NEUROSCIENCE
INTERNATIONAL BRAIN IBRO RESEARCH ORGANIZATION

RESEARCH ARTICLE

M. R. Omrani et al. / Neuroscience xxx (2018) xxx–xxx

Transcription Factors in Regulatory and Protein Subnetworks during Generation of Neural Stem Cells and Neurons from Direct Reprogramming of Non-fibroblastic Cell Sources

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Abstract—Direct reprogramming of non-fibroblastic cells to the neuronal cell types including induced neurons (iNs) and induced neural stem cells (iNSCs) has provided an alternative approach for the direct reprogramming of fibroblasts to those cells. However, to increase the efficiency of the reprogramming process the underlaying mechanisms should be clarified. In the current study, we analyzed the gene expression profiles of five different cellular conversions to understand the most significant molecular mechanisms and transcription factors (TFs) underlying each conversion. For each conversion, we found the list of differentially expressed genes (DEGs) and the list of differentially expressed TFs (DE-TFs) which regulate expression of DEGs. Moreover, we constructed gene regulatory networks based on the TF-binding sites' data and found the most central regulators and the most active part of the network. Furthermore, protein complexes were identified from constructed protein–protein interaction network for DE-TFs. Finally, we proposed a list of main regulators for each conversion; for example, in the direct conversion of epithelial-like cells (ECs) to iNSCs, combination of centrality with active modules or protein complex analyses highlighted the role of POU3F2, BACH1, AR, PBX1 SOX2 and NANOG genes in this conversion. To the best of our knowledge, this study is the first one that analyzed the direct conversion of non-fibroblastic cells toward iNs and iNSCs and we believe that the expression manipulation of identified genes may increase efficiency of the process. © 2018 Published by Elsevier Ltd on behalf of IBRO.

Key words: active modules, direct reprogramming, non-fibroblastic cells, protein complexes, transcription factors, regulatory networks.

INTRODUCTION

Failure in function of central nervous system cells is the origin of neuronal disorders that there are no effective drug treatments or therapeutic strategies for most of them yet. Neurons as the most abundant neuronal cells and neural stem cells (NSCs) attract a lot of attention as they may be used to treat neural disorders or to study them in the laboratory. Acquisition of such cells from human tissues has its own limitation due to the ethical concerns (Breunig et al., 2011). In this regard, generation of them through differentiation of stem cells or direct reprogramming of somatic cells has become a promising approach to replace damaged cells, study central nervous system disorders, and investigate nervous system development. It has been shown that fully differentiated somatic cells can be reprogrammed to a pluripotent state using defined transcription factors (TFs) (Takahashi and Yamanaka, 2006; Takahashi et al., 2007). These pluripotent stem cells can then be differentiated to the functional cells. However, differentiation of iPSCs to somatic cells is a time consuming, non-efficient process, variable among various lines of iPSCs (Hu et al., 2010) and harbors the risk of tumor formation upon *in vivo* transplantation (Pera, 2011). Alternatively, somatic cells can be converted to another type of somatic cells in a process called direct reprogramming (see Fig. 1).

The direct reprogramming allows conversion of somatic cells to each other through forced expression of TFs, miRNA and application of small molecules. So far, extensive efforts have been done for generation of induced neurons (iNs) (Caiazzo et al., 2011; Marro

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Abbreviations: ChEA, Chip-Enrichment Analysis; DEGs, differentially expressed gene; DE-TFs, differentially expressed TFs; ECs, epithelial-like cells; iNs, induced neurons; iNSCs, induced neural stem cells; NRPCs, neural restricted progenitor cells; NSCs, neural stem cells; PRC2, polycomb repressive complex 2; TFs, transcription factors.

https://doi.org/10.1016/j.neuroscience.2018.03.033
0306-4522/

Please cite this article in press as: Omrani MR et al. Transcription Factors in Regulatory and Protein Subnetworks during Generation of Neural Stem Cells and Neurons from Direct Reprogramming of Non-fibroblastic Cell Sources. Neuroscience (2018), https://doi.org/10.1016/j.neuroscience.2018.03.033

