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Direct conversion from skin fibroblasts to functional dopaminergic neurons for biomedical application

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Abstract

Recent progress in tissue engineering research led to the generation of different types of cells from a handful of skin tissue. Lineage reprogramming is a nascent field, which holds great potential to expand its use in regenerative medicine and disease modeling. The concept of somatic cell epigenetic stability has been fundamentally reshaped through the report of direct conversion of somatic identity to another lineage by introducing transcription factors. Here, we review recent advances in lineage reprogramming research, especially direct conversion into dopamine neurons from fibroblasts.

Keywords: Direct conversion, Dopamine neurons, Fibroblasts and iPSC

Background

Parkinson's disease (PD) is a movement disorder that is caused by chronic and progressive degeneration of midbrain dopamine (mDA) neurons in substantia nigra of brain (de Lau and Breteler 2006; Betarbet et al. 2000). Because there is no cure for PD patients, researchers have developed alternative ways to cure PD using cell-based transplantation therapy (Barker et al. 2015; Olanow et al. 1996). Fetal cell transplantation demonstrated that cell-based transplantation therapy is a viable therapeutic approach, showing improvement of PD-related symptoms in some patients (Mendez et al. 2005; Li et al. 2008; Kordower et al. 1996; Kordower et al. 1998; Kordower et al. 2008; Hagell et al. 1999). However, there are significant shortcomings including ethical, technical, and practical issues, as well as variable ranges in effectiveness (Olanow et al. 2003; Freed et al. 2001). After introduction of induced pluripotent stem cell (iPSC) technology by Shinya Yamanaka and his colleagues a decade ago, patient-derived iPSCs have been extensively investigated to generate functional autologous mDA neurons for clinical and research use (Takahashi and Yamanaka 2006; Tapia and Scholer 2016; Takahashi and Yamanaka 2016; Li and Izpisua Belmonte 2016; Karagiannis and Eto 2016; Mertens et al. 2016; Hotta and Yamanaka 2015). Consequently, concept of iPSC generation that somatic tissues can be reprogrammed to early embryonic-like cells by transcription factors raised the question of whether transcription factors could reprogram somatic cell differentiation. This concept was originally demonstrated by the conversion of fibroblasts into myoblasts by introducing expressing plasmid containing *MyoD* (Davis et al. 1987). Subsequently, introduction of transcription factors induces direct conversion of different cell types: (1) glial cells into neuronal cells, (2) liver into pancreas, and (3) B cells into macrophages (Heins et al. 2002; Kulessa et al. 1995; Shen et al. 2000; Xie et al. 2004). Moreover, induction of neuronal cells from fibroblasts using defined transcription factors showed that the direct conversion could be manipulated across different germ layers (Vierbuchen et al. 2010). Transcription factors known to serve crucial roles in dopamine neuron specification and maturation are required for direct conversion of dopamine neurons from fibroblasts (Caiazzo et al. 2011; Pfisterer et al. 2011; Kim et al. 2014; Kim et al. 2011). Subsequently, combination of microRNA (miRNA) and small molecules are being investigated along with the key transcription factors to generate efficient and non-viral integrating neurons (Yoo et al. 2011; Jiang et al. 2015; Lau et al. 2014) (Fig. 1). In this review, we discuss the recent research progress of the direct conversion from fibroblasts to mDA neurons.

