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Review

Reshaping transcription and translation dynamics during the awakening of the zygotic genome

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During the oocyte-to-embryo transition, the transcriptome and proteome are dramatically reshaped. This transition entails a shift from maternally inherited mRNAs to newly synthesized transcripts, produced during the zygotic genome activation (ZGA). Furthermore, a crucial transcription and translation selectivity is required for early embryonic development. Studies across various model organisms have revealed conserved *cis*- and *trans*-regulatory mechanisms dictating the regimes by which mRNA and proteins are produced during this critical phase. In this article, we highlight recent technological and conceptual advances that deepen our understanding of how the tuning of both transcription and translation evolves during ZGA.

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Introduction

In all animals, the first hours of development are controlled by maternal products stocked into the egg before fertilization. Initially, the zygotic genome remains transcriptionally silent while the zygote is reprogrammed. Following this initial phase, gene expression control is progressively handed over to the zygotic genome. The zygotic genome awakens while maternal inputs are gradually degraded. This major developmental transition, conserved among the animal kingdom, is referred to as the maternal to zygotic transition or MZT.

The MZT consists of three key stages: cell cycle control, transcriptional activation of zygotic genes (zygotic genome activation [ZGA]), and the degradation of maternal products. These events are tightly coordinated to orchestrate the precise deployment of gene expression programs and the initial patterning of the embryo that will later give rise to the future body plan. ZGA has been initially described as a two-wave phenomenon (minor and major waves), but we now know that zygotic transcription is gradual, with a scale, timing, and dynamics specific to each species [1]. For example, about 20% of all genes are transcribed during ZGA in mouse, while this fraction represents 35% in *Drosophila* embryos [1–3]. Parallel to this transcription awakening, maternal mRNAs undergo a gradual clearance, initially elicited by maternal products and followed by zygotically synthesized drivers [1]. The combination of maternal mRNA decay and zygotic transcription activation leads to extensive proteome remodeling, altering the concentration and localization of key transcription regulators such as chromatin remodelers or general transcription factors (GTFs) as well as mRNA-binding proteins that adjust mRNA stability and translatability. Consequently, ZGA provides a unique biological context to monitor changes in mRNA and protein synthesis dynamics.

In this review, we focus on *cis* and *trans* mechanisms affecting transcription and translation dynamics during ZGA. For an in-depth consideration of other regulatory mechanisms affecting gene expression during ZGA, such as cell cycle control and chromatin reorganization at various layers, we refer the reader to other reviews [4,5].

Dynamic control of transcription during zygotic genome activation

This section describes the *cis* and *trans* factors that affect transcription dynamics during ZGA. After discussing how the priming of the *cis* code globally prepares for transcription, we present how key TFs/GTFs and their decoding by promoters and enhancers contribute to the tuning of transcription regimes at various scales.

Priming the *cis*-regulatory landscape for transcriptional activation

To prepare for a timely ZGA, the chromatin landscape of *cis*-regulatory sequences (enhancers and promoters) is dynamically reshaped before ZGA. Priming occurs thanks to zygotic genome activator transcription factors. These transcription factors often have pioneering properties, with the capacity to access target motifs occluded by

nucleosomes and enhance chromatin accessibility. Following Zelda, the first zygotic genome activator identified in *Drosophila* [6], a number of zygotic genome activators have been identified in various model organisms. These include Nanog, Pou5f3, and Sox19b in zebrafish, which pioneer chromatin opening through histone acetylation at more than half of active enhancers [7].

During mouse MZT, OBOX regulators have been recently identified as major activators of ZGA [8,9], along with KLF17, which appear to control ZGA by fostering RNA Pol II recruitment [10]. KLF17 was identified as a maternal ZGA factor by screening the proteome of early mouse embryos after treatment with a translation inhibitor [10].

Developing such screening strategies promises future identification of other zygotic genome activators in various model organisms.

The gradual acquisition of accessibility at *cis*-regulatory sequences is coupled to an important epigenome reprogramming during MZT. The development of low-input genomic approaches (such as ultra-low-input CUT &RUN) now allows interrogation of the chromatin landscape at specific embryonic stages during MZT, shedding light on its dynamics. The 'active enhancer' mark H3K27ac, for example, was profiled during the mouse oocyte–embryo transition, revealing a rapid turnover with three distinct waves [11] (Figure 1). The evolution of acetylation patterns is orchestrated by two key protein families, CBP/p300 and HDACs, crucial for preimplantation development and ZGA progression [11]. However, it is important to note that chromatin regulators can also contribute to ZGA regulation independently from their enzymatic activity, as recently demonstrated for CBP in *Drosophila* embryos [12].

