

# Metabolic control of oocyte development: linking maternal nutrition and reproductive outcomes

Ling Gu · Honglin Liu · Xi Gu · Christina Boots · Kelle H. Moley · Qiang Wang

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**Abstract** Obesity, diabetes, and related metabolic disorders are major health issues worldwide. As the epidemic of metabolic disorders continues, the associated medical comorbidities, including the detrimental impact on reproduction, increase as well. Emerging evidence suggests that the effects of maternal nutrition on reproductive outcomes are likely to be mediated, at least in part, by oocyte metabolism. Well-balanced and timed energy metabolism is critical for optimal development of oocytes. To date, much of our understanding of oocyte metabolism comes from the effects of extrinsic nutrients on oocyte maturation. In contrast, intrinsic regulation of oocyte development by metabolic enzymes, intracellular mediators, and transport systems is less characterized. Specifically, decreased acid transport proteins levels, increased glucose/lipid content and elevated reactive oxygen species in oocytes have been implicated in meiotic defects, organelle dysfunction and epigenetic alteration. Therefore, metabolic disturbances in oocytes may contribute to the diminished reproductive

potential experienced by women with metabolic disorders. In-depth research is needed to further explore the underlying mechanisms. This review also discusses several approaches for metabolic analysis. Metabolomic profiling of oocytes, the surrounding granulosa cells, and follicular fluid will uncover the metabolic networks regulating oocyte development, potentially leading to the identification of oocyte quality markers and prevention of reproductive disease and poor outcomes in offspring.

**Keywords** Germ cell · Glucose · Lipid · Amino acid · Biomarker

## Introduction

Mammalian oocyte development is a complex process regulated by a vast number of intra- and extra-ovarian factors. Oocytes originate from primordial germ cells (PGCs). PGCs migrate to the genital ridge where they proliferate by mitosis and transform from oogonia into primary oocytes [1–3]. Around the time of birth, oocytes are arrested within an ovarian follicle at the diplotene stage of the first meiotic prophase, which is also termed the germinal vesicle (GV) stage. After puberty, oocytes are stimulated to reinitiate meiosis after an endogenous LH surge, as indicated by GV breakdown (GVBD). As the microtubules become organized into a bipolar spindle and all chromosomes align at the spindle equator, the oocytes proceed to metaphase I (MI) and then extrude the first polar body. Oocyte maturation is complete upon arrest at metaphase II (MII), waiting for fertilization [4, 5]. Oocyte growth and maturation are believed to be particularly sensitive to changes in nutritional, chemical, and endocrine environments [6].

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L. Gu (✉) · H. Liu  
College of Animal Science and Technology, Nanjing  
Agricultural University, 1 Weigang, Nanjing 210095, Jiangsu,  
China  
e-mail: lgu@njau.edu.cn

X. Gu  
Department of Obstetrics and Gynecology, Rudong Third  
Hospital, Nantong, China

C. Boots · K. H. Moley  
Washington University School of Medicine, St Louis, MO, USA

Q. Wang (✉)  
State Key Laboratory of Reproductive Medicine, Nanjing  
Medical University, 140 Hanzhong Rd, Nanjing 210029,  
Jiangsu, China  
e-mail: qwang2012@njmu.edu.cn

Full developmental competence of an oocyte requires synchronous nuclear maturation and cytoplasmic maturation [7, 8]. Indicative of the requirement for energy production and active synthesis during this process, organelles in the ooplasm such as mitochondria, endoplasmic reticulum, and Golgi complexes become more abundant and experience dynamic changes with oocyte growth [9, 10]. A variety of metabolites and metabolism-related enzymes have been demonstrated to play critical roles in multiple cellular events occurring in oocyte maturation [11–14]. The growing mammalian follicle consists of a single oocyte, one or more layers of surrounding somatic cells (granulosa cells), and an outer rim of theca cells. Oocytes are coupled to granulosa cells by gap junctions. These highly specialized membrane connections mediate the transfer of small metabolites, inorganic ions, and second messengers from one cell to another [15]. Metabolic cooperation between oocytes and granulosa cells in the follicle has long been appreciated [16–18]. Granulosa cells provide various energy substrates for nurturing oocytes, while oocytes control metabolic activity in granulosa cells by secretion of paracrine factors [19, 20].

Obesity, diabetes, and related metabolic disorders are major health issues worldwide. As this epidemic of metabolic disorders continues, the associated medical comorbidities, including those affecting reproduction, increase as well [21]. In particular, women with obesity or poorly controlled diabetes have an increased risk of infertility, miscarriage, obstetric complications, neonatal morbidity and mortality, and birth defects in their offspring. Emerging animal studies and clinical data suggest that metabolic activity in oocytes may be a critical target mediating these reproductive defects.

This review focuses on the recent advances made in the investigation of the metabolic events governing oocyte growth and maturation and the link between maternal nutrition, oocyte metabolism, and reproductive outcomes. In addition, metabolic analysis of oocytes is briefly introduced. Advances in these areas are likely to contribute to the understanding of the mechanisms underlying oocyte development, and as a result, may guide further approaches for the identification of predictors of oocyte quality and for treatment of infertility and poor obstetric and neonatal outcomes. The metabolism during folliculogenesis is not discussed here as it is covered in other recent reviews [22, 23].

## Methods

This article provides a comprehensive review with references from both human and animal studies. Relevant research articles published in English up to August 2014

were obtained from PubMed using the following search terms in various combinations: ‘oocyte’, ‘oocyte quality’, ‘metabolism’, ‘metabolic disorder’, ‘maternal nutrition’, ‘obese’, ‘diabetes’, ‘PCOS’, ‘metabolomics’, ‘follicular fluid’, ‘cumulus cell’, ‘embryo’, ‘reproductive outcome’, ‘pregnancy’, and ‘epigenetics’. Abstracts were evaluated to identify studies appropriate to the review.

## Energy metabolism in oocytes

Oocytes cannot be fully understood in isolation from their follicles (specifically granulosa cells), which create an essential niche for oocyte survival, nourishment, and regulation [24]. Oocytes are deficient in their ability to carry out some key metabolic processes and thus depend on the cooperation of granulosa cells to provide metabolites for their development [19, 25]. Despite the oocytes’ commanding role, communication is bidirectional, and follicular cells are interdependent; for detailed reviews see [20, 26].

As Henry Leese noted [27], metabolic control of oocyte development may be considered at two levels: (1) intrinsic control by enzyme amount/activities, intracellular mediators, and plasma membrane transport systems [28–30] and (2) extrinsic control by providing nutrients derived from the follicular niche, female reproductive tract, or in vitro culture environment [31–34]. Overwhelmingly, the focus of research and practice in this area has been on extrinsic nutrients regulating oocyte maturation. In contrast, the potential contribution of intrinsic pathways controlling oocyte development has received little attention. Some intrinsic enzymes related to metabolism have been examined in mammalian oocytes and are summarized in Table 1. Metabolic control of oocyte development, specifically meiosis, epigenetics and organelles, are outlined in Fig. 1.

## Glucose metabolism in oocytes

Glucose utilization by cumulus-oocyte complexes (COCs) has been systematically reviewed by Sutton-McDowall et al. [35, 36]. Hence, only a specific discussion on metabolic patterns, transport systems, and critical enzymes in oocytes is presented here.

