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# Maternal diabetes and oocyte quality

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## Abstract

Maternal diabetes has been demonstrated to adversely affect preimplantation embryo development and pregnancy outcomes. Emerging evidence has implicated that these effects are associated with compromised oocyte competence. Several developmental defects during oocyte maturation in diabetic mice have been reported over past decades. Most recently, we further identified the structural, spatial and metabolic dysfunction of mitochondria in oocytes from diabetic mice, suggesting the impaired oocyte quality. These defects in the oocyte may be maternally transmitted to the embryo and then manifested later as developmental abnormalities in preimplantation embryo, congenital malformations, and even metabolic disease in the offspring. In this paper, we briefly review the effects of maternal diabetes on oocyte quality, with a particular emphasis on the mitochondrial dysfunction. The possible connection between dysfunctional oocyte mitochondria and reproductive failure of diabetic females, and the mechanism(s) by which maternal diabetes exerts its effects on the oocyte are also discussed.

### Keywords

Diabetes; mitochondria; oocyte quality; embryo; mouse

## 1. Introduction

Diabetes mellitus is a metabolic condition characterized by elevated blood glucose levels secondary to absolute impairment of insulin secretion (type I diabetes). Relative impairment of insulin secretion in combination with varying degree of peripheral resistance to insulin action leads to type II diabetes (Goud et al., 2006). Women with poorly controlled type I or type II diabetes often suffer from a series of reproductive problems such as miscarriage, neonatal morbidity and mortality, and congenital malformations (Becerra et al., 1990; Greene, 1999; Sadler et al., 1988). Despite a drastic decrease in the incidence of spontaneous abortion and congenital malformations in infants of diabetic women due to improvements in glycemic control throughout pregnancy, these women still experience a 3–5 fold higher incidence of these pregnancy complications (Baccetti et al., 2002; Casson et al.,

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1997; El-Sayed and Lyell, 2001; Greene, 1999). These findings indicate that maternal diabetes may have permanent and irreversible effects on female reproduction. Since maternal diabetes in rodents influences embryonic and fetal development in a very similar manner to that of humans, chemically-induced or spontaneously diabetic mice and rats are commonly used as animal models to study reproduction of diabetic women (Amaral et al., 2008; Polanco Ponce et al., 2005). To date, the developmental anomalies during distinct stages induced by maternal diabetes, ranging from gamete and embryo to fetus, have been reported over past decades through animal and human studies (Amaral et al., 2008; Jungheim and Moley, 2008). In this review, we focus on the effects of maternal diabetes on oocyte quality, with a particular emphasis on the mitochondrial function.

## 2. Maternal diabetes and preimplantation embryo development

It has been demonstrated that mammalian embryos are vulnerable to injury during preimplantation stages of development and any damage may cause early embryo loss, embryo resorption and dysmorphogenesis (Moley, 1999). Prior to entering the uterus, pyruvate and lactate as main energy substrates of preimplantation embryo are metabolized aerobically via oxidative phosphorylation. As the developing embryo migrates from the fallopian tube into the anaerobic environment of the uterus, it adjusts to its new surroundings by increasing glucose metabolism via glycolysis (Leese, 1991). Maternal hyperglycemia has been shown to adversely affect progression from a one-cell to a blastocyst stage in rodent models (Diamond et al., 1989; Lea et al., 1996; Moley et al., 1998b; Moley et al., 1991; Moley et al., 1994). Zygotes removed from chemically-induced diabetic mice demonstrate retarded *in vivo* development to 2-cell stage with a lower percentage of 2-cell embryos recovered at 48 h after human chorionic gonadotropin (hCG) treatment compared with nondiabetic controls (Diamond et al., 1989). Similarly, *in vitro* experiments show that 2-cell embryos from control mice cultured in high glucose conditions are developmentally delayed compared with control embryos cultured in normal media (Diamond et al., 1991). It is worth noting that *in vitro*-cultured two-cell embryos that were recovered from diabetic mice still experience significant delay in their progression to the blastocyst stage (Diamond et al., 1989). Vesela et al. also observed that about 50% of two-cell embryos isolated from sub-diabetic rats were unable to develop to the 8-cell stage, even in a non-diabetic tract (Vesela et al., 1994). These results suggest that even brief exposure to diabetic state in periconceptual period may have lasting effects on subsequent embryonic development. Further, by conducting microanalytic assays of single embryos, Moley et al. revealed that hyperglycemia induces a downregulation of the GLUTs (facilitative glucose transporters) at the blastocyst stage in the mouse, which results in decreased glucose uptake and thus lower intraembryonic free glucose levels (Moley, 1999; Moley et al., 1998b). This decrease in glucose transport has been demonstrated to be sufficient to induce apoptosis at blastocyst stage (Chi et al., 2000; Moley et al., 1998a). In addition, an increase in fragmented embryos and a reduction in the number of cells in the inner cell mass of blastocysts recovered from diabetic rats (Lea et al., 1996) are considered to be associated with apoptosis induced by hyperglycemia through cell death effector pathways (Moley, 2001; Pampfer, 2000). Furthermore, our previous work showed the abnormal tricarboxylic acid (TCA) cycle metabolism in the glucose-induced apoptotic blastocyst, suggesting alterations in

