Review Article

Paternal transgenerational nutritional epigenetic effect: A new insight into nutritional manipulation to reduce the use of antibiotics in animal feeding

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ABSTRACT

The use of antibiotics in animal feeding has been banned in many countries because of increasing concerns about the development of bacterial resistance to antibiotics and potential issues on food safety. Searching for antibiotic substitutes is essential. Applying transgenerational epigenetic technology to animal production could be an alternative. Some environmental changes can be transferred to memory-like responses in the offspring through epigenetic mechanisms without changing the DNA sequence. In this paper, we reviewed those nutrients and non-nutritional additives that have transgenerational epigenetic effects, including some amino acids, vitamins, and polysaccharides. The paternal trans-generational nutritional epigenetic regulation was particularly focused on mechanism of the substantial contribution of male stud animals to the animal industries. We illustrated the effects of paternal transgenerational epigenetics on the metabolism and immunity in farming animals and proposed strategies to modulate male breeding livestock or poultry.

1. Introduction

The genetic selection of the growth performance and nutrient optimization in domestic animals has significantly increased their growth performance and shortened their growth cycles (Diao et al., 2018; Gjedrem et al., 2012; Gu et al., 2011; Gutiérrez-Gil et al., 2015). The selection is usually accompanied by increasing metabolic processes that might compromise the immune capacity in the body, leading to the occurrence of epidemiological diseases and retardation of animal growth. To overcome these issues, the use of antibiotics growth promoters (AGPs) was widely adopted in the feed industries. Particularly, AGPs have been used as a growth promoter for a long time to maintain gut health and improve feed conversion efficiency (Dibner and Richards, 2005). However, the use of AGPs has been gradually banned in recent years worldwide due to their harmful roles in disturbing healthy intestinal microbiota and developing antibiotic resistance (Bengtsson and Wierup, 2006; Li et al., 2018d; Wu et al., 2018, 2020a, 2020b). Therefore, the use of AGPs in animal feeding has been gradually banned in recent years worldwide. However, banning the use of AGPs may increase the risk of conditioned pathogen infection in domestic animals and increase the feeding costs, meanwhile, it might increase the risk of infection in human beings (Huyghebaert et al., 2011; Laxminarayan et al., 2016). These situations highlight the need to explore novel alternatives to AGPs, which can support the productive potential and maintain the health of domestic animals. Recently, several classes of AGPs replacers have been studied and suggested, such as probiotics, prebiotics, antimicrobial peptides, polysaccharides, feed enzyme additives (Li et al., 2018d; Wu et al., 2019c; Liu et al., 2020;

Yang et al., 2020a). However, these substitutes have been found not as effective as antibiotics in microecological modulation (Liu et al., 2020; Maria Cardinal et al., 2019; Yang et al., 2020a). Hence, exploring new approaches to decrease the immune and metabolic disorders related to no use of AGPs warrants investigating (Maria Cardinal et al., 2019).

A stable gene expression pattern has been built via genetic selection and the use of AGPs for a century. Briefly, continuous genetic improvement of growth performance has continuously improved the metabolism and feed utilization efficiency. Most of the intake energy and nutrients are used for muscle and bone growth and fat accumulation, but less was provided for immune organs and function development (Berghof et al., 2013). For instance, with the broilers' growth performance improvement, the total antibody titers, immunoglobulin M and immunoglobulin G content, as well as the function of macrophages and natural killer cells of broilers were all significantly reduced (Qureshi and Havenstein, 1994). Further, the heat production of broilers continues to increase, and the anti-stress ability of broilers was significantly decreased (Lara and Rostagno, 2013). Notably, the use of AGPs can help to maintain the health and then improve the growth performance, by overcoming those potential issues induced by the stable gene expression pattern of decreased immune function, increased metabolic heat production, and decreased anti-stress ability (Berghof et al., 2013; Maria Cardinal et al., 2019). In order to maintain the growth performance and health of domestic animals when the AGPs were banned, a novel and stable gene expression pattern should be built, by improving nutritional supplementation through several generations of those domestic animals. The relationships between gene expression patterns and environmental factors, especially nutritional changes, are the core part of the research, which could be easier linked to animal growth performances and immune functions (DelCurto et al., 2013; Uddin et al., 2010; Li et al., 2016; Lv et al., 2019). Therefore, applying transgenerational epigenetic technology to animal production could be an alternative. The altered nutritional supplementation can be transferred to memory-like responses in the offspring through epigenetic mechanisms without changing DNA sequence (Wu et al., 2019a, 2019b). Nutrients that are effective in the regulation of the metabolism and immunity of animals include some functional nutrients and non-nutritional additives, such as amino acids (Phang et al., 2013), vitamins (Joubert et al., 2016), polysaccharides (Wu et al., 2017), probiotics and prebiotics (Kumar et al., 2013), which may be candidates for epigenetic regulation.

