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Review

Transdifferentiation of Fibroblasts by Defined Factors

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Abstract

Cellular differentiation is usually considered to be an irreversible process during development due to robust lineage commitment. Feedback and feed-forward loops play a significant role in maintaining lineage-specific gene expression processes in various cell types, and, in turn, factors secreted by cells may regulate the homeostatic balance of these cycles during development and differentiation. The output of biological responses is controlled by such mechanisms in many regulatory pathways through gene networks involved in transcription, RNA metabolism, signal transduction, micromolecular synthesis, and degradation. The pluripotent stage during cellular conversion may be avoided through ectopic expression of lineage-specific factors. Lineage-specific transcription factors produced during development may strengthen cell type–specific gene expression patterns. Cellular phenotypes are further stabilized by epigenetic modifications. This reprogramming approach could have important implications for disease modeling and regenerative and personalized medicine.

Introduction

Cellular differentiation is usually considered to be an irreversible process during development due to robust lineage commitment, and lineage-specific transcription factors produced during development may strengthen cell type-specific gene expression patterns (Karumbayaram et al., 2009). This view has been reconsidered because the ability to change the pluripotency of a differentiated cell or to change a cell into an entirely different cell type has been demonstrated. Researchers can induce fully differentiated cells to transform into other cell types by reprogramming (Han et al., 2012). It has been shown that somatic cells can be changed into pluripotent cells by methods such as cell fusion, culture-induced reprogramming, and direct reprogramming (Their et al., 2012).

Specifically, direct reprogramming and transdifferentiation of a cell are complex processes that involve many methods and specific factors (Ring et al., 2012). Many regulatory signaling processes control the output of biological responses through mechanisms such as signal transduction, RNA metabolism, micromolecular synthesis, and degradation (Lujan et al., 2012). If cells can be reprogrammed into different cell types, this may constitute a promising method to solve problems related to disease modeling and regenerative medicine. The realization of the great potential of this application both clinically and therapeutically requires more in depth examination (Ladewig et al., 2013).

Regeneration Through the Use of Induced Pluripotent Stem Cells/Embryonic Stem Cells

Pluripotent stem cells are undifferentiated cells that can self-renew, proliferate into undifferentiated cells, and differentiate into other cell types both *in vitro* and *in vivo* and may provide a potential method for cell-based therapies for age-related diseases, wound repair, and degenerative diseases (Gepstein, 2002; Patel and Yang, 2010). Pluripotent stem cells have been classified according to their characteristics. Embryonic stem cells (ESCs) can differentiate into three germ layer cell types—the ectoderm, endoderm, and mesoderm (Nakagami et al., 2006). Fetal stem cells and mesenchymal stem cells have also been recognized as different types of stem cells (Brunt et al., 2012).

Another cell type, termed induced pluripotent stem cells (iPSCs), which are artificially derived from somatic cells, may become seed cells that can differentiate into large numbers of diverse cells for specific cell-based therapy

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(Atala, 2012; Lengner, 2010). Subtle differences have been found between ESC and iPSC lines in the expression of several specific genes (Chin et al., 2009). It has also been reported that differences in expression between these cell lines are not consistent and may result from diverse culture conditions (Gopala Pillai, 2011). Although some controversy remains, the common mode of transcription in ESCs and iPSCs, which can be observed by examining the differences in gene expression, seems to involve the ineffective silencing of gene expression of somatic cells or failure to induce specific genes in the same quantities (Bilic and Belmonte, 2012; Šaric and Hescheler, 2008).

Fibroblasts are the main source of iPSCs, although researchers have also reported other sources for iPSCs, such as mature B cells and hepatocytes. (Yu and Thomson, 2008). Specifically, self-renewing iPSCs, which share many common features with ESCs, can be acquired by reprogramming fibroblasts with a mixture of defined factors consisting of Kruppel-like factor 4 (Klf4), Sry-box-containing gene 2 (Sox2), octamer-binding protein (Oct4), and c-myelocytomatosis oncogene (c-Myc) (Hu et al., 2010; Rufaihah et al., 2013). Various types of somatic cells, such as neurons, osteoblasts, and cardiomyocytes, could be acquired for laboratory studies or clinical cell therapy by inducing iPSCs (Azhdari et al., 2013; Yen et al., 2013; Zhang et al., 2009). Progress in molecular imaging may contribute to transplanted cell tracking *in vivo* (Juopperi et al., 2011). Therefore, there is immense potential for the application of these cells in the field of personalized cell-based therapy, which would overcome the major disadvantages of using differentiated somatic cells (Collado et al., 2007).

