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Mammalian zygotic genome activation

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ABSTRACT

Zygotic genome activation (ZGA) denotes the initiation of gene expression after fertilization. It is part of the complex oocyte-to-embryo transition (OET) in which a highly specialized cell – the oocyte – is fertilized and transformed into a zygote that gives rise to an embryo that will develop into a newborn. From the perspective of gene expression, the OET reflects reprogramming of germ cell gene expression into the new developmental program of the zygote. This reprogramming occurs at transcriptional and post-transcriptional levels. This review will discuss selected aspects of mammalian ZGA, highlighting shared features and evolved differences observed in commonly investigated mammals and non-mammalian model animals.

Contents

1. Introduction

Zygotic genome activation (ZGA) can be likened to logistics[1] required for setting up a new cell-governing system that will ultimately give rise to a new organism while the exchange the cell-governing system has to occur without disturbing cell's regular business. The information for this logistical challenge is stored in ~10^8–10^9 nucleotides of nuclear DNA and the instructions contained therein must be executed in a zygote within a specific time frame. In highly complex human societies, changes in governing systems are accompanied with different degrees of chaos and anarchy before new governing systems establish their control. This anthropomorphic perspective highlights how effectively natural selection has optimized the oocyte-to-embryo-transition (OET) so that its logistics[1] is executed in a timely and orderly fashion.

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[1] logistics /l/ˈdʒɪlogist/, *noun*
the detailed organization and implementation of a complex operation (Oxford Dictionary).
'the management of inventory in motion and at rest.' (businessdictionary.com).

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The initiation of animal development varies. The egg size, yolk distribution, cleavage pattern, and gene activation are among the notably diversified features. Yet, at least three themes appear common across the animal kingdom: rapid cell cleavage, "maturation" of chromatin structures, and a delayed onset of zygotic transcription (for a review of diversity of OET, see, for example, [1]). This review will focus on mammalian ZGA and examine commonalities and differences among mammals and other animals.

There are over five thousand extant species of placental mammals representing clades, that radiated primarily after the Cretaceous-Paleogene event 65–66 million years ago [2]. Two mammalian model systems have been studied the most: *Homo sapiens* and *Mus musculus*, the latter being the most experimentally manipulated mammalian species. However, extant mammals exhibit extreme diversity in size, habitat occupation, and locomotion adaptation [3]. Mammalian radiation did not occur at the same pace in terms of speciation and genome evolution; *Mus musculus* belongs to a group that radiated extensively [4]. The mouse genome evolved faster than that of larger mammals such as humans or bovine because it could produce more generation cycles per a given unit of time. This should be kept in mind when interpreting mouse model data because many traits observed in mice could represent recently evolved characteristics rather than common ancestral traits present in all mammals.

2. Early development in animals – the placenta

Initiation of development in placental mammals differs from other animals such as *Caenorhabditis*, *Drosophila*, zebrafish, *Xenopus* or chicken where the fertilized egg will exclusively give rise to a gastrulating embryo. In non-mammalian models, the initial cleavage typically employs rapid cell cycles (sea urchin or *Drosophila* ~10 min, zebrafish ~15 min, *Xenopus* ~35 min [5]) with little if any transcription of the genome (reviewed in [6]). Different mechanisms may regulate the delayed onset of ZGA (reviewed in [7,8])

Zygotic cleavage in early mammalian development may not be a homologous process to cleavage in non-mammalian species. In mammals (mice, humans, bovine), the initial rate of cleavage is slow while extraembryonic and embryonic lineages are not yet separated. By the time the first cleavage of mouse zygotes is complete, the above-mentioned non-mammalian models have developed far beyond gastrulation (Fig. A). Accordingly, it was proposed that early mammalian development should be aligned with early development of other animals by gastrulation (and not fertilization) to account for the rapid cleavage non-mammalian metazoan zygotes, which appears rather homologous to the accelerated peri-gastrulation cycles in placental mammals [6]. According to this model, fertilization in mammals occurs at a comparatively earlier stage in oocyte development with added cleavage steps before extraembryonic and embryonic lineages are separated [6]. Thus, mammalian preimplantation development should be considered a derived characteristic that evolved in ancestors of placental mammals as an adaptation of terrestrial life.

3. Early development in mammals and animals – the time issue

Numerous experiments in different model systems indicate that zygotic gene products become essential for development only at specific stages that vary among the studied animals. For example, transcriptional inhibition in zebrafish or *Xenopus* embryos results in gastrulation defects, but does not prevent cleavage [9,10]. In *Drosophila*, absence of transcription will prevent cellularization, but preceding cell cycles will occur [11]. Consequently, analysis of RNA synthesis showed that zygotic transcription appears with a species-specific delay after fertilization (reviewed in [8]).

