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Advances in research into gamete and embryo-fetal origins of adult diseases

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The fetal and infant origins of adult disease hypothesis proposed that the roots of adult chronic disease lie in the effects of adverse environments in fetal life and early infancy. In addition to the fetal period, fertilization and early embryonic stages, the critical time windows of epigenetic reprogramming, rapid cell differentiation and organogenesis, are the most sensitive stages to environmental disturbances. Compared with embryo and fetal development, gametogenesis and maturation take decades and are more vulnerable to potential damage for a longer exposure period. Therefore, we should shift the focus of adult disease occurrence and pathogenesis further back to gametogenesis and embryonic development events, which may result in intergenerational, even transgenerational, epigenetic re-programming with transmission of adverse traits and characteristics to offspring. Here, we focus on the research progress relating to diseases that originated from events in the gametes and early embryos and the potential epigenetic mechanisms involved.

gamete, embryo, acquired inheritance, intergenerational/transgenerational transmission, epigenetic modification

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Introduction

In 1989, the British epidemiologist David Barker and his colleagues examined relationships between post-neonatal mortality for the period 1911–1925 and later adult mortality in 1968–1978. They found that regional differences in stroke and coronary heart disease mortality were predicted by birth weight, with lower birth weights associated with an increased risk of death from stroke and coronary heart disease in adults (Barker et al., 1989a, Barker et al., 1989b). In 1992, the evidence was presented in Barker's book "*Fetal and Infant Origins of Adult Disease*" (Barker, 1992), proposing that the roots of cardiovascular disease lay in the effects of undernutrition in fetal life and early infancy.

Subsequent studies in the UK, Europe, USA, and China have confirmed these findings and shown that it is restricted fetal growth, rather than preterm delivery, which carries the risk of later adult diseases (Paneth and Susser, 1995). These observations have been collectively termed the "Barker hypothesis", which is also known as the "Thrifty Phenotype Hypothesis", indicating that intrauterine growth retardation, low birth weight, and premature birth have a causal relationship to the origins of hypertension, coronary heart disease, and non-insulin-dependent diabetes, in middle age.

Intrauterine growth and development includes two phases: the embryonic and fetal phases. The embryonic phase (1–8 weeks) consists of the proliferation, organization, and differentiation of the embryo, whereas the fetal phase (from 9 weeks to birth) involves the continued growth and functional maturation of different tissues and organs (Gluckman and Harding, 1994, Kanaka-gantenbein et al., 2003). In 2010, Motrenko (2010) proposed the "embryo-fetal origin of dis-

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eases" theory, which proposed that abnormal development of embryo, even the gametes, may induce poor health after birth. Embryonic and fetal periods are clearly vulnerable to environmental factors, and the acquired changes can persist trans-generationally, despite the lack of continued exposure. One possible explanation is the epigenetic regulation of the human genome where changes in gene expression or cellular phenotype result from mechanisms other than changes in the underlying DNA (Canani et al., 2011).

In addition to the fetal period, fertilization and early embryonic stages, the critical time windows of epigenetic reprogramming, rapid cell differentiation and organogenesis, are the most sensitive stages to environmental disturbances. Compared with embryo and fetal development, gametogenesis and maturation take decades and are hence more vulnerable to potential damage for longer exposure period. Therefore, we should shift the focus of the origins of adult disease occurrence and pathogenesis further back to gametogenesis and embryonic development events. Based on previous research and new findings, related to the origins of adult diseases in oocyte, sperm, and embryo, Hefeng Huang et al. published the book Gamete and Embryo-fetal Origins of Adult Diseases (GEOAD). Furthermore, the Developmental Origins of Health and Disease (DOHaD) concept has been extended, and the link between the pre-conception, peri-conception, fetus, and early infant phases of life and the subsequent development of metabolic disorders in later life has been highlighted (Hanson and Gluckman, 2014; Vickers, 2014).

