

Maternal control of early mouse development

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Summary

The hiatus between oocyte and embryonic gene transcription dictates a role for stored maternal factors in early mammalian development. Encoded by maternal-effect genes, these factors accumulate during oogenesis and enable the activation of the embryonic genome, the subsequent cleavage stages of embryogenesis and the initial establishment of embryonic cell lineages. Recent studies in mice have yielded new findings on the role of maternally provided proteins and multi-component complexes in preimplantation development. Nevertheless, significant gaps remain in our mechanistic understanding of the networks that regulate early mammalian embryogenesis, which provide an impetus and opportunities for future investigations.

Key words: Maternal-effect genes, *Mater* (*Nlrp5*), *Floped* (*Ooep*), *Padi6*, *Tle6*, *Filia*, Embryonic cell lineage, Cleavage-stage arrest, Embryonic gene activation, Preimplantation development, Subcortical maternal complex

Introduction

Mammalian gametes share an unequal burden in ensuring the successful initiation of development. Following acrosome exocytosis and penetration of the zona pellucida (see Glossary, Box 1), the mouse sperm fuses with the plasma membrane of the egg and is incorporated into the cytoplasm. The haploid sperm provides DNA for the male pronucleus and is essential for egg activation (Saunders et al., 2002). However, the sperm mitochondria (Shitara et al., 1998), the microtubule-organizing center (MTOC) precursors (Schatten et al., 1985) and the stored cellular components of the sperm play no major role in cleavage-stage embryogenesis (Sutovsky and Schatten, 2000). Thus, the early embryo is almost entirely dependent on the egg for its initial complement of the subcellular organelles and macromolecules that are required for survival prior to the robust activation of the embryonic genome at cleavage-stage development (Fig. 1A). These maternal components are encoded by maternal-effect genes.

Maternal-effect genes are transcribed during oogenesis and, by definition, mutant embryonic phenotypes reflect the genotype of the mother rather than that of the offspring. Some maternal-effect genes are expressed only in female gametes, but others are also expressed after activation of the embryonic genome, which complicates differentiating maternal from embryonic effects.

Maternal-effect genes were first described in *Drosophila* and included *dorsal* (Nusslein-Volhard et al., 1980), *bicoid* (Frohnhöfer and Nusslein-Volhard, 1986) and *torso* (Schupbach and Wieschaus, 1986). These early pioneering investigations (St Johnston and

Nusslein-Volhard, 1992) were extended to other model organisms (Morisato and Anderson, 1995; Bowerman, 1998; Dosch et al., 2004; Heasman, 2006), but maternal-effect genes were not described in mammals until 2000 (Christians et al., 2000; Tong et al., 2000).

After fertilization, one of the first roles of maternal factors is the processing of the male genome, which is necessary for its participation in embryogenesis. A second role is the removal of maternal detritus (RNA and protein), and a third is the robust activation of the embryonic genome, which is essential for the development of the embryo beyond two cells. A common phenotype among mouse embryos with mutations in maternal-effect genes is arrested progression during cleavage-stage embryogenesis, which indicates that the transcription and translation of embryonic genes is required to replenish depleted (or degraded) maternal stores of factors involved in cyclical biological processes. However, if maternal genes impose epigenetic marks that are stably inherited (e.g. DNA methylation) or modify structures important for development (e.g. maternal sterile mutants), these maternal effects might become manifest only at later developmental stages. Targeted mutagenesis experiments in mice have provided researchers with a wealth of insight into candidate maternal factors that participate in the regulation of these essential early steps of development.

In this review, we discuss the roles of known maternal-effect genes in early mouse development. The genes were initially discovered serendipitously (Christians et al., 2000; Tong et al., 2000) or through homology with those in other model organisms (Burns et al., 2003; Giraldez et al., 2005). However, the more systematic transcriptome profiling of growing oocytes has begun to identify new candidate factors (Hamatani et al., 2004a; Evsikov et al., 2006). In particular, the categorization of downstream targets of oocyte-specific transcription factors has provided a rich source of additional candidate maternal-effect genes (Joshi et al., 2007). More recently, the repertoire of maternal-effect genes has been further expanded to include multi-protein complexes that have crucial roles in mouse preimplantation development (Li et al., 2008a; Zheng and Dean, 2009). Although the current number of maternal-effect genes in mice is modest (Table 1), we believe that this number is likely to increase dramatically in the near future.

From egg to embryo

During intraovarian growth, the diameter of mouse oocytes increases from ~10 µm to 80 µm, with a concomitant ~500-fold increase in volume. The maternal genome is transcribed and transcripts accumulate (~100 pg) until oocytes reach a diameter of ~65 µm (De Leon et al., 1983). Most transcripts are translated directly into proteins, many of which have been cataloged in proteomic screens (Latham et al., 1991; Vitale et al., 2007). Some transcripts, however, remain dormant, and become activated later in oogenesis by carefully orchestrated polyadenylation (Racki and Richter, 2006). Within 24 hours of fertilization, male and female pronuclei replicate their DNA in the 1-cell zygote and then their chromosomes congress at syngamy (see Glossary, Box 1) prior to mitosis, cytokinesis and formation of the 2-cell embryo.

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Box 1. Glossary

Acrosome. A Golgi-derived subcellular organelle underlying the head of mature sperm. Initial sperm-egg recognition triggers exocytosis of lytic enzymes, the functions of which remain enigmatic.

Ampulla. The portion of the oviduct closest to the ovary and site of fertilization.

Autoimmune oophoritis. A T-cell-mediated inflammation of ovaries induced in C57BL/6 thymectomized mice and a fortuitous source of antibodies that recognize MATER.

Blastocyst. A ≥ 32 -cell embryo with a developing fluid-filled internal blastocoel.

Cleavage-stage embryogenesis. The first three cell divisions of embryonic development prior to compaction to form the morula.

Compaction. After the third cell division, blastomeres increase cell surface contacts with one another to form the morula, with morphologically obscured cell-cell contacts.

Embryonic gene activation. When the embryonic genome initiates transcription at the 1- to 2-cell stage and becomes the primary regulator of development.

Equatorial cleavage. When the plane of cytoplasmic cleavage passes orthogonal to the egg axis (i.e. at right angles to meridional cleavage).

Genomic imprinting. The process whereby a gene or genomic domain is biochemically marked (usually by DNA methylation) with information about its parental origin.

Imprinting control region (ICR). A region of DNA with sexually dimorphic methylation that directs silencing of gene clusters on the maternal or paternal allele to ensure monoallelic expression of a locus.

Inner cell mass (ICM). The ICM is derived from the inner cells of the morula and is eccentrically located in the blastocysts. It provides precursor cells for the developing fetus.

Meridional cleavage. When the plane of cytoplasmic cleavage passes through the animal and vegetal pole of the egg.

Morula. A compacted 8- to 16-cell epithelialized embryo with polarized outer cells and non-polar inner cells, which are precursors of the placenta and fetus, respectively.

Parthenogenesis. Preimplantation development without fertilization by a male.

Preimplantation development. Embryonic development between fertilization and implantation of the blastocyst into the wall of the uterus.

Pseudopregnant. A physiological state characterized by uterine receptivity for embryo implantation following copulation with sterile males.

Regulative development. The ability of the early embryo to adjust to, or substitute for, loss of individual cells.