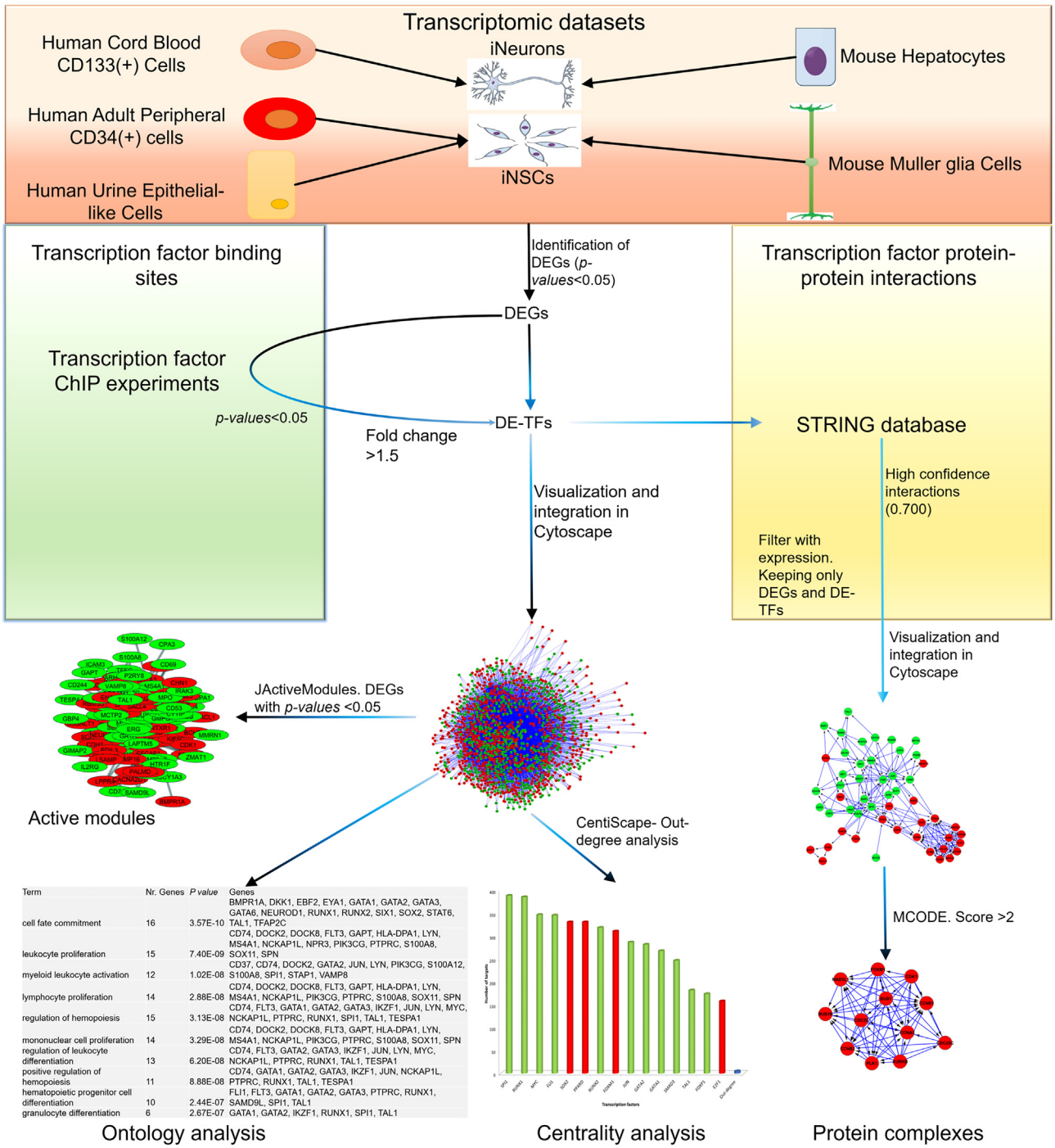

Fig. 1. Overall representation of the methods which we used in our study. Firstly, transcriptomic data sets were obtained from GEO database. Following identification of differentially expressed genes (DEGs), the data of transcription factor (TF)-binding site and protein–protein interactions were recruited to construct integrated gene regulatory network (GRN) and protein–protein interaction (PPI) networks. Finally, the GRN was subjected to different analyses, including identification of the most activated modules, the most central genes and the most affected cellular processes. In addition, the PPI network was analyzed to find the top protein complexes.

et al., 2011a; Son et al., 2011; Ladewig et al., 2012; Liu et al., 2013; Wapinski et al., 2013; Zhou et al., 2014; Colasante et al., 2015; Hu et al., 2015; Li et al., 2015) or NSCs (Lee et al., 2011; Han et al., 2012; Matsui et al., 2012; Ring et al., 2012; Thier et al., 2012; Cassady et al., 2014) from somatic cells, specially fibroblast. However, the direct conversion of somatic cells toward iNs and NSCs is not restricted to the fibroblasts.