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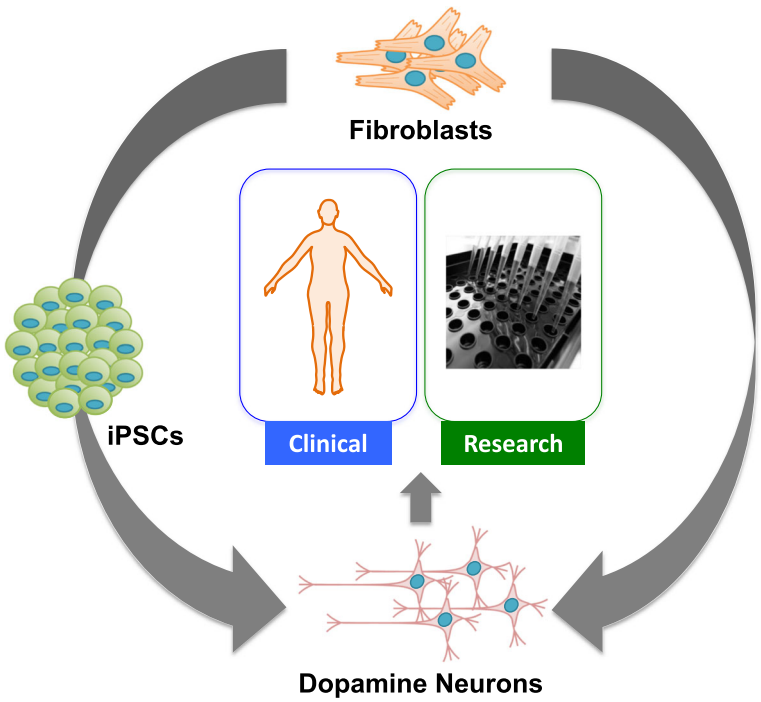

Fig. 1 Schematic comparison between iPSC technology and direct conversion to generate DA neurons from skin fibroblasts in vitro for biomedical application. IPSC geneartion requires a forced expression/induction of reprogramming factors or small molecules. Several differentiation protocols provide robust yields of DA neurons highly resembling DA neuron characteristics with effective recovery of animal PD model. Direct induced dopamine neurons are derived from skin fibroblasts, which minimizes undesired differentiation potential and risks for teratoma formation

Key transcription factors during dopamine neuron development

Mash1 (also known as achaete-scute homolog 1, Ascl1)

Mash1 (mammalian achaete scute homolog-1) is a pro-neural transcription factor, which serves multiple roles in neuronal commitment. In brain development, neurogenesis is an essential process that drives neural progenitors into functional differentiated neurons. This neurogenesis is coordinated by pro-neural transcription factors including Mash1, Ngn1, and Ngn2. Especially, Mash1 is responsible for the neuronal cell specification, by binding with other neural pro-neural genes such as Ngn1 and Ngn2 (Parras et al. 2002; Cau et al. 2002). In sympathetic ganglia, Mash1 facilitates noradrenergic neuron differentiation by inducing expression of the homeobox gene Phox2a and the noradrenaline-synthesizing enzyme dopamine β-hydroxylase 1 (DBH1) (Lo et al. 1998; Hirsch et al. 1998). In the neuroepithelium of the hindbrain, Mash1 is indispensible for the differentiation of central serotonergic neurons (Pattyn et al. 2004). Genome-wide analysis of Mash1-mediated target genes in neural tube during murine embryogenesis revealed that Mash1 directly regulates numerous genes involved in proliferation, differentiation, and maturation of neurons by binding to the specific sequence, E-Box motif (CAGCTG) (Borromeo et al. 2014). Indeed, Mash1-deficient mice exhibit a severe loss of neural progenitors in the subventricular zone and abnormal ventral forebrain differentiation (Casarosa et al. 1999; Horton et al. 1999). Therefore, Mash1 is an important transcription factor, which promotes the neural lineage differentiation and context-dependent proliferation (Vasconcelos and Castro 2014).

Lmx1a and Foxa2

During early brain development, mDA neurons are derived from the ventral midline of the mesencephalon by the combined action of morphogen molecules and transcriptional factors. The initial event of mDA neuron development is regulated by sonic hedgehog (SHH) and wingless-related MMTV integration site 1 (Wnt1) (Arenas et al. 2015). The morphogen, SHH, directly induces the expression of *Foxa2* in the ventral mesencephalon (VM) at embryonic day 8 (E8). Foxa2 regulates the extent of neurogenesis of mDA progenitors by inducing *Ngn2* (Neurog 2) and sequentially differentiates immature mDA neurons by inducing *Nurr1* (Sasaki et al. 1997; Ferri et al. 2007) (Fig. 2). Meanwhile, the glycoprotein Wnt1 secreted from midbrain-hindbrain border (MHB) directly induces the expression *Lmx1* through the β-catenin complex. Lmx1 sequentially induces the expression of *Nurr1* and *Pitx3* for mDA neurons differentiation (Chung et al. 2009; Wurst and Prakash 2014) (Fig. 2). Therefore, transcriptional activity of Lmx1 and

