Cell cycle regulation during early mouse embryogenesis.

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Abbreviations: embryonic stem cells: ESC; inner cell mass: ICM; hematopoietic stem cells: HSC; maternal to zygotic transition: MZT; *Ovum mutant candidate gene 1*: *Omcg1*; spindle assembly checkpoint: SAC; trophoblast giant cells: TGC; zygotic genome activation: ZGA.

Abstract

Elaboration of a multicellular organism requires highly efficient coordination between proliferation and developmental processes. Accordingly, the embryonic cell cycle exhibits a high degree of plasticity; however, the mechanisms underlying its regulation *in vivo* remain largely unknown. The purpose of this review is to summarize the data on cell cycle regulation during the early mouse embryonic development, a period characterized by major variations in cell cycle parameters which correlate with important developmental transitions. In particular, we analyse the contribution of mutant mice to

the study of *in vivo* cell cycle regulation during early development and discuss possible contributions of cell cycle regulators to developmental programs.

Introduction

In mammals, the beginning of embryonic development is mainly devoted to ~~the~~ generation of extraembryonic tissues. These structures not only ensure nutrients supply to the embryo but also play important role in the establishment of the basic body plan of the embryo. Recently, a global gene expression profiling technology has been adapted and applied to pre-implantation embryos. Such studies have revealed that many genes exhibit dynamic variations in transcript level during that period [1,2]. Noticeably, more than half of known genes are differentially expressed during pre-implantation development suggesting that a large number of genes might participate to first steps of development. In apparent contradiction with these observations, gene inactivation leading to an early developmental failure is relatively infrequent. Hence, according to the Jackson database (http://www.informatics.jax.org/), only 296 out of the 4558 (6.5%) gene knock-out listed in the database show an embryonic lethality during the first third of gestation. Moreover, for the majority of those (218 out of 296), lethality occurs after implantation between E4.0 and E8.0. Thus, in total, as little as 1.7% (77 out 4558) of genes disruption results in early embryonic lethality prior E4.0. While this percentage is certainly underestimated (we found many genes falling into that category that was not properly annotated in the database), it is nevertheless surprisingly low considering that not only genes specifically required during pre-implantation development but also essential housekeeping genes were expected to give such a phenotype. Several characteristics peculiar to early mammalian embryo might account for this discrepancy including the persistence of maternally inherited gene products that can sometimes compensate for the lack of zygotic expression during this period but also the extraordinary plasticity of the mammalian pre-

implantation embryo, which has the ability to efficiently adapt its development in response to various perturbations.

To illustrate theses specificities, we chose to focus on the regulation of the cell cycle. Indeed, while the general cell cycle pattern has been highly conserved through evolution, it has been extensively modified to adapt to new developmental programs. Hence, early mouse embryogenesis is characterized by important variations in numerous cell cycle parameters, which correlate with known developmental transitions. Moreover, results obtained from gene targeting have shed some light on the complexity of *in vivo* cell cycle regulation.

Cell cycle parameters of early mouse embryo

Numerous studies have been performed in order to precisely determine the cell cycle parameters during early stages of development and clearly established that these parameters are greatly modified during pre-implantation development. Differences were observed between the values obtained in these studies that stem from differences in experimental procedures as well as influences from the genetic background [3] and the parental origin of the genomes [4,5] (table 1). It is nevertheless possible to synthesize these observations as follows (figure 1 and table 1). The first two divisions last approximately 20h. Four to ten hours after fertilization, replication begins and lasts between 4 and 8h. It should be noted that replication is detected first in the male pronucleus [6,7]. G2/M phase length is estimated to 3-5h. Interestingly, the duration of the first mitosis (120 min) is almost twice longer than the second (70 min) and this increase seems to be due to a transient metaphase arrest independent of the spindle assembly checkpoint (SAC) [8]. The second S phase lasts approximately 6h. Gap phases of the second division are very different since G1 is extremely short (1-2h) [9] and G2 very long (12 to 16h) [3,10-12]. Strikingly, it is during this unusually long G2 phase that occurs the major phase of the zygotic genome activation (ZGA) in the mouse [13]. The following four divisions occurring between st-4 and st-64 are more homogeneous in terms of duration (10-14h; G1:1-2h, S:7h, G2/M:1-5h). Importantly, during the 5th cleavage (between st-16 and st-32), two cellular populations are formed, polarized external cells and apolar internal cells, which seem to differ in their cell cycle parameters [14,15]. As development proceeds, external cells give rise mainly to trophectoderm (polar and mural) while internal cells contribute to the inner cell mass (ICM) that will then

