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Listening to mother: Long-term maternal effects in mammalian development

Meghan L. Ruebel, **Keith E. Latham***

Department of Animal Science, and Reproductive and Developmental Sciences Program, Michigan State University, East Lansing, MI, 48824 U.S.A.

Abstract

The oocyte is a complex cell that executes many crucial and unique functions at the start of each life. These functions are fulfilled by a unique collection of macromolecules and other factors, all of which collectively support meiosis, oocyte activation, and embryo development. This review focuses on the effects of oocyte components on developmental processes that occur after the initial stages of embryogenesis. These include long-term effects on genome function, metabolism, lineage allocation, post-natal progeny health, and even subsequent generations. Factors that regulate chromatin structure, genome programming, and mitochondrial function are elements that contribute to these oocyte functions.

Keywords

oocyte; maternal effect; chromatin; embryo gene regulation

Introduction

In addition to the essential maternal genetic contribution to each offspring, the oocyte has the unique function of providing a vast reservoir of macromolecules that sustain early embryogenesis, control essential metabolic functions, and mediate initial programming of the embryonic genome so that it can execute the appropriate sequence of events to create a new individual. Many maternal effects are readily apparent through early, direct negative consequences during embryo life when they are disrupted. Across diverse species such effects encompass mutations that compromise essential early oocyte functions such as meiosis or yolk deposition, localized ooplasmic determinants in some species, and chromatin regulators and other factors that are required for genome programming and activation (Condic, 2016).

But oocyte factors can also exert long-term effects in development. Early events occurring soon after fertilization may restrict or dictate how later events will unfold, impacting the development or health of the progeny much later, possibly even during post-natal and adult

*Correspondence: 474 S. Shaw Lane, room 1230B, East Lansing, MI 48824, tel. 517-353-7750 fax: 517-353-1699, lathamk1@msu.edu.

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life or even transgenerationally (Figure 1). The scope and impacts of these less immediate and less direct maternal effects continue to be discovered. Such maternal effects are also taking on new and expanding importance as researchers endeavor to understand the oocyte's role in developmental origins of health and disease (DOHaD), particularly in the context of maternal health and nutrition effects on oocyte quality (Andreas, Reid, Zhang, & Moley, 2019; Matorras et al., 2020) and, for example, adult cardiovascular disease (Ferey et al., 2019; Velazquez, Fleming, & Watkins, 2019). Not only might the environment impact the oocyte, and thereby lead to short- and long-term effects on embryogenesis, but genetic variation in the inherent features of oocytes may also determine the responses of oocytes and embryos to different environmental factors and stressors. This lends new relevance to achieving a more complete understanding of maternal effect genes of the oocyte, and how they are connected to long-term health and viability in progeny.

Many other maternal effect genes in mammals have been described that impact key early processes, which, when disrupted, are associated with early embryo demise (Lu, Gao, Qin, & Li, 2017) (Condic, 2016). While the study of such mutations is valuable for understanding essential early developmental processes, its relevance to understanding long-term phenotypic effects is limited. This review focuses on components of mammalian oocytes that have more long-term, less immediate and broader-acting maternal effects on embryo and progeny phenotype. These examples include some specific maternal effect genes, but also include organelle and genome-wide factors in oocytes that have long-term, even life-long impacts on progeny phenotype. The lessons taught to us by recognizing such long-term maternal effects in mammals should provide insight into mechanisms by which early processes that occur in the oocyte set the stage for later developmental events that determine progeny viability and health.

Oocyte histones and histone modifiers

One of the main tasks of oocytes is to progress through meiosis and segregate a haploid complement of chromosomes to the embryo. This task is classified as one of the early acting maternal effects and is essential for normal meiosis and quality of the oocyte and prevent of aneuploidy in the embryo (Figure 1). Recent studies revealed epigenetic changes in the genome that enable meiosis (Huang et al., 2012; Ma & Schultz, 2013). These changes also control gene expression, at least during initial stages of embryogenesis. Additional epigenetic changes in the zygote are mediated by oocyte-expressed histone modifying proteins or mRNAs encoding them. Because such epigenetic changes can exert long-term effects on gene expression, epigenetic actions of oocyte components may dictate more long-term events.

