European Journal of Neurodegenerative Diseases
ISSN 2279-5855 / 2020 vol. 9, ISSUE N. 2, July-December

THE PATHOGENESIS OF NEUROTRAUMA: IMMUNITY AND INFLAMMATION

D. Lauritano*

Department of Medicine and Surgery, Centre of Neuroscience of Milan, University of Milano-Bicocca, Milan, Italy.

Correspondence to:
Dorina Lauritano,
Department of Medicine and Surgery,
Centre of Neuroscience of Milan,
University of Milano-Bicocca,
Milan, Italy.
email: dorina.lauritano@unimib.it

ABSTRACT

Neurotrauma is a serious medical issue, and the mechanisms underlying this pathology are still being studied. It is known that while damaged tissues such as muscles and skin heal without any physiological dysfunction, neurotraumas do not heal properly and undergo functional alterations. Brain injury leads to a neuronal deficit, and the response to glial cell injury involves tissue repair and strengthening in the central nervous system (CNS). In neurotrauma such as spinal cord injury (SCI), various cells are activated, including astrocytes, pericytes, fibroblasts, and Schwann cells, which contribute to glial cell growth and promote fibrotic scarring. Phagocytic cells also participate in the injury by releasing pro-inflammatory cytokines and activating adhesion molecules. Immune cells such as monocytes and neutrophils infiltrate the lesion and mediate inflammation by producing cytokines and chemokines. The neuroinflammation mediated by pro-inflammatory cytokines represents a crucial point of this brain trauma. In this inflammation, where microglia participate, producing pro-inflammatory cytokines and chemokines, endothelial cells are activated with the upregulation of selectins and adhesion molecules. In this complex mechanism, macrophages intervene and contribute to tissue repair and healing. The innate immune response leads to the alteration of the NLRP3 inflammasome with tissue damage and neurological disorders, topics that will be covered here in this paper.

KEYWORDS: *neurotrauma, brain injury, spinal cord injury, central nervous system, neurodegeneration, inflammation, immunity*

INTRODUCTION

Neurotrauma is a sudden injury to the central nervous system (CNS) that includes traumatic brain injury (TBI) and spinal cord injury (SCI). It is a prevalent cause of morbidity and mortality worldwide in the population of individuals aged 45 years and younger (1), with the leading cause being falls and motor vehicle accidents (2).

The injury consists of a sudden, traumatic blow to the brain or spine. SCI involves damage to the spinal cord, resulting in temporary or permanent functional changes. TBI occurs from an external mechanical force to the head that results in an intracranial injury, with damage to the structure or functioning of the brain (3). TBIs are classified based on level of severity and mechanism of injury, but even a minor non-concussive event has the capacity to produce long-term effects (4).

Following the damage induced by the primary injury to the CNS, a secondary pathological injury occurs that causes an inflammatory response, which can help to repair and regenerate neurons or can exacerbate neurodegeneration (5). The

Received: 02 October, 2020
Accepted: 11 November, 2020

2279-5855 (2020)

immune response during this secondary injury process is critical in determining the direction of healing, as it can be beneficial and restorative for tissue repair or create further damage with a prolonged and overactive state of inflammation.

The pathophysiological mechanism of neurotrauma

Damaged tissue such as muscle and skin are generally followed by a healthy tissue repair response through a process involving inflammation, angiogenesis, matrix deposition, and cell recruitment, which allows for healing without physiological dysfunction (6). Neurotraumas differ, as they do not heal properly and undergo functional alterations with structural and chemical disruptions and altered metabolic functioning of neurons (7). The pathophysiological mechanisms accompanying biomechanical injury and tissue damage are still being studied, but growing evidence implicates the role of the immune system in the response and repair process that follows neurotrauma (8-10).

Neurotrauma is associated with increased permeability of the blood-brain barrier (BBB), altered axonal transport, and disrupted functions of neuronal and glial cells (11). The primary, mechanical cerebral injury of TBI results in direct tissue damage and impaired metabolic regulation that can be described as an 'ischemia-like' pattern, which results in lactic acid accumulation due to anaerobic glycolysis and increased membrane permeability and subsequent depolarization and the release of neurotransmitters and other compounds that disrupt intracellular processes (1). Structural changes affecting the biological membranes and nucleosome DNA take place, and cellular structures are degraded with subsequent cell death (12).