*Metabolic patterns of glucose in oocytes* Energy metabolism in primordial germ cells (PGCs) and oogonia remains controversial. Mouse PGCs were originally shown to preferentially oxidize pyruvate over glucose [37]. However, work by Jansen and de Boer [38] suggested that anaerobic glycolysis is the predominant metabolic pattern in PGCs to avoid oxidative damage. Throughout the growth period, pyruvate and oxygen consumption is gradually increased in mouse oocytes [39]. The fully grown

**Table 1** Summary of the intrinsic enzymes related to metabolism in mammalian oocytes

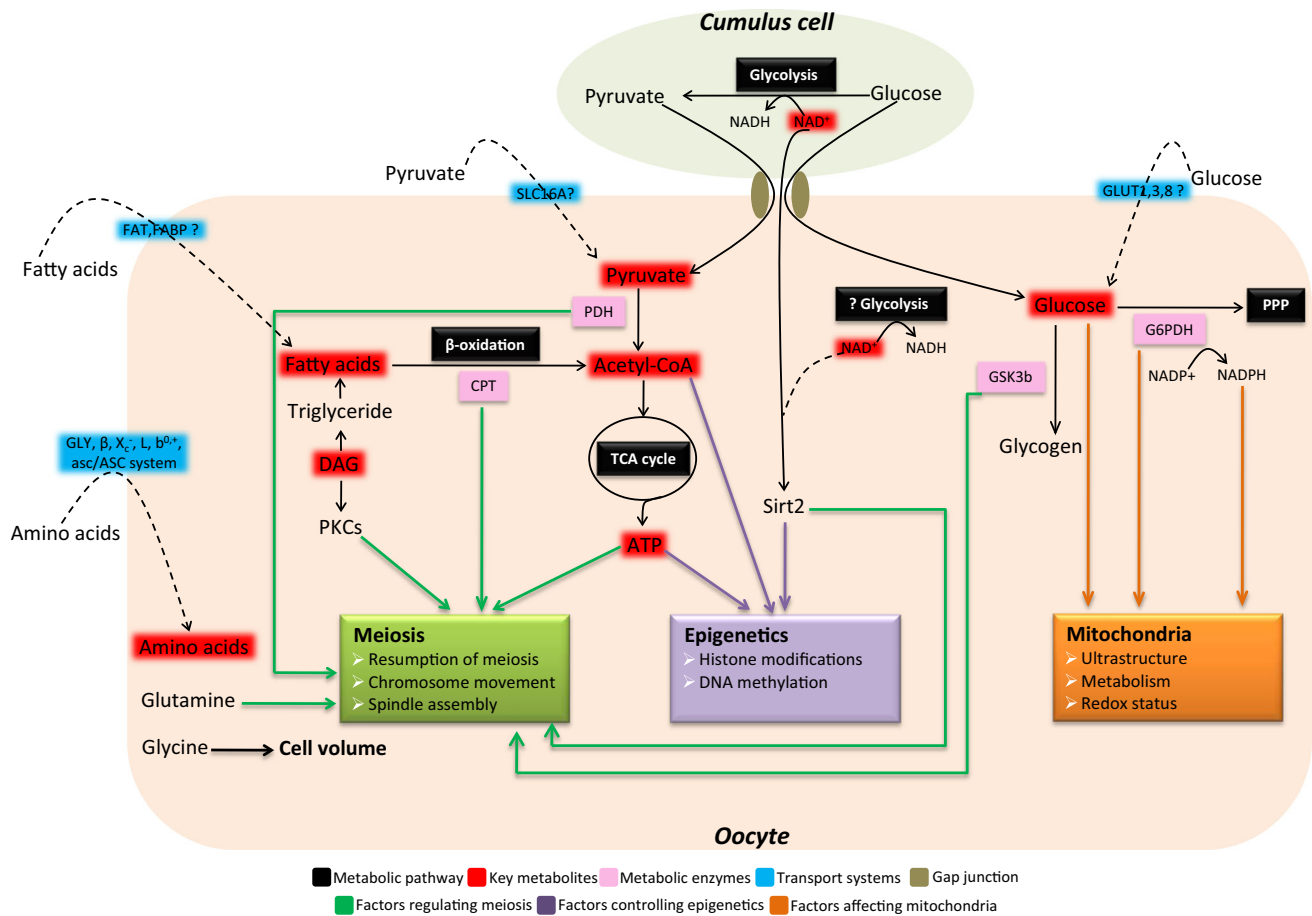
Enzyme	Oocyte/species	Functions	References
Carbohydrate metabolism-related enzymes			
HK	Human; mouse; rat	Detectable activity, no functional analysis	[42, 66, 265, 266]
GPI	Human; mouse	GPI transcript was detectable; <i>Gpi1</i> <sup>-/-</sup> null mouse oocytes show normal function	[65, 68, 265, 267]
PFK	Human; mouse; rat; bovine	Detectable activity, may be associated with oocyte maturation	[66, 94, 265, 268]
G6PDH	Human; mouse; rat; bovine; pig; sheep	Activity is associated with meiotic progression, mitochondrial features and developmental competence of oocytes	[66, 269–274]
GAPDH	Mouse	Detectable activity, no functional analysis	[65]
GS	Human; Mouse	Detectable activity, no functional analysis	[64, 274]
GSK3	Mouse; Bovine	GSK3b regulates mouse oocyte meiosis, particularly chromosome segregation	[275–277]
PK	Human; mouse	Detectable activity, no functional analysis	[64]
PDH	Mouse	<i>Pdha1</i> <sup>-/-</sup> null mouse oocytes are unable to properly complete oogenesis	[12]
ADK	Human; mouse	Detectable activity, no functional analysis	[169]
T-synthase	Mouse	Mouse fertility is enhanced by oocyte-specific loss of T-synthase	[278]
SDH	Rat	Detectable activity, no functional analysis	[279, 280]
AR	Mouse; rat	Detectable activity, and may be important for mouse oocyte meiotic resumption	[279–281]
CS	Human; mouse	Detectable activity, no functional analysis	[169]
MDH	Human; mouse; rat; bovine	Activity increases during oocyte maturation, no functional analysis	[64, 66, 282]
NADP-IDH	Bovine	Detectable activity, no functional analysis	[282]
LDH	Mouse; pig; cattle	Detectable activity, no functional analysis	[65, 283–286]
Lipid metabolism-related enzymes			
Lipase	Bovine	Detectable activity, no functional analysis	[94]
GK	Bovine	Transcript was detectable in oocytes, no functional analysis	[287]
CPT	Mouse	Essential for oocyte developmental competence and early embryo development	[93, 288]
BOAC	Human; mouse	Detectable activity, no functional analysis	[64, 169]
ACADL	Pig	Detectable activity, no functional analysis	[286]
CT	Human; mouse	Detectable activity, no functional analysis	[64]
AC	Human; mouse	Improves the quality of oocytes and embryos and the outcome of IVF	[289, 290]
Amino acid metabolism-related enzymes			
GLDH	Human; mouse		[64]
ALT	Human; bovine	Enzymatic units remained constant in oocytes during IVM	[274, 282]
AST	Human; mouse; bovine	Enzymatic units remained constant in oocytes during IVM	[64, 274, 282]
GPT2	Mouse	Detectable activity, no functional analysis	[169]

