Shock waves induce an evolutionary conserved mechanism of spinal cord regeneration

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1. Introduction

Spinal cord ischemia (SCI) remains a devastating complication after aortic dissection or repair. A primary hypoxic damage is followed by a secondary damage resulting in further cellular loss via apoptosis. Affected patients have a poor prognosis and limited therapeutic options. In this study we aimed to (a) investigate the efficacy of SWT for regeneration of SCI and (b)to highlight underlying mechanisms.

2. Material & Method

SCI was performed in a murine contusion model in wild-type (WT) and **Tlr3-/-** mice with subsequent SWT. Functional performance of animals was evaluated. Spinal cord lesions and bladder size were quantified and evaluated via MRI. Dorsal root ganglia (DRGs) were isolated and neuronal sprouting, survival and metabolism were evaluated. Human spinal slice culture was performed. Zebrafish were subjected to traumatic spinal cord injuries followed by treatment with a TLR3 inhibitor or a TLR3 agonist.

3. Results

SWT improves motor function and decreases lesion size in wild-type but not **Tlr3-/-** mice via inhibition of neuronal degeneration and IL6-dependent recruitment and differentiation of neuronal progenitor cells. SWT reduced the number of ROS positive cells and apoptosis upon ischemia via induction of the antioxidative factor NRF2. Both SWT and TLR3 stimulation enhance neuronal sprouting and improve neuronal survival, even in human spinal cord cultures. We identify TLR3 as crucial enhancer of spinal cord regeneration in zebrafish. To translate our findings into a clinical setting, we treated five patients with spinal cord ischemia using SWT (mean age 65.3 years). Four patients presented with acute aortic dissection (80%), 2 of them exhibited preoperative neurological symptoms (40%). Impairment was ASIA A in 1 patient (20%), ASIA B in 3 patients (60%) and ASIA D in 1 patient (20%) at baseline. At follow up, 2 patients were graded as ASIA A (40%) and 3 patients as ASIA B (60%). SCIM score showed significant improvement. Examination of WHOQOL questionnaires revealed increased scores at follow up.

4. Discussion

Our findings indicate that TLR3-signalling is an evolutionary conserved pathway involved in spinal cord regeneration and suggest its stimulation via SWT could become a potent regenerative treatment option.