After the initial, primary brain injury, there are a series of complex pathophysiological mechanisms that take place, a reaction that is termed the "secondary injury". These two events, the primary and secondary injuries, cause neuropathology.

Brain injury results in neuronal damage and primary cell death in the CNS, and the secondary injury can lead to further neuron death, depending on factors such as metabolic and trophic processes and gene transcription (13). The secondary injury involves changes in the CNS including increased or decreased blood perfusion, dysfunction of cerebrovascular autoregulation, loss of oxygenation, metabolic dysfunction, and cell death resulting from inflammation (1).

A continued state of inflammation that is mediated by microglia can continue the secondary injury and can result in chronic neuroinflammation and the progression and development of neurodegenerative disorders (14).

Secondary injury in neurotrauma: an inflammatory cascade

The damaging mechanical forces of neurotrauma results in tissue damage, disrupted CNS homeostasis, and neuronal cell death. This is followed by a cascade of cellular responses that can be reparative or cause secondary cellular injury.

Following a neurotrauma such as SCI, a neuronal deficit activates the immune response in the CNS of tissue repair and strengthening and axon regeneration. Various glial cells such as astrocytes, pericytes, fibroblasts, endothelial cells, and Schwann cells are activated, which contributes to glial cell growth and promotes fibrotic scarring (15). Glial cells serve supportive functions for neurons by modulating synaptic interactions, providing structural support, and aiding, or sometimes preventing, neuronal recovery following neurotrauma (16).

With sudden injury to the CNS, there is axon damage to neurons which interferes with cell signaling with the loss of synaptic connections and propagation, and cell death (17). Glial cells release toxins and cytokines in response to the mechanical damage of the injury, which can go on to damage surrounding remaining tissue that was not mechanically injured by the initial trauma (15). Signaling cascades ensue with the infiltration of nonresident cells. Successively, fibroblasts are activated and inhibitory extracellular matrix (ECM) proteins such as chondroitin sulfate proteoglycans (CSPGs) are generated that prevent axon growth (18).

Following this, the secondary injury ensues with further disruption to neuronal functioning. These primary and secondary injuries result in activated glial cells and the formation of cellular scars at the injury site of the spinal cord. The fibrotic scar is largely composed of collagen, fibronectin, and laminin deposits in the core of the lesion (17).

Phagocytic cells also participate in the injury. Monocytes and macrophages detect damaged tissues via damage-associated molecular patterns (DAMPs) and when they are activated, they release anti-inflammatory molecules and neurotrophic factors, beneficial for tissue regeneration, but also secrete pro-inflammatory cytokines which can exacerbate secondary injury (19). Studies of monocyte and macrophage processes have revealed that M1 macrophages participate in inflammation by cytokine release and tissue degeneration, while M2 macrophages contribute to neuronal repair and healing (20).

This innate immune response leads to alterations of the NLRP3 inflammasome, which is involved in the physiopathology of diverse neurological disorders such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis (21). The induction of NLRP3 leads to cleavage of caspase-1 and the maturation of IL-1, which is released and recruits further immune cells from the ECM, adding to inflammation and tissue damage (21,22).

Microglia are innate immune cells ubiquitous throughout the CNS that act similarly to macrophage cells. They are quick to respond following brain and spinal cord injury and play a vital role in the reparation process (23). They react swiftly to neurotrauma by releasing pro-inflammatory mediators that recruit other inflammatory cells including neutrophils and monocytes (24). Monocytes, glial cells, and neutrophils, which detect damaged tissue and promote the breakdown and clearance of debris at the injury site, release pro-inflammatory mediators with the activation of endothelial cells and the upregulation of selectins and adhesion molecules. Secondary damage is inflicted with the release of inflammatory cytokines IL-1, IL-6, and tumor necrosis factor (TNF) (25-27).

CONCLUSIONS

With brain trauma, neuroinflammation is mediated by pro-inflammatory cytokines (28). In TBI, If the microglial response subsides after neuronal repair and homeostasis is restored, the secondary injury period is neuroprotective. But continual microglial activation in the CNS and an exaggerated, chronic state of inflammation is damaging to neurons. This harmful inflammatory reaction can cause neuronal dysfunction and interfere with gene suppression and lead to neurological disorders.