Unless stated otherwise, the oocytes mentioned above are fully-grown oocytes

*HK* hexokinase, *GPI* glucose-6-phosphate isomerase, *PFK* phosphofructokinase, *G6PDH* glucose-6-phosphate dehydrogenase, *GAPDH* glyceraldehyde-3-phosphate dehydrogenase, *GS* glycogen synthase, *GSK3* glycogen synthase kinase 3, *PK* pyruvate kinase, *PDH* pyruvate dehydrogenase, *ADK* adenylate kinase, *T-synthase* core 1 beta1,3-galactosyltransferase, *SDH* sorbitol dehydrogenase, *AR* aldose reductase, *CS* citrate synthase, *MDH* malate dehydrogenase, *NADP-IDH* NADP-dependent isocitrate dehydrogenase, *LDH* lactate dehydrogenase, *GK* glycerol kinase, *CPT* carnitine palmitoyl transferase, *BOAC* beta-hydroxyacyl-CoA dehydrogenase, *ACADL* long-chain acyl-CoA dehydrogenase, *CT* cytoplasmic thiolase, *AC* acid ceramidase, *GLDH* glutamate dehydrogenase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GPT2* glutamic pyruvate transaminase 2, *IVF* in vitro fertilization, *IVM* in vitro maturation

oocytes have a limited capacity to utilize glucose [40–43], and glucose first needs to be converted to pyruvate by follicular cells to ensure successful meiotic maturation [18, 44–46]. Pyruvate is transported by the proton-linked

monocarboxylate carrier family (MCT) [47], and mouse oocytes are rich in the SLC16A members of MCT [48] (Fig. 1). Nonetheless, important questions about which MCT(s) and how they mediate the pyruvate uptake by



**Fig. 1** Metabolic control of meiosis, epigenetics and organelles during oocyte development

oocytes remain unanswered. Highlighting the importance of pyruvate during oocyte maturation, mouse oocyte-specific deletion of *Pdhx1* (pyruvate dehydrogenase E1  $\alpha$ ) caused severe meiotic defects [12] (Fig. 1; Table 1). Interestingly, dog and pig oocytes seem to utilize glucose as the primary energy substrate at a much higher rate than that of other species [32, 49], implying the species-specific differences in metabolic pattern of glucose in oocytes.

**Glucose transport in oocytes** Although pyruvate is the preferred substrate, the machinery for glucose metabolism and glucose carrier-mediated uptake have been detected in oocytes [41, 42, 50–54]. Glucose enters cells either actively via sodium-coupled glucose transporters (SGLTs) or through facilitative glucose transporters (GLUTs). Fourteen members of the GLUT family have been identified, including GLUT1–12, the H<sup>+</sup>-coupled myoinositol transporter, and GLUT14 [29, 55]. GLUTs expression has been reported in mouse [56, 57], cow [58], sheep [59], human [60], and rhesus monkey oocytes [61]. The mouse oocyte contains GLUT1, 3 and 8, but GLUT4 (the primary insulin-sensitive transporter) has not been detected [36, 62] (Fig. 1). Up to now, scarce research has been conducted

into the transport mechanisms of glucose in oocytes. Recently, using a non-metabolizable fluorescent glucose derivative, we have revealed an intercellular pathway for glucose transport into mouse oocytes, whereby glucose is taken up in cumulus cells and then transferred into the oocyte through gap junctions [63] (Fig. 1).

**Glucose metabolism-related enzymes in oocytes** In attempting to discover which metabolic pathways are functional in oocytes, it has been necessary to measure the levels and/or activities of related enzymes. Hexokinase (HK), P-fructokinase (PFK), and pyruvate kinase (PK) were measured in single mouse and human oocytes. Although all of them were detectable, the human levels averaged 3–9 times higher than those in the mouse [64], indicating that they may play species-specific roles. Other enzymes related to glucose metabolism and the tricarboxylic acid cycle (TCA) have also been measured in oocytes from different species using either biochemical or cytochemical methods [65–67]. Studies on the functions of most glucose metabolism-related enzymes during oocyte development have not been carried out (Table 1).

A female mouse chimera composed of wild-type cells and homozygous *Gpi*<sup>-/-</sup> null cells (*Gpi* encodes the glycolytic enzyme glucose phosphate isomerase) was able to produce offspring derived from homozygous *Gpi*<sup>-/-</sup> null oocytes [68], supporting the conclusion that mouse oocytes do not require intact endogenous glycolysis for their development. Glucose-6-phosphate dehydrogenase (G6PDH) is a cytosolic enzyme that catalyzes the first step in the pentose phosphate pathway (PPP) and is synthesized within the oocyte during oogenesis (Fig. 1). Since G6PDH can convert the brilliant cresyl blue (BCB) stain from blue to colorless, BCB staining was used to measure G6PDH activity in oocytes. G6PDH has very high activity in the preovulatory oocytes of mice, rats, and cows and experiences dynamic changes during oocyte maturation [65–67]. Numerous reports have shown that low G6PDH activity is associated with a high rate of fertilization and blastocyst formation [69–71], indicating that G6PDH activity may be a good indicator of oocyte quality. Nonetheless, BCB staining has not been used to evaluate the G6PDH activity in human oocytes yet. Moreover, most recently, BCB staining of pig oocytes at the immature stage was found to compromise mitochondrial functions throughout oocyte maturation and, therefore, is not suitable for application in a standard in vitro maturation protocol [72, 73]. Therefore, BCB staining-based oocyte quality evaluation still remains an open issue.

#### *Lipid metabolism in oocytes*

**Lipid stores in oocytes** Intracellular lipid levels within mammalian oocytes vary dramatically among species (4 ng/mouse oocyte, 63 ng/cow oocyte and 161 ng/pig oocyte) [74–76]. Triglycerides are the most abundant lipid in oocytes, constituting over 50 % of all lipid material [77–79] and provide a large potential energy reserve. Lipid droplets accumulate during oocyte growth and undergo temporal and spatial changes during maturation. For example, triglyceride stores sharply decrease over the course of pig and cow oocyte maturation in vitro, despite culturing in the presence of serum [76, 77]. Lipid droplets become larger and more centrally located as the mouse oocyte matures [80]. By contrast, a pronounced peripheral distribution pattern was observed in hamster and pig oocytes [81–83]. It was reported that perilipin-2 and adipose differentiation-related protein (ADRP) surround lipid droplets in mouse and cow oocytes [80, 84], which may control the stabilization of lipid droplets and lipolysis for utilization [85]. Furthermore, using a live cell-imaging method, Sturmey et al. showed the close spatial association between lipid droplets and mitochondria in pig and bovine oocytes [83, 86, 87], indicating the importance of oocyte mitochondria in lipid metabolism.

**$\beta$ -Oxidation of fatty acid in oocytes** Lipase enzymes cleave triglycerides into a glycerol backbone and fatty acids with different chain lengths and saturation degrees. Fatty acid uptake is primarily via fatty acid protein transporters on the cell surface, including fatty acid translocase (FAT), tissue-specific fatty acid transport proteins (FATP), and plasma membrane bound fatty acid binding protein (FABP<sub>pm</sub>) (Fig. 1). Once inside the cell, fatty acids are transported across the outer mitochondrial membrane by carnitine-palmitoyl transferase (CPT) and then couriered across the inner mitochondrial membrane by carnitine. In mitochondria, the long chain acyl-CoA enters the fatty acid  $\beta$ -oxidation pathway, releasing acetyl-CoA. This acetyl-CoA then enters the TCA cycle to produce ATP. CPT1 is believed to be the rate-limiting step in fatty acid oxidation [88] (Fig. 1). In comparison with other macronutrient classes (carbohydrates and protein), fatty acids yield the most ATP by the  $\beta$ -oxidation pathway.

