

HMGB1 as a therapeutic target in spinal cord injury: A hypothesis for novel therapy development (Review)

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Abstract. Historically, clinical outcomes following spinal cord injury (SCI) have been dismal. Severe SCI leads to devastating neurological deficits, and there is no treatment available that restores the injury-induced loss of function to a degree that an independent life can be guaranteed. To address all the issues associated with SCI, a multidisciplinary approach is required, as it is unlikely that a single approach, such as surgical intervention, pharmacotherapy or cellular transplantation, will suffice. High mobility group box 1 (HMGB1) is an inflammatory cytokine. Various studies have shown that HMGB1 plays a critical role in SCI and that inhibition of HMGB1 release may be a novel therapeutic target for SCI and may support spinal cord repair. In addition, HMGB1 has been associated with graft rejection in the early phase. Therefore, HMGB1 may be a promising therapeutic target for SCI transplant

patients. We hypothesize that inhibition of HMGB1 release rescues patients with SCI. Taken together, our findings suggest that anti-HMGB1 monoclonal antibodies or short hairpin RNA-mediated HMGB1 could be administered for spinal cord repair in SCI patients.

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1. Introduction

One of the most serious clinical conditions is spinal cord injury (SCI), the incidence of which has been increasing yearly (1). Spinal cord repair is a problem that has long puzzled neuroscientists (2,3). The repair of the injured human spinal cord with resultant functional recovery is one of the major challenges of contemporary neuroscience (4). Although the mortality rate of SCI has declined to less than 5%, the disability rate associated with SCI remains high (1). One of the most destructive complications after SCI is paraplegia, which has been a constant challenge in clinical medicine (1). Facilitating recovery of spinal cord structure and function after SCI is of great interest to neuroscientists (1). Failure of the spinal cord to regenerate and undergo

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reconstruction after SCI can be attributed to the extremely limited regenerative capacity of most central nervous system (CNS) axons as well as the hostile environment of the adult CNS, with astroglial scars forming within lesioned areas (1).

Over the past 20 years, the survival rate and long-term outcome of patients with SCI has improved, with advances in both medical and surgical treatment (5). However, the efficacy and timing of these adjuvant treatments remain controversial (5). There has been a tremendous increase in the number of basic science and clinical studies on SCI (5). The pathophysiology of SCI is complex, multifactorial and multiphasic (4). Current areas of investigation involve early acute management, including early surgical intervention, as well as new pharmacotherapy and cellular transplantation strategies (5). Transplantation of various cells, such as neural stem cells, human embryonic stem cells, olfactory ensheathing cells, olfactory mucosa, bone marrow stromal cells and induced pluripotent stem cells, is not sufficient for spinal cord repair and is not sufficiently widespread in clinical situations (3,6-15). It is unlikely that a single approach uniformly addresses all of the issues associated with SCI (5). Thus, a multidisciplinary approach is required (5).

2. HMGB1 as a therapeutic target in various diseases

High mobility group box 1 (HMGB1) has pleiotropic effects both inside and outside cells. In the nucleus, HMGB1 bends DNA and promotes the assembly of other nuclear proteins (16). Extracellular HMGB1 released from necrotic or activated cells induces cell permeability, cell recruitment, cell-cell attachment, cytokine production (tumor necrosis factor- α , interleukin-8 and C-reactive protein), T-cell activation, T-helper 1-cell polarization, dendritic-cell maturation, tissue regeneration and coagulant activation (2,17-24). Once secreted, HMGB1 induces inflammatory responses by the transduction of cellular signals through its receptors, such as TLR2, TLR4 (22,25,26) and receptor for advanced glycation end products (RAGE) (17,27,28). HMGB1 levels are markedly increased during severe sepsis in humans and animals, and administration of neutralizing HMGB1-specific antibodies prevents lethality from sepsis (29). Elevated HMGB1 levels characterize various acute and chronic diseases and are implicated in inflammation and tissue injury. In addition, HMGB1 contributes to the pathogenesis of disorders of the brain, heart, liver, lungs, gut, pancreas, joints, blood vessels and periodontium, and is implicated in graft rejection in transplantation as well as sepsis (18-20,23,29-42). Furthermore, the blockade of HMGB1 release using an anti-HMGB1 monoclonal antibody or short hairpin (sh) RNA-mediated HMGB1 has already been shown to be effective in animal models of cancer, rheumatoid arthritis, cerebral infarction, myocardial infarction, hepatic ischemia, acute pancreatitis, hemorrhagic shock and sepsis (29,34,36,43-48). Thus, HMGB1 is a novel inflammatory cytokine that is included in the 'alarmin' family, a group of endogenous factors released into the extracellular space, which activate the inflammatory response through the engagement of membrane receptors (49,50).

