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Novel Gene Therapies Technology for Spinal Cord Injury (SCI) Therapy: Efficient Direct Lineage Reprogramming

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Abstract

What is understood and the goals: For the past few decades, the definition of spinal cord injury (SCI) has been people becoming wheelchair-bound and requiring lifelong medication [1]. The relatively limited medical options for SCI frequently leaves caretakers feeling more frustrated than before because there is no real cure for the disorder. Yet, due to the enormous amount of research conducted recently, neuroscience has advanced significantly through GT, providing better understanding and raising prospects for neuronal regeneration and functional rehabilitation [2]. Many investigations utilising a synthetic virus (AAV, retro, adeno, or lenti) are opening up interesting research paths as GT technology gains popularity as a viable therapeutic technique [3-5]. We discussed Direct Lineage Reprogramming (DLR) technology in this review.new GT technique for those with SCI.

Introduction

Few Adeno-Associated Viruses (AAVs), such as AAV2 and 9, have the ability to penetrate the central nervous system (CNS) and transform neurons after systemic delivery, allowing the GT to emerge as a treatment for conditions that were previously deemed incurable, such as progressive Parkinson's disease and SMA. The severity of SMA, a neuromuscular condition that is generally acquired and recessive and causes muscle atrophy and weakening as a result of a loss in motor neurons, relies on the allelic form-related mutations in Survival Motor Neuron 1. (SMN1). Onasemnogene Abeparvovec (OGA) (formerly AVXS-101, Zolgensma®, Novartis GT EU limited, and Dublin, Ireland) is permitted to treat SMA in more than 40 nations across the world. OGA is an AAV vector-based GT that is administered once intravenously and prepared.to introduce a human SMN gene copy that can cross the blood-brain barrier and function (BBB). As segmented organs with built-in barriers like the BBB that may restrict access, neurological elements including the brain, spinal cord, and sensory organs like the eye and cochlea provide constraints and difficulties for GT. This explains why local vector administration (LVA) is preferable to intravenous introduction or delivery through other fluid-filled compartments.Moreover, the LVA maintains the concentration and lengthens the time the gene transfer agent spends near the target cells, minimising or preventing wide biodistribution and reducing the risk of immunogenicity or toxicities caused by AAV components or ectopic expression of the transgene. LVA of AAV transmission (intraparenchymal injection)is a suitable approach for disorders affecting the eye and spinal cord, and local introduction to ocular conditions has shown to offer clinical benefits. This is due to the fact that it provides better noninvasive monitoring of the prognosis of therapeutic therapies as well as improved access to surgery.

The segmented structure of the eye further reduces the dosage and systemic leaking of the vector.Several researchers are working hard to determine the best course of treatment for patients with spinal cord injury (SCI). Nevertheless, there is currently no treatment strategy for SCI. Reactive astrocytes brought in to the wounded area by the SCI group create a physical barrier known as a "astrocyte scar" and express chemicals that prevent axonal regrowth. According to certain research, early excision of astrocyte scars in a mouse model results in larger lesion sites and less functional recovery. In order to cure SCI, in vivo DLR (IVDR) may therefore be a good candidate for targeting reactive astrocytes. It has been documented that fibroblasts or astrocytes can IVDR become neurons or neuroblasts. Our ultimate objective and several investigations are to develop an IVDR approach for the management of CNS-related diseases.examined the various methods for enhancing DLR effectiveness (Figure 1). Because the bulk of the spinal cord's areas lack neurogenesis, treating adult mammals' spinal cords is more difficult than treating their brains. Therefore, there is a need for novel methods that can replace the missing motor neurons with artificial motor neurons (iMNs), which will be the direction of therapeutic

development in the future. The Brn2, Ascl1, and Mytl1 with Lhx3 (4TF) is the first example of such iMN advancements. Many research teams have recently revealed numerous ways to speed up neural Signaling. The table below lists the several kinds of DLR accelerators, including nanoparticles made of biocompatible materials, miRNA, and tiny molecules. Yoo et al. [14] and his team in particular looked on the precise process to increase the dopaminergic neuronal DLR from astrocyte. They have demonstrated that astrocyte into dopaminergic neuron in vivo Transition is accelerated by gold nanoporous rod by regulating the ROS level and maximising the cell stress and its function. This study has shown that cellular stress and ROS can regulate the DLR's effectivenes.

Discussion

Recent advancements in the field of DLR have made it possible to immediately transform differentiated mature cells into a variety of other cells by avoiding an intermediary pluripotent state. The strategy to convert non-neuronal cells into neurons was motivated by the Transcription Factor's (TF) potent function (Table 3). The transcription factors Ascl1, Brn2, and Myt1l were initially overexpressed in order to induce direct neuronal reprogramming [38]. These three elements transformed fibroblasts into neurons that could express neural markers and create useful connections. Subsequent investigation revealed that ASCL1, BRN2, MYT1L, and NEUROD1 produce human induced neurons (iNs). NEUROD1 is essential for the formation of neurons. Particularly, those with the synapse-capable and functionally profiled. In due course, non-neurogenic cells including astroglia, glial cells, and pericytes will also develop into active neurons. A glutamatergic or GABAergic neuron could be targeted by astroglia with just the Transcription Factors (TF) alone. Similar studies that have expanded TF with reprogramming capability have led to the development of of additional neuronal subtypes, such as intermediate spiny neurons, motor neurons, or dopaminergic neurons. For instance, Caiazzo et al. [39] have demonstrated that human and mouse fibroblasts can

Using Ascl1, Nurr1, and Lmx1a, dopaminergic neurons may be altered. The generated dopaminergic neurons demonstrated dopaminergic neurons' functional similarities. It's interesting how new research has increased the viability of using miRNA for direct reprogramming. Combinations of miRNAs can reprogramme fibroblasts into functioning neurons in a manner similar to transcription factors.

Transcriptional regulators can also strengthen the role of miRNA in brain reprogramming. For instance, miR-9/9* and miR-124 work in conjunction with the transcription factors ISL1 and LHX3 to enhance the conversion of fibroblastic cells into motor neurons [40]. These data collectively highlight the crucial function of TF and miRNA in determining of the destiny of neuronal cells.The brain's ability to replace and repair damaged neurons is restricted. Hence, other cells that are the sources for repair are required in order to intervene in CNS sickness. As IVDR has the potential to be a therapeutic option, it is a developing field that is receiving greater study focus. Correct targeting of a certain cell group is necessary for IVDR in the brain. Using AAV is a sufficient strategy for the best therapy to regulate the ultimate cell type of in vivo reprogramming for therapeutic approaches for CNS diseases. The therapeutic applicability of this intervention is, however, constrained by the fact that the combination of TFs and other combinations showed less success in reprogramming the adult human and mouse cells. A lot of work has been put into developing reprogramming cocktails during the past 10 years that include transcription factors, epigenetic factors, microRNAs, small compounds, or biocompatible materials to produce effective cell fate conversion.

Conclusions

In the realm of GT, cell fate conversion employing a viral system is very intriguing. DLR is used in cell fate conversion methods because of its low efficiency. Numerous scientists have been attempting should look into the technique to improve reprogramming efficiency from a decade ago. The effectiveness of reprogramming can be increased by using specially engineered nanoparticles, such as gold nanoporous rods, by activating cell master regulators such Gsta4, Mt3, Sod1, Cox6b2, Sirt3, etc. [14]. These master regulators could usher in a new age for neurological disorders like Parkinson's, Alzheimer's, and spinal cord injury.

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