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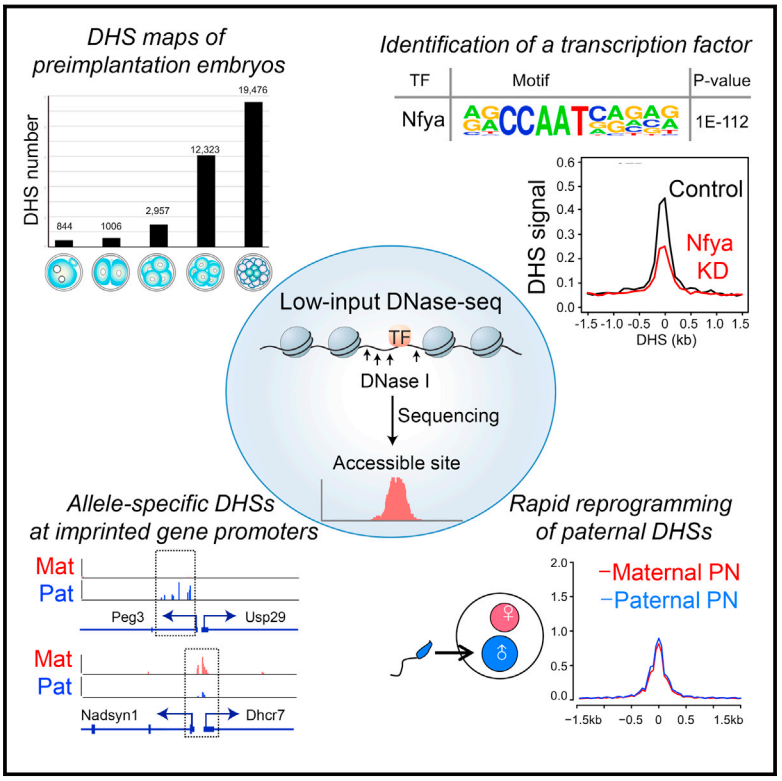
Establishing Chromatin Regulatory Landscape during Mouse Preimplantation Development

Graphical Abstract



Highlights

- Genome-wide mapping of DNase I hypersensitive sites in preimplantation embryos
- DHSs are progressively established with a drastic increase at 8-cell embryos
- Paternal chromatin accessibility is quickly reprogrammed after fertilization
- Nfya and Oct4 contribute to DHSs gained in 2-cell and 8-cell stages, respectively

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In Brief

The DNase I-hypersensitive site mapping of mouse preimplantation embryos reveals how the chromatin regulatory landscape in the mouse embryos is established from differentially packaged sperm and egg genomes and identifies key transcription factors crucial for this process.

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Establishing Chromatin Regulatory Landscape during Mouse Preimplantation Development

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SUMMARY

How the chromatin regulatory landscape in the inner cell mass cells is established from differentially packaged sperm and egg genomes during preimplantation development is unknown. Here, we develop a low-input DNase I sequencing (liDNase-seq) method that allows us to generate maps of DNase I-hypersensitive site (DHS) of mouse preimplantation embryos from 1-cell to morula stage. The DHS landscape is progressively established with a drastic increase at the 8-cell stage. Paternal chromatin accessibility is quickly reprogrammed after fertilization to the level similar to maternal chromatin, while imprinted genes exhibit allelic accessibility bias. We demonstrate that transcription factor Nfya contributes to zygotic genome activation and DHS formation at the 2-cell stage and that Oct4 contributes to the DHSs gained at the 8-cell stage. Our study reveals the dynamic chromatin regulatory landscape during early development and identifies key transcription factors important for DHS establishment in mammalian embryos.

INTRODUCTION

Terminally differentiated sperm and egg genomes are organized in very different ways. While sperm genomes are packaged with protamines, egg genomes are occupied by nucleosomes and are transcriptionally inert (Jenkins and Carrell, 2012). Upon fertilization, the tightly packaged sperm genome undergoes de novo nucleosome assembly before the two parental genomes replicate. This is followed by equal distribution of the replicated chromosomes into the two blastomeres of the 2-cell embryo. After a few round of cleavage divisions, the embryo reaches the morula stage when the first cell lineage specification commences to generate trophectoderm and inner cell mass (ICM) of the blastocyst before implanting to the uterus (Burton and Torres-Padilla, 2014).

Preimplantation development harbors two cell fate transitions. First, the highly differentiated germ cells (sperm and egg) are reprogrammed into a totipotent state characterized by having the highest level of cell fate plasticity (Rossant, 1976). The second cell fate transition takes place when the morula stage cells commit to either the trophectoderm lineage or pluripotent ICM cells (Morgan et al., 2005). Concurrent with the cell fate transitions are dramatic chromatin and transcriptional changes. One of the most notable transcriptional changes taking place during mammalian preimplantation development is zygotic genome activation (ZGA) (Svoboda et al., 2015). In mice, a major ZGA takes place in 2-cell embryos (Hamatani et al., 2004). Despite the fact that ZGA plays an essential role in preimplantation development, no transcription factor (TF) responsible for mammalian major ZGA has been identified. Consequently, the mechanism underlying mammalian ZGA is largely unknown. Recent studies have revealed several TFs, including Zelda, Pou5f1, Nanog, and SoxB1, to be important for ZGA in *Drosophila* and/or zebrafish (Lee et al., 2013; Liang et al., 2008). These TFs are unlikely to be involved in mammalian ZGA as the mammalian counterpart either does not exist or is not expressed at an appreciable level before ZGA. Mammalian ZGA might be mechanistically different from that of *Drosophila* and zebrafish as mammalian ZGA takes place early during preimplantation development, while *Drosophila*/zebrafish ZGA takes place at a much later developmental stage (at cell cycle 14 in *Drosophila* and cell cycle 10 in zebrafish) (Lee et al., 2014).

Cells at a particular state possess a defined set of cis-regulatory elements that are accessible to *trans*-acting factors, which underlies the chromatin regulatory network of the cell state (Bell et al., 2011; Gross and Garrard, 1988). Understanding the dynamics of chromatin accessibility during preimplantation development may provide insights into the chromatin and cell fate regulation during the process. DNase I hypersensitivity is one of the best measures of chromatin accessibility (Bell et al., 2011) and has been widely used to map functional elements, including promoters, enhancers, insulators, and locus control regions, as these regions are relatively more accessible (Gross and Garrard, 1988). Recently, DNase I treatment coupled with high-throughput DNA sequencing (DNase-seq) has allowed high-resolution genome-wide mapping of DNase