Cell Genomics

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Preview

Embryo and prejudice: From diverse first transcriptional impressions to a common developmental path

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https://doi.org/10.1016/j.xgen.2025.100919

Pre-implantation mammalian development culminates in the blastocyst, where embryonic and extra-embryonic tissue founders reside. However, species variations in the underlying mechanisms, starting from zygotic genome activation (ZGA), remain underexplored. In this issue of *Cell Genomics*, Zhang et al.[1] studied RNA Pol II in bovine embryos and discovered super RNA Pol II domains, a regulatory architecture promoting transcription in species with delayed ZGA.

The development of placental mammals, unlike that of many other species, requires ongoing interactions between the fetus and the mother. This is achieved through embryo implantation in the uterus and the generation of the placenta. By analogy to the hourglass model of development,[2] diverse mechanisms may narrowly converge to the generation of a common architectural blueprint, the blastocyst, characterized by an external layer, the trophectoderm (which will give rise to the placenta), and two internal cell populations, the primitive endoderm (which will form the yolk sac) and the epiblast (the founder of the embryo proper). The formation of the blastocyst requires early embryos of placental mammals to rapidly initiate cell differentiation, especially for the trophectoderm. As the establishment of early cell identities in the blastocyst requires distinct gene repertoires, and since the transcripts and proteins inherited from the oocyte sustain the embryo for only a few divisions, early developmental progression relies on the regulated expression of zygotic genes. This implies an early onset of transcription, driven by a process known as zygotic genome activation[3] (ZGA).

Among other species-specific differences, the exact timing of ZGA varies considerably.[3] For instance, ZGA takes place at the 2- and 4-cell stages in rodents and pigs, respectively, while it occurs later in humans (8-cell stage) and cows (16-cell stage). How these distinct timings of ZGA are regulated and how they converge in a similar activation of the genome and the formation of a blastocyst represent key questions that the study from Zhang et al. start to elucidate in this issue of *Cell Genomics*.[1] The authors analyze RNA polymerase II (RNA Pol II) distribution in early embryos of different species displaying early and late ZGA and propose that a peculiar enrichment of RNA Pol II over intergenic regions, which they call super RNA Pol II domains (SPDs), allows late-ZGA bovine embryos to increase the transcription levels of the first genes subject to ZGA, especially those encoding transcriptional activators, such that they quantitatively align with expression levels observed in early-ZGA species (Figure 1).

The authors start by comparing the genomic distribution of RNA Pol II in different organisms (human, bovine, mouse, and porcine) before or after ZGA. First, they show that RNA Pol II pre-configuration[4] is a common phenomenon, observed at promoters in the four species analyzed. Differences appear instead at distal regulatory regions. While RNA Pol II prevalently localizes at the edges of regions displaying partial DNA methylation (partially methylated domains [PMDs]) in mice, bovine and human pre-ZGA embryos show particularly high levels of RNA Pol II throughout the body of these intergenic regions, hence called SPDs, which are also marked by unusually high levels of histone acetylation, a modification characteristic of active regulatory regions. The formation of clusters of RNA Pol II and transcriptional activators, driven by liquid-liquid phase separation, is emerging as a mechanism that allows promoter-enhancer communication and drives gene expression later in development.[5] With this notion in mind, the authors generated chromatin interactions maps and showed that SPDs engage in strong interactions in bovine, but not in mouse or porcine embryos, especially with the genes that are activated first during ZGA. Notably, experiments using CRISPRi to disturb SPD formation showed defective activation of nearby genes. Thus, this study describes the existence of a new functional organization of RNA Pol II over relatively large regions of bovine and, possibly, human embryos that promotes 3D interactions associated with the quick start of transcription during ZGA (Figure 1).

Analyzing the expression of the bovine targets of SPDs in other species led the authors to an interesting observation: the orthologs of one-fifth of the bovine genes driven by SPD interactions are genes transcribed extremely rapidly after fertilization in early-ZGA species, before major ZGA events initiate. SPDs are therefore proposed as a means to boost, in 4- to 8-cell-stage bovine embryos, the expression of general ZGA regulators, such that

