

Review

Receptor for Advanced Glycation End Products (RAGE) and Its Ligands: Focus on Spinal Cord Injury

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Received: 5 June 2014; in revised form: 7 July 2014 / Accepted: 21 July 2014 /

Published: 25 July 2014

Abstract: Spinal cord injury (SCI) results in neuronal and glial death and the loss of axons at the injury site. Inflammation after SCI leads to the inhibition of tissue regeneration and reduced neuronal survival. In addition, the loss of axons after SCI results in functional loss below the site of injury accompanied by neuronal cell body's damage. Consequently, reducing inflammation and promoting axonal regeneration after SCI is a worthy therapeutic goal. The receptor for advanced glycation end products (RAGE) is a transmembrane protein and receptor of the immunoglobulin superfamily. RAGE is implicated in inflammation and neurodegeneration. Several recent studies demonstrated an association between RAGE and central nervous system disorders through various mechanisms. However, the relationship between RAGE and SCI has not been shown. It is imperative to elucidate the association between RAGE and SCI, considering that RAGE relates to inflammation and axonal degeneration following SCI. Hence, the present review highlights recent research regarding RAGE as a compelling target for the treatment of SCI.

Keywords: receptor for advanced glycation end products (RAGE); spinal cord injury (SCI); inflammation; neurite outgrowth; Schwann cell

1. Introduction

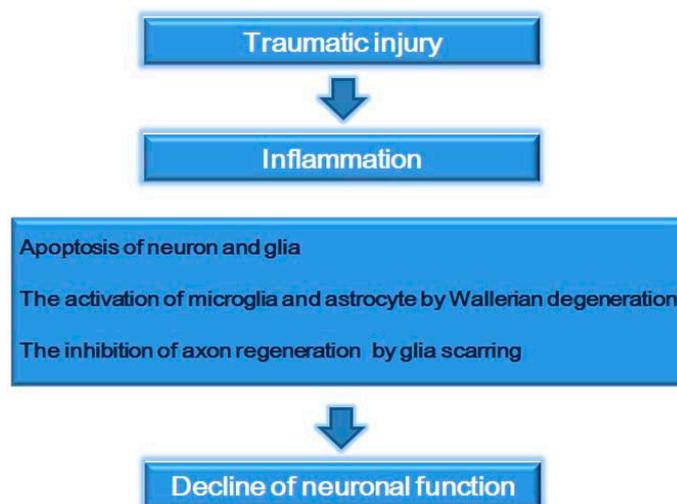
Spinal cord injury (SCI) is considered to be primarily associated with loss of motor function [1] and leads to activate diverse cellular mechanisms in the central nervous system (CNS) to attempt to repair the damaged spinal cord tissue [2]. Potential treatments for SCI, including stem cell therapy [3,4], transplantation of Schwann cells [5,6], neurotrophin and growth factor delivery [7,8], and regulation of inflammatory responses in injured spinal cord [9,10] have recently been investigated. SCI provokes an inflammatory response that causes further tissue damage and neurodegeneration [11]. The inflammation following SCI is considered an important process that promotes secondary damage to neuronal tissue in the spinal cord after traumatic injury and regulates the pathological progress during SCI [12–15]. After SCI, apoptotic cell death is observed in neurons and oligodendrocytes. In addition, Wallerian degeneration of white matter is simultaneously observed [16–18]. The receptor for advanced glycation end products (RAGE), a transmembrane protein and member of the immunoglobulin superfamily, is expressed in endothelial cells, neurons, macrophages, and monocytes [19]. RAGE binds diverse ligands, such as high mobility group box-1 (HMGB1) [20] and S100 β [21], and is implicated in various diseases [22–30]. In this review, we will focus on how RAGE and its ligands are involved in various mechanisms that are activated following SCI. Specifically, we focus on three points: (1) the association between RAGE and inflammation following SCI; (2) the association between RAGE and neurite outgrowth after SCI; and (3) the association between RAGE and Schwann cell growth after SCI. Here, we highlight recent research regarding the rationale behind choosing RAGE and its ligands as potential targets for treating SCI.