One of the changes that appears to be key for meiosis is histone deacetylation. The meiotic spindle assembly is driven in part by the binding of the chromosome passenger complex to the chromosomes via deacetylated histone H3 and H4 (Akiyama, Kim, Nagata, & Aoki, 2004; Akiyama, Nagata, & Aoki, 2006; Balboula, Stein, Schultz, & Schindler, 2014; Bui et al., 2007; Q. Wang et al., 2006). Histone deacetylation also contributes to transcriptional silencing and formation of the surrounded nucleolus nuclear state in oocytes (De La Fuente, Viveiros, Burns, et al., 2004; De La Fuente, Viveiros, Wigglesworth, & Eppig, 2004; Lee,

Wildt, & Comizzoli, 2015). Inadequate histone deacetylation is associated with increased aneuploidy, aberrant oocyte meiosis (Huang et al., 2012; Ma & Schultz, 2013, 2016) and with reduced oocyte quality accompanying aging (van den Berg et al., 2011). Histone deacetylases also regulate the activities of other proteins, and inhibition of this process can also disrupt spindle formation in mitotic and meiotic cells (Chuang, Pan, Hawke, Lin, & Yu-Lee, 2013; Gabrielli & Brown, 2012; X. Li et al., 2017; Shin et al., 2003). Excess histone acetylation may account in part for increased rates of aneuploidy seen in cloned constructs made by transferring somatic cell nuclei to oocytes (Mizutani et al., 2012; Nolen et al., 2005). Although histone deacetylase inhibitors (HDACis) may help program some genes for expression in clones to improve early development (Laguna-Barraza, Sanchez-Calabuig, Gutierrez-Adan, Rizos, & Perez-Cerezales, 2018; Mizutani, Wakayama, & Wakayama, 2015), a potential downside could be disruption of spindle formation and possibly aneuploidy. Histone deacetylation may be sensitive to exogenous factors such as excessive follicle stimulating hormone or stress, which can also induce oocyte aneuploidy (Roberts et al., 2005; Salvador et al., 2001; Xu et al., 2011). The histone deacetylases: HDAC1, HDAC2, HDAC3, RBBP4, RBBP7, and Haspin are implicated in histone deacetylation in oocytes (Balboula et al., 2014; Balboula, Stein, Schultz, & Schindler, 2015; De La Fuente, 2014; Eot-Houllier, Fulcrand, Watanabe, Magnaghi-Jaulin, & Jaulin, 2008; Ma & Schultz, 2013; Q. Wang et al., 2006). One study in porcine oocytes found that class I HDACs in the germinal vesicle were not responsible for global deacetylation, and that instead other cytoplasmic HDACs were responsible (Endo, Kano, & Naito, 2008). Histone methylation may also contribute to meiosis (X. Wang et al., 2014). The correct modulation of histone acetylation and methylation in the oocyte, which regulates not only meiosis but also potentially other transcription factors, may set the stage for long-term effects on development and embryo phenotype.

Histone demethylation driven by oocyte-derived histone demethylases has emerged recently as a key process in remodeling paternal genomes following fertilization (Endo et al., 2008; Hatanaka et al., 2017; Jenkins & Carrell, 2012; Yamagata & Okada, 2011). Additionally, cloned embryos display enhanced developmental potential if the somatic cell nuclei are subjected to increased activities of a range of histone demethylases (Chung et al., 2015; X. Liu et al., 2018; Z. Liu et al., 2018; Matoba et al., 2014; Wei et al., 2017; Y. Zhang et al., 2018). The ability of histone demethylases to positively influence cloned embryo developmental potential implies an important role in the correct programming of normal embryonic nuclei for long-term function and embryo phenotype. Histone demethylation also contributes to embryonic genome activation (Dahl et al., 2016).