Subcortical maternal complex (SCMC). The SCMC forms during oogenesis and is required for cleavage-stage mouse development.

Syngamy. When male and female haploid pronuclei approximate one another after fertilization. Their membranes interdigitate and breakdown and a metaphase plate forms on which chromosomes congress prior to cell division.

Trophectoderm. Precursor of the placenta; the polar trophectoderm is adjacent to the ICM and the mural trophectoderm lines the blastocoel cavity.

Zona pellucida. An extracellular matrix that surrounds the ovulated egg and dividing embryo prior to hatching at the time of implantation.

Zygote. The 1-cell embryo resulting from fertilization of an ovulated egg by a spermatozoon.

Minor activation of the embryonic genome occurs in the male pronucleus of the 1-cell embryo (Nothias et al., 1996), but the two major waves of activation are observed first at the 2-cell stage and then at the 4- to 8-cell transition (Carter et al., 2003; Wang et al.,

2004; Hamatani et al., 2004a). The second and third embryonic divisions occur at ~ 12 -hour intervals, and the resultant blastomeres appear to be morphologically symmetric. However, prior to the next cell division, the 8-cell embryo undergoes a Ca^{2+} -mediated compaction to form the morula (see Glossary, Box 1; Fig. 1B), in which individual blastomeres greatly increase their area of cell-cell contact (Ziomek and Johnson, 1980). Subsequent asymmetric cell divisions result in two distinct cell populations: 'inner' cells that form the embryonic ectoderm/endoderm inner cell mass (ICM); and 'outer' cells, which contribute progeny to the trophectoderm, the precursor of the placenta (Fig. 1B) (Tarkowski and Wroblewska, 1967; Johnson and Ziomek, 1981). The establishment of these two cell fates involves homotypic interactions between maternal stores of E-cadherin along the basolateral membranes; this maternal E-cadherin interacts with subcortical elements of the cytoskeleton (De Vries et al., 2004). In contrast to the flattening of these cell-cell contacts, the apical subcortical region remains rich in microvilli, forming a polar domain that persists in outer cells as preimplantation development progresses (Reeve and Ziomek, 1981).

Thus, following compaction, the embryo becomes an epithelialized sphere with distinct polarization of individual blastomeres and two cell populations. The formation of adhesion complexes (adherens, gap and tight junctions) between outer cells enables the directional translocation of ions via basolateral Na^+/K^+ -ATPase into the embryonic interior. The concomitant passage of water forms a fluid-filled blastocoel at the 32-cell stage that defines the early blastocyst (Fig. 1B), and at embryonic day 4.5 (E4.5) the fully formed blastocyst implants into the wall of the uterus (Madan et al., 2007; Wang et al., 2008). Early embryonic development is regulative (see Glossary, Box 1) and cells derived from blastomeres prior to compaction can participate in all tissues of the adult (Tarkowski, 1959; Rossant, 1976). However, such plasticity does not preclude the existence of differences among embryonic cells during early cleavage stages, although there is controversy as to their effects on subsequent embryonic polarity (Rossant and Tam, 2009).

Maternal RNA and protein degradation

During meiotic maturation in the ~ 12 hours prior to ovulation, mouse oocytes become transcriptionally quiescent and the majority of their polyadenylated RNA disappears (Clegg and Piko, 1983; De Leon et al., 1983) (Fig. 2). Although the mechanisms responsible for this RNA degradation are incompletely understood, small, non-coding RNAs have been implicated in this process (Giraldez et al., 2006). Normally, small RNAs, such as microRNAs (miRNAs) and small interfering RNAs (siRNAs), are loaded into an RNA-induced silencing complex (RISC), which contains Argonaute proteins. miRNAs or siRNAs then target the RISC to specific mRNAs, which are cleaved or translationally repressed. Loss of maternal DICER (DICER1) (Table 1), an endonuclease that cleaves small RNA precursors into mature miRNAs and siRNAs, impairs the completion of meiosis in mouse oocytes (Murchison et al., 2007; Tang et al., 2007), as does the loss of argonaute 2 (*Ago2*; *Eif2c2*), which encodes a catalytically active RNase (Kaneda et al., 2009). Depletion, rather than complete loss of maternal argonaute 2, disrupts gene expression and 2-cell embryos fail to progress to blastocysts (Lykke-Andersen et al., 2008). In a second RNA degradation pathway, a family of CCH tandem zinc-finger proteins has been implicated in destabilizing somatic mRNAs by binding to their 3' untranslated region (Lai et al., 2000). Genetically altered mice with a truncated form of ZFP36L2 (zinc-finger protein 36,

