Original Article

Bioregulators of stem and progenitor cells in preservation solution reduce cold ischemia-reperfusion injury of isolated rat livers

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Abstract

The effects of bioregulators of stem and progenitor cells (BSPC) of fetal tissue cytosol on rat liver during 24h hypothermic storage (HS) and following normothermic reperfusion (NR) were investigated. It was shown that BSPC presence in the preservation medium stabilized pro-oxidant-antioxidant balance impaired in liver after HS and NR, prevented the uncoupling of mitochondrial oxidative phosphorylation and ATP level decline. These consequences led to significant improvement of hepatic morphological integrity and functional state. Powerful protective effect of BSPC on liver at sub-zero temperatures can serve as basis for new approaches to extend safe time for organ preservation and foster understanding of pathways of stem and progenitor cell paracrine action. © 2016 BioFactors, 00(0):000–000, 2016

Keywords: *stem and progenitor cells; bioregulators; preservation solution; liver hypothermic storage; ischemia-reperfusion*

1. Introduction

In spite of great advances made over the past three decades, search for effective approaches to safe hypothermic storage (HS) of isolated organs for further transplantation is in progress [1,2]. This entails the number of general and alternative ways to reduce ischemic and following warm reoxygenation deterioration [3,4]. Application of various biologically active substances in order to maintain the organ functional activity during cold preservation and subsequent normothermic reperfusion (NR) is one example of such method. The ways of use for these agents vary—they can be applied either for donor pretreatment *in vivo* or as the components of storage and/or perfusion solutions.

The possibility to ameliorate organ state before transplantation using a mixture of trophic factors added to preservation medium attracted attention of many researchers. It has been shown that the presence of such mixture (insulin-like, epidermal, and nerve growth factors, bactenicin, substance P) in University of Wisconsin (UW) solution substantially improved viability and reduced the production of hydrogen peroxide by tubular cells from dog kidneys after 3 days of HS [5], protecting mitochondria and preventing apoptosis [6]. Furthermore, the addition of these bioregulators prolonged the storage time (up to 6 days) and maintained the post-transplant renal function [7]. The efficiency of preservation medium, enriched in this way, was also demonstrated on the model of allogenic liver transplantation in pigs [8].

In our previous studies the effects of bioregulators of stem and progenitor cells (BSPC) contained in fetal tissue cytosol of mesenchymal-mesodermal origin in several of experimental pathologies were shown [9–11]. Our choice of this cell type was due to their well-known unique capacity to produce a wide range of biologically active substances that affect the intra- and extracellular processes [12–14]. Bioregulators produced by mesenchymal stromal cells include a number of cytokines, growth factors, chemokines, etc. [15–17].

It was determined that rat pretreatment with BSPC for 4 h before liver long-term HS (24 h) and following NR (60 min) led to decrease of free radical production and normalization of antioxidant system function [18]. Also, animal preconditioning with bioregulators had a positive effect on ATP level and

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