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Review article

Biological computational approaches: new hopes to improve (re) programming robustness, regenerative medicine and cancer therapeutics

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A R T I C L E I N F O

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A B S T R A C T

Hundreds of transcription factors (TFs) are expressed and work in each cell type, but the identity of the cells is defined and maintained through the activity of a small number of core TFs. Existing reprogramming strategies predominantly focus on the ectopic expression of core TFs of an intended fate in a given cell type regardless of the state of native/somatic gene regulatory networks (GRNs) of the starting cells. Interestingly, an important point is that how much products of the reprogramming, transdifferentiation and differentiation (programming) are identical to their *in vivo* counterparts. There is evidence that shows that direct fate conversions of somatic cells are not complete, with target cell identity not fully achieved. Manipulation of core TFs provides a powerful tool for engineering cell fate in terms of extinguishment of native GRNs, the establishment of a new GRN, and preventing installation of aberrant GRNs. Conventionally, core TFs are selected to convert one cell type into another mostly based on literature and the experimental identification of genes that are differentially expressed in one cell type compared to the specific cell types. Currently, there is not a universal standard strategy for identifying candidate core TFs. Remarkably, several biological computational platforms are developed, which are capable of evaluating the fidelity of reprogramming methods and refining existing protocols. The current review discusses some deficiencies of reprogramming technologies in the production of a pure population of authentic target cells. Furthermore, it reviews the role of computational approaches (*e.g.* CellNet, KeyGenes, Mogrify, *etc.*) in improving (re)programming methods and consequently in regenerative medicine and cancer therapeutics.

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1. Introduction

Thousands of genes precisely express and work together in GRNs to warrant the current cell's function, steady-state, survival

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and its transcriptional responses to environment, disease, and age. In addition, specific GRNs are responsible for and determine the cell identity (Macneil and Walhout, 2011; Davidson and Erwin, 2006; Suzuki et al., 2009). Moreover, environmental signals can control cell fate by their impact on transcriptional regulation and the epigenetic landscape (Lang et al., 2014). Direct reprogramming technology has shown that a small number of core TFs are sufficient to establish a new identity in fully differentiated cell types and to control the gene expression programs (Sancho-Martinez et al., 2012; Morris and Daley, 2013; Xu et al., 2015). Identifying core TFs, which define and control GRNs responsible for the cell identity in a specific cell type, is of importance due to the advantages that it offers in improving (re)programming. However, there is not a general standard strategy for selection of core TFs that control individual cell identity for reprogramming purposes. Core TFs of an intended cell fate are identified based on literature, educated guess, trial and error and their differential expression in a specific cell type in comparison with few other cell types. Interestingly, computational approaches can predict candidate factors that control cell identity by utilizing genome-scale technologies. These approaches evaluate the authenticity of the reprogramming products by comparing GRNs of the converted cells with their *in vivo* correlates. Moreover, these approaches can guide efforts to correct incomplete cell-type conversions and to improve reprogramming strategies. This study considers recent findings regarding the imperfection of current reprogramming protocols, the fidelity of cell fate conversion methods, and the capability of computational platforms (*e.g.* CellNet (Cahan et al., 2014; Morris et al., 2014), KeyGenes (Li et al., 2015) and Mogrify (Rackham et al., 2016)) for refining reprogramming strategies and producing authentic functional cell types.