While the very first transcripts may be difficult to detect, the first major wave of RNA synthesis and transcript accumulation occurs at a specific stage of development. The first major surge in RNA synthesis is traditionally denoted the major ZGA wave and is characterized by a global change in gene expression that is essential for continued development. Importantly, some RNA synthesis, traditionally denoted minor ZGA, can be detected prior to major ZGA (reviewed in [1]). However, this traditional distinction has been undermined by next generation sequencing (NGS) methods, which show that transcription at many loci expressed during major ZGA is also detectable at earlier time points.

ZGA timing was proposed to be controlled by nucleo-cytoplasmic ratio changes during cleavage where the geometric increase of genomic DNA titrates transcriptional repression [10], a notion supported by experimental data in zebrafish embryos [12]. More recently, it has been proposed that the concentration of non-DNA bound core histones determines the time for the onset of transcription. The reduction in nuclear histone concentration that coincides with genome activation does not affect nucleosome density on DNA, but would allow transcription factors to compete successfully for DNA binding [13].

Major ZGA in mouse embryos occurs at the 2-cell stage while in other mammals it is delayed several divisions (4–16-cell), although more sensitive NGS data suggest that transcription initiates earlier [14,15]. In terms of major ZGA among mammals, mice are "early genome activators" while humans and bovine are "later genome activators". It is likely that the early genome activation in mice is a derived characteristic while humans and bovine represent a more ancestral state. However, the early/late distinction is relative. Mice undergo major ZGA after the first cleavage (~19 h after fertilization) but at a much later time than major ZGA occurs in zebrafish (~4h), *Xenopus* (~ 6h), or *Drosophila* (~2.5h) [8]).

It is important to highlight that mammalian OET needs only a few replication cycles for ZGA to reprogram embryonic cells to pluripotency. This contrasts with the time and large number of replication cycles needed for artificial establishment of pluripotency in cultured cells [16]. In fact, it has been noted that the number of cell divisions is a key parameter driving epigenetic reprogramming to pluripotency [17]. As mentioned above, other animals (whose development is often deterministic) have multiple cleavages in a short time prior to ZGA while mouse zygotes undergo major ZGA after the first cleavage. Mammalian cell biochemistry is presumably not much different from that of invertebrates. Thus, the "a few days, a few cleavages" mode of OET in mammals appears to be a unique mode of the initiation of development. Only by better understanding the underlying molecular mechanisms can we hope for further improvement in our ability to reprogram cell-fate. Of importance are the replication-dependent and independent chromatin changes in 1-cell and 2-cell mouse zygotes.

4. Chromatin dynamics during ZGA in mice

While there is a complex relationship between chromatin structure, transcription, and post-transcriptional processing, reprogramming gene expression is a matter of the ability of RNA polymerase II (Pol II) to access promoters, which is based on chromatin structure and available transcription factors. Chromatin is extensively remodeled between the 1-cell and 2-cell stages (reviewed in [18–20]). Importantly, both parental genomes remain separated in female and male pronuclei that do not fuse in the 1-cell zygote. Instead of fusing, nuclear envelopes of pronuclei break down during the first cleavage and embryonic nuclei accommodating both parental genomes form in 2-cell blastomeres. Reviewing

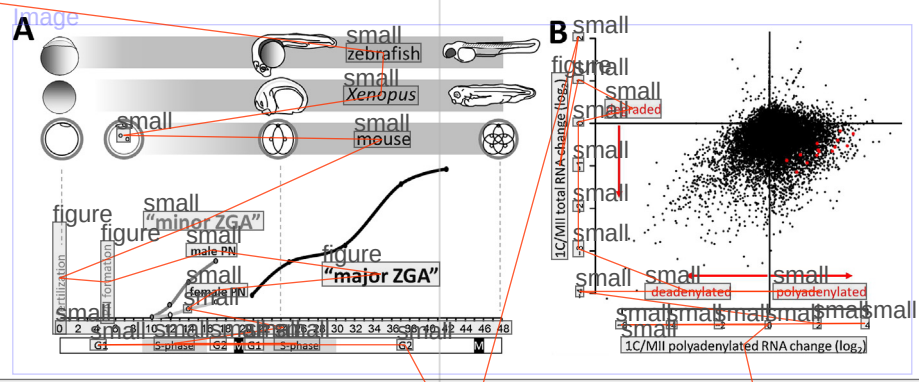

Fig. 1. Zygotic genome activation. (A) Top, development of three vertebrate model organisms during the first two days after fertilization are schematically depicted. Bottom, minor and major ZGA as described in classic experiments measuring BrUTP incorporation in mouse zygotes [53] with the hours post-fertilization and lengths of the cell cycle during the first 2 embryonic cleavages. (B) Comparison of NGS data for total RNA and polyA RNA [65,99]. Each point represents relative exon reads per million per kilobase (FPKM) value of the ratio between fertilized and unfertilized eggs. Red points represent genes proposed to represent the conserved core of minor ZGA genes for humans and mice [15]. Note an apparent shift in relative polyA RNA abundance upon fertilization, which could be interpreted as transcriptional activation, but likely reflects changes in polyadenylation because the NGS data does not indicate a relative increase in total RNA.

in detail the contribution of chromatin to OET is beyond the scope of this work, which will focus just on two key aspects of chromatin structure: (i) the protamine/histone exchange after fertilization, (ii) dynamics of chromatin on the eve of ZGA.

