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General Transcription Factors and Embryonic Genome Activation

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ABSTRACT

Embryonic genome activation (EGA) is a highly complex phenomenon that is controlled at various levels. New studies have ascertained some molecular mechanisms that control EGA in several species; it is apparent that these same mechanisms regulate EGA in all species. Protein phosphorylation, DNA methylation and histone modification regulate transcriptional activities, and mechanisms such as ubiquitination, SUMOylation and microRNAs post-transcriptionally regulate development. Each of these regulations is highly dynamic in the early embryo. A better understanding of these regulatory strategies can provide the possibility to improve the reproductive properties in mammals such as pigs, to develop methods of generating high-quality embryos *in vitro*, and to find markers for selecting developmentally competent embryos.

(Key words : Embryonic gemone activation, Molecular mechanism, Transcriptional activity, Development)

INTRODUCTION

Embryo development, giving rise to a viable offspring, is dependent, at early stages, upon factors that have been stored in oocytes during oogenesis. These factors provide requirements for the oocyte maturation with the adequate stores of information to support complete development. A developmentally competent oocyte is the result of proper growth and nuclear and cytoplasmic maturation of the oocyte. Gene expression provides the information necessary for early development which is stored in the form of RNA or protein.

A transcriptionally active oocyte undergoes a transition to a silenced state in a dynamic manner. After fertilization, transcription activity is reactivated in the early animal embryo. This requires that the basal transcription machinery and the chromatin architecture be reorganized at different levels. Thus, transcription can be modulated in the embryo; a mechanism coordinated with the specific developmental characteristics of each animal and generally established by maternal factors (Zurita *et al*., 2008).

In females, primordial germ cells differentiate into oocytes. Oocytes in mammals are arrested at the prophase of the first meiotic division after birth. At this point, genetic material is dispersed throughout the nucleoplasm (germinal vesicles in oocytes), and this configuration is maintained until the first surge of gonadotropins at the beginning of puberty (Zoccotti *et al*., 2011) Oocytes undergo a change in chromatin shape via increase in size. For instance, two oocyte types are recognizable within antral follicles in mice, based on chromatin configuration. In one type, the huge nucleolus is not surrounded by chromatin (NSN type), while in the other, the nucleolus is encompassed by a dense rim of chromatin (SN type) (Bouniol-Baly *et al*., 1999). A number of studies have suggested that the SN configuration appears after NSN with the progression of oocyte growth (Debey *et al*., 1993; Zoccotti *et al*., 1995; Bouniol-Baly *et al*., 1999). These oocyte types have additionally been observed in other mammalian species, including pigs (Crozet *et al*., 1981).

The above chromatin configuration patterns are accompanied by dramatic changes in the global transcription level in oocytes. Earlier research has shown that in mouse oocytes from large antral follicles, transcriptional activity is completely quiescent (Moore *et al*., 1974), while other studies have reported the incorporation of (^{3}H) uridine in mouse germinal vesicle oocytes (Bloom and Mukherjee, 1972; Rodman and Bachvarova, 1976; Wassarman and Letourneau, 1976; Kopecny *et al*., 1995).

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Furthermore, investigation of the transcriptional activity of preovulatory oocytes in other mammalian species, including human (Miyara *et al*., 2003), cattle (Fair *et al*., 1995), and pigs (Mutlik and Fulka, 1986; Tan *et al*., 2009) has revealed a dramatic decrease in RNA polymerase II (Pol II)-dependent RNA synthesis in growing oocytes.

In mice, only a faint transcriptional activity in the male pronucleus, producing no functional mRNAs, can be detected, and there is little or no transcription between germinal vesicle breakdown (GVBD) and the 4-cell stage in the pig. Thus, it is obvious that the stored information in the oocyte is sufficient to manage the first cell cycles and establish the proper chromatin configuration. Pol II and its transcription factors are maternally inherited to the newly formed zygotes and come to function at the time of EGA. Nuclear translocation and phosphorylation of Pol II carboxyl-terminal domain (CTD) delineate the two phases of embryonic gene activation in mammalian embryos.