mitochondrial physiology (Chi et al., 2002). More importantly, we recently found that one-cell zygote transfer from diabetic to nondiabetic mice still results in significantly increased congenital malformations and growth retardation in the offspring (Wyman et al., 2008), indicating that exposure to maternal diabetes during oogenesis, fertilization, and the first 24h was enough to program permanently the fetus to develop morphological changes. Taking above findings together with depressed ovarian steroidogenesis (Garris et al., 1985; Vomachka and Johnson, 1982), increased granulosa cell apoptosis (Chang et al., 2005) and delayed oocyte maturation (Colton et al., 2002; Diamond et al., 1989) in diabetic mice, it is attractive to hypothesize that maternal diabetes has detrimental effects as early as the oocyte stage, and which may further predispose them to post-fertilization developmental abnormalities and even metabolic diseases in the offspring.

## 3. Effects of maternal diabetes on oocyte quality

In most mammals, oocytes are arrested within ovarian follicles at the diplotene stage of the first meiotic prophase, which is also termed the germinal vesicle (GV) stage, around the time of birth. Fully-grown oocytes are stimulated to reinitiate meiosis by the pituitary luteinising hormone (LH) surge *in vivo* at puberty, as indicated by GV breakdown. As the microtubules become organized into a bipolar spindle and all chromosomes align at the spindle equator, the oocytes proceed to the metaphase I stage and subsequently extrude the first polar body into the perivitelline space, followed by entry into meiosis II and a second arrest at metaphase II (Miao et al., 2009; Wang and Sun, 2007). Full developmental competence of an oocyte requires synchronous nuclear maturation and cytoplasmic maturation (Krisher, 2004). Any dysfunction or dislocation of oocyte components, such as spindle, cortical granules or mitochondria could impair oocyte quality (Combelles and Racowsky, 2005; Coticchio et al., 2004; Sun et al., 2001b). Mounting evidence has suggested that oocyte quality profoundly affects fertilization, early embryonic survival, the establishment and maintenance of pregnancy, fetal development, and even adult disease (Krisher, 2004; Sirard et al., 2006). Thus, investigation of effects of maternal diabetes on oocyte quality may inform us on the origin of reproductive failure in diabetic females. Several developmental abnormalities in oocytes from diabetic animals have been reported. The following sections will give a brief summary of developmental abnormalities, and then focus on our recent findings of mitochondrial dysfunction in oocytes from diabetic mice (Wang et al., 2009).

### 3.1. Maternal diabetes delays meiotic progression of oocytes

Diamond et al. first reported that germinal vesicle breakdown (GVBD), a marker of oocyte meiotic maturation, is attenuated in superovulated oocytes from diabetic mice (Diamond et al., 1989), which has been further confirmed by several other different laboratories (Chang et al., 2005; Colton et al., 2002; Kim et al., 2007; Ratchford et al., 2007). Nevertheless, it is interesting to note that cumulus-enclosed oocytes (CEOs) from diabetic mice exhibit both accelerated spontaneous maturation kinetics and restricted hormone-induced maturation *in vitro*. In addition, ova from diabetic mice were also found to be less likely to progress to metaphase II after induction of ovulation compared with controls (Colton et al., 2002). *In vitro* studies have shown that both the meiosis-inducing and -suppressing effects of glucose on oocyte maturation appear to be mediated by the gap junctional communication pathway

