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Unwind and transcribe: chromatin reprogramming in the early mammalian embryo

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Abstract

Within the first few days of life, the unipotent gametic genomes are rapidly reprogrammed to support emergence of pluripotent cells in the early mammalian embryo. It is now appreciated that this critical stage of development involves dramatic changes to chromatin at multiple levels, such as DNA methylation, histone modifications, histone mobility, and higher-order chromatin organization. Technological advances are beginning to allow genome-wide views of this chromatin reprogramming, and provide new approaches to functionally dissect its regulation. Here we review recent insights into the dynamic chromatin environment of the early mouse embryo. New data challenge long-held assumptions, for example, with regards to the asymmetry of DNA methylation of the parental genomes or the onset of functional zygotic genome activation. We discuss how impaired chromatin reprogramming can lead to early embryonic lethality, but might also have delayed effects that only manifest later in embryogenesis or postnatally, potentially influencing the propensity for adult-onset diseases.

Introduction

A key goal of contemporary biology is to understand the mechanisms that underlie cellular potency, defined as the ability to give rise to different cell types. The highest level of cellular potency is the totipotency of the zygote and early blastomeres of the mammalian preimplantation embryo. This is rapidly followed by pluripotency, which defines the state of the peri-implantation epiblast cells that are no longer able to differentiate into extra-embryonic tissues, but can give rise to any tissue of the embryo proper and thus the organism after birth. While the instructive roles of transcription factors and signaling pathways in these processes have been investigated and described extensively (reviewed in [1]), an increasing body of data suggests that reprogramming of chromatin states plays an important role in allowing, buffering and/or instructing transitions in cellular potency.

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The ability to observe preimplantation development ex vivo and the extensive tools available for genetic and genomic studies make the mouse an excellent model system to dissect chromatin reprogramming in the early mammalian embryo. Moreover, a limited number of studies can be carried out in human embryos, which can also be cultured ex vivo from the zygote to the blastocyst stage. This research represents a pivotal intersection of basic and applied research, as understanding of the epigenetic reprogramming of the gametes towards totipotency and the establishment of pluripotency will be instructive both for reprogramming-based regenerative medicine applications as well as Assisted Reproductive Technologies (ART) in humans. Here we review recent advances in chromatin reprogramming during early mammalian development.

Epigenetic reprogramming of gametic genomes

H3.3 incorporation in nucleosome assembly and transcription

Very soon after a sperm cell enters the oocyte, a dramatic protamine-to-histone exchange takes place in the paternal genome. Recent studies in flies reveal that histone chaperones (TAP/p32, NAP-1, NLP) act to remove protamines from the sperm genome [2]. Maternal Histone 3.3 (H3.3), a histone variant that does not depend on DNA replication to be incorporated and is associated with active transcription, is the main type of H3 incorporated into the paternal genome [3,4], but its functional role in the mouse had remained unclear. Recent work from our lab and others shows that incorporation of H3.3 by its chaperone Hira is not involved in protamine removal, but is indispensable for nucleosome assembly and subsequent DNA replication in the male genome [5,6], as well as for ELYS-mediated nuclear pore complex assembly [7].

An unexpected finding of our studies is that Hira-mediated H3.3 incorporation is required for RNA Polymerase I (Pol I) transcription in both the maternal and the paternal pronuclei, which in turn is essential for zygote development [6]. These results indicate that the female pronucleus is not a passive “bystander” as previously assumed, but rather undergoes active reprogramming. Moreover, these data challenge a decades-old dogma that transcription of the zygotic genome in mouse is minor and not required for the development to the 2-cell stage [8,9]. While phenotypic consequences of zygotic Pol II inhibition only become obvious beyond the 2-cell stage [10], Pol I function is strictly required for the transition to the two cell stage [6]. Thus, Zygotic Genome Activation (ZGA) can be considered to begin at the zygote stage with the transcription of rRNA by Pol I, in preparation for the translation of mRNAs transcribed by Pol II at the 2-cell stage (Fig. 1). While these findings are exciting, they raise several new questions. Further studies should focus on (1) the characterization of the genome-wide location of H3.3 in the parental genomes (2) the mechanisms by which H3.3-containing nucleosomes support DNA replication and rRNA transcription and (3) the kinetics of ribosomal RNA biosynthesis and translation in the zygote.

