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Review Article

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

*Chunggoo Kim, Hyun Soo Shim, Yujung Chang, Hyeonjoo Im and Junsang Yoo**

Cell Reprogramming and Stem Cell Research Center, Stand up Therapeutics, Korea

Abstract

What is known and objectives: Spinal Cord Injury (SCI) is defined for the last few decades as patients getting wheelchair bound and under medication for a lifetime [1]. Medical battery for SCI is very limited which often results in heightened frustration for the caregivers who land up with no solid solution to the condition. However, in recent times due to the huge volume of research, neuroscience has progressed massively through GT offering better insight and high hopes of neural regeneration and functional rehabilitation [2]. As GT technology becomes more popular as an emerging therapeutic method, many studies using a manufactured virus (AAV, retro, adeno, lenti) are opening up promising research avenues [3-5]. In this review, we dealt with Direct Lineage Reprogramming (DLR) technology for a novel GT method for SCI patients.

Methods: Cell reprogramming studies from Pubmed and Google scholar databases were used.

Results and discussion: More than 300 researches about GT were studied since 2010. Especially, DLR, which is called direct conversion, is emerging as a new approach to GT technology [6-10]. Neuronal DLR enables direct astrocytes or fibroblasts to get transformed into functional neurons (motor/sensory neurons, GABAergic neurons, dopaminergic neurons, etc) using a set of lineage-specific transcription factors [9,11-13]. More specifically direct converted induced Motor Neuronal (iMN) properties can be investigated using electrophysiological analysis [14].

What are new and conclusion: There exist many studies to accelerate the efficiency of direct lineage reprogramming. Using nanoparticles during the reprogramming process is one of the approaches. The other approaches can be co-transducing reprogramming master regulator, not lineage-specific transcription factor. These methods can be one of the solutions for GT of SCI patients.

What is known and objectives: Through Gene Therapy (GT), a gene can be planted into a specific cell and its expression can offer good therapeutic results by enhancing the lives of patients suffering from rare diseases, incurable diseases, and hereditary diseases [15-17]. GT uses genetic material in rectifying disease-causing mutations, by either suppressing the effect of the genes that contribute to disease or by delivering the gene encoding molecules that possess therapeutic quality [17-19]. Among the techniques of GT, virus-based GT has been widely used in clinical trials and currently, FDA has approved two marketing applications for AAV-based GT products and one *Lentivirus* based GT product. For AAV-based GT products, Luxturna (GT medication used to treat inherited retinal disease) was approved in, 2017 and Zolgensma (GT medication used for Spinal Muscular Atrophy (SMA)) was approved in 2019 [20-23].

Recent evidence proves that somatic cells can potentially be converted into specific cell types without going through a pluripotent state (stem cell state) through DLR, otherwise known as "trans differentiation or direct conversion". This technology was identified by Davis et al., who showed that mouse embryonic fibroblasts has the potency to get transformed into myoblasts by forced expression of transcription factor MyoD. However, a single factor is not enough for cellular reprogramming for most tissues. After the first report of the direct reprogramming, other transcription factors or combination of them were found to be capable of converting one cell type to another-for example, fibroblasts into neurons, cardiomyocytes, hematopoietic progenitor cells, and pancreatic beta cells. In the past three decades, a substantial body of research has shown that it is possible to manipulate cell fate by using combinations of transcription factors, microRNA (miRNA), small molecules and biocompatible materials. Currently, gene/cell strategies use the induction of lineage-specific progenitor cells (adult stem cells) or genes into the target cells and disease-responsive cell types hosting in the adult organ systems. *In vivo* GT using DLR technic can be a promising strategy to produce functional cells for degenerative disease therapy purposes.

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***Corresponding author:** Junsang Yoo, Cell Reprogramming and Stem Cell Research Center, Stand Up Therapeutics, Ilsin Building, Hannamdaero 98, Seoul, Korea, E-mail: dryoo0912@gmail.com

SCI leads to severe motor and sensory impairment below the point of injury [1]. Damage to the spinal cord mainly confounds signal transmission between the spinal cord and causes dysfunction and organ impairment. Many studies are underway to treat spinal cord injuries, but there are no effective treatments for these injuries yet. In this review paper, we introduced next-generation *In vivo* cell direct conversion-based GT for treatment of SCI recognized as one of the incurable diseases.

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Methods

We have searched Pubmed and Google scholar database for the investigation. The subject words were "cell reprogramming", "direct conversion", "gene therapy", "spinal cord injury", "master regulator", and "biocompatible nanoparticles". Filtered articles were sorted using their titles and abstract and with relevance of these relationships for motor neuron DLR were included to this review.

Results

Search results

Over >300 researches about gene therapy were studied from 2010. Among them 175 papers were published in which DLR method is used as a tool for degenerative disease therapy.