that metabolically couples the oocyte with the somatic compartment of the follicle (Downs, 1995; Downs, 2000; Fagbohun and Downs, 1991). By performing coupling assays on freshly isolated CEOs, Colton and colleagues showed that the cell-cell communication between the oocyte and the cumulus cells was reduced in diabetic mice (Colton et al., 2002). In support of this observation, we recently identified that expression of two gap junction proteins (Cx26 and Cx43) were markedly decreased in diabetic cumulus cells when compared to controls. The levels of Cx37, a gap junction protein known to be predominantly expressed in the oocyte, were also significantly lower in oocytes from control mice than those from diabetic mice (Chang et al., 2005; Ratchford et al., 2008). Moreover, incubating the CEOs with a gap junction blocker carbenoxolone (CBX) *in vitro* dramatically delayed the onset of GVBD in mouse oocytes (Ratchford et al., 2008), although disruption of gap junctional communication with the rat ovarian follicle induces oocyte maturation (Sela-Abramovich et al., 2006). Thus, this decrease in gap junction and connexin expression in CEOs may be responsible for the impaired oocyte maturation in diabetic mice.

In addition, defects in glucose, purine, cAMP metabolism and changes in hydroxyacyl-CoA dehydrogenase (Hadh2), glutamic pyruvate transaminase (Gpt2) and AMP-activated protein kinase (AMPK) activity were detected in CEOs and denuded oocytes from diabetic mice (Colton et al., 2003; Colton et al., 2002; Ratchford et al., 2007). Diabetic rat models demonstrated the altered prostaglandin (PGE2) production in both ovulated and immature CEOs isolated from ovaries, as well as in *in vitro*-matured CEOs (Jawerbaum et al., 1999; Jawerbaum et al., 1996). Each of these conditions is thought to contribute to the disrupted meiotic behavior in oocytes from diabetic animals.

### 3.2. Maternal diabetes causes mitochondrial dysfunction in oocytes

Mitochondria play a primary role in cellular energetic metabolism, homeostasis, and death. They are the most abundant organelles in mammalian oocyte (Van Blerkom, 2004). Mitochondria are directly involved at several levels in the reproductive process since their functional status influences the quality of oocytes and contributes to the process of fertilization and embryonic development (May-Panloup et al., 2007). Recently, we used a streptozotocin (STZ)-induced diabetic mouse model to investigate the effects of maternal diabetes on the mitochondrial status in oocytes. Herein we give a brief summary of our findings, and detailed information can be found in Wang et al. (Wang et al., 2009)

Using transmission electron microscopy, we observed marked structural aberrations in mitochondria of diabetic oocytes including a narrowed intermembrane space and rupture of the outer membrane. These ultrastructural alterations suggest swelling of mitochondria, which in somatic cells is thought to herald mitochondrial dependent apoptosis and degradation (Senoo-Matsuda et al., 2005). Interestingly, we previously discovered the decreased heat shock protein 90 (HSP90) expression in either CEOs or denuded oocytes from diabetic mice (unpublished data), which has been suggested to be able to activate the apoptotic program mediated by mitochondrial pathway (Neckers et al., 2007; Pandey et al., 2000; Sato et al., 2000).

By performing immunofluorescence microscopy, we found that the distribution pattern of mitochondria during meiotic maturation was disrupted in oocytes from diabetic mice. One

pronounced tendency is that the percentage of the perinuclear distribution pattern at GV stage and polarized distribution pattern at MII stage was decreased relative to control whereas the proportion of the homogenous distribution pattern was increased accordingly. In addition, at both GV and MII stages, oocytes from diabetic mice displayed a much higher percentage of clustering mitochondrial distribution. Given that the spatial remodeling of mitochondria may allow maturing oocytes to cater to differing energy requirements of various key events, such as germinal vesicle breakdown and metaphase spindle formation (Van Blerkom, 2004), inadequate translocation of mitochondria therefore perhaps serves as an important factor contributing to the maturation delay (Chang et al., 2005; Colton et al., 2002; Diamond et al., 1989) and spindle defects (Wang et al., 2009) observed in diabetic oocytes.

