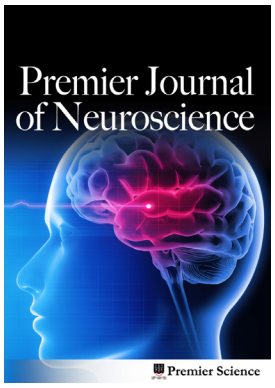

Biomaterials: Advancements in Spinal Cord Injury Treatment

Modinat Olushanu

ABSTRACT

Spinal cord injuries (SCIs) represent some of the most severe forms of trauma, often resulting in irreversible loss of motor and sensory function below the site of injury and profoundly diminishing patients' quality of life. Despite significant advancements in medical science, the development of effective therapies that can restore lost functions and substantially improve outcomes in patients with SCI remains an ongoing challenge. Current therapeutic strategies, including surgical interventions, intensive rehabilitation, and pharmacological treatments, have primarily focused on stabilising the injury and managing secondary complications, such as spasticity, pain, and inflammation. However, these approaches have shown limited success in promoting the repair and regeneration of damaged spinal cord tissues, highlighting the urgent need for innovative treatment modalities. Biomaterials have emerged as promising frontiers in SCI research, offering novel solutions to the inherent challenges posed by SCI. These engineered materials are designed to interact with biological systems in a controlled manner, providing structural support, facilitating cellular growth, and enabling localised delivery of therapeutic agents directly to the injury site.

Furthermore, biomaterials can be tailored to modulate immune responses, reduce inflammation, and create an environment conducive to tissue regeneration. Despite their potential, several critical challenges remain, including ensuring biocompatibility, maintaining long-term stability within the body, and overcoming the risks of immune rejection. Moreover, the translation of biomaterial-based therapies from preclinical studies to clinical applications is a complex and demanding process, necessitating extensive research and rigorous validation. This review aims to critically assess advancements in biomaterials for SCI treatment, focusing on their mechanisms of action, challenges in their application, and future directions.

Keywords: Hydrogel, Nanofibres, Hyaluronic acid, SCI, Alginate, Biomaterial, Scaffold, Fibrin, Inflammation, Functional recovery

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Introduction

Biomaterials: A New Hope for Spinal Cord Injury Treatment

Biomaterials, as engineered substances, represent a novel approach to overcoming the complexities of spinal cord injury (SCI) repair. The literature consistently acknowledges the complex challenges posed by SCI, including the disruption of anatomic organisations and the formation of an inhibitory environment for neural regeneration.[1,2] Biomaterial-based therapeutic strategies hold great promise for reducing secondary damage and promoting repair in SCI.[3] These biomaterials are tailored to interact with biological systems, provide structural support, and facilitate cellular processes that are critical for tissue regeneration.[4,5]

Biomaterial scaffolds, for instance, can bridge gaps in the spinal cord, serve as adhesion sites for cells, and enable sustained release of therapeutic agents, thereby addressing the inhibitory environment and loss of axonal connections characteristic of SCI.[6,7] Interestingly, the efficacy of biomaterials in SCI repair is influenced by their properties, as different materials affect neural tissues and cellular behaviour in distinct ways. For example, the surface properties of biomaterials such as chitosan (CHI), poly (ε-caprolactone) (PCL), and poly (L-lactic acid) (PLLA) are crucial for cell morphology and differentiation, with PCL and PLLA showing particular promise in guiding neuronal differentiation and network development.[8] This underscores the importance of material selection for SCI treatment in tissue engineering.

Biomaterials can also be designed to mimic the natural extracellular matrix, providing structural support and a conducive environment for cell growth and regeneration.[9,10] Researchers have explored various types of biomaterials, including hydrogels, nanofibres, and biodegradable scaffolds, to promote nerve regeneration and functional recovery in SCI patients.[2,4,6–9] One of the primary advantages of biomaterials is their ability to be customised for specific applications.

