CHAPTER SEVEN

Oocyte Quality and Maternal Control of Development

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Contents

Abstract

The oocyte is a unique and highly specialized cell responsible for creating, activating, and controlling the embryonic genome, as well as supporting basic processes such as cellular homeostasis, metabolism, and cell cycle progression in the early embryo. During oogenesis, the oocyte accumulates a myriad of

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factors to execute these processes. Oogenesis is critically dependent upon correct oocyte–follicle cell interactions. Disruptions in oogenesis through environmental factors and changes in maternal health and physiology can compromise oocyte quality, leading to arrested development, reduced fertility, and epigenetic defects that affect long-term health of the offspring. Our expanding understanding of the molecular determinants of oocyte quality and how these determinants can be disrupted has revealed exciting new insights into the role of oocyte functions in development and evolution.

Key Words: Oocyte quality, Epigenetics, Oogenesis, Maternal mRNA, Mitochondria, Preimplantation embryo, Meiosis.

1. Introduction

The traditional Korean Um-Yang concept of nature posits the existence of opposite and complimentary forces that, when in balance, provide for harmonious existence. The feminine, or Um, component is associated with the properties of combining or gathering to establish functionality. This concept applies very well to the oocyte. The oocyte is uniquely endowed with the ability to combine its own components with those of the incoming sperm, and direct the creation of a functional embryo. The oocyte is a highly differentiated, molecularly complex product of gametogenesis, despite its outwardly simple morphological appearance. During oogenesis, the oocyte must accumulate the components that are needed to support early embryo metabolism and physiology, as well as components needed to complete meiosis, initiate cell cycle progression, and direct early developmental events, such as the establishment of the primary embryonic body axes in many species. The oocyte must combine the two haploid genomes into a single embryonic genome, activate transcription of that genome at the correct time, and activate the appropriate array of genes to be transcribed. Additionally, the oocyte must maintain essential epigenetic information, while simultaneously remodeling chromatin and modifying certain other kinds of epigenetic information. In short, the successful development of all embryos is predicated upon correct and efficient execution of many crucial processes by the oocyte to create a functional embryo.

In this review, we will discuss key aspects of oogenesis, oocyte biology, and oocyte components that are responsible for creating a healthy, functional embryo. We will also discuss situations where these processes are disrupted, resulting in poor quality oocytes that are deficient in supporting correct embryo development. Indeed, it is becoming increasingly clear that the phenotype of offspring is largely defined by the quality of the oocytes from which they are derived. This applies to adult phenotypes as well as

embryonic characteristics, and indeed both maternal and grandmaternal effects on development and phenotype can be realized. Accordingly, the review will encompass recent discoveries that link maternal nutrition to defects in organogenesis and physiology in adult stage offspring.

2. Oogenesis

2.1. Stages of oogenesis

There are five stages of oogenesis in mammals, beginning with primordial germ cell (PGC), colonization of the developing gonad and continuing through formation of oogonia, primary oocytes, secondary oocytes, and mature eggs (Fig. 7.1). PGCs are diploid precursors of eggs and sperm, and exist transiently in the embryo before establishing close associations with the somatic cells of the gonad (Hogan, 2001). They can be visualized by alkaline phosphatase staining at 4 weeks of gestation in human embryos. In the mouse embryo, the PGCs are first detectable at day 7.25 postcoitum (dpc) as a small population of alkaline phosphatase-expressing cells in the extraembryonic mesoderm near the base of the allantois (Chiquoine, 1954; Ginsburg *et al.*, 1990). Over several days, the PGCs proliferate and migrate to the genital ridge, the gonadal anlage. By 13.5 dpc in the mouse, PGC proliferation is complete (Chiquoine, 1954; Mintz and Russell, 1957; Ozdzenski, 1967; Tam and Snow, 1981). Upon arrival in the female genital ridge, germ cells, now referred to as gonocytes, give rise to oogonia. The population of oogonia expands through a predetermined, species specific, number of mitotic divisions until the cells enter meiosis and become oocytes (Gosden and Bownes, 1995). For example, oogonia in the mouse ovary undergo ~4 mitotic cycles before entering meiosis between days 14 and 16 of a 20-day gestation period. In comparison, for humans as for other large mammalian species, there are many more rounds of mitotic division over a period of several months until shortly before birth (reviewed by Picton, 2000). In humans, the oogonia begin to differentiate in the 9th week of fetal life (Motta *et al.*, 1995, 2003). Clusters of oocytes or "nests" will break down, some oocytes will degenerate (apoptosis), and primordial follicles will form (Barnett *et al.*, 2006, for an in-depth review of genetic regulation of this process). The oocytes remain arrested in prophase I of meiosis until the female becomes sexually mature.

The primary oocytes synthesize an extracellular coat and cortical granules. Within a few days after birth in rats and mice, the primordial stage oocytes are surrounded by a single layer of flattened cells, also known as pregranulosa cells (Fortune, 2003; Fortune *et al.*, 2000). During the transition from the primary to the tertiary follicle, the granulosa cells (GCs)

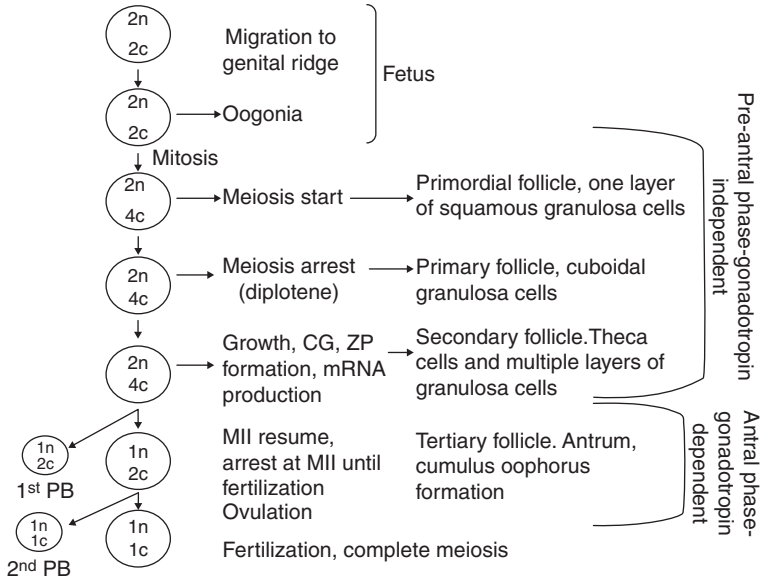

Figure 7.1 The stages of mouse oogenesis. Primordial germ cells (PGCs) migrate to the genital ridge during fetal development and form oogonia. Oogonia proliferate by mitotic divisions, transitioning to primary oocytes as the first meiotic division initiates, and primordial follicles form with one layer of squamous granulosa cells (GCs) before or shortly after birth. Ploidy (*n*) is defined here on the basis of centromere number. DNA content is indicated as "c." After birth, primary oocytes remain meiotically arrested at prophase I and primary follicles form, with oocytes surrounded by cuboidal GCs. Secondary follicle formation proceeds with theca cells and multiple layers of GCs. The stages through secondary follicle formation are Gonadotropin independent. Oocytes continue to grow, synthesizing cortical granules (CGs), zona pellucida (ZP) and mRNA production. After puberty, under the influence of Gonadotropins, secondary follicles proceed to tertiary follicles. At this stage, antrum and cumulus oophorus formation occurs. Cells stop differentiation. Meiosis resumes and nuclear and cytoplasm maturation occurs. Secondary (mature) oocytes extrude the first polar body (PB), which has the haploid number of chromosomes (*n*). Meiosis arrests at metaphase II (MII), waiting for fertilization. Upon fertilization, oocyte activation occurs and meiosis is completed with extrusion of the second polar body.

undergo a transition from a flattened epithelial to a cuboidal epithelial cell morphology, and with further proliferation produce a multilayered collection of cells surrounded by an outer layer of thecal cells and a basal membrane. *In vivo*, follicles with some flattened and some cuboidal GC are frequently observed, and can be very prolonged (Fortune *et al.*, 2000). An extensive network of gap junctions is established, which is essential for folliculogenesis (Ackert *et al.*, 2001). The formation of an antrum inside the GCs leads to the formation of an antral follicle. Within the antral follicle, the oocyte is surrounded by specialized cumulus cells. The antrum is lined by

the follicular epithelium. The whole follicle is shaped by the surrounding connective tissue. The layer of GCs does not contain blood vessels. The next step in oocyte development occurs when the oocyte is stimulated by hormones to resume meiosis as a prelude to ovulation. At this stage, several events occur such as chromosome condensation, nuclear envelope breakdown, and formation of the first polar body and large secondary oocyte. In mammals, oocyte maturation proceeds to metaphase II and then arrests until fertilization.

2.2. Oocyte–follicle cell interactions

The interaction between oocyte and follicular cells has been investigated extensively. Complex bidirectional communication between the oocyte and its surrounding somatic cells is essential for the coordinated development of both germ cell and somatic cell compartments (Fig. 7.2). The oocyte plays an active role in cumulus expansion (Epigg, 2001). The growth and development of the oocyte and the somatic components of the follicle occur in a highly coordinated manner. Previously it was thought that the

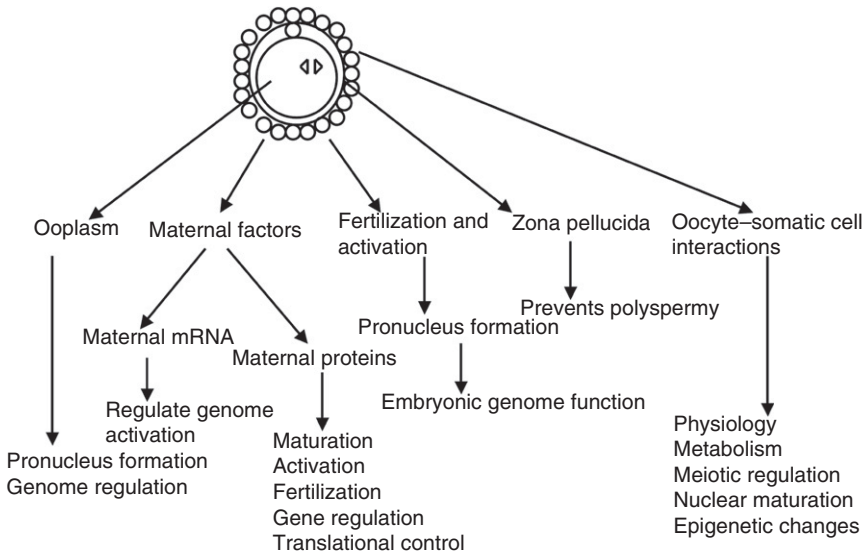

Figure 7.2 Determinants of oocyte quality. The processes affecting oocyte quality are outlined. Ooplasm affects pronucleus formation and embryonic genome activation. Factors in the ooplasm, such as maternal mRNA and proteins, regulate genome activation in the absence of transcription. Bidirectional oocyte–somatic cell interactions help in the proper early development of the oocyte by affecting physiology, metabolism, nuclear maturation, and meiotic regulation.

somatic components of the follicle control the oocyte and its development. Pincus and Enzmann (1934) found that fully grown oocytes removed from antral follicles underwent a spontaneous, gonadotropin-independent resumption of meiosis in culture, and concluded that follicular somatic cells maintain oocytes in meiotic arrest. But recent experiments indicate that the oocyte orchestrates follicular development. Oocytes regulate their own maturation and also affect the functions of the neighboring somatic cells (e.g., cumulus cell expansion) and ovulation rate (Juengel and McNatty, 2005). Follicular somatic cells in turn regulate oocyte transcription (De La Fuente and Eppig, 2001) and promote oocyte competence to undergo fertilization and preimplantation embryogenesis (cytoplasmic maturation) (Buccione *et al.*, 1990). GCs participate in the global suppression of transcription in oocytes that occurs before nuclear maturation. This highly coordinated development requires constant intercommunication between the oocyte and somatic cells. During follicular development, factors from GCs such as Kit ligand (KITL) promote oocyte development, whereas factors from the oocyte influence GC development and function. These interactions, in concert with gonadotropins and other factors, promote the transition to antral follicle. In antral follicles, oocyte-derived factors, such as growth differentiation factor 9 (GDF9), promote the development of the cumulus cell phenotype by suppressing expression of the mural granulosa cell (MGC) phenotype (Elvin *et al.*, 2000; Eppig, 2001; Matzuk *et al.*, 2002; McNatty *et al.*, 2003). GDF9 in culture can promote many of the changes in GC gene expression brought about by oocytes. Interestingly, the oocyte influence is developmentally regulated, with growing oocytes more able to promote GC development than fully grown oocytes (Latham *et al.*, 2004). Bone morphogenetic protein 15 (BMP15), another oocyte-derived factor, is mitogenic for somatic cells and stimulates GC proliferation (Di Pasquale *et al.*, 2004; Otsuka *et al.*, 2000; Shimasaki *et al.*, 2004). Oocytes regulate cumulus cell metabolism (Sugiura *et al.*, 2005) and BMP15 and fibroblast growth factors (FGFs) cooperatively promote increased glycolysis rates in cumulus cells (Sugiura *et al.*, 2007). BMP15-deficient mice demonstrate reduced ovulation, fertilization and developmental potential (Yan *et al.*, 2001). Humans demonstrate a mutation in *Bmp15* that leads to hypergonadotropic ovarian failure in women (Di Pasquale *et al.*, 2004), indicating an important role of BMP15 in follicular development and ovulation. Oocytes also secrete a potent mitogenic factor that promotes mural granulosa and cumulus cell DNA synthesis and cell proliferation (Li *et al.*, 2000; Gilchrist *et al.*, 2001, 2003). Oocytes modulate follicle stimulating hormone (FSH)-induced progesterone and estradiol synthesis by mural and cumulus GCs (Li *et al.*, 2000) and suppress FSH-induced luteinizing hormone receptor (*Lhcgr*) mRNA expression (Eppig *et al.*, 1997). They also regulate the differentiation of the GCs toward the cumulus cell phenotype, which is markedly distinct from the MGC phenotype. The cumulus cells have very

low *Lhcgr* expression compared to MGCs, and possess the capacity to secrete hyaluronic acid and undergo mucification/expansion while MGC do not (Eppig *et al.*, 1997; Li *et al.*, 2000). Mucification of the cumulus cells is needed for fertilization to be successful. With the microsurgical removal of the oocytes from the cumulus–oocyte complex (COC), the cumulus cells display a phenotype similar to MGC, evidenced by less DNA synthetic activity and increased secretion of progesterone (Buccione *et al.*, 1990). Culture of the oocytectomized complex with denuded oocytes restores cumulus cell characteristics. The oocyte also enables cumulus cell expansion in response to epidermal growth factor (EGF) (Diaz *et al.*, 2006). Oocyte-mediated signaling via MAPK1/3 (ERK1/2) and SMAD2/3 within cumulus cells promotes the cumulus cell phenotype (Diaz *et al.*, 2007; Su *et al.*, 2003).