Adaptive responses of the gamete or embryo reacting to adverse factors, such as nutrition, toxins, endocrine disrupting chemicals, culture systems and manipulations in assistant reproductive technology (ART), make them prone to permanent damage of organs, congenital abnormality, and development of chronic adult diseases. This may result in intergenerational, even trans-generational, epigenetic reprogramming with transmission of adverse traits and characteristics to offspring. Accumulating evidence has suggested that a poor developmental experience can increase the risk of non-communicable diseases in later life, including cardiovascular and metabolic comorbidities (such as hypertension, obesity, and type 2 diabetes), cancer, and neurological impairment. This review will mainly introduce the research progress of the diseases originating from gamete and embryo and the potential epigenetic mechanisms involved.

Peri-conceptional environment and GEOAD

The peri-conceptional environment mediated through maternal nutrition can modify development throughout gestation and affect the physiological and metabolic health of adult offspring. In mouse models, maternal protein restriction applied exclusively during the preimplantation period, with normal nutrition thereafter, is sufficient to cause adverse cardiometabolic and neurological outcomes in adult offspring. Evidence for similar effects, whereby environmental factors during the peri-conceptional window can program postnatal disease risk, can be found in humans and large animal models (Fleming et al., 2012; Fleming et al., 2017).

With respect to exposure to the 1944–1945 Dutch famine, Tobi et al. (2015) found that only when famine exposure had been during the first 10 weeks of gestation of their mothers, but not weeks 11–20, 21–30 or 31–delivery, was it associated with differences in offspring in DNA methylation of the genes involved in growth, development and metabolism. Stein et al. (2009) studied 923 individuals and found the maternal exposure to the Dutch famine prior to conception was associated with their offspring being affected by depressive symptoms in adulthood. In the 360 adult offspring (F2) of a cohort of men and women (F1) born around the time of the Dutch famine, offspring from prenatally undernourished fathers, but not mothers, were heavier and more obese than offspring from parents receiving a normal caloric diet before conception. Besides, the increased adiposity in the offspring of prenatally undernourished fathers may lead to increased chronic disease rates in the future (Veenendaal et al., 2013).

Fleming and his colleagues focused on the effect of maternal low-protein diet (LPD) confined to the preimplantation period (Emb-LPD) on offspring. In mice, Emb-LPD with normal nutrition thereafter, leads to offspring with increased weight from birth, sustained hypertension, and abnormal anxiety-related behavior. Embryo transfer (ET) experiments revealed that the increase in perinatal weight was induced within blastocysts responding to preimplantation LPD, independent of subsequent maternal environment during later pregnancy (Watkins et al., 2008a). Elevated offspring systolic blood pressure following maternal gestational protein undernutrition was associated with impaired arterial vasodilatation, elevated serum and lung ACE activity in the offspring (Watkins et al., 2010). Further, they found the induction of metabolic programming following Emb-LPD was achieved through mammalian target of rapamycin complex 1 (mTORC1) signaling which acts as a sensor for preimplantation embryos to detect maternal nutrient levels via branched chain amino acids and/or insulin availability (Eckert et al., 2012). Recently, they found the Emb-LPD and sustained LPD could reduce neural stem cell and progenitor cell numbers through suppressed proliferation rates in both ganglionic eminences and the cortex of the fetal brain, causing short-term memory deficits in adult offspring. The altered expression of fragile X family genes was identified as a potential molecular mechanism, demonstrating that poor maternal nutrition from conception is sufficient to cause

abnormal brain development and adult memory loss (Gould et al., 2018).