The Challenge of Treating Spinal Cord Injury

The spinal cord is an integral part of the central nervous system and functions as a critical communication pathway between the brain and the rest of the body. This pathway allows for the transmission of motor commands from the brain to muscles and the relay of sensory information from the body back to the brain. When the spinal cord sustains damage, the essential neural connections that facilitate communication between the brain and body are disrupted. This disruption can lead to severe consequences, including paralysis, which is the loss of muscle function and sensation, and the inability to feel stimuli in the affected areas.[11–13] While the immediate effects of SCI are often apparent, its long-term implications can extend beyond physical paralysis and loss of sensation. For example, adolescents may experience profound emotional and developmental disruptions due to SCI, necessitating a comprehensive approach to rehabilitation that addresses both physical and psychological needs.[11] Additionally, the severity of SCI is classified using scales such as the American Spinal Injury Association (ASIA) impairment scale, which reflects the degree of functional loss.[12]

The complexity of the spinal cord and its limited intrinsic capacity for regeneration make SCI challenging to treat. The spinal cord comprises various neural cell types, including neurones and glial cells, each of

which plays a specific role in maintaining its function. However, once injured, the spinal cord undergoes a series of pathological changes that exacerbate the initial damage (Figure 1).[14,13,15]

One of the primary pathophysiological mechanisms following SCI is the formation of cystic cavities, which are fluid-filled spaces that replace lost neural tissue. These cavities create physical barriers that prevent axonal regrowth at the injury site.[15] Additionally, the injury induces the formation of astrocytic scars, where astrocytes proliferate and create a dense network of glial fibres around the injury site. While astrocytic scars serve as protective barriers against damage, they also create a hostile environment that inhibits axonal regeneration.[17,18]

Moreover, SCI triggers a cascade of secondary injury processes, including ischaemia, inflammation, and oxidative stress, which further contribute to tissue damage. Ischaemia, or reduced blood flow, deprives the spinal cord of oxygen and nutrients and exacerbates cell death.[19,20] The inflammatory response, initially aimed at clearing debris, often becomes chronic and detrimental, producing cytokines and other factors that inhibit neural repair.[21–23] The accumulation of reactive oxygen species during oxidative stress also damages cellular components, further complicating the repair process.[24]

These secondary injury mechanisms create an inhibitory microenvironment that hinders neural recovery. Cystic cavity formation, astrocytic scarring, and ongoing inflammation obstruct neural conduction pathways, leading to apoptosis (programmed cell death) and necrosis (uncontrolled cell death) of neurones and glial cells. This multilayered damage prevents axon regeneration and leads to progressive degeneration of the neural tissue surrounding the injury site.[25–27]

Biomaterials: Therapeutic Strategy for Treating Spinal Cord Injuries

Hydrogels

Hydrogels have been recognised for their capacity to provide mechanical support and deliver therapeutic agents, including growth factors, to the SCI site. These materials can mimic the extracellular matrix, offering a conducive environment for cell attachment and proliferation, which is essential for tissue regeneration.[28,29] The structural and functional properties of hydrogels can be fine-tuned to achieve the desired mechanical characteristics and the controlled release of therapeutic substances.[28,30] These materials can fill the lesion cavity and provide a scaffold conducive to tissue repair by promoting axonal regeneration, angiogenesis, and functional recovery.[31,32] Fan et al. illustrated that injectable hyaluronic acid-based hydrogels can fill lesion cavities and promote tissue repair by supporting cell compatibility, matching the stiffness of nervous tissue, and facilitating axonal regeneration, remyelination, and angiogenesis.[31]

Furthermore, alginate (ALG) hydrogels have been recognised for their potential to mimic the mechanical properties of neural tissues, which is essential for