The composition, concentration, and localization of molecular drivers of transcription evolve during zygotic genome activation

As gene expression control shifts from maternal input to the zygote, key transcriptional regulators undergo changes in concentration, localization, and stability. Nuclear reorganization, as well as transcription, is very likely to constrain how these transcription factors move through the nucleus and interact within their targets. A myriad of transcription regulators, including Pol II, assemble into clusters of various sizes, concentrations, and compositions [13]. Thanks to new developments in labeling and imaging techniques, exploration of the nanoscale organization of these clusters is now possible. One example is the recent exploration of how Pol II and Nanog form a transcription hub and modulate chromatin organization during zebrafish ZGA [14]. Using expansion microscopy and super-resolution imaging, the authors visualized different classes of Nanog-nucleosome conformations, as well as a specific arrangement of Pol II at transcribed loci (Pol II strings). While carefully controlled in Pownall *et al.*, it is important to note that expansion microscopy can introduce potential artifacts. It is therefore important to challenge the conclusions drawn from expansion microscopy approaches with alternative methods.

Live imaging of endogenously tagged proteins can reveal the sequence of events preceding transcriptional activation. In *Drosophila* embryos, dynamic and unstable Zelda hubs form upon mitosis exit but before transcriptional reactivation [15,16]. A subset of these hubs gain dBRD4, forming heterogeneous clusters that can further recruit Pol II and activate transcription [17]. Interestingly, transcription appears to destabilize these clusters, strongly suggesting that the composition and properties of transcriptional hubs evolve during successive bursts of transcription [18]. This aspect of transcriptional control is not covered in depth here, but we refer to excellent reviews on this topic [19,20].

Key regulators of transcription beyond transcription factors are subject to the major reshuffling of the proteome during ZGA, including initiation and elongation factors. In this section, we will consider the evolving *trans*-control of transcription during ZGA.

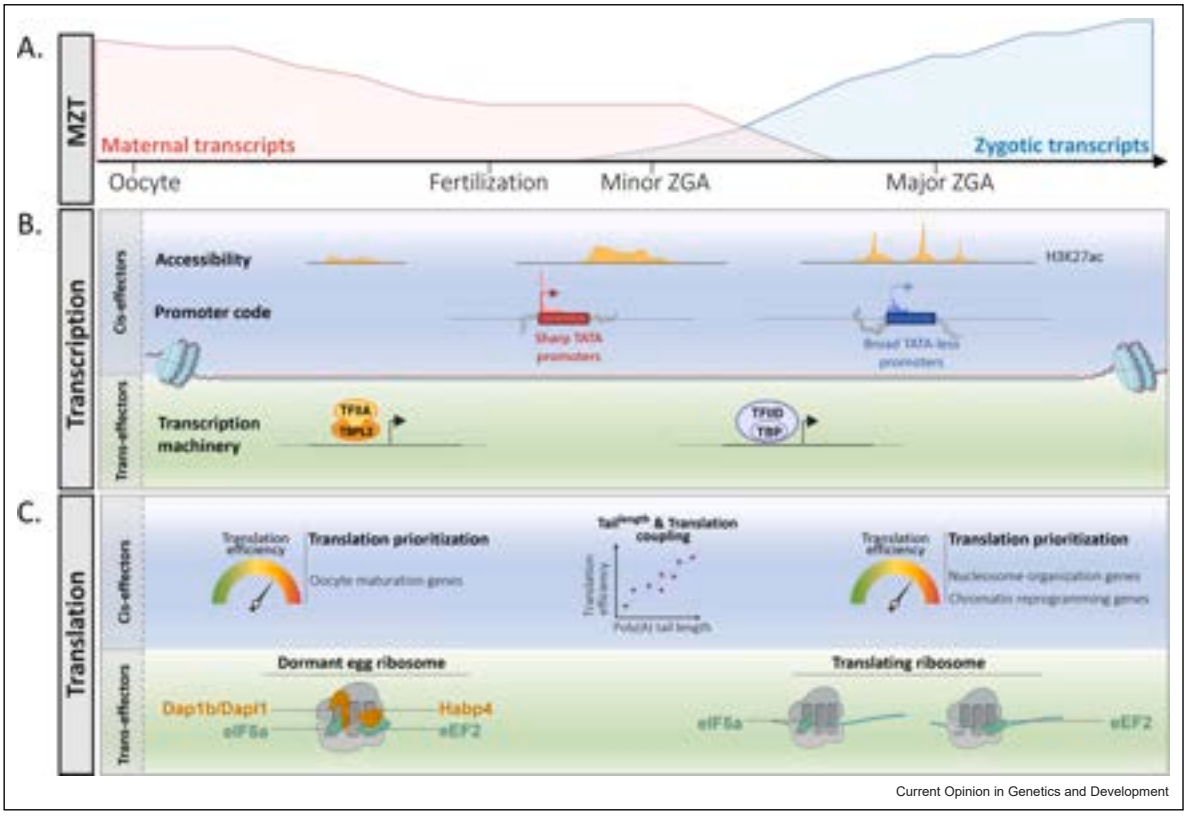
Multiple flavors of the pre-initiation complex