Limitations of iPSC Application

Although the application of iPSC technology has a promising future, obstacles exist. For example, this technology is time intensive and requires complex procedures to induce pluripotency. The cells are first reprogrammed, and then the preferred cell type is induced (Solter, 2000). Because generating iPSCs involves complex stages, the efficiency can be low (Yoshida et al., 2009). Furthermore, the fidelity and safety of iPSC/ESC-derived cells require assessment before these cells can be used clinically (Kanellopoulou et al., 2005; Smith et al., 2013). Tumor formation should be noted when iPSCs are induced into other cell types. Additionally, recombinant formation of iPSCs after transplantation into mouse diploid cells should be a focus, as iPSCs should play a significant role in tissue and tetraploid embryo development (Koche et al., 2011).

In addition, it is difficult to acquire unfertilized oocytes from volunteers for isolation and expansion of ESCs (Ezashi et al., 2009). The efficiency of this process is generally low due to the low availability of cells and dependency on donations (Giorgetti et al., 2012). Considering all of the disadvantages and limitations of iPSC technology, other direct reprogramming methods, which avoid the pluripotent stage, may be more suitable (Li et al., 2011).

Table 1. Examples of Different Types of Cellular Transdifferentiation and Corresponding Reprogramming Factors Used for Directing Cell Fate Switch

Cell origin	*Derived cell type*	*References*
Examples of iPSC technology		
Fibroblasts	iPSCs	
Oct4, Sox2, Klf4, c-MYC		Takahashi (2006)
Oct4, Sox2 + valproic acid		Huangfu et al. (2008)
Oct4, Sox2, c-MYC + kenpaullone		Lyssiotis et al. (2009)
Oct4, Klf4 + CHIR99021 (MEFs)		Li et al. (2009)
Examples of transdifferentiation and direct reprogramming technology		
Pancreatic (exocrine)	Pancreatic (beta cells)	Ferber et al. (2000)
Pdx1		Sapir et al. (2005)
Keratinocyte	Pancreatic cells	Mauda-Havakuk et al. (2011)
Pdx1		
Fibroblasts	Muscle	
ETV2, FLI1, ERG1		Davis et al. (1987)
Fibroblasts	Cardiomyocytes	
Gata4, Mef2c, Tbx5		Ieda et al. (2010)
Gata4, Mef2c, Tbx5, Hand2		Song et al. (2012)
Gata4, Mef2c, Tbx5, VEGF		Mathison et al. (2012)
Mef2c, Myocardin, and Tbx5		Protze et al. (2012)
Myocardin, miR-1, miR-133, GHMT		Nam et al. (2013)
Fibroblasts	Endothelial cells	
Oct4, Sox2, Klf4, c-MYC		Hanemaaijer et al. (1997)
(4-day partial reprogramming)		Margariti et al. (2012)
Oct4, Sox2, Klf4, c-MYC		Ginsberg et al. (2012)
(short reprogramming)		Li et al. (2013)
Fibroblasts	Neurons	
MyoD		Tanji et al. (1994)
Ascl1, Brn2, Myt1l		Vierbuchen et al. (2010)

iPSCs, induced pluripotent stem cells.

Direct Reprogramming Through Transdifferentiation

Direct reprogramming and transdifferentiation may replace the iPSC/ESC method. Several studies have revealed that fibroblasts may be a source for cell-based therapy. Related studies have reported that it is possible to directly reprogram fibroblasts into other cell types using a cocktail of defined factors and microRNAs (miRNAs) (Feng et al., 2009; Laslo et al., 2006; Nam et al., 2013; Qian et al., 2012; Sekiya and Suzuki, 2011).

The history of direct reprogramming

In the 1950s, reprogramming was the subject of various experiments. Some studies showed that direct reprogramming of fibroblasts into different cell types could be achieved by regulating a few specific genes (Caiazzo et al., 2011). These defined genes are usually the primary genes that activate a specific signaling pathway and should also be in place when eliciting responses from additional genes during development (Szabo et al., 2010). In *Drosophila* experiments, defined gene overexpression activated specific lineage genes, influencing these cells and their eventual fate (Gehring, 1996; Schneuwly et al., 1987). These key genes are also found in mammals (Yamanaka and Blau, 2010).

