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Review

Epigenetics of cell fate reprogramming and its implications for neurological disorders modelling

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ABSTRACT

The reprogramming of human induced pluripotent stem cells (hiPSCs) proceeds in a stepwise manner with reprogramming factors binding and epigenetic composition changes during transition to maintain the epigenetic landscape, important for pluripotency. There arises a question as to whether the aberrant epigenetic state after reprogramming leads to epigenetic defects in induced stem cells causing unpredictable long term effects in differentiated cells. In this review, we present a comprehensive view of epigenetic alterations accompanying reprogramming, cell maintenance and differentiation as factors that influence applications of hiPSCs in stem cell based technologies. We conclude that sample heterogeneity masks DNA methylation signatures in subpopulations of cells and thus believe that beside a genetic evaluation, extensive epigenomic screening should become a standard procedure to ensure hiPSCs state before they are used for genome editing and differentiation into neurons of interest. In particular, we suggest that exploitation of the single-cell composition of the epigenome will provide important insights into heterogeneity within hiPSCs subpopulations to fast forward development of reliable hiPSC-based analytical platforms in neurological disorders modelling and before completed hiPSC technology will be implemented in clinical approaches.

Contents

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1. Introduction

Pluripotent cells, which are capable of producing all somatic cell types, provide a valuable resource for developmental studies and regenerative therapies (Ross and Akimov, 2014; Unternaehrer and Daley, 2011). Human embryonic stem cell (hESC) lines can be derived from the inner cell mass of early blastocyst embryos and maintained in vitro (Chan et al., 2013). The unique identity of ESCs is governed by a network of transcriptional factors along with epigenetic factors. The epigenetic status of ESCs features an open chromatin structure with characteristic histone and DNA modification profile (Liang and Zhang, 2013).

Alternatively, human induced pluripotent stem cells (hiPSCs) can be reprogrammed from somatic cells (Lund et al., 2012). Reprogramming of somatic cells to pluripotency can currently be achieved by somatic cell nuclear transfer (SCNT) (Whitworth and Prather, 2010), fusion of somatic and pluripotent cells (Niemann et al., 2008), ectopic expression of defined sets of pluripotency transcription factors (TFs) OCT4, SOX2, KLF4, and MYC (OSKMs) in somatic cells to generate induced pluripotent stem cells (iPSCs) (Takahashi et al., 2007). Somatic cells could also be directly reprogrammed to induced cells e.g. induced neurons (iN) though the use of empirically determined cocktails of neurogenic factors (Han et al., 2012). The first clinical trials using embryonic-stem-cell-derived products have begun (Schwartz et al., 2012).

hiPSCs derived from patients with genetic diseases can be used as cellular models of a disease, thus enabling mechanistic studies and high throughput drug screenings (Lund et al., 2012). Recent findings underline the significant role that hiPSC models can play in epigenetic research to generate patient-specific disease-relevant cells to elucidate disease mechanisms (Qiang et al., 2013). Reprogramming of human fibroblasts into hiPSCs has become a widely applied technique used to create models of neurodegenerative and neurological disorders (Imaizumi and Okano, 2014). Well-described protocols are available to generate patient-derived disease-relevant cell types upon hiPSCs reprogramming. Until now hiPSC models have been applied in order to study a broad spectrum of neurodegenerative disorders (Durnaoglu et al., 2011) including Huntington's disease (Zhang et al., 2010), Parkinson's disease (Byers et al., 2012; Soldner et al., 2009), Amyotrophic Lateral Sclerosis (Bohl et al., 2016), Frontotemporal Dementia (Almeida et al., 2013), Alzheimer's disease (Hossini et al., 2015; D. Zhang et al., 2014), Spinomuscular Atrophy (Ebert et al., 2009; Ebert and Svendsen, 2010) and other polyglutamine diseases (Ross and Akimov, 2014). However, the genetic and potentially epigenetic heterogeneity of stem cell lines contributes to the functional variability of differentiated somatic cells, confounding evaluation of disease modelling experiments (Ichida and Kiskinis, 2015; Sandoe and Eggan, 2013).

In pluripotent cells the accumulation of epigenomic alterations is a concern and it is thus an area of active research. Such variability can be introduced at multiple levels of reprogramming including OSKMs action, in vitro culture, variation in cell culture reagents, and neural generation (Fig. 1).

Reprogramming is a multi-step process characterised by two waves of transcriptome and proteome resetting (Sancho-Martinez and Belmonte, 2013). Early in the reprogramming process, OSKMs induce stochastic gene expression changes in a subset of pluripotency genes which are critical for instigation of the second phase (Buganim et al., 2013). The epigenetic signature of the somatic cell must be erased during the conversion in order to adopt a stem cell-like epigenome. These changes include chromatin reorganisation, DNA demethylation of the promoter regions of pluripotency genes like *Nanog*, *Sox2* and *Oct4*, reactivation of the somatically silenced X chromosome, and genome-wide resetting of histone posttranslational modifications. Confirmation of genetic cell identity is necessary, yet does not provide a full picture of crucial information. Knowledge of the cell state, pluripotency, and other cellular characteristics is not sufficiently advanced at this stage to permit a comprehensive cellular profile based solely on genetic analysis, even with genome sequencing. Table 1 shows the major issues and potential solutions for hiPSC quality control as well contemporary methods of quality testing.

Epigenetic changes, metabolic reprogramming, mitochondrial alterations and remnants of reprogramming components may cause changes in cellular behavior, function and properties (Yaffe et al., 2016). An understanding of the intrinsic properties of stem cells i.e. their pluripotency, self-renewal, and regulatory mechanisms is crucial for the modelling of human diseases. However, a full understanding of how pluripotency and somatic cell reprogramming are controlled is still lacking, meaning that alongside biological cell and molecular mechanisms, the epigenetics underlying these properties becomes of crucial interest (Yaffe et al., 2016).