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# Research progress on the differentiation and apoptosis mechanisms of A9 dopaminergic neurons derived from stem cells and their regulation

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**Abstract.** Current Parkinson's Disease (PD) treatments alleviate symptoms but do not halt progression from degeneration of A9 dopaminergic neurons in substantia nigra pars compacta. Human induced Pluripotent Stem Cells (iPSCs)-based cell replacement therapy has emerged as a promising therapy to PD, but it still faces two significant challenges. One of them is that it is difficult to generate sufficient high-purity and functional A9 neurons effectively; the other is that transplanted neurons readily perish in the hostile brain milieu, which significantly suppresses therapeutic actions. This review presents the fundamental molecular pathways regulating the differentiation of human iPSCs into A9-type dopaminergic neurons in a directional manner. It addresses the systematic control of Shh, Wnt/β-catenin, and SMAD signal transduction, and significant transcription factors such as FoxA2, Lmx1a/b, Nurr1, and Pitx3, a collective of which plays a crucial role in defining the distinct molecular attributes of the A9 neurons. Two practical and efficient differentiation protocols are summarized: a pretreatment system using three small molecules based on CTraS, and an optimized induction strategy targeting SHH/Wnt signaling pathways. Moreover, this review illustrates the fundamental mechanism of neuron apoptosis focusing on mitochondrial pathway and details two viable approaches to enhance the anti-apoptotic ability of A9 neurons via activating Nur77-PARL-BCL-2 signal pathway and enhancing expression of miR-221. Finally, the new concept of functionalization based on efficient differentiation and anti-apoptotic modification proposed in this review is expected to yield ideal high-yield, purity and survival robust A9 neurons. This review refers to theoretical delivery and clinical strategies for stimulating the use of iPSC-based PD cell therapy.

**Keywords:** Parkinson's disease, stem cell, A9 dopaminergic neuron, differentiation, apoptosis

## 1. Introduction

Parkinson's Disease (PD) has a prevalence of approximately 1% in individuals over the age of 60. The primary clinical manifestations in patients include bradykinesia, impaired movement, postural instability, muscle rigidity, and resting tremor, which significantly reduce quality of life.

Presently, PD has no cure, and treatment methods primarily aim to alleviate the symptoms and not prevent disease development [1]. To counter this, cell replacement therapy using transplantation of new dopaminergic

cells, has been explored as a promising means of altering disease course.

With the progress of stem cell biology, the human IPSCs have come to be seen as an extremely promising and acceptable source of these transplantable cells. By carefully manipulating some growth factors and signaling molecules, researchers have devised ways of inducing these stem cells to differentiate into the desired type of midbrain dopaminergic neuron that is destroyed in PD.

Nonetheless, there are two large challenges. First, there are still challenges in current approaches to the production of such specific neurons; efficient production of a large and highly pure population of cells that is functionally relevant is a technical challenge [2]. Second, although the desired cell type has been successfully cultured in vitro, a significant number of them apoptose once implanted into the brain of the patient because of the hostile brain microenvironment, which significantly impairs the effectiveness of the therapy [3].

Thus, a thorough understanding of the regulatory processes of A9 neuronal differentiation and apoptosis, optimization of high-efficiency differentiation regimens, and augmenting the anti-apoptotic homeostasis of neurons are of paramount importance in promoting treatment on the basis of stem cell in PD. The two main aspects of this review are: the molecular processes that control A9 neuronal differentiation and apoptosis and the corresponding procedures. The review also outlines the latest developments and suggest that refinement of anti-apoptotic signaling during stem cell differentiation could yield the production of optimal A9 neurons that would be both high differentiation efficiency and robust post-transplantation survival, thus offering new insights into the development of cell therapies to treat PD.

## 2. Key molecular mechanisms underlying the efficient differentiation of human iPSCs into A9-subtype dopaminergic neurons

Recent studies required accurate recapitulation of development of ventral midbrain floor plate to obtain A9-subtype dopaminergic neurons using human iPSCs. The synergy of Sonic Hedgehog (Shh) and Wnt/b-catenin signaling pathways at the stage is controlled by this process.

The Shh pathway activates ventral specification and is critical to induce a midbrain floor plate fate, upregulating major transcription factors such as FoxA2, Lmx1a/b and Nurr1 [4]. At the same time, the proper Wnt/b-catenin pathway activation, often with GSK3 inhibitor CHIR99021, is essential to form midbrain identity by enhancing the expression of midbrain-specific markers such as OTX2 and EN1, and inhibiting alternative fates [5].

