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Merging Multiple Layers of Cell Regulation during Direct Reprogramming is the Road towards Regenerative Medicine

Sophia Kelaini and Andriana Margariti

Centre for Experimental Medicine, Queen's University Belfast, UK

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Corresponding author:
Andriana Margariti

a.margariti@qub.ac.uk

The Wellcome-Wolfson Building Centre for Experimental medicine south block, 2nd Floor, Queens University Belfast, 97 Lisburn road, Belfast, UK.

Tel: +4428 9097 6476

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Content

Pluripotent stem cells have the ability to differentiate into almost all types of cells in the body [1]. In reverse, latest advances in regenerative medicine have made possible the reprogramming of somatic cells into pluripotent cells using a big diversity of methods [2].

Since the discovery that somatic cells themselves could be reprogrammed to induced pluripotent stem cells (iPSCs) by the addition of only a few defined factors, namely Oct3/4, Sox2, c-Myc, and Klf4 (OSKM) [3], a number of different pathways have been shaped from Waddington's adaptation of the "epigenetic landscape" cell differentiation model [4]. For example, depleting Mbd3, an important member of the Mbd3/NuRD (nucleosome remodelling and deacetylation) repressor complex, along with OSKM-based reprogramming, resulted in deterministic iPS cell reprogramming with a near 100% efficiency within seven days from mouse and human cells [5].

One of the limitations of induced pluripotency is the duration that is necessary to initially reprogram the cells and then subsequently guide them towards the desired fate. The large number of steps needed to generate iPS cells commonly affects the efficiency of generation of the final cell type and it can be as low as 0.01–0.1% [3]. Additionally, concerns about the safety [6] of iPS-derived cells need to be addressed before using these cells in the clinic [7]. Alternative avenues are, thus, being considered that will generate the desired cell type in a faster and safer way. Such an approach we have recently generated partial-iPS (PiPS) cells after short term reprogramming. This was achieved by transferring the four OSKM reprogramming factors to human fibroblasts for short periods of time. PiPS cells have the added advantage that do not form tumours *in vivo* and they additionally display the potential to differentiate into endothelial cells (ECs) in defined culture media and conditions [8]. Consequently, avenues including methods that will be able to bypass the intermediate pluripotent stage, allowing for a more direct approach in generating the final cell type, are currently being considered.

Importantly, based on latest advances in the field of *direct reprogramming* have also made possible the direct conversion of differentiated mature somatic cells into many different cell types whilst bypassing an intermediate pluripotent state. The direct reprogramming approach has exhibited rapid development in recent years and aims at accelerating the cell generation process using a variety of methods and more complex combinations of reprogramming factors.

In a recent study, mouse fibroblasts were directly converted to neuron cells using a cocktail of small molecules, which yielded up to >90% of cells being positive for the neuron-specific marker TUJ1 after 16 days of induction [9]. Furthermore, it was reported that direct reprogramming of human fibroblasts generated induced neural crest (iNC) cells through over-expression of only one transcription factor, SOX10, in combination with environmental cues such as WNT activation [10]. Inactivation of Fbw7, an SCF E3 ubiquitin ligase substrate recognition component, in pancreatic ductal cells, reprogrammed these cells into α, δ, and β cells.

The induced β cells resembled islet β cells morphologically and histologically, expressed genes important for β cell function, and also secreted insulin after a glucose challenge [11]. In a different study, induced hepatocytes (hiHeps) were generated from fibroblasts through over-expression of the hepatic fate conversion factors *HNF1A*, *HNF4A*, and *HNF6* together with the maturation factors *ATF5*, *PROX1*, and *CEBPA* [12]. *Induced* embryonic Sertoli-like cells (ieSCs) were generated by ectopic expression of five transcription factors Nr5a1, Wt1, Dmrt1, Gata4, Sox9 [13]. Generation of beating cardiomyocyte-like cells from mouse fibroblasts using only chemical cocktails has also been achieved. The chemically induced cardiomyocyte-like cells (CiCMs) expressed cardiomyocyte-specific markers. In addition, they also showed characteristic sarcomeric organization, cardiac calcium flux and electrophysiology [14].