segregate into epiblast and primitive endoderm. Based on mitotic index examination, A.J Copp observed that while the number of cells composing the mural trophectoderm increases considerably in late blastocyst embryos, mural trophectodermal cells divide slower than polar ones [16-18]. This observation leads to the proposal that trophectodermic cells are essentially generated in the polar region and then migrate (actively or passively) in the mural region. In the ICM, mitotic index examination revealed partial synchronization of cell divisions between st-30 and st-150 [16]. After implantation in the uterus, the embryo undergoes gastrulation, a very active phase of development during which the three embryonic layers are committed and organized in three dimensions. Important modulations of cell cycle parameters happen during this key developmental process. One of the most salient changes concerned trophoblast giant cells, which undergo endoreplicative cycles, consisting of repeated rounds of S phase without intervening mitosis, until they acquired a DNA quantity equivalent to 500 haploid genomes [19,20]. Endoreplication can be first detected in late blastocysts where approximately 5% of the cells are polyploid [19]. Important modifications are also observed in the epiblast where cell division pace greatly accelerates (table 2). The fact that in all studied species, gastrulation is preceded by fast cell cycles [21], suggests that rapid amplification of embryonic cells is necessary for proper cell type diversification and embryo patterning. Successful gastrulation requires that cell cycle regulation is tightly coordinated to signaling pathways and cell movements. Studies in mice and rat revealed the existence of a region of remarkably fast cell cycle (2-3h), called the proliferative zone, which lies in close proximity to the primitive streak [22,23]. Interestingly, mesodermal cells that are generated from the primitive streak cell

population do not keep proliferation with such a high rate [22-24] (table 2), indicating that the transition between embryonic ectodermal to mesodermal cells implies highly dynamic regulation of cell cycle parameters. How such modifications are controlled and whether they play a direct role in the commitment of the mesoderm and endoderm cell lineages remain unanswered.

Checkpoint activities

Contrary to early mammalian development, rapid cleavage cycles lacking intervening G1 and G2 gap phases are found in early embryos from other major phyla (reviewed for example in [21,25,26]). These rapid cycles either lack or display weak checkpoint activities, a situation which, to some extends, seems to be different to that observed in mouse pre-implantation embryos.

DNA damage checkpoint

Genome integrity maintenance is a key process that requires efficient DNA damage detection and DNA repair processes. In response to DNA damage, different checkpoints are activated leading to a cell cycle delay or arrest. Delayed progression of the cell cycle allows time for either repair or elimination of genetically unstable cells by apoptosis. Such adaptative response seems absent from embryonic cycles of various species. Indeed, inhibition of replication does not prevent mitotic entry in drosophila [27], zebrafish [28] or xenopus [29]. In contrast, similar inhibition induces a strong cell cycle arrest in mouse pre-implantation embryo [30,31]. Early mouse embryos also respond to DNA damages induced by irradiation. While the nature of this response depends largely on the quantity

and the type of radiation used, two main conclusions can be drawn from the literature: i) whatever the age of the exposed embryo, radiations provoke changes in cell cycle parameters [32] and induce apoptosis [11,33,34] ii) sensitivity to irradiation is highly dependent on the developmental stage which is exposed [35]. Interestingly, irradiation of early post-implantation embryos with low doses of X-rays does not result in marked cell cycle delay but rather induces a strong p53 and ATM dependant apoptotic response [36]. Thus, it appears that, at that time of development, the main pathway used by embryonic cells to respond to DNA damage is cell elimination, probably because the cell cycle regulation during this period of extreme proliferation is not compatible with cell cycle arrest and accurate repair of DNA damages. Similar conclusions can be drawn from the analyses of genetic invalidation models. Although *Atm* [37] or *Chk2* [38] are dispensable to embryonic development, embryos lacking *Atr* or *Chk1* die soon after implantation exhibiting high degree of chromosomal fragmentation [39-41]. A similar phenotype was observed in embryos lacking proteins involved in DNA double strand break repair such as *Rad50* [42] and *Nbs1* [43]. Finally, early embryonic lethality was observed following inactivation of several genes encoding for DNA repair machinery components such as *Fen1* [44], *Rad51* [45], *Xab2* [46], or *Xpd* [47]. Interestingly, while non-homologous end joining (NHEJ) repair mechanism has been shown to be extremely active after fertilization [48], inactivation of several genes involved in this process, like *DNA-Pkcs* [49], *DNA ligase IV* [50] or *Xrcc4* [51] does not lead to early embryonic lethality. It is important to note that in cases where early embryonic lethality was observed, defects were manifest by the time of implantation at the earliest. Several explanations might account for this observation. First, the presence of maternal stores might compensate for