GENERAL TRANSCRIPTION FACTORS

Transcription of cellular genomes in all domains of life is carried out by essentially orthologous enzymes, multi-subunit DNA-dependent RNA polymerases (RNAPs). Nuclear RNAPs in eukaryotes are represented by a minimal set of three classes: Pol I transcribing ribosomal RNA genes; Pol II carrying out the synthesis of messenger RNA and a subset of small non-coding RNAs; and Pol III synthesizing transfer RNAs; 5S RNA, and the bulk of small non-coding RNAs (Werner *et al*., 2009, Razin *et al*., 2011; Kuhn *et al*., 2007). All three polymerases are composed of several subunits and have high structural similarities in the enzymatic core. However, only Rpb1, the largest subunit of Pol II evolved a unique, highly repetitive carboxy-terminal domain, termed CTD (Chapman *et al*., 2008; Liu *et al*., 2008), which plays a central role in the complex regulation of genes.

RNA synthesis is carried out by involving many transcription factors. In eukaryotes, Pol II is responsible for transcription of mRNA and most small nuclear RNAs. Transcription of class II genes requires the coordinated assembly of Pol II and six general transcription factors; these are TFIIA, TFIIB, TFIID, TFIIE, TFIIF, and TFIIH (Sikorski and Buratowski, 2009). Mostly using *in vitro* assays, the function of these factors has been experimentally determined (Han, 2004). TFIIA for example, stabilizes TFIID to bind to target DNA (Solow *et al*., 2001). The function of TFIIB is generally attributed to positioning of transcription initiation and stabilization of TATA box-binding protein (TBP) -TATA complex (Orphanides *et al*., 1996; Ranish *et al*., 1999). TBP in addition to more than fourteen other TBP-associated factors (TAFs), forms TFIID and recognizes and binds to promoter elements; in fact, TFIIA and TFIIB incorporations to transcription initiation are mediated by binding of TAFs to DNA closed to transcription start sites (Thomas and Chiang, 2006). Some tissue specific variants of TAFs also have been found in eukaryote. Some animals also have TBP-related factors that show specific and in some cases, equivalent functions to TBP (Thomas and Chiang, 2006; Buratowski *et al*., 1989; Hiller *et al*., 2001). In addition to TFIID, some TAFs also bind to other factors. TBP also can involve in transcription activities such as protein phosphorylation, ubiquitin activation and histone acetylation, which are necessary at some points in different promoters for their transcriptional activities (Thomas and Chiang, 2006; Buratowski *et al*., 1989; Hahn, 2004).

TFIIE also has been shown that binds selectively to inactive form of Pol II (unphosphorylated CTD), interacts with TFIIF and recruits TFIIH, facilitating the formation of an initiation complex followed by promoter clearance (Maxon *et al*., 1994; Goodrich and Tijian 1994). TFIIF also has been shown to recruit TFIIE and TFIIH and involves in the formation of initiation complex. This factor in concert with TFIIB is involved in recognition of transcription initiation site and promotion of elongation phase of transcription (Ghazy *et al*., 2004; Shilatifard *et al*., 2003). Another essential transcription factor is the multifunctional TFIIH complex. It has been shown that TFIIH components are involved in DNA repair process as well as in control of the cell cycle (Zurita and Merino, 2003). Two components of TFIIH with helicase activity, XPB and XPD, facilitate the formation of transcription initiation complex and another TFIIH subunit, CDK7, promotes the phosphorylation of Pol II CTD allowing Pol II to escape from the promoter (Thomas and Chiang, 2006).

