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REGULAR ARTICLE

Human endometrial adult stem cells can be differentiated into hepatocyte cells

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Abstract Liver transplantation is the only choice for patients with end-stage liver diseases. Hepatocyte transplantation is a promising alternative for treatment of these groups. However, the major challenge is insufficiency of donor organs that can provide good-quality cells. Therefore, numerous experimental and clinical studies have evaluated the potential of different sources of adult stem cells, which differentiate into hepatocytes, for cell therapy. Endometrial (stem) stromal cells are readily isolated and expandable; moreover, these cells have more clonogenicity and pose less technical problems, so they are considered to possess great autologous therapeutic potential.

We propose that endometrial stem (stromal) cells could be an invaluable and realistic source in this regard.

Introduction

Liver failure is a growing health problem ranking as one of the supreme causes of death worldwide [1]. Liver transplantation (LTx) is presently the available efficient method for treatment of various end-stage liver diseases [2]. However, it is restricted by the lack of donor organs, immunosuppression and rejection [3]. Therefore, new therapeutic methods are significantly required. Stem cell-based therapy has been proposed as an alternative way to treat liver diseases in an enormous number of patients.

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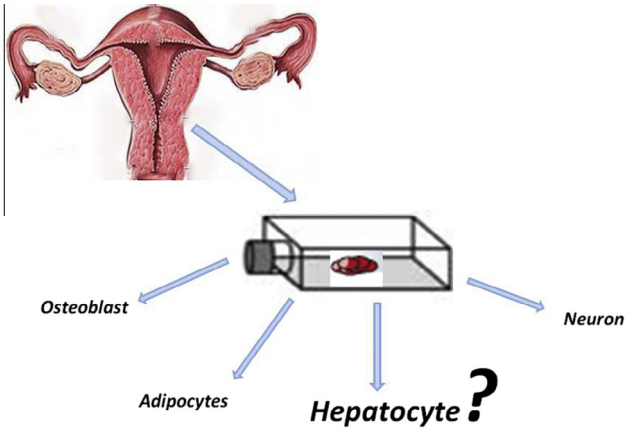

Figure 1 Schematic presentation of our hypothesis.

Cell transplantation is less invasive compared to LTx; it also diminishes mortality in acute liver failure, and can be employed for the treatment of metabolic liver diseases [4–7].

Hepatocyte transplantation (Htx) has been adopted as the credible alternative to LTx [2]. Hepatocyte cells have previously been derived from embryonic stem cells (ESCs), adipose tissue, bone marrow stem cells, mesenchymal cells and multipotent progenitor cells in the human umbilical cord [8–12]. So far, it is not clear as to which stem cell type will be particularly effective in forming cell lines that will be promising in cell therapy. Therefore, it seems vital to investigate the capability of other sources of adult stem cell such as amniotic stem cells and endometrial stem cells to prove their potentiality for medical application.

Human endometrial layers contain a population of stromal (stem) cells, which are presumed to be adult stem/progenitor cells that are responsible for the remarkable regenerative capacity of the endometrium [13–15].

Human endometrial-derived stem cells (EnSCs) have the potential to differentiate into mesoderm-derived cells such as those of chondrogenic and osteoblastic lineages [16,17].

EnSCs are easily isolated and also expand rapidly from patients without leading to major ethical and technical problems, as well as produce a higher overall clonogenicity [13,18]. Previous studies concerning long-term follow-ups of animals treated with endometrial regenerative cells with normal karyotypes, after extended passage (68 doublings), confirmed lack of tumourigenicity of these cells [19]. In addition, autologous transplantation of endometrial stromal cells from a healthy donor should minimise the risks of rejection [20]. Hence, these cells are extremely useful tools for therapeutic application.

Hypothesis

Multipotent adult stem/progenitor cells in the endometrium are characterised by a remarkable regenerative capacity of undergoing repetitive cycles of growth and differentiation. Endometrial regenerative cells possess the potential to differentiate into adipocytes, endothelial cells, pancreatic cells and neurons [19] (Table 1). According to our previous invaluable experiments (un published data), EnSCs have a great potential to differentiate into adipocytes, osteoblasts as well as neurons, and these cells are capable of generating odontoblasts as well as myoblast cells [21,22]. Thus, it is hypothesised that endometrial adult stem (stromal) cells, could be novel candidates for derivation of hepatocytes, and provide an attractive alternative resource for liver cell-based therapies (Fig. 1).

Evaluation of hypothesis

To confirm our hypotheses:

The biopsies are treated with collagenase for cell isolation. The isolated cells were cultured in Dulbecco's modified Eagle's medium (DMEM). Flow cytometry is preformed for cell-surface markers (CD 146, CD31, CD44, CD90, CD105, CD34, CD133 and STRO-1) to characterise EnSCs which were isolated from endometrial biopsies. Consequently, after differentiation of the EnSCs into hepatocytes by using specific mediums, immunocytochemical procedures are preformed for evaluating expression of Oct4 and Sox2, and reverse transcriptase polymerase chain reaction (RT-PCR) is performed to

Table 1 Differentiation capacity of endometrial stem/progenitor cells.

Solid tissue	Menstrual blood cells	Differentiated cells	References
+	–	Adipocytes, osteocytes, smooth muscle cells, chondrocytes	[25,26]
+	–	Adipocytes, osteocytes, smooth muscle cells, chondrocytes	[27]
+	–	Endothelial cells	[28]
+	–	Chondrocytes, dopaminergic neurons	[29,30]
	–	Endothelial cells, Smooth muscle cells	[31,32]
	+	Cardiomyocytes, myocytes, adipocytes, osteocytes, smooth muscle cells, chondrocytes, neural cells, *Hepatocyte*[*]	[33–36,19]

In this hypothesis we want to evaluate the potentiality of stem cells which are originated from endometrium tissue.
[*] Menstrual blood stem cells have been the only source of derived hepatocyte.