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REVIEW ARTICLE

Concise Review : Differentiation of Human Adult Stem Cells Into Hepatocyte-like Cells In vitro

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Adult stem cells (ASCs) are undifferentiated cells found throughout the body that divide to replenish dying cells and regenerate damaged tissues, which are the powerful sources for cell therapy and tissue engineering. Bone marrow-derived mesenchymal stem cells (BMSCs), adipose tissue-derived mesenchymal stem cells (ADSCs), and peripheral blood monocytes (PBMCs) are the common ASCs, and many studies indicated that ASCs isolated from various adult tissues could be induced to hepatocyte-like cells in vitro. However, the isolation, culture protocols, characterization of ASCs and hepatocyte-like cells are different. This review aims to describe the isolation and culture procedures for ASCs, to summarize the molecular characterization of ASCs, to characterize function of hepatocyte-like cells, and to discuss the future role of ASCs in cell therapy and tissue engineering.

Keywords: Adult stem cells, Bone marrow-derived mesenchymal stem cells, Adipose tissue-derived mesenchymal stem cells Peripheral blood monocytes, Hepatocyte-like cells

Introduction

Currently, liver transplantation is the only definitive treatment for the end-stage liver diseases. However, its widely used was limited by the expensive costs, shortage of donor organs and invasive procedure (1). Hepatocyte transplantation has emerged as a feasible alternative to liver transplantation in some liver diseases (2), but it is limited by organ donors and the low cell quality of available liver tissues (3, 4). Thus, searching other sources of cells to replace mature hepatocytes is urgent.

Although human embryonic stem cells (hESCs) and umbilical cord blood stem cells (UCBSC) could be induced into hepatocyte-like cells in vitro (5), their widely used were limited by the low differentiation quality, ethics, and teratoma formation (6). Recently, the adult stem cells (ASCs) derived from various tissues, including bone marrow derived mesenchymal stem cells (BMSCs), adipose tissue derived mesenchymal stem cells (ADSCs), and peripheral blood mononuclear cells (PBMCs) have been developed as new cell sources contributing to liver regeneration for their high efficiency of hepatogenic differentiation using simple procedures and no ethnic issues (7-10).

In the present study, we investigated whether ASCs are the ideal seed cells for the liver regeneration from the followings: ASCs biology, including isolation, culture, differentiation to hepatocytes, and the further role of ASCs in cell therapy and tissue engineering.

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Materials and Methods

Materials

In recent studies, samples of human bone marrow were obtained by Lumbar Puncture (LP), human adipose tissue were obtained from abdominal subcutaneous adipose tissue of gastric cancer patients or liposuction patients, human peripheral blood were obtained from patients with HBV or healthy adult blood donors, in accordance with the local ethics committee.

Isolation and expansion of BMSCs, ADSCs, and PBMCs

Most laboratory data showed that BMSCs could be prepared through the density degree of centrifuge, flow cytometry sorting, and sidewall sieve method (11-14). sidewall sieve method has become popular one for its simple operation, lower cost, less injury to cell (15). Adipose tissue was minced with scissors and scalpels into less than 3mm pieces and isolation of ADSCs proceeded as previously described (16, 17). Generally, human peripheral blood monocytes isolated from donors were isolated by density gradient centrifugation and further purified by adherence separation. In order to obtain more PBSCs in shortly time, PBMCs were mobilized with recombinant G-CSF at 5～10 μg/kg/d, administered subcutaneously daily to mobilize PBMCs from bone marrow to peripheral blood (18, 19). Then PBMCs were collected by means of aphaeresis.

