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ABSTRACT

Harnessing “dancing molecules”: advancements in spinal cord injury recovery through supramolecular chemistry

Aprovechamiento de las “moléculas danzantes”: avances en la recuperación de lesiones de la médula espinal mediante la química supramolecular

Aproveitando “moléculas dançantes”: avanços na recuperação de lesões na medula espinhal por meio da química supramolecular

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Introduction: Spinal Cord Injuries (SCI) represent one of the most challenging conditions in modern medicine, often leading to permanent paralysis and significant loss of function. This condition is notable for its high incidence, substantial costs, significant disability rates, and often early age of onset. The complexity of the spinal cord and its limited capacity for self-repair have historically constrained treatment options, primarily focusing on managing symptoms and preventing further damage rather than restoring lost functions. However, recent advances in regenerative medicine have opened new avenues for potential recovery and rehabilitation for SCI patients[1]. Among these innovations, the concept of “dancing molecules”, particularly pioneered by Dr. Stupp and colleagues from Northwestern University, has emerged as a promising frontier[2,3]. “Dancing molecules” refers to a novel class of bioactive, dynamically moving molecules designed to facilitate neural regeneration. These molecules exhibit dynamic behavior, particularly in the context of supramolecular chemistry. When embedded within an injectable gel, it exhibits a unique capability to interact with cellular receptors, promoting axonal growth, remyelination, and overall neural repair. The dynamic movement of these molecules significantly enhances bioactivity, increasing the probability of beneficial interactions with damaged nerve cells[3,4]. Initial preclinical studies have shown that these “dancing molecules'' can substantially improve motor function and promote the regeneration of axonal pathways in animal models with spinal cord injuries. This innovative approach represents a potential breakthrough in SCI treatment and provides a new paradigm for the design and application of regenerative therapies[3].

Objective: This paper aims to explore the advantages and benefits of “dancing molecules” discovered in Dr. Stupp’s studies in the context of spinal cord injury recovery. We will delve into the underlying mechanisms of this technology, review the latest preclinical and clinical research findings, and discuss the potential implications for future treatments. By examining this cutting-edge development, we hope to highlight the transformative potential of those molecules and their role in advancing the field of regenerative medicine for spinal cord injuries.

Methodology: The methodology for this study involved a comprehensive review of existing literature, focusing on the advantages and benefits of “dancing molecules” discovered in Dr. Stupp’s studies for SCI recovery. A thorough search was conducted in scientific databases to identify relevant studies, using keywords such as “dancing molecules”, “supramolecular polymers” and “spinal cord injury”. The initial search yielded numerous articles, which were filtered based on their relevance, resulting in the selection of 5 key studies, from 2018 to 2023, 4 authored by Dr. Stupp and his colleagues. Data was extracted with particular attention to the types of supramolecular polymers used, injection techniques, and outcomes like axonal growth, remyelination, angiogenesis, cell survival, and functional recovery. The findings were synthesized to understand how “dancing molecules'' promote SCI recovery, with a critical evaluation of study quality. The study highlighted the transformative potential of these molecules in regenerative medicine and recommended future research, emphasizing clinical trials and further mechanistic exploration.