In this review, we explore the potential use of some of these improved nutrients supplementation in epigenetic effects on the growth performance and immune function in domestic animals, especially improving the offspring growth and immune and then eliminating the use of antibiotics in domestic animals.

2. Why should paternal transgenerational epigenetic regulation be the focus?

Epigenetics refers to those studies on the inheritance of altered genes expression without DNA sequence mutation during the processes of cell mitosis, cell meiosis, biological development, and reproduction in animals (Sasaki and Matsui, 2008). DNA methylation, histone modification, chromosome encoding, and non-coding RNAs have been suggested to be involved in the regulation and inheritance of gene expression alterations (Sharma, 2017; Tollefsbol, 2014). Research on livestock epigenetics focuses mainly on 2 aspects: how environmental factors gradually alter epigenetic modifications of the genomes, thereby regulating the expression of associated genes, and how these epigenetic modifications and corresponding phenotypes are transmitted to their offspring. The

latter aspect can be defined as transgenerational epigenetics and likely, the influence of environmental factors is implemented on epigenetic modifications in the germ cells.

Comparing transgenerational epigenetics with traditional genetics, they both have the transgenerational inheritance ability, but transgenerational epigenetics relates to the gene expression alteration that gradually adapts to the resulting environmental changes, likely being continuous, rather than gene mutation or the significantly increased frequency of one genotyping in traditional genetics (Nicoglou and Merlin, 2017; Tollefsbol, 2014). Herein, it refers to the phenotypic alteration of the offspring without DNA sequence changes. Studies on the mechanisms have found that environmental factors could cause the alterations of DNA methylation, histone modifications, and non-coding RNA expression, leading to the changes in gene expression and physiological phenotypes in parent animals, and as a result, phenotypic alterations appear in their offspring (Tollefsbol, 2014). For instance, Dias and Ressler (2014) exposed F0 mice to an odor (acetophenone) fear condition before the conception and found that subsequently conceived F1 and F2 generations had an increased behavioral sensitivity to acetophenone odor, but not to other odors. Sperm DNA CpG hypomethylation in odorant receptor Olfr151 gene in the conditioned F0 males and F1 naive offspring contributed to the transgenerational epigenetic effects. In a rat model, transient exposure of the gestating females during the period of gonadal sex determination to the endocrine disruptors, vinclozolin (an antiandrogenic compound) or methoxychlor (an estrogenic compound), induced a decrease of spermatogenic capacity (cell number and viability) and an increase of incidence of male infertility in the adult F1 generation (Anway et al., 2005). These effects were transmitted through the male germline to nearly all males of subsequent generations (i.e., F1 to F4). The transgenerational effect seemed to be associated with the altered DNA methylation patterns in the germline (Anway et al., 2005). These results prove that the environmental memory in animals could be transmitted to the offspring through paternal transgenerational epigenetic mechanisms.

Although more and more evidence has proved that the changes in the maternal environment, especially the nutritional status during pregnancy, could cause some epigenetic modifications and then influence the gene expression during the embryonic stage, fetal development, and even after birth (Cooney et al., 2002; Lillycrop and Burdge, 2015), and theoretically, maternal and paternal contributions equally to transgenerational epigenetic information to the offspring, more research has concentrated on the paternal effect. Substantially greater influence of stud males than females on the animal breeding is one of the reasons. Less complexity in studying the transgenerational epigenetic mechanisms in a paternal model minimizes the potential influence of other pathways of nongenetic inheritance commonly in females (gestation and lactation). Focusing on males, researchers can focus on the environmental influences on the constituents of sperm and seminal fluid. This male-centered approach, when it is carried out in tightly-controlled laboratory conditions using isogenic populations, has proven highly effective in minimizing genetic (DNA) and environmental confounds. It has also yielded some of the most compelling mechanistic evidence to date that environmentally-induced epigenetic information could be packaged into the germline and transmitted to the offspring, showing the corresponding phenotypes in following generations (Ryan and Kuzawa, 2020). Moreover, when referring to the animal industry, due to the use of artificial insemination techniques, the paternal transgenerational effect can be amplified markedly in the animal industry. For instance, one breeder rooster can produce more than 100 broilers per annum (Berghof et al., 2013; Frank et al., 2003), and the offspring number can be much great in large animals (boars, rams,

bulls). In addition, increasing evidence has shown that trans-generational effects could be maintained for more than one generation (Sasaki and Matsui, 2008; Sharma, 2017).