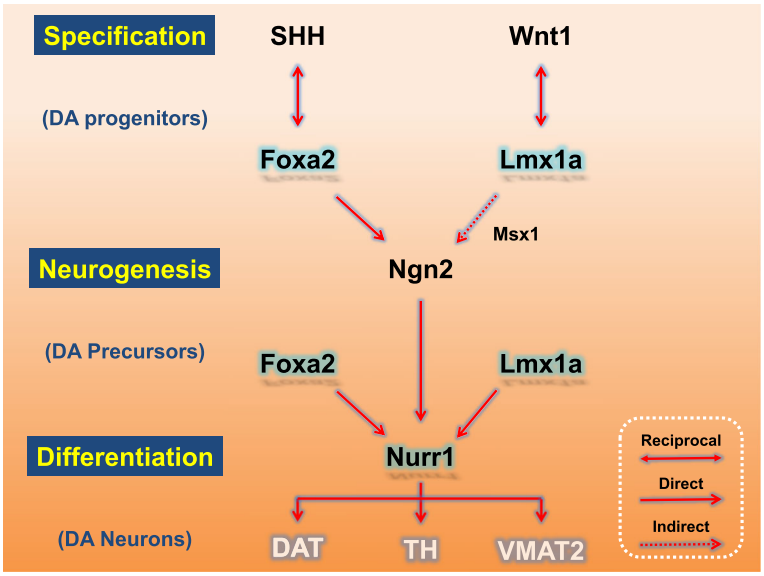

Fig. 2 Schematic interactions between transcription factors and morphogen molecules in the process of the specification, neurogenesis, and differentiation of mDA neurons. Two secreted morphogen molecules (SHH, Wnt1) control the patterning of dopaminergic progenitors through a reciprocal induction of Foxa2 and Lmx1a transcription factors. Subsequently, essential proneural gene, Ngn2, is induced by directly Foxa2 and indirectly Lmx1a (through Msx1) to promote the neurogenesis of dopaminergic precursor cells. Meanwhile, the sustained expression of Foxa2 and Lmx1a begins to induce the dopaminergic differentiation by increasing Nurr1 transcription. The evoked Nurr1 directly leads to the expression of various essential enzymes and transporters in dopaminergic differentiation. The abbreviated designations are the following: sonic hedgehog (SHH), wingless-related MMTV integration site 1 (Wnt1), Msh homeobox homolog (Msx1), neurogenin 2 (Ngn2), nuclear receptor-related factor 1 (Nurr1), dopamine transporter (DAT), tyrosine hydrolase (TH), and vesicular monoamine transporter 2 (VMAT2)

Foxa2 is required in floor-plate formation as well as mDA progenitor induction. Lmx1a is a protein that is involved in the proliferation, specification, and early differentiation of the mesodiencephalic DA progenitors into mDA neurons. In the murine brain development, *Lmx1a* is expressed by E.8.5 in the dorsal midline (roof plate) of the neural tube and in the optic vesicles (Failli et al. 2002). Thereafter, *Lmx1a* is highly expressed in the DA progenitors arising from the VM floor plate. During early neurogenesis of DA progenitors, Lmx1a induces *Msx1* (Msh homeobox homolog 1) expression, which drives the expression of *neurogenin 2* (Ngn2), a key transcription factor involved in neurogenesis and neural specification (Parras et al. 2002; Andersson et al. 2006; Roybon et al. 2008) (Fig. 2). Indeed, a severe reduction in the midbrain is observed in Lmx1a-deficient mice and dreher mutant mice, which are Lmx1a functional mutants (Mishima et al. 2009; Millonig et al. 2000). Therefore, Lmx1a is necessary for mDA neuron characterization. Foxa2 is a transcriptional factor that serves crucial role in mDA neuron specification during E7.5–E9.5. During mDA neuronal development, Foxa1 and Foxa2 are key regulatory factors, which regulate neurogenesis in the mDA progenitors by inducing the expression of *Lmx1a* and *Ngn2* (Ferri et al. 2007; Lin et al. 2009). Lmx1a and Ngn2 cooperatively facilitate mDA neuronal differentiation. Moreover, Foxa1 and Foxa2-induced *Nurr1* and engrailed 1 (*en-1*) increase the expression of aromatic l-amino acid decarboxylase (*AADC*) and tyrosine hydrolase (*TH*) in immature dopaminergic neurons (Ferri et al. 2007). The genetic ablation of Foxa1 and Foxa2 causes a severe loss of TH-positive mDA neurons (Stott et al. 2013). Moreover, a conditional deletion of Foxa1 and Foxa2 in adulthood also leads to the reduction of TH-positive adult dopaminergic neurons in ventral midbrain (Domanskyi et al. 2014). Therefore, the transcriptional activity of Foxa1 and Foxa2 is required in the mDA neuronal development.