Characterization of ASCs

Flow Cytometer was used to identify the surface marker of the adult stem cells. Conget et al indicated that the BMSCs express many surface agents including CD13, CD44, CD29, CD105, but didn't express CD1a, CD14, CD31, CD34, CD56, CD45 (20). ASCs derived from all three sources displayed no expression of hematopoietic markers (CD14, CD34, CD45), of the stem cell marker CD133, or the marker for endothelial cells CD144. More than 90% of MSCs derived from the three sources expressed the typical MSC marker proteins CD44, CD73, CD29, and CD90. However, the intensity of expression of CD90 of PBSCs was significantly below that of the other tissues. More than 90% of the ASCs derived from all three sources expressed HLA I; however, none of the MSCs expressed HLA II. CD105 was expressed by a significantly lower percentage of PBSCs compared with BM- or AD-SCs, whereas, more PB- and BM-SCs expressed CD106 than ADSCs. ADSCs expressed similar surface markers to BMSCs (21, 22). Besides the fact, that they are more heterogeneous (23), they reveal a surface antigen marker profile (22, 24-26), and differentiation potential similar to BMSCs (27-32). ADSCs are characterized as CD45-, CD34+, CD105+, CD31-(33) (Table 1).

Table 1. Identification of different ASCs from gene expression

	BMSCs	ADSCs	PMSCs
CD10	+	+	+
CD13	+	+	+
CD59	+	+	+
CD105	+	+	+
CD166	+	+	+
CD49d	+	+	+
SH3	+	+	+
CD29	+	+	+
CD44	+	+	+
CD71	+	+	+
CD90	+	+	+
CD106	+	+/−	+/−
CD120a	+	+	+
CD124	+	+	+
CD11b	−	−	−
CD14	−	+/−	+
CD31	−	+/−	−
CD34	−	−	+
CD45	−	−	+
CD48	−	−	−
CD135	−	−	−
CD117	+	+/−	+/−

Protocols of ASCs' transdifferentiation

Some studies indicated that functional hepatocytes could be induced from ASCs by some cytokines or through coculture with other cell types. However, the potential of the ASCs' transdifferentiation is generally low. Therefore, researchers are keen to explore new methods to induce ASCs differentiate into functional hepatocytes in vitro currently. The current protocols used in different ASCs are summarized in Table 2.

Functional analysis of hepatocyte-like cells from ASCs

The hepatocyte-like cells from ASCs were confirmed from the gene and protein expression. Gene expressions were identified by RT-PCR, using the common markers of hepatocytes, including ALB, AFP, CK18, CK19, and CYP3A4 (34). Protein expressions were usually identified by immunohistochemistry or mmunofluorescence, western blot, from the expression of albumin, CK18, CYP3A4, CYP1A1, CYP2C9 and NADPH-P450 (35-38). To compare the potential of hepatogenic differentiation of the different adult stem cells in vitro, researches indicated ADSCs have a similar differentiation potential towards the hepatic lineage, similar to BMSCs. However, their longer culture period and proliferation capacity differ from the BMSCs (39-41).

