Transdifferentiation potential of adipose-derived stem cells into neural lineage and their application

Nazem Ghasemi and Shahnaz Razavi*

Abstract
Adipose-derived stem cells are a kind of mesenchymal stem cells which have a higher frequency in the adipose tissue and can be harvested by minimally invasive procedures. These cells are able to differentiate into other cells outside their lineage such as neuron, neurotrophic factor secreting cells and Schwann cells. Many of the identified neurotrophic factors such as brain-derived neurotrophic factor, nerve growth factor, and glial cell line-derived neurotrophic factor can be produced by adipose-derived stem cells. In addition, these cells when differentiated into neurotrophic factor secreting cells are able to secrete a significantly high level of these factors. Neurotrophic factors have a significant role in cellular processes include cell proliferation, differentiation and maturation. This article reviews the in vitro differentiation of adipose-derived stem cells into neural lineage cells and clinical application.

Keywords: Adipose-derived stem cells, neurogenic differentiation, schwann cells, neurotrophic factor secreting cells

Introduction
Stem cells are a population of undifferentiated cells that characterized by their self-renewal ability and multi-potency. So, these cells can create more stem cells and other specialized cells. Generally, there are two kinds of stem cells including embryonic stem cells, which are segregated from the inner cell mass of embryo, and non embryonic stem cells, which are found in various tissues especially in bone marrow. Mesenchymal stem cells (MSCs) are a kind of non embryonic stem cells that can be isolated from various tissues [1], such as bone marrow and blood [2], amniotic fluid [3], dermis [4], umbilical cord blood [5], and in tissues that contain fat [6].

Adipose-derived stem cells (ADSCs) that were first identified in 2001 [7], are a population of mesenchymal stem cells which have a much higher frequency in the fat tissue than in bone marrow (about 8×10^5 to 3.5×10^6 ADSCs per gram fat that is approximately 500-fold more) [8-10]. These cells can be isolated by less invasive procedures but they are not homogenous population cells [11]. In the human body, there are two types of adipose tissue including white and brown which are morphologically and functionally different. Moreover, white fat has greater distribution than other type. Previous studies have shown that ADSCs isolated from these tissues (visceral or superficial layers) have different characteristics [12]. For example, the proliferation of ADSCs isolated from superficial layers is higher than those from the visceral layer [13]. Therefore, ADSCs isolated from both layers express similar levels of the growth factors and some of the stem cell markers such as oct4 and nanog (Kalbermatten et al., 2011). In our previous studies, flow cytometry analysis showed that ADSCs express typical mesenchymal markers such as CD90, CD44, CD105, and are negative for hematopoietic antigens such as CD34, CD45, and CD14 [14-17]. Many of the identified nerve growth factors such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF) can be produced by ADSCs [13,14]. Therefore, ADSCs are considered to be a mediator of tissue regeneration through paracrine effects by modulating angiogenesis, promoting anti-ischemic effects, and neuroprotective effects [18].

ADSCs when cultured in the appropriate conditions are capable to differentiate into other cells outside their lineage such as neuronal, glial and neurotrophic factors secreting cells (NTFs) [14-16,19-24] (Figure 1). Thus, offers the potential to tissue maintenance and regeneration. This review focused on in vitro differentiation of ADSCs to neural lineage cells.

Review
Transdifferentiation potential of ADSCs into neuron cells and clinical application
Nervous tissue is the main component of the central and peripheral...
nerve system which contains specialized cells including neurons and neuroglia that regulate body functions. Furthermore, neural stem cells (NSCs) which are self-renewing and multi-potent cells can be isolated from this tissue. These cells are a type of adult stem cells that under special stimulation can be differentiated into neurons or glial cells which capable to generate nervous tissues during development and to repair damaged area after injury. It is important to mention that NSCs isolation from neural tissue is an impossible process. However, other resources of stem cell have been proposed for treatment in the field of neurodegenerative diseases.