In vivo AAV2 gene therapy

Recently, many investigators have continuously been interesting in using viral vector for gene therapy due to their high efficacy of deliver to cells and expression [24]. The widely used viral vector for *ex vivo* is lentivirus and retrovirus, and *in vivo* are adenovirus, and Adeno-Associated Virus (AAV) [25,26]. Among them, AAV has many profits for gene therapy compared to other viral vector and widely used in *in vivo* clinical study due to their non-genomic integration and low toxicity including immunogenicity, mutagenesis, and genotoxicity [27]. The analysis of GT trials surfaced 149 clinical trials using AAV based viral vector. Among this 94 were already completed (mostly Phase I/II) and the remaining 51 reached the efficacy end point [25]. The former considered both safety and efficacy as two predominant end points, and significantly 80% of these researches were backed by industry based sponsors. Furthermore, the clinical trials using AAV2 serotype were mostly investigated continuously in its study period. The AAV2 found to be very safe and effective, as per 40 completed clinical trials. There are many clinical trials using AAV2 viral vector, which is shown in Table 1.

Central Nervous System (CNS) targeted AAV gene therapy

There are few Adeno-Associated Viruses (AAVs), like AAV2 and 9, which are capable of penetrating the CNS and transforming neurons following systemic delivery that enables the GT to emerge as a solution for disorders that were labeled untreatable, like the progressive Parkinson's disease and SMA. SMA is a generically acquired recessive neuromuscular disorder which leads to muscle atrophy and weakness due to reduction of motor neurons, severity of which depends on the allelic form related mutations in Survival Motor Neuron 1 (SMN1). As a therapeutic approach for SMA, Onasemnogene Abeparvovec (OGA) (formerly AVXS-101, Zolgensma®, Novartis GT EU limited, and Dublin, Ireland) is authorized to treat SMA in more than 40 countries globally. OGA is an AAV vector-based GT administrated through single intravenous introduction and prepared to introduce a functional copy of the human SMN gene penetrating the Blood Brain Barrier (BBB). GT has limitations and challenges while treating neural parts like brain, spinal cord, sense organs like eye, cochlea, as they are compartmentalized organs and possess natural barriers like the BBB that can potentially limit the access. This explains the advantage the Local Vector Administration (LVA) has over the intravenous introduction or through other fluid-filled compartments. Also the LVA retains the concentration and enhances the residence period of gene transfer agent positioning it near to the target cells thereby minimizing or preventing the wide biodistribution and limiting the risk possibility of immunogenicity or toxicities due to AAV components or ectopic expression of the transgene. LVA of AAV delivery (intraparenchymal injection) is appropriate method for eye and spinal cord like, local introduction to ophthalmic conditions had proved to have clinical advantages. This is because this offers the better access to surgery, better noninvasive monitoring of the prognosis of therapeutic interventions. Adding to this the compartmentalized nature of eye minimize the dosage and the systemic leakage of the vector.

Factors influencing iMNDLR

For the Spinal Cord Injury (SCI) patients, many researchers are struggling with find out the ideal way to treat. However, there is no therapeutic methodology for SCI yet. For SCI group, reactive astrocytes recruited in the injured site form a physical barrier called "astrocyte scar" and express molecules that inhibit axonal regeneration. Some studies investigated that early removal of astrocytes scars has been found to increase the size of lesion sites and reduce functional recovery in mouse model. Therefore, reactive astrocytes may be an ideal target for *in vivo* DLR (IVDR) to treat SCI. IVDR of fibroblasts or astrocytes into neurons or neuro blasts has previously been reported. The IVDR strategy for the treatment of CNS related disease is our ultimate goal and many studies investigated the various methodologies to accelerate DLR efficiency (Figure 1).

Treating adult mammalian spinal cord is more challenging than their brain due to the lack of neurogenesis I majority of spinal cord areas. Thus, there is a need for new strategies that can compensate for the lost motor neurons with induced Motor Neuron (iMNs), which is going to be the future of treatment advancement. The first proof for such iMNs advances is the *Brn2*, *Ascl1* and *Mytl1* with *Lhx3* (4TF

Table 1: Clinical trials using AAV2 viral vector.

