cell therapy has attracted great attention for treating SCI by replacing the lost cellular and supporting elements [20,21]. Different types of stem cells at various stages of maturation have been used. Nevertheless, the safety and efficacy of this method has not been well established in humans to date and further animal studies are needed. The mouse model of SCI has been greatly utilized for spinal cord research purpose. This animal-based research can give insight into human research, despite the differences between the two types of cells.

Herein, we will discuss the different types of mouse models of SCI, with emphasis to the prominent studies performed on these models.

2. Chronological development of animal models of spinal cord injury

The first experimental generation of SCI in animal models was performed by Schmaus [26], who studied the effect of concussion on rabbit spinal cord. The injury was induced by tying a wooden board on a rabbit's back and performing a blow trauma to the board. Thereafter, various mechanisms for inducing SCI in different animal models were innovated [34].

Allen [2] developed a weight drop method to induce a spinal cord contusion model in canines. The injury was induced by dropping a weight from a measured height through a perpendicular tube on the exposed spinal cord with intact dura mater. Ayer [4] produced compression injury of spinal cord by injecting paraffin into the epidural space of feline spinal cord. McVeigh [19] produced compression injury in dogs via the fingertip. Thompson [32] produced crush injury in cats' spinal cord via a fingertip and scalpel handle. Ferraro [10] induced spinal cord concussion in rabbits by applying a blow to the back with an iron rod. Craig [7] produced compression injury in cat spinal cords by inserting pieces of bone wax into the intradural space around the spinal cord.

Tarlov et al. [31] developed a hydraulic compression device to produce both acute and chronic compression injuries in dogs. Rubber hydraulic balloons were inserted into the epidural space to produce quantitative degenerative lesions. Gelfan and Tarlov [12] postulated that the conduction block caused by canine spinal cord compression was reversible and was directly related to mechanical deformation rather than anoxia. Coe et al. [6] induced cervical spinal cord flexion compression in a rhesus monkey, by rigid fixation of the head with body acceleration. Harvey and Srebnik [13] induced spinal cord crush injury in rats, using thumb forceps. Ducker and Hamit [9] developed a beagle model of spinal cord contusion, using the weight drop technique. Kelly et al. [15] induced spinal cord contusion in dogs, and reported significant recovery following treatment with hypothermia and hyperbaric oxygen. Yeo and Payne [36] and Yeo et al. [35] developed a contusion model of SCI in sheep by weight drop. Sheep spinal cord more closely resembles the spinal cord of humans compared to other animal models, especially in terms of size. DeGirolami and Zivin [8] developed a spinal cord ischemia model in rabbits by placing a polyethylene catheter around the aorta distal to the renal artery. Sholomenko and Steeves [29] induced a variety of hemisection SCI in Canadian geese and Peking ducks. Wrathall et al. [33], have introduced modifications to the original weight drop method of Allen [2] and used a device in which a weight is dropped along a vertical rod on an impounder applied to the spinal cord. Their technique has been one of the most popular techniques of inducing SCI due to being simple and cheap. Blight [5] developed a guinea pig model of spinal cord compression, by using a modified pair of forceps.

3. Mouse models of spinal cord injury

Mouse models of SCI offer the advantage of being cost effective in terms of buying and maintaining the samples [17]. Moreover, mice are exposed to a diversity of natural mutations as well as genetically engineered ones, which offer a wider scope of possibilities for research.

3.1. Graded contusive model using weight drop method

Kuhn and Wrathall [17] developed a mouse model of graded contusive SCI using a weight drop method. Contusive models of SCI are most appropriate in terms of mimicking human injuries, which are mostly caused by non-penetrating blunt trauma (e.g., fall, vertebral dislocation, and burst fracture). Their method was modified from the impounder weight drop technique used by

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