RNA POLYMERASE II CTD

Transcriptional initiation commences with formation of the first phosphodiester bond and phosphorylation of serine 5 (Ser5) (by TFIIH) in the C-terminal domain (CTD) of the largest subunit of Pol II. CTD is composed of multiple tandem heptapeptides with the evolutionary conserved consensus motif Tyr1-Ser2-Pro3-Thr4-Ser5-Pro6-Ser7. The CTD differs in length dependent on the complexity of the organism (Liu *et al*., 2010). While budding yeast (*Saccharomyces cerevisiae*) has 26 repeats, which nearly all obey the consensus sequence, mamma-

lian CTD comprises 52. The increased number of repeats goes along with deviations from the consensus sequence, mainly in the distal part of the CTD. Non-consensus repeats diverge predominantly at position 7 by replacement of serine to lysine or other amino acids and might execute particular tasks. Genetic analysis revealed that insertion of additional amino acids between single heptads is lethal in yeast, while insertion after tandem repeats is tolerated. This suggests that the minimal functional unit of CTD lies within a di-heptad (Liu *et al*., 2010; Stiller and Cooke, 2004). Although the CTD is dispensable for the catalytic activity of Pol II (Serizawa *et al*., 1993), it is essential for life. Deletion of CTD repeats or extensive truncation of CTD results in inviability (Meininghaus *et al*., 2000). During transcription, the CTD serves as a docking platform for a broad diversity of factors. The capability to interact with different molecules at different stages of the transcription cycle is achieved by the dynamic structural plasticity of CTD together with the variety of binding surfaces generated by extensive posttranslational modification of heptapeptide repeats (Phatnani and Greenleaf, 2006). With tyrosine, threonine and three serines, five out of seven residues of a repeat can be modified by phosphorylation, while the two prolines can undergo isomerization between cis- and trans-conformation. Thus, all amino acid residues of a heptapeptide repeat could potentially be modified. Additionally, serine and threonine residues can also be glycosylated (Kelly *et al*., 1993) and arginine and lysine residues of the non-consensus repeats can be target of methylation.

EMBRYONIC GENOME ACTIVATION

The maternal-zygotic transition is a critical event in early embryogenesis. This transition transforms the highly differentiated oocyte into a totipotent blastomere, and is complete at a species-specific time for instance, by the two-cell stage in mice. During this transition, maternal mRNAs are degraded and the embryonic genome is activated (Schultz, 2002). Genome activation results in the replacement of transcripts common to both the oocyte and the embryo and the generation of new transcripts necessary for further development. Development of mouse embryos unable to accomplish genome activation is terminated at the two-cell stage.

The study of different model organisms has revealed that maternal mRNAs and proteins are deposited into the matured oocyte cytoplasm. For example, about 50% of the mRNAs encoded in the *Drosophila* genome are present in the early embryo by maternal contribution (Tadros *et al*., 2007). The total genome encoded transcripts contain about 40% of mRNAs that maternally deposited into the zygote in mice (Wang *et al*., 2004). In *C. elegans* early development, maternal factors are segregated and then involve in EGA. In this case, the first surge of transcription is seen at 4-cell stage. Interestingly, inactivation of transcription by RNA interference or by α-amanitin, a toxin specifically inhibiting Pol II in low concentrations, has no effect on embryo transcription until post-gastrulation. This indicates that maternally stored information is enough to drive cell divisions until 100-cell stage in *C. elegans.*

Xenopus has been a classical vertebrate model for the study of transcription onset in the early embryo. As a pioneering study in the field, Lanclos and Hamilton (1975) showed that high transcriptional activity occurred during *Xenopus* oogenesis, but transcription was inactivated at oocyte maturation. Similar to post-fertilization *Drosophila* embryos, the *Xenopus* embryo undergoes 11 rapid mitotic cycles that transcriptionally silent (Maller *et al*., 2001), with maternally contributed factors mediating embryonic development. Although a small amount of transcriptional activity can be detected after the sixth mitotic division in *Xenopus* embryos (Maller *et al*., 2001), global EGA begins at the mid-blastula transition (MBT), when the embryo is at the 4,000-cell stage.