In another study, both embryonic and adult somatic fibroblast cells were shown to be efficiently reprogrammed to clonal multilineage hematopoietic progenitors by ectopically expressing the ERG, GATA2, LMO2, RUNX1c, and SCL transcription factors. The reprogrammed cells were also able to exhibit short-term reconstitution ability *in vivo*. In addition, loss of p53 facilitated reprogramming towards blood cells, and p53(-/) reprogrammed cells were able to generate erythroid, megakaryocytic, myeloid, and lymphoid cell types [15].

Moreover, human bone marrow stromal cells (BMSCs) were reprogrammed into renal proximal tubular-like epithelial cells using cell-free extracts from human proximal tubular epithelial (HK2) cells. This resulted in a change in appearance from their usual spindle-shape to cobblestone islands within two weeks [16].

Through studying and shifting the differentiated cell state, new upcoming avenues will open towards the generation of novel research tools providing safer and faster therapeutic resources. Approaches that seem to hold the biggest promise towards improving the efficacy and efficiency of cell conversion, both *in vitro* and *in vivo*, will include methods that combine and merge different layers of cell regulation **(Figure 1)**. Expectantly, the final products of this reprogramming approach could be then effectively applied in regenerative and personalized medicine.

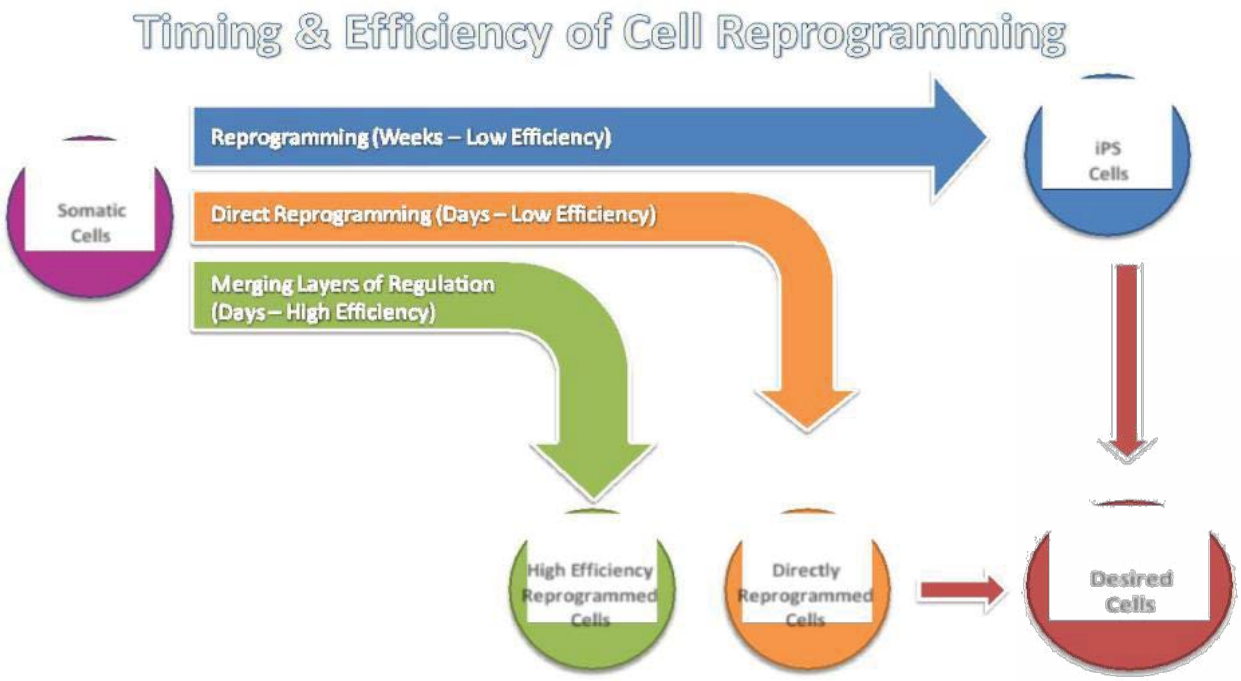

Figure 1 Different approaches towards improving the efficacy and reducing the time needed for the generation of the desired cells using cell reprogramming

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