Following promoter opening, transcription initiates via the sequential recruitment of general transcription factors (GTFs) that assemble to form the pre-initiation complex (PIC). However, the composition of this complex varies from promoter to promoter, for a single promoter, and may evolve during the oocyte to zygote transition (Figure 1). We hypothesize that the promoter-level regulatory layer, including changes in PIC composition, is likely to heavily impact transcription kinetics (rates of transcription) at various stages of ZGA.

PIC plasticity is critical during the transition from oogenesis and zygotic control as shown by the division in murine initiation machineries between transcribing genes in follicular cells (TBPL2/TF2A) compared to the embryo (TBP/TFIID-TAFs) [21] (Figure 1). The evolving nature of GTF usage has also been demonstrated in the *Drosophila* embryo, where TFIIH is highly dynamic throughout the MZT and remains partially associated with chromatin during mitosis [22], potentially indicating a role for the PIC in mitotic bookmarking of active genes for rapid reactivation.

A major challenge in gene regulation at ZGA is the selection of the appropriate transcriptional start site (TSS) or alternative promoter at the right time. Changes in TFIID and PIC compositions may represent a mechanism to preferentially select a specific TSS at different ZGA timings. Although only described in a handful of animals so far, core promoter motifs seem to

Figure 1



Cis and *Trans* control of transcription and translation during MZT. **(A)** Top panel: Maternal transcripts (red) are progressively destabilized and degraded, while zygotic transcripts (blue) are synthesized during a minor and major wave of ZGA. **(B)** Middle panel: Selected examples of molecular mechanisms controlling transcription during oogenesis and early embryogenesis. Control in *cis*: H3K27ac is dynamically regulated during mouse ZGA, with CBP/p300 acetyltransferase opening chromatin at putative enhancers, while HDACs mediate the broad-to-canonical acetylation. Core promoter motifs seem to differ between minor and major ZGA promoters [11]. In zebrafish and fruit flies, early-activated zygotic promoters are generally enriched in TATA motifs, leading to constrained TSS choice and sharp transcription initiation, while promoters activated later tend to be TATA less and exhibit a broader transcription initiation profile [23,24]. Control in *trans*: The composition of the transcription pre-initiation complex changes during oocyte to zygote transition [21]. **(C)** Lower panel: Selected examples of mRNA translation regulations in oogenesis and early embryogenesis. Control in *cis*: The translational capacity of mRNAs changes during early development. mRNAs encoding for oocyte maturation factors are highly translated before fertilization, while mRNAs encoding for chromatin remodelers display a high translation efficiency during ZGA (translation prioritization) [53]. Poly (A) tail lengths correlate with translation efficiency in many species [50,55,56]. Control in *trans*: Translation capacity can be controlled in trans with the activation of ribosomes [68]. In zebrafish, the ribosomal factors Hapb4 and Dap1b maintain ribosomes in a 'dormant state'. They occupy functionally important sites on the ribosome by associating with the initiation/elongation factors eEF2 and eIF5a to repress translation. Upon egg activation, the dormant factors Hapb4 and Dap1b are released from the ribosome, which correlates with the important increase in translation observed after fertilization.

differ between early-activated promoters (enriched in TATA motifs) and late-activated promoters (enriched in initiator elements) [23,24] (Figure 1). In zebrafish embryos, the first locus to be transcribed is the *miR-430* locus, organized as a cluster of gene repeats with extensive TATA motifs at their promoters. Using long-read sequencing, a recent study assembled the entire chromosome hosting the *miR-430* locus and revealed the high promoter density (> 300 promoters) and pervasive TATA box architecture. This organization and promoter architecture are hypothesized to favor precocious transcription of the *miR-430* locus specifically and early ZGA promoters more generally [24].