In addition to undernutrition and LPD, high-glucose or high-fat diet (HFD) during the peri-conceptional period could affect later health in offspring. In mice, Gao et al. (2016) observed that in response to myocardial ischemia reperfusion (MIR), diabetic mother offspring exhibited augmented infarct size, cardiac dysfunction, and myocardial apoptosis compared with offspring born to non-diabetic mice. This was associated with exaggerated activation of mitochondria- and endoplasmic reticulum (ER) stress-mediated apoptosis pathways and oxidative stress. Molecular analysis showed that the impaired myocardial ischemic tolerance in the offspring of diabetic mothers was mainly attributable to blunted cardiac insulin receptor substrate (IRS)-1/Akt signaling. Furthermore, maternal melatonin supplementation in diabetic dams during pregnancy significantly improved the tolerance to MIR injury in their offspring, via restoration of cardiac IRS-1/Akt signaling.

Maternal folate status during periconceptional period and early pregnancy could influence the development in offspring. Padmanabhan et al. (2013) demonstrated that a hypomorphic mutation in the methionine synthase reductase (Mtrr) gene disrupted folate metabolism, resuting in intrauterine growth restriction, developmental delay, and congenital malformations. Remarkably, the transgenerational effect of Mtrr deficiency in mice further signified that abnormal folate metabolism contributes to epigenetic inheritance through the germline. To better understand the biological implications of folate status on the developing fetus, Joubert et al. (2016) examined the association between maternal plasma folate during pregnancy and epigenome-wide DNA methylation in 1,988 newborns from two European cohorts. This work informed how maternal folate could impact the developing epigenome and health outcomes in offspring, and showed that maternal folic acid supplementation modified DNA methylation patterns in the brains of offspring, which was associated with improvement in the early development of sensory-motor function. These findings were consistent with an epigenomic mechanism by which periconceptional folic acid supplementation benefits neurodevelopment in offspring (Li et al., 2018). However, a cohort study in India demonstrated that higher maternal folate concentrations were associated with higher insulin resistance in the children at 9.5 and 13.5 years of age, persisting through childhood into adolescence (Krishnaveni et al., 2014). In mice, the offspring of mothers fed high folic acid-supplemented diet had intrauterine growth delay, short-term memory impairment and altered brain development. Maternal and offspring pseudo-methylenetetrahydrofolate reductase (MTHFR) deficiency with disturbances in choline/methyl metabolism were likely to have contributed to these outcomes (Bahous et al., 2017). Therefore, the mechanism should be further clarified to guide essential and moderate folic acid supplementation, according to individual differences.

In ART, controlled ovarian stimulation (COS) always leads to supraphysiological concentrations of serum estradiol (E_2). The high E_2 environment during peri-conceptional and early pregnant period may have effect on long-term health of the offspring. Previously, we investigated birth weight and maternal serum E_2 levels of 8,869 singletons born after fresh ET, frozen ET, and natural conception (NC). Our findings demonstrated that the maternal high E_2 environment in the first trimester induced by ART was correlated with the increased risks of low birth weight and small-for-gestational-age birth, which may lead to chronic diseases in later life (Hu et al., 2014). Another retrospective cohort study reported that children born to ovarian-hyperstimulated women displayed cardiovascular dysfunctions. The underlying mechanisms may involve the effects of supraphysiological E_2 and progesterone levels, which were identified by a proteomics study and further analysis of umbilical arteries (Xu et al., 2014). Recently, a cohort Study which recruited 86 children born to ovarian hyperstimulation syndrome (OHSS) women, and 172 children conceived with non-OHSS IVF women, confirmed that OHSS offspring displayed reduced intellectual ability (Xu et al., 2017).

The thyroid gland is the first endocrine gland to differentiate in the early embryo at approximately 3 to 5 weeks gestation. A cross-sectional study, containing 949 singletons born after fresh ET, frozen ET, and NC, found that thyroxine (T4), free-thyroxine (FT4), and TSH levels were significantly increased in newborns as well as in children aged 3 to 10 years old conceived by fresh ET compared to NC, suggesting that maternal high E_2 environment in the first trimester was correlated with increased risk of thyroid dysfunction (Lv et al., 2014). Further, in mice, the T4 and FT4 levels were obviously increased in offspring in the high-E_2 group of early pregnancy. Paired box protein Pax8 was significantly up-regulated in thyroid glands, accompanied by the abnormal CpG island methylation status in the promoter region of the high E_2 group. The disturbance of thyroid function was more severe in females than in males (Lv et al., 2016).