4.1. Protamine/histone exchange

In contrast to the maternal genome, which maintains nucleosome-based chromatin structure with global histone modification patterns similar to those of somatic cells (reviewed in [18]), paternal chromatin undergoes major remodeling because the elementary protein component of the sperm chromatin are protamine molecules. Consequently, paternal histone modifications are essentially erased together with the nucleosomal chromatin structure during spermatogenesis in a process of protamine/histone exchange (reviewed in [21,22]). Importantly, 1–10% of histones are retained in the mouse and human spermatozoa, respectively [23]. These residual histones carry specific modifications and thir retention does not appear random [23]. The H3K4me2 (active) mark was found in promoters of genes involved in spermatogenesis and cellular homeostasis, while the H3K27me3 (repressive) mark was associated with developmental promoters. It was proposed that residual histones contribute to paternal heterochromatin formation in human zygotes [24]. However, other studies suggested that nucleosome retention is predominantly associated with gene deserts and not developmental promoters (summarized in [25]). Therefore, the significance of nucleosome retention for OET remains unclear.

Upon fertilization, protamine/histone exchange takes place in reverse in order with help from the histone chaperone HIRA to establish nucleosome chromatin structure of the paternal genome [26]. The consequence of the protamine/histone exchange is that the paternal genome initiates its journey at the beginning of development with “naïve” nucleosome chromatin structures. This correlates with the bulk of initial RNA synthesis in mouse zygotes which takes place in the male pronucleus (Fig. A).

4.2. Chromatin dynamics

Chromatin dynamics is a broadly used term covering changes of covalent modifications of DNA and histones as well as DNA accessibility and higher order chromatin organization into chromatin domains (topologically associating domains - TADs). Because this review focuses on transcriptional aspects of the genome activation, it will only highlight selected aspects of chromatin dynamics.

The most common covalent mammalian DNA modification is 5-methyl cytosine (5mC) (reviewed, for example in [27]). It is a classic epigenetic mark that does not alter DNA sequence, but can carry heritable information (for further reading see [28]). While there is an ongoing debate regarding causes and consequences of DNA methylation with respect to regulation of transcription [27], DNA methylation has been generally associated with transcriptional silencing and genome maintenance through repression of parasitic sequences.

DNA methylation in the mammalian germline undergoes two reprogramming events, in which existing DNA methylation is largely eliminated (reviewed in [29]). In mouse zygotes, maternal and paternal genomes show two distinct demethylation patterns upon staining with a 5mC-recognizing antibody. The paternal genome rapidly loses 5mC signal (6–8 hours after fertilization) while the maternal genome gradually reduces methylation during cleavage-stage development [30,31]. The overall loss of DNA methylation is associated with reduction of repressive chromatin. The molecular mechanism of 5mC loss entails oxidation into 5-hydroxymethyl cytosine (5hmC) by TET dioxygenase and base excision repair (reviewed in [32]). Active paternal DNA demethylation in the zygote is found in many mammals, but is not entirely conserved [33–35] and is incomplete [36]. Apart from imprinted loci, which retain their parent-of-origin methylation pattern in imprinting control regions, intracisternal A-particle (IAP), an active murine endogenous retrovirus also remains methylated despite global demethylation [37].

Histone modifications offer a system for recording additional information concerning the histone-associated DNA. Functionality of key histone modifications is more conserved across eukaryotic kingdoms than DNA methylation (reviewed in [28]). The “histone code” has many roles including regulation of transcription and DNA repair (reviewed in [38,39]). Importantly, some histone marks are generated because of a specific event (e.g. transcription, DNA damage), but are not maintained and do not constitute a true epigenetic mark *per se*.

A detailed catalogue of histone modification dynamics during OET has been provided elsewhere [18,40]. A growing number of chromatin factors has been implicated in establishing the correct epigenetic landscape, including polycomb-mediated gene silencing [41] or histone demethylase KDM1A associated with gene activation or repression in a context-dependent manner [42,43]. Recent advances in analysis of global chromatin architecture allowed also for exploring genome-wide distribution of histone marks, chromatin accessibility and global chromatin architecture during early development [44–47].

