Differentiation 79 (2010) 65–73

Contents lists available at ScienceDirect

Differentiation

journal homepage: www.elsevier.com/locate/diff

Review

Commitment of stem cells into functional hepatocytes ☆

Takahiro Ochiya *, Yusuke Yamamoto, Agnieszka Banas

Section for Studies on Metastasis, National Cancer Center Research Institute, 5-1-1, Tsukiji, Chuoku, Tokyo 104-0045, Japan

ARTICLE INFO

Article history:
Received 4 February 2009
Received in revised form
14 July 2009
Accepted 9 October 2009

Keywords:
Stem cells
ES
iPS
MSC
Hepatocyte
Differentiation

ABSTRACT

Liver transplants represent the only way to treat patients suffering from terminal liver failure, but they are associated with numerous problems, including a chronic shortage of donors, high cost, rejection, and side effects for the donor. It is anticipated that regenerative medicine will provide an alternative to liver transplants for such patients. Regenerative medicine refers to the academic field of eliciting the inherent capacity of organisms for self-regeneration to the greatest possible extent in order to develop new methods of treatment for intractable disorders. From this perspective, much is expected from the use of human embryonic stem cells (ES cells) or induced pluripotent stem cells (iPS cells), and the vigorous development of technology to induce the differentiation of such stem cells into cells possessing hepatic functions is underway. Clinical applications of these human stem cells, however, have yet to reach even the earliest stages of implementation. Facing off against these versatile ES cells are stem cells derived from somatic cells present within organisms, which are attracting attention owing to their superiority in terms of ethics and safety, with many research institutes now in the process of elucidating the details of stem cell separation and identification as well as their plasticity and pluripotency. Bone marrow cells are the best-known somatic-cell-derived stem cells, but the use of mesenchymal stem cells (MSCs) found in adipose tissue has also recently attracted attention. This paper will review the differentiation ability and mechanisms of these various stem cell types to hepatocytes and their application to liver regeneration and the future outlook.

Contents

Abbreviations: AT-MSCs, adipose-tissue-derived mesenchymal stem cells; BMP, bone morphogenetic protein; Dex, dexamethasone; EGF, epidermal growth factor; ES cells, embryonic stem cells; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; HNF, hepatocyte nuclear factor; iPS cells, induced pluripotent stem cells; MET, mesenchymal-to-epithelial transition; MSCs, mesenchymal stem cells; NGF, nerve growth factor; OsM, oncostatin M; VEGF, vascular endothelial growth factor

☆ Join the International Society for Differentiation (www.isdifferentiation.org).

* Corresponding author. Tel.: +81 3 3542 2511x4800; fax: +81 3 5565 0727.
E-mail address: tochiya@ncc.go.jp (T. Ochiya).

0301-4681/$ - see front matter © 2009 International Society of Differentiation. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.diff.2009.10.002

1. Introduction

Many studies on stem cell plasticity are challenging the concept that stem cells contain an intrinsically predefined, unidirectional differentiation program. This means that the developmental fate of a stem cell is dependent on the general potential of the cell as well as on microenvironmental cues, such as stimuli from stem cell niche (Eckfeldt et al., 2005). Despite many reports on the differentiation potential of stem cells, there is little understanding of the molecular basis of stem cell plasticity. Array-based gene expression analyses of "stemness" have been reported. Under normal conditions, the expression of "stemness genes" is tightly regulated by a dynamic array of mediators, including the spatial and temporal expression of inhibitors and the epigenetic modulation of the genome. When stem cells are exposed to microenvironmental cues of tissue or organ injury and regeneration, the balance of regulatory mediators is restored, with the plasticity of stem cells being induced towards differentiation into a specific cell lineage.

In the natural milieu, the hepatic differentiation of stem cells involves multiple pathways (Zaret and Grompe, 2008). This in vivo process may be mimicked in vitro by using a combination of various factors and culturing conditions. It is anticipated that, over the next few years, we will see profound investigations of hepatic stem cells and, particularly, of their mechanisms, transduction pathways, and epigenetic modulations. Hepatic differentiation may certainly be enhanced by further studies and a combination of various techniques, including tissue-engineering technologies. In considering stem cell-based therapy, MSCs have emerged with great potential (Franco Lambert et al., in press). An assortment of studies has documented their contribution in hepatogenic generation in vivo and in vitro. Preliminary results of only a few clinical studies on the administration of bone marrow stem cells to liver cirrhotic patients seem to be very promising, but additional well-designed and controlled studies are needed. We herein present the current knowledge what we obtained from differentiation of functional hepatocytes from several types of stem cells.

2. Differentiation of stem cells

In Table 1, key features of several stem cells including ES cells, iPS cells, MSCs, and tissue stem cells (TSCs) are summarized. Recent years have seen substantial progress in research on stem cell plasticity and regenerative medicine using stem-cell-derived cells, and technologies are now being developed to induce the differentiation of numerous cell types from ES cells and TSCs present in adult organs. For cells such as skin and cartilage, regeneration is already underway at the tissue rather than the cellular level, and clinical applications are being launched. In the field of liver regenerative medicine, the future introduction of clinical applications for real human hepatocytes with multiple liver-specific functions is now anticipated (Fig. 1). Numerous laboratories have reported the differentiation induction of ES cells or MSCs as a stem cells source for hepatocytes (Banas et al., 2006, 2007).

3. Current status of hepatic differentiation of ES cells

The first report of hepatic differentiation of mouse ES cells was in 2001 by Hamazaki et al., who produced an embryoid body from an ES cell and subsequently added fibroblast growth factor (FGF), then hepatocyte growth factor (HGF), and finally oncostatin M (OsM), and dexamethasone (Dex) to induce the differentiation of cells exhibiting hepatocyte-like properties (Hamazaki et al., 2001). In 2003, Yamamoto et al. produced hepatic cells with a high level of liver function by transplanting ES cells into mice with regenerated livers. Viewed under an electron microscope, even in terms of ultrastructural analysis, these ES-derived hepatocytes were genuinely similar to normal hepatocytes, and our work was the first in which ES cell differentiation was induced, in which the resulting cells were cultivated in vitro, in which their hepatic functions were measured, and in which they were transplanted into the livers of immunodeficient mice (Yamamoto et al., 2003). Soto-Gutiérrez et al. (2007) successfully induced the differentiation of hepatocytes with the ability to produce glucose and

Table 1
Characteristics of stem cells.

	Established artificial stem cells		Adult stem cells	
	ES	iPS	MSC	TSC
Autologous transplantation	No	No (possibly Yes)	Yes	Yes
In vitro differentiation	Yes	Yes	Yes	Partial commitment
In vivo differentiation	Yes	Yes	Yes	Yes
Differentiation potency	Very high	Very high	High(limited)	Limited
Growth in vitro	Infinite	Infinite	Semi-infinite	Limited
Ethical issues	Yes	Low or No	No	No
Availability in medicine	No	YES	Yes	Potentially Yes
Legislative/governmental law	YES	No	No	No
Tumorigenesis	YES	YES	Low or No	No
Rejection	YES	No	No	No
Trophic activity *in vivo*	No	No	YES	?

ES: embryonic stem cell; iPS: induced pluripotent stem cell; MSC: mesencymal stem cell; TSC: tissue stem cell.