the absence of a zygotic product. Second, errors or DNA damages accumulation over several cell cycles might be necessary in order to induce a patent phenotype. Anyhow, it probably also reflects the transition in the cell cycle regulation and the increased sensitivity towards DNA damages that occurs after implantation.

Mitotic checkpoint

During mitosis, improper attachment of kinetochores to microtubules triggers the spindle assembly checkpoint (SAC), preventing the onset of anaphase and potential incorrect segregation of the genetic material into daughter cells. Several lines of evidences indicate that SAC is operating during mouse early development. First, pre-implantation embryos exposed to drugs interfering with spindle assembly arrest very efficiently in metaphase [52-55]. Second, key components of the SAC such as MAD2 and BUBR1 localize to kinetochores of unattached chromosomes of zygotes and blastocysts (evoked in [8,56,57]). Finally, early lethality of embryos deficient for various component of the checkpoint such as *Apc10/Doc1* [58,59], *Bub3* [60], *BubR1* [61], *Emi1* [62] and *Mad2* [63] demonstrates that SAC plays a critical role in mitotic progression of early embryonic cells. SAC regulates progression of mitosis by controlling the activity of the APC/C complex, which triggers the degradation of several key mitotic proteins. One of the substrates of APC/C is securin, an inhibitory chaperone of separase, which is the protease triggering sister chromatids separation at the anaphase onset. Not surprisingly, inactivation of *Separase* leads to an early embryonic lethality associated with polyploidy and abnormal centrosomes number [64,65]. In contrast, *Securin* is not essential for either mitosis or meiosis [65-67]. Finally, inactivation of genes encoding centromeres or

kinetochores structural proteins leads to abnormal mitotic figures and to peri-implantation lethality (*CenpA* [68]; *CenpC* [69]; *CenpE* [70]; *Incenp* [71]; *Survivin* [72]).

RB-dependent G1 checkpoint

Cell cycles of the early mammalian embryo not only differ from early mitotic cycles found in other organisms but also from mammalian somatic cell cycles. An important difference concerns cell cycle regulation in G1. In somatic cells, the length of G1 phase can vary considerably in response to environmental stimuli such as for example mitogenic factors that impinge on cell cycle progression through Myc and Rb pathways. Mouse early cleavages are characterized by a short G1 phase. Consistently, pre-implantation development is independent of exogenous growth factors (see for example [73,74]). In addition, although genes taking part in the Rb pathway are expressed dynamically during early mouse development [75-77], they are dispensable for this period of development (for review, see [78,79]). Two non-exclusive explanations might account for the lack of RB-dependent G1 checkpoint activity before implantation. Iwamory and collaborators observed that *Rb* mRNA and proteins were barely detectable before the late blastocyst stage suggesting that low levels of RB is necessary for shortened G1 phase. Accordingly, they observed that forced expression of RB by plasmid injection into zygotes induced developmental arrest before the morulae stage [75]. In another study, Xie and collaborators observed phosphorylated RB proteins throughout pre-implantation development, suggesting that regulation of RB phosphorylation state rather than level of expression might be responsible for the short G1 phase [77]. Interestingly, mouse embryonic stem cells cells (ESC), which derived from the inner cell

mass of blastocyst stage embryo, also lack the RB-dependent control of the G1/S transition that characterizes somatic cells ([80] and reviewed in [81]). Recently, it has been shown that rhesus monkey [82] and human ESC [83,84] share such characteristic. Therefore, studying ESC cycle parameters might be a relevant mean to apprehend cell cycle regulation during human early embryonic development.