A notable feature of chromatin remodeling during OET is reduction of parental heterochromatin prior to ZGA. As mentioned above, most paternal histone modifications, including heterochromatin marks, are almost completely erased during spermatogenesis. Maternal heterochromatin histone marks are also reduced after fertilization in mice. H4K20me3 and H3K64me3 are rapidly lost by the 2-cell stage [48,49] and H3K9me3 is reduced in pericentric heterochromatin up to the 8-cell stage [41]. These patterns suggest that removal of parental heterochromatin marks is part of the reprogramming process that results in totipotent blastomeres. The pattern is also consistent with the open chromatin structure observed during early development [50,51] and reminiscent of the chromatin structure observed in pluripotent embryonic stem cells (ESC) [50,52].

Spatially distinct genome organization was observed using a single-nucleus, high-resolution chromosome conformation capture (Hi-C) in paternal and female pronuclei during mouse OET [47]. Notably, the maternal genome was not segregated into active and inactive compartments (possibly due to inactive transcription in the extended G1 phase) suggesting that its compartmentalization in zygotes is established de novo. In contrast, there was weak, but significant, compartmentalization of the paternal genome which was either rapidly established de novo or inherited from sperm chromatin [47].

5. The onset of ZGA in mouse zygotes – the minor ZGA

Mice have the earliest known onset of ZGA among mammals with new RNA transcripts detected in mouse zygotes as early as ~7 h after pronucleus formation [53–55] (Fig. A); a more sensitive analysis could possibly detect transcription even earlier. Male pronuclei produce more RNA than female pronuclei [53]. The difference historically has been ascribed to the chromatin remodeling in the male pronucleus that is associated with protamine/histone exchange [56]. This remodeling could provide an opportunity for maternal transcription factors to associate preferentially with the male pronuclear DNA [53].

The nature of the initial transcription (minor ZGA) at the 1-cell stage has been unclear. Promiscuous or random transcription is supported by the observations that in 1-cell mouse embryos, repetitive elements such as B2-containing sequences [57] or MuERV-L [58] are expressed. In addition, plasmid-borne reporter gene expression does not require an enhancer for robust expression in 1-cell embryos, whereas an enhancer is required for robust expression in 2-cell embryos [59]. However, apart from detection of MuERV-L retrotransposon transcripts at the late 1-cell stage [58], RNAs produced during minor ZGA could not be detected by microarrays [60,61]. Thus, either minor ZGA did not produce mRNAs or their abundance was too low to be detected by these technologies.

NGS analysis of polyA RNA, which can detect low-abundant and unannotated transcripts, documented hundreds of potential minor ZGA mRNAs [15,62,63]. However, whether these mRNAs reflected transcription or *de novo* polyadenylation that occurs in fertilized eggs [64] was unclear. This issue could be avoided by using total RNA for NGS. Indeed, comparison of published total RNA and polyA RNA NGS data in oocytes and early embryos indicates that polyadenylation of maternal mRNAs could be confused with transcriptional activation (Fig. B). Two NGS studies of total RNA addressed the nature of transcripts produced during the minor wave of ZGA [63,65]. One sequenced total RNA (depleted of ribosomal RNA) and identified ~600 genes whose expression was up-regulated >1.5 fold between oocyte and 1-cell stage. The other sequenced total RNA and observed transcription within ~4000 genes. Altogether, NGS data document that the first wave of zygotic transcription is relatively promiscuous, low-level, genome-wide, and produces transcripts that are inefficiently spliced and polyadenylated [63,65].

Low level, genome-wide transcription that is both inter- and intragenic implies that transcription in 1-cell zygotes only requires minimal promoter features [66]. However, minor ZGA transcription exhibits some selectivity in that oocyte-specific genes are not transcribed. It has been proposed that minor ZGA could be "primed" by the sperm because >300 minor ZGA transcripts are also expressed in sperm, but not in parthenogenetic embryos [63]. However, only a few highly expressed testis-specific genes are detected during minor ZGA and bioinformatic analysis shows that transcription of many genes, known to be expressed during major ZGA, already can be detected during minor ZGA [65]. This implies that transcription factors controlling gene expression specifically during oocyte's growth phase are replaced by the 1-cell stage with transcription factors controlling embryonic genome activation. Elimination of maternal factors (as documented, for example, for NOBOX [67]) would explain the lack of expression of maternal transcripts and expression of major ZGA genes. The promiscuous transcription would then reflect increased accessibility of potential (cryptic) promoters to the available transcription factors. As chromatin structures further matures, this accessibility would be lost and the cryptic promoters would not be engaged.

Another feature of murine minor ZGA is reduced efficiency of splicing and polyadenylation. Spliced transcripts and some degree of termination is detected near the polyA signal [65] and it thus appears that efficiency, rather than specific mechanisms, suppresses processing of nascent transcripts. It may be that the splicing machinery in 1-cell pronuclei has limited capacity that would be overwhelmed by nascent transcripts in pronuclei with chromatin highly permissive for transcription. The relaxed control of splicing and polyadenylation correlates with absent nuclear speckles in 1-cell embryos [65] and disassembly of nuclear speckles is associated with reduced pre-mRNA splicing [68]. While this could explain inefficient processing of nascent transcripts in the larger male pronucleus with its "naïve" chromatin structure, it is unclear how the same would apply to the female pronucleus, where protamine-histone exchange does not occur. However, NGS analysis of parthenogenetic zygotes [63,65] implies that inefficient splicing exists also in female pronuclei.