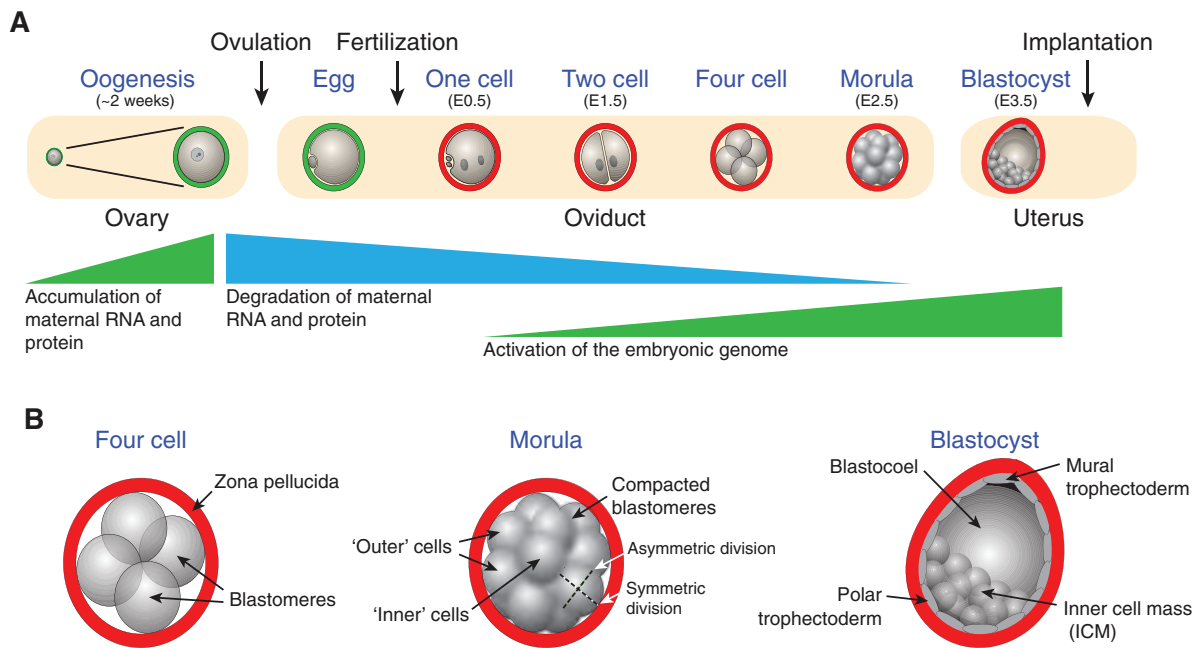


Fig. 1. Preimplantation mouse development. (A) Oogenesis and early development. Maternal RNA and proteins accumulate within individual oocytes during a ~2 week growth phase, but many are degraded during meiotic maturation and ovulation. The zona pellucida surrounds growing oocytes and ovulated eggs (green) and is modified following fertilization (red) to prevent polyspermy and to protect the embryo as it passes through the oviduct. At embryonic day 0.5 (E0.5), 1-cell embryos can be recovered from the oviduct and, by the 2-cell stage (E1.5), there is robust embryonic genome activation. Following the third cell division, embryos undergo a Ca^{2+} -mediated compaction to form morulae (E2.5), and develop a fluid-filled blastocoel cavity from the 32-cell stage to become blastocysts (E3.5) that implant in the uterus wall (E4.5). (B) Late preimplantation development. At four cells, blastomeres with distinct cell boundaries are encased within the protective confines of the zona pellucida. Individual cells remain pluripotent. Following the 8-cell stage, the embryo compacts to form the morula, with increased cell contact that morphologically obscures cell boundaries. Symmetric cell divisions result in similar daughter cells. Asymmetric divisions provide topologically distinct outer cells, which are trophectoderm precursors (forming the placenta), and inner cells, which establish the inner cell mass (ICM) of the fetus. Blastocoel formation defines the blastocyst, and the eccentric localization of the ICM localizes the polar and mural trophectoderm, the latter of which initiates uterine implantation.

C3H type-like 2) do not progress beyond cleavage-stage embryogenesis, although the mechanism of this block remains unknown (Table 1) (Ramos et al., 2004). These mutations do not completely account for the loss of maternal transcripts and it is thus likely that additional pathways are required for the effective degradation of maternal RNA.

Maternal proteins also are degraded early in development (Fig. 2), some by ubiquitin-proteasome pathways (Suzumori et al., 2003; Roest et al., 2004), others by macroautophagy, which involves a cellular program in which superfluous proteins and organelles are rapidly captured in a double-membrane vesicle (autophagosome) for fusion with lysosomes and subsequent degradation. A complex of ATG12-ATG5-ATG16 proteins decorates the outer surface of the developing autophagosome and is recycled into the cytosol for future use (Xie and Klionsky, 2007; Melendez and Neufeld, 2008). Oocyte-specific conditional mutation of *Atg5* has a dramatic effect on early embryogenesis, and *Atg5* mutant mouse embryos do not progress beyond the 4- to 8-cell stage of development (Table 1) (Tsukamoto et al., 2008). Presumably, without the degradation of maternal RNA and proteins, embryonic developmental programs cannot be activated. However, this degradation must have some selectivity (Alizadeh et al., 2005; Su et al., 2007) so as to maintain the maternal factors that are required to bridge the interregnum between the maternal and embryonic control of development.

Chromatin remodeling

During gametogenesis, the haploid male and female genomes are packaged with protamines and histones, respectively. After fertilization, the male genome undergoes decondensation and is repackaged with maternal histones, a process that incurs DNA breaks that must be repaired (Derijck et al., 2006). HR6A (official symbol UBE2A, ubiquitin-conjugating enzyme E2A, RAD6 homolog) has been implicated in DNA repair and histone modification, and mice lacking this protein ovulate eggs that can be fertilized but that arrest at the 2-cell stage (Table 1) (Roest et al., 2004). However, the molecular basis for this early block remains to be determined. Although implicated in decondensation of the male pronucleus in *Xenopus* eggs (Philpott et al., 1991), the absence of nucleoplasmin (encoded by *Npm2*) does not result in a similar phenotype in mice. Instead, abnormalities in histone acetylation and in heterochromatin formation in oocytes and in early embryos derived from *Npm2*-null females are associated with decreased fecundity (Table 1) (Burns et al., 2003).

Once packaged with histones, each haploid genome forms a pronucleus and undergoes DNA replication. At this point of development, low levels of transcription are observed, which are higher in the male than in the female pronucleus. The histones that form the male pronucleus are hyperacetylated compared with those associated with the female genome (Adenot et al., 1997), and the male DNA is hypomethylated (Santos et al., 2002). Either of these

Table 1. Maternal-effect genes in preimplantation development in mice

Gene (official symbol)	Protein	Domains and motifs (Pfam)	Human homolog	Null/RNAi
Degrades maternal factors				
<i>Dicer1</i>	Dicer1	DNA/RNA helicase DEAD/DEAH N; PAZ; DNA/RNA helicase C; Dicer dsRNA-binding fold; RNase III	<i>DICER1</i>	Murchison et al., 2007
<i>Ago2 (Eif2c2)</i>	Eukaryotic translation initiation factor 2C, 2	DUF1785; PAZ; Piwi	<i>EIF2C2</i>	Lykke-Andersen et al., 2008
<i>Zfp36l2</i>	Zinc-finger protein 36, C3H type-like 2	Tis11B N; Znf CCCH	<i>ZFP36L2</i>	Ramos et al., 2004
<i>Atg5</i>	Autophagy-related 5	Autophagy protein 5	<i>ATG5</i>	Tsukamoto et al., 2008
Chromatin remodelling				
<i>Hr6a (Ube2a)</i>	Ubiquitin-conjugating enzyme E2A, RAD6 homolog	UBQ-conjugat E2	<i>UBE2A</i>	Roest et al., 2004
<i>Npm2</i>	Nucleoplasmin 2	Nucleoplasmin	<i>NPM2</i>	Burns et al., 2003
<i>Tif1α (Trim24)</i>	Tripartite motif-containing 24	Znf C3HC4 RING-type; Znf B-box; Znf PHD-finger; Bromodomain	<i>TRIM24</i>	Torres-Padilla and Zernicka-Goetz, 2006
<i>Brg1 (Smarca4)</i>	SWI/SNF related, matrix associated actin-dependent regulator of chromatin subfamily a, member 4	Gln-Leu-Gln QLQ; HAS; BRK domain; Restrict endonuc I R/III Res; SNF2 N; DNA/RNA helicase C; Bromodomain	<i>SMARCA4</i>	Bultman et al., 2006
<i>Brwd1</i>	Bromodomain and WD repeat domain containing 1	WD40 repeat sg; Bromodomain	<i>BRWD1</i>	Philipps et al., 2008
Transcription factors				
<i>Hsf1</i>	Heat shock factor 1	HSF DNA bd; Vert HS TF	<i>HSF1</i>	Christians et al., 2000
<i>Bnc1</i>	Basonuclin 1	Znf C2H2	<i>BNC1</i>	Ma et al., 2006
<i>Ctcf</i>	CCCTC-binding factor	Znf C2H2; AT hook DNA-bd CS	<i>CTCF</i>	Wan et al., 2008
<i>Oct4 (Pou5f1)</i>	POU domain, class 5, transcription factor 1	POU specific; Homeobox	<i>POU5F1</i>	Foygel et al., 2008
<i>Sox2</i>	SRY-box containing gene 2	HMG HMG1/HMG2	<i>SOX2</i>	Avilion et al., 2003
De novo DNA methylation				
<i>Dnmt3a</i>	DNA methyltransferase 3-a	PWWP; C5 DNA methylation	<i>DNMT3A</i>	Kaneda et al., 2004
<i>Dnmt3l</i>	DNA methyltransferase 3-like	No significant matches	<i>DNMT3L</i>	Bourc'his et al., 2001
DNA methylation maintenance				
<i>Dnmt1</i>	DNA methyltransferase 1	DMAP1 bd; Znf CXXC; BAH; C5 DNA methylation	<i>DNMT1</i>	Howell et al., 2001; Hirasawa et al., 2008
<i>Stella (Dppa3)</i>	Developmental pluripotency-associated 3	No significant matches	<i>DPPA3</i>	Payer et al., 2003
<i>Zfp57</i>	Zinc-finger protein 57	Krüppel-associated box; Znf C2H2	<i>ZFP57</i>	Li et al., 2008b
Preimplantation development				
<i>Zar1</i>	Zygote arrest 1	No significant matches	<i>ZAR1</i>	Wu et al., 2003
<i>Mater (Nlrp5)</i>	Maternal antigen that embryos require	NACHT NTPase; Leu-rich repeat	<i>NLRP5</i>	Tong et al., 2000
<i>Floped (Ooep)</i>	Factor located in oocyte permitting development	Atypical KH	<i>OOEP</i>	Li et al., 2008a
<i>Padi6</i>	Peptidyl arginine deiminase (PAD), type VI	PAD N; PAD central; PAD C	<i>PADI6</i>	Esposito et al., 2007
<i>Tle6</i>	Transducin-like enhancer of split 6	WD40 repeat	<i>TLE6</i>	
<i>Filia (2410004A20Rik)</i>	Filia	No significant matches	<i>FILIA</i>	Zheng and Dean, 2009
<i>Tcl1</i>	T-cell lymphoma breakpoint 1	TCL1 MTCP1	<i>TCL1</i>	Narducci et al., 2002
<i>Uchl1</i>	Ubiquitin carboxyl-terminal hydrolase L1	Peptidase C12	<i>UCHL1</i>	Sekiguchi et al., 2006