Mitochondrial DNA (mtDNA) is an essential component of mitochondrial function. Low mtDNA content has been reported to be associated with oocyte incompetence, fertilization failure and even ovarian insufficiency (May-Panloup et al., 2007). Surprisingly, by performing quantitative real time-PCR on single fully-grown oocytes, we found that the average mtDNA copy number in oocytes from diabetic mice was significantly increased as compared with controls. Similarly, mtDNA copy number in oocytes from older women was significantly greater than those from young women (Steuerwald et al., 2000). Such an increase in mitochondrial biogenesis was attributed to a compensatory phenomenon to guarantee sufficient ATP production in the event of either an increased demand or due to a respiratory chain dysfunction. It is also possible to explain this as a decrease in mitochondrial degradation or autophagy (Mammucari et al., 2008; Tsukamoto et al., 2008a; Tsukamoto et al., 2008b). On the other hand, nitric oxide (NO) has been shown to have an effect upon mitochondrial biogenesis. HeLa cells expressing endothelial nitric oxide synthase (eNOS) displayed an increase in mtDNA content (Nisoli et al., 2003; Reznick and Shulman, 2006). It is interesting to point out that NOS activity is also elevated in the ovaries of mild and severe diabetic rats (Jawerbaum et al., 1999; Jawerbaum et al., 1996). Nevertheless, similar experiments have not been performed on diabetic mice yet.

Finally, by conducting microanalytical enzymatic cycling assays, we identified that the levels of ATP and TCA cycle metabolites are dramatically decreased in ovulated oocytes from diabetic mice. Our previous studies also showed the ATP content was significantly lower in preovulatory oocytes and CEOs from diabetic mice (Colton et al., 2003; Ratchford et al., 2007). These results suggest that maternal diabetes results in the reduction of mitochondrial function, which is likely related to their structural abnormalities. Variations in the ATP content have been suggested to significantly affect oocyte quality, embryonic development and implantation process (Quinn and Wales, 1973; Van Blerkom et al., 1995).

Collectively, by performing molecular, cellular and biochemical analysis, we reveal the structural, spatial, genetic and metabolic dysfunction of mitochondria in oocytes from diabetic mice.

## 4. Is mitochondrial dysfunction in oocytes related to reproductive failure of diabetic females?

It is obvious that maternal diabetes has adverse effects on multiple meiotic events during oocyte development. In the following parts, we will just list some correlative evidence to discuss the possible connection between dysfunctional oocyte mitochondria and reproductive failure of diabetic females. However, whether these reproductive problems are mediated through developmental defects in oocytes remains to be determined.

### 4.1. Mitochondrial dysfunction and meiotic defects in diabetic oocytes

The processes of spindle formation and chromatin organization are believed to be particularly sensitive to physical, chemical and endocrine environments (Hunt and Hassold, 2008). Abnormalities in the meiotic spindle and chromosome alignment are known to result in improper chromosome segregation and nondisjunction of the chromatids at the first or second meiotic division, contributing to an increased incidence of aneuploidy (Hassold and Hunt, 2001). By confocal scanning, we revealed that maternal diabetes induces an increased frequency of spindle disorganization and chromosome misalignment in oocytes, as shown in Fig 1. Several lines of evidence have suggested that these meiotic defects may be associated with mitochondrial dysfunction. First, we consistently observed chromosomal congression failure in the ovulated oocytes from diabetic mice that display clustered mitochondria (Fig. 2; lower panel, red arrows), which strongly suggests that deficient chromosome alignment may be directly linked to abnormal mitochondrial distribution. *In vitro* experiments also showed that exposure of maturing mouse oocytes to diazepam to disrupt mitochondrial distribution results in predivision of homologue and aneuploidy (Sun et al., 2001a; Yin et al., 1998). Most recently, association of mitochondria with spindle poles was found to facilitate spindle alignment in *S. pombe* (Kruger and Tolic-Norrelykke, 2008). Second, reduction of mitochondrial function evidenced by decreased ATP content may contribute to the meiotic defects in diabetic oocytes (Wang et al., 2009). Chromatin condensation during meiosis is an ATP-dependent process (Hirano, 2005). Microtubule assembly and chromosome movement also requires ATP (Inoue and Salmon, 1995). It has been suggested that mammalian mature oocytes display a high ATP turnover and that the ATP consumed is supplied by mitochondrial respiration (Dumollard et al., 2004; Igarashi et al., 2005). A recent study revealed that injury of mitochondria in MII oocytes reduces ATP content and disrupts the meiotic spindle (Zeng et al., 2007; Zhang et al., 2006). *Pdha1*-deficient (pyruvate dehydrogenase a1) mouse oocytes experience inadequate ATP levels along with chromatin and microtubular abnormalities (Johnson et al., 2007). Senescence accelerated mice also demonstrated that spindle defects and disturbances in chromosome alignment are associated with mitochondrial dysfunction in oocytes (Liu et al., 2002). Finally, by karyotypic analysis, we confirmed the increased aneuploidy rate in ovulated oocytes from diabetic mice. This is in line with previous reports showing a high frequency of chromosomal numerical anomalies in embryos from diabetic mice (Tatewaki et al., 1995; Yamamoto et al., 1971). Furthermore, mitochondrial dysfunction has been proposed as a factor in the increased incidence of aneuploidy in oocytes from older women (Brenner et al., 1998; Keefe et al., 1995). Collectively, above data support the idea that meiotic defects and aneuploidy in diabetic

oocytes may be associated with mitochondrial dysfunction, which may be involved in reproductive failure and congenital birth defects of diabetic females.

