Cytotherapy, 2016; 18: 925–927

International Society for Cellular Therapy
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LETTER TO THE EDITOR

Ferulic acid pretreatment could improve prognosis of autologous mesenchymal stromal cell transplantation for diabetic neuropathy

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To the Editor:

Neuropathy is one of the most common complications of both type 1 and type 2 diabetes. Patients with diabetic neuropathy (DN) present with pathological features, including impaired vascularity and deficiency of angiogenic and neurotropic factors in nerves. Among various etiologies described for DN, hyperglycemia obviously plays an important role in the onset and progression of disease. Therefore, tight glycemic control and targeting glucose metabolic pathways by specific agents seem to be useful therapeutic strategies for halting the progression of DN. However, clinically, these therapeutic approaches did not show desirable therapeutic efficacy in the established neuronal damage. It underscores the need for requirement of more efficient strategies at the advanced stage of DN, including those activating angiogenic and neurotrophic pathways. Recently, cell therapy based on stem cells has been suggested as an attractive strategy for the treatment of DN [1].

Mesenchymal stromal cells (MSCs) are multipotent cells, capable of moving toward sites of injury, releasing various neurotrophic and angiogenic factors and differentiating into multi-lineage cell types, particularly neuron-like cells. These features make MSCs a suitable candidate for cell-based therapeutic strategies in DN [2]. Autologous MSCs, because they are not subject to immune rejection in contrast to allogeneic MSCs, have been considered an excellent choice for curative angiogenic and neurotrophic therapies [3].

However, oxidative stress as a consequence of high blood glucose causes serious damage to vital mediators in autologous MSCs. Our recent report demonstrated that diabetic MSCs show reduced proliferation rate and impaired paracrine effects including secretion of angiogenic factors [4]. This highlighted that the use of autologous diabetic MSCs as a source for treating diabetic complications may still be controversial. HIF-1 is illustrated as one of the impaired vital mediators [4].

HIF-1, a transcription complex, consists of HIF-1α that contains an oxygen-dependent degradation domain, and HIF-1β. HIF-1α plays a central role in the cellular responses to changes in oxygen availability. Under low-oxygen conditions, HIF-1α degradation via the ubiquitin-proteasome pathway is inhibited. It leads to HIF-1α aggregation in the nucleus and its binding to hypoxia-response elements in the promoters of target genes. HIF-1α regulates the expression of potent angiogenic and neurotrophic factors including vascular endothelial growth factor, platelet-derived growth factor and others [5]. However, protein stability and also transactivation of HIF-1α protein are hampered under oxidative stress. In a high-glucose context, methylglyoxal level increased as a result of oxidative stress and prevented binding of HIF-1α to its

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(Received 15 April 2016; accepted 15 April 2016)

ISSN 1465-3249
http://dx.doi.org/10.1016/j.jcyt.2016.04.006

co-activator [6]. Another disturbing mechanism is the sensitization of HIF-1α to degradation via the ubiquitin- proteasome pathway that is driven by high glucose [5]. It has been shown that pre-conditioning of the cells by an antioxidant could reverse impairment of HIF-1 function [6].

It is also well documented that efficacy of MSC therapy is limited by the poor survival of stromal cells after transplantation [7]. This situation is obviously worsened by the diabetic condition because MSCs isolated from a diabetic population show inherent lower proliferating rate and viable cell fraction [4]. The PI3K-Akt pathway is an important mediator of cell proliferation, growth, survival and angiogenesis in various cell types, including MSCs. Thus, the agents that over-activate this pathway in diabetic MSCs might enhance efficacy of cell therapy [7].

Ferulic acid (FA) is a natural phytochemical compound found in a large number of fruits and vegetables with strong antioxidant activity. Through several mechanisms, FA may correct the impaired functionality of diabetic MSCs. A phenolic nucleus and unsaturated side chain in the structure of FA are related to its antioxidant activity [8]. Hence, FA may reverse high-glucose-related damage in cells by preventing methylglyoxal formation [9].

In a recent report, FA increased HIF-1α in messenger RNA and protein levels and enhanced the binding activity of HIF-1α through phosphoinositide-3 kinase (PI3K). Via the HIF-1 pathway, FA increases the expression of various angiogenic and neuroprotective factors, including vascular endothelial growth factor and platelet-derived growth factor-BB [10].

Another mechanism is attenuation of MSC death by FA pre-treatment. FA inhibits inactivation the PI3K/Akt cascade in stressful conditions [11]. PI3K/Akt pathway regulates multiple cellular processes including cell survival and apoptosis. Akt translocation to the nucleus results in phosphorylating certain transcription factors, which contributes to cell survival [7]. Furthermore, the PI3K/Akt cascade induces the direct induction of bcl-2, a key anti-apoptotic protein [7]. It was shown that FA treatment also inhibits stress-related induction of the pro-apoptotic bax gene [12]. The ratio of bax/bcl-2 determines mitochondrial membrane permeabilization, cytochrome C release and cell apoptosis [7]. Furthermore, some evidence indicates that MSCs differentiate into neuronal cells when exposed to a high concentration of FA. These cells resemble neurons and glial cells, which simultaneously express several neural proteins and are suitable for clinical use [13]. However, there is a need to determine the suitable concentrations and time for FA pre-treatment, providing the best protective paracrine effect along with initiating processes that differentiate cells into neuron.

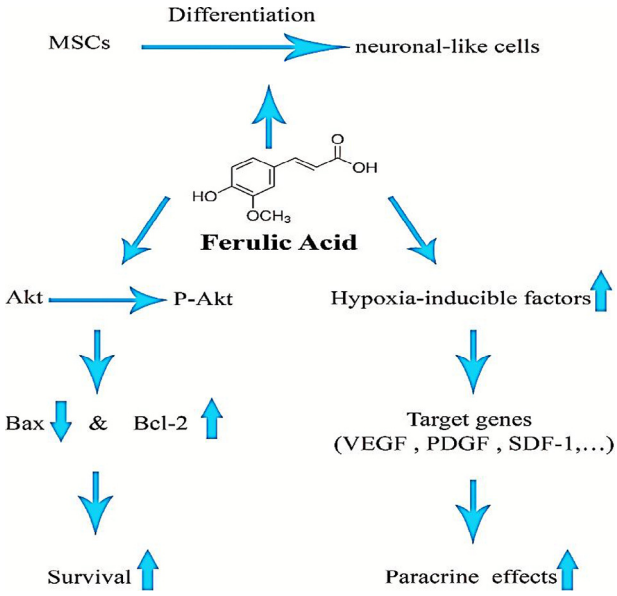

Figure 1. The molecular signaling pathways of FA resulting in increased MSC survival and differentiation capacity.

Taken together, pre-treating MSCs with FA may serve as an effective tool to improve the efficacy of diabetic MSC transplantation for DN by improving the paracrine effect and elevating the viability of diabetic MSCs through affecting HIF-1a and PI3/Akt pathway and, consequently, decreasing apoptosis and accelerating MSCs differentiation into neurons (Figure 1).

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