In mammals, EGA occurs at different developmental stages depending on the species. In mouse, high transcriptional activity occurs during early oogenesis, then after GVBD, the oocytes arrest at metaphase II and no transcription is detected (Bacharova, 1985). This process takes about 14 h; transcription can then be detected only about 10 h later, after fertilization and only when the pro-nuclei are already formed. During this time, several cytoplasmic processes take place, including the translation and systematic degradation of maternally deposited mRNAs (Aoki *et al*., 1997). From the one-cell stage to the two-cell stage, a degradation of about 90% of the stored RNA in the oocyte takes place (Schultz, 2002). Thus, some of the basal transcription factors or their corresponding mRNAs are maternally contributed and used to activate embryo transcription. For still unknown reasons, most of the transcription that occurs at the one-cell stage happens in the male pro-nuclei (Schultz, 2002). In the mouse, two transcriptional stages have been identified: a minor transcriptional wave at the one-cell stage, and a second major wave at the two-cell stage (Forlani *et al*., 1998). These findings are supported by the results of experiments showing that the one-cell stage features significant Pol II-dependent incorporation of bromouridine triphosphate (BrUTP) into RNA, and RNA synthesis is accompanied by an obvious increase in BrUTP incorporation at the two-cell stage. BrUTP uptake during the one-cell stage is only

40% of that at the two-cell stage. The higher levels of BrUTP incorporation seen at the two-cell stage are maintained at subsequent developmental stages (Forlani *et al*., 1998; Aoki and Schultz, 1999). Therefore in the mouse, the basal transcription machinery is ready to activate, after fertilization, the transcription of characteristic genes such as those encoding heat shock proteins, transcription factors, components of the translational machinery and factors involved in splicing (Aoki *et al*., 1997; Forlani *et al*., 1998; Aoki and Schultz, 1999).

EGA and Maternal mRNA Degradation

Recently, it has been considered that maternally encoded mRNAs are liked to activation of embryonic transcripts. For example, maternal mRNA degradation occurs at the same time with embryonic gene activation in *Drosophila* (Bashirollah *et al*., 1999). The zygotic transcripts are especially enriched in transcription factors that modulate the subsequent differentiation program. Interestingly, the earlier zygotic transcripts come from intronless genes that are regulated by a specific transcription factor that enhances its expression at EGA (De Renzis *et al*., 2007).

The mouse early embryonic development also has been studied to discern about the first genes being expressed at the time of EGA. In two recent studies, embryos treated or not with α-amanitin profiled in one-cell to two-cell transition using microarray transcript profiling. One study identified only one transcript sensitive to α-amanitin (Hamatani *et al*., 2004). Another study, reported that mRNA transcripts sensitive to α-amanitin in the one-cell stage were not found (Zeng and Schultz, 2005). A possible explanation is that in the α-amanitin-treated embryos, BrUTP incorporation at the one-cell stage is due to the transcription of polyA− Pol II-dependent RNAs like small nuclear RNA, small nucleolar RNA and histone transcripts. It is also possible that in the methods used, mRNAs with very short polyA$^+$ tails could not be detected. Based on these results, it can be speculated that *de novo* transcription (Pol II-dependent BrUTP-RNA incorporation) in the one-cell-stage embryo only includes a small fraction of the total mature mRNAs detected in the microarray experiments. It is likely that most of them are maternal transcripts that encode components used in mRNA metabolism and protein synthesis that are required for the embryo to continue and maintain development from the one cell to the two cell stage, but not further, since about 90% of the oocyte-stored RNA is degraded by the end of the two-cell stage (Aoki and Schultz, 1999; Evsikov *et al*., 2006) and later developmental stages (Hamatani *et al*., 2004).

CTD Phosphorylation and EGA

Pol II CTD phosphorylation is influenced by basal transcription factors and this influence has been subject of studies to understand the molecular nature of EGA. It has been observed that short before embryonic genome is activated, maternally contributed Pol II as well as components of basal transcription machinery are translocated from the cytoplasm to the nuclei. In fly for instance, large subunit of Pol II and also TATA binding protein begin to be detectable at 7th cell cycle and after on, that is concomitant with the beginning of the first transcriptional activity (Seydaux and Dunn, 1997; Wang and Lindquist, 1998).