### 4.2. Mitochondrial dysfunction in oocytes and developmental abnormalities of diabetic embryos

Mature mammalian oocytes are maternally endowed with thousands of mitochondria that act as the founding population of all daughter-cell mitochondria of the developing embryo (Jansen, 2000; Schatten et al., 2005). Increasing evidence indicates that oocyte mitochondrial dysfunction may be a critical determinant of embryo developmental competence (Fissore et al., 2002; Ramalho-Santos et al., 2004; Ramalho-Santos et al., 2009; Van Blerkom, 2004).

We have observed mitochondrial swelling and even rupture of the outer membrane in ovulated oocytes from diabetic mice (Wang et al., 2009). Similar characteristics were also found in mitochondria of rat embryos exposed to maternal diabetes (Yang et al., 1995; Yang et al., 1998). These ultrastructural alterations have been correlated with an increase of mitochondrial membrane permeability, which is directly regulated by the Bcl-2 family of proteins (Adams and Cory, 2001). Interestingly, we previously identified that expression of Bax, a pro-apoptotic member of the Bcl-2 family, is increased in blastocyst embryos recovered from diabetic mice and that these changes correlate morphologically with increased DNA fragmentation (Moley et al., 1998a). These findings indicate that the structural abnormalities of oocyte mitochondria may be transmitted to the embryo and therefore be involved in the apoptosis in preimplantation embryos in diabetic mice (Chi et al., 2002; Eng et al., 2007; Keim et al., 2001). More importantly, because all mitochondria are maternally inherited, the proportion of genetically compromised mitochondria capable of replication largely determines the extent to which post-implantation development may be compromised, and the probability that certain cytopathologies will develop later in life (Christodoulou, 2000; Jacobs et al., 2006; Van Blerkom and Davis, 2007).

The localization of mitochondria in the egg during maturation and their segregation to blastomeres in the cleaving embryos are strictly regulated. Remarkably, we found that mitochondrial clustering was dramatically increased in oocytes from diabetic mice (Wang et al., 2009). Ovulated eggs by non-diabetic aged mice also displayed a higher percentage of mitochondrial aggregates (Tarin et al., 2001). Such an abnormal distribution pattern may lead to disproportionate mitochondrial segregation during cleavage in embryo, which has been reported to associate with arrested cytokinesis and lysis in the blastomeres that inherited a significantly reduced organelle complement (El Shourbagy et al., 2006; Nagai et al., 2006; Van Blerkom et al., 2000).

*In vitro* studies demonstrated that mitochondrial dysfunction in mouse oocytes induced by photosensitization results in developmental arrest and apoptotic degeneration of preimplantation embryo (Thouas et al., 2004). Treatment of one-cell zygotes with protonophore carbonyl cyanide p-trifluoromethoxy-phenylhydrazone (FCCP) to disrupt mitochondrial function also markedly delayed the cleavage of early embryos (Liu et al., 2002). In addition, sublethal mitochondrial injury in mouse oocyte resulted in the aberrant cytoplasmic patterning of mitochondria (Thouas et al., 2006) and upon IVF these resultant

embryos demonstrated increased miscarriages, growth retardation and neural tube defects similar to that seen with diabetic embryopathy. In combination with other results showing the structural, metabolic and biogenetic alterations in mitochondria of diabetic embryos (Akazawa, 2005; Alcolea et al., 2007; Chi et al., 2002; Yang et al., 1995; Yang et al., 1998), it is possible that dysfunctional mitochondria in diabetic oocyte may be maternally transmitted to the embryo, contributing to the developmental retardation in preimplantation embryos (Diamond et al., 1989; Moley et al., 1991), congenital malformations, and even metabolic disease in the offspring.

## 5. How does maternal diabetes exert its effects on oocyte quality?

Although the adverse effects of maternal diabetes on embryo development have been associated with compromised oocyte competence, however, to date, the pathway(s) by which maternal diabetes exerts its effects on the oocyte remains obscure.

