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Review article

Modulation of human multipotent and pluripotent stem cells using surface nanotopographies and surface-immobilised bioactive signals: A review

Peng-Yuan Wang [a,b,c,d,*], Helmut Thissen [c], Peter Kingshott [a]

[a] Department of Chemistry and Biotechnology, School of Science, Swinburne University of Technology, Hawthorn, Victoria 3122, Australia
[b] Graduate Institute of Nanomedicine and Medical Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei 110, Taiwan
[c] CSIRO Manufacturing, Bayview Avenue, Clayton, Victoria 3168, Australia
[d] Department of Anatomy and Neuroscience, Florey Neuroscience and Mental Health Institute, The University of Melbourne, Victoria 3000, Australia

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ABSTRACT

The ability to control the interactions of stem cells with synthetic surfaces is proving to be effective and essential for the quality of passaged stem cells and ultimately the success of regenerative medicine. The stem cell niche is crucial for stem cell self-renewal and differentiation. Thus, mimicking the stem cell niche, and here in particular the extracellular matrix (ECM), *in vitro* is an important goal for the expansion of stem cells and their applications. Here, surface nanotopographies and surface-immobilised biosignals have been identified as major factors that control stem cell responses. The development of tailored surfaces having an optimum nanotopography and displaying suitable biosignals is proposed to be essential for future stem cell culture, cell therapy and regenerative medicine applications. While early research in the field has been restricted by the limited availability of micro- and nanofabrication techniques, new approaches involving the use of advanced fabrication and surface immobilisation methods are starting to emerge. In addition, new cell types such as induced pluripotent stem cells (iPSCs) have become available in the last decade, but have not been fully understood. This review summarises significant advances in the area and focuses on the approaches that are aimed at controlling the behavior of human stem cells including maintenance of their self-renewal ability and improvement of their lineage commitment using nanotopographies and biosignals. More specifically, we discuss developments in biointerface science that are an important driving force for new biomedical materials and advances in bioengineering aiming at improving stem cell culture protocols and 3D scaffolds for clinical applications. Cellular responses revolve around the interplay between the surface properties of the cell culture substrate and the biomolecular composition of the cell culture medium. Determination of the precise role played by each factor, as well as the synergistic effects amongst the factors, all of which influence stem cell responses is essential for future developments. This review provides an overview of the current state-of-the-art in the design of complex material surfaces aimed at being the next generation of tools tailored for applications in cell culture and regenerative medicine.

Statement of Significance

This review focuses on the effect of surface nanotopographies and surface-bound biosignals on human stem cells. Recently, stem cell research attracts much attention especially the induced pluripotent stem cells (iPSCs) and direct lineage reprogramming. The fast advance of stem cell research benefits disease treatment and cell therapy. On the other hand, surface property of cell adhered materials has been demonstrated very important for *in vitro* cell culture and regenerative medicine. Modulation of cell behavior using surfaces is costeffective and more defined. Thus, we summarise the recent progress of modulation of human stem cells using surface science. We believe that this review will capture a broad audience interested in topographical and chemical patterning aimed at understanding complex cellular responses to biomaterials.

* Corresponding author at: Department of Chemistry and Biotechnology, School of Science, Swinburne University of Technology, Hawthorn, Victoria 3122, Australia.
E-mail address: pengyuanwang@swin.edu.au (P.-Y. Wang).

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Contents

1. Introduction

Stem cells produce their own matrix and interact with this specialised microenvironment during self-renewal and differentiation [1]. This microenvironment, the stem cell niche, in turn regulates the fate of stem cells. The stem cell niche was a term first used by Schofield in 1978 to describe the whole picture of how stem cells survive and interact with their neighbouring cells, the extracellular matrix (ECM), and/or secreted factors (left box, Fig. 1). Since then, scientists are eagerly to understand the stem cell niche and mimic the stem cell niche *in vitro*. However, the stem cell niche is highly complex and dynamic and may thus be very difficult to fully characterise. The first defined stem cell niche was the germ-line stem cell (GSC) niche in *Drosophila* and *Caenorhabditis elegans* [2]. To date, several stem cell niches have been identified in mammalian tissues, including hematopoietic, epithelial, intestinal, muscle, bone, and neural systems, as well as cancer [3,4]. It is believed that there are other stem cell niches that exist but they have yet to be discovered or fully identified.

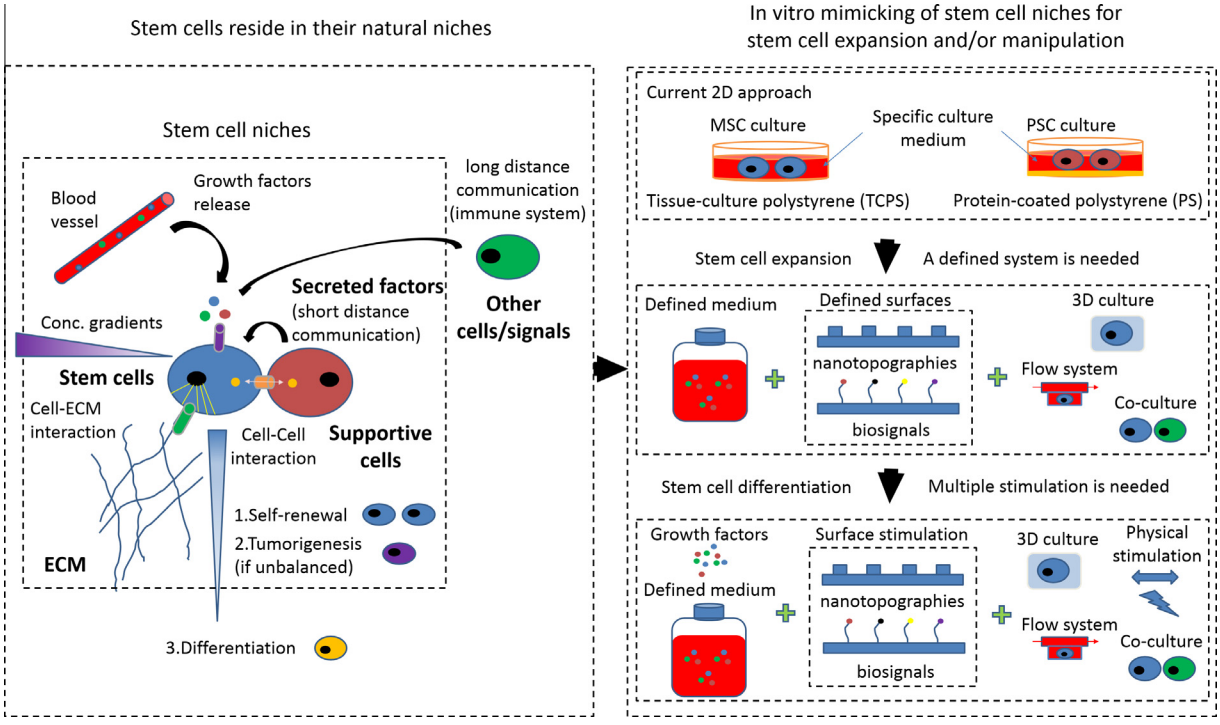

Fig. 1. Summary of the topics discussed in this review. Stem cell niche and cell-ECM interactions are introduced (left box) and classified along with the current protocols for MSC and PSC culture (right box).The state-of-art approaches for MSC and PSC expansion and differentiation using surface nanotopographies and biosignals are reviewed. In addition, other important approaches such as dynamic culture, 3D culture and co-culture systems are discussed. Finally, the design of next generation cell culture tools and protocols for tissue engineered implants are summarised.