bd, binding domain; C, C-terminal; CS, consensus sequence; dsRNA, double-stranded RNA; KH, K homology; MTCP1, mature T-cell proliferation 1; N, N-terminal; NTPase, nucleoside triphosphate hydrolase; Restrict endonuc, restriction endonuclease; sg, subgroup; TF, transcription factor; UBQ-conjugat, ubiquitin-conjugating; vert, vertebrate; Znf, zinc-finger.

epigenetic modifications could provide greater access to the genome for activators of transcription in the male pronucleus, although it is not clear whether the presence of the modified histones is causative or reflective of transcription. At syngamy, the male and female pronuclei approximate one another, their nuclear membranes break

down, and MTOCs form a barrel-shaped mitotic spindle on which chromosomes congress prior to the first mitotic division (Fig. 2A) (Zamboni et al., 1972; Schatten et al., 1986). Despite early transcription in the 1-cell zygote, little de novo embryonic protein synthesis is observed prior to the 2-cell embryo (Flach et al., 1982;

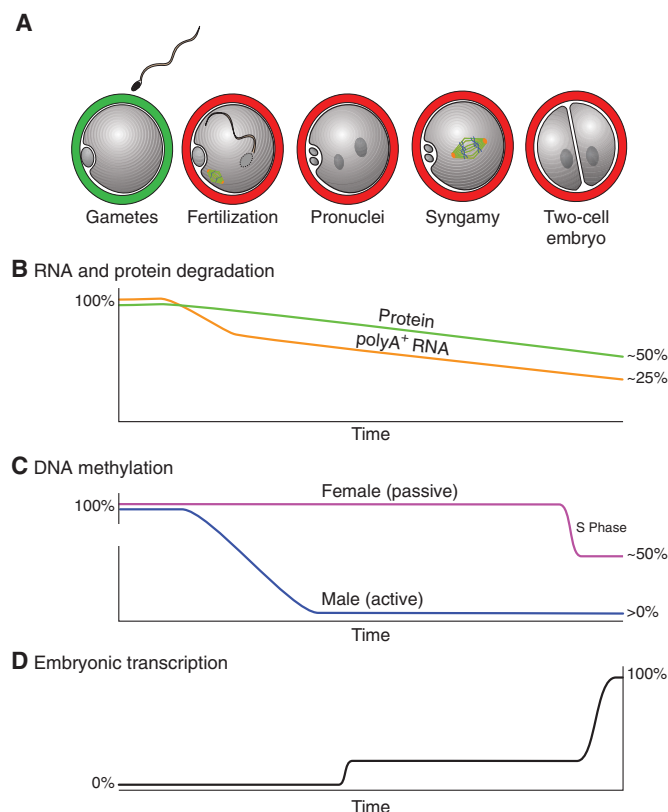


Fig. 2. Molecular changes initiate development. (A) The onset of mouse development. Transcriptionally inert gametes fuse at fertilization and the entire sperm is incorporated into the cytoplasm. The sperm nucleus is decondensed and repackaged with egg-stored histones to form the male pronucleus. The egg completes its second meiotic division and forms the female pronuclei. After syngamy and chromosome congression, cytokinesis establishes the 2-cell embryo. (B) RNA and protein degradation. Maternal stores of RNA and protein are required for cleavage-stage development, but these stores are degraded over time, leaving ~25% of maternal polyA⁺ RNA and ~50% of maternal proteins in the 2-cell embryo (Merz et al., 1981; Clegg and Piko, 1983; De Leon et al., 1983). (C) Demethylation of the embryonic genome. After fertilization, the male genome is actively demethylated prior to DNA replication and male pronucleus formation. By contrast, the female genome undergoes passive demethylation with each cell division (beginning with the first), resulting in cleavage-stage embryos with hypomethylated DNA, except at imprinting control regions (see Glossary, Box 1) (Reik et al., 2001). (D) Embryonic gene activation. Following a minor activation of transcription at the pronuclear stage (more in the male than the female pronucleus), embryonic transcription is robustly activated at the 2-cell stage.

Howlett and Bolton, 1985). *Zar1* (zygote arrest 1) encodes an oocyte-specific cytoplasmic protein of unknown function, and its absence in genetically ablated females affects pronuclear syngamy, a process that is crucial for the progression of the embryo beyond the 1-cell stage (Table 1) (Wu et al., 2003). The molecular signals that activate the transcription of specific embryonic genes remain unknown, and only a few factors that have a global effect on gene activation this early on in development have been identified. These include TIF1 α (transcription intermediary factor 1, alpha; official symbol TRIM24), which translocates from the cytoplasm to the pronuclei and modulates the first wave of activation of the embryonic genome (Table 1) (Torres-Padilla and Zernicka-Goetz, 2006).

Robust activation of embryonic gene expression requires chromatin remodeling, during which well-defined clusters of proteins use the energy of ATP hydrolysis to restructure or move nucleosome constraints to transcription. Four conserved protein families have been described that have specialized functions in this process (Clapier and Cairns, 2009): SWI/SNF (switching defective/sucrose non-fermenting, first described in yeast); ISWI (imitation switch, first described in *Drosophila*); CHD (chromodomain, helicase, DNA binding, first described in *Xenopus*); and INO80 (inositol requiring 80, first described in yeast). Mouse *Brg1* (official symbol *Smarca4*, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4) encodes a component of the SWI/SNF remodeling complex and is required for full activation of the embryonic genome, without which embryos arrest at the 2- to 4-cell stage (Table 1) (Bultman et al., 2006). BRWD1 (bromodomain and WD repeat domain containing 1) interacts with BRG1, and, in its absence, oocytes exhibit defects in meiosis and progress poorly beyond pronuclear formation following fertilization (Table 1) (Philippis et al., 2008). It is likely that other remodeling families play essential roles in the activation of the embryonic genome, but conditional oocyte-specific mutations coupled with genome-wide screens to detect affected genes will be required to dissect out their maternal effects in early development.