Previous studies have used nuclear transfer and transduction based on transcriptional factors as traditional reprogramming methods (Davis et al., 1987). These methods finally showed that the state of differentiation is reversible, adjustable, and flexible (Gurdon, 1962; Blau et al., 1985; Takahashi and Yamanaka, 2006). Groundbreaking cloning experiments in the 1950s demonstrated that cloned organisms be could obtained by nuclear transfer technology in the frog. These experiments were the first to prove the possibility of impermanent gene silencing (Briggs and King, 1952). In the 1980s, researchers first used transcription factors to conduct reprogramming experiments. Srivastava and colleagues successfully reprogrammed embryonic mouse fibroblasts into muscle cells via transfection with the defined gene MyoD (Srivastava and Ieda, 2012). Based on the success of these initial experiments, MyoD was later widely used in additional reprogramming and transdifferentiation experiments in which immature smooth muscle cells and chondrocytes were successfully converted into muscle cells (Choi et al., 1990; Schäfer et al., 1990).

Researchers in the 1990s discovered another significant specific factor, Gata-1, which could induce monocyte precursors into megakaryocytes and eosinophils (Kulessa et al., 1995). In 2004, it was demonstrated that lymphoid progenitors could be converted into descendants of myeloid progenitors (Cobaleda et al., 2007; Nutt et al., 1999; Xie et al., 2004). In early 2002, researchers used direct lineage tracing to reveal that pancreatic and duodenal homeobox 1 (Pdx1)-expressing progenitors in the early embryo give rise to all pancreatic cells in the mouse pancreas (Gu et al., 2002). Kawaguchi's experiments (Kawaguchi et al., 2002) provide evidence that *Ptf1a* expression is specifically associated with the determination of pancreatic fate in undifferentiated foregut endoderm. In 2000, Pdx 1 was used to induce the expression of insulin genes in the liver and to ameliorate streptozotocin-induced hyperglycemia (Ferber et al., 2000). The first example of using Pdx1 to generate functional insulin-producing tissue from adult human liver cells occurred in 2005 (Sapir et al., 2005).

Using a similar strategy, innervated MyoD-converted cells might represent a new source of neuronal cells for studying the molecular events leading to the formation of a functional neuron (Tanji et al., 1994). In 2010, Vierbuchen successfully reprogrammed fibroblasts into neuronal cells using a cocktail of Ascl1, brain-2,Pou class 3 homeobox 2 (Brn2), and Myt11 (Vierbuchen et al., 2010). In 2012, Song's group reported that mouse cardiac fibroblasts could be reprogrammed into beating cardiac-like myocytes using a defined factor set consisting of Gata4, Mef2c, and Tbx5 (GMT) and the Hand2 gene (Song et al., 2012). *In vivo* cardiac transdifferentiation has also been attempted using a combination of factors or epicardin promoters (Jayawardena et al., 2012; Qian et al., 2012; Song et al., 2012). Inagawa used the GMT factor set to induce transdifferentiation in an *in vivo* mouse model of infarction (Inagawa et al., 2012). Additionally, Mathison demonstrated that vascular endothelial growth factor played an important role in promoting the efficiency of reprogramming processes via the GMT factor (Mathison et al., 2012).

Despite these results, the most efficient combination of factors that can promote transdifferentiation into cardiomyocytes remains unknown, because any comparisons were performed using independent and different experimental conditions (Palpant and Murry, 2012). Furthermore, problems in subsequent cardiac reprogramming studies have been found. For example, although heart fibroblasts could be reprogrammed into beating cardiomyocytes, most could not continue beating spontaneously after 1 week or express the cardiac troponin T gene (Addis and Epstein, 2013). Compared to the reprogramming method, a longer duration of spontaneous beating was observed in an experiment involving differentiated iPSCs (Chen et al., 2012; Mummery et al., 2003; Narazaki et al., 2008). This finding may raise questions about the suitability of using heart fibroblasts as a cell pool for reprogramming (Protze et al., 2012; Yi et al., 2013). Despite these limitations, the GMT gene and other defined lineage factors may still play a key role in influencing the processes of cardiomyocyte reprogramming (Small et al., 2010).

Limitations

Reprogrammed cells may show a lower proliferation capacity and less diversity of cell types, which would reduce the potential application of these cells in clinical regenerative therapy (Margariti et al., 2012). Many technical problems must be solved before clinical applications can be considered. The low conversion efficiency and need for purification may represent the primary problems among all of the issues related to reprogrammed cells (Pawlowski and Kotter, 2013). Another difficulty that must be considered is the restricted scalability of cell generation. In the transdifferentiation process, the lack of a proliferative precursor stage largely weakens the capacity of a cell generation system (Pawlowski and Kotter, 2013). Additionally, before clinical trials can be performed, the safety of virus introduction should be investigated. The influences and mechanisms of viruses in humans remain unclear, and viral injection may cause unpredictable side effects, which may result in complications or even cancer (Butel, 2000). Secure methods of conveying reprogramming factors into the human body need

to be considered carefully and may be accomplished by small molecules or specifically modified RNA (Srivastava and Ieda, 2012). Transdifferentiation along alternate adult fates requires only a short-term trigger by ectopic transcription factors; therefore, integration of genetic information is not needed. Last, a mouse model cannot completely simulate the human body, and human cells may be more difficult to reprogram than animal cells (Yan et al., 2010).