Transcription elongation and zygotic genome activation

In addition to modulation of PIC components, regulation at the step of early elongation is also emerging as an important regulatory layer during ZGA. Deletion of maternal transcription regulators generally leads to precocious and severe defects in the germline, precluding further analysis in the early embryo. However, acute and/or reversible knockdown methods (e.g. dTAG or optogenetics) can now reveal the critical window at which a specific regulatory factor is required.

Two recent studies used such approaches to investigate the role of early elongation and paused polymerase during

mouse ZGA [25,26]. Acute depletion of Negative Elongation Factor B (NELFB), a key determinant of promoter polymerase pausing, demonstrated its critical role for minor ZGA wave in mouse embryos. Upon NELFB depletion, premature activation of late ZGA genes is observed at the expense of early ZGA genes [25]. This suggests that the regulation of early elongation plays a key role in timing transcription and progression of mouse ZGA.

Parallel to these findings, experiments involving the P-TEFb subunit CDK9, a kinase that releases paused Pol II, and SPT5, required for pausing and Pol II elongation, show that both are crucial for ZGA in mice [26]. Taken together, these observations suggest a role of early elongation during ZGA, but the importance of pause release regulation at specific steps of ZGA is still under debate.

Interestingly, work performed in zebrafish embryos suggests that the regulation of MZT transcription through pause release may be partially mediated by the sequestration of CDK9 in two large nuclear bodies (seeded by the *mir430* locus). This prevents the transcriptional activation of genes excluded from these bodies. In contrast, loss of *mir430* transcription bodies activates zygotic genes prematurely [27]. It is likely that other major transcription regulators operate similarly through their sequestration in specific nuclear bodies to precisely time their action. It will be important in the future to assess the nuclear distribution of *trans*-acting factors in living embryos to examine their dynamic behavior during the major nuclear reorganization occurring at ZGA.

The multiscale control of transcription bursts during zygotic genome activation

Alongside the reshaping of the *cis*-regulatory code, key *trans*-acting regulators of transcription are modulated during ZGA. In this section, we will discuss how their action is integrated by developmental promoters to affect transcription kinetics.

Tools for investigating the kinetic parameters of transcription

The deployment of labeling tools to monitor mRNA synthesis at the single-cell level in living embryos has transformed our understanding of transcription dynamics during ZGA (Figure 2). These tools provide access to transcription kinetics of promoters, revealing that in most biological contexts studied so far, transcription is a discontinuous process. It is characterized by alternating periods of activity and inactivity with variable timescales. These bursts of transcription are generally modeled as the stochastic switching of the promoter between a competent active state (ON, from which Pol II is released) and one or multiple inactive states (OFF) [20,28].

A major recent discovery regarding bursting during ZGA, albeit primarily observed in the fly embryo, is that these bursts are multiscale [29]. In other terms, the duration of interburst periods can be of various timescales, ranging from seconds to minutes or hours [20,30,31]. Transcription bursts are generally decomposed in terms of burst frequency, amplitude, and duration. However, these qualitative metrics do not provide information on the quantitative parameters of promoter state switching rates. The development of new inference methods [28,32], such as BurstDECONV [28], allows the reconstitution of the sequence of polymerase initiation events responsible for single allele transcription data. When combined with mathematical models, these approaches reveal the number of rate-limiting steps of transcription and estimate promoter switching rates (Figure 3). While promising, such methods do not reveal the biochemical reactions responsible for the rate-limiting steps. Perturbation experiments are required to decode these rate-limiting steps.