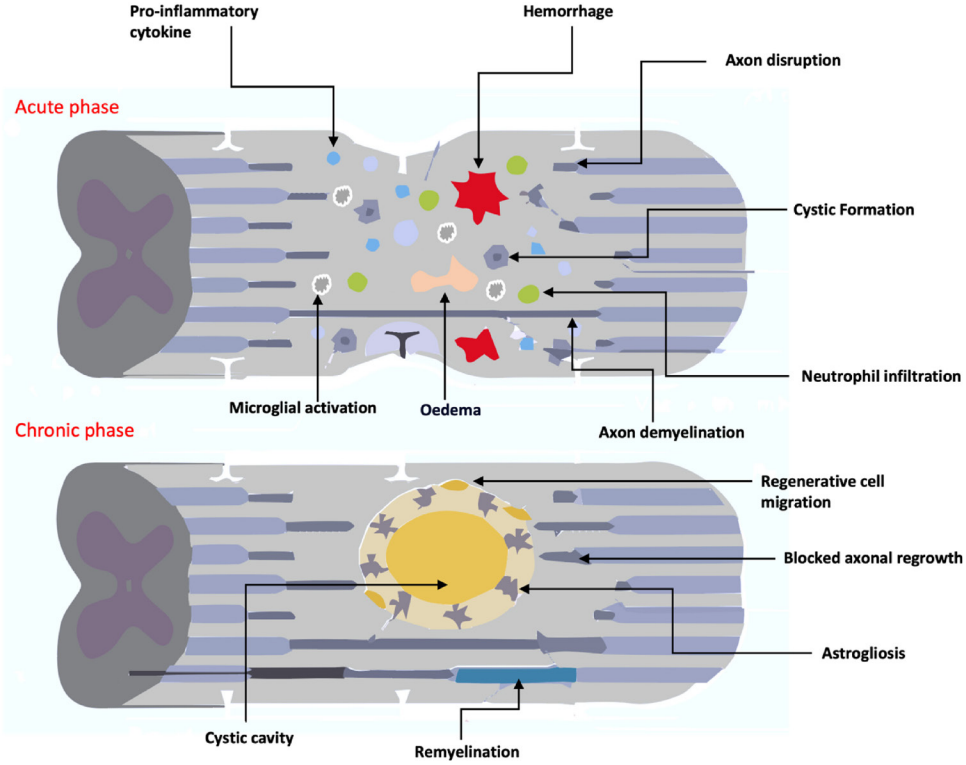

Fig 1 | Spinal cord injury: Pathophysiology of SCI showing primary to secondary response

Source: This "image," is adapted from "Pathophysiology of spinal cord injury (SCI)" by Toshitaka Seki and Kiyohiro Houkin, used under CC BY 4.0. "Pathophysiology of spinal cord injury (SCI)" is licensed under CC BY 4.0 by Modinat Olushanu.[16]

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providing a conducive environment for neuronal regeneration.[33] Karimi et al. demonstrated that alginate hydrogels incorporating short magnetic nanofibres (M.SNFs) exhibited storage moduli within the range of nerve tissues, suggesting their suitability for neuronal regeneration applications.[34] Similarly, Kim et al. described a double-network (DN) hydrogel using alginate and gelatin that exhibited improved mechanical properties such as tensile strength and elastic modulus, which are crucial for fabricating nerve guidance conduits (NGCs) for peripheral nerve repair. Although alginate hydrogels show promise in mimicking neural tissue mechanics, Kim et al. also indicated that single-network (SN) hydrogels may have poor mechanical properties, necessitating the development of more complex hydrogel systems, such as DN hydrogels.[35] Ghaderinejad et al. further supported this finding by demonstrating that alginate hydrogels with magnetic short PCL nanofibres can be externally aligned to form an anisotropic network, which is beneficial for nerve injury repair.[36]

Similarly, fibrin hydrogels have been noted for their biocompatibility and the ability to be modified with cells, ECM proteins, and growth factors to enhance SCI repair.[37] These modifications are crucial as they contribute to the repair of damaged nerve tissue by promoting cell function and tissue regeneration. Although fibrin hydrogels offer a promising platform for SCI repair, variations in their sources and modifications can affect their effectiveness. For instance, fibrin hydrogels derived from different sources may exhibit distinct properties, and the internal topographical guidance during polymerisation can be varied to improve outcomes.[37] Specifically, hierarchically aligned fibrillar fibrin hydrogels have shown potential in directing stem cells towards the nerve lineage and in spinal cord regeneration, as they provide biomimetic biophysical cues that facilitate the rapid construction of nerve-like microtissues.[38] Liu et al. developed an in situ glycidyl-methacrylated silk fibroin/laminin-acrylate (SF-GMA/LM-AC) hydrogel. Activated by ultraviolet (UV) light, this hydrogel quickly forms a network that tightly adheres to the spinal cord and acts as a molecular suture. It provides an optimal environment for neural stem cell growth and enhances neural regeneration when injected into rats with complete SCI.[39]