The development of the oocyte and the somatic cells occurs simultaneously and this is responsible for ensuring an ovulated oocyte ready for fertilization. Disruption of this communication will result in oocyte developmental failure. Oocytes can regulate the rate of development of the somatic cells. This was demonstrated by a set of elegant experiments conducted by Eppig *et al.* (2002). Oocytes from 12-day-old mice were combined with somatic cells from newborn mouse ovaries. Upon grafting, oocytes were surrounded by one or two layers of GCs typical of primary to secondary follicle development. Nine days after grafting, large antral follicles were formed, whereas in the control, which contained oocytes and cumulus cells both from neonatal ovaries, follicles developed at the normal rate, that is, 19–20 days. The rate of development of the follicles was approximately doubled by the presence of later stage oocytes. This demonstrated that oocytes coordinate the development of mammalian ovarian follicles and that the rate of follicular development is based on a developmental program intrinsic to the oocyte (Eppig *et al.*, 2002). Follicles are also regulated by extraovarian factors such as gonadotropin hormones, and require FSH and receptor to become large antral preovulatory follicles (Dierich *et al.*, 1998; Kumar *et al.*, 1997).

2.3. Relevance to oocyte quality

2.3.1. *In vitro* culture effects on oocyte quality

Changes in oocyte development are normally coordinated with follicular differentiation. This coordination, however, can be changed abruptly by accelerating follicular development with exogenous gonadotropins, or other factors. Early recruitment of small antral follicles into the pool of preovulatory follicles results in the ovulation of oocytes incapable of normal maturation, fertilization, or embryogenesis (Eppig *et al.*, 1992a; Hunter, 1998; Schramm and Bavister, 1996a). Many studies in oocyte growth and development *in vitro* were done by the laboratory of John Eppig, employing

cultures of oocyte–GC complexes isolated from the preantral follicles of 12-day-old mice (mid-growth phase) by collagenase digestion. Theca cells were removed and the basal lamina enclosing the GCs and oocytes was degraded. The oocytes at this stage were incompetent to resume meiosis without further development. Between 200 and 300 oocyte–GC complexes were cultured on a collagen-impregnated membrane for 10 days, a period that spans the time of antrum formation and the acquisition of competence to resume meiosis and undergo fertilization and preimplantation development by oocytes *in vivo*. Initially 5% fetal bovine serum was used (Eppig and Schroeder, 1989), and this was later replaced by the serum protein fetuin, which was able to reduce zona hardening (Eppig *et al.*, 1992b, 1996). Serum-free culture medium was supplemented with insulin, transferrin, and selenium (ITS) to promote healthy development of the complexes (Eppig *et al.*, 1992b). The culture system yielded oocytes that could undergo maturation, be fertilized, and develop, but with lower rates compared to *in vivo* oogenesis. Thus, oocyte growth *in vitro* was not equivalent to growth *in vivo* (Eppig and O'Brien, 1996; Eppig and Schroeder, 1989), and some important follicular factors were missing, thus compromising oocyte quality.

Oocytes were also grown *in vitro* from the primordial stage. In the initial studies, the success rate was very low (0.5%) and the first mouse produced from these oocytes displayed abnormal adult characteristics (Eppig and O'Brien, 1996). Two dimensional protein gel analysis revealed a number of proteins altered in expression in GCs and cumulus cells by *in vitro* culture (Latham *et al.*, 1999). Additional effects of FSH and insulin were also seen, and these effects may contribute to differences in oocyte quality and developmental competence. Cultured oocyte–GC complexes fail to undergo appropriate transcriptional regulation (De La Fuente and Eppig, 2001), further indicating the importance of the correct follicular environment for establishing the correct oocyte phenotype. Subsequently, these and other observations were employed to develop a revised culture protocol, differing in the duration of treatment with FSH, and this yielded much greater success in the production of developmentally competent oocytes (O'Brien *et al.*, 2003). This success highlights the critical and dynamic nature of oocyte–somatic cell interactions and the importance of follicular environment in the production of high quality oocytes that can support development and yield healthy offspring.

Other evidence for the importance of these oocyte–follicle cell interactions in establishing oocyte quality comes from studies in the rhesus monkey using *in vitro* oocyte maturation protocols. In rhesus monkeys, *in vitro* maturation remains very inefficient, and has not led to the birth of live young. In unprimed monkeys, oocytes subjected to *in vitro* maturation (IVM) and *in vitro* fertilization (IVF) form blastocysts at an efficiency of less than 1% (Schramm and Bavister, 1996a). Prior stimulation with FSH

elevates the blastocyst formation rate to as high as 40% (Schramm and Bavister, 1996b; Schramm *et al.*, 1994). Interestingly, co-culture of maturing oocytes from nonstimulated females with GCs from FSH stimulated females enhances blastocyst formation by more than tenfold (Schramm and Bavister, 1996a).

2.3.2. Genetic control of oocyte quality

Estrogens extend the action of FSH on GCs by promoting their proliferation and increasing their expression of FSH receptors (Ireland and Richards, 1978). Estrogen signaling is mediated via binding to estrogen receptors (ESRs), which are ligand-dependent transcription factors. Two ESR subtypes exist in humans, ESR1 (ERα) (Menasce *et al.*, 1993; Walter *et al.*, 1985) and ESR2 (ERβ) (Enmark *et al.*, 1997; Mosselman *et al.*, 1996), coded by *ESR1* and *ESR2* genes, respectively. In the ovary, ESR1 is mostly located in the thecal layer, whereas ESR2 can be found in GCs of growing follicles at all developmental stages (Pelletier and El-Alfy, 2000). ESR1, is most abundant, and found in all human reproductive tissues. Studies on male and female *Esr1* knockout (ERKO) mice showed complete infertility (Matthews and Gustafsson, 2003). A study by Altmäe *et al.* (2007) determined the associations between genetic variations in estrogen receptor *ESR1* and *ESR2* genes and etiology of female infertility. They analyzed the influence of these variations on controlled ovarian hyperstimulation (COH) outcome—the quantity and quality of oocytes retrieved. *ESR1 PvuII* T/C (rs2234693) and *XbaI* A/G (rs9340799) single-nucleotide polymorphisms (SNPs) and $(TA)_n$ microsatellite polymorphism, as well as *ESR2 RsaI* G/A (rs1256049) SNP and $(CA)_n$ microsatellite polymorphism were determined in 159 IVF patients. Their results suggested that variations in the *ESR1* gene, in addition to the age of a woman, may predict the COH outcome in IVF.

Follistatin plays an important role in female physiology, regulating FSH levels through blocking activin actions. Failure to regulate FSH correctly has been implicated as a potential cause of premature ovarian failure. Follistatin has been associated with polycystic ovary syndrome (PCOS) in women through genetic linkage studies (Urbanek *et al.*, 2000). PCOS is an endocrine disorder characterized by reduced fertility, hyperandrogenism, and chronic anovulation (Calvo *et al.*, 2001; Liao *et al.*, 2000; Urbanek *et al.*, 1999, 2000). Ovarian failure in women may be diagnosed by high concentrations of the gonadotropins, FSH and luteinizing hormone (LH), and a low concentration of estradiol. A rise in FSH is the most sensitive and the best early marker for ovarian failure (Conway, 2000). Mice lacking follistatin show a drastic reduction in the number of follicles, a reduction in the pool of available oocytes, poor oocyte quality, a failure to ovulate, and increased FSH levels, indicating premature ovarian failure (Jorgez *et al.*, 2004). Women with premature ovarian failure who undergo attempts to

induce ovulation using different regimens have reduced ovulation rates (Johnson and Peterson, 1979; Nelson *et al.*, 1992; van Kasteren *et al.*, 1995).

A long list of genes has been experimentally demonstrated by mutations in mice to control folliculogenesis and oocyte quality. Mice homozygous for a null allele at the *Gdf9* locus (Dong *et al.*, 1996) or for a hypomorphic *Kitl* allele (Donovan and de Miguel, 2001) exhibit female infertility as a result of blocks in follicular development preceding formation of secondary follicles. Females deficient in pentraxin-related gene 3 ($Ptx3^{-/-}$) are subfertile due to defects in the integrity of the cumulus cell–oocyte complex that are reminiscent of $Bmp15^{-/-}/Gdf9^{+/--}$ double mutant and BMP type IB receptor mutant mice. The zona pellucida plays an important role in oocyte–cumulus cell communication as well as controlling sperm penetration and providing physical protection to the embryo. Mice lacking ZP2 and ZP3 proteins are deficient in early antral and preovulatory follicle COC formation and ovulation, and blastocysts from their eggs fail to complete development after transfer to the pseudopregnant mice (Rankin *et al.*, 1996, 2001; Zhao and Dean, 2002). Gap junctions are important for oocyte–granulosa cell communication. Defects in meiotic maturation are evident in mice lacking the GC oocyte junction protein GJA4 (connexin 37) (Carabatsos *et al.*, 2000).

Collectively, these observations further highlight the importance of oocytes in promoting GC proliferation and differentiation (Eppig, 2001), with the oocyte in turn depending on somatic cells to support its growth and development (Brower and Schultz, 1982), regulate meiosis (Chesnel *et al.*, 1994), and modulate global transcriptional activity in the oocyte genome (De La Fuente and Eppig, 2001). The genetic studies to date reveal a wide array of genes that control oogenesis, emphasizing the complexity of the process and the many opportunities for genetic disruption of oocyte quality and subsequent effects on embryogenesis.

2.3.3. Environmental factors affecting oocyte quality

Environmental factors that disrupt follicular function also affect oocyte quality. The potential effects on reproduction by chemicals with hormone-like activity is a growing concern. A number of chemicals in the environment are estrogenic and can disrupt the endocrine system of wildlife and humans by binding to and activating the ESR. These environmental estrogens have the potential to perturb sensitive hormone pathways that regulate reproductive function. Most phytoestrogens and synthetic compounds bind to estrogen receptor ESR1 and ESR2 with relatively low affinity (Kuiper *et al.*, 1997). Diethylstilbestrol (DES) is a synthetic estrogen. It has been used as an estrogen supplement before its carcinogenic effect was recognized (Herbst *et al.*, 1971). In mouse oocytes, DES interferes with centrosomes and microtubule dynamics (Can and Semiz, 2000).

Another important endocrine disruptor is bisphenol A (4,4′-isopropylidene-2-diphenol; BPA). This is a high-volume diphenylalkane used for the production of polycarbonate plastics, epoxy and phenolic resins, polyesters, and polyacrylates, which have wide industrial applications including the manufacture of plastic wares, dental resins, and food can lining. It is proposed to have estrogenic activity (Krishnan *et al.*, 1993; Kuiper *et al.*, 1998; Metcalfe *et al.*, 2001; Welshons *et al.*, 2006). BPA is a widespread contaminant of the aquatic environment (Kawahata *et al.*, 2004; Vethaak *et al.*, 2005). Fish exposed to BPA show testes growth inhibition and maturation delay, altered male sex cell types, lower semen quality, reduced percentage of ovulation in females, altered ovulation timing, and occurrence of ovo-testes (Hassanin *et al.*, 2002; Kang *et al.*, 2002; Lahnsteiner *et al.*, 2005; Mandich *et al.*, 2007; Sohoni *et al.*, 2001; Tabata *et al.*, 2001; Tokumoto *et al.*, 2005). In mice, BPA effects on the oocyte have been revealed by Hunt *et al.* (2003), including a sudden, spontaneous increase in meiotic disturbances, such as aneuploidy coinciding with the accidental exposure of animals to an environmental source of bisphenol (Hunt *et al.*, 2003). In a recent study by Susiarjo *et al.*, (2007), the effect of BPA on meiosis of fetal ovaries was assessed by exposing pregnant mice in their mid-gestation stage to BPA. Oocytes from exposed female fetuses displayed gross aberrations in meiotic prophase, while in mature females BPA exposure increased aneuploidy in oocytes and embryos. In another study (Can *et al.*, 2005), BPA induced cell cycle delay and altered centrosome and spindle microtubular organization in oocytes during meiosis.