High resolution views of DNA demethylation in early mouse embryo

Around the same time that the parental genomes are reprogrammed at the nucleosomal level to support development, they also undergo DNA demethylation on a remarkable genome-

wide scale. Previous low resolution studies based primarily on immunofluorescence staining suggested that the paternal genome undergoes rapid active DNA demethylation via Tet3-mediated oxidation of 5-methyl-cytosine (5mC) to 5-hydroxymethyl-cytosine (5hmC) [11-14]. On the other hand, the female genome was thought to undergo passive DNA demethylation by dilution of 5mC with each DNA replication in the absence of maintenance methylation by Dnmt1 (reviewed in [15]).

Similarly to the case of histone reprogramming (above), this simplistic view of asymmetric DNA demethylation was partially overturned with recent base-pair resolution next-generation sequencing techniques. Wang et al. [16] demonstrated that active DNA demethylation is not restricted to the male genome (Fig 1). Instead, the oxidized 5mC derivatives 5hmC and 5-formylcytosine (5fC), which are products of Tet activity, are detected in both parental genomes. Independent studies [17-19] confirmed the simultaneous involvement of active as well passive DNA demethylation in both pronuclei in the zygote by dissecting the mechanisms genetically (using maternal *Tet3* mutants) or pharmacologically (using the DNA replication inhibitor Aphidicolin). Blurring the lines between active and passive DNA demethylation, some genomic regions were shown to undergo Tet3-mediated conversion of 5mC to 5hmC, followed by DNA-replication dependent conversion to unmodified cytosine (C) [17]. Guo et al. [17] further discovered that TDG (thymine DNA glycosylase), a DNA repair enzyme that can promote the conversion of the 5mC oxidized derivatives to C via base excision repair, is not involved in DNA demethylation in the zygote. Thus, while base excision repair may still contribute to DNA demethylation, it does not involve TDG.

The picture that emerges (Fig. 1) is one where multiple partially redundant demethylation pathways operate in both parental genomes, to varying extents in each genome that may depend on the timing of DNA replication, local chromatin landscape, and accessibility to Tet3. It will be of interest to dissect the contribution of each of these factors, as well as their relationship with other regulators of DNA methylation during early development, such as Dppa3 [20], Zfp57 [21], Prmt5 [22], or Trim28 [23,24]. The observation that H3.3 incorporation is required for DNA replication [6] places histone reprogramming upstream of passive DNA demethylation, but the interplay between histone and DNA reprogramming requires further investigation.

Perhaps more vexing is the question of the function of this massive wave of DNA demethylation, which to date remains unclear. Embryos with a maternal *Tet3* mutation are sub-viable [14], although this defect is also observed in zygotic heterozygous animals, pointing to a functional role of Tet3 later in gestation [25]. DNA demethylation may erase of potential epimutations present in the gametes, facilitate activation of developmental genes or regulatory sequences, contribute to surveillance of transposable elements in the genome, and/or reduction in transcriptional noise during development. Genome-wide analyses of mutants in regulators of DNA demethylation should contribute to shedding light on this question.

Setting up pluripotency during cleavage stages and peri-implantation

Histone modifications

Global removal of DNA methylation during early development allows for the derepression of transposable elements (TEs), such as LINEs, SINEs and IAPs, which have been detected at particularly high levels at the 2-cell stage [26,27], without causing major genomic instability. Maternal-zygotic deletion of Prmt5, an arginine methyltransferase that catalyzes repressive methylation of H2A/H4R3, causes upregulation of IAPs during preimplantation development and subsequent embryonic lethality [22]. These data suggest that histone modifications contribute to keeping TE activity below a critical level in the context of low DNA methylation during preimplantation development. The regulation and potential relevance [28] of the controlled expression of TEs in totipotent cells clearly represents an area of future discovery.

