Open Access Library Journal
2023, Volume 10, e10612
ISSN Online: 2333-9721
ISSN Print: 2333-9705

Evaluating the Role of SEMA3's in Spinal Cord Injuries

Yahvi A. Shah

Biological Sciences, University of Cambridge Research, Paramus, USA
Email: yahvishah13@gmail.com

How to cite this paper: Shah, Y.A. (2023) Evaluating the Role of SEMA3's in Spinal Cord Injuries. *Open Access Library Journal*, **10**: e10612.
https://doi.org/10.4236/oalib.1110612

Received: August 14, 2023
Accepted: September 19, 2023
Published: September 22, 2023

Abstract

Spinal cord injuries (SCIs) are severe and life-changing conditions that result in the disruption of neural pathways and the loss of motor and sensory functions below the site of injury. Finding effective treatment strategies to promote nerve regeneration and functional recovery in SCI patients is a significant challenge for researchers studying neurotrauma. Recent studies have suggested that Semaphorin 3 (SEMA3) proteins, which are primarily involved in guiding nerve growth during development, may also play important roles in SCI pathophysiology and recovery. This research paper aims to explore the various ways SEMA3s contribute to SCI by examining their expression patterns within the injured spinal cord, their impact on axonal growth and guidance, as well as their interactions with other signaling pathways. Additionally, we investigate whether manipulating SEMA3 signaling could be a potential therapeutic approach to enhance axonal regeneration and improve functional recovery using preclinical models of SCI. By conducting a comprehensive review of existing literature, this paper consolidates current knowledge about SEMA3s' role in SCI while identifying possible avenues for future therapeutic interventions.

Subject Areas

Neurology

Keywords

Nervous System, Spinal Cord, Spinal Cord Injuries, Semaphorins, Protiens

1. Introduction

In the mere length of a year between 250,000 to 500,000 individuals experience spinal cord injuries that can result in anywhere from paralysis to an extended duration of pain. A spinal cord injury is damage to any part of the spinal cord at the end of the spinal canal that can result in loss of movement, feeling, or other body functions. These injuries can occur from traumatic events such as car accidents, falls, sports injuries, or from non-traumatic causes such as infections or tumors. Spinal cord injuries can range from minor to severe and can have long term effects on a person's ability to function independently [1]. The two types of neurons that exist in the spinal cord are sensory and motor neurons, injuries to the spinal cord can lead to the death of both types of neurons which can result in the loss of sensation and movement below the level of injury.

Some of the more detailed symptoms and complications can include paralysis, sensory loss, autonomic dysreflexia, bowel and bladder dysfunction, and overarching pain. Rehabilitation options may include surgery, rehabilitation, and the use of assistive divides. When a spinal cord injury takes place the neurons in the affected area can either be damaged or killed, disrupting the normal flow of information between the brain and the rest of the body. The injury can cause a cascade of events that lead to the death of neurons and the formation of a scar at the injury site. The scar, made up of fibrous tissue, can impede the growth of new nerve fibers that are needed for repair and regeneration. The severity of symptoms will depend on the location and size of the lesion as well as the extent of the damage to the spinal cord. This review will particularly look at large stab lesions. Large stab lesions in the spinal cord are severe injuries that can result from a penetrating wound, such as a knife or bullet wound. These types of injuries can cause significant damage to the spinal cord, including the destruction of nerve fibers, the formation of a scar, and the death of neurons. Symptoms of a large stab lesion in the spinal cord can include complete or partial paralysis, loss of bowel and bladder control, chronic pain, and Brown-Sequard syndrome (BSS).

2. Spinal Cord Healing

A new perspective to view spinal cord injuries through, is the healing process and progress that takes place once the injury has occurred. After the injury, the surviving neurons in the spinal cord can undergo changes that allow them to compensate for the loss of function caused by the injury, this process is referred to as plasticity and it can help to preserve some function and sensation below the level of the injury. A key aspect involved in this regeneration and preservation are semaphorins, as shown in **Figure 1**. Semaphorins are a family of proteins that play a role in the development and maintenance of the nervous system. They are involved in the various processes such as axon guidance, synapse formation, and the regulation of neural plasticity. In the spinal cord specifically, semaphorins have been shown to play a role in the growth and guidance of axons which are the long slender projections of nerve cells that transmit signals to other neurons. They also influence the formation and maturation of synapses, which are specialized structures that allow neurons to communicate with each other.