2. Spinal Cord Injury

SCI resulting from mechanical trauma provokes secondary injuries, including severe tissue damage, inflammation, Wallerian degeneration, disruption of the blood-spinal cord barrier, myelin degradation, and glial scarring [2,31–33] (Figure 1). SCI has been reported to have an increased annual incidence [34]. Functional recovery due to the repair of the injured spinal cord is a major challenge in the neuroscience research field [35]. After SCI, inflammation is a major response and source of secondary injury, considering that it modulates the pathogenesis of acute and chronic SCI [36]. Inflammatory responses cause apoptosis of neurons and glia, as well as glial scar formation and the decline of neuronal function [37]. Pro-inflammatory cytokines, such as tumor necrosis factor- α (TNF- α) and interleukin-1 beta (IL-1 β), are expressed by CNS cells, including microglia, astrocytes, neurons, and oligodendrocytes at early time points (one to three hours) after SCI [38–40]. In the injured spinal cord, increased TNF- α and IL-1 β promote vascular permeability, inflammation, release of pro-inflammatory cytokines, and apoptosis of oligodendrocytes and neurons [41–46]. In addition, resident microglia are activated near the injury site with subsequent recruitment of neutrophils, macrophages, and lymphocytes after SCI [47]. Subsequently, Wallerian degeneration triggers the activation of microglia and astrocytes in injured spinal cord tissues [48,49]. Glial scarring from SCI is considered an obstacle for axon regeneration [50,51] and is an inducer of inflammatory cascades [52]. At the site of injury and inflammation, axons are engulfed by macrophages [53]. Subsequently, these direct macrophage–axon interactions can promote axonal degeneration [53]. Several studies have reported that inflammation

caused by SCI contributes to neuronal degeneration and loss of motor function below the injury site [54–56]. Consequently, inflammation should be modulated to reduce secondary injuries and functional decline following SCI. Hence, the study on the mechanisms of inflammation following SCI is important to find the therapeutic solution in SCI.

Figure 1. Schematic representation regarding various responses following spinal cord injury. Spinal cord injury caused by traumatic mechanical injury leads to the secondary damages including inflammatory response, Wallerian degeneration, the activation of glia cells, glia scar formation. Finally, these secondary damages cause decline of neuronal function following spinal cord injury.



3. RAGE

RAGE is a 35-kDa membrane-bound protein receptor and a member of a superfamily of immunoglobulins [57] and shares homology with neuronal cell adhesion molecules such as NCAM or axonin [58,59]. RAGE consists of an extracellular moiety which is required for signal transduction and includes one N-terminal V-type and two C-type Ig domains [60]. RAGE was originally recognized as a receptor of advanced glycation end products (AGEs), which accumulate in diabetes and during aging [61]. Numerous studies demonstrate that AGEs form during metabolic processes involving proteins or peptides and sugars. AGEs are major sources of diabetic complications, such as atherosclerosis [25], nephropathy [27,62,63], and inflammation [26,64,65] due to their interactions with RAGE. RAGE binds to AGEs [66,67], but can also bind to other ligands, including a HMGB1 (amphoterin) [66–70], β -amyloid fibrils [28,71–74], and S100 proteins [24,75–77]. The RAGE VC1 domain has a net positive charge, but the C2 domain has a net negative charge [78,79]. The negatively charged HMGB1 C-domain [80,81], AGEs, and S100 proteins are attracted to the positive charge of the VC1 domain [78,79]. Recent research demonstrates that RAGE is involved in diseases, including CNS diseases, due to interactions with these various ligands [22–27]. RAGE has been reported to induce transduction pathways involving Ras (related with apoptosis through interaction with AGE in response to oxidative stress) [82], Rac/Cdc42 (related with neurite outgrowth through binding with amphoterin) [66], Jak/signal transducer and activator of transcription (Jak/STAT) (related with