Additionally, methacrylate gelatin/ECM-(GelMA)/ECM hydrogel fibrous scaffolds have demonstrated improved mechanical properties and the ability to recruit and differentiate neural stem cells more effectively than traditional scaffolds.[40] Similarly, the incorporation of oxymatrine (OMT) into spinal cord extracellular matrix hydrogel scaffolds has shown enhanced neural stem cell recruitment and differentiation, as well as improved motor function recovery in rat models.[41]

In summary, hydrogels are versatile biomaterials that can be engineered to mimic the mechanical properties of neural tissues and provide localised delivery of therapeutic agents. These properties make these scaffolds ideal for SCI repair, promoting neuronal regeneration, and creating an optimal healing environment. Ongoing research and development to modify and combine these hydrogels continue to advance the field of neural tissue engineering, with the potential to significantly improve functional recovery in patients with SCI.[28,30,34–38]

Nanofibres

Nanofibre scaffolds have garnered attention in the field of SCI treatment because of their extracellular matrix (ECM)-mimicking properties, which are crucial for neural tissue engineering.[9,42,43] These scaffolds provide a conducive environment for cell attachment, proliferation, and differentiation, which are essential for nerve regeneration.[43] They also provide topographical cues that guide the growth of new nerve fibres and potentially bridge the gap created by the injury.[9,44]

Although nanofibre scaffolds offer a promising approach, their efficacy does not solely depend on their architecture. The incorporation of bioactive cues such as protein binding and cellular adhesion epitopes, can further enhance their therapeutic potential by promoting cell adhesion, viability, and neurite outgrowth, as demonstrated by Sever-Bahcekapili et al., using peptide nanofibres in a rat model of SCI.[45] Similarly, silk fibroin nanofibres functionalised with laminin have been found to significantly enhance directional axonal extension, providing both physical and bioactive cues for neurite outgrowth.[46,47] Another promising combination therapy involves the integration of electroactive materials, carbon nanotubes, and graphene, to promote functional recovery by restoring the interconnections between neurones.[48]

Moreover, nanofibre scaffolds can function as effective drug carriers, which may influence the biological behaviour of cells on their surfaces, such as differentiation, proliferation, and migration, thereby promoting tissue regeneration and functional recovery. The literature suggests that nanofibres can serve as local drug delivery systems, aiming to prevent secondary damage through neuroprotection and to promote neuroregeneration by re-establishing neuronal connectivity.[49–51] Similarly, lipid nanovesicles have been identified as highly biocompatible carriers that can penetrate the blood-spinal cord barrier (BSCB), offering targeted treatment for SCI.[52]

In summary, nanofibre scaffolds and nanotechnology-based drug delivery systems are emerging as promising strategies for promoting tissue regeneration and functional recovery in SCI patients. They offer the potential for targeted drug delivery and support for axonal regeneration (Figure 2).[49,52–54]

Overcoming Challenges: Inflammation and Immune Response

Although biomaterials offer significant potential for SCI treatment, several challenges must be addressed before they can be widely adopted in clinical practice. These challenges include ensuring biocompatibility, avoiding immune responses, achieving targeted delivery, controlling drug release, and standardising production and characterisation.[56–58]

