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Epigenetic regulation during mammalian oogenesis

John Bromfield[A,B], *Will Messamore*[A,B] *and David F. Albertini*[A,B,C,D]

[A]Department of Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas City, KS 66160, USA.
[B]The Center for Reproductive Sciences, University of Kansas Medical Center, Kansas City, KS 66160, USA.
[C]Marine Biological Laboratory, Woods Hole, MA 02543, USA.
[D]Corresponding author. Email: dalbertini@kumc.edu

Abstract. The advent of the epigenetic era has sparked a new frontier in molecular research and the understanding of how development can be regulated beyond direct alterations of the genome. Thus far, the focal point of epigenetic regulation during development has been chromatin modifications that control differential gene expression by DNA methylation and histone alterations. But what of events that alter gene expression without direct influence on the DNA itself? The present review focuses on epigenetic pathways regulating development from oogenesis to organogenesis and back that do not involve methylation of cytosine in DNA. We discuss target components of epigenetic modification such as organelle development, compartmentalisation of maternal factors and molecular mediators in the oocyte and how these factors acting during oogenesis impact on later development. Epigenetic regulation of development, be it via cytosine methylation or not, has wide-ranging effects on the subsequent success of a pregnancy and the intrinsic health of offspring. Perturbations in epigenetic regulation have been clearly associated with disease states in adult offspring, including Type II diabetes, hypertension, cancers and infertility. A clear understanding of all epigenetic mechanisms is paramount when considering the increased use of assisted reproductive techniques and the risks associated with their use.

Additional keywords: assisted reproductive technique, developmental programming, embryogenesis, methylation.

Introduction

The notion that the fertilised egg and its subsequent development rely upon the imposition of competencies during oogenesis has been emphasised. At the genetic level, a host of genes and their protein products has been implicated in the post-fertilisation success of mammalian embryos. In some cases, these gene products are stored as either mRNAs, microRNAs or as proteins that linger zygotically for varying amounts of time only to be called into action at a specific developmental transition to sustain embryonic progression. Such products are often referred to as those of maternal effector genes because they represent female germ line entities that are critical for embryogenesis. In addition to the ever-growing list of oocyte genes that are involved in the development of oocytes, follicles or embryos, several epigenetic factors have been identified that play perhaps even more central roles in establishing and maintaining pregnancies resulting in the birth of healthy offspring.

Epigenetics has emerged as a fascinating field within developmental biology, as evidenced when the absence of a specific gene or its protein product cannot adequately address frank embryonic/fetal loss or functional impairments apparent in neonates or adults. In 1942, Conrad Waddington first coined the term epigenetics as 'the branch of biology which studies the casual interactions between genes and their products' (Waddington 1942). Simply stated for the purposes of the present review, epigenetics involves molecular and cellular modifications required during early development that are truly independent of detectable changes in a gene's structure or function, a phenotypic change in the absence of a genotypic change. Thus, the networks of cell behaviours elicited during normal development, including metabolic, signalling and protein interactive events, must reflect patterns of cell organisation laid down in the egg during oogenesis. There can be little doubt that the epigenetic factors elaborated during oogenesis operate and carry out their functions in collaboration with activities and entities that result from activation of the zygotic genome. However, for the purposes of the present review, we will focus on true oogenetic determinants whose functions have been gleaned primarily from studies on mice. For this reason, only generally accepted parallels in domesticated species and humans will be drawn upon. In addition, our emphasis will be on the periods of greatest sensitivity during oogenesis, where impairment of epigenetics will have dire consequences on either pregnancy success or offspring health status. Thus, the notion that perturbation of events at critical junctures during oogenesis impact in lethal or non-lethal ways on the embryo, fetus or neonate will be offered to provide new direction for understanding the effects of maternal ageing on fecundity, as well as possible mechanisms whereby the epigenetic competence of an embryo can be traced back to intraovarian events at various stages of the life cycle. This latter

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Table 1. Post-fertilisation effectors of epigenetic regulation
ICM, inner cell mass

