Title: **The Role of Ferroptosis in Spinal Cord Injury Microenvironment**

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Abstract Spinal cord injury (SCI), for which there currently is no cure, is a heavy burden on patient physiology and psychology. The microenvironment of the injured spinal cord is complicated. According to our previous work and the advancements in SCI research, microenvironment imbalance is the main cause of the poor regeneration and recovery of SCI. Microenvironment imbalance is defined as an increase in inhibitory factors and decrease in promoting factors for tissues, cells and molecules at different times and spaces. There are imbalance of hemorrhage and ischemia, glial scar formation, demyelination and re-myelination at the tissue's level. The cellular level imbalance involves an imbalance in the differentiation of endogenous stem cells and the transformation phenotypes of microglia and macrophages. The molecular level includes an imbalance of neurotrophic factors and their pro-peptides, cytokines, chemokines and ion. For the ion imbalance after SCI, iron plays an important role. The acute phase of traumatic SCI involves immediate hemorrhage and reactive oxygen species accumulation. Moreover, our previous work found that iron is overloaded at the injury site due to hemorrhage. Ferroptosis, a newly identified iron-dependent cell death pathway, shares similar features with these pathogenic changes of SCI. Ferroptosis was identified after spinal cord injury with the featured mitochondrial changes, shrunken mitochondria, occasionally with broken outer membranes in SCI tissues. Ferroptosis pathway associated key proteins glutathione peroxidase 4 (GPX4), glutathione (GSH), Acyl-CoA Synthetase Long Chain Family Member 4 (ACSL4) and system Xc-light chain (xCT) were changed after SCI. Besides, metabolism imbalance and inflammatory cytokines imbalance were also detected following SCI at the molecular level. At cell level, ferroptosis leads to the loss of neurons and the activation of microglia and reactive astrocyte. And the ferroptosis of oligodendrocyte lineage cells causes imbalance between demyelination and remyelination at the tissue level. All these changes caused by ferroptosis result in the poor functional recovery. But the application of ferroptosis inhibitors, such as deferoxamine and SRS 16-86, promote functional recovery by inhibiting ferroptosis pathway after SCI.

In the future, deep sequencing, multi-omics analysis and data sharing are required to reveal the deep pathological changes of the microenvironment about ferroptosis after SCI. And ferroptosis could be a biomarker contributing the diagnosis and prognosis of SCI. Temporal regulation is also a crucial aspect. Stem cells, because of their particular functions, may be a promising therapy for spinal cord injury. Massive findings discovered the role of stem cells in inhibiting ferroptosis, so we have reasons believing that stem cells can function well in inhibiting ferroptosis after SCI. And with the development of tissue engineering and interdisciplinarity, more new treatments combined with stem cells deserve our expecting. Stem cells will provide therapeutic outlook for spinal cord injury, giving a great reference for other nervous system disorders improvement. All these efforts will promote functional recovery, improve outcome and bring a bright future for patients.