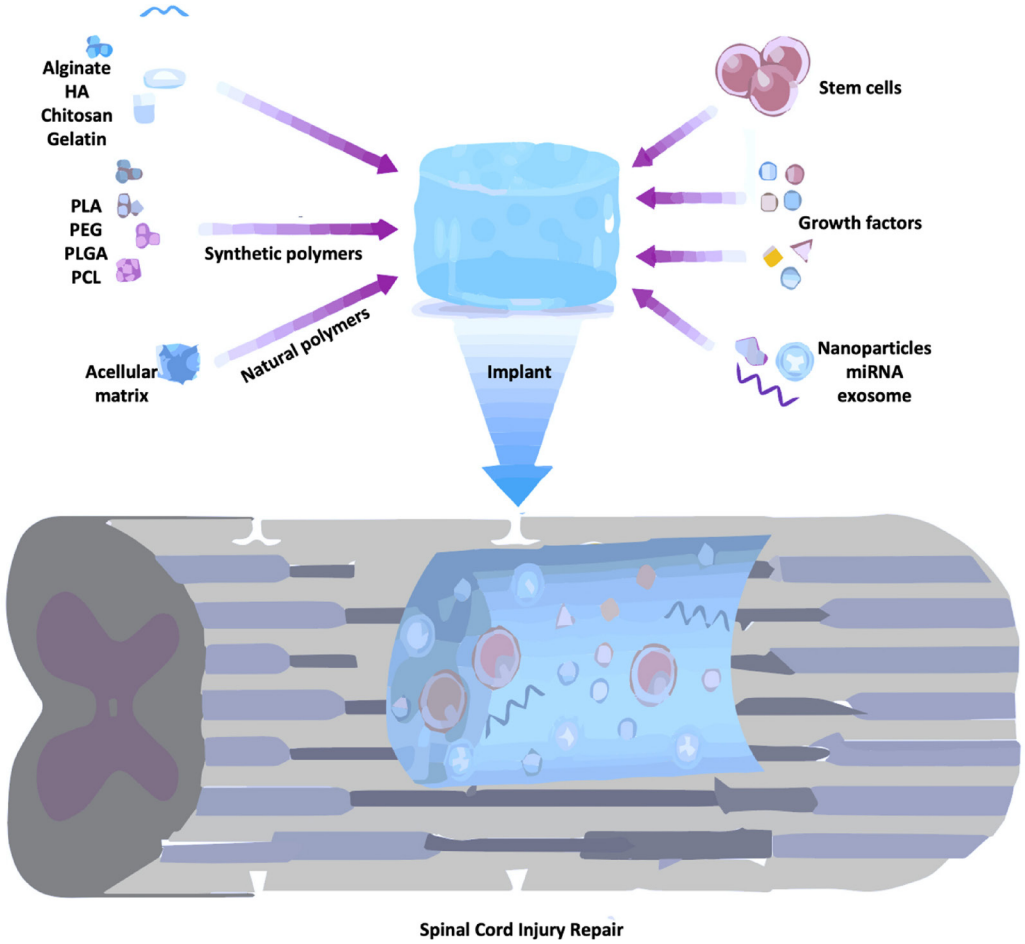

Fig 2 | Schematic diagram illustrating the use of biomaterials in treating spinal cord injuries

Source: This "image," is adapted from "Pathophysiology of spinal cord injury (SCI)" by Toshitaka Seki and Kiyohiro Houkin, used under CC BY 4.0 and a schematic diagram from Ref.[55] "Pathophysiology of spinal cord injury (SCI)" is licensed under CC BY 4.0 by Modinat Olushanu.

Biomaterial scaffolds can be instrumental in addressing the inflammation and immune responses following SCI. They serve not only as structural supports but also actively participate in modulating the inflammatory microenvironment, which is crucial for reducing secondary damage and promoting regeneration.[6,56,59] Biomaterials can inhibit apoptosis, inflammation, and scar formation, while inducing neurogenesis, axonal growth, and angiogenesis.[6]

Although biomaterials alone offer significant benefits, their combination with other therapeutic strategies, such as lentiviral vectors (LVs), may enhance their efficacy. Studies suggest that the synergistic use of LVs and biomaterials can augment the therapeutic effects of each modality in SCI treatment.[60] Additionally, the use of conductive biomaterials in conjunction with regenerative rehabilitation approaches, such as electrical stimulation, may redefine the potential for functional recovery post-SCI.[53]

Other studies have focused on developing biomaterials with inherent anti-inflammatory properties or exploring coatings that can minimise immune responses. You et al. used gold nanoparticle-based nanocomposites for hydrogen gas generation to promote neuroprotective effects during the acute phase of SCI.[61] Stigliano et al. presented a study in which nanoparticles (NPs) containing an MK2 inhibitor selectively targeted and modulated activated microglia/macrophages, reducing the pro-inflammatory cytokine IL-6 and increasing the anti-inflammatory cytokine IL-10 in a rat model of SCI.[62] Similarly, in a study by Gao et al., retinoic acid (RA) and curcumin (Cur) were co-loaded with bovine serum albumin (BSA) to obtain RA@BSA@Cur NPs, which induced polarisation of macrophages towards pro-regenerative phenotypes, reduced the inflammatory response, and promoted functional neurone regeneration after SCI.[63] Guo et al. found that melatonin supports polarisation from pro-inflammatory to anti-inflammatory states in microglia, suggesting that biomaterials could be designed to deliver such agents to modulate immune responses after SCI.[64] This shift could reduce chronic inflammation and support tissue regeneration.

