Opinion

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DNA Methylation Profiles of Human Pluripotent Stem Cells, a Versatile Tool to Investigate Cell Identity and Biosafety

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Abstract

Human pluripotent stem cells (hPSCs) offer numerous functional solutions, but several underlying biological mechanisms, such as epigenetic modifications, still remain to be explored. Recently, there has been an increasing interest in employing whole-genome techniques to profile DNA methylation (DNAm) changes of hPSCs. The results from these studies will increase the knowledge on the molecular mechanisms that underpin hPSCs and their potential use in several fields including disease modelling, drug screening and regenerative medicine.

Keywords: Human pluripotent stem cells; DNA methylation

Abbreviations

DMRs: Differentially Methylated Regions; DNAm: DNA Methylation; hESCs: Human Embryonic Stem Cells; hiPSCs: Human Induced Pluripotent Stem Cells; hPSCs: Human Pluripotent Stem Cells; meDIP-chip: Methylated DNA Immunoprecipitation Coupled to Microarray Technology

Opinion

The interest of the scientific community on the epigenetic landscapes of human pluripotent stem cells (hPSCs) has increased over the past years. Besides the established potential of hPSCs in numerous applications - among which disease modelling, drug screening and regenerative medicine knowledge on the role of epigenetic mechanisms in the regulation of embryonic development, in establishing cell identity and considering the biosafety of these cells in clinical practice will exponentially stimulate progress.

DNA methylation (DNAm) is a heritable epigenetic mark known to influence gene expression through covalent transfer of a methyl group to the C-5 position of the cytosine specific to CpG dinucleotides. Despite the growing knowledge on the genome-wide contribution of DNAm to self- renewal and differentiation, understanding how DNAm changes are able to influence hPSCs and their derivatives is still very limited and not yet fully addressed. Therefore, the application of technological tools to the study of DNAm on hPSCs has multiple implications, both in cell biology and biosafety.

Recently, we have described the DNAm changes at CpG sites occurring during in vitro striatal neuronal differentiation of H9 human embryonic stem cells (H9-hESCs), by means of methylated DNA immunoprecipitation coupled to microarray technology (meDIP-chip) [1]. DNAm underpinned the pluripotency status of H9-hESCs, which were characterized by global DNA hypomethylation [2-4], and in conjunction with other epigenetic marks (such as histone modifications) allowed transcriptionally active decondensed chromatin to activate multiple differentiation programs. Coupling DNA methylome to an ontogeny recapitulating protocol enabled a comprehensive view of the DNAm landscapes characterizing hPSCs during cell commitment in an unbiased manner. Taking into account the mutual reliance between differentiation levels and epigenetic statuses, CpG methylation profiles can help in discriminating the identity of cell types. DNAm represents a dynamic process in cell commitment: differentiating H9-hESCs are characterized by waves of de novo methylation and demethylation, triggering the expression of genes involved in cell specialization and locking cell fate decision. Moreover, the identification of stage-specific differentially methylated regions (DMRs), directly related to peculiar cellular commitments, revealed how the influence between epigenetic regulation and development is close and interdependent. Thus, the study of DNAm also allows the identification of distinct biological entities, which are endowed with peculiar epigenetic signatures, pointing out novel putative biomarkers. Recent studies highlighted the exploitation of microarray-associated data (both from expression and DNAm profiles) to pinpoint quantitative variations in differentiation propensity and efficiency of hPSCs in order to associate a specific scorecard to each cell line [5,6].

Noticeably, differentiating H9-hESCs did not apparently acquire any methylation based oncogenic feature globally; only hypomethylation in the promoter of the oncosupressor gene BCL2L11 was detected in H9-derived neurons. Thus, CpG methylation profiles can be exploited to evaluate the onset of methylation changes that may promote cell proliferation.

Interestingly, the same approach is being adopted to study the methylome of human induced pluripotent stem cells (hiPSCs) in order to understand both reprogramming events and the epigenetic differences compared to hESCs.

Furthermore, the employment of hiPSCs paves the way to unprecedented applications: the creation of hiPSC lines from both healthy and diseased subjects introduces new solutions for disease modelling and translational medicine. In this perspective, we extensively applied the study of the DNAm profiles also on control and disease-specific hiPSC lines in order to identify methylation-based disease associated changes with an impartial approach (data in elaboration). Modifications in the DNAm status of specific genomic regions, which were previously unknown, might be involved in disease susceptibility and/or phenotype modulation.

These changes would not have been identified without the use of hiPSCs as cellular model system coupled with an unbiased whole-genome methylation analysis (reviewed in [7] submitted to Stem Cell Res Ther).

Collectively, these considerations clearly evidence that DNAm introduces an additional level of complexity in the hPSCs field and cannot be underestimated. These conclusions are sustained by the vast influence that DNAm and epigenetics have on several aspects of hPSC self-renewal and differentiation. Therefore, the investigation of the DNAm profiles has numerous readouts: (i) evaluation of pluripotency and differentiation associated chromatin states, (ii) discerning among different cellular identities, creating a database for differentiation associated DNAm changes, (iii) biomarker discovery and (iv) cell biosafety. Despite high-throughput strategies are greatly increasing the knowledge in all these area, the complexity of both epigenetic mechanisms and hPSC biology requires further studies essential to fully understand their real contribution and interplay, in order to entirely harness hPSC power.

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References

1. Baronchelli S, La Spada A, Conforti P, Redaelli S, Dalpra L, et al. (2015) Investigating DNA Methylation Dynamics and Safety of Human Embryonic Stem Cell Differentiation Toward Striatal Neurons. Stem Cells Dev 24(20): 2366-77.
2. Berdasco M, Esteller M (2011) DNA methylation in stem cell renewal and multipotency. Stem Cell Res Ther 2(5): 42.
3. Meissner A, Mikkelsen TS, Gu H, Wernig M, Hanna J, et al. (2008) Genome-scale DNA methylation maps of pluripotent and differentiated cells. Nature 454: 766-770.
4. Mikkelsen TS, Ku M, Jaffe DB, Issac B, Lieberman E, et al. (2007) Genome-wide maps of chromatin state in pluripotent and lineage-committed cells. Nature 448: 553-560.
5. Sugawara T, Nishino K, Umezawa A, Akutsu H (2012) Investingating cellular identity and manipulating cell fate using induced pluripotent stem cells. Stem Cell Res Ther 3(2): 8.
6. Bock C, Kiskins E, Verstappen G, Gu H, Boulting G, et al. (2011) Reference Maps of human ES and iPS cell variation enable high-throughput characterization of pluripotent cell lines. Cell 144(3): 439-52.
7. NetLiPS Consortium members (2015) Network Lombardo iPS (NetLiPS), a stem cell platform to test the pharmacological effects of drugs. Stem Cell Res Ther.