The role of fatty acids during oocyte development in different animal models has been excellently reviewed by Dunning et al. [89] and Mckeegan and Sturmey [90]; therefore, only a brief account of  $\beta$ -oxidation is given here. Palmitic, stearic, oleic, and linoleic acids are the most abundant intracellular fatty acids in pig, cattle, and human oocytes [78, 79, 84]. By employing inhibitors of CPT1, it has been shown that inhibiting  $\beta$ -oxidation of fatty acids during cow and pig oocyte maturation led to a fall in viability of subsequent embryos [76, 91]. Interestingly, although with low lipid reserves, inhibition of  $\beta$ -oxidation during mouse oocyte maturation blocked AMPK-mediated meiotic resumption [92]. In addition, lipase activity during bovine oocyte maturation and CPT1 expression in mouse oocytes following hormone superovulation were found to be up-regulated [93, 94]. Recent studies have shown that supplementation of L-carnitine (a cofactor of CPT1) to cultured follicles enhanced  $\beta$ -oxidation and improved both oocyte nuclear and cytoplasmic maturation in mice and cows [95–97]. Similarly, L-carnitine enrichment of in vitro maturation (IVM) medium increased the concentration of glutathione (an antioxidant) and promoted pig oocyte development [98]. The importance of fatty acid  $\beta$ -oxidation in nuclear maturation has also been demonstrated in mice, cows, and pigs [99]. These findings collectively suggest that metabolism of fatty acids, specifically  $\beta$ -oxidation pathway, is essential for maintaining developmental competence of mammalian oocytes.

**Fatty acids in cellular signaling transduction** In addition to the energy supply for cells, fatty acids and their precursors/metabolites have also been reported to be required for the non-metabolic processes, particularly cellular signaling transduction [100, 101]. Diacylglycerol (DAG), an intermediate in glycerolipid metabolism, is historically the first known lipid second messenger [102–104]. DAG is



generated by the lipid hydrolysis of phosphatidylinositol (4,5)-bisphosphate, and protein kinase C (PKC) is its major effector. The binding of DAG to a conserved C1 domain in PKC leads to PKC activation, modulating the cell cycle, cellular survival, malignant transformation, and apoptosis [105]. It is worth noting that PKC isozymes have been implicated in multiple key steps during oocyte development, such as meiotic resumption, spindle organization, and activation [106–108] (Fig. 1). Ceramide, the immediate lipid product of sphingomyelin hydrolysis, was demonstrated to behave as a bioeffector for meiotic cycle progression in *Xenopus* oocytes [109, 110]. Fatty acids also bind nuclear receptors and transcription factors, such as peroxisome-proliferator activated receptors (PPAR) and sterol-regulatory element binding protein (SREBP) [111]. PPAR and SREBP1 have been detected in mouse and bovine oocytes and may be associated with embryo development and female fertility [112, 113]. Although promising, the role of lipids serving as secondary messengers in the control of mammalian oocyte development is currently an almost unexplored research area.

#### *Amino acid metabolism in oocytes*

Amino acids are transported into cells by an array of specialized systems and play important roles in cellular function, including protein synthesis, energy production, organic osmolytes, and intracellular buffer [114–116]. In the past few decades, amino acids in preimplantation embryos have been extensively investigated. In contrast, much less is known about amino acid transport and utilization during mammalian oocyte growth and development.

*Transport systems of amino acids in oocytes* Amino acid transport systems were defined classically by the range of their substrate specificities and the presence or absence of obligate  $\text{Na}^+$  cotransport [117, 118]. Colonna et al. first examined the amino acid transport systems in isolated mouse oocytes throughout oogenesis. While fully grown GV oocytes were lacking the A-transport system, they demonstrated utilization of the L- and ASC-systems [119]. Van Winkle et al. later showed that glycine transport was mainly via system GLY and cysteine/glutamate transport was via system  $\text{X}_c^-$  in immature oocytes [120, 121]. Similarly, system  $\beta$ , L, GLY,  $\text{X}_c^-$ , and  $\text{b}^{0,+}$  were successively detected in matured oocytes [121–124]. Recently, Pelland et al. [117] measured the transport characteristics of nine amino acids and determined the activity of 11 classically defined amino acid transport systems in mouse oocytes. GLY,  $\beta$ , and  $\text{X}_c^-$  had low activity in growing oocytes and were strongly up-regulated during meiotic maturation. L,  $\text{b}^{0,+}$ , and asc/ASC seemed to be constitutively active throughout oocyte growth and maturation. Consistent with this, oocytes exhibited distinct patterns for amino acid transport [117].

It has been reported that when mouse cumulus cell-enclosed- or cumulus cell-denuded oocytes were cultured in medium containing [ $^{14}\text{C}$ ] L-alanine, the amount of radioactivity in oocytes was higher in cumulus cell-enclosed group [125]. *Slc38a3* (a transcript encoding a sodium-coupled neutral amino acid transporter that has high substrate preference for alanine) was abundantly expressed in cumulus cells as compared to oocytes in mice [126]. To date, the enhanced transport rates of glycine, alanine, taurine, and lysine into oocytes have been demonstrated in the presence of granulosa cells [117, 120, 125]. These findings strongly imply that metabolic cooperation between oocytes and follicular cells involves the uptake of amino acids. Surprisingly, follicular cells did not confer additional amino acid transport capabilities on the enclosed oocyte, and in some cases, they appeared to inhibit the uptake of leucine by oocytes in mice [117].

*Utilization of amino acid in oocytes* The presence of numerous transport systems in oocytes indicates their capacity to utilize amino acids from the external environment. Glutamine has been suggested to be an efficient energy substrate to support oocyte development. For example, using glutamine as a sole energy source is sufficient to initiate meiotic resumption of mouse oocytes within COC, despite the inability to progress through the MII stage [127]. Addition of glutamine to the culture medium promoted oocyte maturation in cow, hamster, dog, rabbit, and rhesus monkey [115, 128–131] (Fig. 1). Glutamine, aspartate and valine also can prevent polyspermic fertilization of pig oocytes [132].

Animal cells control their volume by actively adjusting the cytoplasmic concentrations of osmotically active solutes, thus altering intracellular osmotic pressure [133]. Tartia et al. [134] have done elegant work to examine volume regulation in mouse oocytes. They found that GLYT1, a glycine transporter, is quiescent in immature GV oocytes, which also contain very little endogenous glycine. However, within several hours of the initiation of ovulation, GLYT1-mediated glycine transport becomes activated in oocytes. Concomitantly, oocytes become able to use glycine to regulate their volume. These observations indicate that the glycine-dependent cell-volume-regulatory mechanism exists in oocytes (Fig. 1).