Maternal high serum E_2 concentration during early pregnancy also influences glucolipid metabolism in the offspring. By *in vitro* and *in vivo* experiments, we found that a COS induced high maternal serum E_2 environment could up-regulate enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) expression in fetal hepatocytes via an estrogen response element (ERE) in the promoter, which induced elevated levels of TC and LDL-C in newborns (Meng et al., 2015). Developmental influences can cause persistent structural changes in hypothalamic circuits regulating food intake in the service of energy balance. The crosstalk be-

tween developing circuits regulating different modalities of food intake shapes future behavioral responses to environmental challenges, demonstrating maternal nutrition is associated with the behavioral responses in offspring (Zeltser, 2018). It is noteworthy that male human offspring resulting from fresh ET present a higher risk of insulin resistance than NC. In mice, prenatal exposure to high E_2 leads to sex-specific insulin resistance via elevated methylation of the hypothalamic insulin receptor (INSR) promoter, and, chronic food restriction reversed insulin resistance by correcting abnormal INSR promoter methylation (Wang et al., 2018).

Sperm and acquired inheritance

Accumulating animal models have provided evidence that the paternal environment plays a role in a non-genetic inheritance of pre-conceptional exposures through the male germ line. The environment of the father before conception can increase the risk that his children will develop chronic diseases (Soubry, 2018). Epigenetic regulation of gene expression is critical during spermatogenesis (Zamudio et al., 2008). In humans, cytosine demethylation in pre-implantation embryos shares tremendous similarity with mouse embryos at the equivalent stage. However, by whole-genome bisulfite sequencing and RNA-sequencing of human prenatal germline cells from 53–137 d of development, the transcriptome and methylome of human germline is distinct from both human pluripotent stem cells and the inner cell mass of human blastocysts (Gkountela et al., 2015). Environmentally induced aberrant DNA methylation patterns in the germline could be one of the explanations for paternal germline inheritance.

In our previous study, we established a gestational diabetes mellitus (GDM) mouse model of intrauterine hyperglycemia. The female (♀) and male (♂) F1 adults of control and GDM mice were intercrossed to obtain F2 offspring of four groups: (i) C♂-C♀, (ii) C♂-GDM♀, (iii) GDM♂-C♀ and (iv) GDM♂-GDM♀. After exposure to intrauterine hyperglycemia, parental characteristics were inter-generationally transmitted to the F2 offspring. For F2 offspring, paternal line factors were more prone to transmission compared to maternal line factors. Both F1 and F2 offspring demonstrated dysregulated expression of the imprinted gene *Igf2* and abnormal methylation status. Additionally, altered imprinting gene expression was also found in the sperm of adult F1-GDM with, or without, impaired glucose tolerance, suggesting the transmission of epigenetic changes in male germ cells (Ding et al., 2012). Further, we selected nondiabetic F1- and F2-GDM male mice as founders to examine metabolic changes in the next generation and performed methylome sequencing of day 13.5 primordial germ cells (PGCs) from F1-GDM to explore the underlying epigenetic mechanisms. The findings suggested that intrauterine exposure alone was sufficient to cause the epigenetic inheritance in F2 offspring, and the epigenetic memory carried by DNA methylation patterns could be erased by the second wave of methylation reprogramming in the F2 PGCs during fetal development. The intrauterine hyperglycemia exposure per se contributes to intergenerational metabolic changes in the F2 but not F3 generation (Ren et al., 2018). In addition, paternal prediabetes altered the overall methylome patterns in sperm with a large portion of differentially methylated genes overlapping with that of pancreatic islets in offspring, indicating that paternal prediabetes increased the susceptibility to diabetes in offspring through gametic epigenetic alterations (Wei et al., 2014).