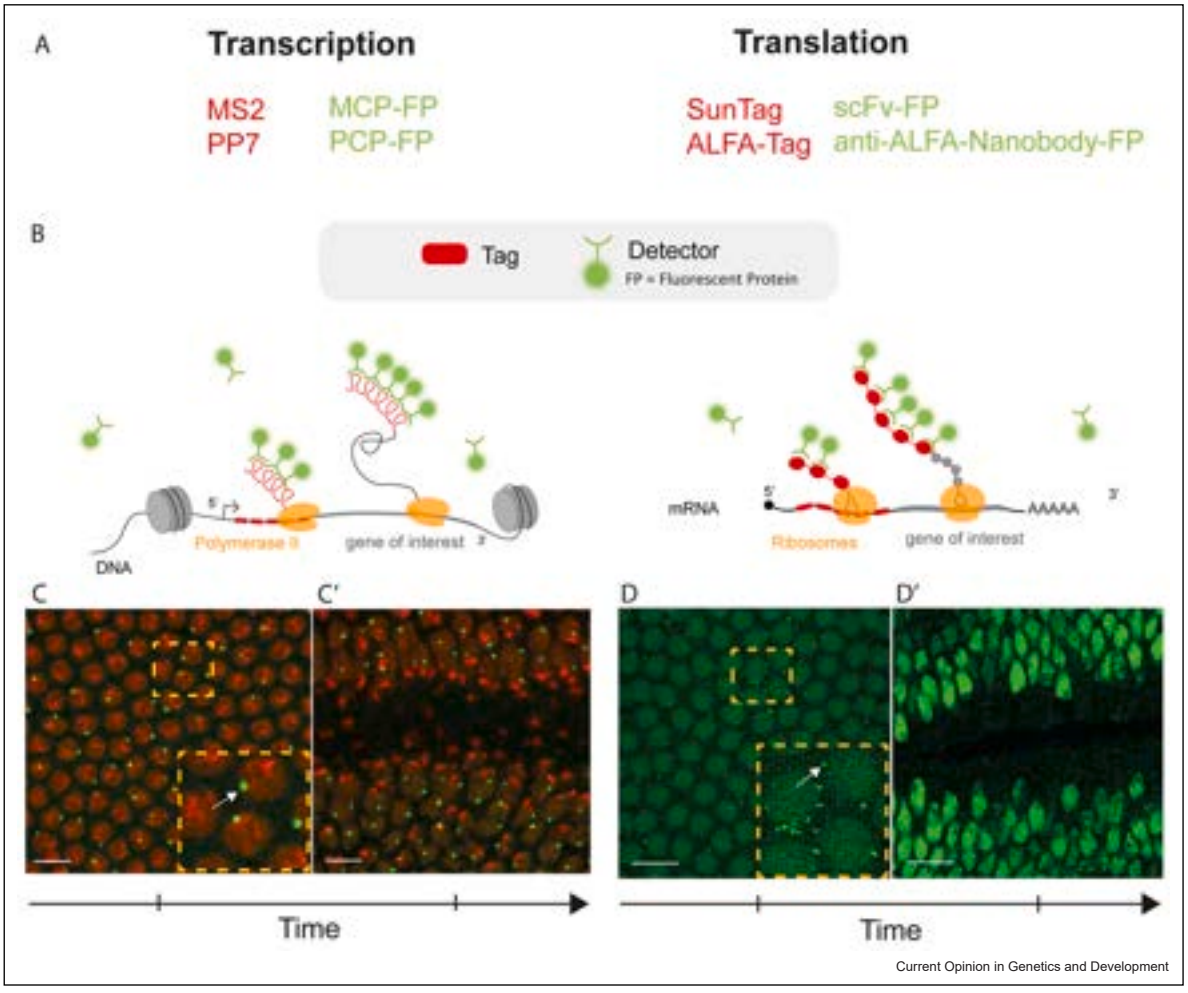
Promoter state switching rates during zygotic genome activation

As summarized in the previous sections, major regulators of transcription see their composition, concentration, and localization evolving during ZGA. In addition, the *cis*-regulatory code also exhibits major changes, such as the choice of alternative promoter TSS. How these *cis* and *trans* changes affect the kinetics of transcription and particularly the rates of promoter switching between distinct states remains largely unexplored. In the fly embryo, recent studies specifically questioned the impact of promoters on transcription kinetics [30,33,34].

Through mutation analysis in synthetic transgenes, TATA promoters were shown to generate long active states with short OFF periods, whereas promoters containing an Initiator element were associated with two inactive promoter states of distinct timescales [30,33]. This variability in bursting behavior may be directly related to the composition and stability of the PIC and/or to early elongation factors. To better interpret these evolving bursting kinetics, it will be important to quantify the residence time of PIC members on chromatin during ZGA, as recently assessed in *S. cerevisiae* and mouse Embryonic Stem cells [35,36].

Besides promoters, enhancers contribute to integrating input signals to modulate transcription rates during ZGA. Enhancer priming, particularly by pioneer factors, determines the precise timing at which a gene is activated during ZGA as well as how gene activation is synchronized between neighboring cells within a tissue [15,37–39]. While several studies show that enhancers influence the frequency of transcription bursting and to a lesser extent burst amplitude, burst durations appear as being largely independent of enhancers [40,41]. However, how the binding of specific input Transcription Factors (TFs) is decoded by enhancers to elicit specific promoter dynamics remains challenging to address. Indeed, the presence of multiple co-acting enhancers, their