No.	Name	Application	status	Phase	Identifier
1	AAV2-BDNF	Alzheimer's disease	Recruiting	Phase 1	NCT05040217
2	AAV2-GDNF	Parkinson's disease	Recruiting	Phase 1	NCT04167540
3	AAV2-hRPE65v2	Inherited retinal dystrophy	Active, not recruiting	-	NCT03602820
4	AAV2/5-RPGR	X-linked retinitis pigmentosa	Completed	Phase 1/2	NCT03252847
5	rAAV2.REP1	Choroideremia	Completed	Phase 2	NCT02671539
6	AAV2-REP1	Choroideremia	Completed	Phase 2	NCT02553135
7	AAV2hAQP1	Squamous cell head and neck cancer radiation induced xerostomia salivary hypofunction	Recruiting	Phase 1	NCT02446249
8	AAV2-hCHM	Choroideremia	Active, not recruiting	Phase 1/2	NCT02341807
9	rAAV2.REP1	Choroideremia	Completed	Phase 1/2	NCT02077361
10	AAV2-GDNF	Parkinson's disease	Completed	Phase 1	NCT01621581
11	AAV2-sFLT01	Macular degeneration	Completed	Phase 1	NCT01024998
12	AAV2-NTN	Parkinson's disease	Completed	Phase 1	NCT00252850

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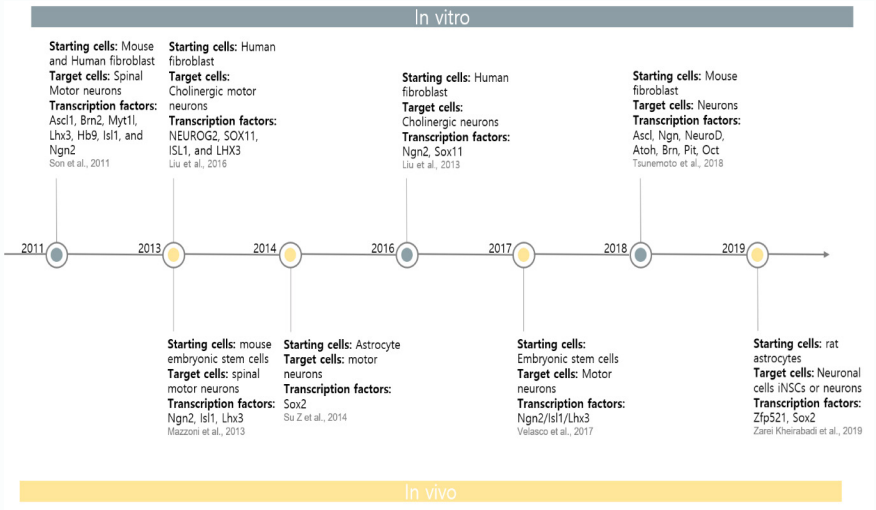

Figure 1: Various methodologies to accelerate DLR efficiency.

cocktail) and *Neurog2*, *Hb9*, or every genes with Isl1 (5TF cocktail) in adult rodent tail tip fibroblasts [28]. The 4 and 5 TF-induced MNs produced action potential and formed a neuromuscular junction according to Son and his colleagues in 2011. Mazzoni and his team in 2013, tried to improvise with 3TF Cocktails (3TFC) with the help of Neurog2, Isl1, and Lhx3. The 3TFC was introduced into the mouse embryonic stem cells to induce differentiation of iMNs [29]. Based on these results, it was possible to know deeply about the same TF that induced MN differentiation. Velasco et al. [30] in 2017 illustrated that there are two steps in which Neurog2, Isl1, and Lhx3 first bind to the same transcriptional region, and then Lhx3 and Isl1 bind to the new regulation site in the genome to trigger differentiation. To apply these advances among human fibroblasts, 4 TFs were required to generate a functional choline iMNs: NEUROG2, SOX11, ISL1, and LHX3 as per the research work of Liu et al. [31]. Interestingly, Liu et al. [31] proved that although NEUROG2 alone when symbiosed with small size molecules can initiate the acquisition of a cholinergic iMN fate, giving no consideration to MN markers (ISL1, LHX3) [31]. These studies demonstrate that there are number of different TFs exist that can initiate conversion of the iN system in fibroblasts. These results were further strengthened by large screening of 598 TFs that found 76 TF pairs capable of generating iN [32]. Therefore, it can be seen that the type and design of TF are very important for the formation of iMN *in vivo*.

Additionally, previous studies reported that resident astrocytes can be reprogrammed into functional motor neurons using single transcription factors in SCI. Su et al. [33] investigated that SOX2 can induce the conversion of resident astrocytes to doublecortin (DCX)-positive neuroblast. Also, Zarei-Kheirabadi et al. [34] demonstrated that the expression of ZFP521 reprograms astrocytes into induced iNSCs or iMNs and restores motor function and in SCI rat model.

Neuronal DLR accelerator

Recently, many research groups demonstrated the various methods to accelerate neuronal DLR. The table below shows the various type of DLR accelerator: small molecules, miRNA and biocompatible materials: nanoparticles. Especially, Yoo et al. [14] and his group investigated the specific method to boost up the dopaminergic neuronal DLR from astrocyte. They have revealed that gold nanoporous rod accelerates astrocyte into dopaminergic neuron *in vivo* DLR by controlling the ROS level and optimize the cell stress and its function. From this research, it has been revealed that efficiency of DLR can be controlled by ROS and cellular stress (Table 2).