In utero nutritional exposures during critical windows of germ cell development can affect the male germline methylome, associated with metabolic disease in offspring. In an intergenerational developmental programming model affecting F2 metabolism, Radford et al. (2014) demonstrated that the in utero nutritional environment of F1 embryos altered the germline DNA methylome of F1 adult males in a locus-specific manner. Differentially methylated regions were hypomethylated and enriched in nucleosome-retaining regions. Undernutrition during prenatal life, even when followed by normal postnatal nutrition, can compromise male germline development and epigenetic reprogramming. Alterations in adult gamete methylation may serve as a legacy of earlier developmental exposures which may contribute to the intergenerational transmission of environmentally-induced disease. Siklenka et al. (2015) generated transgenic mice in which overexpression of the histone H3 lysine 4 (H3K4) demethylase KDM1A during spermatogenesis reduced H3K4 dimethylation in sperm. In these mice, the epigenetic inheritance of aberrant development could be initiated by histone demethylase activity in developing sperm, without changes to DNA methylation at CpG-rich regions.

Small RNA-induced gene silencing can persist over several generations via trans-generationally inherited small RNA molecules in *C. elegans*. The starvation-induced developmental arrest leads to the generation of small RNAs that were inherited through at least three consecutive generations, targeting genes with roles in nutrition (Rechavi et al., 2014). More recent studies have further demonstrated that sperm RNAs can play a role as molecular carriers that transmit paternally acquired characteristics to the offspring. In the model of chronic paternal stress, microRNAs were increased in the sperm of stressed sires and associated with reduced hypothalamic-pituitary-adrenal stress axis reactivity in offspring (Rodgers et al., 2015). Traumatic stress in early life altered expression of mouse microRNAs, and the behavioral and metabolic responses in the progeny. Injection of sperm RNAs from traumatized males into fertilized wild-type oocytes reproduced the behavioral and metabolic al-

terations in the resulting offspring (Gapp et al., 2014). One proof of a direct causal role of sperm RNAs in transferring acquired traits across generations in mammals is that the injection of a subset of sperm tsRNAs (also known as tRNA-derived RNA fragments) into normal zygotes can generate metabolic changes in offspring that recapitulate paternal phenotypes (Chen et al., 2016). Another independent group showed that the microinjection of either testis or sperm RNA of male mice fed a high-fat and/or high-sugar diet into normal zygotes generated offspring that fully recapitulated the paternal metabolic disorders (Grandjean et al., 2015). Deletion of a mouse tRNA methyltransferase, Dnmt2, could prevent the elevation of RNA modifications that were induced by HFD, alter the sperm small RNA expression profile, and abolish sperm sncRNA-mediated transmission of high-fat-diet-induced metabolic disorders to the offspring (Zhang et al., 2018). These studies demonstrated that sperm RNA modifications and RNA-editing events are active participants in the inter-generational transfer of epigenetic information.

Oocyte and intergenerational/transgenerational transmission

Early in 1999, Morgan and colleagues described the inheritance of an epigenetic modification at the agouti locus in mice. In viable yellow (A(vy)/a) mice, transcription originating in an intra-cisternal A particle (IAP) retrotransposon inserted upstream of the agouti gene (A) caused ectopic expression of the agouti protein, resulting in yellow fur, obesity, diabetes and increased susceptibility to tumors. The maternal epigenetic effect was due to incomplete erasure of an epigenetic modification when a silenced Avy allele is passed through the female germ line (Morgan et al., 1999). In 2011, researchers revealed the role of Tet3 DNA dioxygenase in epigenetic reprogramming by oocytes. Female mice depleted of Tet3 in the germ line showed severely reduced fecundity and their heterozygous mutant offspring lacking maternal Tet3 suffered blocked paternal genome reprogramming and markedly increased developmental failure of the embryo. Deficiency in oocyte Tet3 could also cause weakened or delayed activation of the somatic Oct4 in nuclear transfer embryos (Gu et al., 2011). DNA methylation, small regulatory RNAs, and histone modifications have been implicated as carriers of epigenetic information across generations. However, the mechanisms underlying transgenerational epigenetic inheritance and *de novo* establishment of the zygotic epigenome are poorly understood. A study found H3K27me3 inter-generationally inherited from the maternal germ line resisted reprogramming events during early embryogenesis in *Drosophila* (Zenk et al., 2017). Since H3K27me3 was recently shown to be present on pre-implantation embryo chromatin in the mouse, they speculated that H3K27me3 could have similar functions during mammalian embryogenesis (Liu et al., 2016). They further proposed that environmentally induced alterations of histone modifications in the adult germ line could contribute to transgenerational epigenetic inheritance.

