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Complete canine spinal cord transection model: a large animal model for the translational research of spinal cord regeneration

Sufang Han†, Xing Li†, Zhifeng Xiao† & Jianwu Dai*

State Key Laboratory of Molecular Developmental Biology, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing 100080, China

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Traumatic spinal cord injury (SCI) usually results in devastating neurologic deficits and disability. In the United States, approximately 12,500 new cases are reported each year, while an estimated 100,000–140,000 new cases occur every year in China (National Spinal Cord Injury Statistical Center, 2016). Spinal cord injuries are highly disabling and primarily affect young adults, and therefore create great psychological and financial burden on the affected individuals and their families.

Methylprednisolone (MP) therapy and early surgical techniques are currently used to treat SCIs in clinic. MP had been demonstrated to reduce inflammation in acute SCI in early clinical studies, but recent research into the clinical efficacy of MP treatment has shown mixed results and harmful side effects (Mothe and Tator, 2012). While early spinal stabilization or decompression could prevent further injury, but did not promote neural regeneration. The recent advancement of regenerative medicine brings a hope for SCI repair. Stem cell transplantation, biomaterial scaffold implantation and neurotrophic factors application have been demonstrated to facilitate the creation of a regenerative microenvironment in injured spinal cords (Han et al., 2010; Li et al., 2013; Shrestha et al., 2014). A collagen-based scaffold (NeuroRegen scaffold) combined with stem cell was firstly tested in patients with complete SCI (Xiao et al., 2016; Zhao et al., 2017).

During product development, sufficient preclinical data from suitable animal models is essential. Over the past few decades, rodents have been the main SCI animal model due to its low cost, easiness to care for, and low incidence of surgical infections (Lukovic et al., 2015). In addition, a variety of experimental interventions have been shown impressive functional outcomes in rodents. However, rodents are greatly different from human in body size, anatomy and response to spinal cord injury (Nout et al., 2012). It is thus difficult to directly extrapolate the preliminary results from rodent models to clinical cases. Therefore, beagle dogs may be a suitable model between rodents and human due to easily neurological examinations, and similar clinical signs to the human counterparts.

Since the first rat weight-drop contusion model created by Allen in 1911, a range of animal models, such as contusion, compression, distraction, dislocation, transection or chemical models, have been developed to evaluate the efficacy of therapeutic interventions for SCI repair (Cheriyan et al., 2014). Partial transection, contusion and compression are the currently three main model of SCI; however, these models could not precisely evaluate axonal regeneration owing to compensatory sprouting of axons from nearby undamaged axons to form new connections with resident fibers (Figure 1A and B) (Tuszynski and Steward, 2012). These models often lead to heterogeneous degrees of injury severity and are difficult to inflict a consistent injury in each experimental animal.

†Contributed equally to this work
*Corresponding author (email: jwdai@genetics.ac.cn)

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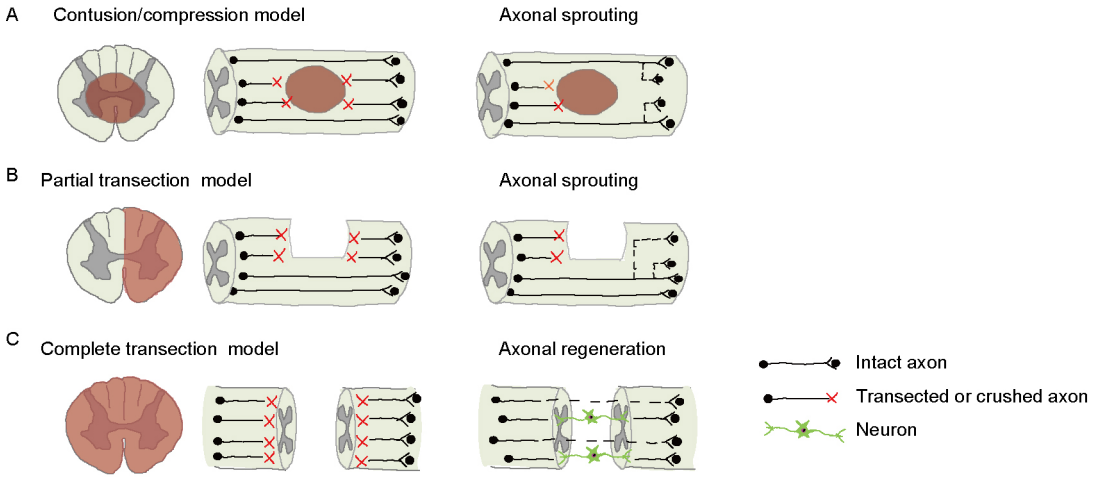

