Microglia-Astrocyte communication through spinal cord injury - Alexandra Kisucka - Biomedical Research Center of SAS

Alexandra Kisucka

Abstract

Understanding the mechanisms of inflammation and glial scar formation after spinal cord injury (SCI) is not possible without the comprehension of reactive astrocytes and resident microglia activation, and the infiltration of macrophages in the major pathogenesis of SCI. Early after SCI, both the microglia and astrocytes are activated into two polarization states: the pro-inflammatory phenotypes (M1 and A1) and the anti-inflammatory phenotypes (M2 and A2). This fact plays an important role in the regulation of immune responses under various pathological conditions and repair. We aimed to study the behavior of reactive astrocytes and microglia/macrophages and their polarization states after Th9 compression (40g/15 min) at the lesion site and in adjacent spinal cord sections. Adult Wistar rats were divided into three experimental groups: 1) sham control, and 2-3) a group of animals that survived 7 and 14 days after SCI. The results show that microglia/macrophages and astrocytes transformation after Th9 compression is mostly impacted at the lesion site and 3 mm caudally from the injury epicenter. While the gene expression of reactive microglia/macrophages was strongly upregulated one week after SCI in each segment studied, reactive astrocytes were considerably expressed two weeks post-injury. The study of particular phenotypes indicates that the first post-injury week is critical for the modulation of reactive microglia/astrocytes into their neuroprotective states and that inhibiting M1/A1 and/or promoting M2/A2 polarization may be a very effective treatment strategy to improve functional recovery after SCI. Supported by APVV-15-0766; APVV-19-0324; VEGA 2/0145/21; VEGA 2/0098/20; ERDF-IMTS 313011V344. The nature and extent of a spinal cord injury (SCI) is diverse and complicated. There are many symptoms, including, but not limited to, paralysis, myelopathy, and damage to white matter and grey matter. The complexity of injury is increased manifold as nerve fiber damage compromises sensation and motor signal transmittance to and from the brain, while grey matter damage results in segmental losses of interneurons. The utilization of corticosteroid (methylprednisolone sodium succinate), surgical interventions, and physiotherapy are the only methods for treatment in current health care, and these methods display limited success. Yet, recent advances in the fields of stem cell biology have revolutionized neuroprotective and regenerative interventions. Neuropathic pain (NP), because of its relatively unexplored molecular mechanism and widespread clinical morbidity, is extremely debilitating for SCI patients.

In addition, NP is extremely resistant to treatment with current analgesic drugs, solidifying the necessity to find efficacious treatment options. Acknowledged in the current research are the emerging role of WNK1; cation-dependent chloride transporters (NKCC1) activation and inhibition by bumetanide cannabinoid receptor (CB2) and anti-hyperalgesia effect of WIN 55,212-2 bradykinin (B1) and vanilloid-1 (TRPV1) receptor antagonists and PPAR-gamma agonists in preventing neuropathic pain. Time-specific changes in expression of matrix metalloproteinase-2 (MMP-2) in SCI-induced NP (SCINP) and improved functional recovery with folic acid therapy has been found. Likewise, bone marrow stromal cells (BMSCs) following lumbar puncture have shown some promising results in alleviating NP, including allodynia and hyperalgesia in chronic constriction injury (CCI) and spared nerve injury mice models. Delving further into NP research, glia-mediated inflammatory reactions have been found to play a pivotal role in the introduction and development of NP. Microglia plays a fundamental role in proliferation, differentiation, and synaptic hemichannel growth in neurons. They are also known to be involved in the regulation of infection in brain tissue through innate and adaptive immune responses and maintaining homeostasis, respectively. Because of its major role in the neuroinflammatory process for neurodegenerative diseases, the study and utilization of microglia awakened from its relative dormancy. A noteworthy discussion on microglial cells history reveals their origin, differentiation, homeostasis, and implication in health and disease. For example, microglia have been recognized to have a critical role in Alzheimer's, Parkinson's, and Adrenoleukodystrophy. Another glial cell type involved in providing neuroprotection is spinal cord astrocytes that release astrocytic mediators, for example, cytokines, chemokines, and growth factors for this purpose. Unfortunately, the mechanism behind how astrocytes release astrocytic mediators is unclear, due in part to the lack of research on astrocytes because of their complexity in differentiation and seeding. Although astrocytic connexin-43 is implicated in gap junctions and communication of cytosolic contents via glial syncytia and to the extracellular space, the mechanism for this contribution remains unclear. Despite this, many studies have implicated astrocytes in facilitating or maintaining NP. Studying molecular mechanisms, discovered in the murine nerve injury model, MMPs activate and sustain NP. MMP-9 induces NP through interleukin-1beta cleavage and microglia activation at the acute stage.

Alexandra Kisucká

Institute of Neurobiology, Biomedical Research Center of SAS E-mail: kisucka@saske.sk

Similarly, latent stage MMP-2 maintained NP through the continuation of interleukin-1beta cleavage, though instead activating astrocytes. Tissue inhibitors of MMPs (TIMPs) inhibit the activity of MMPs by regulating tissue proteolysis. As discussed, earlier, microglia and astrocytes help in tissue repair and breakdown in CNS. Therefore, studying the role of these glial cells in relation to NP may provide new insights into NP treatments.

Bottom Note: *This work is partly presented at 27th Annual Summit on Neuroscience and Neurological Disorder at December 01-02, 2021 | Barcelona, Spain*