The endogenous metabolite of 17β-estradiol (E_2), 2-methoxyestradiol (2-ME), is a natural component of follicular fluid produced by the GCs (Dehennin *et al.*, 1984; Hammond *et al.*, 1986; Spicer *et al.*, 1987). Concentrations of 2-ME can be increased by exposure to environmental pollutants that activate the expression of enzymes in the metabolic pathway from 17β-estradiol to 2-ME. Exogenous estradiol does not affect maturation, whereas its metabolite 2-ME impairs the acquisition of full developmental competence (Lattanzi *et al.*, 2003). There are marked alterations in the spindle assembly of oocytes exposed to 2-ME during maturation, leading to gross chromosomal aberrations after fertilization and subsequent developmental arrest at the morula stage (Lattanzi *et al.*, 2003). Another recent study by Eichenlaub-Ritter *et al.* (2007) found that a high concentration of 2-ME produces a minor increase in GV-arrested dictyate-stage oocytes, blocked progression from first to second meiotic metaphase, caused delays in the formation of a typical bipolar spindle at meiosis I, induced severe spindle abnormalities and aberrant spindle pole organization at metaphase II, disrupted centrosome integrity, and induced nondisjunction and aneuploidy. Other chemicals, such as triclorofon (Cukurcam *et al.*, 2004; Yin *et al.*, 1998), chloral hydrate (Eichenlaub-Ritter and Betzendahl, 1995), nocodazole (Eichenlaub-Ritter and Boll, 1989; Everett and Searle, 1995;

Shen *et al.*, 2005; Sun *et al.*, 2005), mancozeb (Rossi *et al.*, 2006), diazepam (Sun *et al.*, 2001), okadaic acid (de Pennart *et al.*, 1993; Zernicka-Goetz and Maro, 1993), and taxol (Mailhes *et al.*, 1999), affect the meiotic spindle as well. Such effects on the oocyte can affect embryonic development by compromising genome integrity.

3. Oocyte Activation

Immediately after fertilization, egg activation leads to a complex series of events associated with blocks to polyspermy and additional downstream events that culminate in cleavage and eventually activation of gene transcription to complete the oocyte to embryo transition. The activation stimulus normally arises via actions of sperm-derived components (Fujimoto *et al.*, 2004; Stice and Robl, 1990). Artificial activation of oocytes can be achieved through a variety of treatments, including brief ethanol treatment, exposure to calcium ionophores, electrical pulses, treatment with strontium chloride, and treatment with the protein phosphorylation inhibitor 6-Dimethylamino purine (DMAP). Artificial oocyte activation is an essential component of experimental procedures such as nuclear transfer (NT) and parthenogenesis to produce potentially useful stem cell lines, and may also be advantageous in combination with clinical procedures involving subnormal sperm. Considerable interest has thus arisen in understanding oocyte activation and how it relates to embryo quality. An optimized activation protocol could enhance reprogramming of NT embryos, and could enhance the quality of embryos obtained by artificial activation.

3.1. Molecular mechanisms

Egg activation is a complex process involving multiple mechanisms. One key mechanism is calcium signaling. At fertilization, a massive increase in intracellular calcium abundance occurs in the egg, which leads to the formation of pronuclei and resumption of cell divisions (Miyazaki and Ito, 2006). Calcium is released from the endoplasmic reticulum by the 1,4,5-triphosphate receptor (Miyazaki, 2006). This calcium wave starts at the site of sperm entry and travels across the whole egg, thus activating it. Swann (1994) injected sperm head extract into eggs, which resulted in oocyte activation. This led to the hypothesis that there is a factor called Ca^{2+} oscillation-inducing protein (COIP) in the sperm responsible for egg activation. Phospholipase C (PLC) family members have been prime candidates for this factor. Most PLCs fail to induce calcium oscillations upon injection. Saunders *et al.* (2002) found that PLC-zeta, which is specifically expressed in sperm, induces calcium oscillations upon injection of its mRNA into

oocytes, implicating it as a putative COIP protein. Fujimoto *et al.* (2004) demonstrated that PLC-zeta is a sperm-borne oocyte activation factor associated with the perinuclear matrix in the postacrosomal region. Once oocyte activation is initiated by the sperm, additional activation-associated processes are executed by the egg in response to oscillations in intracellular free calcium ion.

3.2. Comparative effects of natural and artificial activation on development

While the sperm provides the natural stimulus for oocyte activation, a variety of artificial stimuli can trigger oocyte activation and initiate development. The occurrence of one or more transient increases in free calcium ion is the key trigger of meiotic resumption during fertilization, and a wide range of procedures for artificial oocyte activation have been established to elicit calcium transients, including mechanical, chemical, and physical stimuli that elicit one or several Ca^{2+} transients in the oocyte. Chemical activation can be induced by exposure to the Ca^{2+} ionophore (Kline and Kline, 1992), ionomycin (Loi *et al.*, 1998), 7% ethanol (Presicce and Yang, 1994), strontium chloride (Cuthbertson *et al.*, 1981), phorbol ester, and thimerosal. Ionophore A23187 promotes the release of intracellular Ca^{2+} stores but also facilitates the influx of extracellular Ca^{2+} ions (Kline and Kline, 1992). When a combination of calcium ionophore A23187 and puromycin is used, the activation rate is ~90% and the proportion of parthenotes displaying one pronucleus with extrusion of the second polar body is ~80% in mouse oocytes and human aged oocytes (Nakagawa *et al.*, 2000; Sengoku *et al.*, 2004; Yamano *et al.*, 2000). Ionomycin is another potent Ca^{2+} ionophore currently used in NT protocols (Cibelli *et al.*, 1998; Wells *et al.*, 1999). It mobilizes intracellular Ca^{2+} from Ca^{2+} stores. Ionomycin has been used widely with human intracytoplasmic sperm injection (ICSI) as well as in bovine NT experiments. Exposure of matured oocytes to 7% ethanol for 5–7 min induces successful activation and pronucleus formation by promoting the formation of inositol triphosphate (IP_3) and the influx of extracellular Ca^{2+} (Presicce and Yang, 1994). Strontium chloride induces multiple Ca^{2+} transients, probably by displacing bound Ca^{2+} in the oocyte (Whittingham and Siracusa, 1978), but also by inducing intracellular Ca^{2+} release (Kline and Kline, 1992). Strontium chloride has been used successfully to activate mouse oocytes after NT (Chung *et al.*, 2002; Gao *et al.*, 2003, 2004; Vassena *et al.*, 2007a,b; Wakayama *et al.*, 1998). Phorbol ester, which mimics endogenous diacylglycerol, activates the calcium- and phospholipid-dependent protein kinase C (Nishizuka, 1984) and induces calcium oscillations and pronucleus formation in mouse oocytes (Cuthbertson and Cobbold, 1985). However, the activation rate is lower when compared to calcium ionophore (Uranga *et al.*, 1996). This compound

has not been used in other mammalian oocytes. Thimerosal, a sulfhydryl-oxidizing agent that induces repetitive Ca^{2+} oscillations, has been used successfully for the activation of bovine oocytes (Fissore *et al.*, 1992, 1995). However, the peak and the duration of the calcium oscillations induced by thimerosal are shorter than those of the first rise induced by spermatozoa during fertilization (Nakada and Mizuno, 1998). Electrical stimulation is an alternative to chemical activation to induce Ca^{2+} influx through the formation of pores in the plasma membrane. The success of this procedure depends on the size of the pores formed and the ionic content of the medium. Moreover, the time to restore membrane integrity depends on the temperature, which affects the fluidity of lipids and proteins in the plasma membrane (Zimmermann *et al.*, 1985). Periodically repeated electrical stimulation mimics the pattern of oscillations observed during fertilization (Ozil, 1990). The single Ca^{2+} rise recorded after electrical stimulation is dependent on the presence of extracellular Ca^{2+} ions. However, when rabbit oocytes are pulsed in the presence of lithium (which prevents the production of IP_3), oocyte activation is inhibited (Ozil, 1990). This suggests that electrical stimulation induces the production of IP_3 that leads to intracellular Ca^{2+} release. Electroporation of IP_3 in a calcium- and magnesium-free medium followed by incubation in 6-DMAP has been used to activate parthenogenetic and NT rabbit embryos (Mitalipov *et al.*, 1999). Another physical stimulus used for oocyte activation is the exposure of oocytes to room temperature before NT (Stice *et al.*, 1994).

The number and pattern of calcium oscillations control essential early processes, such as cortical granule exocytosis, cell cycle resumption, and gene transcription (Ducibella *et al.*, 2002, Ozil *et al.*, 2005). The pattern of calcium oscillations affects gene expression and developmental potential (Ozil *et al.*, 2006). Too few oscillations can alter expression of 20% of genes analyzed, preferentially affecting the expression of mRNAs related to transcription and mRNA processing. Hyperstimulation has a much lesser effect on gene expression, but is associated with effects on progeny growth. Thus, the mode of oocyte activation can have long-term consequences on embryo development.

4. Oocyte Components Controlling Early Development

The oocyte contains a rich supply of macromolecules and organelles that collectively support and regulate vital processes in the early embryo. This includes processes such as ion homeostasis, metabolism, cell cycle progression, DNA repair, apoptosis, transcriptional activation of the embryonic genome, epigenetic modifications and reprogramming of the genomic

material, and in some species early cell fate determinative events that control subsequent morphogenesis and differentiation.

4.1. Spindle formation and function

The establishment of a bipolar spindle is essential for the accurate segregation of chromosomes during mitosis and meiosis. In somatic cells, a centrosome, consisting of a pair of centrioles surrounded by proteins called pericentriolar material (PCM), determines both the location of the microtubule organizing center and the polarity of microtubule arrays with their growing plus ends extending away from the microtubule organizing center. During the S phase, the centrosome is duplicated, and just before mitosis the duplicated centrosomes are separated to enable them to serve as two mitotic spindle poles. Microtubules, which are nucleated from the centrosomes, alternate rapidly between growing and shrinking phases, until some are captured and stabilized by interactions with kinetochores through a "search and capture" mechanism of mitotic spindle formation (Kirschner and Mitchison, 1986). Thereafter, a centrosome together with an accompanying set of chromosomes is distributed into each daughter cell at the end of mitosis, thus ensuring that both the centrosome and chromosome number are accurately conserved through successive cell generations (Mazia, 1987). Meiotic spindles in mammalian oocytes (with the exception of rodents) lack centrioles, which are present only up to the pachytene stage during oogenesis (Szollosi *et al.*, 1972), and have to be inherited from fertilizing sperm (Schatten, 1994). In mouse oocytes, antibodies to PCM react with the acentriolar meiotic spindle poles as well as in the cytoplasm (Maro *et al.*, 1985).

The faithful transmission of chromosomes during both meiosis and mitosis is fundamental to the survival and reproduction of all living organisms. Errors during this process result in aneuploidy. Whereas sister chromatids segregate from each other during anaphase in mitotic cells, homologous chromosomes do so at the equivalent stage of the first meiotic division. Incorrect segregation of chromosome 21 during human meiosis is the cause of Down's syndrome, whereas that of other chromosomes is the cause of many spontaneous fetal abortions (Hassold and Hunt, 2001). Aneuploidy during mitotic divisions is associated with many forms of human cancer (Sen, 2000). Studies of human embryos have revealed that chromosomal aneuploidies are common (Angell *et al.*, 1986, Magli *et al.*, 2001; Munne *et al.*, 1993; Plachot *et al.*, 1986; Wolstenholme, 1996). The greater the fraction of aneuploid cells, the lower the developmental potential of the embryo (Baltaci *et al.*, 2006; Bielanska *et al.*, 2002). Interestingly, aneuploid cells may be excluded from the inner cell mass (ICM) (Johnson *et al.*, 1993), or cells may lose supernumerary chromosomes (Munne *et al.*, 2005). Aneuploidy rates increase with maternal age (Fujimoto *et al.*, 1978).

Thus, one component of decreased oocyte quality is disruption in spindle function, which can affect long-term embryo development.

The spindle can also control embryo genotype and phenotype by participating in meiotic drive processes. Meiotic drive is a process wherein chromosome segregation occurs in a nonrandom fashion. It is mediated by genetic elements, called segregation distorters that actively bias segregation, resulting in transmission of itself and linked chromosome material to more than half of the functional gametes. The most studied examples affect gamete viability, including *Segregation Distorter* in *Drosophila melanogaster* (fruit fly), the *t* haplotype in *Mus musculus* (mouse), and *spore killer* (*sk*) in *Neurospora* sp. (fungus) (Lyttle, 1991; Ripoll *et al.*, 1985; Turner and Perkins, 1979). Segregation distorters that are present in sexual chromosomes (e.g., the X chromosome in several *Drosophila* species; Atlan *et al.*, 2004) are denominated sex-ratio distorters, as they induce a sex-ratio bias in the offspring of the carrier individual. Selective death of subsets of gametes involves two tightly linked loci, a "Killer" locus and a "Target" locus. The segregation distorter set is composed of a "Killer" allele and "Resistant" allele, while its rival set is composed of "Non-killer" and "Non-resistant" alleles. In *Drosophila*, sperm receiving sensitive alleles of *Responder* (*Rsp*) on chromosome 2 are subject to dysfunction (Houtchens and Lyttle, 2003). The Segregation Distorter locus (also on chromosome 2) has been discovered to encode a mutant RanGAP protein that is mislocalized to the nucleus, diminishing nuclear RanGTP and disrupting nuclear RAN pathway signaling (Kusano *et al.*, 2001).