Another important maternally derived histone is the histone variant H3.3. Although present in both sperm and egg, paternally-derived H3.3 is lost after fertilization (Kong et al., 2018). Maternally-derived H3.3 associates with the paternal chromatin, remains detectable in the nuclei until the morula stage, and is essential for correct transcription from the paternally derived chromosomes, the correct expression of the key pluripotency gene *Oct4/Pou5f1*, and embryo pre-implantation viability (Kong et al., 2018). This latter effect on *Oct4/Pou5f1* suggests a possible long-term maternal effect of oocyte-derived H3.3 level on progeny phenotype.

The histone demethylase, KDM1A, also exerts-long-term maternal effects, as well as contributing to embryonic genome activation. Conditional knockouts achieving complete ablation of oocyte-expressed KDM1A using the *Gdf9* or *Zp3* promoters in mice prevents embryonic genome activation and arrests embryos by the two-cell stage (Wasson et al., 2016). However, an alternate conditional knockout allele using the *Vasa* promoter that reduces KDM1A by about 67% allows approximately 5% blastocyst formation and a low rate of development to birth. But this is followed by a significant rate of perinatal mortality and abnormal behavior (excessive scratching, digging and food grinding, and anxiety in survivors as well as imprinting defects (Wasson et al., 2016), demonstrating a long term maternal effect of reduced oocyte expression.

The euchromatic histone lysine N-methyl transferase (EHMT2, a.k.a., G9A), may contribute to essential lineage-regulation during preimplantation development. Ablation of both maternal and embryonic sources of this protein leads to a failure to repress certain genes at the four-cell stage, and subsequent dysregulation of lineage segregation at the blastocyst stage (Zylicz et al., 2018). This suggests that the maternally expressed EHMT2 could contribute to the correct programming of later gene expression patterns that contribute to optimum lineage formation, but long-term studies would be needed to confirm this.

These observations highlight the dramatic remodeling of histones associated with meiosis and early embryogenesis, and mediated by oocyte-expressed histones and histone modifiers. They also provide a powerful demonstration of how the histone modifications driven in oocytes and by oocyte-expressed factors contribute to long-term gene regulation and developmental phenotype.

Other oocyte-expressed chromatin remodeling factors impacting later events

Besides the histone variants and histone modifiers described above, other ooplasmic factors drive early events that regulate the genome in the embryo, with long-term impacts. In mammals, for example, many studies have been published describing roles for oocyte-expressed factors in mediating initial embryonic transcriptional genome activation, such as double homeobox (DUX) (De Iaco et al., 2017; Hendrickson et al., 2017), a homolog of yeast Sin3 (SIN3A), Yes-associated protein (YAP), tripartite motif-containing 24 (TRIM24, a.k.a. TIF1A), mediator complex-13 (MED13), histone demethylases, components of the Polycomb Repressor Complex 1 (e.g., Ring finger proteins 1 and 2) and many others (Ancelin et al., 2016; Dahl et al., 2016; Jimenez et al., 2015; Miao et al., 2018; Posfai et al., 2012; Torres-Padilla & Zernicka-Goetz, 2006; Winata et al., 2018; Yu et al., 2016). Here, however, we focus on a special class of maternal effect genes comprised of oocyte-expressed chromatin and transcription regulators that exert long-term effects well beyond the initial stages of early embryonic gene expression (Figure 1).

One such factor is TET3, which oxidizes 5-methylcytosine in DNA as a step in removing cytosine methylation, and plays a key role in embryonic genome reprogramming at the two-cell stage in mice. Ablation of oocyte expressed TET3 does not impede oogenesis, fertilization, or development to birth, but increases embryonic gene transcription at the two-

cell stage and results in post-natal growth deficiency and death (Tsukada, Akiyama, & Nakayama, 2015), a striking example of the impact of oocyte-expressed chromatin regulators on long-term embryo development.