Most of the studies focused on ADSCs because these cells are capable to differentiate to cells of ectodermal, mesodermal and endodermal lineage [6,25,26]. In addition, ADSCs possess additional characteristics including immunomodulatory properties that can alter the cytokine secretion profile of immune cells and act as source of variety of growth factors. In our previous study, in vitro differentiation of ADSCS into neuron cells is achieved by culture with media (by BDNF, NGF, NT3 and neurotrophin (NT)-4 secretion), and stem cells that under special stimulation can be differentiated stem cells (NSCs) which are self-renewing and multi-potent cells containing selective lineage specific induction factors [21].

 Recently, stem cell-based therapies using ADSCs are suggested as a potential novel paradigm for the treatment of neural tissue injuries. ADSCs by neurotrophic factors secretion have the ability to protect neuronal population (by BDNF and neuro-trophin (NT)-3 secretion), enhance neuronal survival (by BDNF, NGF, NT3 and neurotrophin (NT)-4 secretion), and promote axon regeneration [27-30]. Luo et al., reported that transforming growth factor beta 1 (TGFβ1) enhanced the regenerative capacity of ADSCs transplanted by protecting these cells from apoptosis and decreasing inflammation and promoting vascular endothelial growth factor (VEGF dependent angiogenesis [30].

Another study's results demonstrated that implanted ADSCS into the lumen of polycaprolactone (PCL)-based nerve conduits in peripheral nerve injury capable to promote the nerve formation [31]. The same group demonstrated that ADSC are capable to alleviate symptoms of Alzheimer’s disease and diminish cognitive decline through modulate microglial activation [32]. Chen et al., revealed that ADSCs transplantation in rat model of brain ischemia can promote neuronal regeneration by inhibiting the expression of Glial fibrillary acidic protein (GFAP) and increasing the expressions of Neuritin and NF-200 in the brain [33].

**Transdifferentiation potential of ADSCs into Schwann cells and clinical application**

Schwann cells (SCs) are the chief glia cell in the peripheral nervous system (PNS) which play a major function in many important aspects of peripheral nerve biology including nerve development and neurodegenerative processes [34,35]. Moreover, SCs possess additional performance including generation of the nerve extracellular matrix, regulate of neuromuscular synaptic activity, offering of antigens to immune cells and trophic support for neurons through neurotrophic factors secretion [34,37].

After peripheral nerve injury, SCs are necessary for nerve regeneration and according to previous published data, transplanted Schwann cells can remyelinate and restore neural function [38,39]. Unfortunately, autologous SCs isolation is an invasive procedure and it is difficult to get sufficient number of SCs for clinical application. However, recent studies demonstrated that ADSCs seems to be one ideal cell source for transdifferentiation into SCs [40]. In our previous study, using a standard protocol, ADSCs were induced into SCs [22].

There are a large number of experimental studies showing positive effects of SCs transplantation as a therapy for neurodegenerative disease and for spinal cord injury [41-43].

Yang et al., demonstrated that simultaneous transplantation of Schwann cells and ADSC can effectively promote locomotor functional recovery and diminish reactive gliosis after contusion brain injury in rats [44]. In addition, Kanno et al., in their study concluded that the combination of SC transplants engineered to secrete neurotrophin and chondroitinase further improves axonal regeneration and sensorimotor function [45].

In our previous study, we indicated that ADSC are a good option to induce SCs-like for transplantation in demyelinating disease [22]. Moreover, these cells were able to generate components of myelin shell when exposed to Leukemia inhi-bitory factor (LIF) [24]. Thus, these cells are a potential cell source for the treatment of nerve injuries in central nervous system (CNS) and PNS.

Mantovani et al., illustrated that ADSCs can differentiate into SCs lineage which have functional properties and growth factor synthesis activities alike native SC [46]. Thus, during nerve
regeneration, these cells could prepare nerve fiber support and promote locomotors functional recovery.