Additionally, surface modifications of biomaterials, such as altering their chemistry or topography, can further reduce the immune response by making the materials less recognisable to the immune system, thereby decreasing the likelihood of a foreign body reaction (FBR). FBR is indeed a significant impediment to the integration of biomaterial scaffolds following SCI, as

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it can lead to the encapsulation of the implant and its isolation from surrounding tissues, thereby hindering the healing process.[65] A recent study by Zheng et al. suggested that optimising the mechanical properties of scaffolds, such as stiffness, may alleviate FBR and promote better integration with host tissue.[66]

Additionally, the use of natural biomaterials, such as collagen, hydrogels, or chitosan, can also influence immune responses by affecting immune cell behaviours such as activation and differentiation, and can be engineered to release immunomodulatory factors to promote a tolerogenic immune response.[67] Wang et al. illustrated that polycitrate-based nanocomposite hydrogel (PMEAC) scaffolds provide biomimetic mechanical and electrical properties that promote locomotion recovery and reduce in vivo inflammation.[68] In a study by Gao et al., HA hydrogels were shown to possess properties such as damage-associated molecular pattern (DAMP) scavenging and sustained release of anti-inflammatory cytokines, which contribute to the reduction of lymphocyte accumulation and modulation of the immune response, thereby enhancing the survival and function of transplanted tissues after acute SCI.[69] Although HA-based biomaterials generally support anti-inflammatory responses, they can also be engineered to target specific pathways or cells. For instance, HA-selenium nanoparticles (HA-Se NPs) target the CD44 receptor, which facilitates their internalisation by astrocytes and leads to the suppression of pro-inflammatory cytokines by microglia, thus enhancing functional recovery post-SCI.[70] Furthermore, Liu et al. reported that a dopamine-modified chitosan hydrogel improved cell survival and modulated immunity by promoting macrophage polarisation to the M2 phenotype, which is associated with anti-inflammatory and tissue repair functions.[71]

By incorporating these strategies, biomaterials can create a more conducive environment for healing, reduce the likelihood of chronic inflammation, and ultimately improve the outcomes of treatments for conditions such as spinal cord injuries.[59,72,73]

Overcoming Challenges: Clinical Translation

Clinical trials involving biomaterials for the treatment of SCI are of increasing interest, as evidenced by the current literature on their use.[74] These biomaterials are designed to be compatible with spinal cord tissues and have the potential to improve outcomes in patients with SCI by providing a scaffold for tissue regeneration and a medium for targeted drug delivery. However, although the development of biomaterials represents a promising direction, the literature does not provide extensive details on the specific clinical trials currently underway or their outcomes. This indicates a gap between the research phase and its application in clinical settings, which is not uncommon in the field of regenerative medicine. In summary, the current academic discourse suggests that biomaterials hold promise for the treatment of SCI, with their properties aligning well with the requirements for supporting tissue regeneration and drug delivery.[74] However, the lack of detailed information on ongoing clinical trials and their results highlights the need for further research to bridge the gap between laboratory findings and clinical application.

Conclusion

The field of biomaterials for SCI treatment is still, to some extent, in its initial stages of development; however, advancements made thus far are promising.[3] The complexity of SCI pathology and the unique post-injury microenvironment have historically made complete repair challenging; however, as our comprehension of the intricate biology of the spinal cord and the characteristics of biomaterials continues to expand, the possibility of devising effective treatments becomes increasingly feasible. Although no single treatment can fully address the multifaceted challenges associated with spinal cord injuries, combining biomaterials with cutting-edge technologies, such as gene editing and bioengineering, could further amplify their therapeutic potential.[75]

Biomaterials offer a promising solution for enhancing recovery from SCI by fostering an environment conducive to nerve regeneration, reducing inflammation, and complementing modern therapeutic approaches. The potential to improve patient outcomes is substantial.

Clinical trials are a critical step in the process of transferring the achievements observed in animal models to human patients. These trials aimed to assess the safety, effectiveness, and feasibility of biomaterials to treat SCIs. If these trials are successful, biomaterials could significantly change the way SCI treatment is approached, potentially offering a promising solution for individuals who currently face a lifetime of disability.

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