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The differentiation of MSCs into functional hepatocyte-like cells in a liver biomatrix scaffold and their transplantation into liver-fibrotic mice

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ABSTRACT

Hepatocytes derived from mesenchymal stem cells (MSCs) hold great potential for cell-based therapies for liver diseases. The cell-based therapies are critically dependent on the hepatic differentiation of the MSCs with a high efficiency and on a considerable scale. Recent results have shown that decellularized organs provide a three-dimensional extracellular matrix for the lineage restriction of stem cell maturation. In this study, we compared the cell proliferation and hepatic differentiation of murine MSCs in a biomatrix scaffold from rat liver and in the presence and absence growth factors (GF) with a two-dimensional substrate. In the absence or presence of GF, the dynamic cultured scaffold (DCS) stimulated the MSCs to express endodermal and hepatocyte-specific genes and proteins associated with improved functions, and the cells exhibited the ultrastructural characteristics of mature hepatocytes. When transplanted into CCl_4-injured mice, the cells pretreated with a combination of the DCS and GF exhibited increased survival, liver function, engraftment into the host liver and further hepatic differentiation. The paracrine effect of the transplanted cells on hepatic stellate cells and native hepatocytes played a key role in the treatment of the liver pathology. These studies define an effective method that facilitates the hepatic differentiation of MSCs exhibiting extensive functions and support further research into the use of a decellularized liver matrix as a bioscaffold for liver tissue engineering.

1. Introduction

Liver transplantation remains the definitive treatment option for end-stage liver disease. However, the surgical complications, chronic rejections, critical shortage of donor organs and high cost of this procedure have sparked tremendous interest in finding new treatments [1]. Cell-based therapies, such as cell transplantation and bioartificial liver devices, have emerged as alternative therapies [2,3]. Because of the difficulties associated with obtaining autologous hepatic tissue and maintaining the phenotype of the primary hepatocytes in culture, the scarcity of human hepatocytes remains a serious roadblock for the development of cell-based therapies [4]. Therefore, the promise of a renewable supply of functional hepatocytes from an alternative source represents an important goal in current studies.

Stem cells are considered an alternative cell source for functional hepatocytes. Increasing evidence suggests that the differentiation of stem cells into hepatocytes is achieved in the appropriate microenvironment following stimulation with hepatic growth factors [5–7]. Mesenchymal stem cells (MSCs) are a type of adult stem cell and, compared to hepatocytes, are more suitable for cell therapy because of their adequate availability, easy accessibility, rapid proliferation, multipotent differentiation, and successful integration and immunological tolerance in the host tissue [8]. Meanwhile, MSCs could be derived from a patient's own tissues rather than blastocyst or embryos, and are considered more appropriate for clinical use [9]. In addition, it has been shown that the transplantation of MSCs or MSC-derived hepatocyte-like cells improves the liver function in rodents [10,11] or patients [12] suffering from liver damage. However, the several traditional protocols used to date have had limited success, and these hepatocyte-like cells exhibit only a portion of the markers and

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