Oocyte metabolism, maternal nutrition, and reproductive outcomes: connecting the dots

Evidence is growing that excessive body fat has a detrimental effect on female fertility and pregnancy. Obese women take longer to conceive, even if cycling regularly, and have a high risk of miscarriage, preeclampsia, gestational diabetes, and congenital defects in the offspring [135–137]. Likewise, women with poorly controlled

diabetes often suffer from a series of reproductive problems, such as miscarriage, neonatal morbidity and mortality, and congenital malformations [138–140]. Moreover, despite the glycemic control throughout pregnancy, these women still experience a three to fivefold higher incidence of the pregnancy complications [141], indicating that maternal diabetes may have permanent and irreversible effects on female reproduction. Meanwhile, animal studies also have demonstrated that deficiencies or excesses in a range of macro- and micronutrients are associated with significant impairments in reproductive performance, fertility, fetal development, and long-term offspring health [142–144].

### *Maternal nutrition and reproduction*

In the past 30 years, most studies examining the effects of maternal nutrition on reproduction in humans and animal models have been focused on early embryo and offspring development. We will not include a discussion of metabolic fuel for female reproduction and the effects on fetus/offspring, which have been the subject of other recent reviews [142, 145–147].

Maternal hyperglycemia and obesity have been shown to adversely affect progression from a one-cell zygote to a blastocyst in rodent models [148–153]. Recently, we found that a one-cell zygote transfer from diabetic to non-diabetic mice still results in significantly increased congenital malformations and growth retardation in the offspring [154]. Similar phenotypes were also observed in mice fed a high-fat diet (HFD) [153]. These findings indicate that exposure to disturbed metabolic conditions during oogenesis and fertilization was enough to permanently program the fetus to develop morphological changes.

Data from human clinics have shown that implantation and pregnancy rates are [155, 156] lower in obese women than those of normal weight [157, 158]. Oocyte donation models have been used to determine whether oocyte/embryo quality or uterine receptivity is the main cause of decreased pregnancy rates. There are several systematic reviews illustrating this topic, and conflicting results were produced [159–165]. Nonetheless, the majority of retrospective studies imply that body mass index (BMI) is less likely to negatively affect endometrial receptivity, and it is more likely that poor-quality oocytes or resulting embryos are the cause of reproductive problems experienced by overweight women [161, 162]. Most recently, a very large analysis of 45,000 assisted reproductive technology (ART) cycles concluded that increasing obesity correlated with decreasing likelihood of achieving pregnancy. This effect was only observed when autologous oocytes were used. If donor oocytes from a lean woman were used, the effect was

mitigated [166], supporting the idea that the source of the oocyte determines the reproductive outcome.

Together, it is attractive to propose that maternal metabolic disorders have detrimental effects as early as the oocyte stage, which further predisposes them to embryo developmental abnormalities and even metabolic diseases in the offspring. Direct causative relationships between maternal nutrition, oocyte quality, and reproductive outcomes have not been unequivocally established. Nevertheless, evidence for such relationships continues to solidify. Herein, we will summarize the data from both experimental animal models and infertility clinics related to the effects of maternal nutrition on oocyte development, with a specific perspective on oocyte metabolism.

### *Nutritional effects on oocyte metabolism*

Upon leaving the primordial resting pool and during the follicular growth phase, oocytes are particularly sensitive to changes in the follicular environment, especially those stressors induced by nutrient changes [167]. The follicular environment is a reflection of the physiologic status of the animal. Thus, variance in maternal nutrition is likely to have a significant effect on the metabolic activity of oocytes. As outlined above, inappropriate metabolism of oocytes inevitably compromises oocyte quality and the resultant embryo development.

Diabetes mellitus is a metabolic condition characterized by elevated blood glucose levels. Using a type I diabetic mouse model, we found that maternal diabetes markedly results in structural and spatial alterations of mitochondria in oocytes [168]. Consistent with this, the levels of ATP and TCA cycle metabolites including citrate, malate, and aspartate are decreased in preovulatory and ovulated oocytes from diabetic mice [155, 156, 168, 169]. Similar phenomenon was also seen in HFD mice and mice with hyperinsulinemia [153, 170]. Variations in the ATP content have been suggested to affect oocyte quality, embryonic development, and the implantation process [171, 172]. Specifically, microtubule assembly and chromosome movement during meiosis require ATP [173]. Injury of mitochondria in mouse oocytes could decrease ATP content and disrupt the meiotic spindle [174]. *Pdhx1*-deficient mouse oocytes show inadequate ATP levels along with chromatin and microtubular abnormalities [12]. Oocytes from senescence-accelerated mice demonstrated spindle defects and disturbances in chromosome alignment associated with mitochondrial dysfunction [175]. Recently, association of mitochondria with spindle poles was found to facilitate spindle alignment in *Schizosaccharomyces pombe* [176]. Furthermore, low mtDNA and ATP content also may contribute to the absence of birefringent spindles imaged with the PolScope in human oocytes [177]. Hence,

it is hypothesized that disrupted mitochondrial metabolism may be associated with the spindle defects and chromosome misalignment observed in oocytes from diabetic, obese, and insulin-resistant mice.

Formation of reactive oxygen species (ROS) is a by-product of oxidative phosphorylation in the mitochondria [178, 179]. Igosheva et al. [180] reported increased NAD(P)H content and reduced FAD autofluorescence in oocytes from obese mice, indicating an elevation of ROS generation. Wakefield et al. [181] found that feeding of a diet enriched with long-chain  $n-3$  polyunsaturated fatty acids (PUFA) leads to mitochondrial dysfunction and elevated ROS levels in mouse oocytes, with reduced fertilization capacity and blastocyst formation. These data suggest that excess maternal nutrition could adversely impact mitochondrial status in oocytes, particularly energy production and oxidative stress, and ultimately disrupt oocyte metabolism.

Polycystic ovary syndrome (PCOS) is also associated with metabolic disturbance. Women with PCOS and hyperandrogenism are typically characterized by increased number of oocytes retrieved during in vitro fertilization (IVF). However, these oocytes are often of poor quality, leading to lower fertilization/implantation rates and a higher miscarriage rate [182]. By feeding mice chow supplemented with dehydroepiandrosterone (DHEA), we used a hyperandrogen model to show that citrate levels, G6PDH activity, and lipid content in oocytes from DHEA-exposed mice were significantly lower than those in controls [183], suggesting abnormal TCA and PPP metabolism. Inconsistent with the results derived from animal models, oocytes from PCOS patients show elevated glucose/pyruvate consumption and lower intracellular NAD(P)H content compared to oocytes from control patients [184]. This discrepancy may be explained by the following: (1) although various animal models have been shown to mimic key phenotypes of women with obesity or PCOS, no one model provides complete replication of the complex clinical disorders [185–187]; or (2) the data from human oocytes are sometimes variable because of the limited number of control oocytes from young and healthy women.

HFD mice have higher levels of lipid within oocytes of preovulatory COCs [188–190]. Likewise, both an in vivo hyperglycemic environment and an in vitro high-glucose culture increase free glucose levels in mouse oocytes [63]. Glycogen content is also higher in immature oocytes of diabetic mice, whereas fructose-1, 6-phosphate (FBP) levels are elevated with the resumption of meiosis [169], indicating that a hyperglycemic environment leads to accumulation of glucose stored as glycogen before maturation in oocytes. In contrast, the activity of two enzymes that are major representatives of fatty acid metabolism

(hydroxyacyl-CoA dehydrogenase; *Hadh2*) and amino acid metabolism (glutamic pyruvate transaminase; *Gpt2*) are lower in diabetic oocytes than controls. In addition, diabetic rat models showed altered prostaglandin (PGE<sub>2</sub>) production in both ovulated and immature COCs isolated from ovaries [191, 192]. Some of these conditions are thought to contribute to the disrupted meiotic behavior in oocytes from diabetic animals.