Embryonic gene activation

After remodeling, the embryonic genome becomes accessible to activation by transcription factors. Heat shock factor 1 (HSF1), a master regulator of stress-inducible genes, is highly expressed in mouse oocytes. Although its expression is not limited to oocytes, *Hsf1*-null females have defects in meiosis (Metchat et al., 2009), and embryos derived from their ovulated eggs arrest, primarily at the 1-cell stage (Table 1) (Christians et al., 2000). Two zinc-finger transcription factors are also required for early embryogenesis. The first is basonuclin 1 (encoded by *Bnc1*), which is abundant in keratinocytes and germ cells and affects RNA polymerase I- and II-mediated transcription. Its depletion in mouse oocytes is associated with defects in oogenesis, fertilization and cleavage-stage embryogenesis, leading to decreased fecundity (Table 1) (Ma et al., 2006). A second zinc-finger DNA-binding protein, CCCTC-binding factor (CTCF), is ubiquitously expressed in mice. It has well-reported roles in genetic and epigenetic regulation (Filippova, 2008), including in X chromosome inactivation in embryonic stem (ES) cells via its interactions with the pluripotency transcription factor OCT4 (POU5F1) (Donohoe et al., 2009). Maternal depletion of CTCF results in widespread defects in meiosis, maternal transcription and preimplantation development (Table 1) (Wan et al., 2008).

Following fertilization, the zygote, derived from two terminally differentiated gametes, is endowed with totipotency through the reprogramming of its DNA. The pluripotency transcription factor OCT4 is expressed during oogenesis and its mRNA persists in 1- and 2-cell embryos. It has recently been reported that depletion of *Oct4* mRNA at the 1-cell stage causes embryonic arrest during cleavage-stage development. The data suggest that maternal OCT4 both facilitates zygotic genome activation and enhances maternal RNA degradation, including that of *Zar1* and *Nobox*, two known oocyte-specific transcription factors (Table 1) (Foygel et al., 2008). Another pluripotency transcription factor, SOX2, is also abundantly expressed in oocytes, where it is sequestered in the cytoplasm, presumably to prevent activation of gene targets. Maternal SOX2 translocates to the nucleus of 2-cell embryos, where it remains in the

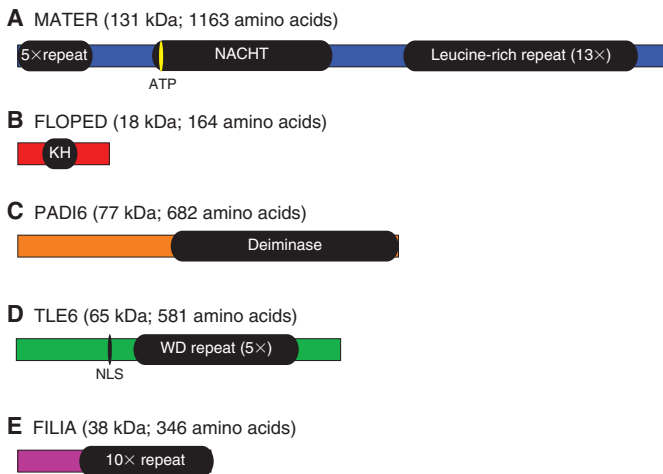


Fig. 3. Proteins of the subcortical maternal complex (SCMC).

(A) MATER is the largest protein in the complex and has a novel 5× N-terminal repeat, a NACHT domain (<http://pfam.sanger.ac.uk/>) and a 13× leucine-rich repeat that is implicated in protein-protein interactions. (B) FLOPED is the smallest SCMC protein and contains a single, atypical KH domain. (C) PADI6 is an enzyme that converts arginine to citrulline; its specific substrates have yet to be identified in the early embryo. (D) TLE6 is a member of the Groucho co-repressor family that is unique to mammals and lacks the N-terminal Q domain found in other members. NLS, nuclear localization signal. (E) FILIA binds to MATER, but not to FLOPED or TLE6. For a summary of null phenotypes, see Table 2. These proteins are encoded by: *Filia*, official symbol 2410004A20Rik; *Floped*, factor located in oocytes permitting embryonic development, official symbol *Ooep*; *Mater*, maternal antigen that embryos require, official symbol *Nlrp5*; *Padi6*, peptidylarginine deiminase 6; *Tle6*, transducin-like enhancer of split 6.

cells of the ICM, but redistributes to the cytoplasm of trophectodermal cells, where, again, it is sequestered from the nucleus. Its embryonic expression is not detected until the morula stage (Fig. 1A), and *Sox2*-null embryos do not survive past early implantation (Table 1) (Avilion et al., 2003). It seems likely that maternal SOX2 has an effect on the early embryo, which could be investigated in greater detail using conditional mutant mice that lack maternal SOX2.

The subcortical maternal complex

Beyond the effect of individual maternal proteins, a subcortical maternal complex (SCMC) has been described that is essential for embryonic progression past the 2-cell stage (Table 1) (Fig. 3). The founding member of this complex is encoded by *Mater* (maternal antigen that embryos require; official symbol *Nlrp5*), which was

originally characterized as an antigen associated with a mouse model of autoimmune oophoritis (see Glossary, Box 1) (Tong and Nelson, 1999). Additional members of the complex are encoded by *Floped* (factor located in oocytes permitting embryonic development; official symbol *Ooep*) (Pierre et al., 2007; Herr et al., 2008; Li et al., 2008a), *Tle6* (transducin-like enhancer of split 6) (Li et al., 2008a) and *Filia* (RIKEN cDNA 2410004A20) (Ohsugi et al., 2008). The interactions of these proteins, which co-localize in the subcortex as seen by confocal microscopy, have been confirmed by co-expression of Myc- or HA-tagged recombinant proteins in heterologous cell lines and by co-immunoprecipitation (Ohsugi et al., 2008; Li et al., 2008a). Based on its subcortical localization in the oocyte/embryo and on its null phenotype (see below), *Padi6* (peptidylarginine deiminase 6) might also encode a protein that participates in the SCMC (Yurttas et al., 2008).

The absence of MATER, FLOPED, PADI6 or FILIA following genetic ablation in mice does not affect intraovarian follicle formation or germ cell development. Adult male and female *Mater*- and *Floped*-null animals appear normal, but the absence of either protein precludes the formation of the SCMC. Male mice are fertile, but females produce no offspring. Ovulated eggs can be fertilized, but embryos progress poorly past the first cell division and perish prior to implantation. This phenotype is not rescued by normal males, and neither *Mater* nor *Floped* is expressed from the embryonic genome (Tong et al., 2000; Li et al., 2008a). A similar phenotype is observed in embryos derived from *Padi6*-null females, which lack the cytoplasmic lattices in eggs that are thought to store maternal ribosomes for the early embryo (Yurttas et al., 2008). In the absence of these lattices, embryos derived from *Padi6*-null females do not develop significantly past the 2-cell stage (Esposito et al., 2007). Although defects in embryonic transcription are observed in embryos derived from *Mater*- and *Padi6*-null females, the severity of the embryonic lethal phenotype makes it difficult to determine whether these metabolic abnormalities are causative or reflective of impending cell death (Table 2).