Newer research has enriched knowledge on SMAD signaling. Although dual SMAD inhibition is a common approach to induce neural development, the BMP/SMAD signal pathway per se plays a crucial role in midbrain dopamine neuron development, which cannot be ignored. Hence, it is possible to increase the expression of A9-subtype-defining genes, such as PITX3, GIRK2, and ALDH1A1, by optimizing the length of SMAD inhibition-such as by making it shorter [6].

After patterning, the terminal maturation and the A9-subtype differentiation is performed by transcription factors Nurr1 and Pitx3. Nurr1 plays a crucial role in the regulation of the dopaminergic gene battery, such as, Tyrosine Hydroxylase (TH), the Dopamine Transporter (DAT), and Vesicular Monoamine Transporter 2 (VMAT2) [7].

Pitx3 works together with Nurr1, plays a role in mediating the expression of A9-enriched enzyme ALDH1A1, and it is also involved in the establishment of the final GIRK2+/CALBINDIN-molecular signature of A9 neurons [8]. The sequential, stage-selective timing of signaling pathways and transcription factors constitutes the underlying logic that is utilized by later high-efficiency differentiation plans.

## 2.1. Efficient differentiation method 1: CTraS-based neurosphere system pretreated with three small molecules

The first efficient differentiation approach is a new system that is founded on CTraS (chemically transitional embryoid-body-like state) chemical pretreatment and neurosphere culture that provides a breakthrough in generating high-purity midbrain dopaminergic progenitor cells without flow cytometry sorting [9].

Day 0 to Day 5 Researchers start by pre-treating human iPSCs with three small molecules, including SB431542 that is a TGF-b/SMAD inhibitor, Dorsomorphin that specifically inhibits the BMP signaling, and CHIR99021 that is a GSK3 inhibitor and capable of activating the Wnt/b-catenin pathway as early.

These three molecules work together to quickly drive the iPSCs into a CTraS that not only makes the neural specification process faster, but also efficiently removes the undifferentiated iPSCs that can lead to tumorigenicity of later transplantation at the source [9].

Following the pretreatment, Day 5-19, cells are grown as single-cell suspensions to produce primary neurospheres, which is a recreation of the aggregated microenvironment of neural precursor cells within the body [9]. On Day 8, there is a critical junction point where the identity of the midbrain anteroposterior axis is achieved by continuous stimulation of the Wnt pathway by CHIR99021 and the ventralization of cells and attainment of floor plate fate is induced by Purmorphamine (PM) as a Shh pathway agonist.

High-purity midbrain dopaminergic progenitor cells can be consistently obtained on Day 19 after induction using this system [9]. Their molecular core has been confirmed by immunofluorescence/qPCR: the positivity rates of core transcription factors like FOXA2 (79.2 ± 2.11%), LMX1A (88.2 ± 2.63%), and NURR1 (98.0 ± 0.79%) all over 80%; the positivity rates of clinically relevant sorting surface mark.

These cells exhibit strong EN1 expression and weak FOXG1/SIX3 and HOXB4 expression. This profile definitively excludes contamination from forebrain, hindbrain, or spinal cord lineages and confirms, with 100% fidelity, a ventral midbrain dopaminergic progenitor cell fate.

In in vitro maturation culture using these progenitor cells, they are able to effectively differentiate into TH+ functional A9 neurons [9]. In transplantation of 6-OHDA-induced PD model mice, more than 90% of the transplanted cells differentiate into dopaminergic lineage, with about 14% of these developing into A9 dopamine synthesis and release functions that drastically reduced apomorphine-induced rotational behavior of the animals, without the formation of teratoma post-transplantation [9].

It is easy to use, highly scalable, reproducible and does not require complex sorting procedures and therefore, it is cost-effective in clinical translation and is an effective differentiation protocol that can be used in the preparation of clinical-grade cells [9].

## 2.2. Efficient differentiation method 2: precision optimization of SHH and Wnt pathways for generating functional A9 pacemaking neurons from iPSCs

The second effective differentiation approach involves an optimized SHH and Wnt signaling approach tailored to the epigenetic memory property of human iPSCs, namely, to induce mature A9-type dopaminergic neurons with natural autonomous pacemaking activity [6]. Such approach tackles the bottlenecks of low differentiation efficiency and immaturity of conventional floor plate approaches in iPSCs [6].

