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Cell cycle regulation during early mouse embryogenesis

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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.

Keywords: Cell cycle; Checkpoints; Early mouse development; Endoreplication; Gene targeting; *Ovum mutant candidate gene 1*; Peri-implantation lethality

1. Introduction

In mammals, the beginning of embryonic development is mainly devoted to 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 (Hamatani et al., 2004; Wang et al., 2004a). 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 were 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.

2. 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

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

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Table 1
Cell cycle parameters of the first four divisions of the early mouse embryo

1st division				2d division				3rd division				4th division				References
G1	S	G2	M	G1	S	G2	M	G1	S	G2	M	G1	S	G2	M	
4	4	3-5														[6]
9	6-7	5														[121]
8	4															[7]
	7-8															[122]
	4	8		0.5	7	11.5		1	7	2						[3]
	5	5		2	6	14		1	7							[3]
				1	4											[123]
				1	6	12										[10]
				1.3	6.1	15.4	1.3	1.6	7.4	0.5	1.2					[12]
								1	7	2-5		2	7	1-3		[124]
7	**5.3**	**6.5**		**1.2**	**5.8**	**13.5**		**1.1**	**7.1**	**2.9**		**2**	**7**	**3**		**Average**
19				**20**				**11**				**11**				**Total lenght**

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.

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 (Molls et al., 1983a) and the parental origin of the genomes (Shire and Whitten, 1980a,b) (Table 1). It is nevertheless possible to synthesize these observations as follows (Fig. 1 and Table 1). The first two divisions last approximately 20 h. Four to ten hours after fertilization, replication begins and lasts between 4 and 8 h. It should be noted that replication is detected first in the male pronucleus (Abramczuk and Sawicki, 1975; Luthardt and Donahue, 1973). G2/M phase length is estimated to 3–5 h. 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) (Sikora-Polaczek et al., 2006). The second S phase lasts approximately 6 h. Gap phases of the second division are very different since G1 is extremely short (1–2 h) (Gamow and Prescott, 1970) and G2 very long (12–16 h) (Molls et al., 1983a; Luthardt and Donahue, 1975; Molls et al., 1983b; Sawicki et al., 1978). Strikingly, it is during this unusually long G2 phase that occurs the major phase of the zygotic genome activation (ZGA) in the mouse (Flach et al., 1982). The following four divisions occurring between st-4 and st-64 are more homogeneous in terms of duration (10–14 h; G1: 1–2 h, S: 7 h, G2/M: 1–5 h). 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 (Barlow et al., 1972; MacQueen and Johnson, 1983). As development proceeds, external cells give

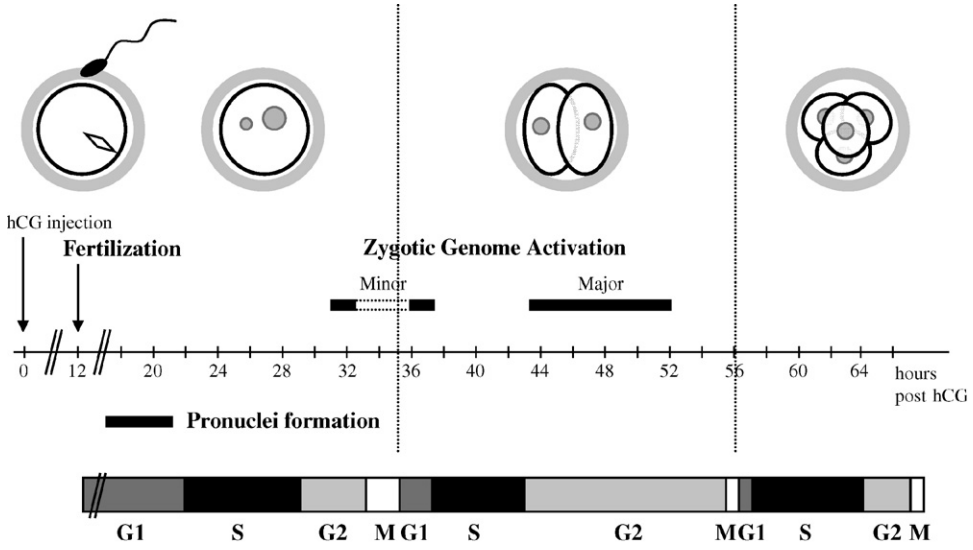

Fig. 1. Summary of the first three cleavages of the mouse embryo. Major developmental events are represented such as the formation of pronuclei that occurs shortly after fertilization and takes between 2 and 4 h, the zygotic genome activation that is initiated at the end of the first division but takes 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.