Increased body mass index (BMI) has been associated with suboptimal reproductive outcomes. Following adjustments for the respective BMI of the oocyte donor and recipient, a retrospective cohort study of two hundred and thirty five consecutive fresh donor oocyte IVF cycles demonstrated an association of preconception BMI with subsequent IVF outcomes. The observations of this study were consistent with prior animal studies, suggesting a possible effect of BMI at the oocyte level prior to fertilization and implantation (Cardozo et al., 2015). Maternal obesity has adverse effects as early as the oocyte and pre-implantation embryo stage and these effects may contribute to lasting morbidity in offspring. Compared with controls, diet-induced obese mice had significantly more apoptotic ovarian follicles, smaller and fewer mature oocytes, decreased embryonic IGF-IR staining, smaller fetuses, increased placental Igf2r mRNA, and smaller pups. The pups demonstrated catch-up growth, glucose intolerance and increased cholesterol and body fat, suggesting early development of a metabolic-type syndrome (Jungheim et al., 2010). Using the IVF technology, the sperm of normal chow diet (NCD) fed male mice and the oocytes of HFD fed female mice were fertilized *in vitro* to obtain embryos, which were transferred into NCD females. It is interesting that the offspring of donor oocytes from HFD showed decreased glucose tolerance, increased body weight, with the risk of obesity and insulin resistance. The ingenious experiment suggested that the offspring of mothers exposed to HFD before conception were more susceptible to developing obesity and diabetes in a parent of origin-specific mode, with the epigenetic inheritance of acquired metabolic disorders (Huypens et al., 2016).

In a HFD-based female mouse model of obesity, a marked reduction of Stella protein in oocytes was identified. Establishment of pronuclear epigenetic asymmetry in zygotes from obese mice was severely disrupted, inducing the accumulation of maternal 5-hydroxymethylcytosine modifications and DNA lesions. Notably, overexpression of Stella in the oocytes of HFD-fed mice not only restored the epigenetic remodeling in zygotes but also partly ameliorated the maternal-obesity-associated developmental defects in early embryos and fetal growth. Therefore, embryonic defects induced by maternal obesity in mice derived from Stella insufficiency in oocytes (Han et al., 2018). Another animal study showed that HFD induced obesity and obesity due to genetic mutation of the leptin gene (*ob*/*ob*) both impaired oocyte meiotic maturation, disrupted spindle morphology, and reduced oocyte polarity. The 5mC levels and H3K9 and

H3K27 methylation levels were altered in oocytes from obese mice, which indicated that DNA methylation and histone methylation had been affected by the obesity (Hou et al., 2016).

Zhang et al. (2015) identified that Sirt3 plays an important role in modulating reactive oxygen species homeostasis during oocyte development, and indicated that Sirt3-dependent deacetylation of Superoxide dismutase 2 (SOD2) could protect against oxidative stress and meiotic defects in oocytes under conditions of maternal obesity. A pharmacological study demonstrated that obesity before conception imparts a legacy of mitochondrial loss in offspring that is caused by ER stress. In obese female mice, cumulus-oocyte complexes exhibited ER stress, high levels of intracellular lipid, spindle abnormalities and reduced pentraxin 3 (PTX3) extracellular matrix protein production, whereas by treatment with the ER stress inhibitor salubrinal or the chaperone inducer BGP-15 (an amidoxim derivative) before ovulation, this effect was reversible during the final stages of oocyte development and maturation (Wu et al., 2015).