The significance of minor ZGA in mouse zygotes remains unclear. Why would the zygote produce nascent transcripts across the genome that would be inefficiently processed? Inefficient post-transcriptional processing could have a protective role against mis-expression of genes that would compromise development. This could also explain, at least in part, the uncoupling of transcription and translation observed for plasmid-borne reporter genes in 1-cell embryos [69]. It is also possible that some transcripts among genes transcribed in 1-cell embryos are efficiently spliced and translated into functional proteins important for continued development. Notably, low splicing efficiency would favor protein expression from intron–less genes – in fact, a cluster of intron-less double homeobox genes recently has been implicated in ZGA [70–72]. Investigation of intron-less genes transcribed during minor ZGA is thus one research direction that could shed more light of the significance of minor ZGA. Finally, as transcription itself is required for some cellular processes, e.g., genomic imprinting [73], it should be considered that pioneering transcription itself (i.e. not its products) helps to remodel the chromatin during minor ZGA to set the stage for reprogramming gene expression during major ZGA. This notion resonates with the above-mentioned HiC data showing male pronucleus compartmentalization into active and inactive compartments that aligns with H4 hyperacetylation [47], which was known to accumulate rapidly in the male pronucleus [74].

6. The major ZGA in mouse zygotes

Major ZGA in mouse zygotes takes place during the 2-cell stage and results in a dramatic change in gene expression. While maternal mRNA degradation can be viewed as an oocyte identity-erasing mechanism, major ZGA is a zygotic identity-generating mechanism. This transition is manifested in transcriptome similarities among different stages of OET. Transcriptome profiling by microarrays as well as NGS documents an oocyte-like identity of the 1-cell transcriptome while the 2-cell stage transcriptome profile is shifting to that of the later preimplantation stages (Fig.). This shift reflects loss of oocyte-like identity through maternal mRNA degradation and accumulation of a novel zygotic transcriptome which conveys cellular totipotency.

Importantly, minor and major ZGA differ not only in the volume of transcription, but also in what is transcribed, i.e., the major wave of ZGA is not simply more of the same transcripts expressed during minor ZGA [63,65]. The estimates of genes transcribed during major ZGA vary according to filtering conditions. For example, microarray profiling of mouse early embryos identified ~3000 α-amanitin-sensitive genes in 2-cell embryos [61]. The bulk of transcription (RNA synthesis) in 2-cell embryos occurs in its long G2 phase (Fig. A). A small population of genes activated during major ZGA continue their expression in 2-cell embryos, but become silenced upon establishment of transcriptionally-repressive chromatin at the end of the 2-cell stage. NGS, however, documents that microarrays underestimate the number of expressed genes because arrays lack many non-annotated genes while NGS has the sensitivity to detect low abundant transcripts. In addition, single-cell sequencing of hybrid zygotes suggested existence of stochastic monoallelic expression and de novo activation of the paternal X chromosome [62]. In any case, ZGA and reprogramming gene expression entails thousands, not hundreds, of genes.

7. Minor and major ZGA in mammals – common and species-specific features

The minor/major ZGA concept developed in mouse zygotes cannot be generalized for all mammals. Human and bovine embryos undergo ZGA several cleavage divisions later (4–16 cells), although NGS data suggest that transcription could initiate earlier than previously thought [14,15]. Expression profiling of 2-cell mouse zygotes identified >3000 major ZGA genes [61–63]. Profiling early bovine development identified ~ 100 transcripts up-regulated at the 4-cell stage and ~1000 and ~1300 transcripts up-regulated at the 8-cell and 16-cell stages, respectively [14]. Profiling of human early development identified ~2500 genes whose expression increased between 4-cell and 8-cell stages [75]. According to another study, human ZGA occurs in three waves, with ~2000 genes up-regulated between 2-cell and 4-cell embryos ("early risers"), ~1500 genes up-regulated between 4-cell and 8-cell embryos ("middle risers"), and ~1400 genes up-regulated after 8-cell ("late risers") [76].

It might seem that with more sensitive analysis, the ZGA timing in other mammals would shift into earlier stages and the minor ZGA could occur as early as in mice. In fact, Xue et al. reported minor ZGA in human 1-cell embryos [15]. However, there are two arguments against this possibility. First, some of the evidence for early human genome activation is possibly an experimental artifact, especially when the analysis is restricted to polyA RNA (Fig. B). Second, the whole transcription correlation data paint a different picture when comparing mice with human or bovine early embryos (Fig.)