Nurr1 (also known as NR4A2)

Nurr1 is an orphan nuclear receptor that serves essential roles for the differentiation, maturation, and maintenance of mDA neurons. In the murine brain development, *Nurr1* is expressed around E10.5 in the ventral midbrain prior to expression of *TH*, which is a key enzyme to generate dopamine at E11.5. Nurr1 expression is retained in DA neurons of the substantia nigra and ventral tegmental area (SN-VTA) throughout adulthood. Therefore, Nurr1 may be involved in the early stage of mDA neuronal differentiation as well as in the postnatal stage of mDA neuron maintenance. Moreover, SHH-Foxa2 and Wnt1-Lmx1 axis orchestrate the expression of *Nurr1*, suggesting that *Nurr1* expression is a molecular cue for the development of mDA neurons.

Three conserved DNA-binding domains of Nurr1 are important for its transcriptional activity. NGFI-B response element (NBRE, AAAGGTCA) is crucial for Nurr1

function as a monomer, Nurr response element (NurRE, AAAT(G/A)(C/T)CA) is important for homodimers or heterodimers with NR4A family (Nur77 or Nor1), and direct repeat of AGGTCA with a five-base-pair spacer (DR5) is required for heterodimer with RXR (Campos-Melo et al. 2013). Importantly, Nurr1 induces the expression of *TH* as well as dopamine transporter (*DAT*) to maintain dopamine levels in synaptic cleft (Sakurada et al. 1999; Schimmel et al. 1999; Sacchetti et al. 2001). Subsequent studies have revealed that Nurr1 induces essential genes for the mDA neuronal function such as vesicular monoamine transporter 2 (*VMAT2*), aromatic amino acid carboxylase (*AADC*), and Ret (*GDNF* receptor) (Hermanson et al. 2003; Smits et al. 2003; Li et al. 2009).

Indeed, Nurr1-deficient mice are incapable of generating mDA neurons in the SN and VTA. However, these mice eventually died within the first 2 days of birth due to milk-suckling difficulty (Zetterstrom et al. 1997). A study using conditional *Nurr1*-gene targeted mice, in which *Nurr1* is selectively ablated in mature DA neurons, showed progressive reduction in both developing and adult striatal DA neurons (Kadkhodaei et al. 2013). Moreover, selective *Nurr1* deletion in mature DA neurons at adulthood (~ 5 weeks) results in typical pathological phenotypes seen in PD patients: (1) degeneration of DA neurons, (2) reduced dopamine and dopamine-related metabolites, and (3) impaired motor behaviors. Collectively, Nurr1 plays an indispensable role for generating and maintaining DA neurons by regulating numerous genes including dopamine-related enzymes, transporters, and transcription factors.

Generation of DA neurons from fibroblasts

Research on the generation of DA neurons from fibroblasts was inspired from the finding of direct conversion that generation of neurons using three transcription factors Ascl1, Brn2 and Myt1l (Vierbuchen et al. 2010). To determine which transcription factor is required for induced mDA neuron generation, Pfisterer and colleagues examined 10 genes involved in patterning and specification of DA neurons (*En1*, *Foxa2*, *Gli1*, *Lmx1a*, *Lmx1b*, *Msx1*, *Nurr1*, *Otx1*, *Pax2*, and *Pax5*). They found that Foxa2 and Lmx1a in combination with the three known genes (*Ascl1*, *Brn2*, and *Myt1l*) are required for induced DA neuron generation (Pfisterer et al. 2011). Consequently, Caiazzo and colleagues reported the minimal transcription factor combination (*Ascl1*, *Nurr1*, and *Lmx1a*) for generating induced DA neurons from mouse and human fibroblasts (Caiazzo et al. 2011). Induced DA neurons from murine fibroblasts alleviate symptoms in a mouse model of PD (Kim et al. 2011). Transcription factors including Axcl1, Nurr1, and Lmx1b induce direct conversion into DA neurons from astrocytes (Addis et al. 2011). Collectively, the ectopic expression of genes that are known to serve crucial function in the DA neuron specification and development is required for the generation of induced DA neurons.

