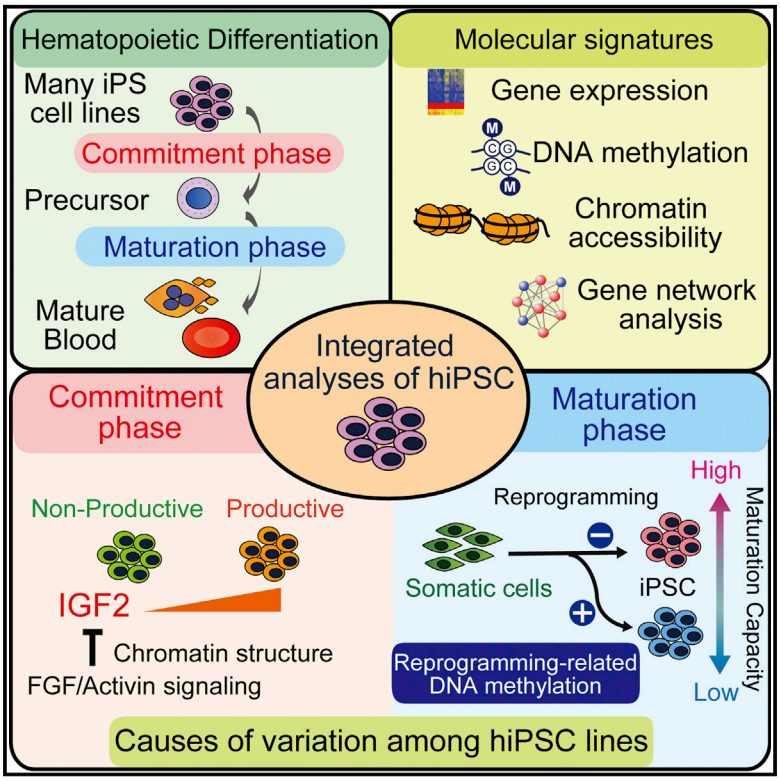
Article

Cell Stem Cell

Epigenetic Variation between Human Induced Pluripotent Stem Cell Lines Is an Indicator of Differentiation Capacity

Graphical Abstract



Highlights

- Human PSC hematopoietic commitment capacity correlates with IGF2 expression
- IGF2 expression depends on signaling-dependent chromatin accessibility
- Maturation capacity is associated with reprogramming-related DNA methylation
- Epigenetic features can help identify human PSC lines with differential capacities

Authors

Masatoshi Nishizawa, Kazuhisa Chonabayashi, Masaki Nomura, ..., Akifumi Takaori-Kondo, Shinya Yamanaka, Yoshinori Yoshida

Correspondence

yoshinor@cira.kyoto-u.ac.jp

In Brief

Nishizawa et al. integrate analysis of differentiation outcome and molecular characterization to identify features of human iPSCs associated with high and low capacities for hematopoietic specification and maturation. Prospective use of this type of information could help in choosing iPSC lines best suited to different applications.

Accession Numbers

GSE60924
GSE74967

Nishizawa et al., 2016, Cell Stem Cell *19*, 341–354
September 1, 2016
http://dx.doi.org/10.1016/j.stem.2016.06.019

Cell Stem Cell
Article

Epigenetic Variation between Human Induced Pluripotent Stem Cell Lines Is an Indicator of Differentiation Capacity

Masatoshi Nishizawa,[1,2] Kazuhisa Chonabayashi,[1,2] Masaki Nomura,[1] Azusa Tanaka,[1] Masahiro Nakamura,[1] Azusa Inagaki,[1] Misato Nishikawa,[1] Ikue Takei,[1] Akiko Oishi,[1] Koji Tanabe,[1] Mari Ohnuki,[1] Hidaka Yokota,[1] Michiyo Koyanagi-Aoi,[1] Keisuke Okita,[1] Akira Watanabe,[1,3] Akifumi Takaori-Kondo,[2] Shinya Yamanaka,[1,3,4] and Yoshinori Yoshida[1,*]