Influencing factor	Location	Time	Action	References
Maternal nutrition	Ovary, oviduct, uterus	Periovulatory → third trimester	Indirect: fetal programming of metabolic framework Direct: DNA methylation	Roseboom *et al*. 2001; van Engeland *et al*. 2003; Elias *et al*. 2005
Organelle topography	Oviduct	Preimplantation	Mitochondrial number and distribution	McConnell and Petrie 2004; Taylor *et al*. 2005
Cellular allocation	Fertilisation	Fertilisation → blastocyst	Changes in ICM: trophectoderm ratio	Kwong *et al*. 2000
Embryonic promoting factors	Oviduct, uterus	Preimplantation	Growth factors and buffering agents to promote and protect embryonic development	Sjoblom *et al*. 1999; Schultz and Heyner 1993
Embryonic disrupting factors	Oviduct, uterus	Preimplantation	Environmental toxins, oxidative stress, ammonium	Susiarjo *et al*. 2007; Lane and Gardner 2003
Placental development		Implantation → term	Fetal stress and undernutrition	Kind *et al*. 1995

topic is especially relevant to mounting concerns in the arena of assisted reproductive technology (ART).

The epigenetic egg: thinking beyond oogenesis

Although the emphasis of the present review is focused towards understanding the epigenetic mechanisms that may be occurring during oogenesis, and ultimately impacting on embryo development and postnatal health, a concise review of these mechanisms would not be complete without consideration of the research focused on epigenetic mechanisms affecting the zygote during the post-fertilisation period.

The earliest of studies defining post-fertilisation effects on postnatal development focused on a cohort of individuals who underwent gestation during the Dutch famine during World War II. Extensive medical records during this time allowed researchers some 50 years later to identify individuals whose mothers suffered caloric restriction during one of the three trimesters of pregnancy (Roseboom *et al*. 2001; Elias *et al*. 2004, 2005*a*, 2005*b*). Many of these retrospective studies have been able to demonstrate a link between these periods of caloric restriction and specific predispositions to disease states during adulthood, particularly, but not restricted to, those of a metabolic nature, including Type II diabetes, hypertension and obesity (Roseboom *et al*. 2001). Most of these studies did not specifically identify epigenetic modifications as a cause of the phenotypes witnessed in many of these individuals, but it is difficult to perceive another mechanism that could be responsible. Predominately, these effects have been associated with a programming of the fetus' own metabolic pathways in response to the environment to which its mother is being exposed, to ready the fetus for the ensuing environment in which it must survive (Hales and Barker 2001). Since these earlier studies, many groups have undertaken research strategies to identify particular pathways in which this programming may occur in a post-fertilisation setting (Table 1). Many groups have persisted with using various models of caloric restriction in animal models, altering the nutritional value of the maternal diet (high caloric, low protein/isocaloric) and, of greater interest, the time and duration in which these actions occur. It has been demonstrated that an isocaloric/low-protein diet during the peri-implantation or peri-ovulatory period can drive the development of obesity and early onset hypertension in subsequent offspring, the latter (peri-ovulatory) implicating that even the final stages of meiotic maturation may be affected by as little as an 8% reduction in maternal protein consumption for only 3 days before ovulation (Kwong *et al*. 2000; Watkins *et al*. 2007).

Since the 1960s, dietary folate intake during and before pregnancy has been associated with establishing and maintaining a healthy pregnancy (Lowenstein *et al*. 1966). More recently, van Engeland *et al*. (2003) have demonstrated that enzymes involved in methylation and demethylation of the genome during epigenetic imprinting are regulated by folate intake and availability, suggesting that maternal diet may directly influence epigenetic programming of the conceptus during development. In addition, it has been shown that, in mice, methyl dietary supplements can alter methylation of specific imprinted genes (Cooney *et al*. 2002). Although these dietary and nutritional restriction models are invaluable for understanding the development of adult disease, they are yet to lead to elucidation of the epigenetic pathways leading to these and other aetiologies.