In addition to contributing to genome defense, intriguing new evidence suggests that histone modifications may also play instructive roles in directing cell fates prior to or in parallel with lineage-specific transcription factors, such as Cdx2 and Oct4. Burton et al. identified Prdm14, a Carm1-interacting protein that attenuates H3R26me2 levels and biases cells towards the inner cell mass (ICM) fate already at the 4-cell stage [29]. Along these lines, Saha and colleagues found that disrupting the balance of KDM6B and EED affects the levels of H3K27me3 and transcription at key trophectoderm regulators, and interferes with normal blastocyst formation [30].

Histone variants and mobility

Histone variants have also been shown to have an impact on the epigenetic landscape of the preimplantation embryo. We found that H3.3 is required for development to the blastocyst stage by preventing over-condensation and mis-segregation of chromosomes during cleavage [31]. At the molecular level, H3.3 is required to maintain high levels of H3K36me2 and H4K16ac, marks of decondensed chromatin, and to antagonize excessive incorporation of linker histone H1 [31]. These results highlight the intricate interplay between histone variants, histone modifications and chromosome structure, and support the notion that there is a critical sensitivity to aneuploidies at the morula-to-blastocyst transition.

While the genome-wide location of histone variants and histone marks during cleavage stages remains to be determined, the mobility of several GFP-tagged histones has recently been investigated using FRAP [32]. Interestingly, the mobility of H3.3 remains unchanged between the 2- and the 8-cell stages, while H2A, H3.1 and H3.2 mobility decreases along with an increase in heterochromatin. Pluripotent cells of the ICM display a lower histone mobility than totipotent cleavage stage cells but higher than trophectoderm cells [32]. Similarly, ES cells have higher histone mobility than differentiated cells derived from them [33]. Thus, histone mobility in the preimplantation embryo appears to correlate with developmental potency of cells (Fig. 1). The functional relevance of this intriguing observation remains to be investigated.

Euchromatin vs Heterochromatin

While a globally decondensed chromatin is associated with totipotency, Jachowicz et al. recently explored the significance of the localization of pericentromeric heterochromatin at the periphery of nucleolar precursor bodies [34]. Pericentromeric DNA was tethered to the nuclear lamina using a fusion protein between Zn fingers that bind to major satellite repeats and emerin, an integral protein of the inner nuclear membrane. Interestingly, this resulted in major satellite de-repression and defective development to the blastocyst stage [34]. These findings suggest that the developmental defect may be caused by impaired heterochromatin silencing, although unrelated effects on fidelity of mitosis cannot be excluded. Nevertheless, the results point to a nuclear partitioning of silenced vs active chromatin domains in totipotent/pluripotent cells that is distinct from that of differentiated cells.

Overall, little is known about the molecular regulation of the decondensed chromatin state of pluripotent cells. Chd1, a chromatin remodeler that binds to the active histone mark H3K4me3, had previously been implicated in maintenance of decondensed chromatin in embryonic stem (ES) cells [35]. Following up on these studies, we recently showed that *Chd1−/−* ES cells have a self-renewal deficit and a 25-30% reduction in transcriptional output genome-wide, including of ribosomal RNA. In vivo, we found that Chd1 is specifically required in the epiblast for development past E5.5, and that *Chd1−/−* mutant epiblast cells have abnormal nucleolar morphology and greatly reduced rRNA expression [36]. These results reveal that Chd1 is a critical regulator of the globally elevated transcriptional output of pluripotent cells, which in turn may be required for their rapid cell proliferation. In support of these findings, in vitro studies have recently showed that silencing of nucleolar ribosomal DNA nucleates heterochromatinization of non-nucleolar DNA and promotes exit from pluripotency [37]. Clearly, the role of the nucleolus as an orchestrator of the euchromatic state of pluripotent cells deserves further exploration.