Environmental effects

Environmental perturbations also arrest embryogenesis at the 2-cell stage. α -Amanitin is a mushroom toxin that binds to RNA polymerase II and blocks elongation of transcription (Vaisius and Wieland, 1982). Exposure of late 1-cell zygotes to doses of this toxin that inhibit RNA polymerase II (Flach et al., 1982; Vaisius and Wieland, 1982) induce arrest at the 2-cell stage (Warner and Versteegh, 1974). In addition, embryonic cytoplasmic components appear to play a role in making 2-cell embryos competent to complete embryonic cleavage. For example, in vitro development from the 1-cell to the blastocyst stage is restricted in certain inbred mouse strains and F1 hybrids (Shire and Whitten, 1980). In some strains, the 1-cell embryo becomes arrested at the 2-cell stage, which has been termed the ‘in vitro 2-cell block’ (Whittingham and

Table 2. Null phenotypes of subcortical maternal complex (SCMC) components

Gene	SCMC	Development	Phenotype	References
<i>Mater</i>	Absent	2-cell arrest, sterile	Decreased transcription, translation	Tong et al., 2000
<i>Floped</i>	Absent	2-cell arrest, sterile	Delayed cell cycle progression, abnormal cleavage	Li et al., 2008a
<i>Padi6</i> *	ND	2-cell arrest, sterile	Decreased transcription, translation, absent cytoplasmic lattices	Esposito et al., 2007
<i>Filia</i>	Present	Delayed embryonic progression, decreased fecundity	Aneuploidy, abnormal spindles and spindle regulators, defective SAC	Zheng and Dean, 2009

ND, not determined.

SAC, spindle assembly checkpoint.

*Not a proven participant in SCMC.

Biggers, 1967). This block can be surmounted by injecting small amounts of cytoplasm from embryos that do not exhibit this block (Muggleton-Harris et al., 1982). This rescue occurs independently of the presence of maternal chromosomes, indicating the importance of stored, rather than newly synthesized, components (Zanoni et al., 2009). It has been suggested that in some types of clinical infertility, the transfer of donor ooplasm into human eggs might permit successful embryonic development (Cohen et al., 1997). However, the specific maternally provided cytoplasmic proteins that control embryonic development have not been identified. The in vitro 2-cell block in mice can also be circumvented by modifications to the culture conditions (Lawitts and Biggers, 1993), which has implications for human in vitro fertilization, in which embryos are cultured prior to transfer to recipients.

Most maternal effects are observed early in mouse development, which reflects the rapid degradation of the encoded products in the absence of compensatory expression from the inactive embryonic genome. Although progress has been made, there remains a significant shortfall in the number of maternal-effect genes that have been identified and characterized (Table 1) and a gap in our knowledge of the transcriptome of mouse oocytes (Hamatani et al., 2004b; Evsikov et al., 2006). It is likely that the combined approaches of biochemistry, cell biology and more sophisticated genetics will help to define the interactions of these maternal proteins to provide a more inclusive picture of the regulatory networks that initiate the onset of mouse development.

Beyond two-cell embryogenesis

After activation of the embryonic genome, stored maternal factors play a smaller role in preimplantation development and a surprising number of degraded maternal proteins are replaced immediately by newly synthesized embryonic gene products (Hamatani et al., 2004a; Evsikov et al., 2006). However, the phenotype of mutations in some maternal-effect genes only becomes manifest later in development, including those genes required to impose epigenetic marks that are inherited by the progeny of early embryonic cells.

DNA methylation patterns

The haploid genomes of egg and sperm are methylated during gametogenesis. However, within hours of fertilization, the male pronucleus is actively demethylated, whereas female genes are passively demethylated during rounds of semiconservative DNA replication in the early embryo (Fig. 2). By the blastocyst stage, the bulk of embryonic DNA has been demethylated, except for the differentially methylated imprinting control regions (ICRs; see Glossary, Box 1) (Reik et al., 2001; Santos et al., 2002). Both a male and a female haploid genome are needed for successful embryogenesis, and parthenogenetically activated eggs do not progress beyond the blastocyst (McGrath and Solter, 1984; Barton et al., 1984). The major barrier to parthenogenesis (see Glossary, Box 1) appears to be the monoallelic expression that results from epigenetic modifications (primarily DNA methylation) of imprinted genes (Kono et al., 2004). To date, ~130 imprinted genes have been identified (http://www.har.mrc.ac.uk/research/genomic_imprinting). Those with monoallelic male expression would not be available to parthenotes.

Although epigenetic modifications to sperm chromatin may contribute to embryonic development (Hammoud et al., 2009), maternal factors have been proven to play crucial roles in regulating epigenetic marks. For example, during oogenesis de novo DNA methylation is accomplished by DNA methyltransferase 3A (DNMT3A) (Table 1) (Okano et al., 1999; Kaneda et al., 2004),

which forms a complex with the enzymatically inactive co-factor DNA cytosine-5-methyltransferase 3-like (DNMT3L) (Table 1) (Bourc'his et al., 2001). This complex is targeted by DNMT3L to the N-terminal tail of histone H3 (Kaneda et al., 2004), and the methylase modifies adjacent DNA to establish imprinted loci. The tethering of DNMT3A-DNMT3L to the tail of histone H3 depends on the methylation status of lysine 4 on this histone (H3K4) and is required for the de novo DNA methylation of differentially methylated regions (Ooi et al., 2007; Ciccone et al., 2009).

Maternal factors also maintain DNA imprints during preimplantation development, a process that is complicated by ongoing passive demethylation associated with the semiconservative DNA replication noted above. DNA methyltransferase (cytosine-5) 1 (DNMT1), which has oocyte- and somatic-specific isoforms, is both necessary and sufficient to ensure monoallelic expression of imprinted genes (Table 1) (Hirasawa et al., 2008). *Stella* (*Dppa3*, developmental pluripotency-associated 3) is an oocyte-specific maternal-effect gene that is required for early development (Table 1) (Payer et al., 2003; Bortvin et al., 2004). STELLA binds to Ran-binding protein 5 (RanBP5; importin 5, IPO5) and is transported into the nucleus, where it maintains methylation marks on most of the maternal genome (Table 1) (Nakamura et al., 2007). Another maternal-effect gene, *Zfp57* (zinc-finger protein 57), is not only required for the establishment of germline methylation, but also plays a broad role in maintaining maternal and paternal methylation patterns in early embryos (Table 1) (Li et al., 2008b).