Mammalian ovarian follicles are highly specialized structures that support the growth and development of oocytes. Bidirectional communication between oocytes and their associated follicular somatic cells, granulose cells, constitutes a regulatory loop essential for the development of both cell types (Eppig, 2001). The oocyte and granulosa cells are metabolically coupled throughout follicular development by membrane specializations known as gap junctions (Albertini and Anderson, 1974; Sugiura and Eppig, 2005). Glucose is a necessary energy substrate for oocyte maturation in the presence of cumulus cells (Downs and Utecht, 1999; Preis et al., 2005; Zheng et al., 2007; Zuelke and Brackett, 1992). Nevertheless, oocytes carry out glycolysis poorly and require cumulus cells to metabolize glucose into products that can be used by oocytes as energy production substrates to support maturation (Biggers et al., 1967; Sugiura and Eppig, 2005). Hence, the somatic compartment is a critical mediator in the interaction of glucose in oocyte development. Notably, significant reductions in metabolic coupling and gap junction communication have been demonstrated in cumulus-oocyte complexes from diabetic mice (Colton et al., 2003; Ratchford et al., 2008). These alterations may be responsible for the delay in oocyte growth and maturation and the altered energy resources seen in diabetic mice (Diamond et al., 1989; Ratchford et al., 2007). In addition, we detected an increased apoptosis in granulose cells from diabetic mice (Chang et al., 2005), which has been correlated with compromised oocyte quality and poor pregnancy outcome (Lee et al., 2001; Nakahara et al., 1997). Recently, we revealed the structural and metabolic dysfunction of mitochondria in cumulus cells of diabetic mice, which was further demonstrated to be involved in the increased apoptosis of cumulus cells exposed to maternal diabetes (Wang Q, et al., unpublished data). Together these data suggest that maternal diabetes may indirectly impair oocyte competence by disturbing the metabolism in granulosa cells and their communications with the oocyte.

We previously found that glycogen levels were significantly higher in oocytes from diabetic mice than controls (Ratchford et al., 2007), which indicates that the hyperglycemic environment may lead to accumulation of glucose stored as glycogen. In support of this idea, our most recent data showed around 2-fold increase in glucose levels in oocytes from diabetic mice compared with those from control mice (Ratchford A, et al., unpublished data). The deleterious effects of high glucose on mitochondria have been widely documented

in various cell types (Rolo and Palmeira, 2006; Russell et al., 2002; Yu et al., 2008). It is interesting to point out that elevated glycogen levels have been reported to inhibit AMPK activation (Kawanaka et al., 2000; Polekhina et al., 2003; Wojtaszewski et al., 2002), which is in line with our result showing the drop of AMPK activity in diabetic mouse oocytes (Ratchford et al., 2007). Moreover, activation of AMPK was demonstrated to participate in the regulation of oocyet maturation (Chen and Downs, 2008; Chen et al., 2006; Downs et al., 2002). On the other hand, Wellen et al. recently identified that glucose availability can influence histone acetylation in an adenosine triphosphate-citrate lyase (ACL) dependent manner (Wellen et al., 2009). Histone acetylation is required for meiotic resumption, spindle assembly and chromosome segregation during oocyte development (Akiyama et al., 2006; Kageyama et al., 2007; Nagashima et al., 2007; Wang et al., 2006). Importantly, epigenetic modifications linked to early nutrition can be transmitted to subsequent generations and may contribute to “intergenerational programming” of diabetes risk (Drake and Walker, 2004; Woo and Patti, 2008). Taking above data together with our results showing mitochondrial dysfunction and meiotic defects in diabetic oocytes, it is plausible to speculate that maternal hyperglycemia could directly disrupt meiotic events by inducing glucose accumulation in the oocyte.

It is known that the type I diabetic mouse is characterized by hyperglycemia and hypoinsulinemia. Therefore, hypoinsulinemia could also be a contributory factor affecting oocyte quality, as the insulin signaling pathway has been reported to function in chromatin remodeling during oocyte growth (Acevedo et al., 2007).

## 6. Concluding remarks

Maternal diabetes adversely affects oocyte developmental competence. In particular, mitochondria have been demonstrated to be dysfunctional in oocytes from diabetic mice. Those abnormal oocyte mitochondria may be maternal transmitted to the embryo and then be propagated during embryogenesis and fetal development, contributing to the reproductive problems experienced by diabetic females. More work is necessary to explore the pathways by which maternal diabetes impairs oocyte quality and to identify the potential mediators during this process. This information is essential in order to more effectively improve reproductive outcomes for diabetic women.