X chromosome reactivation during preimplantation development

Likely the most extreme form of facultative heterochromatinization is displayed by the inactive X chromosome in female cells. The re-activation and inactivation of the X chromosome (XCR/XCI) in females represents a special case of epigenetic regulation that appears to encompass all previously discussed modes of regulation. While the paternal X chromosome remains inactive in the extra-embryonic trophoblast cells, cells of the ICM reactivate the imprinted X by E3.5 and undergo subsequent random XCI. These inactivation events have been investigated in great detail and will not be discussed here (for a recent review, see [38]).

The regulation of XCR remains much less understood than that of XCI. It was recently shown that the non-coding RNA Tsix and the transcriptional regulator Prdm14 are important for efficient XCR prior to implantation [39], but the molecular details underlying these defects remain unclear. Consistent with the in vivo findings that Tsix is a positive regulator of XCR efficiency, but is not absolutely required, both Payer et al. and Pasque et al. found Tsix to be dispensable for XCR during induced pluripotent stem cell (iPSC) generation in vitro [39,40]. Pasque and colleagues further identified several intermediate steps of epigenetic reprogramming during XCR in individual female cells in vitro, establishing a

paradigm that may allow for the generation of testable hypotheses for the regulation of XCR in vivo.

Do environmental factors modulate epigenetic states during early mammalian development?

There is a growing appreciation that environmental factors can impact chromatin states, at least in part by modulating metabolic pathways [41]. Given the extensive chromatin reprogramming that occurs during early mammalian development, it is possible that environmental influences during this window of time lead to alterations in the chromatin state of pluripotent cells that are epigenetically inherited into adulthood (Fig. 1). Such epimutations could affect disease propensity in the adult or possibly across generations [42]. Epidemiological data support the so-called developmental origin of health and disease (DOHaD) hypothesis [43,44], but the underlying molecular mechanisms remain unknown.

ART [reviewed in [45,46]] and nutritional cues [47] are among the most common and better studied environmental stresses that can alter epigenetic marks in preimplantation embryos. Overall there is a lack of genome-wide data in this field. Recent evidence from low-resolution studies using immunofluorescence indicate a decrease in H3K4me3 levels following ART [48] or acute dietary zinc deprivation [49]. Tian and Diaz further report a reduction in DNA methylation and an increase in the mRNA levels of some TEs in zinc-deficient oocytes [49]. Taking a candidate gene approach, Feuer et al. found that a glucose-sensitive gene, Thioredoxin-interacting protein (*Txnip*), is expressed at significantly higher levels in in vitro fertilization (IVF) blastocysts, and adipose tissue and muscle of adult IVF females [50]. This dysregulation of *Txnip* expression was associated with enrichment for H4 acetylation at the *Txnip* promoter, detected both at the blastocyst stage and in adult adipose tissue. There were no detectable DNA methylation differences at the *Txnip* promoter [50]. Interestingly, analyses of DNA methylation at a select group of imprinted genes at E10.5 reveal an increase in stochastic errors associated with ART in the placenta, but not the embryo [51]. These studies lend some support to the notion that early mammalian development is a window of opportunity for environmental modulation of epigenetic states. Given that the environment of the preimplantation embryo is by design artificially manipulated during human ART, this is a question of high relevance where basic science can make an important contribution. Much work lies ahead in understanding the extent to which environmental factors affect chromatin states genome-wide, whether chromatin alterations are cause or consequence of dysregulation of gene expression, what are direct effects on the embryo vs those modulated by effects in the uterine environment or the placenta, how epigenetic information is inherited into adulthood, and how it can affect disease propensity.

