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Views & Comments

A Comprehensive Study of Gene Expression and Molecular Regulation Following Spinal Cord Injury

Kwok-Fai So [a,b]

[a] Ministry of Education CNS Regeneration Collaborative Joint Laboratory, Guangdong-Hong Kong-Macau Institute of CNS Regeneration, Jinan University, Guangzhou 510632, China
[b] The State Key Laboratory of Brain and Cognitive Sciences & Department of Ophthalmology, The University of Hong Kong, Hong Kong 999077, China

Spinal cord injury will cause temporary or permanent changes in spinal cord function, leading to devastating physical, social, and vocational consequences for patients. A better understanding of the pathophysiological cascade after spinal cord injury will facilitate therapies for spinal cord injury. This research applied whole-transcriptome sequencing to analyze the rostral and caudal regions to the lesion at different time points (0 h, 0.5 h, 3 h, 6 h, 12 h, 1 d, 3 d, 7 d, 14 d, 21 d, and 28 d) after hemisection of the spinal cord in rats. Differentially expressed genes between injured and sham-operated animals were identified. Significantly altered biological processes after spinal cord injury in different types of cells (astrocytes, microglia, oligodendrocytes, immune cells, and vascular endothelial cells) were enriched with these differentially expressed genes by ingenuity pathway analysis (Fig. 1). The dynamic trends in these processes were illustrated by calculating the average expression profiles of the differentially expressed genes. Gene expression-regulatory networks of astrocyte activation, microglia activation, oligodendrocyte differentiation, blood-vessel hypoxia, sprouting, and remodeling following spinal cord injury were constructed and key genes in these processes were selected for experimental validation (Fig. 2).

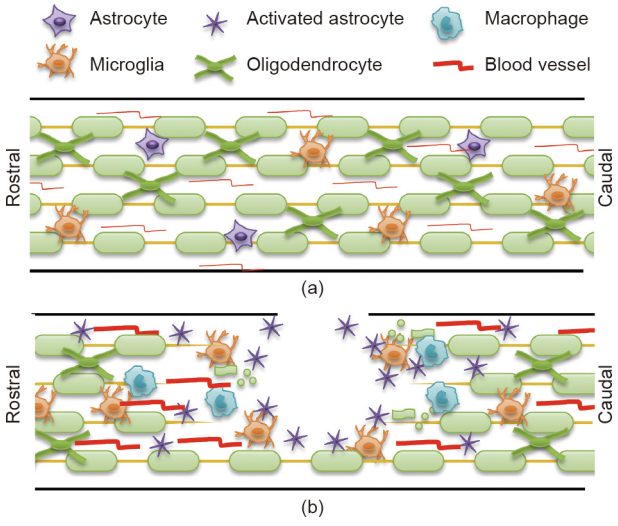

Fig. 1. Summary of the changes in biological processes (a) before and (b) after spinal cord injury in different types of cells.

Rather than the recent and growing single-cell sequencing technology, whole-transcriptome sequencing were used for spinal cord tissues. Since spinal cord injury is a complex and multifaceted disease process accompanied by a cascade of pathophysiological events and cellular activities, it is difficult and unsuitable to analyze this complicated process in just one kind of cell without paying attention to the whole microenvironment system after an injury. They applied RNA sequencing of injured tissues to facilitate the investigation on multicellular and multi-system interactions and to provide a comprehensive analysis of the complicated events that occur after spinal cord injury.

Based on the results of their studies on spinal cord injury, several conclusions were made: ① Astrocyte activation was the main event for astrocytes after spinal cord injury, and was highly activated on Day 3 following spinal cord injury. Genes involved in astrocyte activation, such as *MMP9*, *SERPINE1*, *IL1B*, *TLR2*, and *CEBPB*, were upregulated after spinal cord injury. However, *SNCA* was downregulated during this process, suggesting that *SNCA* may inhibit astrocyte activation after spinal cord injury. ② Microglia was mainly activated from Day 3 to Day 28 after spinal cord injury. Genes involved in microglia activation, such as *HMOX1*, *IL-6*, *CYBB*, *ERBB2*, and *TGFB1*, were highly upregulated. ③ The processes of oligodendrocyte apoptosis, survival, development, and differentiation sharply decreased on Day 1 after spinal cord injury. The expressions of *BMP2*, *HGF*, *TP53*, *LINGO1*, *TNC*, and *VCAN*, which are involved in oligodendrocyte differentiation, were altered after spinal cord injury. ④ Spinal cord injury triggers a sequential recruitment of inflammatory cells to the lesion site, including neutrophils, monocytes, and lymphocytes. The expressions of several cytokine and chemokines were upregulated at 0.5 h after spinal cord injury. Inflammation-related transcriptional factors, such as ATF3 and FOS, were also upregulated. ⑤ The density of the blood vessels was increased after spinal cord injury, which might be associated with the migration, proliferation, and activation of

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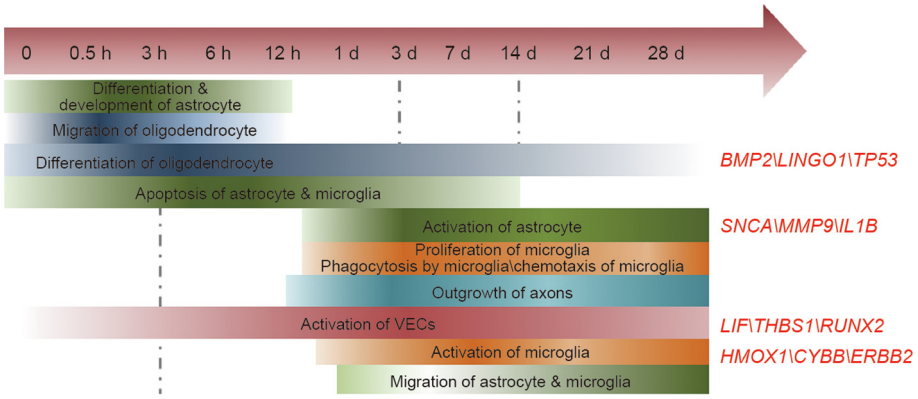

Fig. 2. Changes in key genes and biological process after spinal cord injury. VECs: vascular endothelia cells.

vascular endothelia cells. Blood vessels underwent hypoxia, sprouting angiogenesis, and blood-vessel remodeling during angiogenesis after injury, with expression changes of key genes including *LIF*, *THBS1*, and *RUNX2*.

In general, this research broadens the current understanding of molecular pathology for spinal cord injury; depicts for the first time different pathological processes and microenvironment changes in the rostral and caudal regions to the lesion at different time points after spinal cord injury; and provides helpful insights for comprehensive therapeutics for spinal cord injury, which might integrate multiple targets, drug interference, cell interference, and engineering technology.