Similar to other species, mouse oocytes also contain a large amount of Pol II. The CTD shows a dynamic phosphorylation pattern during the course of oocyte maturation and fertilization, since, the levels of phosphorylated CTD decrease during oocyte maturation and increase after fertilization at the end of the one-cell stage, concomitant with the first surge of transcription (Bellier *et al*., 1997). In these embryos, about 9 h after fertilization, Pol II accumulates in the pronuclei especially in the male pronucleus. Inhibition of RNA or protein synthesis does not impair this nuclear translocation, and therefore the program established during oocyte development is followed. Therefore, the nuclear translocation of Pol II and its CTD phosphorylation are determinants of developmental regulation for EGA in the mouse (Bellier *et al*., 1997). In addition, components of the TFIID factor like TBP and TAF1 are practically undetectable in the pro-nuclei after fertilization. TBP can be identified inside the male mouse pro-nuclei after 4 h post-fertilization and TAF1 after 6 h. Therefore, the nuclear localization of TBP and TAF1 together with Pol II translocation from the cytoplasm to the nuclei correlates with EGA. Data from *Drosophila* and mice suggest that activation of the basal transcription machinery is a limiting step for genome activation (Wang *et al*., 2006; Worad *et al*., 1994). However, these experiments cannot distinguish if the regulated translocation of the basal transcription machinery causes transcription onset or, due to transcriptional activation, the basal transcription components accumulate in the early embryo nuclei.

RNA POLYMERASE II CTD KINASE

P-TEFb

Searches for enzyme(s) responsible for the Pol II CTD phosphorylation revealed that the CTD is a major target of CDK9 kinase activity, and the distinct phosphorylation states of the enzyme are associated with different functionalities. This oscillation of CTD phosphorylation regulates recruitment of various factors re-

quired throughout transcription (Sims *et al*., 2004).

Positive transcription elongation factor b (P-TEFb), also termed CDK9/cyclin T1, the metazoan Pol II CTD kinase, regulates transcription elongation by phosphorylating Ser2 of the CTD and Negative Elongation Factor-E (NELF-E) (Reese, 2003; Orphanides and Reinberg, 2002; Price, 2000; Bres *et al*., 2008). Phosphorylation of NELF-E removes the block against early transcriptional elongation induced by binding of the NELF complex to the nascent transcript (Yamaguchi *et al*., 1999; 2002). Within the cell, P-TEFb exists in two forms, designated the large and the free forms (Yang *et al*., 2001; Nguyen *et al*., 2001). The kinase-active free form contains CDK9 and one of several cyclin regulatory subunits (cyclin T1, cyclin T2a, cyclin T2b, or cyclin K) with cyclin T1 being predominant in many cell types (Peng *et al*., 1998; Fu *et al*., 1999). The kinase-inactive large form of P-TEFb additionally contains 7SK RNA (Yang *et al*., 2001; Nguyen *et al*., 2001) and either hexamethylene bisacetamide-induced protein 1 (HEXIM1) (Yik *et al*., 2003; Michels *et al*., 2003) or HEXIM2 (Byers *et al*., 2005). In HeLa cells, 50-90% of P-TEFb exists as the large form, with the remaining protein being in the kinase-active free form (Yang *et al*., 2001; Nguyen *et al*., 2001; Michels *et al*., 2003; Byers *et al*., 2005). It is hypothesized that the large form of P-TEFb serves as a reservoir for the free form.

Flavopiridol is a potent anti-cancer and -HIV therapeutic agent currently under investigation in clinical trials (Senderowicz and Sausville, 2000; Kelland, 2000). This compound is the most potent inhibitor of P-TEFb identified to date and the first reported CDK inhibitor that acts in a manner that is not competitive with ATP (Chao, 2000). Flavopiridol inhibits transcriptional elongation *in vitro* by targeting CDK9; the IC50 value of this effect is 5-10-fold lower than that noted when effects on other CDKs are assessed (Chao and Price, 2001). Nuclear run-on transcription assays have shown that flavopiridol inactivates P-TEFb and blocks most Pol II-mediated transcription *in vivo* (Chao and Price, 2001).