Ruminant livestock species are also important models to reveal the significance of periconceptual nutritional status and its effects on reproductive performance. In dairy heifers, it was shown that a high-starch diet had negative effects on oocyte developmental competence, and these were avoided when leucine intake was increased [193]. Crude protein overfeeding also compromises the subsequent capacity of bovine oocytes to develop to blastocysts, probably via direct toxic effects of elevated ammonia and urea concentration in the follicular environment [194, 195]. Nevertheless, the nutritional effects on oocyte metabolism in ruminant species remain poorly evaluated. The relationships between metabolic disturbance and follicle/embryo metabolism of these animals have been extensively reviewed [142, 196, 197].

#### *Potential mechanisms: oocyte metabolism as a link between maternal nutrition and reproductive outcomes*

The effects of the metabolic condition on oocyte metabolism and development are summarized in Table 2. A schematic diagram for the proposed pathways through which maternal nutrition exerts its effects on oocyte metabolism and reproductive outcomes is shown in Fig. 2.

*Metabolic effects on oocyte mitochondria and meiosis*  
Mitochondria are double-membrane organelles composed of an outer membrane, inner membrane, intermembrane space, and matrix. A large number of enzymes involved in different metabolic pathways exist in the mitochondrial matrix, serving as the major site for energy generation in cells. Mitochondria are also characterized by having their own, maternally inherited genome, mitochondrial DNA (mtDNA). As the most abundant and prominent organelle in oocytes, mitochondria undergo stage-specific changes in ultrastructure and distribution during oocyte maturation in response to differing energy requirements [198]. ATP synthesis by oxidative phosphorylation (OXPHOS) is the primary function associated with mitochondria. Most ROS are produced when electrons leak from the mitochondrial respiratory chain. Although mitochondria are major sites of ROS production, excessive ROS can damage mitochondrial functions in oocytes [199]. Mitochondrial function in the oocyte has been extensively reviewed [10, 167, 179, 200].



**Table 2** Effects of maternal nutritional status on oocyte metabolism and development

Maternal nutrition	Affected organelles or events in oocytes	Changes in oocyte metabolism	References
<b>Obesity</b>			
Mouse model	Mitochondria Endoplasmic reticulum DNA methylation Spindle assembly/chromosome alignment	mtDNA content↑; Citrate levels ↓; NADPH levels↑; ROS production↑; Lipid content↑	[153, 180, 188, 220]
Women	Spindle assembly/chromosome alignment	Not determined	[214]
<b>Diabetes</b>			
Mouse model	Mitochondria Endoplasmic reticulum Meiotic resumption Epigenetic modifications Spindle assembly/chromosome alignment	mtDNA content↑; ATP levels ↓; Citrate levels ↓; Malate levels ↓; Aspartate levels ↓; ROS production↑; Glucose levels↑; Glycogen levels↑; FBP levels↑; Hadh2 activity ↓; GPT2 activity ↓	[156, 168, 169, 213, 218, 219, 291]
Rat model	Meiotic resumption	Prostaglandin E production in COCs↑	[192, 292, 293]
<b>PCOS</b>			
Hyperandrogenism mouse model	Pentose phosphate pathway metabolism	Citrate levels ↓; Lipid content ↓; G6PDH activity ↓	[183]
Hyperinsulinemia mouse model	Mitochondria Spindle assembly/chromosome alignment	mtDNA content↑; ATP levels ↓; GSH levels↓; GSH/ GSSG ratio ↓; ROS production↑	[170]
Women	Spindle/chromosome organization	Glucose consumption↑; Pyruvate consumption↑; NAD(P)H content↑	[184, 294]
<b>Dietary supply or deficiency of nutrients</b>			
Mouse fed high PUFA diet	Mitochondria Epigenetic modifications	ROS production↑; Expression of SOD2 for scavenging ROS↑; Expression of COX2 for producing prostaglandins ↑	[181, 295]
Mouse fed low protein diet	LPD fed exclusively during mouse oocyte maturation leads to behavioral and cardiovascular abnormalities in offspring	Not determined	[296]
Pig fed high fiber diet	Oocyte maturity	Not determined	[297, 298]
Mouse fed zinc deficient diet	Meiotic resumption	Not determined	[299]

Unless stated otherwise, the oocytes mentioned above are fully-grown oocytes

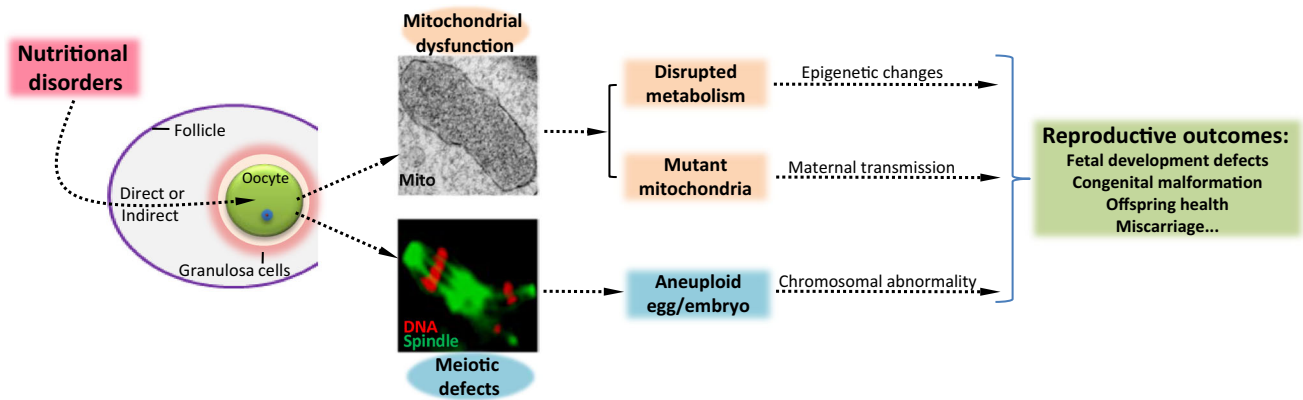
*mtDNA* mitochondrial DNA, *NADPH* nicotinamide adenine dinucleotide phosphate, *ROS* reactive oxygen species, *FBP* fructose-1,6-phosphate, *Hadh2* hydroxyacyl-CoA dehydrogenase, *GPT2* glutamic pyruvate transaminase 2, *COCs* cumulus-oocyte complexes, *PCOS* polycystic ovary syndrome, *G6PDH* glucose-6-phosphate dehydrogenase, *GSH* glutathione, *GSSG* glutathione disulfide, *PUFA* polyunsaturated fatty acid, *SOD2* superoxide dismutase 2, *COX2* cyclooxygenase 2, *LPD* low protein diet

↑ indicates an increase in content; ↓ indicates a decrease in content

Follicular fluid is derived from blood in the thecal capillaries. As follicular development progresses, fluid accumulates in the antrum of the follicle, bathing the oocyte and providing the milieu needed for oocyte development [201]. Data from animal models and human clinics have suggested that metabolic disorders are reflected in the microenvironment of pre-ovulatory follicles [182, 202, 203].