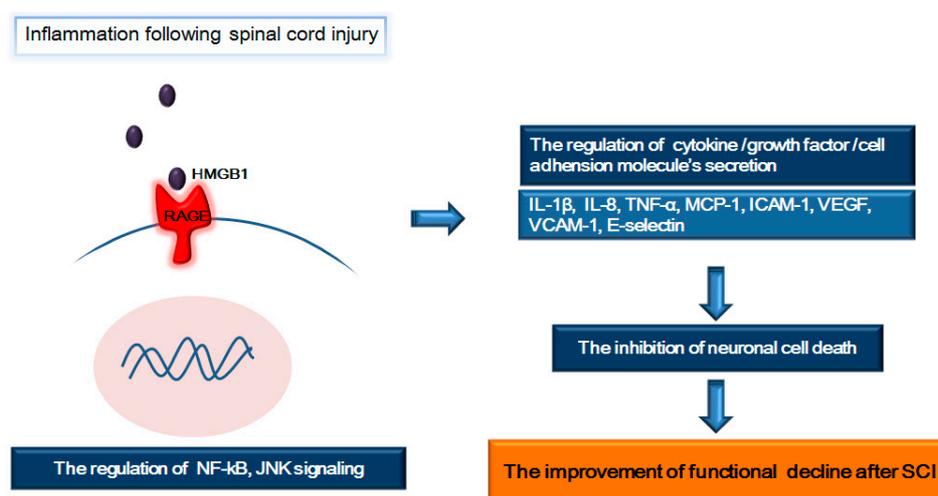
alteration of gene expression/cytokine production through interaction with HMGB1) [22–26,64,83,84], extracellular signal-regulated kinase (ERK) (related with cell survival/cell proliferation with activation of Rac-1 and Cdc42) [85–87], nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B) (related with cell apoptosis/cytokine production) [69,88–90]. RAGE is involved in various inflammatory mechanisms and participates in numerous diseases including CNS disorders by binding diverse ligands. In particular, several studies reported that RAGE was upregulated after SCI in rats and mice [91,92]. Also, by confirming using RAGE deficiency animals, RAGE was demonstrated that it plays a cardinal role in the various pathophysiological process of SCI [93]. Hence, RAGE should be examined to understand the mechanisms leading to secondary damage after SCI, particularly because RAGE is associated with inflammatory responses following SCI.

4. RAGE and Its Ligands (HMGB1 and S100 β): Focus on Inflammation Following SCI

Among RAGE's ligands, HMGB1 and S100 β protein should be focused on the SCI's research because these ligands participate in secondary mechanisms after SCI along with RAGE. RAGE is a major cellular binding site for HMGB1 (amphoterin) [57,94,95]. It acts as a pattern recognition receptor and participates in the innate immune response [61,96]. HMGB1 is generally expressed in cellular nuclei and cytoplasm in brain regions, including the hippocampal dentate gyrus, olfactory bulbs, cell lining of the telencephalic ventricles [97], the nuclei of adult neurons and astrocytes [98], spinal cord oligodendrocytes [99], choroid plexus endothelial cells [100], microglia [101], and Schwann cells [102]. S100 β is abundantly expressed in astrocytes and binds to RAGE in the CNS [21]. HMGB1 and S100 β protein has been reported to modulate both beneficial and harmful effects in *in vitro* study [103,104]. The interactions of RAGE with these ligands activate diverse mechanisms, including inflammation, oxidative stress, neurodegeneration, promotion of neurite outgrowth, cell survival, and neuronal differentiation [20,60,67,68,105,106]. Several studies demonstrate that mechanical injury following SCI results in secondary injuries, such as inflammatory responses [12,107], hemorrhage, ischemia, excessive free radical generation, vascular dysregulation, and immune cell infiltration [108–110]. Specifically, inflammation following SCI has been known to play an important role in the regulation of remyelination and neuronal and glial cell death [12,15,107,111–115]. Inflammation has been recognized as an important process that affects the progression of neuronal tissue damage following SCI [15,116,117]. Cell death caused by inflammation is affected by injury-promoting factors, such as pro-inflammatory cytokines [15,92]. Within one hour post-SCI, TNF- α and interleukin-6 (IL-6) are strongly upregulated around the contused site [38,118]. Inhibition of cell death is important for improving neurologic dysfunction following SCI [15,92]. Inflammation during SCI has been regarded as be important the regulation through NF- κ B [119]. A transgenic mouse model of SCI, in which NF- κ B was selectively suppressed in astrocytes, showed reduced inflammation and increased axonal sprouting [120,121]. RAGE activation perpetuates NF- κ B p65 activation by de novo synthesis of NF- κ B p65 which is directly associated with cell proliferation and that the interaction of RAGE and HMGB1 increases the expression of NF- κ B p65 [122]. Among the ligands of RAGE, HMGB1 is specifically associated with neuronal cell death following SCI [15,91]. HMGB1 has been found to be elevated in injured spinal cord tissues of rodents [92,123–125]. HMGB1 binds to RAGE on neurons, glia, and endothelial cells in the CNS [126–128]. HMGB1 in living cells resides [129] mostly in the nucleus whereas necrotic