The maternal undernutrition has adverse effect on maturing oocytes as well. Normal protein diet (NPD) or isocaloric LPD was restricted to one ovulatory cycle (3.5 d) prior to natural mating in female mice. After mating, all females received NPD for the remainder of gestation. Although no difference in gestation length, litter size, sex ratio or postnatal growth was observed between the two groups, maternal LPD induced abnormal anxiety-related behavior and cardiovascular abnormalities such as elevated systolic blood pressure in offspring (Watkins et al., 2008b). For female offspring of maternal diabetes, by using streptozotocin-induced and nonobese diabetic mouse models, the study showed the adverse effects on DNA methylation of maternally imprinted paternally expressed gene 3 (Peg3) in oocytes of a diabetic female as a time-dependent manner, but normal methylation in offspring's oocytes (Ge et al., 2013). Further study showed that high-glucose concentrations altered DNA methylation levels of Peg3 and adiponectin in human *in vitro* maturation oocytes (Wang et al., 2018).

In addition, the abnormal endocrine environment could disturb oocyte epigenetic modifications and induce long-term effects. In humans, oocytes from women with hyperandrogenism showed increased Igf2 expression. Treatment of human oocytes with dihydrotestosterone could up-regulate Igf2 and down-regulate DNA methyltransferase 3a (DNMT3a) levels. Consistent with the findings in humans, hyperandrogenism also increased Igf2 expression and decreased DNMT3a in rat oocytes. Pre-gestational hyperandrogenism may predispose offspring to glucose metabolism disorders in later life via Igf2 hypomethylation in rat offspring pancreatic islets, which were inherited from the oocyte (Tian et al., 2017).

As part of the first step for all ART procedures, the ovarian stimulation protocols that administer exogenous hormones may prevent the gamete from establishing an appropriate epigenetic state (Marshall and Rivera, 2018). Oocyte *in vitro* maturation (IVM) is used for patients at high risk of OHSS or for female fertility preservation. Animal models have generally demonstrated correct methylation imprint establishment for *in vitro* grown and matured oocytes. For human IVM, optimized human IVM procedures had no significant effects on the establishment of maternal DNA methylation patterns at three maternally methylated (LIT1, SNRPN and PEG3) and one paternally methylated (GTL2) imprinted genes (Kuhtz et al., 2014). No statistically significant impact was found of IVM on chorionic villus and cord-blood DNA methylation, at the developmentally important genes that were studied, and interspersed repeats, suggesting IVM-induced epigenetic changes in offspring, if any, are relatively small in magnitude and/or infrequent (Pliushch et al., 2015). Human oocyte cryopreservation is an important technology in ART, during which oocytes show tolerance to osmotic stress by vitrification. Hyperosmosis induces up-regulation of Aquaporin7 (AQP7) via Aurora cytoplasmic polyadenylation element binding protein (CPEB) phosphorylation mediated by the phosphatidylinositol 3-kinase (PI3K) and protein kinase C (PKC) pathways, which plays an important role in improving of tolerance to hyperosmotic stress and survival of oocytes during cryopreservation by vitrification (Tan et al., 2015). In bovine, oocyte vitrification decreased the levels of DNA methylation and H3K9me3 in oocytes and early cleavage embryos, but the level of acH3K9 increased during the early cleavage phases. DNA methylation and H3K9 modification suggested that oocyte vitrification may excessively relax the chromosomes of oocytes and early cleavage embryos (Chen et al., 2016).