Examples

Conversion into neurons

Previous studies have shown that fibroblasts from mice and humans could be directly reprogrammed to become neurons by transfection with a combination of defined factors (Wernig et al., 2002). Torper's study showed that human fibroblasts and astrocytes could be transplanted and converted into neurons when specific genes were activated (Torper et al., 2013). In addition, Torper also found that mouse astrocytes could be directly reprogrammed into neurons with nuclei expression *in vivo*. Doxycycline-regulated lentiviruses (LVs) were chosen as vectors to deliver the neuron-related factor combination of Ascl1, Brn2a, and Mytl1 (Pfisterer et al., 2011; Shi and Jiao, 2012). To determine the effect of doxycycline, these vectors were used to activate specific neuronal genes for the conversion process *in vivo* (Grealish et al., 2010; Pang et al., 2011).

Previous studies have shown that the neuron-related gene ABM [achaete-scute complex-like 1 (Ascl1), brain-2 (Brn2a), and myelin transcription factor-like 1 (Myt1l)] could successfully reprogram fibroblasts into functional neurons *in vitro* using a combination of factors. Reprogramming of fibroblasts and astrocytes into neurons was shown to be feasible in the brain parenchyma (Heinrich et al., 2011). Then, Son and colleagues used a stereotaxic injection of Cre-regulated LVs to convert endogenous brain cells into parenchymal astrocytes in glial fibrillary acidic protein (GFAP)-Cre mice (Son et al., 2011). The results demonstrate that reprogramming GFAP-expressing glia into NeuN-expression neurons is feasible using a combination of ABM genes *in situ*. Generally speaking, the study results show that it is possible to perform direct neural reprogramming using endogenous mouse cells as a starting cell (Chambers and Studer, 2011).

Transdifferentiation into retinal pigment epithelium-like cells

The retinal pigment epithelium (RPE), which participates in the metabolic and cellular processes of retinal photoreceptors, is a pigmented monolayer of epithelium. Degeneration and dysfunction of the RPE results in many sight-threatening diseases due to injury to the photoreceptor, including age-related macular degeneration (AMD), the leading cause of blindness (Lim et al., 2012). Currently, the available therapy for these diseases is limited, and replacement of receptor loss is impossible. Therefore, the generation of functional RPE cells is a promising finding in the field of regenerative medicine and may provide possible cures for retinal degenerative diseases, such as AMD (Schwartz et al., 2012).

Previous studies have successfully induced RPE differentiation of iPSCs and ESCs (Carr et al., 2009; Lu et al., 2009; Zhu et al., 2013). Although the conversion of RPE cells from ESCs is promising, the application of human ESCs (hESCs) for clinical purposes remains controversial due to ethical concerns (Zhang et al., 2013). Although iPSC technology has a bright future as a means to produce specific cells required for transplantation, ethical controversies still exist (Takahashi et al., 2007). In addition, the efficiency of conversion from iPSCs to RPE cells is low, and diversity exists among different iPSC lines (Buchholz et al., 2009). There is also a risk of tumor formation in clinical treatment (Panopoulos et al., 2011). Recently, progress in transdifferentiation has yielded a potential solution to these issues. The required cell type can be easily acquired by the conversion of somatic cells (Ben-David and Benvenisty, 2011). Using different combinations of defined factors, direct reprogramming technology has been applied to generate various cell types, such as neurons and hepatocytes (Huang et al., 2011; Kim et al., 2011; Lowry et al., 2008; Sekiya and Suzuki, 2011).

Recently, a new RPE-specific reporter system, the Best1::green fluorescent protein (GFP) reporter, which can be used for reprogramming cells, has been reported (Zhang et al., 2014). Using this reporter system, human fibroblasts can be directly reprogrammed into Best1::GFP+ colonies by transfection with a specific combination of transcription factors. This study not only provided clarification of the transcriptional mechanism by which RPE cell fate determination is regulated but also described promising methods to acquire functional RPE cells, complementing the use of pluripotent stem cells for drug selection, disease modeling, and even new cell therapy for retinal degenerative diseases.

