Biotechnology Advances 29 (2011) 815–829

Contents lists available at ScienceDirect

Biotechnology Advances

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

Research review paper

Stem cell cultivation in bioreactors

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ARTICLE INFO

Article history:
Received 22 December 2010
Received in revised form 11 June 2011
Accepted 12 June 2011
Available online 25 June 2011

Keywords:
Stem cells
Bioreactors
Cell culture
Stem cell engineering
Stem cell bioprocessing
Regenerative medicine

ABSTRACT

Cell-based therapies have generated great interest in the scientific and medical communities, and stem cells in particular are very appealing for regenerative medicine, drug screening and other biomedical applications. These unspecialized cells have unlimited self-renewal capacity and the remarkable ability to produce mature cells with specialized functions, such as blood cells, nerve cells or cardiac muscle. However, the actual number of cells that can be obtained from available donors is very low. One possible solution for the generation of relevant numbers of cells for several applications is to scale-up the culture of these cells in vitro. This review describes recent developments in the cultivation of stem cells in bioreactors, particularly considerations regarding critical culture parameters, possible bioreactor configurations, and integration of novel technologies in the bioprocess development stage. We expect that this review will provide updated and detailed information focusing on the systematic production of stem cell products in compliance with regulatory guidelines, while using robust and cost-effective approaches.

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Contents

Abbreviations: 2D, Two-Dimensional; 3D, Three-Dimensional; BFU-E, Burst-Forming Units-Erythrocyte; CFCs, Colony-Forming Cells; CFU-F, Colony-Forming Units-Fibroblast; CFU-GEMM, Colony-Forming Units-Granulocyte-Erythrocyte-Macrophage-Megakaryocyte; CFU-GM, Colony-Forming Units-Granulocyte-Macrophage; EBs, Embryoid Body; EMEA, European Medicines Evaluation Agency; ESCs, Embryonic Stem Cells; FDA, Food and Drug Administration; GMP, Good Manufacturing Practices; HARV, High Aspect Ratio Vessel; HSCs, Hematopoietic Stem Cells; HSPCs, Hematopoietic Stem and Progenitor Cells; iPSCs, Induced Pluripotent Stem Cells; LIF, Leukemia Inhibitory Factor; LTC-ICs, Primitive Long-Term Culture Initiating Cells; MAPCs, Multipotent Adult Progenitor Cells; MEF, Mouse Embryonic Fibroblast; MESCs, Mammary Epithelium Stem Cells; MNCs, Mononuclear Cells; MSCs, Mesenchymal Stem Cells; NSCs, Neural Stem Cells; PB, Peripheral Blood; PET, Polyethylene Terepthalate; PSCs, Pluripotent Stem Cells; Ri, ROCK Inhibitor; SBs, Stirred-Suspension Bioreactors; STLV, Slow Turning Lateral Vessel; UCB, Umbilical Cord Blood.

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0734-9750/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.biotechadv.2011.06.009

1. Introduction

Stem cells are undifferentiated cells with self-renewal capacity and the ability to differentiate into mature cells (Passier and Mummery, 2003). These properties are very appealing for therapeutic applications, but the actual number of cell therapy products that have reached the market is still very low (Parson, 2008). Most likely, the success of these approaches will be dependent on the development of novel technologies that allow the systematic production of cells in a robust and cost-effective manner (*e.g.* bioreactors) (Kirouac and Zandstra, 2008).

In fact, for some applications the number of cells needed to treat an adult patient greatly surpasses the number of cells available from donors (Laflamme and Murry, 2005; Sohn et al., 2003). Moreover, the need to develop fully controlled large-scale bioreactors arises not only from the limited number of cells that can be obtained from available donors, but also from the need to comply with strict regulatory guidelines (FDA, EMEA) (Cabral, 2001). Since the desired products are cells, further challenges related to good manufacturing practices (GMP) and product safety also need to be overcome (Unger et al., 2008) (Fig. 1a). Donor-to-donor variability, microbiological contamination, potential tumorigenicity of the transplanted cells, among others, are examples of such issues (Ahrlund-Richter et al., 2009).

Furthermore, stem cell engineering strategies can also contribute for studying the mechanisms controlling cellular events such as proliferation and differentiation (Vazin and Schaffer, 2010), and consequently greatly benefit process development (Amanullah et al., 2010). Additional empirical and mechanistic modeling, along with other rational approaches for process optimization (Lim et al., 2007), may also contribute to further comprehend the factors that affect a given system. Successful in vitro models will therefore enable the study of the mechanisms and dynamics of stem cell differentiation and organ development (Abranches et al., 2009). Moreover, meaningful pharmacological studies can also be carried out using such strategies (Lee et al., 2008).