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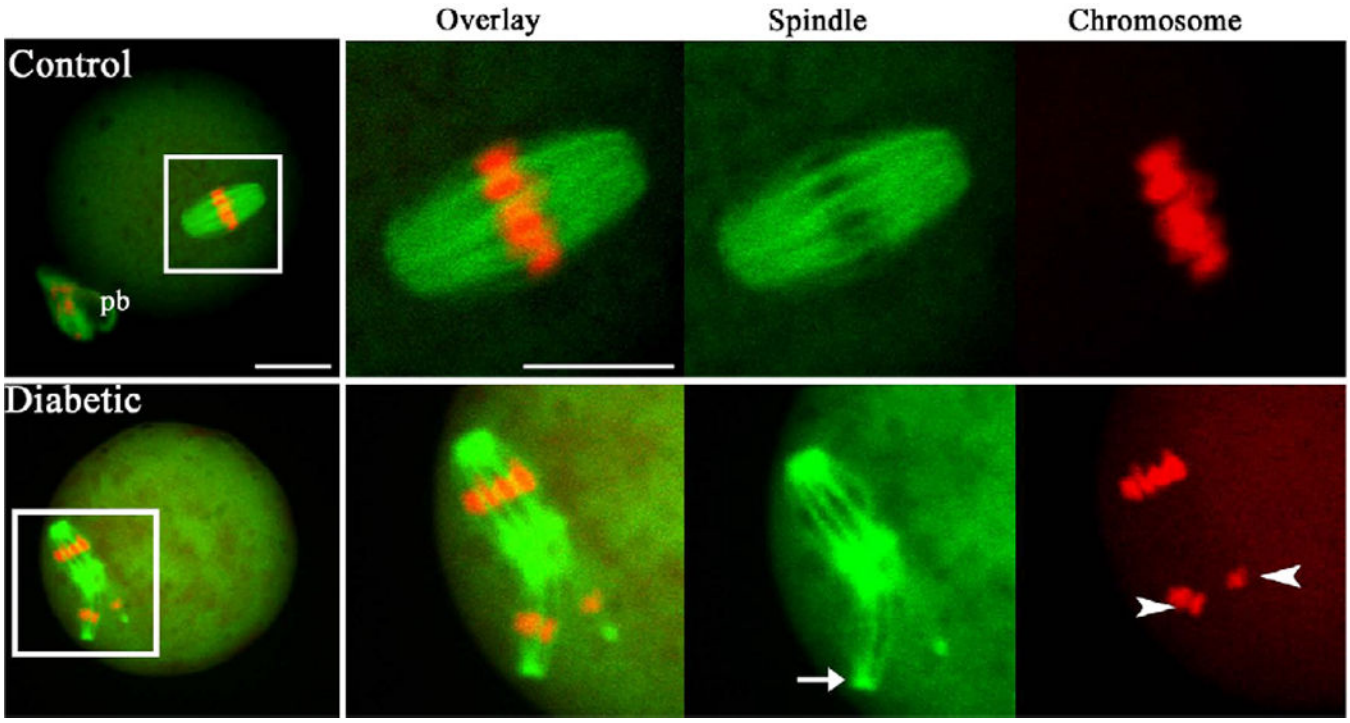


**Figure 1. Spindle defects and chromosome misalignment in oocytes from diabetic mice**

Ovulated MII oocytes from control and diabetic mice were stained with β-tubulin antibody to visualize the spindle (green) and counterstained with TO-PRO to visualize chromosomes (red). MII oocytes from control mice present a typical barrel-shape spindle and well-aligned chromosomes on the metaphase plate. In MII oocytes from diabetic mice, spindle defects (arrows) and chromosome misalignment (arrowheads) were readily observed. Representative confocal sections are shown. Scale bars: 20 μm. (From Wang Q, et al. Maternal diabetes causes mitochondrial dysfunction and meiotic defects in murine oocytes. Mol Endocrinol 2009, 23:1603–1612, with minor modifications.)