Protein-enriched cell cortex

The subcortex of the egg and early dividing embryo contains a plethora of proteins important for early development. For example, maternal E-cadherin (encoded by *Cdh1*) is present in the cortex and is required for the adherence of early blastomeres. However, if the proximity of the blastomeres is assured by the zona pellucida, the dividing embryo can survive the absence of maternal E-cadherin and can undergo normal compaction at the morula stage because of the embryonic expression of paternal *Cdh1* (De Vries et al., 2004). As noted above, the absence of MATER or FLOPED prevents the formation of the SCMC (Table 2), another subcortical complex, and embryos do not progress beyond cleavage-stage embryogenesis (Li et al., 2008a). Although FILIA also participates in the SCMC, its absence in genetically ablated mice has a less catastrophic phenotype (Table 2). Importantly, the absence of FILIA does not preclude the subcortical localization of other components of the SCMC, and *Filia*-null female mice have a ~50% decrease in fecundity rather than sterility. Ovulated eggs from *Filia*-null mice are fertilized, but cell cycle progression is delayed by 6-8 hours during cleavage-stage embryogenesis. This more subtle phenotype provides mechanistic insight into the role of the SCMC in ensuring the fidelity of chromosome segregation during preimplantation mouse development. A relatively high rate of aneuploidy in embryos derived from *Filia*-null females implicates FILIA (and, by extension, the SCMC) in normal spindle formation via a RHOA signaling pathway and in maintaining the integrity of the spindle assembly checkpoint (Zheng and Dean, 2009).

Other maternal proteins become geographically polarized during preimplantation development, some as early as the 2-cell stage, such as T-cell leukemia/lymphoma 1 (TCL1) and ubiquitin carboxy-terminal hydrolase L1 (UCHL1). TCL1 shuttles between the cortex and nucleus in a cell cycle-dependent manner, and embryos derived from *Tcl1*-null females have delayed cleavage-stage progression with decreased fecundity (Table 1) (Narducci et al., 2002). TCL1 heterodimerizes with AKT (thymoma viral proto-oncogene 1,

AKT1; also known as protein kinase B, PKB), a serine/threonine kinase implicated in cell growth. Rather than activating AKT by phosphorylation, TCL1 promotes blastomere proliferation by translocating AKT to the nucleus of early blastomeres, although the targets of the kinase remain unknown (Fiorenza et al., 2008). UCHL1, which participates in the ubiquitin-proteasome pathway for protein degradation, is also expressed during oogenesis. It has a subcortical location and is excluded from cell-cell contacts, as occurs with the SCMC. Decreased fecundity is observed in mice lacking UCHL1, which might be partly due to increased rates of polyspermy, the basis of which remains unknown (Table 1) (Sekiguchi et al., 2006). Whether or not these proteins directly participate in the SCMC remains to be determined.

These results emphasize the participation of maternal proteins in maintaining the epigenetic marks that are necessary to prevent embryonic lethality and that are required to foster the progressive transition from maternal to embryonic control of development. The increasingly detailed characterization of interacting proteins in the subcortex and of the ability of components to shuttle to the nucleus might provide insight into protein networks, some of which might ensure the pluripotency of embryonic blastomeres.

Establishing embryonic cell lineages

Although gene products expressed after fertilization are key in establishing initial embryonic cell lineages (Rossant and Tam, 2009; Zernicka-Goetz et al., 2009), maternal factors may also play a role in this process. The 1-cell embryo normally divides into two totipotent blastomeres. These cells then divide sequentially, either parallel (meridional) or orthogonal (equatorial) to the initial cleavage plane of the 2-cell embryo (see Glossary, Box 1; Fig. 4). If parallel-oriented division occurs, the 4-cell embryo establishes a planar structure (~20%), whereas if orthogonal division occurs (~80%), a tetrahedron results (see Fig. 4) (Gardner, 2002). When the cleavage of the first dividing blastomere is meridional and the second is equatorial (or vice versa), the progeny of the early dividing blastomere will preferentially contribute to the embryonic axis of the blastocyst (Piotrowska-Nitsche et al., 2005). The vegetal blastomere that lies beneath the other three cells in the tetrahedron has an altered epigenetic mark on histone H3 (H3R26me) (Torres-Padilla et al., 2007), as well as increased levels of *Cdx2* mRNA (Jedrusik et al., 2008), which might contribute to a trophectodermal cell fate (Bischoff et al., 2008). The diminished level of cell-cell contact of the vegetal blastomere, coupled with the exclusion of the SCMC from such regions (see below), predicts a greater occupancy of the cortex by the SCMC, but its role in initial cell lineage establishment remains to be determined.

After compaction and formation of the morula, the SCMC segregates to the outer cells of the morula and blastocyst, where the complex is asymmetrically restricted to the apical cortex of the outer cells (Fig. 5B). The exclusion of the SCMC from cell-cell contact is reversed when blastomeres are separated (Ohsugi et al., 2008; Herr et al., 2008; Li et al., 2008a), which indicates that a dynamic equilibrium exists between a cytoplasmic pool of preassembled complex (or components of it) and the subcortical complex (Fig. 5). Cell division non-parallel to the apicobasal axis of the polarized blastomeres results in cell populations that are marked by the presence or absence of the SCMC. These observations are consistent with a model in which the early embryo differentially accumulates a maternally expressed protein complex in topologically distinct blastomeres. The progeny of those outer cells that contain the SCMC are known to preferentially form the trophectoderm, whereas those without the complex preferentially become the ICM of the

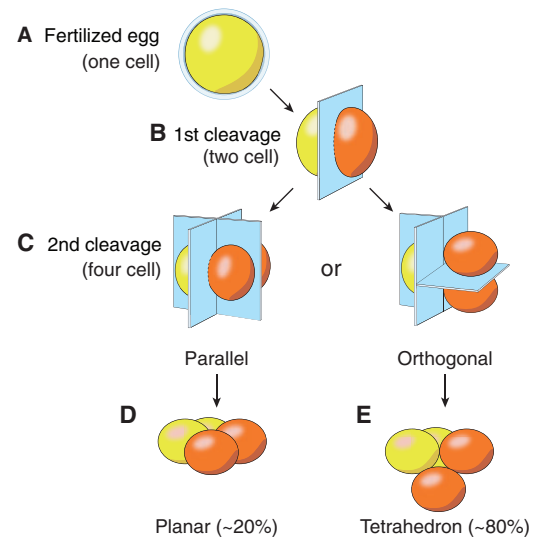


Fig. 4. Initial embryonic cleavages. (A,B) The first cleavage of the fertilized egg forms the symmetric 2-cell embryo, in which each blastomere (orange and red) remains totipotent. (C) The second embryonic cleavage occurs sequentially and can either be parallel to the first cleavage (left) or orthogonal to the first cleavage (right). (D) If the former occurs, the pluripotent blastomeres of the 4-cell embryo are present on a single plane. (E) Most commonly (~80%), however, orthogonal division occurs and the blastomeres form a tetrahedron.

blastocyst. One could envision a role for the SCMC in sequestering macromolecules that eventually trigger, either directly or indirectly, a commitment of the outer cell progeny to becoming trophoblasts (Johnson and McConnell, 2004). The localization of *Cdx2* transcripts in the periphery of outer cells (Jedrusik et al., 2008) and the observation that FLOPED binds to ribonucleotide homopolymers (Herr et al., 2008) are consistent with the complex having a role in sequestering RNA in outer cells to influence the subsequent pathways that direct cells into trophectoderm or ICM lineages.