Advances in epigenetic modification of germ cells

An environmental factor can promote epigenetic transgenerational inheritance of germline epimutations and appearance of genetic mutations in later generations. The combination of genome-wide locations of differential DNA methylation regions and genetic mutations demonstrated that the transgenerational phenotype will likely involve an integration of epigenetics and genetics (Skinner et al., 2015).

At single-cell and single-base resolutions, approximately 10 to 11 weeks after gestation, the human PGCs are nearly devoid of any DNA methylation, with only 7.8% and 6.0% of the median methylation levels in male and female PGCs, respectively (Guo et al., 2015). During preimplantation development, demethylation of the paternal genome is much faster and thorough than that of the maternal genome. From the two-cell to the post-implantation stage, methylation of

the paternal genome is consistently lower than that of the maternal genome (Zhu et al., 2018). The map of H3K9me3-dependent heterochromatin undergoing dramatic reprogramming during early embryonic development provides valuable resources for further exploration of the epigenetic mechanism in early embryos (Wang et al., 2018). The recent advance in low-input technologies has provided novel insights into epigenetic dynamics during gametogenesis and the earliest events of embryonic development in mice. The evaluation of epigenetic profiles in the early embryo suggested that there is widespread erasure of the gametic epigenetic patterns after fertilization, and subsequent re-establishment of DNA methylation, histone modifications, chromatin accessibility and nuclear organization (Hanna et al., 2018).

Wu et al. (2016) have reported a genome-wide map of accessible chromatin in mouse preimplantation embryos using an improved Assay for Transposase-Accessible Chromatin with high throughput sequencing (ATAC-seq) with CRISPR/Cas9-assisted mitochondrial DNA depletion. Using a single-nucleus high-resolution chromosome conformation capture (Hi-C) protocol, Flyamer et al. (2017) showed that chromatin architecture is uniquely reorganized during the oocyte-to-zygote transition in mice, and is distinct in paternal and maternal nuclei within single-cell zygotes. Features of genomic organization including compartments, topologically associating domains (TADs) and loops are present in individual oocytes when averaged over the genome, but the presence of each feature at a locus varies between cells. Notably, the TADs and loops, but not compartments, are present in zygotic maternal chromatin, suggesting that these are generated by different mechanisms. In the studies of Ke et al. (2017) and Du et al. (2017), the 3D chromatin architecture of mouse gametes and early embryos found that mature oocytes at the metaphase II stage do not have TADs. In sperm, extra-long-range interactions (>4 Mb) and interchromosomal interactions occur frequently. The high-order structures of both the paternal and maternal genomes in zygotes and two-cell embryos are obscure but are gradually re-established through development (Ke et al., 2017). Chromatin may exist in a markedly relaxed state after fertilization, followed by progressive maturation of higher-order chromatin architecture during early development (Du et al., 2017).

Partly due to single-cell and low-cell number epigenomic studies, our understanding of the epigenetic and chromatin landscape of preimplantation development has improved considerably. Although numerous transcription factors and epigenetic regulators have been proposed to regulate the maternal-to-zygotic transition, some activate only a subset of zygotic genome activation transcripts. What initially activates these factors remains to be determined. Moreover, how additional chromatin modifications, as well as transcription factors and epigenetic regulators, change during this time of development remains an important area for future research (Eckersley-Maslin and Alda-Catalinas, 2018).

In conclusion, environmental epigenetic information can be transmitted through germ cells. Not only DNA methylation, but also chromatin protein, small RNA and other molecules may be the carriers of environmental epigenetic information transmission. Understanding the epigenetic reprogramming process of gametes and early embryos has benefited from work in both mice and humans, with the development of single-cell and low-cell number epigenomic technology, providing the possibility for further study of the potential mechanisms. Investigation of the epigenetic regulation mechanisms of cell programming and reprogramming in the process of gamete/embryo development, and the mechanism of intergenerational/transgenerational transmission effect, is of great significance, and important for early detection of disease targets and the control of disease sources.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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