The mouse model is exceptional in that minor and major ZGA produce distinct sets of RNAs that are separated by the cleavage between 1-cell to 2-cell embryos. This can be visualized as a difference in developmental stage transcriptome correlations when separating exon and intron NGS data in mice (Fig.). When such analysis is done on mouse NGS, intron data show that the 1-cell zygote is already establishing a "zygotic" nature. This is apparently because introns in maternal mRNAs were already spliced out and degraded while nascent transcripts transcribed at the 1-cell stage come often from genes expressed at the 2-cell stage, but never from oocyte-specific genes. At the same time, exon data from the 1-cell zygote show its "maternal" identity (because of the high abundance of residual maternal mRNAs). However, such a phenomenon is not observed in bovine early development (Fig.) where one cannot place a clear boundary between minor and major ZGA. Bovine and human early embryos exhibit the major shift between maternal and zygotic transcriptomes at 8–16 cells and 4-8-cells, respectively (Fig.), indicating a later onset of major ZGA in these species compared to mouse.

Mice thus activate their genomes fast (in terms of cleavage stages) and their minor and major ZGA waves are separated by the first cleavage event. This appears as a novel feature that evolved in the mouse lineage while the delayed major ZGA observed in humans and bovine could be the an ancestral trait. It also seems that transcriptional activation in other mammals is more incremental during the early cleavage divisions than the two bursts of transcription in 1-cell and 2-cell mouse embryos.

8. ZGA and the nature of the "zygotic program"

While the set of genes that are transcribed during early development can be described by transcriptome profiling, the entirety of the "zygotic program" remains poorly defined. In mammalian development, the priority of the post-fertilization "zygotic program" is establishing totipotency, i.e. the ability to develop in all cell types, including extraembryonic tissues. During subsequent embryonic lineage commitment [77], the totipotency is reduced to pluripotency, i.e. ability to give rise to all cell types within the developing embryo, but not extraembryonic lineages. Thus, for oocyte-to-embryo reprogramming, three types of transcription programs (or transcription factor networks) can be distinguished:

maternal –the oocyte transcription factor network includes oocyte-specific proteins such as FIGLA, NOBOX, LHX8, SOHLH1/2, FOXO3A (reviewed in [78]), which are responsible for accumulation of maternal mRNAs. As mentioned above, NGS data suggest that germ cell-specific transcription factors, which control expression during oocyte growth, do not contribute to ZGA in mouse embryos [65]. This implies efficient removal or repression of these transcription factors during ovulation and after fertilization. For example, NOBOX becomes undetectable in already preovulatory oocytes [67]. In contrast to somatic cells, where transcription factors are retained on mitotic chromosomes and mark promoters for transcription following entry into interphase, this is not the case for condensed metaphase II chromosomes [79].

zygotic totipotent –a transcription factor network which forms in mice during the 2-cell stage by maternally-provided zygotic genome-activating transcription factors and transcription factors expressed during minor and major ZGA. It is poorly understood how oocytes produce transcription factors that would be recruited for genome activation while not contributing to transcription in the oocyte. While an obvious candidate mechanism is dormancy, where translationally repressed mRNAs become translated in response to developmental stimuli (reviewed in [80]), dormancy of maternal transcription factors acting in ZGA has not been explored. Nevertheless, cloning experiments document that the oocyte's ability to reprogram gene expression of a somatic nucleus into a totipotent state resides in the cytoplasm [81,82]. The totipotent program forms before lineage commitment and is responsible for the totipotency of early embryo blastomeres. It