The advent of the epigenetic era, in conjunction with available molecular and microscopy technologies, has allowed researchers to begin to determine some of the biochemical and cellular pathways leading to anomalous epigenetic modifications during development. It is believed that any manipulation of or adverse effect on the oocyte or zygote will drive compensatory cellular responses, ultimately leading to alterations in gene expression during early development. Alterations in gene expression may arise from either changes in direct epigenetic programming of the egg or, alternatively, through changes in transcriptional activity. These observations have clearly been demonstrated using

in vitro-produced embryos where culture conditions lead to altered patterns of gene expression (Niemann and Wrenzycki 2000). Differential methylation of the genome has also been demonstrated as a result of *in vitro* embryo culture, showing a clear susceptibility of the conceptus to epigenetic reprogramming at this time (Khosla *et al*. 2001; Young *et al*. 2001). Embryo-promoting factors, including growth factors, or buffering agents have also been used in *in vitro* culture to aid in embryonic development and survival. Rinaudo and Schultz, using a microarray approach, demonstrated that even changes in the composition of the culture media can change global gene expression patterns in the embryo (Rinaudo and Schultz 2004; Rinaudo *et al*. 2006). This work has aided in the development of culture media supplemented with exogenous embryo-promoting factors and buffering agents to support embryonic development under conditions that better reflect the *in vivo* developmental environment. This reinforces the notion of a more Lamarckian evolutionary principle, because environmental conditions lead to marked changes in gene expression during mammalian development.

Any stressor affecting the embryo during development may influence gene expression and therefore alter the developmental competence of the embryo. Changes in intracellular redox state have been shown to alter expression of oxygen-sensitive genes (Harvey *et al*. 2007), whereas exposure to environmental toxins has been shown to alter gene expression and embryonic developmental competence (Susiarjo *et al*. 2007). Ammonia accumulation within *in vitro* culture media can again lead to perturbed embryonic developmental competence via altered gene expression (Lane and Gardner 2003). Changes in organelle number and distribution have been associated with stressors during development. Mitochondrial DNA is derived solely from the maternal genome and is replicated for only a very short period following fertilisation, suggesting a very short period when external factors can influence mitochondrial number. Mitochondrial number and function have been shown to be altered in embryos following either altered maternal protein consumption or *in vitro* embryo culture and are maintained beyond postnatal development (McConnell and Petrie 2004; Taylor *et al*. 2005). Perturbations to embryonic development due to *in vitro* culture have demonstrated imbalances in the allocation of blastomeres between inner cell mass and trophectoderm cell lineages (Lee *et al*. 2004). In this light, embryo culture has been shown to alter placental morphology and function (Sjoblom *et al*. 2005). In addition, placental insufficiencies adversely affect fetal development, including the onset of adult disease (Hayashi and Dorko 1988; Anderson *et al*. 2006). Early alterations in gene expression, particularly of imprinted genes, may be a key driving force in perturbing placental development and function, resulting in altered fetal development, and may impact blastomere fate allocation during earlier development. Several imprinted genes have now been identified, many of which have direct roles in placental development (Coan *et al*. 2005).

Children arising from *in vitro* embryo culture have been shown to have altered birthweights, which have been the most historical epidemiological link in the onset of adult metabolic diseases (for a review, see Barker 1998). Approximately 2–3% of the national birth rate of many Western countries comprises babies born from ART, resulting in babies of an increased incidence of preterm birth, lower birthweight for gestational age and some suggestion of increased birth defects. Imprinting disorders, such as Angelman and Beckwith–Wiedemann syndromes, have also been closely associated with babies derived from ART, suggesting that the improper imprinting that occurs to the embryo as result of *in vitro* culture may be the penultimate cause for the disposition to these syndromes (Cox *et al*. 2002; DeBaun *et al*. 2003; Maher *et al*. 2003; Orstavik *et al*. 2003).