With respect to spindle function, meiotic drive can also occur by a process that does not involve gamete destruction, but rather relies upon an asymmetry of meiosis in females: the driving allele ends up in the oocyte instead of in the polar bodies with a probability greater than one half. This is termed true meiotic drive, as it does not rely on a postmeiotic mechanism. This form of drive is unique to female meiosis wherein a single functional gamete is produced from amongst the four meiotic products, thereby providing a mechanism whereby nonrandom segregation can direct enhanced transmission via the oocyte. One example of this is the DDK mouse strain. In this system, segregation distortion in favor of DDK alleles of the *Om* locus is due to nonrandom segregation of chromatids at the second meiotic division (Wu *et al.*, 2005). Additionally, nonrandom segregation of Robertsonian translocations occurs during the first meiotic division in humans (Pardo-Manuel de Villena and Sapienza, 2001b,c,d), and during the second division of murine meiosis (Pardo-Manuel de Villena *et al.*, 2001a,b). This is likely a key process contributing to speciation and genome evolution toward predominantly acrocentric or metacentric chromosomes (Pardo-Manuel de Villena and Sapienza, 2001a). Such nonrandom chromosome segregation in the oocyte requires asymmetry in the meiotic spindle and in the manner in which chromosomes associate with

the spindle. Nonrandom chromosome segregation can affect oocyte quality by biasing inheritance of specific alleles of genes linked to the distorter locus.

Spindle defects may play a special role in limited success of cloning by somatic cell nuclear transfer (SCNT). During SCNT, the second meiotic spindle is removed from the ovulated oocyte and replaced with a donor cell nucleus. Western blot analysis revealed that some proteins are depleted slightly by this procedure, but recover in abundance within a matter of hours (Miyara *et al.*, 2006). Despite this, the spindle that forms anew in the oocyte after SCNT is deficient in specific proteins, and this same deficiency is recapitulated at mitotic divisions in the embryo (Miyara *et al.*, 2006). Examination of cloned blastocysts revealed increased rates of aneuploidy and tetraploidy (Booth *et al.*, 2003; Nolen *et al.*, 2005; Shi *et al.*, 2004); however, the fraction of abnormal cells is small, indicating that mitotic errors are not obligatorily coupled to the earliest cleavage divisions. Rather, the spindle deficiencies likely create an enhanced risk of aneuploidy at each cell division.

4.2. Maternal mRNAs

During oogenesis, a high rate of gene transcription leads to the accumulation and storage of mRNAs as message-ribonucleoprotein (mRNP) complexes for use during oocyte maturation and early development. These maternal mRNAs can be released from the mRNP compartment and recruited for translation in a stage-specific manner, thereby providing for a changing array of proteins produced in the embryo during a period of transcriptional quiescence (Fig. 7.2).

4.2.1. Diversity of the maternal mRNA population

The maternal mRNA population is highly diverse, and supports a range of different functions during oocyte maturation and after fertilization. The maternal mRNA population also changes extensively during these periods. During murine oocyte maturation, the total amount of mRNA bearing long poly(A) tails diminishes greatly, as actively translating mRNAs become either degraded or deadenylated (Bachvarova *et al.*, 1985; Paynton *et al.*, 1988). Following fertilization, the amount of poly(A) mRNA in the cell increases dramatically, detectable by a rapid incorporation of radioactive ATP into poly(A) mRNA (Clegg and Piko, 1982, 1983a,b; Piko and Clegg, 1982) as stored maternal mRNAs undergo elongation of their poly(A) tails. This increase in poly(A) mRNA content is insensitive to transcription inhibitors, emphasizing the role of maternal mRNA polyadenylation. The overall effect of this maternal mRNA recruitment is an extensive shift in the protein synthesis pattern during the first cell cycle. Over half (60%) of the proteins being synthesized during the 1-cell stage change by twofold or more (27% by more than fourfold) in rates of synthesis during this period (Latham *et al.*, 1991). This represents a vast amount of change in the protein

synthetic activity, and exceeds the amount of difference observed between such extreme situations as proliferating versus quiescent fibroblast cultures. Moreover, a microarray analysis of polysomal mRNA populations before and after fertilization revealed that 29% of the detected mRNAs undergo twofold or greater changes in translation during this transition (Potireddy *et al.*, 2006). Thus, the recruitment, translation, and degradation of maternal mRNAs after fertilization are major processes that lead to profound changes in the array of proteins being produced in the cell.

The vast change in maternal mRNA recruitment is not chaotic, but rather seems to follow a very carefully orchestrated pattern wherein large groups of maternal mRNAs may be coordinately recruited, translated, and degraded at specific times during the first cell cycle. Cluster analysis of individual protein synthesis patterns (sampling at 3 h time intervals using synchronized groups of embryos) revealed four major patterns of synthesis (Latham *et al.*, 1991). One group represents proteins that cease to be produced, most likely encoded by maternal mRNAs that are degraded. A second group includes proteins that increase in rates of synthesis from the mid 1-cell to late 1-cell stage onward, and most likely reflects maternal mRNAs that are recruited. A third class of proteins peak in synthesis at the mid 1-cell stage, also most likely representing recruited maternal mRNAs that are recruited and then degraded. The fourth class represents proteins that diminish in rates of synthesis progressively until the very end of the 1-cell stage, when they display a transient and dramatic reappearance. This class includes the 32K complex of proteins encoded by *Spin*, a gene that produces multiple transcript variants that are recruited at specific stages and under the control of different combinations of cis regulatory elements (Oh *et al.*, 1997, 1998, 2000).

Evidence that maternal mRNA recruitment during the first two cell cycles is critical for early development has come from studies to elucidate the requirements for transcriptional activation. Cycloheximide treatment at the late 1-cell stage prevents the major genome activation event (Wang and Latham, 1997). Similarly, treatment with cordycepin, a chain terminating analogue that blocks maternal mRNA polyadenylation also prevents genome activation, affecting a wide range of housekeeping genes as well as stage-specific transiently induced genes (Aoki *et al.*, 1997, 2003). Taken together, these observations indicate that maternal mRNAs are recruited for translation at multiple stages after fertilization, that this is essential for development, and that recruitment is carefully orchestrated, most likely in coordination with the cell cycle (Hara *et al.*, 2005).

4.2.2. Functions of maternal mRNAs

One key role played by maternal mRNAs in many species relates to early cell fate determination, with key mRNAs localized to specific regions of oocytes either before or after fertilization. This is seen in a wide range of

vertebrates (e.g., amphibians) and invertebrates (e.g., nematodes, mollusks, insects). Localized messenger ribonucleoprotein complexes contain proteins or mRNAs that encode protein determinants of the germ lineage, such as P granules in *Caenorhabditis elegans* and polar plasm in *Drosophila* and other insects (Amikura *et al.*, 2005; Dworkin and Dworkin-Rastl, 1990; Hird *et al.*, 1996; Illmensee and Mahowald, 1974; Micklem, 1995; Olesnicky and Desplan, 2007; Schisa *et al.*, 2001; Semotok *et al.*, 2005; Strome and Wood, 1982; Strome *et al.*, 1994; Tadros and Lipshitz, 2005; Warn, 1975). In other cases, localization of maternal mRNAs during oogenesis is progressively translated into axial patterning during embryogenesis. This occurs as a result of the localized production of proteins to generate molecular gradients, which in turn define downstream gene expression programs. An ideal example of this is seen with regulation of the *hunchback* (*hb*) gene in *Drosophila*. The maternally produced bicoid mRNA must be localized at the anterior tip of the oocyte, from where translation produces a bicoid protein concentration gradient. Above a certain concentration, *bcd* activates embryonic transcription of the *hb* gene, whilst below that concentration transcription is inhibited (Struhl *et al.*, 1989; Tautz, 1988). Additional proteins, particularly nanos and torso, inhibit *hb* expression posteriorly thereby sharpening the gradient (Irish *et al.*, 1989; Struhl, 1989). Recent studies indicated that in *Drosophila* embryos, concentration gradients of morphogens are established by an mRNP complex, the Nos Response Element (NRE) complex which includes Nanos, Pumilio, and Brain tumor proteins and interacts with the NRE in the 3′ untranslated regions (3′UTRs) of *hb* and *caudal* mRNA (Cho *et al.*, 2006). d4EHP, a cap-binding protein is involved in repression of *caudal* and *hb* mRNA translation. The same protein is also involved in the translation inhibition of *hb* mRNA by interacting with the mRNA 5′ cap structure and brain tumor. Another excellent example is the localization of a variety of mRNAs (e.g., *VG1*, *VEGT*) at the vegetal pole in *Xenopus* embryos (White and Heasman, 2008).

Maternal mRNAs encode a wide range of essential proteins other than determinants of cell fate, too numerous to be covered in a single review. Of particular note amongst the essential functions regulated by maternal mRNAs are control of the cell cycle and control of embryonic genome activation. An excellent example of cell cycle control is regulation of appearance of the protein MOS. In *Xenopus laevis*, the production of MOS protein in response to hormonal stimulation is essential for germinal vesicle breakdown and initiation of meiosis (Sagata *et al.*, 1988), and MOS also controls meiotic progression in the mouse oocyte (Paules *et al.*, 1989), a process that occurs via activation of mitogen-activated protein kinase (MAPK) in a positive regulatory loop (Matten *et al.*, 1996). A protein called *Musashi* (which otherwise functions as a neural stem cell regulator) is involved in translational control of MOS production. The *Musashi* protein

interacts with the *MOS* mRNA. Inhibition of *Musashi* by a dominant inhibitory form prevents meiotic cell cycle progression. Early *Musashi*-dependent translation of *MOS* mRNA is required for late cytoplasmic polyadenylation-dependent (CPE) temporal regulation of maternal mRNAs (Charlesworth *et al.*, 2006).

Maternal mRNA translation is also likely to provide a key timing mechanism to control transcriptional activation of the embryonic genome. The ability of an embryo to undergo the process of gene transcription arises after fertilization. In the mouse embryo, this occurs during the second half of the 1-cell stage, as evidenced by endogenous gene transcription, transgene expression, and the acquired ability to transcribe genes in transplanted cleavage stage nuclei (Latham, 1999). Despite this early acquisition of the ability to transcribe genes, the actual rate of gene transcription can remain quite low until after one or more cleavage divisions. Transcriptional activation is not a single, discrete event, but rather occurs in periodic waves. In rodents, the major embryonic genome activation event occurs at the late 2-cell stage, whereas in other mammalian species this occurs at the 6- to 8-cell stage. This delay in embryonic genome activation is likely attributable to the stage-specific synthesis of transcription regulatory factors encoded by maternal mRNAs. The genome activation event is protein synthesis dependent, and can be inhibited with cycloheximide (Wang and Latham, 1997). Moreover, enhancers first become required for a high rate of transcription at the 2-cell stage (Henery *et al.*, 1995), and a maternal mRNA encoding at least one enhancer-binding protein (TEAD2) is recruited specifically at that stage (Kaneko *et al.*, 1997, 2004; Wang and Latham, 2000). In addition to providing for stage-specific production of essential transcription factors like TEAD2, maternal mRNAs encode chromatin regulators and factors that regulate RNA polymerase II (Zheng *et al.*, 2004). In fact there appears to be a significant transition in chromatin regulatory proteins encoded by maternal versus embryonic transcripts (Zheng *et al.*, 2005), such that changes in the level of gene transcription and the array of genes being transcribed could be driven by a transition in utilization of these two populations of mRNAs.

An in-depth microarray-based analysis of mouse maternal polysomal mRNAs that are recruited for translation either before or after fertilization (Potireddy *et al.*, 2006) revealed substantial differences in the biological functions supported by proteins being produced at the two stages. The mRNAs enriched in the polysomes of ovulated eggs were predominantly related to homeostatic processes, whereas those enriched on 1-cell polysomes were predominantly related to metabolism and biosynthesis. This latter group has many mRNAs- encoding transcription factors, again pointing to regulated maternal mRNA recruitment as playing a key role in controlling transcriptional activation in the early embryo. Interestingly, this transition in the polysomal mRNA population is mirrored at the level of total cellular mRNA (Zeng *et al.*, 2004), indicating that as the relevant

maternal mRNAs are recruited for translation they also become degraded, so that the overall mRNA population changes dramatically.

The correct control of maternal mRNAs is crucial for development. In the rhesus monkey, incorrect regulation of maternal mRNAs is associated with poor oocyte quality and arrested embryo development (Zheng *et al.*, 2005). *In vitro* maturation of oocytes from small antral follicles appears to be associated with precocious recruitment and then degradation of many maternal mRNAs, with the result that cleaving embryos produced by *in vitro* fertilization of these oocytes are deficient in these mRNAs. Cell cycle regulatory mRNAs appear to be particularly susceptible to this mode of disruption, possibly accounting for the early cleavage arrest (Mtango and Latham, 2008).

Another intriguing example of how disruptions in maternal mRNA regulation may compromise development is seen with cloned embryos produced by SCNT. A detailed array analysis of the transcriptomes of mouse 2-cell stage cloned, fertilized, and parthenogenetic embryos revealed that cloned embryos display either aberrant persistence or precocious loss of hundreds of maternal mRNAs (Vassena *et al.*, 2007b). The predominant effect is the persistence of maternal mRNAs, suggesting that many maternal mRNAs are simply not recruited and degraded as required. This is an interesting observation, as it indicates a role for the nucleus in controlling maternal mRNA translation after fertilization, a role that is not readily filled by a somatic cell genome.