[1]Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto 606-8507, Japan
[2]Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto 606-8507, Japan
[3]Institute for Integrated Cell-Material Sciences, Kyoto University, Kyoto 606-8501, Japan
[4]Gladstone Institute of Cardiovascular Disease, San Francisco, CA 94158, USA
*Correspondence: yoshinor@cira.kyoto-u.ac.jp
http://dx.doi.org/10.1016/j.stem.2016.06.019

SUMMARY

Variation in the differentiation capacity of induced pluripotent stem cells (iPSCs) to specific lineages is a significant concern for their use in clinical applications and disease modeling. To identify factors that affect differentiation capacity, we performed integration analyses between hematopoietic differentiation performance and molecular signatures such as gene expression, DNA methylation, and chromatin status, using 35 human iPSC lines and four ESC lines. Our analyses revealed that hematopoietic commitment of PSCs to hematopoietic precursors correlates with IGF2 expression level, which in turn depends on signaling-dependent chromatin accessibility at mesendodermal genes. Maturation capacity for conversion of PSC-derived hematopoietic precursors to mature blood associates with the amount and pattern of DNA methylation acquired during reprogramming. Our study therefore provides insight into the molecular features that determine the differential capacities seen among human iPSC lines and, through the predictive potential of this information, highlights a way to select optimal iPSCs for clinical applications.

INTRODUCTION

The potential of human induced pluripotent stem cells (iPSCs) (Takahashi et al., 2007; Takahashi and Yamanaka, 2006) to differentiate into many cell types makes them a promising source for regeneration therapy, drug screening, and pathogenetic study. However, this potential is compromised by the large variation that exists among human iPSC lines in their differentiation capacity to specific lineages. One of the factors attributed to this variation is the residual DNA methylation signatures that remain after the reprogramming process to pluripotency, a phenomenon known as somatic memory (Kim et al., 2010, 2011; Lister et al., 2011; Ohi et al., 2011; Polo et al., 2010). Another factor that could cause variation among iPSC lines is aberrations during the reprogramming process, with aberrations in DNA methylation being most investigated (Huang et al., 2013; Koyanagi-Aoi et al., 2013; Lister et al., 2011; Nazor et al., 2012; Ruiz et al., 2012; Stadtfeld et al., 2010). A third factor is genetic differences among individual donors of human pluripotent stem cells (PSCs) (Kajiwara et al., 2012). While all these theories deserve consideration, overall, reports that have investigated variations in human iPSC lines used sample numbers that were too small for reliable conclusions.

In the present study, we assessed the hematopoietic differentiation capacity of 35 human iPSC lines from four parental tissues and four embryonic stem cell (ESC) lines by evaluating both the early phase (commitment phase) and the late phase (maturation phase) of hematopoietic differentiation. In addition, we investigated gene expression, DNA methylation, and open chromatin accessibility and performed correlation analysis of the differentiation capacities and these molecular signatures. The analysis revealed that in iPSCs, commitment capacity was associated with insulin-like growth factor 2 (IGF2) gene expression, which was under the control of fibroblast growth factor (FGF)-activin signaling-dependent chromatin accessibility. In contrast, maturation capacity was associated with aberrant DNA methylation acquired during the reprogramming process. Our study provides important insights on the molecular mechanism of differentiation capacity and ways to select optimal iPSCs for clinical applications.

RESULTS

Hematopoietic Commitment Capacity Is Associated with Expression Levels of IGF2 in Undifferentiated PSCs, but Not with Original Cell Type

To investigate the differentiation capacity among human iPSCs from different origins, we first assessed the hematopoietic differentiation capacities of 35 iPSC lines derived from four types of somatic tissues—human dermal fibroblasts (HDFs), hematopoietic cells such as cord blood (CB) and peripheral blood (PB), dental pulp (DP) cells, and keratinocytes (Kera)—from 15 donors