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Review

Guided differentiation and tissue regeneration of induced pluripotent stem cells using biomaterials

Yung-Chih Kuo[1,*], Rajendiran Rajesh[1]

Department of Chemical Engineering, National Chung Cheng University, Chia-Yi 62102, Taiwan, ROC

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ABSTRACT

Differentiated somatic cells can be engineered into pluripotent stem cells, which have the ability to differentiate into any type of cell lineage; these are known as induced pluripotent stem cells (iPSC). Different techniques are used for the generation of iPSC from somatic cells. The discovery of iPSC has led to the opening of a wide variety of applications in the fields of regenerative medicine, tissue engineering, disease modeling, nanotechnology, and drug discovery. In this review, we discuss reprogramming techniques for the derivation of iPSC and the advantages of iPSC over embryonic stem cells, and mainly focus on the relevance to regenerative medicine of several types of biomaterial-guided differentiation of iPSC to different cell types. In recent years, the fabrication of biomaterial has grown from basic materials to the development of biomaterial scaffolds with the ability to guide processes like proliferation, differentiation and morphogenesis. Natural extracellular matrix offers a perfect microenvironment for biochemical, topographical and electric signals for cell attachment, proliferation and differentiation. Hence, there is a need to fabricate a biomaterial scaffold with the properties of immunologically inert, biodegradable, biochemical and physical cues with high biocompatibility for iPSC differentiation. This review outlines the rationale for using biomaterial-guided differentiation in tissue engineering and regenerative medicine through the use of appropriate biomaterial that can permit the iPSC to adhere, proliferate and finally differentiate into particular functional somatic cells.

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1. Introduction

Advances in the field of tissue engineering and nanotechnology have opened up a wide range of applications in drug discovery, *in vitro* and *in vivo* disease modeling and regenerative medicine [1–3]. Regulating cell behavior and tissue development using synthetic biomaterial scaffolds that mimic natural extracellular matrix (ECM) and that can support three dimensional (3D) cell culture and regeneration of tissue are important elements in the field of tissue engineering and regenerative medicine. Biodegradable and immunologically inert, with high biocompatibility and porosity for vascularization and cell migration and 3D matrices with suitable physical properties to simulate ECM are essential characteristics of a synthetic biomaterial scaffold for tissue regeneration [4-9]. Different fabricating techniques like electrospinning, gas foaming, nanofiber self-assembly, liquid-liquid phase separation, computer-aided design and manufacturing techniques and emulsification/freeze-drying are being used for fabricating biomaterial scaffolds used for tissue engineering purposes [10–14].

Induced pluripotent stem cell (iPSC)-generating techniques have rapidly evolved in recent years. These techniques are important for parallel research protocol development of biomaterials with efficacy in inducing differentiation of these iPSC to particular desired cell phenotypes. iPSC can differentiate into all three germ layers, *i.e.*, mesoderm, ectoderm, and endoderm. The proper guidance and control of iPSC using biomaterials can be potential in regenerating organ and tissue in human [15]. Hence, the aim of this review involved in addressing the biomaterials in regenerative medicine followed by biomaterial-guided differentiation of iPSC for regenerating various organs and tissues, along with the rationale behind the selection of particular biomaterial scaffolds for effective tissue engineering. Although biomaterial-guided differentiation of iPSC into tissues has been explored, only limited works have been published. To the best of our knowledge, all the published scientific reports in this emerging field have been discussed in this review. This review also provides opportunities of approaching to further researches in biomaterial-guided differentiation of iPSC and in tissue regeneration for biomedical applications.

* Corresponding author.
E-mail address: chmyck@ccu.edu.tw (Y.-C. Kuo).
[1] Authors have equally contributed to this work.

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Table 1
Generation of iPSC from various tissues using different reprogramming factors.

No.	Source	Reprogramming factor	Ref.
1	Mouse embryonic or adult fibroblasts	*Oct3/4, Sox2, c-Myc* and *Klf4*	[16,17,29]
2	Human somatic cells	*Oct3/4, Sox2, Klf4* and *c-Myc*	[22]
3	Human somatic cells	*Oct3/4, Sox2* and *Klf4*	[30]
4	Primary fibroblasts from a type 1 spinal muscular atrophy patient	*Oct4, Sox2, Nanog and Lin28*	[31]
5	Human cord blood-derived endothelial cells	*Oct4, Sox2, Nanog and Lin28*	[32]
6	Mouse embryonic fibroblas	Poly-arginine protein fused to the C terminus of *Oct4, Sox2, Klf4* and *c-Myc*	[33]
7	Human newborn fibroblasts	*Oct4, Sox2, Klf4*, and *c-Myc* fused with a cell penetrating peptide	[34]
8	Human keratinocytes	*Oct4, Sox2, Klf4* and *c-Myc*	[35]
9	Human peripheral blood cells	*Oct4, Sox2, Klf4* and *c-Myc*	[36]
10	Primary hepatocytes and gastric epithelial cells	*Oct3/4, Sox2, Klf4* and *c-Myc*	[37]