2. Native GRNs as barriers to reprogramming and transdifferentiation

A potential drawback of reprogramming is that silencing expression of the transgenes causes the cells to revert back toward the starting cell (*e.g.* fibroblast) morphology and to lose their newly acquired program (D'Alessio et al., 2015; Buganim et al., 2012; Huang et al., 2011; Lujan et al., 2012). Although it has been neglected, to engineer a given cell type to another fate, silencing or disruption of the native identity-associated GRNs seems essential because they can hinder the conversion process and robust establishment of the desired fate. Therefore, native/somatic GRNs that characterize a particular cell type could be considered as barriers to direct reprogramming strategies (Ebrahimi, 2015). Indeed, somatic transcriptional programs and chromatin factors act as safeguard mechanisms in fully differentiated somatic cells by protecting the cells from aberrant transformations (Tomaru et al., 2014; Cheloufi et al., 2015). Thus, for the establishment of a fully self-sustaining identity in reprogrammed cells, disruption of the starting cell program appears to be of importance to ensure robustness of reprogramming process. In this regard, Morris et al. (2014) indicated that residual expression of native master regulators in the converted cells represses target fate specification. Interestingly, Tomaru et al. showed that combinatorial depletion of four fibroblastic master genes (OSR1, PRRX1, LHX9 and TWIST2) disrupts somatic transcriptional regulatory network (TRN) in human fibroblasts and induces a plastic state. They analyzed FANTOM5 data and Illumina microarray data to identify fibroblast-enriched TFs and systematic siRNA knockdown of selected TFs to find the minimal influential set. Moreover, they indicated that the ectopic expression of the four fibroblastic master genes impedes adipogenic differentiation of mesenchymal stem cells (Tomaru et al., 2014). Furthermore, Morris et al. (2014) revealed that knockdown of B cell regulators (*i.e.* Pou2af1 and Ebf1) during the macrophage conversion of B cells considerably improves direct reprogramming robustness at least in part through the extinguishment of native GRNs. Similarly, Cheloufi et al. (2015) recently showed that the histone chaperone CAF-1, as a key determinant of cellular identity, safeguards somatic cell identity and that its inhibition enhances the transdifferentiation of mouse B cells into macrophages and fibroblasts into neurons. Recently, Li et al. (2015) identified a chemical cocktail of four small-molecules capable of driving direct lineage conversion of mouse fibroblasts into functional neurons. Interestingly, in their chemical cocktail small-molecule I-BET151 promotes neural reprogramming by disruption of the fibroblast GRN (Li et al., 2015). Indeed, in this reprogramming paradigm, disruption of the native GRN enabled few small-molecules to convert fibroblasts into neurons without ectopic expression of master regulators. Therefore, native identity-associated gene or transcriptional regulatory networks seem to be potent barriers to pluripotent reprogramming and transdifferentiation. In the case of pluripotent reprogramming, OSKM (Oct4, Sox2, Klf4, and c-Myc) expression effectively silences fibroblast GRN in induced pluripotent stem cells (iPSCs) (Cahan et al., 2014). However, fibroblast program appears to be a barrier during the reprogramming process. Suggestively, by transient disruption of the native GRNs and subsequently unlocking the cells from somatic program diverse transformations may be possible (Tomaru et al., 2014). Moreover, identification of master genes responsible for the native/somatic state in distinct cell-types and their knockdown could be a new strategy for enhancing the efficiency and fidelity of direct reprogramming to both pluripotent and differentiated cells.

3. Aberrant and target GRNs

An important question about the effectiveness of direct reprogramming strategies and directed differentiation is that how much (re)programmed cells are identical to their *in vivo* counterparts? Indeed, during reprogramming, the installation of new identity-associated GRNs in the presence of native GRNs can lead to a “confused or plastic state” instead of a mature fate in the converted cells. For example, in the reprogramming of B cells to macrophages (Bussmann et al., 2009) and fibroblasts to induced hepatocytes (iHeps) (Huang et al., 2011; Sekiya and Suzuki, 2011), CellNet network biology platform revealed the presence of both native and target GRNs and the establishment of a progenitor state instead of the intended somatic program (Morris et al., 2014). Moreover, Cahan et al. (2014) showed the establishment of aberrant GRNs in the products of every reprogramming strategy that is, at least in part, due to off-target effects of the reprogramming factors and then the partial establishment of alternate fates. Surprisingly, in every reprogramming paradigm, one or more regulators of a defined set of reprogramming factors can potentially target aberrant sub-networks leading to the partial establishment of alternate fates (Cahan et al., 2014). For instance, CellNet has indicated that iHeps with the potential of functional engraftment into both damaged mouse colon (Morris et al., 2014) and liver (Sekiya and Suzuki, 2011) are indeed induced endodermal progenitors (iEPs) rather than fate-restricted hepatocytes (Morris et al., 2014). Moreover, it has been suggested that products of directed differentiation and direct conversion are not exactly identical to their *in vivo* counterparts in molecular and functional features. In addition to these problems, low network influence score of a special set of core TFs could adversely affect the degree of target fate specification (Cahan et al., 2014). Regarding these concerns, recent findings (Morris et al., 2014; Roost et al., 2015) have challenged existing differentiation and reprogramming strategies in the way that they could not robustly specify a defined cell

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