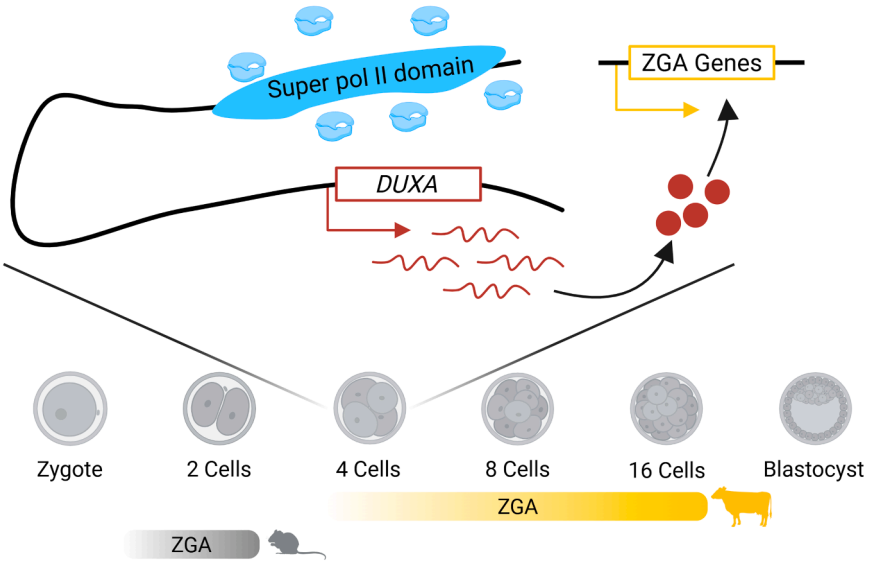

Figure 1. Super Pol II domains: Catching up for ZGA
Intergenic regions proximal to genes that are first transcribed during ZGA often display unique patterns of low DNA methylation and widespread deposition of H3K4me3 in oocytes and zygotes of species with fast ZGA, such as mice. Zhang et al. propose that in late-ZGA species, such as cows, RNA Pol II strongly accumulates in these regions, forming super Pol II domains that boost expression of the first genes transcribed by the embryos, notably that of transcription factors controlling ZGA itself. The quick expression rise of these genes may serve the purpose, in bovine and possibly human embryos, to align their levels with that observed shortly after fertilization in early-ZGA species. Created in BioRender: https://BioRender.com/1cd268z.

they can quantitatively catch up with early-ZGA species. In this regard, the authors' proposal that SPDs represent an evolutionary adaptation to late ZGA is interesting and provocative, especially because, so far, SPDs appear as unique features of early embryos, calling into play exquisitely specific mechanisms to restrict SPDs to this early developmental stage. Lending support to the existence of such temporal specificity, ZGA genes and the surrounding distal regulatory regions have been shown to localize at PMDs in early-ZGA species and to be marked by atypical, kilobase-long domains of H3K4 trimethylation, a histone modification normally found restricted to active promoters. These atypical patterns, which present differences between species, resolve at ZGA, converging to a common organization typical of mature cells.[3] Regardless of these considerations, ZGA appears to be controlled by a variety of unusual transcriptional and chromatin properties, which converge in a common post-ZGA mode of gene regulation. Understanding the causes of such diversity may involve considering distinct evolutionary histories regarding the invasion by and the domestication of retrotransposons, which play a key role in the emergence of placental mammals by contributing essential genes and regulatory elements involved in placental development and are prominent players of ZGA in mice[6] and, as suggested in this study, also in bovines.

While ZGA is differentially initiated across placental mammals, whether the convergence of gene regulatory mechanisms culminates with ZGA or later, when embryonic versus extra-embryonic lineage decisions set up the different cell identities constituting the blastocyst, remains unclear. For instance, the control of promoter-proximal RNA Pol II pause-release is fully established only at the 8-cell stage in mice,[7] coinciding with the onset of lineage segregation mechanisms. Whether this process, as well as the transcription factors that control gene expression during the period that links ZGA to the beginning of lineage specification in mice,[8–10] is conserved in late-ZGA species becomes a particularly important question. In any case, just as Jane Austen's characters in *Pride and Prejudice* (1813) move from diverse first impressions to enduring truths and meaningful connections, all placental mammals must establish a deep connection with the mother, despite the early diversity in their engagement with ZGA. Understanding the convergence into a progressively unified, "Austenian" journey toward the blastocyst will offer new insights into pre-implantation development.

ACKNOWLEDGMENTS

The authors acknowledge the Institut Pasteur (P.N.), the CNRS (P.N. and N.F.), and the Labex Revive (ANR-10-LABX-73, P.N.) for recurrent support and the ANR (Dev-NucleR ANR-22-CE13-0008, N.F.; CHRODYNE ANR-20-CE12-0028, P.N.) for funding.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT in order to check readability. After using this tool, the authors reviewed and edited the content as needed, and they take full responsibility for the content of the publication.

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