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Biomaterials control of pluripotent stem cell fate for regenerative therapy

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ABSTRACT

Pluripotent stem cells (PSCs) derived from either the embryo or reprogramming processes have the capacity to self-renew and differentiate into various cells in the body, thereby offering a valuable cell source for regenerative therapy of intractable disease and serious tissue damage. Traditionally, methods to expand and differentiate PSCs have been confined to 2D culture through the use of biochemical signals; the use of biomaterials beyond the commercially available culture dish has not been widespread. Nevertheless, biomaterials with tailored physical, chemical, and geometrical cues can mimic the native stem cell niche to tune the microenvironmental conditions for PSCs to preserve their self-renewal capacity or to switch their phenotype, a status ultimately needed to gain regenerative functions *ex vivo* and *in vivo*. Recently efforts to explore biomaterials to regulate PSC behavior have accelerated. The biomaterials properties investigated include surface chemistry, immobilized ligand, nano-/micro-topography, matrix stiffness, geometrical complexity, 3D configuration, and combinations thereof. This review aims to cover the current advances of biomaterials-based control over PSCs, particularly for the preservation of self-renewal capacity as well as for their differentiation into target cells. Furthermore, it aims to suggest future research directions that would facilitate the eventual translation of these advances.

Contents

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1. Introduction

Patients suffering from various degenerative diseases create a high demand for effective treatments. To satisfy the therapeutic needs of these degenerative diseases, regenerative medicine offers an exciting promise [1–3]. Regenerative medicine seeks to utilize the therapeutic capacity of stem cells because most of tissues in the body have their own endogenous stem cells to regenerate upon injury [4]. When the damage exceeds the capacity of the injured tissues to regenerate, transplantation with exogenous stem cells is required [5].

Stem cells have a capacity to self-renew and differentiate [6–8]. While adult stem cells are multipotent or unipotent, embryonic stem cells (ESCs), embryonic germ cells (EGCs), and embryonic carcinoma cells (ECCs) are pluripotent [9–14]. Induced pluripotent stem cells (iPSCs), recently developed by epigenetically reprogramming somatic cells, are also pluripotent [15]. PSCs have several advantages over adult stem cells: (i) they can proliferate indefinitely *in vitro* under proper conditions, whereas adult stem cells have a limited proliferation capacity, (ii) they are capable of differentiating into most cell types in the body, while adult stem cells are only able to differentiate into cells of lineages from which they originate, and (iii) they are permissive to genetic modification, while adult stem cells are largely resistant to genetic engineering [9–11].

The establishment of human ESCs and EGCs is thus a milestone in the medical applications of stem cells, including modeling embryonic development and disease progression in human, drug screening using ESC-derived somatic cells *in vitro*, and regenerative therapy using ESC-derived somatic cells as donor cells [16–19]. The shortage of donor tissues and organs has always been a concern in tackling organ failure and intractable diseases [20]. In fact, the treatments of injured tissues and organs have been carried out by transplantation of physiologically functional cells, tissues or organs derived from stem cells. Although adult stem cells, such as hematopoietic stem cells (HSCs), have been used for the treatment of leukemia [21], their use in organ failure or degenerative diseases is still far from being practical due to their limited proliferation capacity *in vitro* [22,23]. PSCs in contrast can provide an inexhaustible cell source. Some of the life-threatening diseases and injuries, like hematopoietic disorders, liver damage and spinal cord injuries, have started to utilize the PSCs-based regenerative approaches [24].

Above all, for the successful clinical applications of the PSCs, two major assets of PSCs – unlimited self-renewal and differentiation into all types of cells – should be defined and controlled well. Securing a large population of cells is a prerequisite to achieve therapeutic capacities in stem cell based regenerative medicine. Maintaining the characteristics and phenotype of PSCs over prolonged passages is not easy – often the cells loose the pluripotency with a heterogeneous population of unwanted or poorly-defined differentiated cells. Directing the secured large number of PSCs toward a targeted lineage is a challenging issue for safe and potential use of them in clinical settings. In fact, human PSCs were potentially tumorigenic upon their transplantation into the body [25,26], limiting their clinical uses. Therefore, strategies and technologies to target tissue differentiation *in vivo* as well as the control of the differentiation level *in vitro* should be explored. Substantial effort has been given to this. For example, antibody-based strategy was used to remove the undifferentiated cells before transplantation [27–29]; however, the lack of specificity of the targeted PSC markers limits their clinical availability. Some cells originated from PSCs have also been shown to spontaneously dedifferentiate into a pluripotent state after transplantation, leading to a teratoma formation [30]. A method to inhibit the pathways in the generation of pluripotency and teratoma was thus used; NANOG, known as a key gene for the pluripotency, was suppressed to reduce the teratoma formation [31–33].

Apart from the biological strategies that have employed 2D culture plates and soluble molecules, other culture parameters like 3D environments and substrate physico-chemical properties can be considered to overcome those limitations of PSCs – *how to multiply cell population without losing a pluripotency and to differentiate to specific cell types in vitro and in vivo* – ultimately to satisfy safety and therapeutic efficacy. A substantial body of literatures has recently witnessed the