3. HMGB1 in spinal cord injury

Recently, HMGB1 has been shown to be elevated in the spinal cord tissue of rodents with spinal cord compression injury and

is associated with neuronal cell apoptosis (51,52). Furthermore, HMGB1 has been shown to be elevated in both the spinal cord tissue and the serum of rodents with spinal cord ischemic injury (53,54). Moreover, melatonin, ethyl pyruvate and hydrogen gas were found to reduce motor neuron apoptosis, improve motor dysfunction and attenuate the release of HMGB1 in rodents with SCI (51,53,54). Previous studies have implicated that HMGB1 directly induces apoptosis in neural cells (32,33), aggravates infarction volume and exacerbates the neurological deficit in transient cerebral ischemia in rats (36,55).

It is known that the mode of delayed neuronal cell death after SCI is apoptosis (52,56). Apoptosis is influenced by several injury-promoting factors which include pro-inflammatory cytokines (52,56). Inhibition of apoptosis promotes neurologic improvement following SCI (52,56). Therefore, it is expected that inhibition of HMGB1 release may be a novel therapeutic strategy for treating SCI as well as various acute and chronic diseases.

4. HMGB1 in transplantation

Several lines of evidence suggest that HMGB1 may play a major role in graft rejection. First, administration of thrombin and HMGB1 together in rats was found to result in excessive fibrin deposition, demonstrating pro-coagulant activity (19), and to trigger the RAGE signaling pathway, in which HMGB1 is a ligand, to activate complement (57), suggesting that HMGB1 may contribute to both vascular events and complement activation in acute rejection. Second, treatment of allograft recipients with RAGE, an anti-HMGB1 antibody or HMGB1 box-A (amino-terminal region), which specifically blocks endogenous HMGB1, was found to significantly prolong the survival of transplanted hearts in murine models (58,59). Furthermore, neutralization with an anti-HMGB1 antibody has been suggested to prevent fibrogenesis in post-orthotopic liver transplantation liver grafts (60), and treatment with an HMGB1-specific antibody prevented early islet graft loss following islet transplantation in mice (61). Therefore, it is expected that HMGB1 may become a novel therapeutic target for transplant patients following SCI, as well as other transplantations.

5. Hypothesis

The present hypothesis focuses on HMGB1 as a therapeutic target in spinal cord repair. Currently, there is no effective treatment for SCI. First, it is necessary to study the outcome of anti-HMGB1 monoclonal antibody or shRNA-mediated HMGB1 administration in animal models with SCI. Second, it is necessary to study the outcome of anti-HMGB1 monoclonal antibody or shRNA-mediated HMGB1 administration in animals that have been transplanted with various types of cells after SCI. We hypothesize that inhibition of HMGB1 as a therapeutic target for the treatment of SCI may support spinal cord repair and may be advantageous in the treatment of SCI in a clinical setting. We suggest that patients with SCI should be administered anti-HMGB1 monoclonal antibodies or shRNA-mediated HMGB1, and we predict that administration will result in positive outcomes for SCI patients. Clearly, further studies are required to confirm the effects of anti-

HMGB1 monoclonal antibody or shRNA-mediated HMGB1 administration on patient outcomes.

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