Contribution of mutant mice to the study of *in vivo* cell cycle regulation during early development

Plasticity and functional redundancy

For the last 15 years or so, gene targeting experiments have challenged the canonical view of cell cycle regulation, generating a tremendous amount of data. One of the most striking conclusions raised by these studies is that most key cell cycle regulators are largely dispensable during development (reviewed in [78,79,85,86]). To date, regarding Cyclin/Cdk complexes, early developmental failure was observed after disruption of only *Cyclin A2* [87,88], *Cyclin B1* [89] and *Cdk1* [90]. Consistent with the fact that several members of a given type of cyclin or Cdk are present in the mouse genome, more severe phenotypes were observed in compound mutants. For example, while mice defective for a single member of the cyclin D family (D1, D2 or D3) are viable [91-93], combined invalidation of the three *CyclinD* genes leads to an embryonic lethality around E16.5 [94]. Similarly, double knock-out of *Cyclin E1* and *E2* leads to a lethality towards E16.5 whereas the simple knock-outs are viable [95,96]. Lastly, the double knock-out of *Cdk4* and *Cdk6* is embryonic lethal around E14.5-E16.5 whereas simple knock-outs are viable [97,98]. Strikingly, progression to late developmental stage of the aforementioned double

and triple mutant embryos demonstrates that removal of all these ''key'' regulators of proliferation provides a surprisingly minimal barrier to cell proliferation in the early mouse embryo. It also suggests that the embryonic cell cycle has a high degree of plasticity more sophisticated than simple redundancy (figure 2). Hence, in some circumstances functional compensatory mechanisms may occur between proteins acting on different aspects of the cell cycle regulation. An evidence for such mechanism was recently provided by the analysis of embryonic fibroblasts deficient for *Cdk2*. Indeed, in the absence of CDK2, CDK1 normally regulating mitotic progression is able to bind Cyclin E and to drive cells into the S phase [99]. Other examples of functional compensation will certainly arise from future studies on genetically modified mice. In these studies, an important question will be to determine whether such compensatory mechanisms are essentially activated following the disequilibrium induced by gene disruption or whether they represent accessory pathways normally used in wild-type context.

Control of endoreplication

Another striking fact uncovered by gene knock-out studies is that many cell cycle regulators happen to have tissue-specific functions. Even in the case of a combined inactivation of several genes leading to an embryonic lethality, one finds defects restricted to some embryonic structures. Thus, the inactivation of cyclins D1, D2 and D3 induces problems in the formation of the heart at the origin of the lethality of embryos towards E16.5 [94]. Contrarily to the situation found in *Drosophila* [100] and *C. elegans* [101] where cyclin E is absolutely required for normal development, the E-type cyclins

appear to be dispensable for the development of the embryo proper in the mouse. However, the disruption of cyclin E in mice brought some important informations on the control of endoreplicative cell cycle *in vivo*. Indeed, lethality of embryos deficients for both *cyclin E1* and *E2* is essentially due to abnormal placental development consecutive to failure of endoreplicative cycles of trophoblast giant cells (TGC) [95,96]. This shows that E-type cyclins are key players in the control of endoreplication. Regulation of cyclin E levels is therefore expected to be critical for TGC endoreplication. Interestingly, *Skp2* deficient mice display elevated cyclin E levels and polyploidy in several tissues of postnatal animals [102]. Abnormally high levels of cyclin E and early embryonic lethality have been observed in mice deficient for other components of ubiquitin and ubiquitin-like modification pathways as for example *Cul1* [103] or *Cul3* [104], two members of the SCF complexes, *Csn2* [105], a subunit of Cop9 signalosome and *Uba3* [106], the catalytic subunit of NEDD8-activating enzyme. Importantly, in *Cul3* or *Uba3* deficient embryos, constitutive expression of cyclin E in trophoblast cells has been shown to correlate with a block in endoreplication. Gene disruption studies also provide evidences that other pathways regulate endoreplicative cycle progression *in vivo*. Indeed, inactivation of *Mat1*, coding for a subunit of the trimeric Cdk7-CylinH-Mat1 kinase, results in peri-implantation lethality [107]. *Mat1* deficient TGC are rapidly arrested in the cell cycle progression, although they underwent several cycles of endoreplication. Finally, genetic ablation of *Geminin*, an inhibitor of pre-replication complex assembly, causes premature endoreplication and trophoblast cell differentiation of inner cells [108]. In wild-type blastocysts, *Geminin's* down regulation in trophoblast cells correlates with

active endoreplication. Altogether these observations suggest that *Geminin* is involved in suppression of endoreplication and trophoblast differentiation.