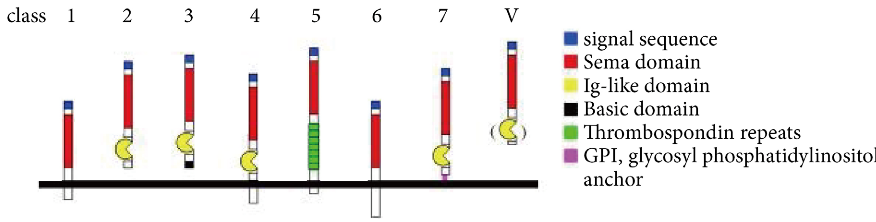

Figure 1. There are eight total classes of semaphorin classes categorized based on sequence similarity and structural features. Semaphorins can exist as both secreted and membrane-associated proteins. The most prominent in spinal cord recovery are the vertebrate secreted semaphorins. Semaphorin receptors neuroplexin and plexin are the most prominent in axon regeneration which is a key facet of spinal cord recovery.

3. Spinal Cord Injuries and the Development of the Nervous System

Spinal cord injury (SCI) can have a significant impact on the development of the nervous system. The spinal cord is an essential component of the central nervous system (CNS), responsible for transmitting signals between the brain and the rest of the body. When an injury occurs, it can result in a range of physical and cognitive symptoms, depending on the severity and location of the injury. In the immediate aftermath of an SCI, there is often an initial phase of inflammation and swelling. This can cause further damage to the already injured tissues and lead to the formation of scar tissue, which can obstruct the flow of signals in the spinal cord.

This can result in loss of motor function and sensation below the level of the injury. In the weeks and months following the injury, the nervous system begins to undergo a series of changes in an attempt to compensate for the injury [2]. For example, the brain may develop new neural connections to bypass the damaged portion of the spinal cord. This process is known as neuroplasticity, and it can help to improve motor and sensory function in some cases. However, SCI can also lead to long-term changes in the nervous system that can interfere with normal development. For example, the injury can cause the overproduction of certain chemicals that can lead to chronic pain, muscle spasms, and other symptoms.

Additionally, the injury can result in the death of nerve cells, leading to a reduction in the overall size and function of the nervous system. In conclusion, spinal cord injury can have a profound impact on the development of the nervous system, leading to both short-term and long-term changes (**Figure 2**).

It is important for people with SCI to receive prompt medical attention and ongoing rehabilitation to help improve their outcomes and maximize their recovery.

4. Role of SEMA-3S in Nervous System Development

SEMA-3S (Semaphorin 3S) is a type of semaphorin protein that plays a role in the development of the nervous system [4]. Semaphorins are a large family of