Results and Discussion: The studies from Dr. Stupp and his colleagues, especially in the articles "Bioactive Scaffolds with Enhanced Supramolecular Motion Promote Recovery from Spinal Cord Injury"[2] and "Supramolecular Polymers: Dynamic Assemblies of 'Dancing' Monomers"[3] present significant advancements in the use of bioactive scaffolds to facilitate recovery from spinal cord injury (SCI). These scaffolds promote axonal regrowth, reduce glial scar formation, enhance angiogenesis, and support functional recovery. The study is a preclinical research that involves in vitro (lab-based) experiments and animal models to test the efficacy and mechanism of action of the molecules. They are supramolecular polymers designed to enhance motion at the molecular level, with specific functional groups enabling dynamic and reversible interactions to form a responsive network. Detailed characterization using nuclear magnetic resonance (NMR) spectroscopy, gel permeation chromatography (GPC), and dynamic light scattering (DLS) confirmed the formation of polymers with the desired molecular weight and structural features, capable of self-assembling into supramolecular structures under physiological conditions. The term "dancing molecules'' might be used metaphorically to describe the dynamic nature of these interactions. In a sense, the molecules are "dancing" as they constantly associate and dissociate, responding to changes in their environment. This dynamic behavior is crucial for the formation of supramolecular assemblies, which can have various applications in fields such as materials science, drug delivery, sensing, and catalysis. The concept of "dancing molecules" has emerged as a transformative approach in tissue engineering and regenerative medicine, harnessing the dynamic interactions of molecules to orchestrate the complex processes involved in spinal cord regeneration. The dynamic nature of the "dancing" monomers significantly improved bioactivity by better mimicking the natural extracellular matrix. In the SCI study, this enhanced motion facilitated cell attachment, proliferation, and differentiation. In vitro tests demonstrated that cell cultures on dynamic scaffolds exhibited higher viability and more pronounced neurite outgrowth compared to static scaffolds. The motion activated mechanotransduction pathways, enhancing critical cellular responses for tissue repair. The gel is typically injected directly into the spinal cord at the site of injury to maximize its regenerative effects. The procedure involves preparing the gel in a sterile environment to ensure it is contaminant-free, using imaging techniques like MRI or CT scans to precisely identify the injury location and extent, and carefully injecting the gel into the damaged area with a fine needle a catheter, either during surgery or via a minimally invasive technique depending on the injury's severity and location. Once injected, the gel spreads throughout the injury site, integrates with the existing tissue, and initiates its regenerative work. Also, the gel is composed of supramolecular polymers, which are assemblies of monomers that interact through noncovalent bonds, allowing the polymers to exhibit dynamic and reversible behavior like molecules in constant motion. This "dancing" motion is crucial as it enables the gel to mimic the natural extracellular matrix (ECM) more closely, providing a supportive environment for cell growth and differentiation. When injected into the site of spinal cord injury, the gel's dynamic nature facilitates its integration into damaged tissue. The monomers within the gel interact with cellular receptors on nerve cells, promoting several key regenerative processes: the dynamic motion of the molecules encourages axons to extend. bridging the gap caused by the injury; the gel supports the regeneration of myelin sheaths around axons, essential for proper nerve cell function; and the overall bioactivity of the gel enhances cellular repair mechanisms, contributing to the restoration of neural pathways. A pivotal finding is the inhibition of glial scar formation, a major barrier to axon regrowth following SCI. The dynamic scaffolds promoted significant axonal regrowth, evidenced by immunohistochemical staining for neurofilament and growth-associated protein 43 (GAP-43). This regrowth was attributed to the scaffold's ability to modulate the local microenvironment, reducing inhibitory cues and providing physical support for regenerating axons. Moreover, dynamic scaffolds were found to promote angiogenesis, crucial for supplying necessary nutrients and oxygen for tissue repair and regeneration. Enhanced cell survival was observed, likely due to the improved microenvironment and mechanical cues provided by the scaffold, supported by increased expression of survival markers and reduced apoptosis. Most importantly, the SCI study demonstrated significant functional recovery in animal models. Behavioral tests, such as the Basso Mouse Scale (BMS) for locomotion, showed that animals treated with dynamic scaffolds regained more motor function compared to controls. The study extended its in vitro analysis to human neural progenitor cells (hNPCs) to validate the translational potential of the scaffolds. hNPCs cultured on the dynamic scaffolds showed enhanced differentiation into neurons and glial cells, accompanied by increased expression of lineage-specific markers. This suggested that the scaffold's dynamic environment supports cell maturation and functional integration, consistent with findings on "dancing" monomers. To understand the role of supramolecular motion, physical experiments were combined with computer simulations. Techniques such as atomic force microscopy (AFM) and rheometry measured the mechanical properties and dynamic behavior of the scaffolds, confirming the desired level of supramolecular motion and mechanical responsiveness Molecular dynamics simulations provided insight into how supramolecular interactions at the molecular level translated into macroscopic properties, elucidating mechanisms by which dynamic scaffolds influenced cell behavior and promoted tissue repair.

Conclusion: By leveraging the responsive and adaptable nature of dynamic supramolecular polymers, researchers have developed advanced bioactive scaffolds that significantly improve outcomes for patients with spinal cord injuries. These scaffolds promote axonal regrowth, reduce glial scar formations, enhance angiogenesis, and support functional recovery, offering a multifaceted approach to SCI treatment. This innovative strategy not only addresses the

complexities of spinal cord repair but sets a promising direction for future regenerative medicine, potentially revolutionizing the treatment and rehabilitation of SCI patients.

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