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The experiments	No. of dogs	Injured segment	Injured distance	Observation time
Nanjing I (Acute, 2011)	36	T12	7 mm	12 weeks
Nanjing II (Acute, 2012)	46	T12	5 mm	38 weeks
Tianjin (Acute, 2013)	36	T8	5 mm	36 weeks
Suzhou (Acute, 2014)	30	T8	5 mm	36 weeks
Changsha I (Chronic, 2014)	36	T8	5 mm	15 months
Changsha II (Acute, 2016)	46	T8-9	10 mm	36 weeks

Figure 1 A variety of SCI animal models and beagle dogs carried out in our lab. A and B, The contusion, compression and partial transection could induce compensatory sprouting of axons from nearby undamaged axons to form new connections with resident fibers. C, Neural regeneration in complete transection model. D, Acute and chronic completely transected SCI model on beagle dogs carried out in our lab since 2011.

We pioneered complete spinal cord transection animal models and the models show the genuine axonal regeneration since the two stumps of the spinal cord are completely separated with no residual axons left in the lesion site (Figure 1C) (Han et al., 2010; Han et al., 2015). Our previous study demonstrated that NeuroRegen scaffold alone or in combination with neurotrophic factors or stem cells could guide neurite outgrowth along its fibers, reduce scar formation and promote functional recovery in completely transected SCI rats (Han et al., 2010). We then developed the complete spinal cord transection canine model to further validate the function of NeuroRegen scaffold (Han et al., 2014; Han et al., 2015; Han et al., 2017).

The difficulty of the postoperative care increases with the severity of the injury. The postoperative care for completely transected SCI model in canine is a major challenge. Diverse secondary medical complications including pressure ulcers, deep vein thrombosis (DVT), osteoporosis, muscle spasms, urinary tract infections, and respiratory complications occur with completely transected spinal cord injury. We explored methods suitable for beagle dogs postoperative care, including (i) empty bladder manually every 12 h until the dogs were observed to urinate without assistance; (ii) keep the skin clean and free of body fluids or feces; (iii) keep the cage with very soft blankets to avoid excessive pressure; (iv) regularly apply tannic acid for preventing pressure ulcers; (v) a balanced diet that includes plenty of proteins.

Six independent experiments were performed and nearly 300 beagle dogs were used for the complete spinal cord transection canine model (Figure 1D). We evaluated the effects of NeuroRegen scaffold combined with collagen binding brain-derived neurotrophic factor (LOCS+CBD-BDNF) on the restoration of function in a canine T12 completely transected spinal cord through a short-term (12 weeks) observation (Han et al., 2014). We then prolonged the observation time up to 38 weeks and found the combined therapy could reduce the collagen deposits, and large number of neural fibers could grow into the lesion site. The therapy significantly promoted the locomotor recovery, and more than 40% of dogs in the LOCS+CBD-BDNF group at weeks 26–38 could stand unassisted and even walk, which is the first time to report such breakthrough in complete transection SCI in large animals (Han et al., 2015).

In conclusion, we have established the complete transection SCI model for the first time in beagle dogs. This model is reliable for evaluating the neural regeneration and can be used in the translation research for SCI repair.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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