Phosphorylation of the CTD plays a further important role in co-transcriptional mRNA processing *in vivo*. Specifically, the phosphorylated protein serves as a binding platform for factors involved in 5' end capping, splicing, and 3' end-processing of pre-mRNA, as well as chromatin modification (Pirngruber *et al*., 2009).

P-TEFb is required for transcription of most genes, including heat-shock genes and c-Myc, and also for HIV-1 transcription by trans-activator of transcription (TAT) (Zhou and Yik, 2006). Shim *et al*. (2002) reported that P-TEFb was, in general, essential for expression of early embryonic genes in *C. elegans*. Notably, P-TEFb is essential for the expression of early embryonic genes and the phosphorylation of Ser 2 in the CTD and the elongation factor SPT-5. Experiments in *C. elegans* have shown that P-TEFb and SPT-4/SPT-5 have opposing functions during Pol II elongation, and P-TEFb is thought to mediate several different post-initiation pathways (Shim *et al*., 2002). However, it is not yet known how P-TEFb functions in these differential pathways. In addition, the role of P-TEFb in early gene expression has not yet been analyzed in the four-cell *C. elegans* embryo or 2-cell stage mouse embryo when genome activation occurs.

In the first genetic study of P-TEFb components, Shim *et al*. (2002) showed that Ser2 phosphorylation is eliminated upon genetic inactivation of CDK9 or its cyclin T1 subunit. *C. elegans* development is arrested at the 100-cell stage in the absence of cyclin T1 or CDK9; this is precisely what is noted upon knockdown of the large subunit of Pol II. Experiments using yeast and *Drosophila* have shown that CDK9 is vital for all of appropriate 3' end-processing of pre-mRNA (Ni *et al*., 2004; Ahn *et al*., 2004), gene expression, histone methylation, and elongation factor recruitment (Eissenberg *et al*., 2007).

TFIIH

TFIIH, composed of CDK7, Cyclin H and MAT1, is the kinase responsible for the phosphorylation of the CTD at Ser5. This kinase has been studied using mutations and RNAi in *C. elegans* to understand embryonic transcription in very early stages of development. Although, embryonic transcripts are not needed until 100-cell stage, CDK7 inactivation led to developmental arrest at 50-cell stage. It suggested that CDK7 also had a role in cell cycle regulation. Inactivation of CDK7 either by antibody injection or by mutation in *Drosophila* shows a similar observation in other studies (Aguilar-Fuentes *et al*., 2006; Larochelle, *et al*., 2001; Leclerc, *et al*., 2000). In both *C. elegans* and *Drosophila,* the early expression patterns of the zygotic genes were changed. Additionally, CTD phosphorylation was reduced and the cell cycles were prolonged (Larochelle, *et al*., 2001; Leclerc, *et al*., 2000). Surprisingly, genetic inactivation of CDK7 in mice reveled that this kinase is dispensable for global transcription (Ganuza *et al*., 2012). In embryonic fibroblasts generated from *CDK7* null mice, CTD phosphorylation was unaffected but phosphorylation levels of CDK1 and CDK2 were reduced indicating the importance of this kinase in cell cycle regulation.

RNA POLYMERASE CTD PHOSPHATASE

TFIIF-associated CTD phosphatase, FCP1, has been characterized as first Pol II CTD phosphatase in HeLa cells (Chambers and Dahmus, 1994). In 2007, Walker *et al*. proposed a model, based on analyses of CTD phosphorylation dynamics in *C. elegans,* suggesting that trans-