By enzymatically measuring intracellular free glucose in individual oocytes, glucose content among oocytes from diabetic mice was shown to be higher than that from control mice [63]. Mitochondrial dysfunction resulting

from high glucose has been reported in various cell types [204, 205]. In line with this, altered mitochondrial properties, specifically mitochondrial swelling and increased ROS generation, were observed in diabetic mouse oocytes [168] (Fig. 1). Associated with elevated levels of follicular free fatty acid, obvious lipid accumulation was detected in oocytes from HFD mice [188]. When exposed to a high-lipid environment, cells accumulate triglyceride droplets and free fatty acids, causing significant damages to other cellular organelles, such as mitochondria and endoplasmic reticulum (ER); this process is termed lipotoxicity [206]. Mitochondrial dysfunction and ER stress in oocytes from



**Fig. 2** Schematic diagram for the proposed pathways through which maternal nutritional status exerts its effects on oocyte metabolism and, therefore, reproductive outcomes

obese and insulin-resistant mice have been reported by different groups [153, 170, 180, 188, 189, 200]. Collectively, disrupted energy metabolism of oocytes in response to nutritional cues could result in reduced potential for meiotic maturation and fertilization, as well as impaired preimplantation embryonic development. Additionally, these abnormal oocyte mitochondria may be maternally transmitted to the embryo and then be propagated during embryogenesis and fetal development, leading to the reproductive problems experienced by females with metabolic disorders (Fig. 2).

In addition to the direct action of the follicular environment on oocyte metabolism, the deleterious effects on granulosa cells may disrupt trophic and signaling interactions with the oocyte and indirectly contribute to oocyte incompetence and thus poor pregnancy outcomes. Oocytes are deficient in their ability to use glucose as an energy substrate and require cumulus cell-provided glycolytic byproducts for their own development. Pyruvate and ATP, as related products of glycolysis by cumulus cells, can be transferred to oocytes [20, 207]. It is worth noting that abnormal metabolism increased apoptosis, and diminished mitochondrial function are detected in granulosa cells from obese and diabetic mice [156, 188, 208–210]. In particular, glucose uptake is dramatically reduced in cumulus cells of diabetic mice and shows a strong correlation with the lowered ATP levels in the enclosed oocyte [211]. After the resumption of meiosis, oocytes become transcriptionally inactive. At this stage, ATP is only needed to sustain basal metabolism and spindle formation in oocytes [212]. Consistent with this notion, mouse models have revealed that maternal diabetes, obesity, and hyperinsulinemia induce diverse, malformed spindles and misaligned chromosomes in oocytes [153, 168, 170, 213]. Similarly, Machtinger et al. have directly assessed a possible association between severe obesity (class II and III obesity) and oocyte characteristics in women. In severely obese patients, they have

shown a high prevalence of cytoskeletal abnormalities in oocytes that failed to fertilize [214]. Any error in the spindle assembly and chromosome movement could result in oocyte chromosomal imbalance, which is the leading genetic cause of miscarriage and congenital birth defects [14, 215, 216]. It is, therefore, possible that the limitation of energy substrates in granulosa cells disrupts the metabolic homeostasis of the oocyte, producing an aneuploid germ cell and contributing to the reproductive problems induced by metabolic disorders.

*Metabolic regulation of epigenetics* As discussed above, maternal metabolic disorders adversely affect oocyte quality leading to fetal growth retardation and developmental defects, even when removed from the stressful milieu and transferred into a normal uterine environment. Since these fetal abnormalities occur long after the environmental insult, the nutritional effect on the oocyte is likely to be propagated by an epigenetic pathway. Imprinting is an epigenetic mechanism where genes are expressed in a parent of origin specific manner. The chromosomal basis of the epigenetic inheritance of imprinting is methylation of CpG sequences. Imprinting establishment occurs in the germline of the parental generation and maintenance of the parental imprinting commences at the being of embryonic development [217]. Methylation status of several imprinted genes during oocyte development of diabetic mice has been examined. Results showed that the methylation pattern of *Peg3* differential methylation regions (DMR) was altered in a time-dependent manner by maternal diabetes, with no significant changes in *H19* and *Snrpn* DMRs [218].

In addition, the differences in acetylation patterns of histone H3 and H4 have also been observed during oocyte maturation in diabetic mice [219]. In striking contrast, DNA methylation of imprinted genes in oocytes was not altered in either obese dams or their offspring. However, DNA methylation of metabolism-related genes was

changed. In oocytes of obese mice, the DNA methylation level of the *Leptin* promoter was significantly increased and that of the *PPAR- $\alpha$*  promoter was reduced [220]. Interestingly, rosiglitazone was able to normalize oocyte developmental competence from obese mice [221], indicating that its target, *PPAR- $\gamma$* , may be a key regulator of metabolic mechanisms controlling oocyte quality. Failure to establish or maintain germ cell methylation patterns may result in abnormal fetal growth, placental failure, and human diseases [222].

A less studied but recently emerging concept is the integration of information about a cell's metabolic state into the regulation of epigenetics [223]. Various enzymes responsible for adding or removing epigenetic modifications have been identified. These enzymes that play important roles in epigenetic gene regulation utilize substrates or cofactors generated by cellular metabolism, thereby providing a potential link between nutrition, metabolism, and epigenetic modifications [224]. Most cytosolic acetyl-CoA comes from citrate exported from mitochondria in mammalian cells. Tracing experiments with radiolabeled glucose revealed that about half of the acetyl groups on histone H4K16 came from glucose-derived acetyl-CoA [225] (Fig. 1). Similarly, abrogation of acetyl-CoA generating enzymes leads to global histone hypoacetylation [226]. *S*-Adenosyl methionine (SAM) is derived from the essential amino acid methionine in an ATP-dependent manner. Both histone and DNA methylation require SAM as the high-energy methyl donor [227]. In response to a low ATP/AMP ratio, AMPK can translocate to chromatin and phosphorylate histone H2B serine 36 [228] (Fig. 1). There is also evidence that changes in glucose and glucose metabolism can leave lasting epigenetic marks [229]. Of particular note, metabolic disorders in oocytes, such as reduced citrate levels, ATP/AMP ratio, and glucose/lipid accumulation have been discovered under nutrition-deficient conditions. The findings outlined herein provide a mechanistic framework for understanding how nutritional effects on oocyte metabolism could impact epigenetic modifications and, therefore, embryo/offspring development where epigenetic alterations play a role (Fig. 2). Future focus should be directed towards identifying how specific metabolites and metabolic co-substrates interact with chromatin to epigenetically alter gene expression.