Discussion

The field of DLR has gone through significant development in recent years making it possible to directly convert the differentiated mature cells into a range of other cell, through bypassing an intermediate pluripotent state. The approach to turn non-neuronal cells into neurons was inspired by the powerful role of the Transcription Factor (TF) (Table 3). Direct neural reprogramming was initially achieved through the overexpression of the transcription factors Ascl1, Brn2 (also called Pou3f2), and Myt1l [38]. These three factors converted fibroblasts to neurons with the ability to express neuronal marker and form functional synapses. Further research illustrated that the production of human induced-neuron (iNs) by ASCL1, BRN2, MYT1L and NEUROD1. NEUROD1 plays a vital part in neuronal development. In particular, human iN that has the ability to synapse and possess a functional profile. Soon thereafter, non-neurogenic cell, like astroglia, glial cells and pericytes, shall be transformed into functional neurons as well. The Transcription Factors (TF) was enough to direct astroglia towards a glutamatergic or GABAergic neuron. There are similar researches that have extended TF that have reprogramming capacity, resulting in the production

Table 2: Efficiency of DLR can be controlled by ROS and cellular stress.

Species	Starting cells	Target cells	Materials	Efficiency	Reference
Mouse	Fibroblast	Dopaminergic neurons	Electromagnetized gold nanoparticles	~ 55 %	[9]
Mouse	Fibroblast	Dopaminergic neurons	Electromagnetized graphene nanosheet	~ 20 %	[35]
Mouse	Fibroblast	Dopaminergic neuron-like cells	Mesoporous silica nanoparticles	~ 81 %	[36]
Mouse	Fibroblast	Dopaminergic neurons	Elongated nanoporous gold nanorod	~ 40 %	[14]
Human	Fibroblast	Neuron	Polymer-functionalized Nanodot	~ 40 %	[37]

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of other neuronal subtypes, such as dopaminergic neurons, motor neurons or intermediate spiny neurons. For instance, Caiazzo et al. [39] have showed that fibroblasts of the mouse and human can be potentially reprogrammed into dopaminergic neuron suing Ascl1, Nurr1, and Lmx1a. The induced dopaminergic neurons exhibited functionally similar to dopaminergic neurons. Interestingly recent literature strengthens the feasibility of utilizing miRNA for direct reprogramming. Similar to transcription factor, combination of miRNAs can reprogram into functional neuron from fibroblasts. Furthermore, transcription factors can enhance the role of miRNA in neural reprogramming. For example, miR-9/9* and miR-124 with other TF, ISL1 and LHX3, enhancing the reprogramming of fibroblastic cells in to a motor neurons [40]. All together these evidences underline the vital role of TF and miRNA in determination of neuronal cell fate.

Brain has limited capacity to repair and replace the damaged neurons. Hence to intervene CNS disease, there is a necessity of other cell which is the sources for repair. IVDR is an emerging area which attracts more research attention as it is a potential therapeutic prospect. To conduct IVDR in Brain, correct targeting of specific cell population is inevitable. To control the final cell type of *in vivo* reprogramming for therapeutic approaches for CNS disease, using AAV is adequate method for the optimal therapy.

However, the combination of TFs and other combinations illustrated less success in reprogramming the adult human and mouse fibroblasts, limiting the clinical translation of this intervention. During the last ten years significant effort has been dedicated to optimizing reprogramming cocktails comprised of transcription factors, epigenetic factors, microRNAs, small molecules, or biocompatible materials to yield efficient cell fate conversion.

What is new and conclusion?

Cell fate conversion using virus system is of great interest in the field of GT. The reason that cell fate conversion method including DLR is because it's low efficiency. Many researchers have been trying to investigate the method to accelerate the reprogramming efficiency from decade ago. Recently, couple research groups have revealed that specifically modified nanoparticles: gold nanoporous rod can boost up the reprogramming efficiency by activating cell master regulators: Gsta4, Mt3, Sod1, Cox6b2, Sirt3, etc [14]. Incorporation of these master regulators into neuronal reprogramming may open a new era for neurological disease such as PD, AD and SCI (Figure 2).

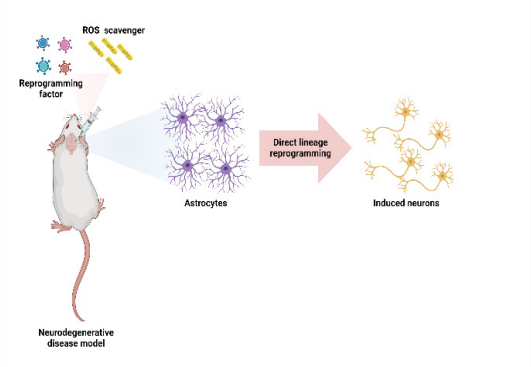

Figure 2: The master regulators into neuronal reprogramming.

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