cription activation is prepared during oocyte maturation. Depletion of FCP1 by RNA interference in transcriptionally inactive oocytes showed that CTD phosphorylation at Ser5 is elevated in these cells. On the other hand, RNAi inhibition of FCP1 together with CDK7 or components of preinitiation complex does not increase Ser5 CTD phosphorylation, suggesting that the CTD phosphorylation occurs in the context of the preinitiation complex. This model proposes that in oocytes, gene expression is silenced due to abortive transcription. The basal transcription machinery, however, is already positioned at gene promoters that require rapid activation at EGA. When oocyte maturation is stimulated, there is also an increase in the Ser5-phosphorylated CTD, supporting the above hypothesis. Importantly, this study reveals that the balance and regulation between CTD phosphatases and CTD kinases play a major role in EGA. However, other components of the PIC are required for CTD phosphorylation and it has not been demonstrated that phosphorylated Pol II and the rest of the basal transcription machinery are positioned in chromatin that is going to be transcribed at EGA. An utmost important task will be answering this question, since the system is highly dynamic. In *Xenopus*, CTD phosphorylation is a key aspect in the initiation of mRNA synthesis (Palancade, *et al*., 2001a). After fertilization, the CTD is rapidly dephosphorylated in the *Xenopus* embryo. This unphosphorylated state is maintained throughout several divisions, and then the CTD is rapidly phosphorylated at the mid-blastula transition (Palancade, *et al*., 2001b). In *Drosophila*, using transgenic lines in which the function of FCP1 was misregulated, Tombacz *et al*. (2009) showed that FCP1 function is essential throughout *Drosophila* development and ectopic up- or down-regulation of FCP1 results in lethality. The role of FCP1 in CTD dephosphorylation and its potential impact on EGA in mammals are largely unknown. Altogether, data from the experiments on model organism reveal the dynamics of P-TEFb, TFIIH and FCP1 and their fundamental in CTD phosphorylation. Additional work will be required to examine the mechanisms governing post-fertilization CTD dephosphorylation in mice and other organisms.

CONCLUSIONS AND PERSPECTIVES

Although the time of EGA differs among various species, it is demonstrated that basal transcription factors including Pol II itself, are generally maternally inherited from the oocyte to the embryos. Among the events studied in early embryonic development, it seems that phosphorylation of Pol II CTD and its effects on general transcription determine the status of transcription factors in EGA in all animals.

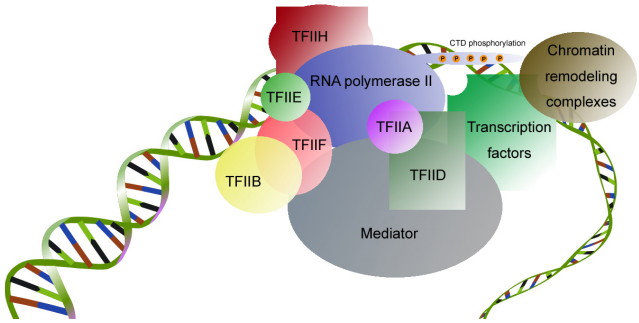

Fig. 1. Schematic representation of RNA polymerase II and general transcription factors. TFIIH is fundamental for triggering DNA melting around transcription initiation site. CDK7 component of TFIIH phosphorylates Pol II CTD and promotes initiation of transcription. For more details see the text.

It is now known that animals discussed in this review have two waves of transcription during EGA. The first wave promotes a selected few genes to be transcribed in early stage of development (for example in the mouse, in one cell stage) which are likely needed for proper cell division and/or for triggering the second wave of transcription in which a large number of genes are transcribed (Zeng and Schultz, 2005; Hamatani *et al*., 2006).

Understanding the time of transcription in different animals has provided an insight about the pathways controlling early animal development. It will also be interesting to investigate how factors promoting EGA are coordinated with the general transcription factors, and how genome architecture determines the activation of a somatic cell nucleus inserted into early embryo (Inoue *et al*., 2006). Future advance in somatic cell cloning and tissue engineering as well as address the questions such as why so few cloned embryos survive to develop to maturity depend on to understand the mechanisms regulating early embryonic development. In summary, it can be proposed that factors and components of general transcription machinery are maternally deposited into the egg cytoplasm. Although several lines of evidence support this model, questions such as what mechanism(s) regulate the nuclear translocation of transcription factors before EGA remain to be answered. However, accumulation of new findings and availability of more advanced techniques raise the hope to answer these questions.

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