Structural maintenance of chromosome flexible domain containing 1 (*Smchd1*) is a maternally expressed chromatin regulator that provides early actions that contribute to long-term viability. siRNA *Smchd1* knockdown inhibits the termination of the first wave of embryonic gene transcription, revealing an important early maternal effect role for SMCHD1 (Ruebel, Vincent, Schall, Wang, & Latham, 2019; Schall, Ruebel, & Latham, 2019). But in addition, transient reduction of maternal plus early embryonic sources of this protein through the morula stage by siRNA knockdown leads to reduced blastocyst formation and hatching, reduced total cell number, reduced inner cell mass allocation, and disruptions in gene regulation, with increased expression of genes related to the trophectoderm lineage (Midic et al., 2018). Importantly, these modest preimplantation developmental effects are accompanied by a nearly 40% reduction in term development from the two-cell stage (Midic et al., 2018). *Smchd1* knockdown also reduced expression of the mRNA encoding the essential cell cycle driver, S-phase kinase associated protein 2, (SKP2). These results contrast with previous studies of *Smchd1* mutations, in which homozygous mutant embryos from heterozygous mothers displayed mid-gestation lethality with no apparent early effect. Because those studies did not limit maternally expressed SMCHD1, the viability through the mid-gestation stage indicates that the oocyte-derived *Smchd1* expression remaining in these early mutant embryos contributed to long-term viability, possibly through support of correct lineage segregation and stem cell proliferation.

Subcortical maternal complex (SCMC) effects

In addition to the above mentioned oocyte-expressed chromatin and transcription regulators, the subcortical maternal complex (SCMC) can exert long term effects on future progeny. The SCMC in mammalian oocytes and embryos includes a number of maternal effect proteins, including NLRP5, OOEP, TLE6, and KHDC3L and proteins NLRP5 (Mater), Fila, OOEP (Floped), and KHDC3L (TLE6) (Amoushahi, Sunde, & Lykke-Hartmann, 2019). This complex is required for development of the mouse embryos past the 2-cell stage and controls formation of cytoplasmic lattices, F-actin dynamic, distribution of ER and mitochondria, and mRNA degradation during the oocyte to embryo transition (Amoushahi et al., 2019). A recent clinical study showed that mutations in SCMC genes lead to embryonic arrest, with embryos failing to form blastocysts, including arrest well after the earliest SCMC actions and indicates more long-term impacts of early SCMC functions (Figure 1) (X. Wang et al., 2018).

Maternal antigen that embryos require (MATER), also known as Pyrin domain (PYD) containing proteins 5 (NLRP5), was one of the first maternal effect genes to be identified in mammals and a component of the SCMC, but it is still incompletely understood how NLRP5 controls embryo development (Fernandes et al., 2012; Kim & Lee, 2014). *Nlrp5* mRNA is highly expressed in germinal vesicle stage oocytes but not detected in early embryos, although NLRP5 protein is detected throughout preimplantation development (Amoushahi et al., 2019). NLRP5 protein is localized in nucleoli and mitochondria of the

oocyte, demonstrating that it has both nuclear and cytoplasmic functions (Amoushahi et al., 2019). MATER has also been reported to play a role in forming cytoplasmic lattices (B. Kim, Kan, Anguish, Nelson, & Coonrod, 2010), mRNA translation, spindle positioning, and epigenetic genome modification (Bebbere, Masala, Albertini, & Ledda, 2016) (Bebbere et al., 2016). The first *Nlrp5* knockout mice demonstrated an essential role in early embryo development. Deficient embryos arrested at the 2-cell stage, despite there being no difference in follicle distribution or number of ovulated oocytes compared to control mice (Kim & Lee, 2014). This observation was expanded in non-human primates, where depletion of *NLRP5* caused a disruption in embryo development with embryos arresting before the 16-cell stage (X. Wu, 2009). Importantly, while some studies demonstrate such short-term maternal effects of SCMC component deficiency, other studies reveal that oocyte deficiency can also have longer-term effects, impairing blastocyst formation and later development (Amoushahi et al., 2019).