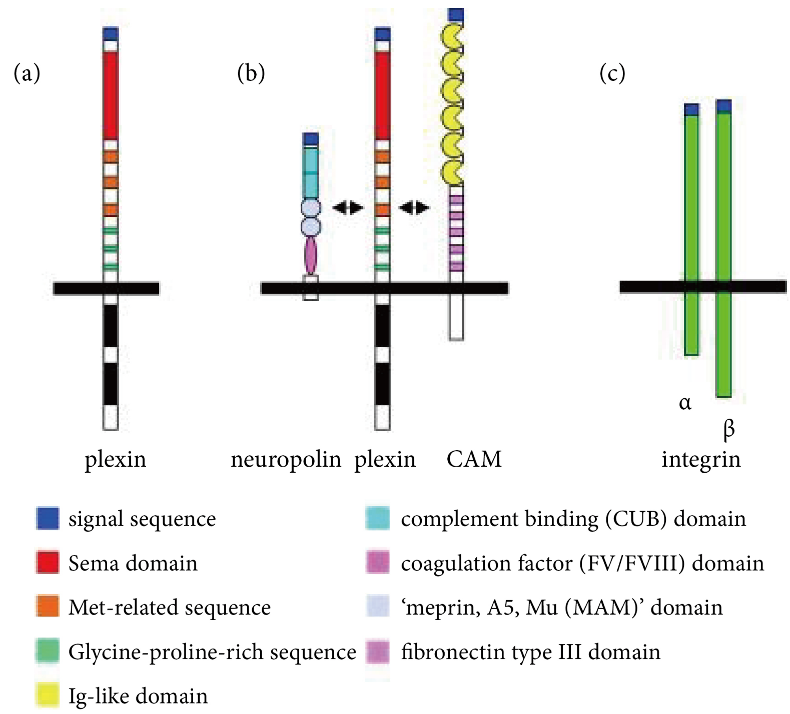

Figure 2. Both neuroplexins and plexins are keys to axon regeneration in spinal cord recovery. Semaphorins belonging to classes 4 - 7 directly interact with plexins. Secreted class 3 semaphorins can signal through both neuroplexin and plexin receptors [3].

signaling molecules that play important roles in various aspects of nervous system development, including axon guidance, cell migration, and neural circuit formation.

SEMA-3S is particularly interesting because it has been shown to play a role in the regulation of axon growth and guidance during the development of the nervous system. Axons are the long, thin fibers that extend from neurons and transmit signals to other neurons or muscles. The proper growth and guidance of axons is crucial for the formation of functional neural circuits. Studies have shown that SEMA-3S acts as a repulsive cue for axons, preventing them from growing into certain areas and guiding them towards their appropriate target regions. This is important for establishing the proper connections between neurons and ensuring the proper formation of neural circuits.

In addition to its role in axon guidance, SEMA-3S has also been shown to play a role in other aspects of nervous system development, including the regulation of neural stem cell proliferation and differentiation, and the formation of the blood-brain barrier [5]. Overall, the role of SEMA-3S in the development of the nervous system highlights the importance of semaphorins in regulating various aspects of nervous system development and ensuring the proper formation of functional neural circuits.

Overall, the role of SEMA-3s in nervous system development can be summarized into four key features: axonal regeneration, re-vascularization, re-myelination, and immune response.

Axonal regeneration refers to the process by which damaged or injured nerve fibers (axons) in the nervous system attempt to regrow and reestablish connections with their target cells. Unlike some other cells in the body, neurons in the central nervous system (CNS), which includes the brain and spinal cord, have limited intrinsic regenerative capacity. This is due to various inhibitory factors in the CNS environment that prevent robust axonal regrowth. In contrast, neurons in the peripheral nervous system (PNS), which includes nerves outside the CNS, exhibit greater regenerative potential. Following an injury to peripheral nerves, axonal regrowth can occur with the assistance of Schwann cells, which form a regenerative pathway and produce growth-promoting factors. In the CNS, ongoing research aims to identify strategies to enhance axonal regeneration by overcoming inhibitory factors and stimulating intrinsic growth mechanisms.

As shown in **Figure 3**, re-vascularization, or angiogenesis, is the process of forming new blood vessels in the nervous system after injury. When the nervous tissue is damaged, the blood supply to the affected area may become compromised, leading to ischemia (insufficient blood flow) and cell death. Angiogenesis helps in restoring blood flow to the damaged region, providing oxygen and nutrients essential for tissue repair and regeneration.

Myelin is a fatty substance that forms a protective sheath around nerve fibers, enabling faster conduction of nerve impulses and maintaining the integrity of the axons. In demyelinating diseases (e.g., multiple sclerosis), myelin is damaged, leading to impaired nerve signal transmission and neurological dysfunction [6]. Re-myelination is the process by which new myelin sheaths are formed around demyelinated axons, restoring their function. In the CNS, re-myelination

