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Impact of Transgenic Adipose Derived Stem Cells in the Healing of Spinal Cord Injury of Dogs

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Abstract : The primary spinal cord injury (SCI) causes mechanical damage to the neurons and blood vessels. It leads to secondary SCI, which activates multiple pathological pathways, which expand neuronal damage at the injury site. It is characterized by vascular disruption, ischemia, excitotoxicity, oxidation, inflammation, and apoptotic cell death. It causes nerve demyelination and disruption of axons, which perpetuate a loss of impulse conduction through the injured spinal cord. It also leads to the production of myelin inhibitory molecules, which with a concomitant formation of an astroglial scar, impede axonal regeneration. The pivotal role regarding the neuronal necrosis is played by oxidation and inflammation. During an early stage of spinal cord injury, there occurs an abundant expression of reactive oxygen species (ROS) due to defective mitochondrial metabolism and abundant migration of phagocytes (macrophages, neutrophils). ROS cause lipid peroxidation of the cell membrane, and cell death. Abundant migration of neutrophils, macrophages, and lymphocytes collectively produce pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1beta (IL-1β), matrix metalloproteinase, superoxide dismutase, and myeloperoxidases which synergize neuronal apoptosis. Therefore, it is crucial to control inflammation and oxidation injury to minimize the nerve cell death during secondary spinal cord injury. Therefore, in response to oxidation and inflammation, heme oxygenase-1 (HO-1) is induced by the resident cells to ameliorate the milieu. In the meanwhile, neurotrophic factors are induced to promote neuroregeneration. However, it seems that anti-stress enzyme (HO-1) and neurotrophic factor (BDNF) do not significantly combat the pathological events during secondary spinal cord injury. Therefore, optimum healing can be induced if anti-inflammatory and neurotrophic factors are administered in a higher amount through an exogenous source. During the first experiment, the inflammation and neuroregeneration were selectively targeted. HO-1 expressing MSCs (HO-1 MSCs) and BDNF expressing MSCs (BDNF MSC) were co-transplanted in one group (combination group) of dogs with subacute spinal cord injury to selectively control the expression of inflammatory cytokines by HO-1 and induce neuroregeneration by BDNF. We compared the combination group with the HO-1 MSCs group, BDNF MSCs group, and GFP MSCs group. We found that the combination group showed significant improvement in functional recovery. It showed increased expression of neural markers and growth-associated proteins (GAP-43) than in other groups, which depicts enhanced neuroregeneration/neural sparing due to reduced expression of pro-inflammatory cytokines such as TNF-alpha, IL-6 and COX-2; and increased expression of anti-inflammatory markers such as IL-10 and HO-1. Histopathological study revealed reduced intra-parenchymal fibrosis in the injured spinal cord segment in the combination group than in other groups. Thus it was concluded that selectively targeting the inflammation and neuronal growth with the combined use of HO-1 MSCs and BDNF MSCs more favorably promote healing of the SCI. HO-1 MSCs play a role in controlling the inflammation, which favors the BDNF induced neuroregeneration at the injured spinal cord segment of dogs.

Keywords : HO-1 MSCs, BDNF MSCs, neuroregeneration, inflammation, anti-inflammation, spinal cord injury, dogs
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