Table 2. Overview of ASCs expansion, and hepatic differentiation

	Expansion Medium	Hepatic Differentiation Medium	Ref.
BMSCs	DMEM, 10% FBS	500 ml Williams Medium E with-out L-glutamine, 50 mg/l L-glutamine, 100 IU/l penicillin/streptomycin, 20 mM HEPES, 20 mM sodium pyruvate, 5 nM Dex, 10 ng/ml EGF, 5 ng/ml HGF; 20 mU/ml insulin, 10% FBS, and 10% horse serum	42
	DMEM, 10% FBS	100 U/ml penicillinG, 100 μg/ml streptomycin, 50 ng/ml amphotericin B and 100 ng/ml aprotinin in William's medium E. Medium A contained 10% FBS;medium. Medium Bcontained 1 nM insulin and 1 nM Dex in medium A and Coculture with Hepatocytes	43
	DMEM, 5% FBS	0.03 mM nicotinamide, 0.25 mM sodium-pyruvate and 1.623 mM glutamine,10 ng/ml FGF-4, 20 ng/ml HGF, 1×ITS and 20 lg/l Dex	44
	60% DMEM-LG/5% FBS, 40%MCDB -201, 1x ITS, 10-9M Dex, 10-4M ascorbic acid 2-phosphate, 10 ng/ml EGF, 100 U penicillin, 1000 U streptomycin	DMSO (0.1%), HGF (10 ng/ml), OSM (10 ng/ml)	45
	DMEM-LG,15% human serum, 50 μg/ml gentamicine	EGF (20 ng/ml), bFGF (10 ng/ml), HGF (20 ng/ml), nicotinamide (4.9 mmol/l), OSM (20 ng/ml), Dex (1 μmol/l), ITS (10 μl/ml), BSA (1.25 mg/ml), linoleic acid (190 μmol/l)	46
ADSCs	DMEM, 10% FBS	Transferrin (5 μg/ml), hydrocortisone-21-hemisuccinate (10^{-6} M), BSA (0.5 mg/ml), ascorbic acid (2 mM), EGF (20 ng/ml), insulin (5 μg/ml), Dex (10^{-8} M), HGF (150 ng/ml), FGF1 (300 ng/ml), FGF4 (25 ng/ml), OSM (30 ng/ml), Dex (2×10^{-5} mol/l)	47
	DMEM, 10% FBS	Activin A (20 ng/ml), FGF4 (20 ng/ml), transferrin (5 μg/ml), hydrocortisone-21-hemisuccinate (10^{-6} mol/l), BSA (0.5 mg/ml), ascorbic acid (2 mmol/l), EGF (20 ng/ml), insulin (5 μg/ml), Dex (10^{-8} M), HGF (150 ng/ml), FGF1 (100 ng/ml), FGF4 (25 ng/ml), OSM (30 ng/ml), Dex (2×10^{-5} mol/l), 1x ITS, nicotinamide (0.05 mmol/l), DMSO (0.1%)	48
	60% DMEM, 40% MCDB, 5 mg/ml apotransferrin, 5 ng/ml selenous acid, 5 mg/ml linoleic acid, 5 mg/ml bovine insulin, 100 mM ascorbic acid 2-phosphate, 1 nM Dex, 10 ng/ml PDGF, 10 ng/ml EGF, 100 U/ml penicillin, 10 mg/ml streptomycin, 15% FCS	5' Azacytidine (20 μM), human hepatocyte maintenance medium, FCS (2%), HGF (40 ng/ml), EGF (20 ng/ml)	49
	60% DMEM-LG, 40% MCDB-201, 1x ITS, 1 nM Dex, 100 mM ascorbic acid 2-phosphate, 10 ng/mL EGF, 5% FBS	Dex (1 nM), ascorbic acid (100 μM), EGF (10 ng/ml), bFGF (10 ng/ml), HGF (10 ng/ml), OSM (10 ng/ml), DMSO (0.1%)	50
PMSCs	RPMI 1640 medium,10% human ABserum, 2 mmol/L glutamine, 100 U/mL penicillin, and 100 μg/mL streptomycin	RPMI 1640 medium,10% human ABserum, 2 mmol/L glutamine, 100 U/mL penicillin, and 100 μg/mL streptomycin, 140 μmol/L β-mercaptoethanol, 5 ng/mL M-CSF, 0.4 ng/mL human IL-3, 3 ng/mL [FGF]-4	51

Discussion

In the present study, we described different ASCs could be induced into hepatocyte lineage cells in different culture systems in vitro. It is very safe and easy to acquire the enough ASCs, and then induce them into functional hepatocytes in vitro. Based on this progress, ASCs transplantation might be a novel therapy for the severe liver diseases, and also will be ideal seed cells for liver tissue engineering. However, which ASCs are better still needs us to investigate from their preparation, molecular characterization, and functional assay. This paper firstly pro-

vides such a concise review focused on ASCs' biology and differentiates potential, indicating ASCs might be an ideal seed cells in cell transplant therapy and tissue engineering. We also believe in the future, some studies will show us the most appropriate ASCs for cell transplant or tissue engineering.

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Potential conflict of interest

The authors have no conflicting financial interest.

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