In clinical studies, mutations of *NLRP5* are associated with spontaneous abortions, reproductive wastage, and multi-locus imprinting disorders, through aberrant methylation of imprinted loci (Amoushahi et al., 2019), which can have significant long term consequences. Additionally, NLRP5 deficiency in mice alters mitochondrial localization and increases ATP levels compared to controls (Fernandes et al., 2012). This leads to increased cellular stress through increased reactive oxygen species (ROS) production and changes to mitochondrial membrane potential, which caused depletion of mitochondria in the oocyte (Fernandes et al., 2012), possibly impacting long-term phenotype. NLRP5 deficiency in the oocyte is thought to cause mitochondrial damage by triggering premature activation of the mitochondrial pool (Amoushahi et al., 2019; Fernandes et al., 2012). However, the exact involvement of NLRP5 and the SCMC in redistribution or translocation of mitochondria within the embryo is still not fully understood. Regardless of mechanism, these observations reveal both short-term and long-term effects of NLRP5 and SCMC. The extent to which other SCMC components may contribute to long-term effects in the embryo (beyond initial cleavage divisions) remains to be determined.

Mitochondrial legacy

The foregoing discussion makes repeated reference to mitochondrial function in the oocyte. The health and development of the mitochondria, which are exclusively matrilineally transmitted, are critical for oocyte quality and long-term embryo viability, as well as diverse aspects of progeny phenotype. The oocyte mitochondrial legacy can have a large impact on long-term embryo development, adult phenotype, and even transgenerational effects in progeny health (Andreas et al., 2019; Ferey et al., 2019; St John et al., 2019; Udagawa & Ishihara, 2019). Through ATP production, oocyte mitochondria not only support essential metabolic and homeostatic needs of the oocyte and early embryo, but also provide the energy required for meiosis, the vast amount of genome reprogramming that occurs, DNA replication and repair, and the production of the glutathione that is needed for mitigating effects of ROS. Because disruptions in these broader processes can impact long-term phenotype, oocyte mitochondrial function constitutes a significant maternal effect factor relevant to understanding long-term effects of oocyte factors (Figure 1).

A key point to bear in mind regarding mitochondrial activity in the oocyte is that the precise level of mitochondrial activity appears to be critical (Leese et al., 2016). Mitochondrial insufficiency is highly detrimental to short-term embryonic phenotype (Al-Zubaidi et al., 2019), but, conversely too much mitochondrial activity can be detrimental, as it can be associated with excess production of ROS (Leese et al., 2016). The production of excess ROS is especially problematic for oocytes and zygotes because, compared to somatic cells, they are deficient in some of the enzymes that are needed to eliminate ROS, acquiring these ROS scavenging molecules instead from the follicular or oviductal fluid (Guerin, El Mouatassim, & Menezo, 2001; Ufer & Wang, 2011). Indeed, oocyte mitochondria appear to be adapted during oogenesis to minimize the risk of excess ROS production. An “under-developed” mitochondrial state emerges during oogenesis, where in mitochondria are small, spherical, contain under-developed cristae, and have lower ATP production (Babayev & Seli, 2015; Van Blerkom, 2004, 2011). Correct regulation of oocyte ROS production is key for oocyte quality and early embryo survival (Johnson & Nasr-Esfahani, 1994; Mihalas, Redgrove, McLaughlin, & Nixon, 2017). Interestingly, recent studies revealed roles for DNA methyltransferases in the epigenetic modulation of nuclear encoded mitochondrial protein genes (Ruebel et al., 2018). Additional evidence that this regulation contributes to reducing ROS production was obtained from oocytes treated with antioxidants (Cao et al., 2019). That the oocyte genome is subject to such epigenetic control of mitochondrial protein genes raises the possibility of long-term effects of such changes on later development. Factors that impact this regulation could thus have long-term effects. These results indicate that correct regulation of oocyte mitochondrial gene activity, mitochondrial function, and cellular reactive oxygen species production may be key for generating high-quality oocytes, which in turn support long-term development of healthy progeny. A recent study also provided evidence for an epigenetic effect of maternal diet on progeny cardiac mitochondrial function in mice (Ferey et al., 2019).