CNS axon regeneration with glial cells is now being targeted as a focus of therapeutic efforts in neurotrauma, as damaged cells are involved in scar formation and an ensuing inflammatory process that prevents neuronal axon growth (29).

In conclusion, the immune response is vital to neurological tissue repair and regeneration after neurotrauma, but also can cause a harmful inflammatory response that contributes to neuronal death and neurodegeneration.

Conflict of interest

The author declares that they have no conflict of interest.

REFERENCES

1. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. *British Journal of Anaesthesia*. 2017;99(1):4-9. doi:https://doi.org/10.1093/bja/aem131
2. Langlois JA, Rutland-Brown W, Wald MM. The Epidemiology and Impact of Traumatic Brain Injury. *Journal of Head Trauma Rehabilitation*. 2006;21(5):375-378. doi:https://doi.org/10.1097/00001199-200609000-00001
3. Fehily B, Fitzgerald M. Repeated Mild Traumatic Brain Injury. *Cell Transplantation*. 2017;26(7):1131-1155. doi:https://doi.org/10.1177/0963689717714092
4. Makinde HM, Just TB, Cuda CM, Perlman H, Schwulst SJ. The Role of Microglia in the Etiology and Evolution of Chronic Traumatic Encephalopathy. *Shock (Augusta, Ga)*. 2017;48(3):276-283. doi:https://doi.org/10.1097/SHK.0000000000000859
5. Ray S, Dixon CE, Banik NL. Molecular mechanisms in the pathogenesis of traumatic brain injury. *Histology and histopathology*. 2002;17(4):1137-52. doi:https://doi.org/10.14670/HH-17.1137
6. Eming SA, Martin P, Tomic-Canic M. Wound repair and regeneration: Mechanisms, signaling, and translation. *Science Translational Medicine*. 2014;6(265):265sr6-265sr6. doi:https://doi.org/10.1126/scitranslmed.3009337
7. Solstrand Dahlberg L, Becerra L, Borsook D, Linnman C. Brain changes after spinal cord injury, a quantitative meta-analysis and review. *Neuroscience & Biobehavioral Reviews*. 2018;90:272-293. doi:https://doi.org/10.1016/j.neubiorev.2018.04.018
8. McKee CA, Lukens JR. Emerging Roles for the Immune System in Traumatic Brain Injury. *Frontiers in Immunology*. 2016;7. doi:https://doi.org/10.3389/fimmu.2016.00556
9. Balu R. Inflammation and Immune System Activation After Traumatic Brain Injury. *Current Neurology and Neuroscience Reports*. 2014;14(10). doi:https://doi.org/10.1007/s11910-014-0484-2
10. Plesnila N. The immune system in traumatic brain injury. *Current Opinion in Pharmacology*. 2016;26:110-117. doi:https://doi.org/10.1016/j.coph.2015.10.008
11. Chodobski A, Zink BJ, Szmydynger-Chodobska J. Blood–Brain Barrier Pathophysiology in Traumatic Brain Injury. *Translational Stroke Research*. 2011;2(4):492-516. doi:https://doi.org/10.1007/s12975-011-0125-x