Conventional floor plate differentiation approaches are primarily established on human ESCs; the epigenetic memory of iPSCs means that they are much less sensitive to the ventralizing signal Shh, and thus do not differentiate into floor plate markers such as FOXA2 and CORIN, and fulfill their differentiation with only 56% efficiency [6].

To address this challenge, the approach executes three fundamental optimizations: First, Shh pathway refinement-recombinant Shh protein is substituted with Purmorphamine and its concentration is elevated to 3

μM depending on the nature of iPSCs, greatly boosting the strength of Shh pathway activation, which effectively promotes the expression of FOXA2 and CORIN, and suppresses the forebrain marker.

Second, accurate control of Wnt pathway-CHIR99021, being a GSK3 inhibitor, is strictly regulated at a dose of 0.8 μM that is capable of stabilizing the Wnt pathway to preserve the expression of midbrain-specific genes including OTX2, SOX6, and LMX1A/B, without hindbrainization that occurs when the dosage is higher than 1.

Third, there is an optimization for duration of SMAD inhibition—traditional dual SMAD inhibitors (SB431542 + Dorsomorphin) have a time of action of 9 days, which is now reduced to 6 days [6]. Research has confirmed that the BMP/SMAD pathway is crucial for the development of midbrain dopaminergic neurons, and the inhibition for a longer duration results in decreased expression of essential transcription factors such as FOXA2, CORIN, LMX1B, and PITX3. However, a 6-day inhibition period is sufficient to effectively start neural induction, and sustain the pathway's activity in promoting dopaminergic specification in midbrain neurons, which is a critical factor in improving the efficiency of differentiating iPSCs to match that of ESCs [6].

Also, the technique further prolongs the ventral midbrain specification phase to Day 16 (traditionally only 9 days) to permit the sustained activity of PM and CHIR99021 to sustain the high expression of genes including FOXA2, CORIN, LMX1A/B, and PITX3, finally achieving homogeneous midbrain floor plate dopaminergic progenitor cells.

On Day 20, BDNF + GDNF + TGFb3 are induced to stimulate the differentiation of dopaminergic neurons, dcAMP is induced to increase ion channel expression, DAPT is inhibited to stimulate neuronal differentiation and inhibit glial cell formation, and PM and CHIR99021 are progressively removed [6].

After induction under this protocol the overall purity of the mature neurons on Day 60 are excellent: TuJ1+ is 98% and MAP2+ is 95.7% and the percentage of TH+ neurons is as high as 72.5 +14.3, with high A9 subtype selectivity: GIRK2+ and ALDH1A1A1+ are both over.

More to the point, these neurons recapitulate the fundamental functional properties of the natural A9 neurons in electrophysiology: L-type Ca 2 channel dependent spontaneous action potentials (frequency of about 5 Hz) can be recorded Day 80-120 and they are not inhibited by DNQX or AP5, but can be fully blocked by Nimodipine and TTX.

The transplantation of Day 37 A9 dopaminergic precursor cells into the striatum of athymic rats with medial forebrain bundle lesions induced by 6-OHDA leads to the survival of human-derived cells and the formation of extensive nerve fibers, which are capable of integrating into the host striatal neural network, and significantly improves the rotational behavior of the animals and the retention time The motor function recovery effect is far much better than the conventional protocols, and as such it is the most effective differentiation strategy to date that is used to produce neurons that are closely related to endogenous A9 neurons [6].

## 3. Core molecular mechanisms underlying the enhanced anti-apoptotic capacity of A9 dopaminergic neurons

The pathology of the PD brain has an extremely high apoptotic vulnerability of A9 dopaminergic neurons, and their central mechanism is highly concentrated on the abnormal activation of the intrinsic mitochondrial apoptotic pathway, with multiple regulatory axes functional disorders [10].

In neurons, the ratios between pro-apoptotic and anti-apoptotic signals are disturbed under a variety of pathological conditions including cumulative oxidative stress, structural and functional damage to

mitochondria, and calcium overload: the amount of the pro-apoptotic factors Bim and Bax increases substantially, with Bax translocating to the mitochondrial membrane where he forms pores.

This eventually causes the opening of the mitochondrial permeability transition pores and discharge of cytochrome c into the cytoplasm out of the mitochondrial matrix [10-12]. The free cytochrome c binds Apaf-1 to create apoptosomes, which then activate caspase-9 to set off the apoptotic cascade reaction and eventually cleave downstream substrates using caspase-3, leading to the condensation of nuclear chromatin and the fragmentation of DNA, and neuronal apoptosis [10].