Another mechanism for long-term impact of the oocyte mitochondrial legacy on progeny phenotype relates to the control of mitochondrial dynamics, which ultimately determine mitochondrial number in the early embryo and beyond. Normal somatic cells undergo mitophagy to eliminate damaged mitochondria, but there appears to be little to no activation of mitophagy in the oocyte, leading to an increase in the number of mitochondria susceptible to damage (Boudoures et al., 2017; Igosheva et al., 2010; Luzzo et al., 2012). How the oocyte reduces the transmission of impaired mitochondria to the early embryo is unclear (Tworzydlo, Sekula, & Bilinski, 2020). Recent studies revealed roles for GAS6 and PINK1 in this process (Boudoures et al., 2017; Kim, Kim, Ko, & Lee, 2019; Niu, Nie, Shin, Zhou, & Cui, 2019). Wu et al. also demonstrated a connection between mitochondrial damage, mitochondrial dynamics, and endoplasmic reticulum (ER) stress (L. L. Wu, Russell, Norman, & Robker, 2012). The uncoupled protein response (UPR) can play a role in the regulation and function of the mitochondrial dynamics (Senft & Ronai, 2015) by inducing mitophagy, regulating mitochondrial biogenetics, and reducing mitochondrial membrane potential in somatic cells and increasing ROS production (Senft & Ronai, 2015). Dysregulation of mitochondrial dynamics in oocytes can also have long-term consequences. Imbalanced mitochondrial dynamics in oocytes and other somatic cells is associated with increased ATP levels, increased mtDNA levels, ROS production, and oxidative

phosphorylation (Liesa & Shirihai, 2013; Udagawa & Ishihara, 2019; Wai & Langer, 2016). Overexpression of mitofusion proteins in oocytes negatively affects both mitochondrial morphology and dynamics, and is associated with chromosome misalignment when compared to control oocytes (Wakai, Harada, Miyado, & Kono, 2014). Other observations reveal the sensitivity of mitochondrial dynamics to stress and metabolic alterations, and the attendant sensitivity of oocyte developmental potential to mitochondrial regulation (Babayev et al., 2016; Igosheva et al., 2010; Saben et al., 2016). Bu the changes in oocyte mitochondrial dynamics have long-term effects as well as immediate effects on the oocyte and early embryo energetics. One striking series of studies found that a high fat/high sucrose maternal diet can damage oocyte mitochondria (Boudoures et al., 2017; Grindler & Moley, 2013; Saben et al., 2016), and that this can lead to changes in cardiac mitochondrial structure and function for multiple generations (Ferey et al., 2019), as well as oocyte and skeletal muscle (Andreas et al., 2019; Saben et al., 2016). Thus, correct regulation of a healthy oocyte mitochondrial legacy contributes to long-term healthy progeny phenotype.

Understanding the large impact of abnormal mitochondrial function on oocyte and embryo development has also led to new research looking at the effects of mitochondria replacement therapy. The thought behind these techniques, which can include pronuclear transfer, mitochondria spindle transfer, ooplasm transfer, or mitochondrial microinjection, is that the mutant or defective mitochondria can be replaced or augmented with healthy donor mitochondria (Mobarak et al., 2019). However, these techniques are subject to both ethical and safety concerns (Adashi & Cohen, 2018). One study reported a healthy baby boy born after oocyte spindle transfer to prevent transfer of a mitochondrial disease, Leigh syndrome, in a woman undergoing IVF treatment (J. Zhang et al., 2017), and other reports of using oocyte spindle transfer to treat infertility have surfaced since. In non-human primates, mitochondria spindle transfer experiments led to viable progeny that showed growth and development comparable to control offspring (Adashi & Cohen, 2018; Tachibana et al., 2009). In addition, mouse studies yielded progeny from mitochondria replacement procedures designed to overcome mitochondrial genetic defects (Adashi & Cohen, 2018; Sato et al., 2005). These methods generally had low mtDNA carryover, but heteroplasmy can be seen in progeny (Mobarak et al., 2019). However, studies to date from mitochondrial microinjection indicate that benefits may be limited in some contexts and may be affected by the cellular source of the mitochondria (Igarashi et al., 2016; Mobarak et al., 2019). The possible transgenerational effects of any heteroplasmy that would result from these methods have not been well studied. Potential epigenetic changes in the progeny genomes have also not been rigorously studied. Further studies are needed to understand the safety and efficacy of this method.