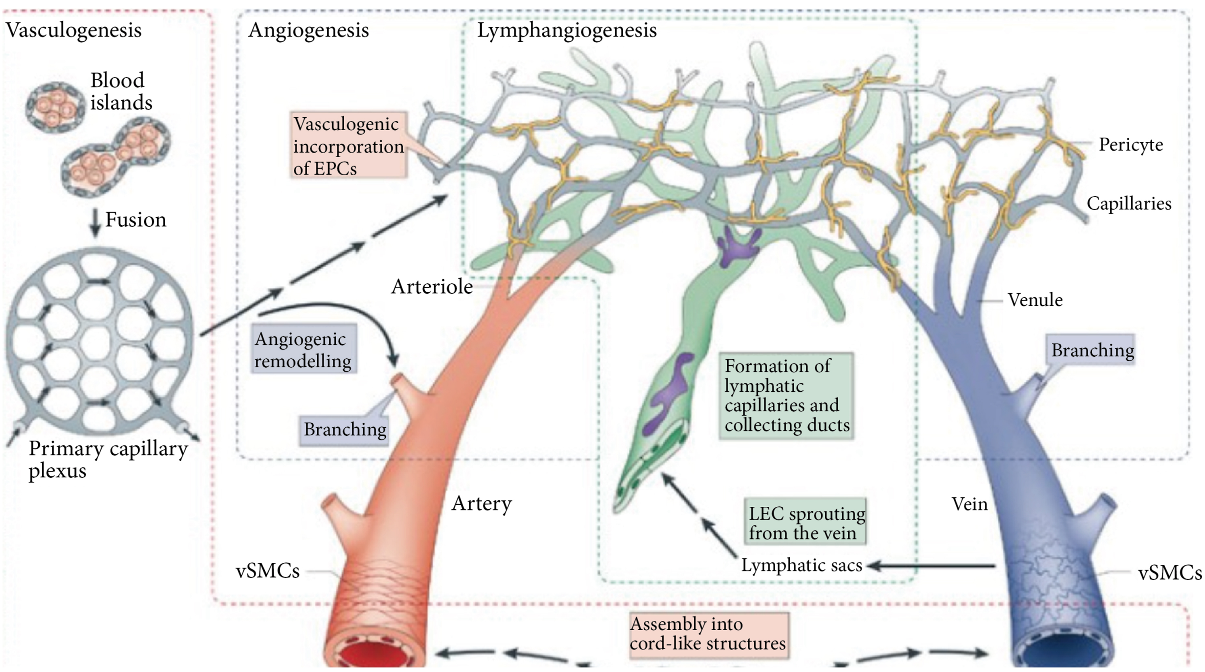

Figure 3. Angiogenesis in the CNS.

is mainly carried out by oligodendrocytes, specialized cells that produce myelin. However, the re-myelination process can be complex and often incomplete, depending on factors such as the extent of damage, the presence of inflammatory responses, and the age of the individual.

The immune response in the nervous system is a double-edged sword. It plays a crucial role in clearing debris, pathogens, and damaged cells after injury, thus facilitating the healing process. However, excessive or dysregulated immune responses can also cause secondary damage to healthy tissues. In the CNS, immune cells, such as microglia, act as resident immune cells and participate in the immune response to injury or infection. Inflammatory responses can attract additional immune cells from the bloodstream to the site of damage, creating a complex immune environment. A balanced immune response is crucial to support tissue repair while minimizing collateral damage. Therapies aimed at modulating the immune response in the nervous system are actively being explored to promote better recovery from injuries and diseases.

Overall, these processes-axonal regeneration, re-vascularization, re-myelination (as shown in Figure 4), and immune response-work together to promote recovery and repair in the nervous system after injury or damage. Understanding these mechanisms can help researchers develop targeted interventions to improve outcomes for individuals affected by neurological conditions.

5. SEMA-3S on Synapse Formation

SEMA-3s can play a role in the formation of synapses, which are the specialized structures that allow neurons to communicate with each other. In particular, SEMA-3s can contribute to the formation of synapses by regulating the growth and guidance of axons, which are the long, thin fibers that extend from neurons and transmit signals to other neurons or muscles. Studies have shown that SEMA-3s act as repulsive cues for axons, preventing them from growing into certain areas and guiding them towards their appropriate target regions. This is