In theory, initial cell lineages (trophectoderm versus ICM) could be set at the 2-cell stage, but by deferring this dichotomous fate choice until eight cells, the risk of embryonic lethality from the loss or damage of a single cell is substantially reduced. However, this requires pluripotency to be maintained in all cells during the first three cell divisions and for compensatory mechanisms to exist for the loss of a single blastomere. Following asymmetric cell division at the 8-cell stage, the absence of the SCMC in the inner cells may initiate developmental lineage decisions in the ICM. This formulation is consistent with models in which cell fate is determined by cleavage pattern and by the positions of blastomeres (or by the molecular determinants in them) in the embryo (Tarkowski and Wroblewska, 1967; Johnson and McConnell, 2004; Zernicka-Goetz et al., 2009). The ability of the SCMC to redistribute during cleavage-stage embryogenesis (Ohsugi et al., 2008; Herr et al., 2008; Li et al., 2008a) may play an important role in the regulative nature of early mammalian development, in which ablation of individual blastomeres need not prevent normal development (Tarkowski, 1959; Tsunoda and McLaren, 1983). The observation that some inner cells become outer cells with trophectoderm descendants after incubation with morulae (Ziomek and Johnson, 1982) might reflect the restoration of the SCMC (from cytoplasmic stores) in the absence of cell-cell contact, as observed

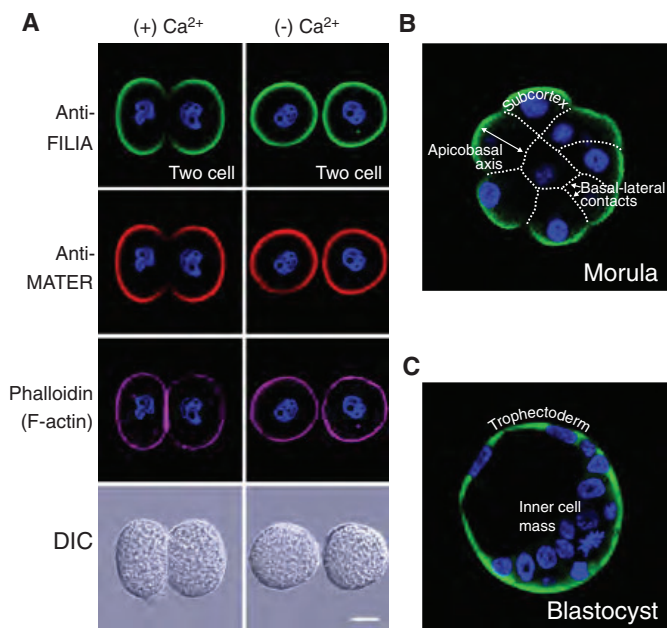


Fig. 5. Localization of the SCMC in the early mouse embryo.

(A) Exclusion from cell-cell contacts. Zona-pellucida-free 2-cell mouse embryos incubated in the presence (+) or absence (–) of calcium, and fixed, permeabilized and stained with antibodies to FILIA (green), MATER (red) or with phalloidin to stain F-actin (purple), prior to imaging by confocal microscopy or differential interference optics (DIC). The exclusion of the SCMC from regions of cell-cell contact of 2-cell embryos (left) is readily reversible upon disaggregation of the two blastomeres in the absence of calcium (right). Scale bar: 20 μ m. (B) Absence of SCMC from inner cells. Morula fixed, permeabilized and stained with antibody to FILIA prior to imaging by confocal microscopy. Dotted lines superimposed on the morula represent basal-lateral contacts of cell membranes. The SCMC (as defined by antibodies to FILIA) is located in the subcortex of outer cells that are polarized (apicobasal) and is not detected in the non-polarized inner cells of the morula. (C) Same as B, but showing a blastocyst. The restriction of the SCMC to the outer cells of the blastocyst provides a marker for trophoblast cells, which give rise to the placenta. The SCMC is excluded from the ICM. Modified, with permission, from Ohsugi et al. (Ohsugi et al., 2008).

after immunosurgery (Ohsugi et al., 2008). Alternatively, the complex might participate in maintaining the pluripotency of cleavage-stage blastomeres.

Other proteins expressed by the embryonic genome, including ezrin and the partitioning defective protein 3 (PAR3, also known as PARD3)–atypical protein kinase C (aPKC) complex, do not become geographically polarized until later in preimplantation development. Ezrin, a member of the ERM (Ezrin–Radixin–Moesin) family of proteins (Sato et al., 1992), has been reported to be an early marker of blastomere polarization and of trophoblast precursor cells (Louvét et al., 1996). Ezrin is widely expressed in the adult mouse, in which it localizes to the apical cortex of epithelial cells (Berryman et al., 1993). Although not essential for development (Saotome et al., 2004), ezrin, derived from maternal and embryonic transcripts, remains symmetrically present at the periphery of blastomeres until the 8-cell stage, when it becomes confined to the apical cytocortex. The PAR3–aPKC complex is also asymmetrically located in the 8-cell embryo, and the experimental disruption of either protein in individual blastomeres *in vitro* at the 4-cell stage partially redirects their cell fate towards that of an inner cell after the fourth embryonic

cleavage (Plusa et al., 2005). Whether these aforementioned proteins interact with the SCMC beginning at the 8-cell stage of development has not been ascertained.

Conclusions

Following fertilization, successful preimplantation development depends on: the degradation of maternal detritus; the activation of the embryonic genome; cell cycle progression that is orchestrated to ensure the proper allocation of initial cell lineages; and the formation of a blastocyst that implants on the uterine wall. The molecular basis of these physiological processes is heavily dependent on components that are stored in the oocyte and encoded by maternal-effect genes.

Compared with other model organisms, relatively few maternal-effect genes (fewer than 30) have been investigated in mice since the first two were described in 2000. Thus, there continues to be major gaps in our knowledge of what are very fundamental developmental processes, concerning, for example: selectivity in the initial turnover of maternal RNA and proteins; the chromatin reprogramming that is required to restore totipotency in terminally differentiated gametes; the activation of the embryonic genome; the initiation of embryonic cell division; the compaction to form the morula; and the plasticity of genetic programs and how they might relate to the regulative nature of early development. However, a more complete cataloguing of the egg transcriptome and proteome, as well as the advent of the genome-wide analysis of epigenetic marks, transcription factor regulatory networks and small RNAs promises future advances in understanding these events of early development.

Mouse transgenesis continues to play an important role in identifying the genes that are essential for normal development. The most accessible maternal-effect genes are those that are oocyte, or at least gamete, specific, because genetic ablation provides phenotypes that offer insight into their function in embryos derived from homozygous null mothers. More challenging to study are those genes that are expressed both maternally and in the zygote. However, the creation of conditional mutants should make these genetic circuitries more amenable to investigation and should dramatically broaden our understanding of early development. Heterozygous mutants might also provide a useful means of studying the molecular interactions of genetic networks that might be more subtly perturbed and thus do not produce overt phenotypes that arrest development.

The initial cohort of maternal-effect genes that has been studied to date has been used to identify binding partners and to investigate other potential participants in specific developmental signaling and metabolic pathways. In addition, recently described oocyte-specific transcription factors offer powerful tools for use in mouse genetics, particularly when coupled with genome-wide screens to identify potential downstream maternal-effect genes. Investigating such genes in mice could afford new mechanistic insights into the reprogramming of terminally differentiated cells into pluripotent embryonic cells, with possible therapeutic implications for treating human disorders such as diabetes, cardiovascular and neurodegenerative diseases. The genetic ablation of individual, or groups of, maternal-effect genes might also provide useful models for investigating abnormal human physiology that can affect early development and reproduction.

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Competing interests statement

The authors declare no competing financial interests.

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