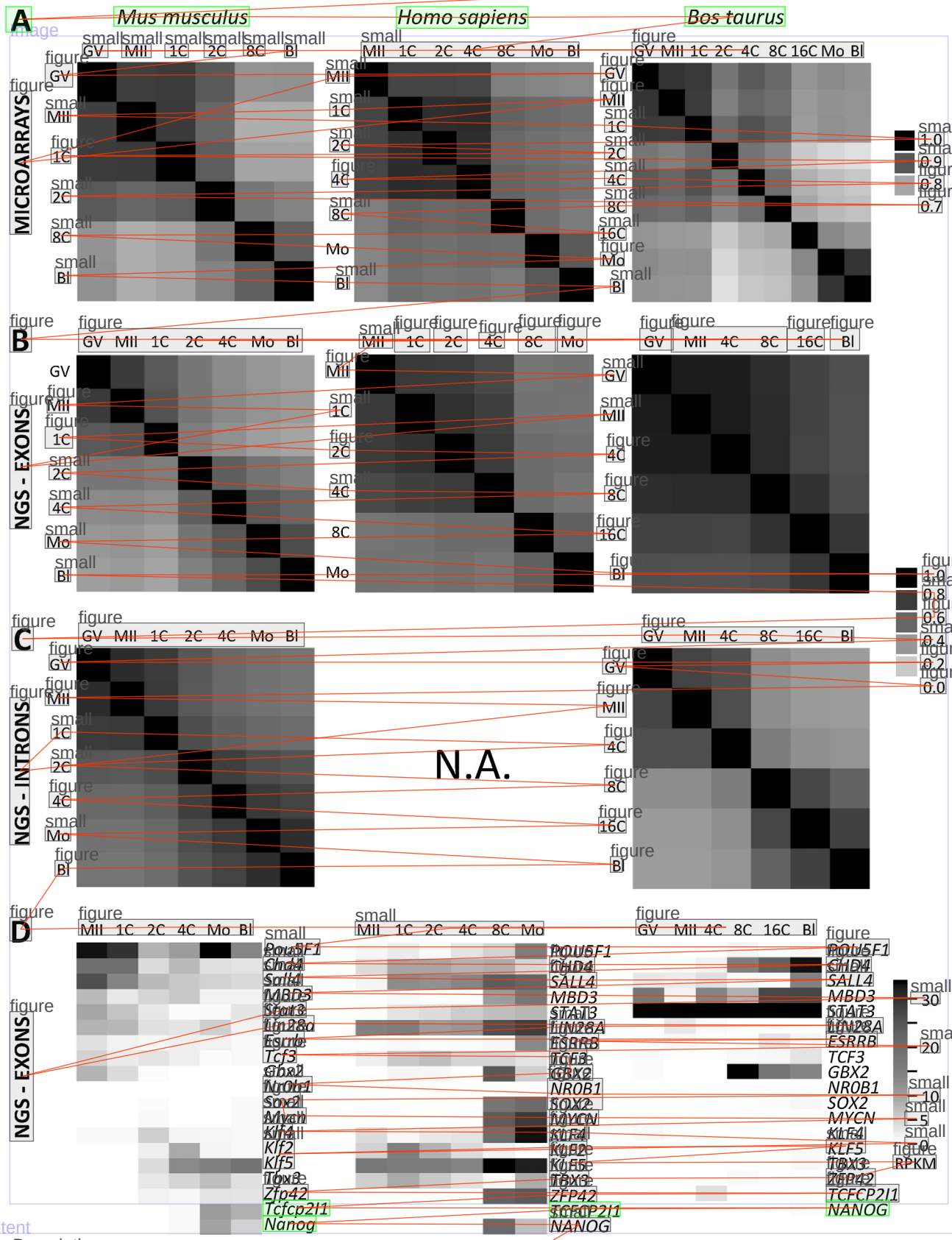

Fig. 2. ZGA transcriptome remodeling and the core pluripotency network during mouse, human and bovine early development. (A–C) Heatmaps depict correlation of pairwise comparisons of (A) microarray [85] and (B,C) NGS datasets from indicated species [14,15,65]. N.A. indicates that the NGS dataset for human polyA RNA was insufficient to analyze introns. (D) Expression of the core pluripotency network factors during OET in mice, bovine, and humans. Heatmaps depict reads per million per kilobase (RPKM) for indicated genes in published datasets [14,15,65]. MII, ovulated eggs; 1C, zygote; 2C-16C, 2-cell to 16-cell embryos; Mo, morula; Bl, blastocyst.

is unclear whether this transcription program can exist as a stable program as it has two transient components: transcription factors encoded by maternal RNAs and by genes silenced at the end of the 2-cell stage. Interestingly, analysis of ESCs revealed a minor subpopulation of cells with 2-cell-like expression pattern (e.g. expressing MuERV-L) suggesting that the zygotic totipotent program might be induced in cultured cells) [83].

embryonic pluripotent – this transcription factor network is equivalent to that of ESCs and gives cells their pluripotent properties (reviewed in [84]). A subset of these transcription factors, the famous "Yamanaka" factor combination of *Pou5f1*, *Sox2*, *Klf4*, and c-*Myc*, is sufficient to reprogram gene expression and induce pluripotency in differentiated somatic cells [16]. Importantly, the pluripotent program is inter-related with the zygotic transcription factor network because its formation is initiated during ZGA (Fig.).

The set of transcription factors and binding sites in the regulated genes that constitute mammalian ZGA is poorly defined, but details of these gene regulatory networks are emerging. A part of the mammalian ZGA gene regulatory network appears to be the pluripotency network [85]. This raises the question to what extent is ZGA related to induction of the core pluripotency network. The answer is that although the major ZGA and induction of the core pluripotency network have some overlap, the two events are distinct. The contribution of core pluripotency factors to mammalian major ZGA seems small judging by the frequency of known binding sites of the core pluripotency factors [86] in proximity of genes transcribed during major ZGA (Svoboda and Franke, unpublished observation). Furthermore, zygotes lacking both maternal and zygotic *Oct4a* expression can still activate the genome and form a *Nanog*-expressing inner cell mass [87]. This situation contrasts with zebrafish where a conserved core network component consisting of *Nanog*, *Pou5f1*, and *SoxB1* family members represent >75% of transcripts during the first wave of zygotic gene expression [88].