The links between the pre- and post-fertilisation events that impact the epigenetic programming responsible for altered development postnatally have yet to be defined clearly. However, the accumulation of evidence from epidemiological, *in vitro* and *ex vivo* culture, in addition to many observational studies defining actions resulting in perturbations at any stage of development, are now beginning to demonstrate a process of epigenetic reprogramming throughout development from oogenesis, organogenesis and back. The recent demonstration of the transgenerational effects of environmental stressors (Skinner 2007) is evidence of the continuum of susceptibility from oogenesis throughout development; this is of particular relevance when considering the foundation for the next generation and its establishment in the oocyte during gestation.

Epigenetic principles governing oocyte development

There are many generally acknowledged features of the mammalian oocyte that link basic architectural aspects of egg design to the more immediate consequences apparent in the preimplantation embryo. Before reviewing these, it is important to point out that the production of epigenetically competent oocytes is a by-product of the germ cell's life history within the ovary. The coordination of folliculogenesis with oogenesis clearly requires a balance of cellular interactions between the ovarian somatic components and the oocyte and the feedback interactions that are mediated by hormones and growth factors within the hypothalamic–pituitary–gonadal axis (Combelles *et al*. 2004). How circadian rhythms participate in this complex multicellular dialogue is only now being uncovered (Karman and Tischkau 2006) and is beyond the scope of the present review. Many elements of these feedback mechanisms are resolved, but suffice to say that disturbances in somatic physiology are likely to impact the epigenetic quality of oocytes depending on the stages of oogenesis that are at risk during fetal, prepubertal or adult phases of the life cycle.

Among the hallmarks of oocytes that successfully complete oogenesis are those that relate to specific post-fertilisation functions in the egg (Table 2). Thus, the elaboration of the zona pellucida illustrates one of the earliest structures that will ultimately present a substrate for interaction with sperm and cumulus cells. Similarly, the hypertrophic growth of the mammalian oocyte requires reduplication of most intracellular organelles, such as mitochondria, Golgi complex, lysosomes and endoplasmic reticulum, not only for sustaining adequate levels of protein synthesis, but also the sequestration of calcium within vesicles that are invoked at fertilisation. That the germinal vesicle is modified at the level of chromatin patterning has been studied in many mammals and generally these alterations in the location and extent of heterochromatisation are linked to

Table 2. Hallmarks of oocyte epigenetic competence
MTOCs, microtubule-organising centres

Target component	Developmental modification
Organellar	Composition/number
	Positioning
Nuclear	Architecture
Cortical	Differentiation
	Cortical granules
	Microvilli
	Actin
	MTOCs
Zona pellucida	Sperm and cumulus interaction
Molecular mediators	Cell cycle factors
(mRNA and protein)	Spindle assembly
	Polar body extrusion
	Localisation machinery
	Protein synthesis and degradation
	Calcium sequestering

timely changes in transcription that assure large-scale repression before fertilisation. Interestingly, it is at the later stages of oocyte growth that heterochromatisation is initiated, a time when both oocyte imprints are established (Obata and Kono 2002) and hormone-regulated oocyte–granulosa interactions are diminished (Combelles *et al*. 2004). Finally, although often overlooked, a large degree of cortical differentiation is required in the oocyte for its successful transition into embryogenesis. Multiple Golgi complexes mediate the synthesis and packaging of cortical granule contents and the cortical granules themselves must adopt a subplasmalemmal position in spatial compliance with the calcium-sequestering vesicles alluded to earlier. When combined with the deployment of microvilli, and the dynamic web of actin filaments that will mediate cytokinesis during polar body extrusion and blastomere cleavage, this complex network is likely to be central to protein localisation for prolonging the lifespan of maternal gene products well into embryogenesis (refer to the example of DNA methyltransferase (dMNT1) (Table 3) or below). Thus, careful positioning of both organellar components, including the germinal vesicle, and components of the cytoskeleton represents the macromolecular outcome of oogenesis. That additional cytoskeletal and extracellular signals modulate this cortical differentiation observed in mammalian oocytes has also been proposed (Albertini and Carabatsos 1998).