In the meantime, important regulatory defects in pathological conditions further enhance the apoptotic signal: stress-induced shuttling of Nur77 between the nucleus and the mitochondria is impaired, and the concentration of PARL, which is one of the essential proteins on the mitochondrial membrane, decreases; the two do not create a functional complex to stabilize BCL-2 and prevent Bax activation [11].

Also, the dramatic down-regulation of miR-221 frees its post-transcriptional suppression of the pro-apoptotic Bim protein, which is then over-accumulated, and further enhances the mitochondrial apoptotic pathway activation [12].

Thus, the very key to improving the anti-apoptotic capability of A9 neurons is to precisely adjust the expression of the above mentioned molecular nodes: by increasing the expression of those anti-apoptotic molecules, blocking the major members of the pro-apoptotic pathways, and stabilizing the mitochondrial structure and functioning, and in particular, by balancing the Nur77-PARL-BCL-2 axis and the miR-221-Bim-Bax axis.

### 3.1. Method 1 for enhancing A9 neuronal resistance: activating the Nur77-PARL-BCL-2 pro-survival signaling cascade

Activation of Nur77-PARL-BCL-2 mitochondrial pro-survival cascade is the first key approach to increasing the anti-apoptotic capabilities of A9 neurons. Being one of the primary endogenous defense systems to ensure the survival of dopaminergic neurons, the malfunction of this regulatory module is a major left in selective degeneration of A9 neurons in PD [11].

The level of PARL (Presenilin-associated rhomboid-like protein) in the plasma and the substantia nigra of the patients under the pathological condition of PD is significantly reduced [11]. Being a major regulatory protein on the mitochondrial membrane, the lack of PARL directly inhibits the stable binding and protection of the anti-apoptotic protein BCL-2, leading to an increased degradation rate and reduced functional activity of BCL-2 [11].

This approach does not adequately suppress the activation and mitochondrial translocation of the pro-apoptotic protein Bax. Consequently, Bax undergoes oligomerization, leading to increased mitochondrial membrane permeability, activation of caspase-3 via cleavage, and the induction of apoptosis in A9 neurons [11].

Research has established that the orphan nuclear receptor Nur77 is a molecular switch, which trafficks between the nucleus and the mitochondria in reaction to pathological stress [11]. It directly binds to PARL to construct an active complex to stabilize the binding affinity between PARL and BCL-2 to a large extent, stabilizing the protein concentration and anti-apoptotic form of BCL-2, preventing Bax activation and the development of mitochondrial membrane pores, and eventually preventing the initiation of the mitochondrial apoptotic pathway [11].

In order to activate this pathway, the Nur77-specific agonist Csn-B (Cytosporone B) has been found to highly induce the translocation efficiency of Nur77 into the mitochondrion, its binding affinity with PARL and additional stability of the PARL-BCL-2 complex [11]. It is able to dramatically increase BCL-2 protein

content, decrease the amount of Bax and active caspase-3, and successfully suppress A9 neuronal apoptosis in both cellular and animal models [11].

Mechanism validation experiments have demonstrated that when PARL is knocked down using shRNA, Nur77 is no longer able to stabilize BCL-2 and that its neuroprotective response is completely abolished, which directly demonstrates that PARL is a core mediator that can not be rescued by this pathway [11].

Moreover, clinical studies prove that the plasma PARL level in patients with PD is significantly lower as compared to control participants. This protein level exhibits a strong negative relationship with severity of disease (H&Y staging, UPDRS score), and a positive relationship with cognitive function (MMSE score), implying that PARL not only plays a crucial role in regulation, but also could be used as a biomarker to assess treatment outcomes [11].

The main benefit of this approach is that it is not based on gene editing technology, but merely triggers the endogenous protective pathway with small-molecule agonists, with high safety, low immunogenicity, and high compatibility [11]. It can be directly incorporated into the stem cell directed differentiation system- by aligning Nur77-PARL-BCL-2 axis activation with the critical phase of A9 neuronal differentiation, it can not only guarantee the normal differentiation efficiency and functional maturation of neurons, but also considerably increase their anti-apoptotic capacity and survival under pathological conditions of the PD brain, which is a safe and efficient approach to clinical translation [11].