MicroRNA-mediated conversion into dopamine neurons from fibroblasts

miRNA is an endogenous small non-coding molecule found in many organisms including plants, animals, and viruses (Dethoff et al. 2012). miRNA regulates gene expression by binding to complementary sequences (Vidigal and Ventura 2015). Numerous studies showed the close relationship between microRNA and neuronal development (Behm and Ohman 2016). Especially, miR-133b is expressed in the DA neurons and is deficient in PD patients. MiR-133b regulates function and maturation of DA neurons (Kim et al. 2007). Subsequent study showed that miR-9 and miR-124 repress BAF53a in post-mitotic neurons, regulating essential transition of neurogenesis (Yoo et al. 2011; Yoo et al. 2009). Interestingly, ectopic expression of miR-9 and miR-124 induces neuron-like morphological change in fibroblasts (Yoo et al. 2009). Combination of miR-124 and two transcriptional factors, Ascl1 and Myt1l, promote into human-induced neuron (ihN) generation from human primary dermal fibroblasts (Yoo et al. 2011). Collectively, these studies suggest that miRNAs involved in neuronal development could play an important role for generating neurons directly from fibroblasts. A more rigorous approach will be required to elucidate molecular mechanism of miRNA-mediated neuronal differentiation, specifically DA neuron differentiation.

Recent studies of induced DA neurons

The lentiviral vector system has been widely used to generate induced neurons from fibroblasts (Caiazzo et al. 2011; Pfisterer et al. 2011; Kim et al. 2014; Kim et al. 2011). Although this system is efficient to generate induced neurons, it is not safe for clinical use due to the possibility of transformation by lentiviral elements. Thus, alternative methods including non-integrating vector and chemical (small molecules) combinations have been investigated (Yoo et al. 2011; Jiang et al. 2015; Lau et al. 2014). The advantage of small molecules is the rapid, reversible, and dose-dependent effect, which allows control of the outcome by applying different concentration and combinations. Small molecules target key factors including transcription factors that regulate cell differentiation and reprogramming. Thus, small molecules have been widely used for generating iPSC and iPSC-derived DA neurons (Hou et al. 2013; Zhu et al. 2010; Li et al. 2011; Chen et al. 2011; Huangfu et al. 2008; Mali et al. 2010; Kriks et al. 2011; Studer 2012; Sundberg et al. 2013; Doi et al. 2014; Kirkeby et al. 2012; Ma et al. 2011). For example, epigenetic-related small molecules including

HDAC inhibitors promote mouse embryonic fibroblasts reprogramming into iPSC (Huangfu et al. 2008; Mali et al. 2010). GSK3 inhibitors support embryonic stem cell (ESC) self-renewal and also facilitate rapid and efficient generation of iPSC (Li et al. 2009). Furthermore, there are small molecules that induce neural differentiation. SMAD inhibitors efficiently drive hESC to neural precursors through floor plate. SHH and FGF8 accelerates efficient generation of DA neuron precursors (Chambers et al. 2009). For ALK2, 3 and 6 inhibitors, LDN193189 facilitates neural conversion of human fibroblasts (Dai et al. 2015). Multiple studies have demonstrated direct conversion of DA neurons from fibroblasts using combination of small molecules and known transcription factors (summarized in Table 1).