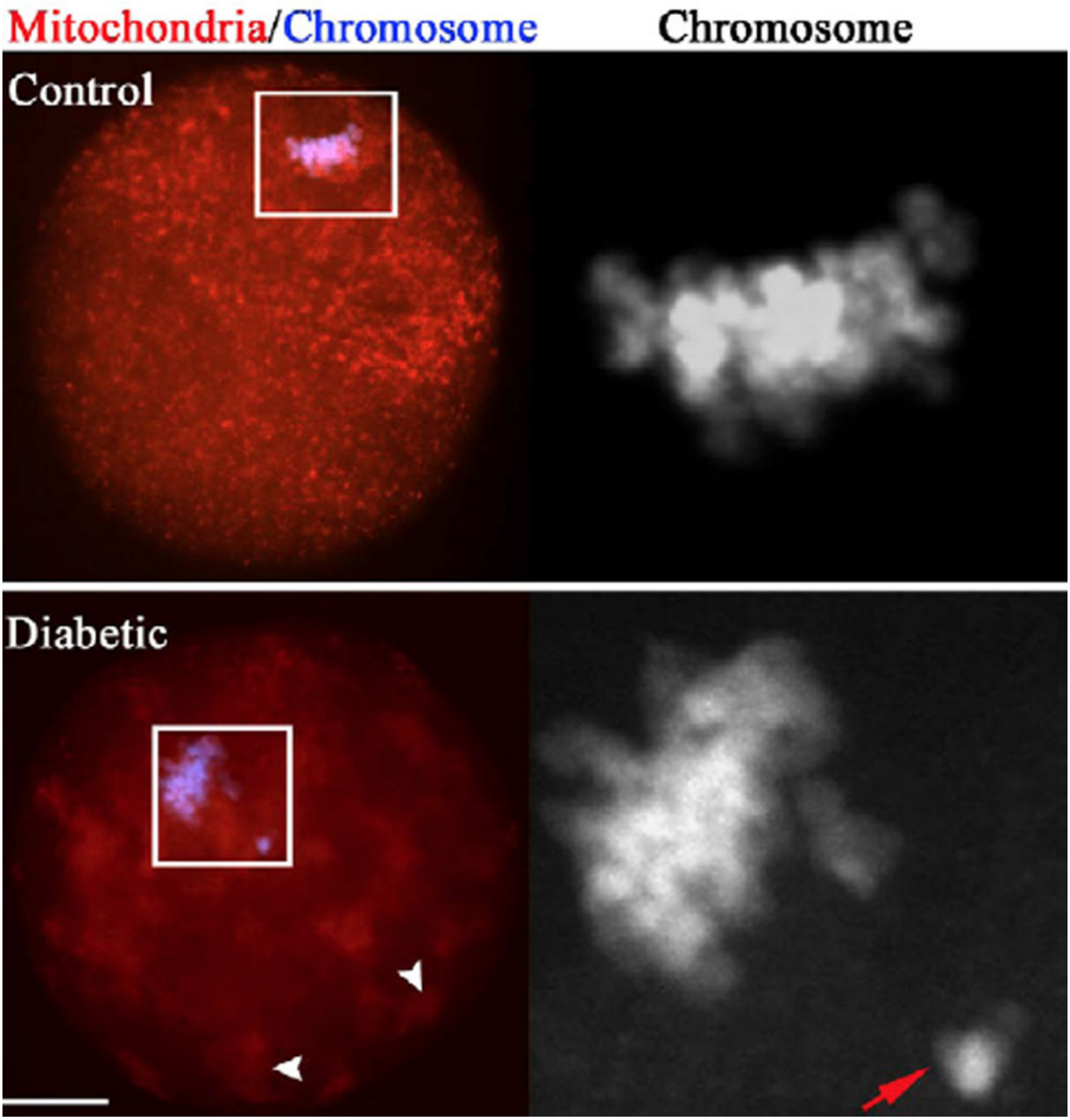


**Figure 2. Mitochondrial clustering and its relationship with chromosome congression failure in diabetic oocytes**

Ovulated MII oocytes from control and diabetic mice were labeled with MitoTracker Red to visualize mitochondrial localization and counterstained with DAPI for nuclear status. In most control oocytes, mitochondria display a polarized distribution pattern and chromosomes well align on the metaphase plate. However, we consistently detected chromosomal congression failure (abnormal alignment; lower panel, red arrows) in diabetic oocytes that display clustered mitochondria (white arrowheads). Scale bars: 20 μm. (From

Wang Q, et al. Maternal diabetes causes mitochondrial dysfunction and meiotic defects in murine oocytes. Mol Endocrinol 2009, 23:1603–1612, with minor modifications.)