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Transgenic Zebrafish Lines as Valuable Tools to Understand Successful Spinal Cord Regeneration

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Spinal cord injury (SCI) is a devastating condition that in humans leads to permanent disability. Currently, there is not yet a satisfactory treatment to cure and completely repair the damaged spinal cord in humans. Therefore, it is of great importance to follow different lines of research to increase our knowledge of this condition and to develop new therapies. In contrast to mammals, lampreys and fishes are capable of repairing their spinal cord and regaining locomotion after a complete SCI [1-4]. In the last decade, zebrafish has appeared as a very valuable genetically tractable model that can be used to understand the mechanisms that control successful spinal cord regeneration in aquatic animals. Lampreys and other species of teleost fishes are being mainly used for this type of studies [lampreys: [5-8]; teleosts: [9,10]. For example, studies performed using the lamprey model of SCI have shown that different reticulospinal descending neurons projecting in a similar region of the spinal cord have different regenerative abilities after axotomy [4,5] even in the presence of functional recovery. Recent findings using lampreys have also shown that those brain neurons that are "bad regenerators" usually die after a complete spinal cord transaction [3,5]. Other studies in lampreys have suggested that changes in the expression of axonal guidance molecules or neurotransmitter receptors could be responsible for the success/failure of the regeneration process after injury [11-13]. These and other studies have shown that lampreys are great models to study successful spinal cord regeneration. However, lampreys have a very long and complex life cycle (approximately 9 years long) involving a metamorphosis process, which makes them not suitable to generate transgenic or mutant lines that would facilitate to design and perform more functional studies.

On the other hand, zebrafish is an animal model with a short life cycle, which has facilitated greatly the generation of different transgenic and mutant lines. Transgenic and mutant animals can be used to understand the molecular mechanisms that lead to successful regeneration of the spinal cord in fishes. Recent studies using transgenic mice have shown that new cells are produced in the mammalian spinal cord after injury, although only glial cells are generated [14,15]. We could translate the knowledge acquired in zebrafish studies to design new therapies to promote neuronal and axonal regeneration in mammals including humans. For example, Dias and co-workers [16] have recently used a double-transgenic zebrafish line [*Tg(hsp70l:Gal4)×Tg(UAS:myc-notch1a-intra)*], in which a heat-shock promoter drives expression of the active intracellular domain of notch1a, to show that Notch signalling controls the generation of new motor neurons after SCI in adult zebrafish. Also, a transgenic zebrafish line, *Tg(shha:GFP),* has been used as a sonic hedgehog reporter line to show that hedgehog signalling is involved in the generation of new serotonergic interneurons after SCI in adult zebrafish [17]. Also, a recent study from Goldshmitand co-workers [18] used different transgenic and mutant zebrafish lines *[Tg(GFAP:GFP), Tg(nestin:GFP)Tg(Isl1:EGFP),Tg(mpeg1:GFP),Tg(mpx:GFP),Tg(hsp70l:dn-fgfr1-EGFPpd1), spry4-/-fh117*] to shown that Fgf signalling controls the formation of a "glial bridge" that facilitates axonal regeneration after SCI in zebrafish. These are just three of several examples of the types of functional SCI studies that can be done using transgenic zebrafish lines. So, this model appears as a very useful genetic tool to understand the mechanisms that control the production of new neurons, or for instance the regeneration of descending axons, after SCI in adult fishes. This will clearly help to propose new research lines in mammalian SCI models or to design new therapies for SCI in humans.

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