In addition, accumulating evidence suggests that the metabolic mTOR/PTEEN/PI3K signaling pathways play crucial roles during follicular growth and oocyte development in mice [230, 231]. Genetic data have shown that all primordial follicles become depleted in early adulthood of mice lacking PTEEN in oocytes, causing premature ovarian failure [232]. PI3K-AKT-mTOR pathway is involved in somatic regulation of oocyte mRNA translation, affecting

its developmental competence [233]. It is interesting to note that HFD-induced obesity accelerates the ovarian follicular development and the rate of follicle loss through activating mTOR signaling in rats [234]. mTOR has also recently been indicated to function in the PCOS mouse ovary [235]. However, whether these metabolic pathways in oocytes mediate the nutritional effects on pregnancy outcomes remains unknown. This topic would be a valuable research direction and deserves more attention in the future. Additionally, in response to the changes in maternal nutrition, the fluctuation of a series of extra- and intra-ovarian factors, such as epidermal growth factor (EGF), insulin-like growth factors (IGFs), and leptin, have been identified [182, 236, 237]. Whether, and if so how, they influence oocyte quality and reproductive outcomes requires further clarification and will not be discussed here as it is beyond the scope of this review.

In summary, increasing evidence supports a model where maternal nutrition imbalance disrupts energy metabolism in oocytes. This disruption further contributes to reproductive problems via the metabolic control of meiosis, mitochondria, or epigenetic modifications. As a consequence, meiotic defects result in nondisjunction inducing embryonic aneuploidy. The dysfunctional complements of mitochondria are maternally transmitted and epigenetic changes are likely to be propagated during embryogenesis, leading to the developmental abnormalities of the offspring. Further clarification is needed to exclude other possible metabolism-related pathways in oocytes that mediate the maternal nutritional effects on reproductive outcomes.

## Metabolic analysis and oocyte quality

### *Metabolite measurement in oocytes*

Metabolic analysis of mammalian oocytes started in the 1980s, which mainly used radiolabeled substrates to define the metabolites that oocytes require for their growth and maturation. A series of fundamental findings in this area have been discovered successively, such as utilization of glucose and pyruvate, uptake and metabolism of ribonucleoside and hypoxanthine, and transport of amino acids during oocyte development [40, 52, 117, 238–242]. Alternatively, we have developed a technique to measure metabolites and enzyme activities in single oocytes or preimplantation embryos, using not radioactivity but enzymatic cycling reactions that are based on the amplification of a fluorescent signal of pyridine nucleotide [243]. NADH and NADPH have identical absorption bands near UV light, which peak at 340 nm. NAD<sup>+</sup> and NADP<sup>+</sup> do not absorb at this wavelength. Therefore, changes in oxidation or reduction can be measured in the

spectrophotometer. According to this principle, separate assays are developed for each metabolite and are designed to link reactions ending with NAD/NADH or NADP/NADPH, which then are enzymatically amplified in a cycling reaction, and a byproduct of the amplification step is measured in a fluorometric assay. The detailed assay conditions have been described in our previous papers [64, 169, 244].

#### *Metabolomic search for markers of oocyte quality*

Very recent attempts are looking beyond a single substance to the totality of the biochemical constituents in the follicular environment, which is referred to as metabolomics. Metabolomic analysis seeks to identify and quantify the entire collection of intracellular and extracellular metabolites. Conceptually, there are two basic analytical methodologies used in metabolomics: target analysis (analysis restricted to single or selectively defined metabolites) and metabolite profiling (study of selective groups of target compounds and their metabolic intermediates using a single analytical technique) [245]. The application of metabolomics has been widely pursued. Nevertheless, it is currently still an enormous challenge for the direct metabolomic analysis of the oocyte itself, due to the requirement of large amounts of material. Thus, development of a technique for metabolic profiling of nano- and femtomolar amounts of sample down to even the single-cell level [246–248] would greatly advance our understanding of oocyte metabolism and improve in vitro maturation systems.

As a key factor in the reproductive technologies, oocyte quality profoundly affects fertilization, early embryonic survival, pregnancy maintenance, and even the offspring health. Thus, one of the important puzzles for reproductive biologists today is the search for the reliable noninvasive predictors of oocyte quality for both human and animal reproduction. In general, the use of morphological characteristics as predictors of oocyte quality is still controversial because of its subjectivity and inaccuracies. The follicle provides a very important microenvironment for the development of COC. This makes factors in follicular cells and those secreted in follicular fluids to be an ideal source of non-invasive and operational predictors of oocyte quality. Global assessment strategies involving genomic, transcriptomic, proteomic, or metabolomic profiling of follicular fluid, cumulus cells, or culture media have been applied to assisted reproduction [249]. Metabolomics allows the understanding of biological processes to be completed, as it is capable of providing biological end-point markers of the cellular processes that occur as a result of the disease, drug exposure, or nutritional alteration [250].

Currently, assessment of the metabolite profile is based on spectroscopic/spectrometric and chromatographic techniques such as nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry (MS; often combined with chromatography), and optical spectroscopy. Both NMR and MS can generate information on multiple compounds with a sample and have applied to analysis of culture media and follicular fluid [251–255]. For the first time, NMR was used to document a change in lipoprotein concentration in follicular fluid during follicular development [256]. NMR analysis of granulosa cells from rats has shown that follicle-stimulating hormone (FSH) increases the activity of the pentose phosphate pathway [257]. Using gas chromatography mass spectrometry (GC/MS)-based metabolomics, Bender et al. [258] found higher concentrations of saturated fatty acids in follicular fluid from cows and higher docosahexaenoic acid levels in follicular fluid from heifers. The elevated content of detrimental saturated fatty acids in cows will have a negative impact on oocyte maturation and early embryo development, which may explain the differences in fertility between heifers and lactating cows.

Liquid chromatography-tandem mass spectrometric (LC-MS/MS) analysis of follicular fluid revealed an increased aromatic amino acid content in PCOS patients independent of obesity, whereas the levels of branched-chain amino acid, glutamic acid, phenylalanine, alanine, and arginine are elevated with body mass index [259]. The disruptions in specific amino acids in the follicular fluid might impair oocyte quality, accounting for the inferior pregnancy outcome in obese and PCOS women. Analysis with high-performance LC also indicates that non-invasive amino acid profiling can be used to measure bovine oocyte developmental competence [260]. The most popular types of optical spectroscopy used in metabolic analysis are near infrared (NIR) and Raman spectroscopy. Although metabolite analysis obtained by these two approaches was successfully correlated with the developmental potential of embryos [254, 261, 262], opposing results have been also reported [263, 264]. Overall, there is a lack of the direct metabolomic analysis of oocytes and the surrounding cumulus cells. Data from this field will undoubtedly provide an essential network for metabolic regulation of oocyte development.

#### **Concluding remarks**

In conclusion, this review summarizes the metabolic pathways essential for oocyte development. The focus of this field has been overwhelmingly on extrinsic nutrients, and hence the intrinsic regulation of oocyte growth and development by transport systems and metabolic enzymes



has been relatively neglected. Metabolic disorders, such as obesity and diabetes, have major adverse effects on fertility, pregnancy, and the health of offspring. In the present review, we highlight the importance of endogenous oocyte metabolism linking maternal nutrition and reproductive outcomes, with emphasis on the metabolic control of meiosis, mitochondria, and epigenetic modifications.

Clearly, further research is needed to uncover mechanistic details for understanding how nutritional effects on oocyte metabolism are propagated during embryogenesis and offspring development. Global assessment strategy via metabolomic profiling of follicular fluid, cumulus cells, and culture media has been applied to assisted reproduction. Data from metabolomics may serve as a proxy to predict oocyte quality and thereby prevent reproductive defects, but its application is still in the infantile stages.

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