Previously uncharacterized cell cycle regulators

In some cases, gene knock-out mouse models may help to uncover novel cell cycle regulators. Recently, three genes, the function of which had not been previously ascribed to cell cycle regulation, have been shown to regulate cell cycle progression *in vivo*. Hence, the *Cdc2P1* gene encodes two kinases originally identified as regulators of RNA transcription and processing that have been renamed CDK11 ten years ago because of their possible interaction with cyclin L. The first evidence that *Cdc2P1* is indeed involved in cell cycle progression came from the observation that *Cdc2P1* deficient embryos exhibit mitotic arrest followed by massive apoptosis at the blastocyst stage [109]. Further studies have shown that the CDK11 p58 small isoform, the synthesis of which occurs through an internal ribosome entry site which is specifically used during the G2/M transition, is critical for centrosome maturation, bipolar spindle formation and proper completion of cytokinesis [110,111]. The second gene is *E4f*, one of cellular target of E1A oncoprotein during adenoviral infection, which encodes a protein required for both transcriptional repression and activation of adenoviral genes. *E4f* deficient embryos die at the end of pre-implantation development and exhibit mitotic progression defects, chromosomal missegregation, and increased apoptosis [57], suggesting that, *in vivo,* E4F participates to the cell cycle control. Recently, it has been demonstrated that E4F directly regulates p53 [112]. It will be therefore interesting to monitor the contribution of p53 to the phenotype of *E4f* deficient embryos. The third gene is *Ovum mutant candidate gene 1*

(*Omcg1*), which codes for a nuclear zinc finger protein [56]. *Omcg1* invalidation leads to an embryonic lethality by the end of pre-implantation development. This lethality is preceded by a dramatic reduction in the total cell number, a high mitotic index, and the presence of abnormal mitotic figures at the late blastocyst stage. Importantly, *Omcg1* disruption results in the lengthening of M phase rather than in a mitotic block. This mitotic delay is associated with neither dysfunction of the spindle checkpoint nor abnormal global histone modifications. Further analyses will help to decipher the molecular mechanisms underlying the role of *Omcg1* in mitotic progression.

Control of developmental transitions by cell cycle regulators

Highly dynamic modulations of the cell cycle parameters occur during embryonic development. It is clearly established that the various signalling pathways at works during embryonic development trigger variations in the cell cycle progression that are necessary for proper coordination of essential developmental processes such as proliferation, growth, patterning and differentiation. Conversely, it is reasonable to assume that cell autonomous genetic control of the cell cycle regulation may be a potent way to allow developmental transitions. However, only few examples of such mechanisms have been documented so far, most of which concern non-mammalian species. Hence, while checkpoints mainly act as gatekeepers of cell division integrity, their ability to regulate cell cycle progression has also been employed for developmental purposes. In drosophila, the maternal to zygotic transition (MZT), which occurs by the 13^{th} mitosis and is equivalent to the mouse ZGA, requires a functional DNA damage checkpoint. Indeed, removal of either *Mei-41* (*Atr* ortholog), *Grapes* (*Chk1* ortholog) or *Wee1* maternal stores causes a developmental arrest at the 13^{th} division [113-115]. These