iPSC-derived DA neuron vs. induced DA neuron

James Thompson and his colleagues established human embryonic stem cells (hESC) in 1998 (Thomson et al. 1998). hESC offers unlimited cell source not only for the inaccessible tissue but also for the development of diverse protocols including efficient generation of DA neurons. These efficient protocols are being used to generate iPSC-derived DA neurons, but there is a variation in differentiation potential of iPSCs (Hu et al. 2010). A subsequent study showed that treatment by a combination of small molecules efficiently induces hESC, iPSC, and PiPSC-derived DA neurons that (1) express dopamine neuronal markers in vitro, (2) exhibit robust TH positive neuritis innervation of the host striatum, and (3) show recovery in 6-OHDA PD rat model (Sundberg et al. 2013). This result indicated that iPSC-derived DA neurons could be a potent alternative cell source for PD. However, eliminating undifferentiated and undesired cell populations during iPSC-derived DA neuron generation is one of the major hurdles for clinical use of iPSC-derived DA neuron (Trounson and DeWitt 2016; Gutierrez-Aranda et al. 2010; Katsukawa et al. 2016; Lu and Zhao 2013). Especially, undifferentiated autologous iPSC can form teratoma, which does not fulfill clinical criteria. Induced neurons directly generated from fibroblasts that undergo senescence after several passages do not require cell proliferation, which is a necessary condition for iPSC reprogramming, eliminating the risk of teratoma. Although generation of DA neurons by direct conversion is faster compared to iPSC-derived DA neuron generation, there is a practical limitation to generate sufficient numbers of induced neurons by direct conversion for therapeutic use (Yang et al. 2011). Based on postmortem analysis from fetal VM transplantation in PD patients, large numbers of TH-positive cells (200,000~400,000) are required (Mendez et al. 2005; Li et al. 2008; Kordower et al. 1996; Hagell et al. 1999; Mendez et al. 2008). Therefore, it

Table 1 Summary of studies on induced mDA neuron differentiation from fibroblasts

Reference	Dopamine neuron differentiation				
	Transcription factor	miRNA	Chemical	Characteristics	Functional test
Pfisterer et al. 2011	Ascl1, Brn2, Myt1l, Foxa2, and Lmx1a	N/A	N/A	-16.43 ± 4.3% conversion efficiency to neuron -Less than 10% of TH^+ cells among neurons	-Electrophysiology -Spontaneous action potentials and rebound action potentials are comparable with mDA neuron
Caiazzo et al. 2011	Ascl1, Nurr1, and Lmx1a	N/A	N/A	-ICC TH^+ (~ 5%), VMAT2, DAT, ALDH1A1, and calbindin -Gene expression pattern	-Electrophysiology -Spontaneous action potentials and rebound action potentials are comparable with mDA neuron -HPLC:DA release
Kim et al. 2011	Ascl1 and Pitx3	N/A	Shh + FGF in N3 media (N2 + bFGF)	-ICC TH^+ (~ 5%), Tuj, DAT, and AADC -Gene expression pattern	-Electrophysiology -HPLC:DA release -About 50% recovery in amphetamine-induced rotation -About 2000 TH^+ cells in grafted with elevated dopamine level
Addis et al. 2011	Ascl1, Lmx1b, and Nurr1	N/A	N/A	-ICC 35.15% of $Tuj1^+$ 50.9 ± 3.3% of TH^+ among $Tuj1^+$ cells (18.2 ± 1.5% conversion rate) -Gene expression pattern	-Electrophysiology -HPLC:DA release
Jiang et al. 2015	Ascl1, Lmx1a, Nurr1, and p53 shRNA	miR-124	Y27632/CHIR/VC/DM/SB/ BDNF/PMN/NGF/GDNF/TGF-β	-ICC 93.3 ± 1.6% of $Tuj1^+$, 59.2 ± 3.7% TH^+	-Electrophysiology -HPLC:DA release

would be desirable to generate DA neuron precursors from fibroblasts that are expendable (Kim et al. 2014; Tian et al. 2015; Lim et al. 2015).