In a previous study, human ADSCs (hADSCs) differentiated into Schwann-like cells by a mixture of glial growth factors and then assessed their ability to act as Schwann cells in vitro and in vivo. The results of this study showed that hADSCs can differentiate into SC-like cells and have ability to secrete neurotrophic factors as well as to form components of myelin sheath in vivo. So, hADSCs may be an interesting prospect for cell-based transplantation therapy for various nerve disorders [47].

In another study, adipose derived stem cells of different anatomical regions, differentiated into Schwann-like cells. Finally it was concluded that the differentiated cells had a same features and function to primary Schwann cells in vitro. So, this would support the application of autologous transplantation of these cells for therapeutic delivery and potential treatment of nerve injuries [48].

**Transdifferentiation potential of ADSCs into Neurotrophic factor secreting cells and clinical application**

Neurotrophic factor secreting cells (NTF-SCs) by secreting a large amount of neurotrophic factors that are necessary for neuronal development and survival, paves the way to use NTFs cells for the treatment of patients that suffering from neurodegenerative disease. Neurotrophic factors are small molecule polypeptides including NGF family, GDNF family ligands and neuropoietic cytokines [29]. These factors have a significant role in regulating of neuronal development in the PNS and CNS through intracellular signaling by specific receptors.

The application of neurotrophic factors as therapeutic agents is a new idea for preserving and restoring neuronal function during neurodegenerative disorders. Contrary to this view, since the half-life of these agents is low, direct application of them is limited [49]. Moreover, when delivered peripherally, their efficacy diminished due to the blood–brain barrier. So, transplantation of NTF-SCs instead of neurotrophic factors may be an ideal strategy for delivering neurotrophic factors into the neural tissue. In our previous study, the results demonstrated that ADSC are able to secrete a variety of growth factors that strongly supporting the process of neuronal differentiation. In addition, NTF-SCs derived from ADSCs are able to secrete more of these factors [14]. Therefore, NTF-SCs can be transplanted safely into neural lesions and thereby serve as vehicles for delivering NTFs. ADSCs can be differentiated into NTF-SCs when cultured in NTF-SCs differentiation media. This induction can be done according to our previous method [23].

Recent studies have shown that NTF-SCs transplantation can efficiently improve the symptoms of some types of neurodegenerative diseases [50-52]. Thus, these cells may be an ideal cell source for cell based therapy in neurodegenerative diseases.

Sadat et al [53]. Evaluated the migration ability and efficacy of neurotrophic factor-secreting cells in animal models of Parkinson's and Huntington's disease. In this study by a two-phase medium-based induction, mesenchymal stem cells were differentiated into NTF-SCs and then these cells transplanted into induced striatal lesions. The histological evaluation demonstrated that the transplanted cells migrated and acted to regenerate the damaged nerve cells. Therefore, these finding showed that the induced MSCs may be a potential therapy in the treatment of neurodegenerative diseases due to their paracrine effects and their ability to migrate towards the lesions.

**Conclusion**

ADSCs are a promising cell source for neural regenerative due to their ability to differentiate into neural lineages cells, and ability to secrete various neurotrophic factors. A large number of clinical examinations using ADSCs have already performed and many of them showed ADSCs are effective on neural tissue regeneration.

**List of abbreviations**

ADSCs: Adipose-derived stem cells  
BDNF: Brain-derived neurotrophic factor  
CNS: Central nervous system  
GDNF: Glial cell line-derived neurotrophic factor  
GFAP: Glial fibrillary acidic protein  
hASCs: Human adipose-derived stem cells  
LIF: Leukemia inhibitory factor  
MSCs: Mesenchymal stem cells  
NSCs: Neural stem cells  
NTF-SCs: Neurotrophic factor secreting cells  
NGF: Nerve growth factor  
NT: Neurotrophin  
PCL: Polycaprolactone  
PNS: Peripheral nervous system  
SCs: Schwann cells  
TGFβ1: Transforming growth factor beta 1  
VEGF: Vascular endothelial growth factor  

**Competing interests**

The authors declare that they have no competing interests.

**Authors' contributions**

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