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Research Article

Protective Effect of Adipose-Derived Mesenchymal Stem Cell Secretome against Hepatocyte Apoptosis Induced by Liver Ischemia-Reperfusion with Partial Hepatectomy Injury

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Ischemia-reperfusion injury (IRI) is an inevitable complication of liver surgery and liver transplantation. Hepatocyte apoptosis plays a significant role in the pathological process of hepatic IRI. Adipose-derived stem cells (ADSCs) are known to repair and regenerate damaged tissues by producing bioactive factors, including cytokines, exosomes, and extracellular matrix components, which collectively form the secretome of these cells. The aim of this study was to assess the protective effects of the ADSCs secretome after liver ischemia-reperfusion combined with partial hepatectomy in miniature pigs. We successfully established laparoscopic liver ischemia-reperfusion with partial hepatectomy in miniature pigs and injected saline, DMEM, ADSC-secretome, and ADSCs directly into the liver parenchyma immediately afterwards. Both ADSCs and the ADSC-secretome improved the IR-induced ultrastructural changes in hepatocytes and significantly decreased the proportion of TUNEL-positive apoptotic cells along with caspase activity. Consistent with this, P53, Bax, Fas, and Fasl mRNA and protein levels were markedly decreased, while Bcl-2 was significantly increased in the animals treated with ADSCs and ADSC-secretome. Our findings indicate that ADSCs exert therapeutic effects in a paracrine manner through their secretome, which can be a viable alternative to cell-based regenerative therapies.

1. Introduction

Hepatic ischemia-reperfusion injury (HIRI), a precursor to liver dysfunction and liver failure [1], is an inevitable complication of shock, trauma, hepatectomy, liver transplantation, and other surgical procedures [2–4]. The pathophysiological process of HIRI involves excessive production of reactive oxygen species (ROS), activation of Kupffer cells and other inflammatory cells, and calcium overload, which eventually lead to hepatocellular apoptosis [5]. Although orthotopic liver transplantation (OLT) is an effective treatment for terminal liver dysfunction, it is limited by organ shortage, high costs, immune rejection, and transplant-related complications [6]. HIRI is still an unresolved clinical issue, and an effective strategy is urgently needed to alleviate HIRI and improve patient prognosis.

Stem cell therapy is a promising approach for tissue repair and regeneration [7–9]. Mesenchymal stem cells (MSCs) in particular have shown encouraging results against inflammatory, degenerative, and ischemia-reperfusion diseases [10–12] since they can be isolated from multiple sources, including adipose tissue [13], bone marrow, dental pulp [14], umbilical cord blood [15], tonsils [16], oral cavity [17], and amniotic fluid [18]. Adipose-derived stem cells (ADSCs) are increasingly being considered a promising tool for cellular therapy and tissue engineering [19]. Depending on the environmental stimuli, ADSCs can differentiate into osteoblasts, adipocytes, and hepatocytes [20] and are therefore highly suitable for cell-based therapy in multiple organ systems. However, the clinical application of stem cells is limited by long-term safety concerns, such as unwanted differentiation [21], potential tumorigenicity [22], and elimination