Therefore, the propagation and differentiation of stem cell populations under controlled conditions remains a major technical challenge due to the complex kinetics of the heterogeneous starting culture population, the transient nature of the subpopulations of interest, the lack of invariant measures, and multiple interactions between culture parameters, such as growth factor concentration, dissolved oxygen tension, or cell–cell interactions. Advances in bioreactor culture have been reviewed for specific populations of stem cells, like mesenchymal stem cells (Godara et al., 2008), hematopoietic stem cells (Cabral, 2001; Cabrita et al., 2003; Safinia et al., 2005), neural stem cells (Kallos et al., 2003) or pluripotent stem cells (Azarin and Palecek, 2010a; Kehoe et al., 2010). Interesting points of view were also published regarding key issues related with this field, like stem cell bioprocessing (Placzek et al., 2009), challenges for the development of novel cellular therapies (Kirouac and Zandstra, 2008) and the application of engineering principles to understand and manipulate stem cell behavior (Ashton et al., 2011). In this review, we focus on the fundamental issues related to bioprocess and bioreactor development towards the in vitro expansion, maintenance and/or controlled differentiation of stem cells, while keeping their functional characteristics, including the ability to differentiate into appropriate tissues. In the following sections we give an overview of the progress already achieved with different stem cell populations, in different bioreactor systems, and describe recent developments and new technologies for stem cell cultivation. We expect to provide an updated and integrated perspective based on initial reports from the literature, and also on recent developments from this field.

1.1. Stem cell isolation and characterization

The isolation of stem cells from donor sources and their functional characterization represent the initial steps in the design of a new process (Kirouac and Zandstra, 2008). In fact, different stem cell populations can be used for the clinical production of cellular products. Cells isolated from embryonic, fetal or adult tissues and, more recently, pluripotent stem cells (PSCs) generated using cellular reprogramming (Takahashi and Yamanaka, 2006), represent available sources of cells for potential clinical use.

Embryonic stem cells (ESCs), for example, have the potential to generate all the cell types derived from the three embryonic germ layers, a property best known as pluripotency (Smith, 2001). However, their clinical usage is undermined by their innate tumorigenicity (*i.e.* ability to form teratomas upon implantation), lack of efficient culture systems to control their differentiation, and ethical constraints due to the destruction of the embryo. On the other hand, ethical concerns are alleviated with adult stem cells that can be directly obtained from available donors. Nonetheless, cell features are quite dependent on donor characteristics (*e.g.* age, sex, genetic background, etc.). In addition, they possess limited proliferative capacity in vitro and their differentiation potential is restricted to the original cell lineage. Nevertheless, hematopoietic stem cells have been widely used in the clinic since the 1960s (Thomas et al., 1957), and more recently mesenchymal stem cells have been already tested with success in cell therapy settings as well (Caplan and Bruder, 2001).

In the adult, bone marrow was originally the cell source of excellence for transplantation, but other tissues like peripheral blood after mobilization, adipose tissue, placenta and umbilical cord, are also promising alternatives. For instance, the isolation of hematopoietic stem cells (HSCs) from these sources can be performed by magnetic or fluorescence-activated cell sorting based on surface antigen expression ($CD34^+$, $Thy1^+$ and $CD38^-$) (Wognum et al., 2003). Likewise, human mesenchymal stem cells (MSCs) have been characterized based on cell adherence to tissue culture plastic and a specific pattern of surface antigen expression — more than 95% of expression of CD73, CD90 and CD105, without expressing hematopoietic markers (Dominici et al., 2006; Pittenger, 2008). In addition, cell surface antigen expression is not only useful for cell isolation from donor tissues, but also as a quality control measurement during *ex-vivo* cell culture.

On the other hand, human ESCs have been isolated and derived from blastocysts using feeder cell layers and serum-containing medium (Thomson et al., 1998). The maintenance of these cells in culture may also be assessed using the expression of key pluripotency markers, such as the cell surface markers SSEA3, SSEA4, TRA-1-60, and TRA-1-81, and the transcription factors Oct4, Nanog, Sox2 or Rex-1 (Carpenter et al., 2003). Importantly, ethical concerns related with the destruction of human embryos have led to the establishment of several protocols for derivation of pluripotent stem cell lines that do not require embryo destruction (McDevitt and Palecek, 2008). Among these, reprogramming adult cells to generate induced pluripotent stem cells (iPSCs) (Takahashi et al., 2007) is of great interest, not only due to the ethical concerns surrounding human ESCs, but also because it allows the derivation of patient-specific pluripotent stem cell lines

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