cells release HMGB1 immediately [130,131]. HMGB1 accelerates inflammatory responses through the binding with RAGE [20,132–134]. RAGE contributes to inflammatory responses [135] by regulating the production of cytokines, such as interferon-gamma (IFN- γ) [136], interleukin-6 (IL-6), and TNF- α [137,138], IL-1 β [139] in monocytes and macrophages [140–142] after binding with HMGB1. In addition, interaction of RAGE and HMGB1 regulates the production of chemokines [143,144] to activate the immune cells such as dendritic cells [145,146] and monocytes [147]. Moreover, the binding of HMGB1 to RAGE regulates the migration of immune cells and the upregulation of interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP1), vascular endothelial growth factor (VEGF), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin [133,148–150]. Subsequently, the binding of HMGB1 to RAGE participates in neovascularization after injury [133,148–150]. In addition, HMGB1-induced signaling through RAGE activates diverse signaling pathways, such as the JNK and NF- κ B pathways [66,149], in inflammatory environments. The binding of HMGB1 to RAGE seems to contribute to the inflammatory response generating the secondary damage of SCI by controlling the secretion of cytokine and chemokine and by mediating apoptosis signaling (Figure 2).

Figure 2. Schematic representation regarding the role of receptor for advanced glycation end products (RAGE) in inflammation following spinal cord injury. After spinal cord injury, RAGE binds to high mobility group box-1 (HMGB1) and subsequently follows in the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) or JNK pathway. The interaction RAGE and HMGB1 regulates the production of a variety of cytokines, adhesion molecules and growth factors and finally inhibits neuronal cell death. Thus, the interaction RAGE and HMGB1 may improve the functional decline after spinal cord injury.

