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Research review paper

Bioreactor engineering of stem cell environments

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ABSTRACT

Stem cells hold promise to revolutionize modern medicine by the development of new therapies, disease models and drug screening systems. Standard cell culture systems have limited biological relevance because they do not recapitulate the complex 3-dimensional interactions and biophysical cues that characterize the in vivo environment. In this review, we discuss the current advances in engineering stem cell environments using novel biomaterials and bioreactor technologies. We also reflect on the challenges the field is currently facing with regard to the translation of stem cell based therapies into the clinic.

Contents

1. Introduction

Stem cells provide enormous opportunities for improving human medicine, through the development of tissue replacement therapies, human in vitro models of disease, screening of therapeutic and toxic effects of chemical libraries, and "personalized" medicine. Furthermore, recent advances in stem cell biology, biomaterials, genetic engineering and biomedical engineering have allowed an unprecedented ability to create controlled environments and ask specific biological questions. The progression from historical culture plates with animal cells and immortalized cell lines towards embryonic stem cells (ES) and induced pluripotent stem cells (iPS) in 3-dimensional (3D) bioreactors is truly paving the way for new applications in tissue engineering and regenerative medicine, the study of disease, and drug screening (Fig. 1). Here we review advances in engineering stem cell environments using dynamic bioreactor systems, and discuss the importance of these novel

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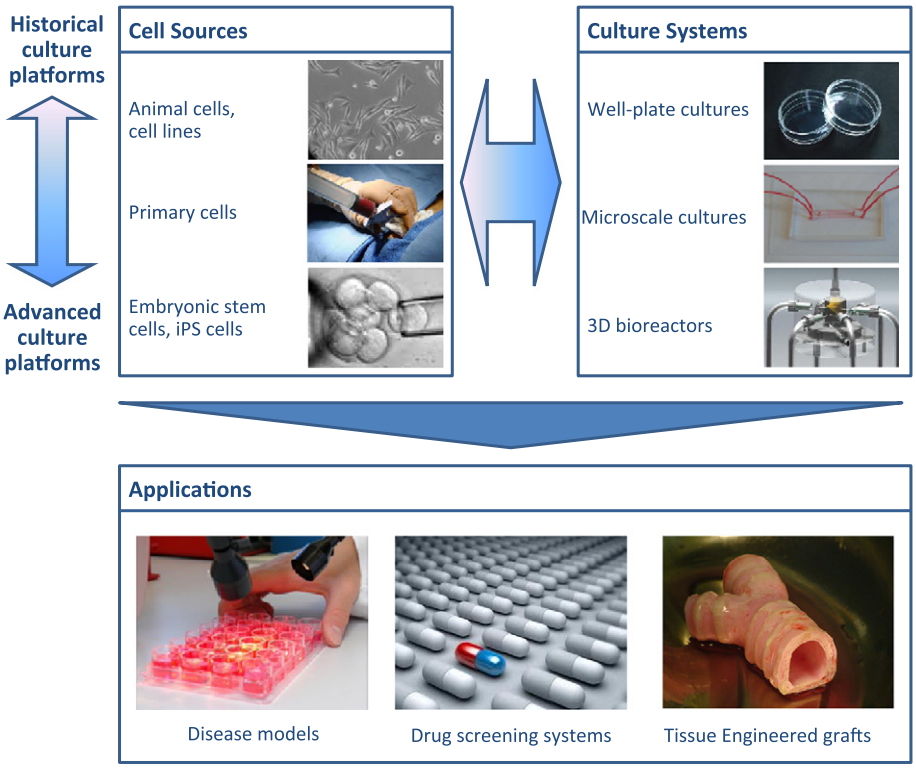

Fig. 1. Development of cell culture systems. The progression from traditional cultures with animal cells and cell lines towards scaffold–bioreactor systems with human adult, embryonic and iPS cells. The new tissue engineering technologies are paving the way to the new generation of in vitro disease models, drug screening systems, and tissue-engineered implantable grafts.

tools to stem cell research as well as the applications of stem cells in pre-clinical and clinical settings.

2. Limitations of current stem cell research models

Ever since the time of Galen, the famous physician who reportedly dissected pigs and goats, researchers have sought experimental models of human biology. More recently, the Petri dish, invented at the end of the 19th century, has proven invaluable for experiments in cellular biology. And in fact, standard Petri dish cultures are still widely used: adherent cells are grown on synthetic surfaces (i.e. tissue culture plastic), basement membrane or extracellular matrix protein coatings (i.e. laminin, vitronectin, collagen), or feeder cells (i.e. mouse embryonic fibroblasts), and are bathed in culture medium containing appropriate nutrients and signaling molecules. Changing of cell culture medium is conducted batch-wise, resulting in the variation of medium composition over time.

In Petri dishes, the cells are essentially cultured in two dimensions. Stem cells generally grow in dense colonies with defined borders, which expand in size and merge with other colonies in the culture dish (Takahashi et al., 2007; Thomson et al., 1998). At confluence, cells are passaged for further expansion, or subjected to differentiation protocols. While this culture format recapitulates some aspects of tissues that are essentially two-dimensional (2D), such as skin or bladder, it falls short of providing environments experienced by most cells in the organism. In particular, Petri dish culture lacks the 3D cell–cell and cell–matrix interactions, provision of spatial and temporal gradients of biochemical and physical signals, and systemic regulation including cross-talk between different organ systems (Kaplan et al., 2005; Vunjak-Novakovic et al., 2005). Findings obtained in Petri dish cultures are therefore not always predictable of whole tissues and organs, and are difficult to translate into the in vivo settings of pre-clinical studies in animals, and clinical trials in human subjects.

In contrast to the controlled environments of cell culture systems, animal models allow the assessment of stem cell developmental potential within whole organisms, and are therefore invaluable for studies of development, disease pathogenesis and toxicity testing (Cheshier et al., 1999; Sacco et al., 2010; Wobus and Loser, 2011). After the discovery of mouse ES cells and the completion of human genome sequencing, creation of mice with specific gene knockouts and gene reporters has enabled the study of gene function during development, and cell lineage tracking experiments (Lloyd, 2011). Furthermore, specific rodent strains with compromised immune systems have been developed that allow us to study the function of human cells in vivo without immune rejection (i.e. humanized mice) (Shultz et al., 2011).

However, despite these advantages, animal models present several limitations when used in disease modeling and toxicological studies. First, very few animal models faithfully reproduce human pathophysiology. Therefore it is important that all disease models — whether surgically or pharmacologically induced or genetic, are clearly defined with regard to the pathology that is being modeled, and to how it relates to the human condition. Second, there are important interspecies differences in pharmaco-toxicological effects between experimental animals and humans (Wobus and Loser, 2011), which are only exacerbated when human cells are transplanted into immune-suppressed hosts, potentially also affecting physiological healing responses (Goldring et al., 2011). In this respect, progress in the preparation of iPSc from large animals, such as pigs, would advance transplantation studies (Montserrat et al., 2012). Finally, for studies of transplanted cells, in vivo models offer less control over the cell microenvironment, and are challenging for on-line monitoring of the outcomes, compared to in vitro systems, which are better defined and better controlled.

A critical application highlighting the importance of developing better in vitro systems to model human biology and physiology is that of drug development. A number of high-profile drugs have been recently withdrawn from the market, most commonly due to the cardiotoxicity, neurotoxicity and hepatotoxicity that were not observed until clinical trials (Report, 2011). These negative side effects were not detected because of the limited functional capacity and genetic diversity of current research models, resulting in drugs that pass animal studies but fail in human

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