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Commentary

Carbon monoxide releasing molecule-3 inhibits inflammasome activation: A potential therapy for spinal cord injury

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Spinal cord injury (SCI) is a devastating condition for which an approved therapy is yet to become available. Approximately 11,000 new cases of SCI occur each year [1], and it generally affects patients at a young age. As a result, patients find themselves having to live with the consequences of SCI for several decades. In the acute phase, current care of patients with SCI aims at surgical stabilization and decompression of the spinal cord as well as using anti-inflammatory approaches to decrease the amount of spinal cord damage [2]. Chronic care of patients with SCI seeks to decrease the devastating effects of comorbidities associated with the injury such as chronic pain. Despite significant improvement in the care of patients with SCI and despite the promise of new interventions such as cell-based regenerative therapies or spinal cord stimulation [2], there is still a significant need for more specific and efficient therapies in the care of this patient population.

In a study published in *EBioMedicine*, Zheng and colleagues show the neuroprotective effects of carbon monoxide releasing molecule-3 (CORM3) in a compression model of thoracic spinal cord injury in rodents [3]. Accordingly, CORM3 delivery after SCI resulted in improved histopathological and functional outcomes by decreasing inflammasome activation and the inflammasome-mediated cell death mechanism of pyroptosis. The inflammasome is a key component of the inflammatory innate immune response after SCI [4]. The inflammasome is a multiprotein complex involved in the activation of the inflammatory cysteine aspartase caspase-1. Upon activation of caspase-1, this inflammatory caspase processes the pro-inflammatory cytokines interleukin(IL)-1β and IL-18. [5]

Carbon monoxide (CO) at low concentrations has been shown to be anti-inflammatory. [6] Endogenous levels of CO result from the presence of haem oxygenase 2, which is constitutively expressed, and of haem oxygenase 1 enzymes, which are inducible enzymes responsible for the catabolism of haem products. Pharmaceutical-grade inhalable CO is currently under investigation in animals and humans. Previous evidence suggests a therapeutic potential for CO in conditions such as heart, lung and kidney graft rejections as well as in acute lung injury, bacterial infections, rheumatoid arthritis and myocardial infarctions, among others. In the Zheng et al. study, the authors extend our understanding of the therapeutic potential of CO by identifying the inflammasome as a target for the anti-inflammatory effects of this gas. Moreover, in such study, the authors describe the potential benefits that this approach may have for the SCI patient population.

In addition to inhalable CO, it is also possible to deliver CO in the form of exogenous CO donors such as CORM1 or CORM3. Zheng et al. used CORM3 delivered immediately after SCI and showed that CORM3 inhibited the activation of the inflammatory caspases caspase-1 and caspase-11 as well as of IL-1β and IL-18. Inflammasomes are named after the pattern recognition receptors that comprised them such as the NOD-like receptors NLRP1 or NLRP3. [7] In the central nervous system (CNS), these receptors have been identified in neurons, astrocytes, oligodendrocytes and microglia. In the Zheng et al. study [3], the authors show that CORM3 decreases the protein expression of NLRP1 and NLRP3 after SCI when compared to the untreated group. Taken together, these findings indicate that CORM3, and potentially inhalable CO, inhibits activation of the NLRP1 and NLRP3 inflammasomes.

In the CNS, the inflammasome-mediated cell death mechanism of pyroptosis was first described in neurons [8]. More recently the substrate of pyroptosis was found to be gasdermin-D (GSDM-D). Accordingly, caspase-1 and caspase-11 cleave GSDM-D between the amino and carboxy terminal domains, which are required for pyroptosis. [9] In addition to inhibiting inflammasome activation after SCI, CORM3 also inhibited the expression of GSDM-D, indicating that this intervention also decreased pyroptosis. Since CORM3 is present in neurons, these findings suggest that the improved histopathological and functional outcomes reported are the results of increased neuronal survival resulting from decreased pyroptotic cell death. Thus, whereas for many years apoptosis has been the most studied cell death mechanism following CNS injury and in general, here the authors highlight the importance of targeting pyroptosis to improve outcomes after SCI.

Inositol-requiring enzyme 1 (IRE1) is a transmembrane receptor activated by endoplasmic reticulum stress. IRE1 activation results in increased thioredoxin Interacting Protein (TXNIP) levels and NLRP3 inflammasome activation. [10] Zheng and colleagues show that CORM3 inhibits IRE1 phosphorylation in neurons, resulting in inflammasome inhibition, which gives a mechanistic insight as to how the inflammasome is inhibited by CORM3.

In conclusion, the study of Zheng and colleagues [3] shines light into a potential therapy for SCI patients where CO, in the form of CORM3 and – although not a part of the Zheng et al. study – inhalable CO, can be

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used in the treatment of SCI in order to improve histopathological and functional outcomes by inhibiting inflammasome activation and pyroptotic cell death in neurons by inhibiting the phosphorylation of IRE1. Future studies should aim to identify the therapeutic window of CORM3 as well as whether inhalable CO has a similar effect and mechanism of action in an animal model of SCI and in other conditions affecting the CNS.

Disclosure

I am a co-founder and managing member of InflamaCORE, LLC and have patents on inflammasome proteins as biomarkers of injury and disease as well as on targeting inflammasome proteins for therapeutic purposes.

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