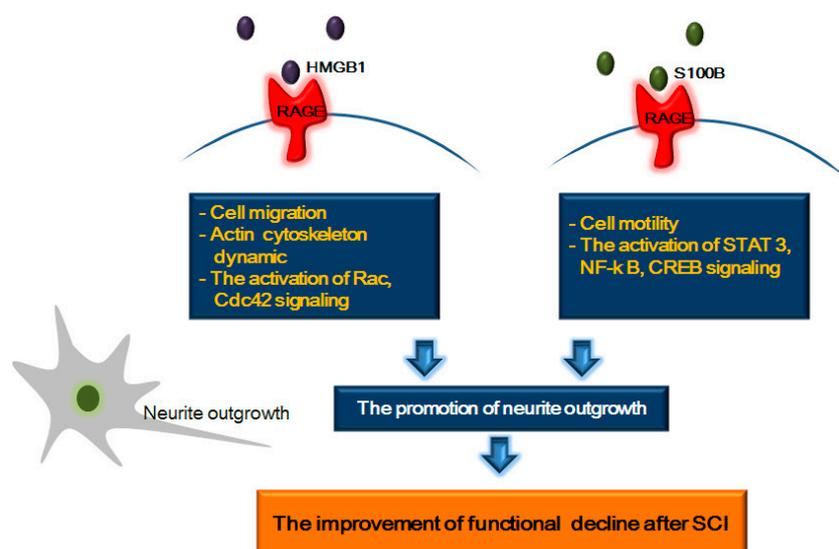


5. RAGE and Its Ligands: Focus on Neurite Outgrowth Following SCI

SCI results in the failure of axonal regeneration, leading to functional decline [151]. To improve function after SCI, various solutions, such as neural precursor cell transplantation to increase remyelination, have been proposed [152–157]. Axon regeneration and neurite outgrowth are key to treating functional decline following SCI. Several studies demonstrate that HMGB1 promotes neurite

outgrowth, cell migration after injury [68,92,101,158]. Binding of amphoterin to RAGE has been known to promote neurite outgrowth [20,66,68,104,159,160]. HMGB1 binds to RAGE-associated *N*-glycans and subsequently promotes neurite outgrowth [161,162]. Hori *et al.* demonstrated that anti-RAGE IgG/(Fab')₂ inhibited HMGB1-RAGE activation and blocked HMGB1-induced neurite outgrowth [20]. Several studies demonstrated that RAGE-amphoterin interaction involves Rac and Cdc42, and promotes the neurite outgrowth [66,163]. In addition, several studies show the role of RAGE in cell migration [143,144,164–167] and in the dynamics of the actin cytoskeleton [143]. RAGE signaling mediates neurotrophin-dependent neurite outgrowth [168]. Among the RAGE ligands, S100 β also has known to promote neurite outgrowth and induce translocation of transcription factors, such as NF- κ B and CREB, following interaction with RAGE [21,104,169–171]. In detail, S100 β -RAGE activation regulates neurite outgrowth through STAT3 and p44/p42 MAP kinases via RAGE [172]. S100 β -mediated RAGE activation also participates in cell motility [164]. In a study on the function of RAGE in cell motility, transfectants exposed to amphoterin induced neuritis [66]. Collectively, the interaction between RAGE and HMGB1/S100 β may activate cell motility and neurite outgrowth after SCI (Figure 3). Hence, RAGE and its ligands may improve functional decline after SCI by promoting neurite outgrowth, considering that regulation of neurite outgrowth is important for neurite regeneration after nerve injury [173].

Figure 3. Schematic representation of the relationship between RAGE and neurite outgrowth after spinal cord injury. The binding RAGE to HMGB1 promotes Rac, Cdc42 pathway and is involved in the dynamics of actin cytoskeleton. Also, the binding RAGE to S100B increases cell motility and is related to CREB, NF- κ B, STAT3 signaling. These mechanisms result in the promotion of neurite outgrowth and finally may improve the functional decline after spinal cord injury.