Conclusions

Despite the short amount of time since the report of direct conversion into neuronal cells from fibroblasts, it already represents a significant shift that cell fate plasticity can be manipulated by transcription factors (Vierbuchen et al. 2010; Pfisterer et al. 2011; Kim et al. 2011). Although the molecular mechanism is still poorly understood, this new methodology may be a strong and attractive tool to expand our knowledge on the relationship between transcription factors and various repressive/active chromatin states to regulate cell fate decision. Moreover, direct conversion of DA neurons provides an alternative for the cell-based therapy using iPSC technology. Recently, disease modeling using iPSC-derived neurons has provided new insights into the cellular aspect of diseases by recapitulating patient derived cells (Nishizawa et al. 2016; Mucci et al. 2016; Li et al. 2016; Heman-Ackah et al. 2016; Jang and Ye 2016; Choi et al. 2016; Mekhoubad et al. 2012; Marchetto et al. 2011; Soldner and Jaenisch 2012). Consequently, progerin-mediated late-onset disease modeling provides the possibility of using iPSC-derived DA neurons in late-onset age-related diseases (e.g., Parkinson's diseases) (Miller et al. 2013). Along with the advance of iPSC-based disease modeling, induced mDA neurons from patient-derived fibroblasts will be beneficial for recapitulating diseases in vitro. Although small molecule-mediated generation of functional DA neuron from iPSC has been established, direct conversion of fibroblasts into DA neurons using only small molecules has not been established. This may be due to the different epigenetic control and chromatin statuses that are involved in cell fate plasticity, compared to those in iPSCs. Thus, more rigorous approaches are required to screen effective small molecules that regulate epigenetic changes in fibroblasts. Recent studies showed the close relationship between metabolites and epigenetic control in stem cell self-renewal and differentiation (Donohoe and Bultman 2012; Inagaki et al. 2016; Ryall et al. 2015; Berger and Sassone-Corsi 2015; Menendez 2015; Ryall et al. 2015; Ost and Pospisilik 2015; Meier 2013; Agathocleous and Harris 2013; Kaelin and McKnight 2013; Lu and Thompson 2012; Hanover et al. 2012). Acetyl-CoA, methionine, and α-ketoglutarate are the key metabolites that are either a source or cofactor of acetylation, methylation, and dimethylation. Moreover, metabolites like glucosamine-induced stem cell proliferation and differentiation by regulating both epigenetic control and anabolic metabolism (Hwang et al. 2016; TeSlaa et al. 2016; Carey et al. 2015; Jung et al. 2016; Jang et al. 2012). Thus, metabolic reprogramming is one of the candidates to further examine for regulation of cell fate plasticity. Future investigation will need to overcome the low efficiency of induced DA neurons from adult human fibroblasts.

Abbreviations

6-OHDA: 6-Hydroxydopamine; AADC: Aromatic l-amino acid decarboxylase; ALK2: Activin A receptor type 2; BAF53a: BAF complex 53 KDa subunit; BDNF: Brain-derived neurotrophic factor; Brn2 also POU3F2: POU class 3 homeobox 2; CHIR: CHIR99021; DA neurons: Dopamine neurons; DAT: Dopamine transporter; DBH1: Noradrenaline-synthesizing enzyme dopamine β-hydroxylase 1; DM: Dorsomorphin; DR5: Five-base-pair spacer; en-1: Engrailed 1; FGF8: Fibroblast growth factor 8; Foxa2: Forkhead Box A2; GDNF: Glial cell line-derived neurotrophic factor; Gli1: Gli family zinc finger1; GSK3: Glycogen synthase kinase 3; HDAC: Histone deacetylase; ihN: Human-induced neuron; iPSC: Induced pluripotent stem cell; Lmx1a: LIM homeobox transcription factor 1 α; Mash1 also known as Ascl1: Mammalian achaete scute homolog-1; mDA neuron: Midbrain dopamine neuron; MHB: Midbrain-hindbrain border; miRNA: MicroRNA; Msx1: Msh homeobox homolog 1; MyoD: Myogenic differentiation 1; Myt1l: Myelin transcription factor 1 like; NGF: Nerve growth factor; Ngn1: Neurogenin 1; Ngn2: Neurogenin 2; Nurr1: Nuclear receptor-related 1 protein; Otx1: Orthodenticle homeobox1; Pax2: Paired box 2; Pax5: Paired box 5; PD: Parkinson's disease; Phox2a: Paired like homeodomain 2a; PiPSC: Primate iPSC; PMN: Purmorphamine; RXR: Retinoic X receptor; SB: SB431542; SHH: Sonic hedgehog; SN: Substantia nigra; TH: Tyrosine hydrolase; VC: Vitamin C; VM: Ventral mesencephalon; VTA: Ventral tegmental area; Wnt1: Wingless-related MMTV integration site 1; Y27632: Rock inhibitor

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YJ and JHJ wrote the manuscript and figures. JHJ decided on the content, had editorial input on all sections, and designed the layout of figures. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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