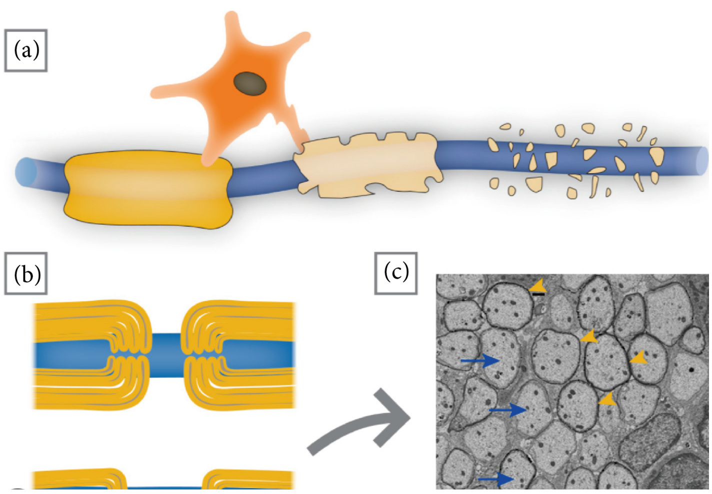

Figure 4. Remyelination in the Central Nervous System.

important for the formation of synapses because it helps ensure that axons reach their correct target neurons and form functional connections.

In addition to its role in axon guidance, SEMA-3s can also play a role in regulating the formation and refinement of synapses by modulating the activity of presynaptic neurons. This can occur through the regulation of the release of neurotransmitters, which are the chemical signals that neurons use to communicate with each other. Overall, the role of SEMA-3s in the formation of synapses highlights the importance of semaphorins in regulating various aspects of nervous system development and ensuring the proper formation of functional neural circuits.

6. Conclusion

In conclusion, the research presented in this paper has shed light on the critical role of Semaphorin 3 (SEMA3) proteins in spinal cord injuries. Through a comprehensive evaluation of existing literature and experimental findings, it is evident that SEMA3s play a multifaceted role in guiding axonal growth and modulating the regenerative response after spinal cord injury. The inhibition of SEMA3 signaling has shown promising results in promoting axonal regeneration, re-vascularization, and re-myelination, thus offering potential therapeutic avenues for enhancing recovery and functional outcomes in patients with spinal cord injuries. Nevertheless, it is essential to acknowledge the complexities of the nervous system and the challenges in translating these findings to clinical applications. Further research is needed to elucidate the intricate molecular mechanisms underlying SEMA3 signaling and to explore safe and effective delivery methods for targeted interventions. By unraveling the intricacies of SEMA3s in spinal cord injuries, this research provides a stepping stone towards developing innovative therapies that may one day transform the lives of those living with devastating spinal cord impairments.

Conflicts of Interest

The author declares no conflicts of interest.

References

[1] National Clinical Guideline Centre (2016) Spinal Injury: Assessment and Initial Management. National Institute for Health and Care Excellence (NICE), London. https://www.ncbi.nlm.nih.gov/books/NBK344254/

[2] Pasterkamp, R.J. and Verhaagen, J. (2006) Semaphorins in Axon Regeneration: Developmental Guidance Molecules Gone Wrong? *Philosophical Transactions of the Royal Society of London*, *Series B*, **361**, 1499-1511. https://doi.org/10.1098/rstb.2006.1892 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1664670/

[3] Sharma, A., *et al.* (2014) Changes in Expression of Class 3 Semaphorins and Their Receptors during Development of the Rat Retina and Superior Colliculus. *BMC Developmental Biology*, **14**, 34. https://doi.org/10.1186/s12861-014-0034-9 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4121511/

[4] Carulli, D., *et al*. (2021) Semaphorins in Adult Nervous System Plasticity and Disease. *Frontiers in Synaptic Neuroscience*, **13**, Article 672891.
https://doi.org/10.3389/fnsyn.2021.672891
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8148045/

[5] De Winter, F., Oudega, M., Lankhorst, A.J., Hamers, F.P., Blits, B., Ruitenberg, M.J., Pasterkamp, R.J., Gispen, W.H. and Verhaagen, J. (2002) Injury-Induced Class 3 Semaphorin Expression in the Rat Spinal Cord. *Experimental Neurology*, **175**, 61-75.
https://doi.org/10.1006/exnr.2002.7884
https://pubmed.ncbi.nlm.nih.gov/12009760/

[6] Dietrich, W.D. (2015) Protection and Repair after Spinal Cord Injury: Accomplishments and Future Directions. *Topics in Spinal Cord Injury Rehabilitation*, **21**, 174-187.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4568099/
https://doi.org/10.1310/sci2102-174