mutant embryos fail to undergo syncitial to blastoderm transition and to initiate major zygotic gene activation. In wild-type embryos, a lengthening of the 11th and 12th division precedes the MZT. In defective embryos, the MZT does not take place and there is no change in the cell cycle duration before the 13th division. Thus, it seems that maternally derived ATR, CHK1 and WEE1 collectively participate in the slowing down of cleavage speed, which in turn allow time for the initiation of the MZT and embryo cellularisation. In nematode, *Atl-1* (*Atr* ortholog) and *Chk1* are necessary for the asynchrony of division observed between AB and P1 blastomere during the second embryonic mitosis [116]. Thus, in this species also, the DNA damage/DNA replication checkpoint contributes to modulation of cell cycle duration during early development. Interestingly though, *Atr* [39], *Chk1* [40,41] and *Wee1* [117] disruption in mice lead to an early embryonic lethality. However, the critical requirement for these checkpoint genes at that period of development may be explained by the higher rate of errors that is likely to occur in rapidly dividing cells of the epiblast. To our knowledge, requirement of maternally derived ATR, CHK1 and WEE1 has not been monitored in mouse. Considering the unusual lengthening of G2 phase observed before ZGA during the second division of the mouse embryo and given the role of these checkpoint proteins in drosophila MZT, one might expect that mouse oocyte specific inactivation of these genes results in very early developmental failure.

Unsuspected links between cell cycle regulators and developmental programs have also been reported in the mouse. For example, inactivation of *Xrcc2*, a member of Rad51 family involved in DNA repair by homologous recombination, leads to a mid-gestation lethality between 12.5 and 18.5 dpc [118]. Surprisingly enough, several anomalies

observed in mutant embryos, mostly defects in neurogenesis and somitogenesis, can be explained by a severe reduction of expression of *Dll1* coding for one of the Notch receptor ligand. How the removal of a gene involved in DNA damage repair affects expression of a member of one of the key signalling pathway at works during development remains unclear. Another example has been provided by the study of hematopoiesis in *Mad2* heterozygous mice [119]. Under cytokine stimultion, c-KIT physically associates with MAD2 and this interaction plays a role in regulating hematopoietic stem cells (HSC) self-renewal/differentiation balance. It has been proposed that local cytokine signalling modulates the duration of mitosis in HSC, allowing or not the correct positioning of the spindle and therefore asymmetric division [120]. Future investigations will determine whether an interaction between members of the SAC and signalling pathways is a common mechanism regulating asymmetric division.

Concluding remarks

In vivo cell cycle regulation is extraordinarily complex. Gene knock-out studies have highlighted the great plasticity of embryonic cell cycle that can compensate for the lack of one or several regulatory proteins by various mechanisms including redundancy and functional compensation. Acquisition of lineage-specific cell cycle duration is a central issue during development. In the embryo, the modulation of the cell cycle progression is achieved by both time- and tissue-specific expression of cell cycle regulatory proteins as well as the integration of external cues generated by cell-cell contact and signalling pathways. Unique features of early mammalian embryos such as the switch from a maternal to a zygotic developmental program and the rapid diversification of embryonic and extra-embryonic cell lineages contribute to this complexity. It is clear that the

regulation of the cell cycle during early mouse development has not yet delivered all its secrets and the generation of more and more sophisticated mouse models will help us to better understand all its facets.

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Figure legends

Figure 1. Summary of the first three cleavages of the mouse embryo.
Major developmental events are represented such as the formation of pronuclei that occurs shortly after fertilization and takes between 2 to 4h, the zygotic genome activation that is initiated at the end of the first division but takes place during G2 phase of the second division. Such developmental events are accompanied by cell cycle changes particularly in term of length of the gap phases.

Figure 2. Different types of functional compensation.
❶ Schematic representation of a developmental transition from a state A to a state B. The product of gene 1 is involved in this transition, however disruption of gene 1 has no effect on the progression from state A to state B. Three types of functional compensatory mechanisms might explain such observation. ❷ Another gene, gene 2, which in the normal situation is also involved in the A to B transition, can compensate for the lack of gene 1 product. ❸ In absence of gene 1 product, gene 3 product, which in the wild type situation is acting on a different process, is recruited to ensure correct transition from state A to state B. ❹ A to B transition is achieved through a different route involving gene 4.

Table legends

Table 1. Cell cycle parameters of the first four divisions of the early mouse embryo.
This table combines data collected from several studies. Variability of the estimation of the length of the different phases (in hours) between the studies should be noted..

Table 2. Estimation of cell cycle length of post-implantation embryos in mice at E7.5 dpc [24] and at egg-cylinder stage [22] and in rat at E8.5 dpc [23].