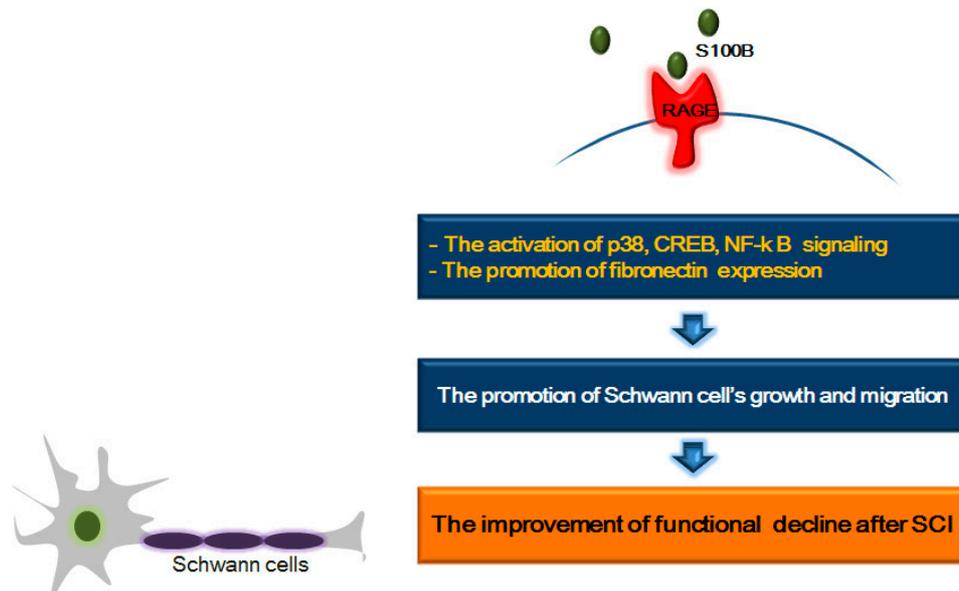


6. RAGE and Its Ligands: Focus on Schwann Cell Growth and Migration after SCI

Schwann cells have important roles in tissue repair after CNS injury because Schwann cells are involved in various mechanisms, including differentiation, migration, proliferation, and myelination of axons [174,175]. In addition, Schwann cells promote the secretion of a variety of neurotrophic factors,

subsequently inducing axonal regeneration after CNS injury [174]. After SCI, Schwann cells are sometimes observed in remyelinating axons in the spinal cord [110,176–179]. The remyelination by Schwann cells in the spinal cord is regarded as the result of migration from the periphery [176]. Williams *et al.* reported that the implantation of Schwann cells in injured spinal cords supports regeneration of axons, reduces cyst formation, and improves functional decline [180]. Schwann cell myelination occurs through increased fibronectin expression [181]. S100 β -mediated RAGE activation promotes mRNA expression of fibronectin [182,183]. Several studies demonstrated that Schwann cells, RAGE, and S100 β are necessary for peripheral nerve regeneration [182–184]. RAGE plays a key role in Schwann cell's function during regeneration of injured nerves [185]. Moreover, S100 β -activated RAGE has been reported the association with Schwann cell migration during the repair procedure of injured peripheral nerves through activation of p38 MAPK, CREB, and NF- κ B [186]. These researches indicate that the interaction between RAGE and its ligands may promote the Schwann cell's beneficial function including secretion of neurotrophic factors, myelination of axons and axonal regeneration for treating after spinal cord injury (Figure 4).

Figure 4. Schematic representation of the association between RAGE and Schwann cell growth and proliferation after spinal cord injury. After spinal cord injury, the interaction RAGE and S100 β promotes the activation of NF- κ B, CREB, p38 signaling and the expression of fibronectin. These mechanisms may promote the growth and proliferation of Schwann cells and finally improve the functional decline after spinal cord injury.



7. Conclusions

In the present review, we discuss the association of RAGE and its ligands with SCI from various perspectives. We addressed three points: (1) Binding of RAGE and its ligands appears to contribute to the inflammatory response caused by SCI by regulating the secretion of cytokines and chemokines and modulating apoptosis signaling; (2) RAGE and its ligands may improve functional decline after SCI by promoting neurite outgrowth, which is crucial for neurite regeneration after CNS injury; (3) RAGE and its ligands may promote the myelination of axons and axonal regeneration as treatments for

injured spinal cords by activating Schwann cells. This review indicates that further studies of RAGE and its ligands in SCI are necessary for a good understanding of the various mechanisms leading to functional decline after SCI.

Acknowledgments

This research was supported by the DGIST R&D Program of the Ministry of Science, ICT and Future Planning (14-BD-06).

Author Contributions

Juhyun Song gleaned the materials and wrote the preliminary draft. Won Taek Lee reviewed and helped to revise the manuscript. Kyung Ah Park and Jong Eun Lee revised every single details of the manuscript and provided overall supervision.

Conflicts of Interest

The authors declare no conflict of interest.

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