Endogenous antioxidant level of stem cell is important for the transplantation efficacy

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Stem cell transplantation has been applied to clinical trials and obtained certain curative effect, but due to the severe environmental such as oxidative stress, the efficiency of stem cell transplantation is still low. However, oxidative stress on stem cells, the influence of the transplantation efficiency and its molecular mechanism are not fully understood. In our recent research, we have confirmed that oxidative stress is the mainly reason that caused the low efficiency of hUCMSCs transplantation. In vitro, antioxidants pretreatment of the hUCMSCs can decrease cell apoptosis through the MAPK-PKC-Nrf2 pathway. In vivo, antioxidants pretreatment can accelerate the host hepatic regenerative process and improve the expansion efficiency of stem cells. In this research, the antioxidant we used is edaravone which is now widely used in clinic. Thus, our study has answered how the oxidative stress affects stem cell transplantation efficiency and puts forward a clinical antioxidant which can improve the endogenous antioxidant level of stem cells.

Keywords: Stem cell transplantation; Oxidative stress; Edaravone

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Stem cell transplantation has already been applied to clinical trials for a variety of diseases [¹], such as acute lymphoblastic leukemia [²], acute liver failure [³], and osteoarthritis [⁴] certain proven curative effects. However, the overall disease improvement outcome is below expectation and stem cell transplantation is still inefficient [⁵-⁶]. For example, a study demonstrated that on the first day of transplantation, more than 99% of implanted mesenchymal stem cells (MSCs) have been apoptosized[⁷]. Another random meta-analysis study of autologous bone marrow stem cells (BMMSCs) transplantation in clinical coronary heart disease (CHD) treatment showed that the stem cell therapy could not promote left ventricular reconstruction, and the improvement of left ventricular ejection fraction was only 5% to 10% [⁸]. The low efficacy of stem cell transplantation might be attributed to unfavorable pathologic environment at the injured sites such as strong oxidative stress and inflammation [⁹-¹⁰]. To solve this problem, several studies applied exogenous antioxidant treatments before transplantation and they hypothesized that the endogenous antioxidant level of stem cell was crucial for the cellular survival time post-implantation and the overall treatment efficacy. An important study conducted by Drowley and colleagues found that pre-treatment with antioxidant agent N-acetyl cysteine (NAC) in muscle stem cells before transplantation had a better improving effect on the cardiac functions in a mice myocardial ischemia model, when compared with naïve control [¹¹]. The detailed molecular mechanism of how oxidative stress influences stem cells is not fully understood which warrants further solid mechanistic studies.

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Figure 1. Cellular redox signaling pathway influenced by pre-treatment with antioxidant edaravone or pro-oxidant diethyl maleate (DEM). In an acute cell damage model induced by the co-treatment of hydrogen peroxide and lipopolysaccharides (LPS), excessive reactive oxygen species (ROS) were accumulated in human umbilical cord mesenchymal stem cells (hUCMSCs) which induced the activation of MAPK/PKC-Nrf2 pathway and following cell oxidative injuries. Edaravone pre-treatment, in contrast with DEM, significantly attenuated MAPK/PKC activation and increased Nrf2 activity, leading to enhanced cellular endogenous antioxidant level and promoted cell regenerative ability.

In our recent research,[12] we found that pre-treat human umbilical cord MSCs (hUCMSCs) with antioxidant edaravone or pro-oxidant diethyl maleate (DEM) could significantly further increase or reduce cell viability impaired by exogenous challenge of oxidative stress, which also induced evident apoptosis of hUCMSCs through both intrinsic and extrinsic apoptotic pathways. Edaravone pre-treatment decreased cellular reactive oxygen species (ROS) production through repairing the GSH/GSSG balance and restoring of endogenous level of antioxidant enzymes, such as catalase (CAT) and superoxide dismutase 1 (SOD1), while DEM showed completely opposite effects. Since a number of studies have shown that both mitogen-activated protein kinase (MAPK) and protein kinase C (PKC) pathway directly controlled the transcription activity of nuclear factor erythroid-2 related factor 2 (Nrf2), a center transcriptional regulator of entire body’s redox status via regulating the transcription activity of its downstream genes,[13-14], this study also found that pre-treatment with edaravone decreased the phosphorylation level of both p38 MAPK and ERK1/2, and increased the transcriptional activity of Nrf2, while the inhibition of ERK 1/2 or PKC pathway abolished this effect from edaravone. Inhibition of Keap1, a cellular inhibitor of Nrf2, attenuated the deleterious impact from DEM on stem cells. Thus, we confirmed the key role of MAPK-PKC-Nrf2 pathway in regulating hUCMSCs endogenous antioxidant levels. Moreover, in an acute liver injury mice model induced by galactosamine/lipopolysaccharides (Gal/LPS), we found that hUCMSCs transplantation could promote to host hepatic regenerative process, but the efficacy was quite limited. Edaravone pre-treatment significantly improved the engraftment and expansion efficacy and decreased the apoptotic ratio of stem cells. It also promoted the expression of two regeneration-related genes, oncostatin M (OSM) and epidermal growth factor (EGF), as well as the secretion of hepatocyte growth factor (HGF), which was shown to be beneficial for hepatic injury recovery primarily through a paracrine pattern from nourishing cells.[13]. Taken together, the data suggests that antioxidant pre-treatment enhanced hUCMSCs anti-stress ability and therapeutic efficacy in an acute liver failure model.

In summary, improving the level of endogenous antioxidant of stem cells before transplantation is likely to be a strategy to improve stem cell transplantation. Our research has confirmed that oxidative stress is a major factor that influences the efficiency of stem cell transplantation which is consistent with the previous studies[14-15]. In vitro antioxidant pre-treatment can increase the hUCMSCs viability and reduce its apoptosis impaired by the oxidative challenge, which at least is partly through the MAPK-PKC-Nrf2 pathway (Fig. 1). Other studies consistently show that stem cells have a variety of others pathways to regulate its endogenous antioxidant levels, such as protein kinase B (Akt) activation which leads to stem cells premature aging in oxidative stress[16]. Thus, there is an urgent need for more mechanistic investigations to confirm the detailed antioxidant stress pathway network to improve the clinical stem cell transplantation efficiency. Although we found that antioxidant pre-treatment could faster the host hepatic regenerative process and improve liver function, it should be noted that whether antioxidant pre-treatment causes stem cell neoplasia is another severe security issue. Before its clinical application, improving transplantation efficacy and preventing its tumorigenesis are currently two urgent problems need to be solved.

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Conflicts of interest

The authors declare no conflict of interest.

Author contributions
JX, YL conceived and designed the paper. MY, JX, YL wrote and edited the paper.

References