2. Induced pluripotent stem cells (iPSC)

Yamanaka and colleagues first retro-differentiated somatic cells to an embryonic stem cell (ESC)-like state, namely iPSC, and various reports in more efficient methods for generating iPSC for clinical applications have since been published (Table 1) [16-18]. Genetic reprogramming of adult somatic cells into iPSC, which have limited differentiation potential, can allow the iPSC to acquire plasticity and differentiate into all cell types upon reprogramming [16]. During the initial period, the stem cell transcriptional regulator genes *Oct4*, *Sox2*, *Lin28*, and *Nanog* or *Oct4*, *Sox2*, *Klf4*, and *c-Myc* were transduced into adult fibroblasts for the development of human iPSC (hiPSC) [19–21]. Reprogrammed hiPSC exhibit surface antigen expression and the epigenetic status of pluripotent genes, morphology, proliferation rate, and telomerase activity, the same as that of human embryonic stem cells (hESC). Also, hiPSC acquire the capability to differentiate into cell types of the three germ layers *in vitro* and *in vivo* [22]. However, a difference in expression of some genes at the transcriptional level has also been reported between hiPSC and hESC [16,23–26]. Also, variations in the expression of genes have been documented in iPSC lines [25], due to the genetic variability in the reprogramming methodology and somatic cell source [27] and/or in the degree to which the cells are genetically reprogrammed [28]. Different methodologies have been employed for reprogramming iPSC to attain a maximum degree of pluripotency, and have had their own merits and demerits with respect to future clinical use.

3. Reprogramming techniques

Cell reprogramming is an approach to developing ESC-like cells or pluripotent cells from differentiated somatic cells by controlled expression of defined factors (Table 1) [16,29–38]. The iPSC-generating field is rapidly growing, which makes these cells a supreme candidate in therapeutic strategies (Fig. 1). The efficacy of obtaining pluripotent stem cells from transfected somatic cells was reported to be less than 1% in the first study, from 2007, but near 100% efficiency was achieved in a study from 2013 by inhibiting an important protein associated with blocking the transcription of transfected genes [39]. Takahashi et al. were the first to report that, by inducing the expression of specific transcription factors and genes in human adult differentiated fibroblast cells (somatic cells), the cells could be reverted back to behave like ESC with pluripotency [22]. *Oct4*, *Sox2*, *Nanog*, and two oncogenes (*c-Myc* and *Lin28*) are the core regulatory genes responsible for reprogramming the epigenetic program of differentiated adult somatic cells and achieving pluripotency [40–42]. iPSC derived through the reprogramming techniques have all the characteristic features of hESC, like gene expression, morphology and growth profile [43].

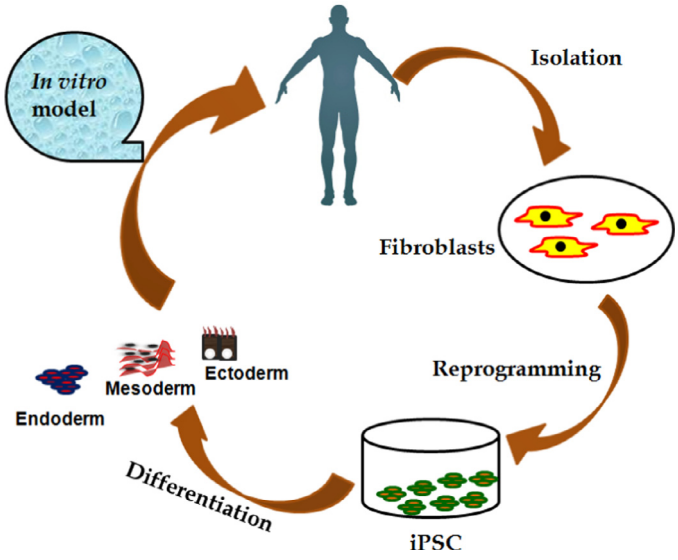

Fig. 1. Schematic representation of isolation and differentiation of iPSC and utilization of them for *in vitro* model.

During the initial period, retroviruses and/or lentiviruses were used for iPSC generation by transducing regulatory genes either into a single expression vector or separately into somatic cells. iPSC generated by viral transduction will have the viral particle integrated into host chromosomes, which carries the risk of insertional mutagenesis and leads to malignancy; hence, they are not suitable for clinical applications [44]. Moreover, these cells may also cause an immunogenic response due to the presence of viruses [45]. To counteract this, new methodologies for the generation of iPSC are being developed quickly and continuously. Currently, iPSC are generated by inducing synthesized RNAs [46], proteins [34] and plasmids [17,47] into somatic cells to achieve a pluripotent state. To avoid the risk of malignancy in retroviral transduction, non-integrating transfection methods are employed for iPSC generation. The use of high concentrations of plasmids for reprogramming somatic cells is one of the non-integrating transfection methods [17], but the reprogramming efficacy of this method cannot match retroviral transduction. Another safety issue is related to the constant proliferation of implanted cells. To overcome this safety issue in therapeutic applications, a protocol was developed to evaluate non-tumor-forming “safe” iPSC lines [48,49]. iPSC have a lower risk of tumor formation, compared to ESC, when this screening process is used. These methodologies are much safer and acceptable for clinical studies than viral transduction. Even though these methods increase the rate of obtaining iPSC from somatic cells, there is the risk of these cells becoming malignant and causing genetic damage

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