12. Miller MA, Zachary JF. Mechanisms and Morphology of Cellular Injury, Adaptation, and Death11For a glossary of abbreviations and terms used in this chapter see E-Glossary 1-1. *Pathologic Basis of Veterinary Disease*. Published online 2017:2-43.e19. doi:https://doi.org/10.1016/b978-0-323-35775-3.00001-1
13. Kermer P, Klöcker N, Bähr M. Neuronal death after brain injury. *Cell and Tissue Research*. 1999;298(3):383-395. doi:https://doi.org/10.1007/s004410050061
14. Faden AI, Wu J, Stoica BA, Loane DJ. Progressive inflammation-mediated neurodegeneration after traumatic brain or spinal cord injury. *British Journal of Pharmacology*. 2015;173(4):681-691. doi:https://doi.org/10.1111/bph.13179
15. Gaudet AD, Fonken LK. Glial Cells Shape Pathology and Repair After Spinal Cord Injury. *Neurotherapeutics*. 2018;15(3):554-577. doi:https://doi.org/10.1007/s13311-018-0630-7
16. Kou Z, VandeVord PJ. Traumatic white matter injury and glial activation: From basic science to clinics. *Glia*. 2014;62(11):1831-1855. doi:https://doi.org/10.1002/glia.22690
17. Orr MB, Gensel JC. Spinal Cord Injury Scarring and Inflammation: Therapies Targeting Glial and Inflammatory Responses. *Neurotherapeutics*. 2018;15(3):541-553. doi:https://doi.org/10.1007/s13311-018-0631-6
18. Jones LL, Sajed D, Tuszynski MH. Axonal Regeneration through Regions of Chondroitin Sulfate Proteoglycan Deposition after Spinal Cord Injury: A Balance of Permissiveness and Inhibition. *The Journal of Neuroscience*. 2003;23(28):9276-9288. doi:https://doi.org/10.1523/jneurosci.23-28-09276.2003
19. Popovich PG, Guan Z, McGaughy V, Fisher L, Hickey WF, Basso DM. The Neuropathological and Behavioral Consequences of Intraspinal Microglial/Macrophage Activation. *Journal of Neuropathology & Experimental Neurology*. 2002;61(7):623-633. doi:https://doi.org/10.1093/jnen/61.7.623
20. David S, Kroner A. Repertoire of microglial and macrophage responses after spinal cord injury. *Nature Reviews Neuroscience*. 2011;12(7):388-399. doi:https://doi.org/10.1038/nrn3053
21. Eren E, Özören N. The NLRP3 inflammasome: a new player in neurological diseases. *Turkish Journal Of Biology*. 2019;43(6):349-359. doi:https://doi.org/10.3906/biy-1909-31
22. Jorgensen I, Lopez JP, Laufer SA, Miao EA. IL-1β, IL-18, and eicosanoids promote neutrophil recruitment to pore-induced intracellular traps following pyroptosis. *European Journal of Immunology*. 2016;46(12):2761-2766. doi:https://doi.org/10.1002/eji.201646647
23. Perry VH, Teeling J. Microglia and macrophages of the central nervous system: the contribution of microglia priming and systemic inflammation to chronic neurodegeneration. *Seminars in Immunopathology*. 2013;35(5):601-612. doi:https://doi.org/10.1007/s00281-013-0382-8
24. Loane DJ, Byrnes KR. Role of microglia in neurotrauma. *Neurotherapeutics*. 2010;7(4):366-377. doi:https://doi.org/10.1016/j.nurt.2010.07.002
25. Pineau I, Lacroix S. Proinflammatory cytokine synthesis in the injured mouse spinal cord: Multiphasic expression pattern and identification of the cell types involved. *The Journal of Comparative Neurology*. 2006;500(2):267-285. doi:https://doi.org/10.1002/cne.21149
26. Lawrence CB, Allan SM, Rothwell NJ. Interleukin-1β and the interleukin-1 receptor antagonist act in the striatum to modify excitotoxic brain damage in the rat. *European Journal of Neuroscience*. 1998;10(3):1188-1195. doi:https://doi.org/10.1046/j.1460-9568.1998.00136.x
27. Ferguson AR, Christensen RN, Gensel JC, et al. Cell Death after Spinal Cord Injury Is Exacerbated by Rapid TNF -Induced Trafficking of GluR2-Lacking AMPARs to the Plasma Membrane. *Journal of Neuroscience*. 2008;28(44):11391-11400. doi:https://doi.org/10.1523/jneurosci.3708-08.2008
28. Kempuraj D, Ahmed ME, Selvakumar GP, et al. Brain Injury–Mediated Neuroinflammatory Response and Alzheimer's Disease. *The Neuroscientist*. 2019;26(2):134-155. doi:https://doi.org/10.1177/1073858419848293
29. Sami A, Selzer ME, Li S. Advances in the Signaling Pathways Downstream of Glial-Scar Axon Growth Inhibitors. *Frontiers in Cellular Neuroscience*. 2020;14. doi:https://doi.org/10.3389/fncel.2020.00174