Figure 2



Imaging transcription and translation in living embryos. **(A)** Top panel: overview of signal amplification labeling systems currently employed to detect transcription [76,77] or translation in living embryos [74,75,78]. These systems comprise a tag, generally multimerized to enhance the signal (shown in red) and a corresponding detector, an RNA-binding protein for mRNA labeling and a small tag binder, such as single-chain fragments (scFv) or nanobodies for protein labeling (shown in green). **(B)** Schematics of transcription (left) and translation (right) processes enabled by RNA Pol II or ribosomes (shown in orange) in the context of these labeling systems. Upon transcription, the free detector (e.g. MS2 Coat Protein, MCP) recognizes the repeated tag (e.g. MS2 array) in the nascent mRNA. Similarly, upon translation, the tag present in the nascent peptide (e.g. an array of Gcn4 epitopes for the SunTag system) is recognized by the corresponding genetically encoded detector (scFv in the case of SunTag). In both cases, the detectors are coupled to a fluorescent protein and fluorescence intensity scales with mRNA or protein synthesis rates. Lower panel: Live imaging snapshots from early *Drosophila* embryos showing transcription sites and translation spots (white arrows, left and right panels respectively) **(**C, D**)** before and **(C', D')** during gastrulation. Scale 10 µm.

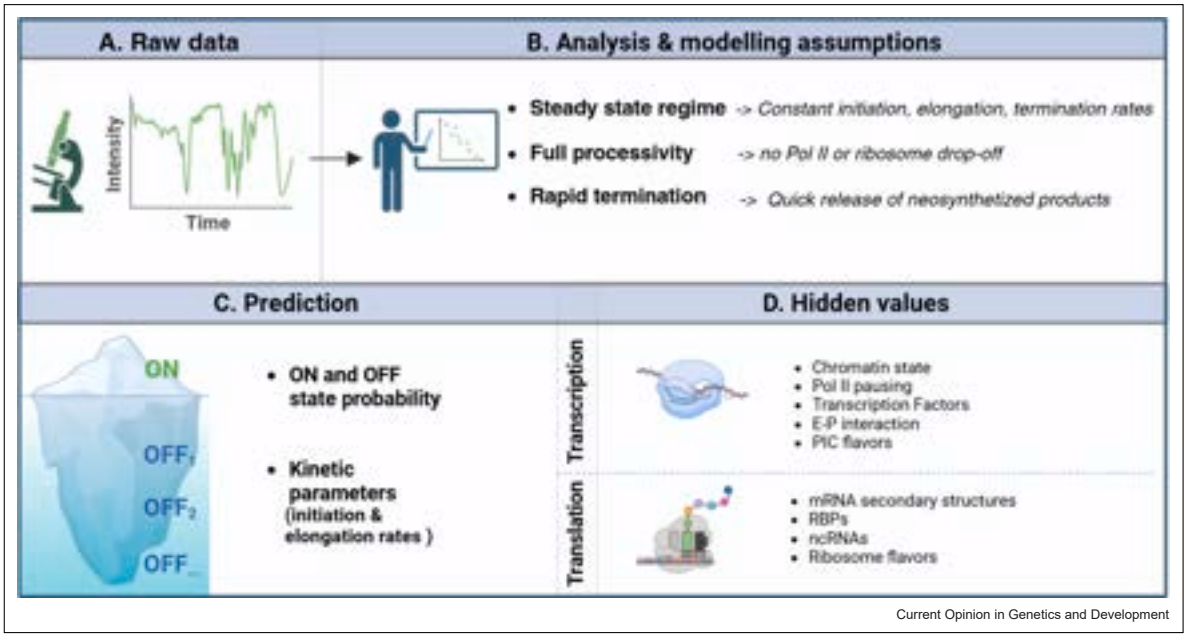
combinatorial regulation by multiple TFs, as well as their potential cooperativity significantly complexifies our capacity to decode enhancer action. To reduce this complexity, minimal synthetic transgenes are often employed, where single TF-binding site affinities can be modulated [15,42,43]. Moreover, how enhancer navigation within the nucleus (mobility, promoter search, interactions with transcription hubs) affects bursting is still poorly described during ZGA. The development of new labeling technologies [44,45] and their spatiotemporal manipulation with optogenetics [46,47] promises a bright future for these fundamental questions.

Dynamic control of translation during zygotic genome activation

Paired transcriptome and proteome time course data sets during *Drosophila* and vertebrate embryogenesis show only a moderate correlation between mRNA abundance and protein levels [48,49]. Mathematical models suggest that discordances between the two may largely result from protein translation and degradation dynamics.

In this section, we will discuss how the fine-tuning of translation is emerging as an important regulatory layer during ZGA.