Environmental factors impacting long-term maternal effects

A growing body of evidence suggests that environmental factors that create stress in the oocytes as well as the peri-conception stage embryos can have substantial long-term effects on progeny phenotype. Stressors can include oocyte in vitro maturation medium, embryo culture, medium, maternal low-protein diet, maternal obesity, diabetes, environmental toxins and chemicals, ethanol consumption, and excess hormonal stimulation (Andreas et al., 2019; Ecker et al., 2004; Eichenlaub-Ritter & Pacchierotti, 2015; Fleming, Eckert, & Denisenko,

2017; Hart, 2016; L. Li et al., 2020; Mann et al., 2004; Ng, Lau, Yeung, & Ho, 2003; Snider & Wood, 2019; VandeVoort, Grimsrud, Midic, Mtango, & Latham, 2014; Velazquez, 2015). Of particular interest here, is the impact of such factors on the oocyte. In rhesus macaques, administration of ethanol to simulate binge drinking can compromise oocyte quality, even after the treatment is terminated (VandeVoort et al., 2014). Exposure to environmental endocrine disruptors can impact meiosis and oocyte quality and have multi-generational and transgenerational effects in the ovary (Rattan & Flaws, 2019). Maternal diets deemed unhealthy can lead to mitochondrial dysfunction, inflammation, changes in ER stress and UPR related gene expression (*Atf4, Xbp1s, Hspa1a, Hapa1b*) and reduced developmental competence in ovulated oocytes compared to control litter mates (Boudoures et al., 2017; Ruebel et al., 2017; Snider & Wood, 2019; L. L. Wu et al., 2015). Effects of unhealthy maternal diets have also been observed transgenerationally. Abnormal mitochondrial function, morphology, and dynamics of oocytes from F1 and F2 generation offspring were demonstrated in offspring that were exposed to maternal high fat/high sucrose diet (Boudoures et al., 2017; Jaeger, Saben, & Moley, 2017; Saben et al., 2016). These observations indicate that the oocyte is a sensitive target for effects of diverse exogenous and endogenous factors that exert multi-and transgenerational effects. The mechanism responsible for such effects remain incompletely understood, but these studies highlight the importance of oocyte quality in the next and even subsequent generations, highlighting the crucial role played by maternal factors in the oocyte.

Perspectives

The oocyte is richly supplied with a multitude of factors that support not only early embryogenesis, but also long-term progeny health. Many of these factors play crucial roles in early programming of the embryonic genome for correct transcription, correct regulation of mitochondria, essential production of ATP, metabolism, repairing DNA damage, preventing ongoing damage to DNA and other macromolecules from ROS, and many other vital processes. One impressive observation to emerge in the last decade is the finding that early insults to the mother can negatively impact the oocyte and lead to transgenerational effects. Studies in cattle revealed that even mild nutrient restriction during a narrow peri-conceptional window of time can lead to reduced ovarian reserve, aorta malformation, and hypertension in female progeny (Mossa, Latham, Ireland, & Veiga-Lopez, 2019), demonstrating the high potential of maternal factors in impacting progeny health. Maternal exposure to low levels of environmental toxins (Hunt et al., 2003; Hunt, Susiarjo, Rubio, & Hassold, 2009; Lawson et al., 2011; Muhlhauser et al., 2009; Susiarjo, Hassold, Freeman, & Hunt, 2007), maternal obesity (Boudoures et al., 2017; Grindler & Moley, 2013), and potential effects of ovarian stimulation and oocyte/embryo *in vitro* culture and manipulations likewise can disrupt the fragile biology of the oocyte, impacting progeny health. These observations are important because they suggest that a significant fraction of adult health disorders and disease, including the number one killer in our society—cardiovascular disease—may emerge in part through the impact of comparatively mild and seemingly innocuous factors affecting the oocyte, by compromising these long-term functions of the oocyte in supporting progeny development and health. Genetic factors that increase or decrease susceptibility to such exogenous influences warrant further study, as do potential

approaches to mitigate the effects of these factors following exposure, as well as approaches to reducing exposure. Additionally, recognition that oocyte functions that are related to progeny health may be compromised well in advance of conception provides an incentive for further research and education related to identifying and minimizing such detrimental exposures throughout reproductive life.