Conclusions

Recent advances highlight the importance of chromatin reprogramming for the establishment of totipotent and pluripotent states during early mammalian development. We are beginning to gain mechanistic insight into the intricate network of interactions of many layers of chromatin-level regulation, including DNA methylation, histone marks, histone

variants, nucleosome positioning, chromatin mobility, higher-order chromatin organization, and nuclear compartmentalization that contribute to the remarkably precise unfolding of transcriptional states and lineage decisions in the early mammalian embryo. Due to the limited amount of material available from preimplantation embryos, however, these phenomena have to date often been explored using specific loci and exceptional situations, such as imprinting and XCI/XCR. It is imperative to test how the models that are emerging fare on a genome-wide scale, particularly with regards to histone modifications. Recent advances in low cell number ChIP-seq applied to freshly isolated embryonic cells [52,53] should be particularly useful in this regard. An area that deserves further attention pertains to the potential role of non-coding RNAs in the regulation of chromatin states during early development, as suggested by studies linking satellite repeat expression to heterochromatin formation [54,55]. In parallel, the use of pluripotent (ESCs, EpiSCs, iPSCs) and extra-embryonic stem cells (TSCs, XEN cells) provides opportunities to investigate epigenetic phenomena in vitro that will need to be tested thoroughly in vivo, preferably using rigorous genetic strategies that avoid artifacts of gene over-expression or knockdown approaches. Whenever possible, maternal gene manipulation using Cre/loxP technology will continue to be a method of choice, and new CRISPR/Cas9-based approaches will likely accelerate discovery on this front. Finally, most studies have investigated the effects of chromatin abnormalities that are dramatic and frequently lethal by the blastocyst stage. However, the preimplantation period might also be a sensitive window for sub-lethal insults that result in epigenetic changes impacting later events in the life. It will be important to rigorously assess if, when and how environmental factors may epigenetically affect postnatal propensity for disease. Considering the increasing availability of sophisticated technologies to probe in depth chromatin states in the early mammalian embryo, the years ahead should prove fertile ground for fundamental discoveries in this field.

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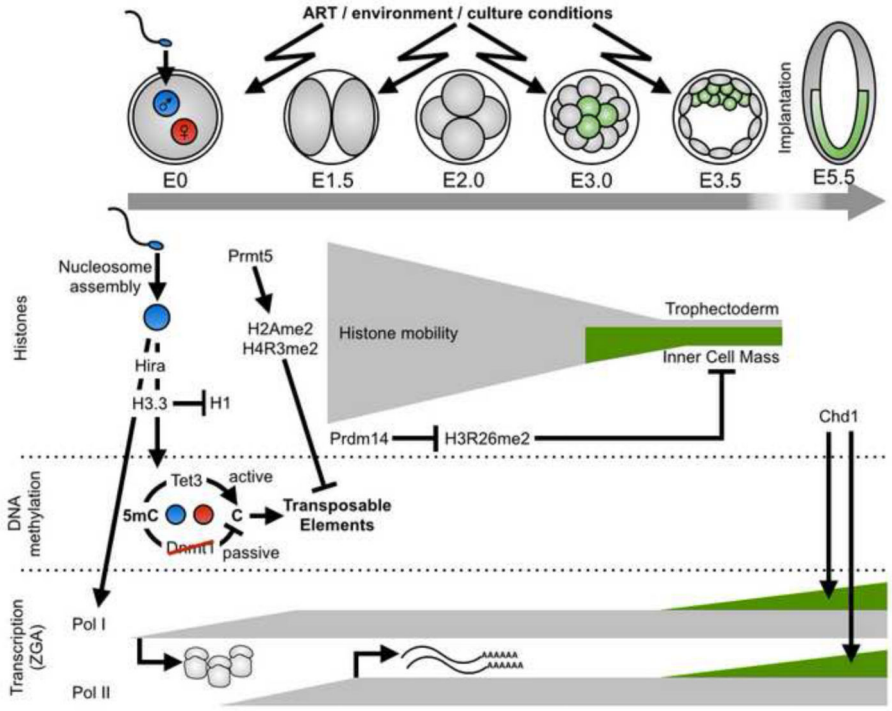

Figure 1.

Summary of key recent advances in epigenetic reprogramming during early mouse development at the level of histones, DNA (de)methylation, and transcription. Paternal and maternal pronuclei are indicated in blue and red, respectively. Pluripotent cells are indicated in green. See text for details.