## 3.2. Method for enhancing A9 neuronal resistance via miR-221 overexpression: inhibition of the Bim-Bax-caspase-3 apoptosis pathway

The second important strategy for increasing the anti-apoptotic ability of A9 neurons involves overexpressing miR-221. This leads to a broad increase in neuronal resistance due to the specific targeting and inhibition of the Bim-Bax-caspase-3 pro-apoptotic pathway, in conjunction with an increase in anti-oxidative stress ability [12].

It has been clearly established in clinical studies that miR-221 levels in plasma as well as in the substantia nigra pars compacta of patients with PD are markedly reduced, and that the extent of its suppression is positively related to the death of A9 dopaminergic neurons, closely linked with PD disease progression, suggesting that miR-221 deficiency is a significant contributor to neuronal apoptotic vulner.

At the mechanistic level, both bioinformatics prediction and luciferase reporter assays have verified that miR-221 can directly bind to the 3'UTR region of the pro-apoptotic protein Bim using its seed sequence, which directly inhibits the translation and expression of Bim protein and its downstream apoptotic cascade response mediated by Bim [12].

Since Bim is a pro-apoptotic Bcl-2 family member, its inhibition can greatly decrease the oligomerization and translocation of Bax to the mitochondrial membrane, and thus the chance of mitochondrial permeability transition pore formation. This further reduces cytochrome c leakage out of mitochondria and eventually inhibits the proteolytic maturation of caspase-9 and caspase-3, thus preventing the spread of apoptotic signals [12].

The upregulation of miR-221 via lentivirus or adeno-associated virus in Parkinson disease models induced by 6-OHDA exposure can partially reverse the loss of TH-expressing dopaminergic cells and increase the level of dopamine in the striatal area and confer a dual protective effect of anti-apoptosis and anti-oxidation [12].

Vital validation experiments have demonstrated that when a Bim overexpression plasmid is co-transfected whilst overexpressing miR-221, the neuroprotective effect of miR-221 is fully overturned, the number of TH-positive neurons reduces yet again, and the percentage of apoptotic cells increases in tandem directly confirming that Bim is the critical downstream effector by which miR-2 acts.

The specificity of action, target effects, and high safety: miR-221 can only perform its activity by post-transcriptional control, and does not form abnormal proteins, without causing the off-target effects of gene editing; miR-221 can be stably expressed in a variety of ways, including lentivirus, adeno-associated virus, or small-molecule mimics, and can adapt to different.

Reconstitution of the miR-221 overexpression approach into the iPSCs directed differentiation system can maintain the overhead of the apoptotic signal during the entire differentiation of A9 neurons, and allow the neurons to remain at high survival rates during the preparation, purification, transplantation and intracerebral integration phases without affecting the specification of the midbrain floor plate or the molecular phenotypic maturation.

Ultimately, this approach achieves an optimal balance between effective neuronal differentiation and strong resistance to cell death. Consequently, it provides a promising source of cells for stem cell–based replacement therapies targeting Parkinson's disease [12].

## 4. Conclusion

To conclude, maturing of A9-type dopaminergic cells and enhancing their survival in adverse pathological microenvironment are two key pillars of successful PD-related cellular replacement therapy. By carefully controlling Shh, Wnt and SMAD signaling, current protocols have facilitated differentiation of iPSCs to A9 fate with high purity and high efficiency. At the same time, two different types of anti-apoptotic approaches, Nur77-PARL-BCL-2 axis activation, and miR-221 overexpression have been confirmed to be effective to inhibit mitochondrial apoptosis and promote neuronal survival.

Drawing from the progress described above, the review presents a novel and clinically relevant hypothesis: It may be possible to generate A9 dopaminergic neurons that are characterized by both high differentiation efficiency and significant post-transplant survival ability by integrating high differentiation efficiency protocols, anti-apoptotic engineering at the stem cell level, and A9 dopaminergic neurons.

For instance, in CTraS-based or SHH/WNT-optimized differentiation, simultaneous activation of the Nur77-PARL pathway or stable overexpression of miR-221 can prevent A9 neurons from undergoing apoptosis during differentiation, maturation, and after transplant integration. These engineered neurons would maintain high purity and true functional phenotypes, and also be able to tolerate oxidative stress, mitochondrial dysfunction, and apoptosis in the Parkinsonian brain.

This combinatorial strategy is anticipated to address the persistent issue of low graft survival rates. Consequently, it could significantly enhance the efficacy, safety, and potential for clinical translation of stem cell-based therapies for Parkinson's disease.

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