Figure 3



Deciphering transcription and translation kinetics from live imaging data. **(A)** Raw data here represent transcription or translation site intensity over time, monitored using fluorescent microscopy in a living embryo. **(B)** Using different modeling strategies, fluctuations in signal intensities are analyzed based on specific assumptions regarding transcription and translation events. **(C)** Mathematical modeling allows to estimate key parameters and rate-limiting steps characterizing the transcription and translation processes [28,70–75]. **(D)** Multiple hidden values can control transcription and translation. Their impact on transcription and translation kinetics can be tested experimentally and quantified using live imaging data.

Prioritizing the translation of specific maternal mRNAs

Several studies have shown major changes in the translational capacity of mRNAs in mice, zebrafish, *Xenopus*, and *Drosophila* at the MZT [50–53]. A specific set of maternal mRNAs encoding essential proteins for the early steps of zygotic life exhibit a time-dependent translation control (Figure 1). For example, maternal *zelda* mRNAs show a strong translational boost soon after fertilization in *Drosophila* embryos, presumably to load the embryo with high amounts of this master ZGA factor [6,54]. Translation is an energetically demanding process, and it can be imagined that mechanisms exist to ensure that the translation of specific mRNAs would be prioritized to prepare for ZGA.

Using an improved low-input Ribo-seq approach, a recent study unmasked which mRNAs are subject to translational control upon fertilization in mice [53]. Maternal *Smarcd2* appears as the most translated chromatin factor–encoding mRNA, showing a translation increase already detectable at the one-cell stage of zygotic development. This study further demonstrates the functional relevance of *Smarcd2* active translation in preimplantation development. It therefore appears that the load of maternal proteins is insufficient to sustain the demands of ZGA and that *de novo* production of key proteins (including ZGA and chromatin remodeling factors) in a timely controlled manner is essential (Figure 1). It also offers the possibility to identify new ZGA factors through the analysis of translationally upregulated genes in the zygote.

Controlling translation in *cis*: a role for poly(A) tails and UnTranstaled Regions

In this section, we will focus on *cis*-based mechanisms regulating translational capacity, such as UnTranstaled Region (UTR) sequences and poly(A) tail lengths, in the specific context of the oocyte-to-embryo transition (Figure 1).

In many species, mRNA with long poly(A) tails tend to be translated more efficiently than shorter tail mRNAs [50,55,56]. This correlation suggests that polyadenylation is a well-conserved and tunable switch controlling the translatome. A recent study comparing large mRNA 3'UTR and translation libraries from developing embryos and oocytes identified specific mRNA motifs controlling both tail length and translation efficiency [57] (Figure 1). Poly(A) and translation efficiency coupling was absent in nonembryonic samples (i.e. at later stages and in cell culture), suggesting the coordinated control of tail length and translation is specific to the oocyte-to-embryo transition. Interestingly, during egg activation in *Drosophila*, large-scale switches in translation efficiency seem to be controlled by the protein kinase complex PAN GU (PNG) that becomes active during the oocyte-

to-embryo transition [58]. PNG substrates remain to be discovered, but this complex seems to regulate translation primarily through poly(A)-tail length and possibly via poly(A)-binding protein (PABP) recruitment. PABPs are believed to be involved in translation initiation and termination regulation. Interestingly, the Bartel group suggested that the concentration of PABPs could be limiting during MZT [55]. In a context where tail length and translation efficiency are coupled, it is possible that mRNAs compete for PABP, favoring the translation of transcripts with longer poly(A) tails. We could generalize this view and wonder whether large amounts of newly transcribed zygotic mRNAs could compete for translation initiation factors and ribosomal subunit recruitment. In such a scenario, zygotic mRNAs properly packed with appropriate RNA-binding proteins (RBPs) and correctly polyadenylated would have an advantage in recruiting ribosomal subunits, favoring their translation.

Multiple studies also identified 5'UTRs as major *cis*-regulatory elements adjusting translation. Indeed, they often include internal ribosome entry sites, G-quadruplex structures, and microRNA-binding sites, all of which influence translation initiation [59]. Two recent studies used massive parallel reporter assays to examine the contributions of 5'UTRs sequences to translational control in zebrafish embryos [60,61]. The authors identified conserved motifs within the 5′UTRs, with various effects on ribosome recruitment and translational control. They further characterized the motif grammar within 5'UTR isoforms driving different translation initiation capability. Such approaches offer an unprecedented view of the genetic code modulating translation initiation dynamics during developmental transitions.