On a more subtle level, but equally important in terms of epigenetic regulation, molecular mediators have been identified in many systems that function to render key catabolic, metabolic or signalling pathways functional or not. A few examples relevant to oocyte epigenetics are listed in Table 3. As will be considered below, many factors that regulate key transition points in the cell cycle assume non-random localisation in order to generate rapid and complete effects, assuring synchronisation of kinase activation and timely ubiquitinisation at M-phase cell cycle entry and exit, respectively. Regulating cytoplasmic access is accomplished by nucleolar sequestration in yeast (Carmo-Fonseca *et al*. 2000). Centrosomes, in contrast, function to limit the diffusional capacity of the many components involved in cell cycle progression by complexing these factors to motor molecules that target and maintain their presence at microtubule-organising centres (MTOCs). Finally, the spindle itself serves to harbor and stabilise many factors that are involved in the timely degradation of cyclins that elicits the metaphase–anaphase transition during the M phase. Collectively, then, the emerging concept that, through specific interactions with the cytoskeleton and other organelles, mRNAs and proteins can be localised, stabilised and/or rendered available for activating post-translational modification or gaining access to the nuclear compartment deserves consideration in the context of oocyte epigenetics. In fact, provocative findings suggest this to be an important element of egg design with immediate relevance to embryogenesis.

One of the first examples of the importance of protein localisation during mouse development came from the studies of Ratnam *et al*. (2002). These authors characterised an oocyte-specific splicing variant of the dimethyltransferase 1 gene, known as *Dmnt1o*, and showed that knocking out this gene resulted in arrest of development at the morula stage, a time that would coincide with the remethylation of male and female genomes. One possibility was that the mRNA for this protein was stored for regulated translation at this stage. Instead, it was found that the mRNA was translated during the growth phase of oogenesis and the protein product was localised in the oocyte cortex, where it remained until the eight-cell stage. At this point, *Dmnt1o* moved into the nucleus, where it effected its chromatin-modifying activity. Interestingly, another variant of *Dmnt1* was also translated during oogenesis and served to methylate maternal imprints but was degraded once this was accomplished (see Table 3). These elegant studies illustrate several important epigenetic principles, namely that protein localisation ensures functional activity and protection from degradation and prevents premature nuclear localisation. This mechanism for regulating nuclear access is also likely to underscore the regulation of the meiotic cell cycle in oocytes because, as mentioned earlier, catalytic events that must be coordinated temporally are often spatially segregated in order to limit spurious activation during meiotic resumption (Mitra and Schultz 1996; Albertini and Carabatsos 1998).

There is a growing list of epigenetic regulators that impact the completion of meiosis, the transition into the embryonic mitotic cell cycle and subsequent events related to morphogenesis and chromatin remodelling (Table 3). Although this list is not comprehensive, it does serve to illustrate how the chronological readout of oocyte-specific gene products dictates key transition points in early embryogenesis and the importance of mRNA or protein processing well after transcription has occurred. For example, cMOS, a proto-oncogene, has long been known to effect the block in the meiotic cell cycle at metaphase 2 in mammalian oocytes (Colledge *et al*. 1994). In mice, the relevant knockout phenotypes have been documented and, in the case of cMOS, its elimination results in the unregulated transition from meiosis to mitosis that causes parthenogenetic activation of the egg. Nucleoplasmin 2 (NPM2) causes arrest at the one-cell stage due to impairment of pronuclear apposition (Burns *et al*. 2003). Expectedly, some maternal effect genes disrupt compaction, the process during which inner cell mass and trophectoderm allocation takes place as outer cells acquire the properties of a polarised

Table 3. Examples of molecular epigenetic regulators
Specific maternal effect genes are designated based on storage as either mRNA (r) or protein (p). PB, polar body; MII, meiosis stage 2; NMP2, nucleoplasmin 2; KO, knock out