It is worth noting that translational control of maternal mRNAs is a widespread and essential component to early development in a wide range of multicellular plants and animals (Benoit *et al.*, 2005; Caldwell and Emerson, 1985; Crosby *et al.*, 1988; Dworkin *et al.*, 1985; Grainger and Winkler, 1987; Harris and Dure, 1978; Kuligowski *et al.*, 1991; Lieberfarb *et al.*, 1996; Lublin and Evans, 2007; Rosenthal and Ruderman, 1987). Thus, understanding how this regulation is achieved is an important question in developmental biology.

4.2.3. Mechanisms of translational regulation

Our understanding of the molecular mechanisms regulating maternal mRNA translation in oocytes and embryos has increased greatly in recent years. The mechanisms can best be considered by examining two principal components: molecular mechanisms that promote silencing and storage of mRNAs, and the regulation of interactions between factors binding to the 5′ and 3′ regions of mRNAs that regulate formation of the translation initiation complex.

Maternal mRNAs are stored in mRNP particles in the oocyte until they are translated. This protects the mRNAs until they are recruited for translation at specific stages. The RNA-associated protein LSM14A, aka RAP55, is localized to mRNP cytoplasmic foci in oocytes, where it also associates

with the protein YBX2 (aka FRGY2, MSY2), a principal component of mRNP particles along with mRNP3, and with other associated proteins including DEAD-box ATPase Xp54, and the protein arginine methyltransferase PRMT1 (Murray *et al.*, 1992; Sommerville and Ladomery, 1996; Tafuri and Wolffe, 1990, 1993; Tanaka *et al.*, 2006; Yang *et al.*, 2006). Other components of mRNPs, include embryonic poly(A)-binding proteins, ePAB and ePABP2 (Cosson *et al.*, 2004; Good *et al.*, 2004; Ladomery *et al.*, 1997; Voeltz, *et al.*, 2001; Weston and Sommerville, 2006). The RAP55 protein also localizes to processing bodies (P bodies) and stress granules in somatic cells under stress conditions (Yang *et al.*, 2006). The Y-box proteins like YBX2 are responsible for the packaging of mRNAs into mRNPs (Matsumoto *et al.*, 2003; Skabkin *et al.*, 2004). The mRNP material, or nuage, in mammalian oocytes also includes the homologues of *Drosophila* germ cell marker VASA (DEAD/H Box 4, DDX4) and the maternal effect gene product Tudor, specifically Tudor repeat domain proteins 1, 6, and 7 (TDRD1, 6, and 7) (Hosokawa *et al.*, 2007). Mice deficient in TDRD1 display only male infertility, even though TDRD proteins localize to the nuage (intermitochondrial cement) in both male and female germ cells, indicating that, while some aspects of mRNP formation are essential and conserved between male and female gametes (e.g., YBX2), other components provide for sex-specific functions in germ cells (Chuma *et al.*, 2006; Hosokawa *et al.*, 2007).

XP54 and its human homologue RCK repress translation *in vitro* and in oocytes (Coller and Parker, 2005; Minshall *et al.*, 2001). XP54 interacts with cytoplasmic polyadenylation element-binding protein (CPEB) in oocytes (see below), associates with nascent transcripts in the nucleus, and is involved in the assembly of storage mRNPs (Smillie and Sommerville, 2002). Furthermore, yeast genetic studies demonstrated that Dhh1p, which is the yeast homologue of XP54, is involved in general translational repression (Coller and Parker, 2005). In aged *C. elegans*, large ribonucleoprotein foci form if fertilization is delayed because of lack of internal sperm. These foci contain RNA-binding proteins and nuclear pore proteins, and maintain the integrity of the oocytes until fertilization (Jud *et al.*, 2007). Recently, Buchet-Poyau *et al.* (2007) demonstrated that human MEX3A and MEX3B colocalize with decapping enzyme DCP1A and EIF2C1 (AGO1) proteins in the P bodies. Mutation in the MEX3B prevents the accumulation of the mRNAs in the P bodies, indicating that interaction with the above protein is necessary for the localization of the mRNAs, where nontranslated transcripts will be degraded or sequestered (Buchet-Poyau *et al.*, 2007).

Stored mRNAs are maintained in an untranslated state by preventing formation of a translation initiation complex. A widely held model of how translation is initiated is the closed loop model, in which the 5′ and 3′ ends of the mRNA are believed to make a contact via respective binding proteins. In this model, the poly(A) tail has a major role in circularizing

the mRNA. The interaction between the 5′ and 3′ ends is mediated by EIF4G and the poly(A)-binding protein, PABP, which binds to the poly(A) tail. This interaction facilitates binding of EIF4G to EIF4E, which is associated with the 5′ mRNA cap. The interaction between EIF4G and EIF4E is critical for forming the translation initiation complex (Hernandez and Vazquez-Pianzola, 2005), and can be regulated by a combination of eIF4E phosphorylation and binding of the inhibitory EIF4E binding proteins EIF4EBP1 and EIF4EBP2 (Clemens, 2004; Feigenblum and Schneider, 1996; Fingar and Blenis, 2004; Fingar *et al.*, 2002; Haghighat *et al.*, 1995; Hernandez and Vazquez-Pianzola, 2005; Huang *et al.*, 1987; Jagus *et al.*, 1992; Mader *et al.*, 1995; Salaun *et al.*, 2003, 2005; Zhou *et al.*, 2005). Circularization is likely also helpful in reinitiating the translation process on the same mRNA once the translation is terminated at the 3′ end and also in protecting the mRNA from degradation (Gingras *et al.*, 1999; Mazumder *et al.*, 2001).

In general, stored mRNAs have short poly(A) tails, and extending the poly(A) tail leads to activation of translation by recruiting PABP molecules and promoting interaction with the 5′ end of the mRNA. Decreasing the length of the poly(A) tail has the opposite effect. Maternal mRNAs are synthesized in the nucleus and polyadenylated under the influence of the nuclear polyadenylation signal AAUAAA. Once the synthesis is completed, they are transported into the cytoplasm where they become deadenylated and stored for later use, or polyadenylated further for immediate translation.

Two elements in mRNAs have well-documented roles in regulating polyadenylation. The cytoplasmic polyadenylation element, CPE, resides in the 3′UTR and regulates which mRNAs are polyadenylated and when this occurs. The CPE function is provided by a diverse array of sequences identified amongst amphibians and mammalian mRNAs that are recruited during oocyte maturation (Oh *et al.*, 2000). The second element is the polyadenylation signal, or hexanucleotide, of the consensus AAUAAA. The CPE and AAUAAA are required for polyadenylation. In developing *Xenopus* oocytes, deadenylation is a default mechanism occurring in the absence of a CPE (Varnum and, Wormington, 1990; Fox and Wickens, 1990). EDEN, the embryonic deadenylation element (Bouvet *et al.*, 1994), is a cis acting element that can promote deadenylation (Paillard *et al.*, 1998). In *Xenopus* oocytes, the AU-rich element (ARE) regulates mRNA deadenylation. The embryonic poly(A)-binding protein (ePAB) binds to the ARE and to the poly(A) tail, and immunodepletion of ePAB accelerates ARE-mediated default deadenylation, with subsequent mRNA degradation, indicating its role in deadenylation and accumulation of maternal mRNAs (Voeltz *et al.*, 2001). SMAUG, a multifunctional posttranscriptional (translational) regulator is conserved from yeast to humans. In *Drosophila*, maternal mRNA regulation by smaug triggers the translational repression and deadenylation of maternal mRNAs by independent mechanisms, and the

yeast homologue *Vts1* stimulates degradation of mRNAs containing the smaug recognition element (SRE) (Baez and Boccaccio, 2005).

The 3′UTRs exert critical control over the translation of maternal mRNAs. The 3′UTR plays a role in a number of processes, including polyadenylation of the mRNA, temporal regulation of mRNA translation by stage-specific polyadenylation, mRNA deadenylation, and mRNA stability. The 3′UTRs contain elements for regulating maternal mRNAs during maturation. Evidence for the role of 3′UTR in translation came from antisense-mediated truncation studies of the 3′UTR, which prevented mRNA activation (Strickland *et al.*, 1988). Two elements of the 3′UTR are involved: one that directs the selective polyadenylation, and the AAUAAA hexanucleotide, which functions as a cleavage and polyadenylation signal in the processing of nuclear transcripts (Proudfoot and Brownlee, 1976; Wickens and Stephenson, 1984). In mammals, the presence of the poly (A) tail is sufficient for mRNA translation (Vassalli *et al.*, 1989). Polyadenylation of tPA mRNA requires active protein synthesis during the first hours after GVBD (Huarte *et al.*, 1987), indicating that synthesis of a new protein is necessary, which could be a poly(A) polymerase or another protein involved in recognition of the mRNA by the polymerase.

Identification of the CPE led to the discovery of the CPE-binding protein, CPEB. CPEB is a 62-kDa protein that contains two RNA recognition motifs, and within this region, it is 62% identical to orb, an oocyte-specific RNA-binding protein from *Drosophila* (Hake and Richter, 1994). CPEB is involved in oocyte maturation and is degraded by prophase of meiosis I in *Xenopus* (Mendez *et al.*, 2002). Injection of a nondegradable form of CPEB into *Xenopus* oocytes interferes with translation of cyclin B1 mRNA and progression to meiosis II (Mendez *et al.*, 2002). CPEB binds to the CPE and also interacts with the protein maskin, which binds to eIF4E. The binding of maskin to eIF4E prevents eIF4E–eIF4G interaction, thereby suppressing translation (Barnard *et al.*, 2004, 2005; Cao and Richter, 2002; de Moor and Richter, 1999; Groisman *et al.*, 2002; Richter, 1999; Richter and Sonenberg, 2005; Stebbins-Boaz *et al.*, 1999). In response to specific stimuli to induce oocyte maturation, phosphorylation of both maskin and CPEB promote polyadenylation and translation of maternal mRNAs. MAPK phosphorylates CPEB on four residues (T22, T164, S184, S248), but not on S174, a key residue for activating CPEB function (Keady *et al.*, 2007) (Fig. 7.3). MAPK may prime CPEB phosphorylation, but the activation of CPEB by phosphorylation of S174 is achieved by another kinase, EG2 (current symbol AURKC, aka Aurora A, AIE2, AIK3, STK13, IPL1-like kinase), which also phosphorylates maskin (Hodgman *et al.*, 2001; Mendez *et al.*, 2000). This induces the recruitment of the cytoplasmic form of cleavage and polyadenylation-specific factor, CPSF (comprised of three subunits of 30, 100, and 160 kDa) to the hexanucleotide. Associated with the CPSF is poly(A) polymerase (PAP), which

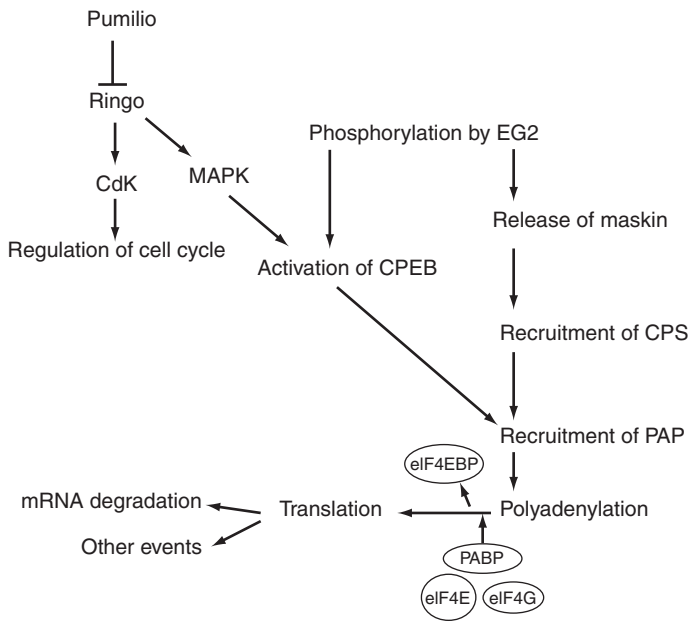

Figure 7.3 Translational regulation of maternal mRNAs. Schematic of the various regulator proteins controlling the translational recruitment. Ringo, a cell cycle regulator binds to the cyclin-dependent kinase inhibitor 1B (CDKN1B, aka p27/Kip1) needed for cytoplasmic polyadenylation element-binding protein (CPEB)-mediated translation. Pumilio 2 protein binds to the Pumilio-binding element in the 3′UTR of RINGO mRNA leading to the repression of its translation. RINGO activates mitogen-activated protein kinase (MAPK), leading to the phosphorylation of CPEB. Activation of CPEB is through phosphorylation by EG2 kinase. EG2 also phosphorylates Maskin, leading to its release from CPEB. Cleavage and polyadenylation specificity factor (CPSF) binds to the AAUAAA and interacts with CPEB on the CPE. This interaction recruits poly(A) polymerase (PAP), leading to polyadenylation of the mRNA. The poly(A) tail is bound by poly(A)-binding protein (PABP), which interacts with the 5′ end of the mRNA, recruiting the various translation initiation factors, including EIF4E, EIF4G, and ribosomes, as EIF4E-binding protein (EIF4EBP) is released. Once translated, the mRNA is degraded.

catalyzes poly(A) tail elongation (Fox *et al.*, 1992). This polyadenylation event results in the translation of *MOS* mRNA, which in turn activates CDC2 kinase to phosphorylate CPEB at multiple sites (Mendez *et al.*, 2000). This leads to dissolution of maskin-EIF4E, which permits binding of ElF4E to ElF4G and the translational activation of CPE-containing mRNAs (Stebbins-Boaz *et al.*, 1999).

