Untangling the mysteries of maternal inheritance with polyCOMB

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The inheritance of maternal factors in oocytes plays a crucial role in development, particularly in non-mammalian species, where asymmetric segregation of developmental factors among early blastomeres regulates early patterning of the embryo. Whereas this role is less important in mammals, a number of studies have shown that maternal inheritance is equally critical for regulating development through epigenetic instructions and initiating transition from the zygote to embryonic transcription programme (Li *et al*, 2010). A recent study by Posfai *et al* (2012) now shows the important role played by maternally inherited Polycomb complexes during development of the mouse oocyte, and thereafter during early development.

Germ cell development is a highly dynamic process, which has to be precisely orchestrated to ensure proper development of the embryo. A totipotent embryo has the ability to

give rise to all the three germ layers including extra embryonic tissues. Development follows after the formation of a totipotent zygote, which involves fusion between two differentiated cell types, the sperm and the oocyte. However, nuclear transfer experiments (whereby a somatic nucleus is injected into an enucleated oocyte) can also result in development to term, albeit infrequently. Thus, the cellular milieu of the oocyte has a unique composition, which enables the oocyte to reprogram the nucleus of even a terminally differentiated somatic cell (Meissner and Jaenisch, 2006). To understand the mechanisms that govern totipotency, it is essential to know what maternal factors give an oocyte this unique potential.

Upon fertilization, the maternal and paternal nuclei undergo dramatic chromatin changes, wherein the sperm nucleus is stripped off its protamines, which are rapidly replaced by

Figure 1 Maternally provided PRC1 components Rnf2 and Ring1 are crucial for proper embryonic development. Genetic deletion of Rnf2 and Ring1 in oocytes results in developmental arrest of embryos at the two-cell stage, following replication defects and impaired zygotic gene activation. Rnf2/Ring1 double-mutant oocytes show a loss of H2AK119ub1 and genome-wide mis-regulation of transcription in which PRC1 target genes are particularly affected. Nuclear localization of other PRC1 complex proteins in the growing oocyte and two-cell embryo is also disrupted in the absence of Rnf2 and Ring1 (Posfai *et al*, 2012).

maternally provided histones (Wright, 1999). Epigenetic reprogramming is also marked by loss of DNA methylation of the male pronucleus and deposition of replication-independent histone variants such as H3.3 (Torres-Padilla *et al*, 2006). Alongside, the maternal transcription programme is turned off and a zygote-specific gene activation (ZGA) programme ensues. This switch in transcription from a maternal to a zygotic programme is thought to involve epigenetic factors and oocyte-derived microRNAs (Giraldez, 2010). ZGA marks the acquisition of totipotency. The SWI/SNF complex ATPase Brg1, provided maternally, has been shown to be crucial for ZGA in mice (Bultman *et al*, 2006), although other epigenetic factors may also contribute to this specific process.

The Polycomb family, comprising PRC1 and PRC2 complexes, mediate gene repression in diverse cellular contexts. The recent study by Posfai *et al* (2012) has focused their role in mouse oocytes and early development. Polycomb proteins are thought to silence a key set of developmental genes in embryonic stem cells to set the stage for lineage commitment (Pietersen and van Lohuizen, 2008). In agreement, PRC2-dependent H3K27me3 also targets developmental genes *in vivo* in the inner cell mass (ICM) (Dahl *et al*, 2010). Previous studies showed that both PRC1 and PRC2 have histone-modifying activities: PRC1 mediates mono ubiquitination of H2A at lysine 119 (H2AK119ub1), whereas PRC2 is involved in histone H3 lysine 27 trimethylation (H3K27me3). Loss-of-function mutants of PRC1 and PRC2 complex members have uncovered distinct as well as redundant functional roles for these proteins. Loss of PRC2 activity results in early embryonic lethality in mice, whereas PRC1 loss is associated with later developmental phenotypes, possibly owing to redundancy (Surface *et al*, 2010). Embryonic lethality phenotypes, however, make it difficult to study the contribution of the Polycomb group to normal development.

Posfai *et al* (2012) take a step backward and rewind into the oocyte to study whether the PRC1 complex is important during oogenesis by deleting key components of PRC1, Rnf2 and Ring1 in growing mouse oocytes. The double mutants show an upregulation of developmental and differentiation-inducing genes in the oocyte and zygote (see Figure 1). A previous study by the same group demonstrated that sperm chromatin contains histones enriched for PRC2-dependent H3K27me3, on developmental genes as well (Brykczynska *et al*, 2010). Therefore, the polycomb complex likely safeguards developmental and differentiation-inducing genes in the sperm as well as in the oocyte from being expressed early in the zygote. This points towards Polycomb's role as a central epigenetic factor in creating a chromatin state that favours totipotency at the onset of embryonic development.

Posfai *et al* (2012) also explored the role of PRC1 by nuclear transfer and metaphase-II chromosome swap experiments in the oocyte, which showed that the cytoplasm of PRC1 double, mutant oocytes fails to support proper embryonic development. Loss of PRC1 severely impairs ZGA and abrogates cell cycle progression, resulting in the arrest of embryos at the two-cell stage (see Figure 1). Rnf2 and Ring1 appear to play redundant functions during oogenesis, thereby mutually reinforcing a tight control over the chromatin state and consequently over the cytoplasmic composition of an oocyte. Whether the phenotype may be attributed to misregulation of specific PRC1 target genes and whether DNA methylation is compromised in the mutants need to be addressed in future work. This study importantly marks Polycomb as a key component in defining the maternal toolkit of inheritance.

Conflict of interest

The authors declare that they have no conflict of interest.

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