Trans-regulation and translational switches

Translation fine-tuning by RNA-binding proteins

Along the entire lifecycle of an mRNA, RBPs can modulate its localization, translatability, and stability. Yet, the precise combination of RBPs bound to key developmental mRNAs and how they influence their fates remains largely unknown. One of the best-characterized examples of such an RBP-based spatial control of translation is provided by *Drosophila oskar* maternal mRNA [62,63]. *Oskar* transcripts are actively transported to the posterior pole of the embryo in a microtubule-dependent manner through the association of their 3'UTRs with specific RBPs [64]. *Oskar* translational control is tightly coupled to this localization mechanism. Before reaching the posterior pole, *oskar* mRNAs are bound by the RBPs Bruno and Cup to block translation initiation [65,66]. While the precise mechanisms leading to the activation of translation remain unclear, several proteins binding the 3'UTR and the poly(A) tail are believed to displace translation repressors. However, a recent spatial transcriptomic and proteomic study performed in the fly follicular epithelium showed that the transport machinery is essential to keep transcripts translationally silent until they reach their final localization [67]. These results emphasize the idea that coupling of the translation status with the subcellular distribution can be mediated by regulatory RBPs, acting both as localization and translation regulators.

Ribosome awakening can be concomitant to genome awakening

In addition to a *trans* control of translation mediated by RBPs, a switch in ribosome states has recently been proposed [68]. The Pauli group discovered that ribosomes can be present in a 'dormant' state in zebrafish and *Xenopus* eggs. Using polysome fractionation and mass spectrometry, they showed that most ribosomes are not engaged in translation before egg activation (Figure 1). Furthermore, cryo-EM experiments revealed that ribosomes associate with Habp4–eEF2 and Dap1b/Dap–eIF5a modules, occluding the mRNA entry channel to keep translation repressed. The authors propose a model in which, upon fertilization, dormant factors are released from the ribosome, while already-bound initiation factors eEF2 and eIF5a allow the resumption of translation [68]. The ribosome state switch constitutes an elegant mechanism to temporally fulfill the high demand of translation during egg activation and subsequent MZT. Such a ribosome-dormant state, in which the translation initiation factors are present but ineffective, is reminiscent of transcription priming whereby enhancers are prepared prior to their activation.

Compartment-specific translation efficiencies during development

Most of our understanding of translatome reshaping during MZT comes from ensemble methods. While these approaches offer a genome-wide view of translation, they lack the resolution to quantify translation at the single-molecule level. This limitation has now been overcome with imaging-based techniques such as SunTag/scFv labeling, which enable the direct visualization of translation with single-molecule precision. By monitoring nascent translation events in live cells, these approaches have uncovered translation bursts similar to those previously observed during transcription [69–73] (Figure 2). Combined with analytical models, these approaches can be used to estimate key translation kinetic parameters such as initiation rates and elongation speed (Figure 3). This labeling method has recently been deployed in the early *Drosophila* embryo and revealed when, where, and at which rates a specific mRNA is translated [74,75]. Interestingly, the zygotic *twist* mRNA, encoding a key transcription factor, shows a differential translation efficiency depending on its subcellular localization. *Twi* transcripts located in the basal juxtanuclear compartment display a higher ribosome density

compared to identical mRNAs located in the apical compartment [74]. This observation highlights the existence of a spatial translational heterogeneity *in vivo*.

The molecular mechanisms governing such heterogeneity, as well as its functional relevance in development, remain to be investigated. However, this observation suggests compartment-specific protein synthesis rates and could represent an efficient strategy for establishing protein gradients and patterning in embryos.

Conclusions and outlook

The progressive awakening of the zygotic genome represents a unique physiological context to investigate how the kinetics of transcription and translation are regulated in space and time. The development of live imaging approaches to monitor these two pillars of the central dogma at single-molecule resolution in a developing embryo opens unlimited opportunities. The combination of state-of-the-art technologies coupled with deep knowledge of the regulatory genome gained from decades of functional genomics and genetics will allow a more causal and quantitative understanding of gene expression control during ZGA.

Discoveries made in the context of ZGA will set the stage for our understanding of transcription and translation control when an organism faces abrupt drastic changes, such as during regeneration or dedifferentiation.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

We declare no conflict of interest.

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- • of special interest
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This paper demonstrates that minor wave zygotic genes, including the *mir430* cluster, exhibit a common promoter architecture (present a TATA motif), distinct from that of zygotic genes activated later during major zebrafish ZGA. This work also reveals that the *mir430* locus contains the highest density gene cluster in the zebrafish genome, which allows the formation of transcription bodies.

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