RINGO (rapid inducer of G2–M in oocytes)/SPY (speedy) protein, is an activator of cyclin-dependent kinases (cdks), and is required for CPEB-directed translation (Padmanabhan and Richter, 2006). Overexpression of RINGO/SPY induces MOS synthesis, MAPK and MPF activation, and oocyte maturation. RINGO/SPY binds to CDKs and associates with

CDKN1B (p27), a CDK inhibitor, indicating a role in cell cycle regulation (Dinarina *et al.*, 2005; Karaiskou *et al.*, 2001; McAndrew *et al.*, 2007; Porter *et al.*, 2003). RINGO/SPY translation precedes maturation and is required for polyadenylation and translation of Mos mRNA and also for all CPEB-mediated processes (Padmanabhan and Richter, 2006) (Fig. 7.3). In immature oocytes, Pumilio 2 (PUM2) binds to the PUM2-binding elements (PBE) within the RINGO/SPY mRNA 3′UTR and represses its translation. PUM2 also interacts with other proteins, such as deleted in azoospermia-like (DAZL) (Cooke and Elliott, 1997), and embryonic PABP (Voeltz *et al.*, 2001). PUM2 dissociates from the RINGO/SPY mRNA when its translation is activated upon maturation, while DAZL and ePAB still interact with RINGO/Spy mRNA. PUM2 inhibits ePAB activity (Collier *et al.*, 2005) and this impacts EIF4G, EIF4B, or poly(A) interacting protein (PAIP). PUM2 may affect the interaction of EIF4E with EIF4G (Cao and Richter, 2002; Stebbins-Boaz *et al.*, 1999), or EIF4E with the cap (Cho *et al.*, 2005). Irrespective of the mechanism, PUM2-mediated repression of RINGO/SPY RNA during maturation is necessary for controlling translation.

Other elements exist in the 3′UTR to control translation. Cyclin B1 (*CCNB1*) mRNA is regulated by maturation promoting factor signaling (de Moor and Richter, 1997; Howard *et al.*, 1999). In contrast to cyclin B1, *MOS* mRNA translation can be stimulated by the MAPK pathway independently of CDC2 activity (Howard *et al.*, 1999). Aside from the requirement for the CPE in *MOS* mRNA translation (Mendez *et al.*, 2000), another regulatory element exists distinct from CPE. This element links MAPK signaling to the early progesterone-stimulated induction of *MOS* mRNA translation, and is named the PRE, for polyadenylation response element (Charlesworth *et al.*, 2002). Charlesworth *et al.* (2002) reported that the initial translation of the Mos mRNA is mediated by the PRE. In Mos, even though this element overlaps the CPE, the two elements have different roles, so that MAPK signaling targets PRE-directed mRNA translation, whereas cdc2 activation promotes the later CPE-directed mRNA translation.

The scenario outlined above for the regulated deadenylation, storage, polyadenylation, and translation of maternal mRNAs is likely incomplete. Most of what has been learned of maternal mRNA regulation has come from studies of events that occur during oocyte maturation. As described above, however, many maternal mRNAs are likely recruited for translation after fertilization to meet early, stage-specific demands of the embryo. Oocyte maturation requires the synthesis of new proteins (Uzbekova *et al.*, 2008). This new protein synthesis is achieved by the translational recruitment of stored mRNAs in a stage-specific manner, compensating for an absence of transcription. This requires mechanisms to prevent recruitment of subpopulations of maternal mRNAs during oocyte maturation, and

additional mechanisms to promote stage-specific recruitment. Comparison of the mRNA populations undergoing translation at the egg and the zygote stage indicated dramatic differences in the 3′UTRs of the transcripts being preferentially translated at the two stages. Sequence analysis indicates that CPEs are prevalent in transcripts translated preferentially at the MII oocyte stage, with 84% containing known CPEs in the 3′UTRs. By contrast, only 41% of the mRNAs enriched on polysomes at the 1-cell stage possessed known CPEs (Potireddy *et al.*, 2006). This indicates that other novel motifs likely control the process of stage-specific recruitment of maternal transcripts. Additionally, multiple genes encoding CPEBs exist, raising the possibility of further diversity in function and complexity in mRNA translational regulation.

Micro RNAs (miRNAs) and small RNAs (sRNAs) also regulate maternal mRNAs. In zebrafish embryos, miRNAs play a major role in regulating the maternal mRNA pool. Murchison *et al.* (2007) reported that elimination of the oocyte supply of DICER results in arrest during meiosis I, indicating its critical role in eliminating a group of maternal mRNAs that must be degraded in order to accomplish this critical transition (Su *et al.*, 2007). Schier and Giraldez (2006) developed transgenic embryos lacking the enzyme DICER, which is involved in synthesizing miRNAs, so that the embryos are devoid of the miRNAs. In the absence of miRNAs, the embryos showed morphogenetic defects. But with the addition of miR430, maternal mRNAs are subjected to decay through deadenylation. Giraldez *et al.* (2006) also reported that maternal mRNAs are subjected to degradation by the miR430 in zebrafish. This degradation is not the result of nonproductive translation, as repression of translation of the reporter gene with morpholino antisense oligonucleotides does not result in the decay to the same extent as the miRNA-mediated decay. MiR430 is expressed at the onset of zygotic transcription and accelerates the deadenylation and decay of a large set of maternal mRNAs in zebrafish. Lack of miR430 does not block development but results in a mixed maternal–zygotic state. This suggests that miR430 facilitates the developmental transition from maternal to zygotic states. In contrast, however, of 1000 *Drosophila* oocyte proteins examined, only a minor fraction (4%) of maternal mRNAs was increased in the *dicer* mutants (Nakahara *et al.*, 2005).

Another small RNA involved in early development is the PIWI interacting piRNA. Polar granules contain the piRNA-binding protein, PIWI (Megosh *et al.*, 2006). Depleting the levels of PIWI leads to defects in pole plasm maintenance and PGC formation. The mouse PIWI homologue, MIWI, associates with DICER, piRNAs, and mRNAs resident either on polysomes or within mRNPs (Grivna *et al.*, 2006). It is suggested that small RNAs likely play diverse roles in regulating the maternal mRNA population at the level of translation and mRNA stability, contributing to overall oocyte quality.

4.3. Maternal proteins

The foregoing discussion of maternal mRNA regulation makes it clear that the oocyte is endowed with a rich supply of maternal mRNAs to direct a changing array of proteins being synthesized, as well as a network of regulatory proteins to control the translation of these mRNAs in coordination with transit through the cell cycle. The oocyte also contains a vast array of proteins that provide key regulatory functions, such as transcriptional activation, cell cycle control, and many other regulatory processes, as well as proteins to support basic cellular homeostasis and metabolism (Fig. 7.2). The importance of many of the regulatory proteins has been revealed by spontaneous mutations and gene targeting, yielding classical maternal effect phenotypes.

4.3.1. Maternal effect mutations

Many maternal proteins regulate gene transcription. One such maternal factor is tripartite motif containing protein 24 (TRIM24, aka transcription intermediary factor 1α, TIF1A). This protein translocates from the cytoplasm into pronuclei enriched with chromatin remodelers SMARCA4 (BRG1) and SMARCA5 (SNF2H). Inhibition of TRIM24 expression by RNA interference leads to developmental arrest of the embryos at 2- to 4-cell stage (Torres-Padilla and Zernicka-Goetz, 2006). TRIM24 plays a major role in remodeling of the chromatin during the first major wave of transcription. SMARCA4 is also an important maternal factor involved in chromatin remodeling. Conditional mutation of mouse Smarca4 results in oocytes that completed meiosis and undergo fertilization normally, but yields embryos that arrest at the 2-cell stage and show reduced transcription in 30% of expressed genes (Bultman *et al.*, 2006). NLRP5 (aka MATER, for Maternal Antigen that Embryos Require), first identified in mouse, is distributed in the cytoplasm, and is required for the oocyte–embryo transition. Even though the function of NLRP5 still needs to be established, a decrease in transcription in embryos lacking NLRP5 indicates a role of this protein in transcription and the resulting oocyte–embryo transition (Tong *et al.*, 2000). *Nlrp5* null females ovulate normally but produce no litters, whereas homozygous null males and heterozygous females have normal fertility. Fertilization is normal in null females, but the embryos arrest at the 2-cell stage and degenerate. Zygote arrest 1 (*Zar1*) is another maternal effect gene, and is expressed in oocytes and embryos. ZAR1 decreases in abundance by the 2-cell stage and is absent thereafter. Most *Zar1* null embryos arrest at the 1-cell stage, and show suppression of genome activation (Wu *et al.*, 2003). A mouse homolog of *Xenopus* nucleoplasmin (nucleoplasmin 2, NPM2) is also critical for development. Embryos from *Npm2*-null females have defects in nuclei and nucleolar organization specifically evident in the loss of heterochromatin from these organelles (Burns *et al.*, 2003). Although some embryos are able to proceed through the 2-cell stage and some offspring are born to null females, most

embryos show reduced cleavage to the 2-cell stage. Another recent maternal effect factor identified is *Dppa3* (developmental pluripotency-associated 3, aka *Stella*). Embryos from DPPA3-deficient oocytes progress to the 4-cell stage but are defective in further cleavage and in preimplantation development (Bortvin *et al.*, 2004; Payer *et al.*, 2003).

Maternal proteins also provide for correct epigenetic modifications of the embryonic genome. The DNA (cytosine-5)-methyltransferase, DNMT1, is responsible for maintenance of DNA methylation. RNA silencing of the *Dnmt1* leads to activation of the zygotic genome two cycles earlier than normal in *Xenopus* embryos (Stancheva and Meehan, 2000). The methylation patterns in the embryonic genome are programmed and depletion of the DNMT1 leads to disruptions in the programmed changes of the promoter regions. This leads to altered gene expression in the embryos (Stancheva *et al.*, 2002). Another critical role for DNMT1 in the early embryo is maintenance of genomic imprints. Mammalian oocytes possess a specific oocyte form of the protein, termed DNMT1o, and express only very slight amounts of the somatic form (DNMT1s) during preimplantation development (Ratnam *et al.*, 2002). Deficiency for DNMT1o leads to embryonic lethality and loss of genomic imprinting information, even in wild-type nuclei transferred to mutant ooplasm (Howell *et al.*, 2001). Interestingly, cloned embryos produced by SCNT display reduced nuclear localization of DNMT1o, and this correlates with imprinting defects (Chung *et al.*, 2003).

Maternal proteins also play a role in repackaging chromatin. An oocyte-specific form of histone H1, called H1FOO, displays enhanced binding to DNA compared to somatic forms. Within as little as 5 min after sperm injection or SCNT, H1FOO associates with the incoming DNA, and within an hour can completely displace the incoming chromatin bound proteins, resulting in a complete replacement of somatic H1 after SCNT (Gao *et al.*, 2004). The H1FOO is then eliminated by the 2-cell stage in both normal and cloned embryos. These transitions may involve proteolytic events (Gao *et al.*, 2005). The ability of the oocyte to mediate these transitions is developmentally regulated, so that by 2 h after oocyte activation somatic histone removal is inhibited (Gao *et al.*, 2004). One curious aspect of these events is that the mouse 2-cell stage embryo experiences a period during which histone H1 of any kind is sparse, creating a potential for promiscuous gene transcription before the somatic forms become fully assembled on the chromatin (Gao *et al.*, 2004). This may contribute to a transient pattern of gene expression at the 2-cell stage.

4.3.2. Elimination of maternal proteins

While both maternal mRNA and protein play critical roles in early development, it is just as important to accomplish a successful transition from maternal to embryonic control of development. This requires degradation of

maternal mRNAs and proteins. The degradation of the mRNAs is coupled to translational recruitment, as discussed above. The ubiquitin-proteasome pathway forms the major channel of degradation of maternal proteins. In *C. elegans*, degradation of the MEI1 oocyte protein is tightly regulated by phosphorylation mediated by the minibrain kinase homolog, MBK2. MBK2 is tethered to the cortex by EGG3, an oocyte protein required during egg activation. During meiotic divisions, EGG3 is degraded. This causes MBK2 release from the cortex, leading to MEI1 phosphorylation and degradation. The phosphorylated MEI1 is recognized by the MEL26/CUL3 (DeRenzo and Seydoux, 2004). The phosphorylation of MEI1 by MBK2 increases the affinity of the protein to the MEL26/CUL3. The first hint for involvement of cullins came from RFL1, a homolog of UBA3 and a member of the neddylation pathway, which activates cullins. RNAi screening of the cullins led to the identification of CUL3 as an important factor for degradation of the MEI1. MBK2 is also involved in phosphorylation of other proteins such as OMA1, which is degraded after first mitosis with the phosphorylation by the second kinase (Nishi and Lin, 2005). Loss of MBK2 delays and/or blocks the degradation of MEI1, OMA1, and CCCH-finger proteins (Pellettieri *et al.*, 2003; Quintin *et al.*, 2003).

VASA, a regulator of germ cell fate in *Drosophila* is localized to the posterior pole by recruitment by *Oskar* (Hay *et al.*, 1990; Lasko and Ashburner, 1990). The ubiquitin pathway plays a role in Vasa localization to the posterior pole. Localization requires the deubiquitinating enzyme *fat facets* and the SOCS-box protein *Gustavus*. In the absence of the deubiquitinating enzyme, *vasa* is polyubiquitinated and accumulated at lower levels. Even though the exact role of SOCS-box protein in the localization of *vasa* is not known, in general it functions as a substrate-recruitment factor for E3 ubiquitin ligases (Kile *et al.*, 2002), which bind to specific targets and stimulate their ubiquitination and degradation.