In mice, transcripts of most of pluripotency factors are present in the blastocyst, which is consistent with the origin of ESCs (Fig. D). About a half of the factors are expressed maternally while the other half appear in early embryos. Among *Pou5f1*, *Sox2*, and *Nanog*, whose homologs constitute the maternal foundation of ZGA in zebrafish [88], only *Pou5f1* is expressed maternally, whereas *Sox2* is transiently expressed at the 2-cell stage and then again in blastocysts. *Klf4* is one of the few pluripotency factors strongly expressed during major ZGA in mice. *Nanog* is first expressed in 2-cell embryos and its transcripts accumulate until the blastocyst stage. Taken together, the mouse model suggests that a fraction of the core pluripotency factors is provided maternally to initiate a reprogramming transcription factor cascade that forms the core pluripotency network controlling the pluripotent state of inner mass cells.

However, when performing a similar expression analysis in bovine or human embryos, striking differences in terms of temporal/stage expression of pluripotency factors emerge (Fig. D). This high variability implies that the core pluripotency network during early mammalian development could be established in multiple ways. Also, this evolving variability in maternal and zygotic appearance of pluripotency factors could contribute to reproductive barriers emerging during speciation. One could envision that maternally provided pluripotency transcription factors initiating the core pluripotency network formation (and genome activation in general) in a defined sequence would fail to activate the genome in another species. Such a post-zygotic reproductive barrier would be a more cos-effective solution than hybrid sterility. In any case, the mammalian core pluripotency circuitry appears linked to ancestral vertebrate ZGA, but in mammals it evolved into a pluripotency program in inner cell mass cells upon their separation from extra-embryonic lineages.

If the core pluripotency circuitry makes a minor contribution to mammalian zygotic transcription programs, can other contributory factors be defined? An important insight into the murine zygotic transcription programs comes from detailed analysis of ESCs. As mentioned above, a small fraction (~1%) of ESCs express an LTR retrotransposon mouse endogenous retrovirus type L (MuERV-L) [83]. MuERV retrotransposons [89,90] are transiently expressed during ZGA where they comprise a significant fraction of mRNAs [58,91]. This minor ESC population expressing MuERV-L sequences has unique characteristics in terms of gene expression and totipotency which is normally found in blastomeres of the 2-cell zygote [83]. This finding suggests that the pluripotent potential of ESCs does not only stochastically fluctuate "forward" towards differentiation, but also "back" towards a totipotent state [83] and that "totipotency" indeed might exist as an expression program driven by a defined set of transcription factors.

Whether MuERV-L is an active player in this fluctuation and whether it is a unique feature of the mouse model is an open question. MuERV-L engagement in transcription in 2-cell zygotes appears primarily a consequence of MuERV-L survival strategy. Retrotransposon expansion in the genome requires retrotransposition to occur during the germline cycle. Consequently, retrotransposons sequences adapt such that they would be recognized and transcriptionally activated during the germline cycle. Accordingly, MuERV-L LTRs evolved to recruit transcription factors initiating gene expression in zygotes. Consequently, as MuERV-L had been spreading through the mouse genome, it would be distributing zygotic genome activation platforms that could be recruited for novel functions during ZGA. In fact, many LTRs of the ERVL retrotransposon family to contributed to the separation of maternal and zygotic programs in mammals [92]. Studies of transcriptional control of MuERV-L thus reveal factors/mechanisms contributing to murine ZGA [93–97]. One of the remarkable MuERV-L regulators is a double homeobox gene *Dux4*, which has been recently implicated in ZGA [70–72]. *Dux4* becomes transiently expressed during minor ZGA[65] and, as an intron-less gene localized in a tandemly duplicated locus, is the primary candidate for a transcription factor involved in ZGA. *Dux4* also fits into the model that the earliest transcribed genes are short and newly evolved [98].

9. Conclusions

Mammalian OET is characterized by relatively long transition between the maternal and zygotic gene expression which involves only a small number of cleavages a zygote. This likely reflects the need to produce a totipotent early embryo, which undergoes separation of extraembryonic and embryonic lineages. There is a variable timing of the major ZGA; the early onset in mice seems to be a derived character while blastomeres of other mammals undergo several cleavages before the major ZGA. Advances in high throughput methods have been providing a comprehensive picture of gene expression and, lately, also chromatin dynamics during OET. However, there is a number of issues that still need to be addressed. Of a particular interest are determination of variable and constitutive parts of genome reprogramming and identification of the set of maternally provided transcription factors, which would be sufficient to drive OET. Also of interest are mechanisms assuring that transcription factors driving the maternal and zygotic transcription do not interfere as well as events that lead to the early genome activation during evolution of mice. Improved understanding of molecular mechanisms underlying OET will translate into more efficient manipulation of a cell-fate, which is of fundamental importance for biotechnology and medicine.

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