Conversion into cardiomyocyte-like cells

Cardiovascular disease is a leading cause of death worldwide, and current treatment options are limited. Because the regenerative capacity of heart tissue is limited, the regeneration of cardiac tissue is an attractive form of treatment (Bondue et al., 2008). Transdifferentiation of human cardiac fibroblasts into cardiomyocytes may be a promising therapy for cardiovascular disease.

Previous research results have shown that a diverse range of cell types can be acquired through direct reprogramming. These cell types include neurons, blood progenitors, hepatocytes, and pancreatic cells (Li et al., 2013; Lujan et al., 2012; Sancho-Martinez et al., 2012; Szabo et al., 2010). Ieda et al. showed that the GMT combination may be able to directly reprogram fibroblasts into cardiomyocyte-like cells *in vivo* and *in vitro* (Ieda et al., 2010). Their finding that GMT alone could not successfully convert fibroblasts into cardiomyocytes encouraged them to evaluate additional transcription factors that promote reprogramming. Compared to GMT alone, the combination of GMT, Mesp1, and Myocd resulted in the upregulation of more cardiac-lineage genes in human cardiac fibroblasts (HCFs), which produced more efficient cell transformation (Fu et al., 2013; Small et al., 2010). Some findings have also shown that this combination could change the cell morphology to a polygonal shape and that such cells exhibit spontaneous Ca^{2+} oscillations.

Following this report, other researchers have conducted similar experiments with multiple combinations of specific

factors, including either GMT plus Mef2c, Myocd, Hand2, and Tbx5 or other miRNAs (MicroRNAs) (Amabile and Meissner, 2009; Chen et al., 2012; Mathison et al., 2012; Protze et al., 2012). Although direct reprogramming of cells into beating cardiomyocytes is not feasible *in vitro*, transdifferentiation could produce new cardiomyocytes from endogenous cardiac fibroblasts and improve cardiac function after myocardial injury (Bauersachs and Thum, 2007; Hansson and Chien, 2012; Ieda et al., 2010; Inagawa and Ieda, 2013). Ongoing studies indicate that cardiac reprogramming may be a promising method for the regeneration of injured cardiac tissues. It is important for researchers to determine other feasible and efficient combinations for the application of this technology (Bauersachs and Thum, 2007; Oh et al., 2004; Wada et al., 2013). These findings have established that this technology could play a significant role in regenerative medicine in the near future (Wang et al., 2011).

Clinical Applications

Although an increasing number of progressive clinical trials are currently using regenerative therapy, there are still many challenges for clinical applications. One major issue is the reduced availability of resources needed for treatments. A significant example emphasizing the requirement for a large number of appropriate cells can be found in the field of cardiac disease, which is a top killer worldwide (Ignarro et al., 2007). The regeneration of adult heart tissue is limited and urgently requires new treatment options that are both rapid and robust (Rasmussen et al., 2011). Importantly, the vascular endothelium is of great importance to cardiovascular homeostasis. An early and common event in the process of atherosclerosis is triggered by structural changes and endothelial cell dysfunction (Weber and Noels, 2011). Furthermore, alterations in endothelial cell function facilitate the infiltration of inflammatory cells and control the regulation of proliferation of vascular smooth muscle and the aggregation of platelets (Wong et al., 2012). Therefore, the generation of a large number of endothelial cells, which are usually limited in number, would be very beneficial in the clinical treatment of this disease.

Summary and Perspectives

Some novel findings in regenerative research have reduced the dependence on retroviral delivery via the introduction of new methods to convey reprogramming factors into cells. Such methodologies include episomal plasmids, mRNAs, miRNAs, and cell-penetrating recombinant proteins (Zhou et al., 2009). Although technical progress in transdifferentiation has shown much promise in the short term, the process remains slow and inefficient. Further improvements are required for the technology to become a feasible and convenient. Additionally, with respect to direct reprogramming, the limited cell diversity and capacity of proliferation may place obvious restrictions on regenerative therapy. Advances contributing additional means of reprogramming, such as specific molecules and even physical-aided enhancements, could possibly solve the safety problems and counteract the epigenetic changes that occur during transdifferentiation (Vaskova et al., 2013). This idea could be possible through the avoidance of viral vectors generated by iPSCs, in which the recombinant genome could increase the tumorigenicity and genetic abnormalities in the reprogrammed cells. By accessing and changing the differentiated state, new solutions may provide new research tools and treatment resources for diseases (Blum and Benvenisty, 2008; Ohi et al., 2011). The final achievements of cell reprogramming may be applied to personalized regenerative therapy for clinical purposes.

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Author Disclosure Statement

The authors declare that there are no conflicts of interest.

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