Correct elimination of maternal proteins is essential for normal development. Protein degradation eliminates proteins that are useful early in the development but are harmful later. For example, CPEB functions early during oocyte maturation and is degraded later. But use of a nondegradable form of CPEB interferes with the translation of cyclin B1 and progression to meiosis II (Mendez *et al.*, 2002). CPEB is a PEST domain containing protein that is degraded during maturation, and deleting the PEST domain or use of proteasome inhibitors prevents the degradation of CPEB (Reverte *et al.*, 2001).

Studies in the rhesus monkey have revealed complex temporal patterns of regulation of maternal and embryonic mRNAs encoding components of the ubiquitin-proteasome pathway (Mtango and Latham, 2007). Differences in expression of these mRNAs between oocytes of different qualities indicate a role for the ubiquitin-proteasome pathway in determining oocyte quality and embryo development.

4.4. Effects of maternal mitochondria

The maternal mitochondrial population constitutes a major determinant of oocyte quality, via its role in embryonic metabolism and its role in controlling apoptosis. Apoptosis is the process of programmed cell death, either as a part of normal tissue differentiation or as a means of eliminating defective cells. A central regulator and mediator of apoptosis is the caspase family, which consists of cysteine-dependent aspartate-specific proteases. These are divided into two groups, initiator caspases such as caspase-8 and caspase-9 that activate other caspases, and executor caspases such as caspase-3, -6, and -7 that are responsible for degrading cellular proteins. Three general mechanisms are known, and their effects may be interrelated: (i) disruption of electron transport, oxidative phosphorylation, and adenosine triphosphate (ATP) production; (ii) release of proteins that trigger activation of caspase family proteases; and (iii) alteration of cellular reduction–oxidation (redox) potential (Green and Reed, 1998). Mitochondria contain many pro-apoptotic proteins such as apoptosis-inducing factor (AIF), SMAC/DIABLO, and cytochrome *C*. These factors are released from the mitochondria following the formation of pores in the mitochondrial membrane called the permeability transition, or PT pores (Chipuk *et al.*, 2006; Lemasters, 2005; Skommera *et al.*, 2006). These pores are thought to form through the action of the pro-apoptotic members of the *Bcl2* family of proteins, which are activated by apoptotic signals such as cell stress, free radical damage, or growth factor deprivation. Mitochondria also play an important role in amplifying apoptotic signals from the death receptors, with receptor-recruited caspase 8 activating the pro-apoptotic *Bcl2* family protein, BID.

Mitochondria distribution and localization in maturing embryos and oocytes are mediated primarily by microtubules, although there is evidence for actin-based localization as well (Barnett *et al.*, 1996; Haggeness *et al.*, 1978; Hales, 2004; Muggleton-Harris and Brown, 1988; Pozo *et al.*, 1990; Van Blerkom, 1991). The localization is presumably in response to localized energy needs. Available data indicate that correct mitochondrial distribution within the blastomeres is correlated with developmental potential, and hence oocyte and embryo quality (Barnett *et al.*, 1996). The mechanism responsible for this relationship is not entirely known, but may relate to providing local high concentrations of ATP within the cell.

Mitochondrial genome integrity may be sensitive to procedures that may affect oocyte quality. An increase in the incidence of mitochondrial mutations was reported for rhesus monkey oocytes produced by assisted reproduction methods (Gibson *et al.*, 2005). This indicates that unknown processes may affect maintenance of the mitochondria, and long-term health of offspring.

The mammalian oocyte and sperm are designed to achieve strictly matrilineal inheritance of mitochondria. Mitochondria and mitochondrial

DNA (mtDNA) are transmitted through the female germ line (Birky, 1995, 2001; Giles *et al.*, 1980; Hutchinson *et al.*, 1974). Mitochondria cannot be made *de novo*, only elaborated from other mitochondria, and thus derived from the oocytes (Cummins, 2000; Dawid and Blackler, 1972; Jansen, 2000; Shoubridge, 2000). The spermatozoon introduces up to 100 functional mitochondria into the ooplasm at fertilization; however, these are degraded rapidly in the preimplantation embryo via a ubiquitin-dependent process that targets ubiquitinated proteins on the sperm mitochondria (Nishimura *et al.*, 2006; Sutovsky, 2003; Sutovsky *et al.*, 1999, 2000). The mandatory destruction of sperm mitochondria may provide an evolutionary and developmental advantage (Ankel-Simons and Cummins, 1996; Cummins, 1998, 2000), because the paternal mitochondria and their DNA (mtDNA) may be compromised by the action of reactive oxygen species encountered by the sperm during spermatogenesis and fertilization (Aitken, 1994, 1995; Aitken and Fisher, 1994; Aitken *et al.*, 1999). The work on mitochondrial inheritance provided an explanation of how the fertilized egg destroys paternal mitochondrial genes (Sutovsky, 2003; Sutovsky *et al.*, 1999, 2000; Thompson *et al.*, 2003). As a consequence of such selective sperm mitochondrion destruction, mitochondria in humans and other mammals are typically inherited only from the mother. This inheritance pattern allows scientists to determine the lineage of human and animal evolution and to calibrate the evolutionary clock.

The destruction of paternal mitochondria should result in homoplasmic individuals, but there is evidence of sperm mtDNA persistence in human polyploid IVF-generated blastocysts (St. John *et al.*, 2000). The surveillance system that targets paternal mtDNA can apparently be abrogated in interspecific crosses, as shown in studies with mice (Gyllensten *et al.*, 1991; Kaneda *et al.*, 1995), fruit flies (Kondo *et al.*, 1990), sheep (Zhao *et al.*, 2004), and nonhuman primates (St. John and Schatten, 2004).

The coexistence of two or more mtDNA variants within a cell (heteroplasmy) can result from sperm transmission, interspecific crosses, or from supplementation arising through microsurgical procedures such as germinal vesicle transfer (GVT), cytoplasmic transfer (CT), pronulear transfer (PNT), or SCNT. The mixing of diverse nuclear and mtDNA fusion partners could compromise electron transfer channel (ETC) function and be disadvantageous for preimplantation or fetal development, and for survival of the offspring. Heteroplasmy can change amino acid composition, as shown in interspecific NT-offspring (Steinborn *et al.*, 2002; St. John *et al.*, 2005), and thus potentially alter protein conformation of the components of the ETC. Furthermore, as both mitochondrial and chromosomal genes contribute proteins to the ETC, the genetic divergence between the gene products of these genomes could also affect ATP output. The mtDNA can be either inherited from the recipient oocyte only or from both the donor cell and recipient oocyte (heteroplasmy) in NT. Such transmission has been

observed in both NT embryos (Lloyd *et al.*, 2006; Steinborn *et al.*, 1998) and their offspring (Evans *et al.*, 1999; Hiendleder *et al.*, 1999; Meirelles *et al.*, 2001; St. John and Schatten, 2004; Steinborn *et al.*, 2002).

Microsurgical techniques thus contravene the strict mechanism that regulates mtDNA transmission postfertilization. Intraspecific crosses in mice eliminate sperm mitochondria by the late 1-cell stage (Kaneda *et al.*, 1995; Shitara *et al.*, 2001), and before the 8-cell stage in cattle and rhesus macaque via a mechanism that requires mitochondrial protein ubiquitination (Sutovsky *et al.*,1999). With interspecific crosses, however, the ubiquitin-mediated proteolysis is avoided and sperm mitochondria persist at low levels (Gyllensten *et al.*, 1991; Shitara *et al.*, 1998). In cytoplasm transfers, successful human births have been achieved, and there is evidence that infants resulting from "ooplasm transfer" exhibit heteroplasmy (Brenner *et al.*, 2000; Harvey *et al.*, 2007; Van Blerkom *et al.*, 1998). Furthermore, the outcome of IVF in couples who underwent ooplasm transfer was poor due to low oocyte and embryo quality, possibly due in part to mitochondrial dysfunction (Harvey *et al.*, 2007). Some studies in mice failed to reveal detrimental effects of heteroplasmy on mouse development (Levron *et al.*, 1996; Meirelles and Smith, 1997, 1998; Takeda *et al.*, 2000). A recent study by Acton *et al.* (2007), however, screened basic physiological functions for heteroplasmic mice (NZB mtDNA on a BALB/cByJ background). The mice were tested for cardiovascular and metabolic function, hematological parameters, body mass analysis, ovarian reserve, and tissue histological abnormalities over a period of 15 months, and defects were seen in heteroplasmic mice in all tests.

4.5. Effects of the maternal pronucleus

Left unfertilized, oocytes are destined to die. One of the earliest things a fertilized embryo must do is to divert itself from a pathway of death to a pathway of life. Failure to suppress apoptotic events after fertilization leads to blastomere fragmentation, DNA fragmentation, and other typical signs of apoptosis, and indeed it has been suggested that insufficient suppression of these processes may constitute an important quality control mechanism to eliminate abnormal embryos at an early stage (Jurisicova *et al.*, 1998). Numerous recent studies have reported oocyte or blastomere fragmentation and/or apoptosis in a number of different mammalian species, including cow, mouse, and human (Antczak and Van Blerkom, 1999; Bergeron *et al.*, 1998; Bolton *et al.*, 1989; Brewster *et al.*, 2000; Byrne *et al.*, 1999; Casper and Jurisicova, 2000; Erenus *et al.*, 1991; Hardy, 1999; Hardy *et al.*, 1999; Jurisicova *et al.*, 1995, 1996, 1998; Liu and Keefe, 2000; Moley and Mueckler, 2000; Morita *et al.*, 1999, 2000; Otoi *et al.*, 1999; Pampfer, 2000; Perez *et al.*, 2000a,b; Van Blerkom and Davis, 1998; Watson *et al.*, 2000). Clinically, this reduces the number of high-quality embryos available

for establishing pregnancy of human embryos produced by IVF, >80% exhibit some degree of cellular fragmentation, and this propensity appears to be programmed by the 1-cell stage (Jurisicova *et al.*, 1996). The maternal pronucleus appears to play a commanding role in suppressing apoptotic processes. Mouse embryos produced with eggs from C3H/HeJ females display enhanced rates of blastomere fragmentation as compared to those made with eggs from C57BL/6 mothers (Han *et al.*, 2005). An extensive series of maternal pronuclear transfer experiments indicated that a C57BL/6 maternal pronucleus can suppress cytofragmentation regardless of the strain of origin of the ooplasm or paternal pronucleus, and conversely a C3H/HeJ maternal pronucleus can enhance the process (Han *et al.*, 2005). This is an interesting discovery, because other studies revealing greater rates of gene transcription in paternal as compared to maternal pronuclei (Aoki *et al.*, 1997; Henery *et al.*, 1995) indicated that the paternal pronucleus might exert a greater level of control over early development than the maternal pronucleus. However, it appears instead that the maternal pronucleus is endowed with the very important attribute of controlling apoptosis in early embryos, which is in fact the earliest documented effect of the embryonic genome on embryo phenotype. Interestingly, a parental origin effect of the maternal strain has also been observed (Han *et al.*, 2005; Hawes *et al.*, 2001), indicating a possible role for genomic imprinting in controlling apoptosis. This could account for why the maternal pronucleus plays such a predominant role in this early process, which would also make this the earliest known effect of imprinting on embryonic phenotype.

4.6. Effects of the ooplasm on paternal pronucleus function

While the maternal pronucleus itself exerts a commanding influence over early embryo apoptotic processes, a broader effect of the maternal genotype is seen in the potent influences over the early embryo via the ooplasm, particularly controlling the paternal genome. The ooplasm plays a key role in establishing early embryo phenotype by transforming the paternal genome into an integral component of the embryonic genome. Once fertilization occurs, the ooplasm directs the breakdown of the sperm nuclear envelope. The ooplasm then creates a paternal pronucleus (pPN) from the decondensed haploid sperm genome. This process involves extensive restructuring of the chromatin, as histones replace protamines and then subsequently undergo extensive posttranslational modifications in preparation for the onset of embryonic gene transcription (Latham, 1999; Latham and Schultz, 2001). Moreover, the paternal pronucleus undergoes enhanced changes in DNA methylation and histone acetylation, and displays evidence of increased transcriptional activity of injected transgenes as well as endogenous genes, relative to the maternal pronucleus (Adenot *et al.*, 1997; Aoki *et al.*, 1997;

Henery *et al.*, 1995; Lepikhov and Walter, 2004; Santos *et al.*, 2005; Van der Heijden *et al.*, 2005, 2006; Wiekowski *et al.*, 1993; Yeo *et al.*, 2005).

The interactions between the ooplasm and the paternal genome are subject to genetic variation. One example of this is the polar phenotype exerted by the Ovum mutant (*Om*) locus. This locus is responsible for the peculiar incompatibility between the DDK mouse strain and other strains, wherein DDK female X non-DDK male crosses produce 95% lethality by the morula stage, while the reciprocal cross is fully fertile (Wakasugi *et al.*, 1967). The trait is controlled by the *Om* locus on chromosome 11, and appears to consist of multiple genes, at least one of which is expressed as an mRNA and/or protein in the oocyte and at least one other gene that is expressed from the paternal genome and responds to this ooplasmic constituent to yield a nonviable phenotype (Baldacci *et al.*, 1992; Bell *et al.*, 2006; Mann, 1986; Pardo-Manuel de Villena *et al.*, 1997; Renard and Babinet, 1986; Renard *et al.*, 1994; Sapienza *et al.*, 1992).