Gene	Function	Impact of loss	KO phenotype
cMOS (r)	Arrest meiosis (MII)	Dysregulated first cell cycle	Pathogenesis Large PB
E-Cadherin (p)	Compaction	Impaired lineage allocation	Arrested morula
NMP2 (p)	Pronuclear maturation	Cell cycle delay	Arrested one cell
Dmnt1o (p)	Chromatin methylation	Modified methylation	Arrested morula
γ-Tubulin (p)	Embryonic mitosis	Arrested cell cycle	Arrested morula

epithelium (Selwood and Johnson 2006). These factors include E-cadherin, a protein essential for altering blastomere adhesive properties that result from the insertion of cytoplasmic protein into the blastomere plasma membrane (Selwood and Johnson 2006), and γ-tubulin. γ-Tubulin is a key regulator of microtubule assembly owing to its localisation to the centrosome. Gamma tubulin 1 (GT1) is a ubiquitous variant that, if deleted, results in the arrest of embryos at the time of compaction (Yuba-Kubo *et al*. 2005). Although these embryos do proceed to compact, they are unable to progress through the cell cycle due to the role GT1 plays in the centrosome to harbour and regulate the activation of cdk1/cyclin complexes. The fact that zygotic gene activation coincides with the massive depletion of maternal mRNAs serves to emphasise what may be a general rule for epigenetic control of early development: oocyte gene products as proteins are better served to effect their regulatory activities than their respective mRNAs owing to mechanisms that allow for their selective localisation and protection from degradation. It will be interesting to determine whether such mechanisms operate in eggs of other mammalian species, where current emphasis has been placed on mRNA displays rather than protein products. In this light, recent work on mouse oocytes has documented a role for tyrosine kinases in the regulation of the first embryonic cell cycle and, here too, components of the signalling machinery for the pathway exhibit distinct patterns of localisation to both the spindle and cell cortex (McGinnis *et al*. 2007).

In summary, this section has illustrated the importance of spatial localisation, as documented in the experimentally tractable murine model system. The success of a zygote is contingent on the zygote's ability to sequester and stabilise maternal effector genes as mRNAs, microRNAs or proteins, as well as the zygote's ability to recruit these effectors for embryonic progression at proper time-points. Thus, establishing and maintaining positional information is likely to be regulated by cytoskeletal elements within the zygote. Future studies will be needed to assess the relative roles of nuclear cytoplasmic transport, cortical binding and cytoskeletal interactions that may dictate the properties of stability and spatial patterning relevant to the early stages of development in mammals.

Future directions

The concept of an epigenetically competent oocyte has been introduced to explain how the design of the mammalian oocyte impacts directly on the post-fertilisation development of the conceptus independent of zygotic gene regulation. How these regulatory principles are modified by environmental factors is not understood, but two areas in reproductive biology seem to be likely targets for study in this vein. First, the widespread use of ART in animals and humans often draws attention to the epigenetic burdens that are placed on gametes and embryos that may affect the viability and health of offspring produced with these technologies. Chromatin remodelling, as noted earlier, is often cited as a cause for developmental failures and, in most cases, defects in DNA methylation have been identified as a contributing factor. However, it remains to be shown discriminately what mechanistic defects underlie inappropriate imprinting. Perhaps, with new technologies that would allow for an assessment of the dynamic nature of chromatin remodelling factors, new insights of relevance to improvements in ART will be obtained.

A second area of active investigation is the problem of reproductive ageing in the practice of human ART. Current models to explain defects in oocytes that underlie age-related pregnancy loss and congenital defects focus on the status of oocyte chromatin during oogenesis and the impact that chiasma or telomeres may have on the processes of chromosome segregation before and after fertilisation (Susiarjo *et al*. 2007). It seems equally relevant to consider that gradual changes in lifestyle, environmental exposure and hormonal imbalance target aspects of the epigenetic regulation in the oocyte that bear directly on compromised developmental competence. These prospects are already being realised and are indicating that many steps during oogenesis may be at risk to modifications in epigenetic programming that will have long-term consequences on the health of offspring. Realising the imperative to expand research in this area will advance the quality of life in humans and animals for years to come.

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