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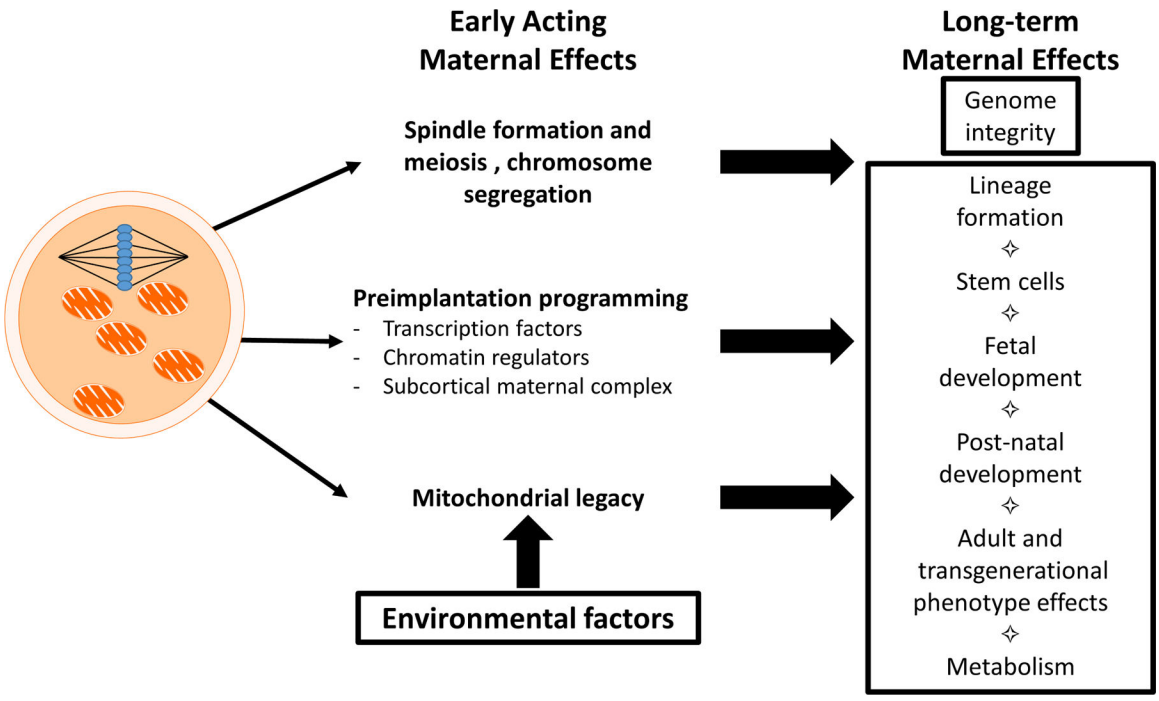

Figure 1.

Short-term and long-term maternal effects mediated by oocyte components and processes. Short-term effects include immediate effects of oocyte components on processes in the oocyte and early embryo before the embryonic genome assumes control of development. These include spindle formation, meiosis and chromosome segregation, early aspects of genome programming that determine initial transcriptional activity, and the precise control of oocyte mitochondrial activity. Long-term effects are those that are observed after the embryonic genome assumes control of development, with effects on later preimplantation stages, fetal development, adult phenotype, and even transgenerational impacts. Such long-term effects emerge through persistent epigenetic programming of the early embryonic genome, impacts of these programming events on lineage formation and stem cell formation and later developmental processes, consequences of early programming of mitochondrial function and dynamics. Such long-term effects can also impact later generations. Environmental factors acting upon the oocyte an also impact long-term phenotype via effects on mitochondrial function.