Another example of ooplasmic control of paternal genome function is seen with androgenetic mouse embryos, which are prepared by microsurgery to contain two paternal pronuclei and no maternal pronuclei. Such embryos display differences in developmental potential to the blastocyst stage depending on the cytoplasm in which the paternal pronucleus forms (Latham, 1994; Latham and Solter, 1991). This reflects an effect of the ooplasm on the paternal genome very early during the 1-cell stage, and is attributed to two independently segregating loci on mouse chromosomes one and two (Latham and Sapienza, 1998; Latham and Solter, 1991). Collectively, these observations indicate that the paternal pronucleus undergoes extensive modifications that affect later paternal genome function and embryo phenotype, and that this is under the control of genes expressed in the oocyte.

A third possible instance of this interaction between ooplasm and paternal pronucleus can be seen with certain genetic combinations of mouse inbred strains C57BL/6 and C3H/HeJ, and outbred strains including CD1. The rate of cytofragmentation can be higher in simple crosses between these strains as compared to intrastrain crosses, so that oocytes from one strain will display enhanced fragmentation when fertilized by the sperm of one strain as compared to another (Jurisicova *et al.*, 1998; Han *et al.*, 2005; Hawes *et al.*, 2001). The genetic basis for this effect has not been revealed. It is possible that this relates to differences in sperm function, sperm components, and the quality of egg activation by the sperm (Ducibella *et al.*, 1993; Kono *et al.*, 1996; Moore *et al.*, 1993; Schultz and Kopf, 1995).

Why do such effects of the ooplasm exist over paternal genome function? One explanation is that genomic imprinting, like any biological process, is subject to genetic variation, and so is not identical between strains (Forejt and Gregorova, 1992). The epigenetic modifications of the paternal genome may require editing or modification in order to ensure

complementarity with the maternal strain. Without such editing, embryos could either over-express or lack expression of imprinted genes. Such effects may thus be revealed only in certain genetic combinations wherein the editing is imperfect, or via the extreme measure of performing pronuclear transfer to create unusual combinations of ooplasm and pronuclear genotypes. With respect to clinical practice, one can only speculate whether certain genetic combinations within couples may create similar incompatibilities, and thereby affect fertility or progeny phenotype.

5. Oocyte Polarity and Development

Across a wide range of animals, localized molecules in the oocyte provide information that directly determines cell fate or participates in the patterning of embryonic axes. Whether such determinants exist in mammalian oocytes has recently become an active area of study and subject of much debate. The mammalian oocyte is indeed polarized, with asymmetric distributions of microvilli and surface proteins, as well as an asymmetrically located meiotic spindle (Van Blerkom and Bell, 1986). The question thus arises whether cleavage occurs in such a way as to distribute materials unequally between daughter cells and whether this alters subsequent cell fates. Recent studies in the mouse involving marking the sperm entry point with lectin, monitoring the relationship between polar body position and blastocoel location, and marking the zona pellucida with oil droplets have led to the suggestion that this may occur (Gardner, 1997, 2001; Piotrowska *et al.*, 2001; Piotrowska and Zernicka-Goetz, 2001). The blastomere inheriting the sperm entry point is believed to divide first and this is believed to affect the fate of cellular progeny (Piotrowska and Zernicka-Goetz, 2001). Additionally, the sperm entry point and position of polar body are believed to define an early embryonic axis that provides an early bias affecting the position of blastocoel formation (Piotrowska and Zernicka-Goetz, 2001). These observations, while remarkable, have been called into question (Alarcon and Marikawa, 2003, 2005; Chroscicka *et al.*, 2004; Hiiragi and Solter, 2004; Louvet-Vallée *et al.*, 2005; Motosugi *et al.*, 2005). For example, upon detailed examination of time lapse videos of immobilized embryos, the positions of surface lectins and polar bodies are seen to change dramatically, and moreover the embryo can rotate within the zona pellucida, invalidating oil droplets in the zona pellucida as landmarks (Hiiragi and Solter, 2004, 2005, 2006). Mechanical forces rather than molecular specialization biases formation of the embryonic–abembryonic axis (Motosugi *et al.*, 2005). Lineage tracing studies in the mouse indicate that both blastomeres at the 2-cell stage contribute equally to the developing embryo (Alarcon and Marikawa, 2005; Chroscicka *et al.*, 2004; Motosugi *et al.*, 2005).

Moreover, twinning by embryo splitting is successful, as is development of demi-embryos when performed either at early cleavage (2-cell or 4-cell) stages or at the morula–blastocyst stage (Allen and Pashen, 1984; Johnson *et al.*, 1995; Matsumoto *et al.*, 1989; Oppenheim *et al.*, 2000; Ozil, 1983; Papaioannou *et al.*, 1989; Robl and First, 1985; Saito and Niemann, 1991; Seike *et al.*, 1991; Tarkowski, 1959a,b; Tsunoda *et al.*, 1984; Voelkel *et al.*, 1985; Yanagimachi, 2002). Two-cell stage blastomeres display equivalent developmental capacities in a substantial number of experimentally separated monozygotic pairs (Mitalipova *et al.*, 2002; Wildasen, 1979). Procedures that eliminate one blastomere at the 2-cell stage within the zona pellucida yield a high efficiency of blastocyst formation (Illmensee *et al.*, 2006; Tojo and Ogita, 1984). Demi-embryos can regulate their size during gestation (Lewis and Riossant, 1982; Papaioannou *et al.*, 1989; Rands, 1986; Tsunoda and McLaren, 1983). These observations that the fates of individual blastomeres are plastic and can be regulated are inconsistent with the idea that localized determinants exist in the mammalian oocyte and play an essential role in controlling early development (Alarcon and Marikawa, 2003).

6. Maternal Nutrition and Diabetes Affecting Oocyte and Embryo Quality

Beyond the need to support early embryogenesis, the importance of oocyte quality in determining future health of the progeny is becoming increasingly appreciated. One of the most startling discoveries in recent years has been that the health and disease status of adult offspring may be determined by maternal food consumption during a brief period at the time of conception. A low protein diet (LPD) given to female rats for the brief period of 4.5 days between fertilization and implantation, followed by a normal diet thereafter, reduces embryonic cell number, affects birth weight, and subsequently can lead to compensatory weight gain, hypertension, and alterations in organ/body weight ratios in adults (Kwong *et al.*, 2000). Periconception LPD (i.e., LPD during the preimplantation period) also can affect expression of imprinted and nonimprinted genes in progeny liver and affects the hypothalamo–pituitary–adrenal axis in fetal sheep (Kwong *et al.*, 2006, 2007). Interestingly, these effects display sex-dependent differences, suggesting either differential sex-dependent sensitivity or sex-dependent compensatory mechanisms. These observations collectively suggest that a range of adult diseases, including hypertension and subsequent kidney and heart disease, in many cases constitute birth defects arising during the first few days of life as a result of seemingly innocuous, short-term variations in maternal diet, a situation that has substantial clinical and societal importance.

The mechanisms by which maternal diet and the preimplantation embryo milieu affect long-term development are likely complex. The best-studied example of this relates to glucose availability. Exposure of embryos to elevated glucose levels (including via maternal hyperglycemia) leads to downregulation of glucose transporters and IGF1 receptors, followed by reduced glucose uptake, altered carbohydrate metabolism, and induction of apoptosis via a p53-dependent mechanism involving cell death effector pathways (Chi *et al.*, 2000a,b, 2002; Gäreskog *et al.*, 2007; Keim *et al.*, 2001; Moley, 1999, 2001; Moley *et al.*, 1996, 1998a,b; Riley and Moley, 2006). Insufficiency for glucose transporters compromises the ability of preimplantation stage embryos to cope with hypoxic stress (Heilig *et al.*, 2003). Reduced amino acid availability leads to reduced rates of cell division and later effects on blastocyst quality and stem cell lineages (Lane and Gardner, 1997). Amino acids are beneficial for blastocyst development and implantation (Biggers *et al.*, 2000; Devreker *et al.*, 1998, 2001; Lane and Gardner, 1997). Peri-conception LPD in the rat leads to a significant increase in maternal serum glucose and decrease in insulin between days 3 and 4 of treatment, returning to normal values by 2 days after return to normal diet. Coincidentally, the LPD led to depletion of six amino acids by day 4 of treatment (Kwong *et al.*, 2000).

The fact that LPD can both elevate glucose and reduce amino acids in maternal serum indicates that the embryos of these mothers may be forced to respond to both adverse conditions. The reduced cell number in both ICM and trophectoderm (TE) of blastocysts from mothers treated with peri-conception LPD could be explicable on the basis of either reduced cell proliferation, increased cellular apoptosis, or a combination of these, might result from the combined effects of elevated glucose and reduced amino acid availability. A slow rate of cleavage is correlated with reduced cell numbers in blastocysts, and reduced developmental potential, either to term (Gonzales *et al.*, 1995; Lonergan *et al.*, 1999; Lundin *et al.*, 2001; Sakkas *et al.*, 1995, 1998; Scott *et al.*, 2007; Wharf *et al.*, 2004) or for the *in vitro* production of embryonic stem (ES) cell lines (Chen *et al.*, 2005). Growth factors that promote cell proliferation and suppress apoptosis can improve development of embryos with reduced cell numbers (Glabowski *et al.*, 2005; Kurzawa *et al.*, 2004; Lin *et al.*, 2003), and can enhance the formation of stem cells (Lin *et al.*, 2003). Subsequently, the sizes of specific stem cell populations arising from downstream development of the ICM can affect the formation of specific organs (Stanger *et al.*, 2007). Thus, the size of the initial ICM population (the forerunner of all embryonic lineages) could significantly affect organogenesis by affecting the numbers of cells available to form critical units (e.g., nephrons). Moreover, a small ICM may contribute to fetal growth retardation and large placenta (Kwong *et al.*, 2000; Lane and Gardner, 1997), so that early effects on the ICM size can greatly affect fetal development, including

direct effects on the fetus itself as well as indirect effects via changes in maternal–fetal waste, nutrient, and oxygen exchange.

Even more striking than the relatively immediate effects of maternal diet during the preimplantation period is the potential for long-term effects even transcending generations—a grandmaternal effect. Maternal undernutrition during pregnancy and lactation can seriously compromise the health of offspring. Effects include low birth weights, obesity, type 2 diabetes, defects in organ development, hypertension, vascular and heart disease, and effects on brain, liver, and muscle function (e.g., Akahoshi *et al.*, 2006; Armitage *et al.*, 2007; Barker, 1997; Cox *et al.*, 2006; Godfrey *et al.*, 1994; Kelly *et al.*, 2005; Lau and Rogers, 2004; Oreffo *et al.*, 2003; Ozaki *et al.*, 2000; Painter *et al.*, 2006; Patera *et al.*, 2006; Petry *et al.*, 2006; Pires *et al.*, 2006; Ravelli *et al.*, 1998, 2005; Sayer and Cooper, 2005; Symonds *et al.*, 2007; Thone-Reineke *et al.*, 2006). Alternatively, modulating maternal diet can ameliorate genetic predispositions to certain diseases, and dietary antioxidants can ameliorate some effects of LPD (Cahill *et al.*, 2007; Sankaran *et al.*, 2006). Maternal diet prior to conception can affect oocyte quality (Adamiak *et al.*, 2005; Cambonie *et al.*, 2007; Hunter *et al.*, 2005). This effect on oocytes affects embryo quality and potentially fetal development and adult health, raising the possibility of effects on oocytes in the next generation, possibly producing further trans-generational effects. The effect of nutrient restriction is also believed to exert transgenerational effects in humans and rodents (Barker *et al.*, 1994).

7. Perspectives and Significance

The results summarized in this review highlight the truly remarkable qualities of the oocyte, along with the remarkable and complex oocyte–somatic cell interactions that endow the oocyte with these qualities. The oocyte is endowed with a rich legacy of proteins, mRNAs, and other macromolecules that direct and regulate early development. This legacy arises through essential biosynthetic processes that are directly affected by interactions with the follicular environment. Disruptions in these interactions can compromise oocyte quality. The creation of high-quality oocytes is thus sensitive to genetic and environmental factors. Additionally, the oocyte and early embryo can respond to exogenous stimuli and stressors, modulating their phenotype accordingly; however, these responses may compromise the ability of the oocyte to respond appropriately to the developmental milieu it encounters at a later stage. Thus, along with genetic and environmental factors, procedural variables employed for assisted reproduction methods in human and nonhuman species have the potential for long-term effects on embryo development and health of the offspring.

Our appreciation is increasing rapidly for the potential long-term effects of oocyte quality on embryo developmental capacity and adult health, as well as potential transgenerational effects that may arise through self-perpetuating rounds of effects of maternal physiology and oogenesis/oocyte quality on each other. As our understanding of the molecular mechanisms that drive early development and control oocyte and embryo responses to their environments improves, so too should we see increases in our understanding of what specific characteristics denote high-quality oocytes, what specific stimuli or factors compromise or enhance oocyte quality, and how the availability of high-quality oocytes can be improved for clinical and applied purposes. The prospects for improved efficiencies in infertility treatment, contraception, bioengineering of domestic species, and species preservation of endangered species are therefore quite favorable. From a basic science perspective, anticipated advances in understanding oocyte control of nuclear function would yield broadly applicable lessons for understanding gene regulation, and for achieving new success in the development of emerging technologies for stem cell derivation and stem cell-based therapeutic applications. The oocyte indeed provides the essential life-generating force for combining gametes to create a new, functional, and viable individual. Continued improvement in understanding the mechanisms at play should provide us with a much greater appreciation for the remarkable fact of our very existence, where we came from, and what lies on the road ahead.

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