3. Paternal imprinted genes and mechanism of paternal trans-epigenetics

Imprinted genes or genome provided the first mechanical evidence for epigenetic research. In 1984, McGrath and Solter identified that the completion of mouse embryogenesis required both the maternal and paternal genomes (McGrath and Solter, 1984). Soon after, the identification of 3 imprinted genes, *IGF2*, *IGF2R*, and *H19*, were reported respectively (Dean et al., 1998). Since then, more imprinted genes involved in growth and development have been identified (Edwards and Ferguson-Smith, 2007), and the underlying mechanism of the imprinted genes has gradually been revealed. DNA methylation has been proved to regulate the paternal and maternal expression of *IGF2* and *H19* genes. In addition, *H19* could also serve as a long non-coding RNA to regulate the expression of *IGF2*. And then the line between the imprinted gene expression and the epigenetic modification, especially DNA methylation, has been drawn (Murrell et al., 2004; Zhou et al., 2015). So far, there are around 260 imprinted genes that have been identified in mice (Tucci et al., 2019). Although the recent genome-wide characterization of imprinting suggests that there may be more than 1,000 loci with parent-of-origin allelic effects in embryonic and adult mouse brains (Gregg et al., 2010a, 2010b). Of these genes, the paternally expressed genes and their DNA methylation could influence the gene expression and development process in the offspring, which could lay the foundation for the paternally transgenerational epigenetic regulations (Liang et al., 2014; Soubry et al., 2016; Zhang et al., 2019). With the development of whole-genome methylome sequencing, the epigenetic reprogramming events during the embryonic period or after birth have been identified in mammals. In mammals, the development from fertilization to gametogenesis does involve several major epigenetic "reprogramming" events that reset the epigenetic state in germ cells (Table 1). The first event occurs immediately following fertilization, when the cellular differentiation states involved in programming sperm and egg cells are cleared passively (through division without re-methylation) or actively (through maternally-derived ten-eleven translocation enzyme [Tet] DNA demethylase) (Li et al., 2018c; Santos et al., 2002; Smith et al., 2012). The second event occurs during the formation of primordial germ cells (PGCs) when PGC lineage-specific epigenetic marks are cleared and replaced with sex-specific DNA methylation (DNAm) in the developing germline (Guibert et al., 2012; Seisenberger et al., 2012). These 2 epigenetic reprogramming events form the barriers of inter-and trans-generational epigenetic inheritance, subclasses of epigenetic inheritance which can be defined by the timing of the exposure in relevance to the stages of epigenetic reprogramming. Following these 2 events, spermatogonia stem cells (SSCs) undergo the third epigenomic reprogramming as they pass through the blood-testis barrier (Phillips et al., 2010). However, although the epigenetic reprogramming immediately after fertilization is extensive, it is not absolute. In mammals, DNA demethylation occurs in the whole-genome level after fertilization, but not in some loci, such as intracisternal A particle (IAP) and some other imprinting regions (Hackett et al., 2013). As the representation of oviparous, sperm DNA methylome is inherited in zebrafish early embryos (Jiang et al., 2013). These remained regions contribute to the transgenerational inheritance of epigenetic information from the father. In male animals, differential methylation in imprinted regions also persists through spermatogenesis, including the process of chromatin repackaging (Sanford et al., 1987; Trasler, 2009). Thus, the epigenetic state of imprinted genes in sperms is retained to varying degrees in individual tissues throughout their lives and provides an example of intergenerational epigenetic inheritance.

Different from mammals, Zebrafish and other non-mammalian (anamniote) vertebrates lack global 5-methylcytosine (5-mC) erasure (Bogdanovic et al., 2011; Hontelez et al., 2015; Jiang et al., 2013; Macleod et al., 1999; Potok et al., 2013; Veenstra and Wolffe, 2001), which occurs after fertilization and persists during blastula stages in mammals (Oswald et al., 2000; Smith et al., 2012). However, zebrafish inherit the paternal DNA methylome configuration (Jiang et al., 2013; Potok et al., 2013) (Table 1). Recent studies demonstrated the absence of global DNA methylation erasure in the zebrafish germline and extensive amplification and demethylation of the oocyte-specific fem-rDNA cluster during gonad transformation, which suggested the retention of paternal epigenetic memory in the developing zebrafish germline (Iwanami et al., 2020; Skvortsova et al., 2019). These studies have proved the existence of paternal transgenerational epigenetics in non-mammalian (anamniote) vertebrates.

4. Paternal transgenerational epigenetic mechanisms relating to the environmental changes in animals

DNA methylation that occurs in the 3 reprogramming periods in mammals and the retention of paternal DNA methylome in both offspring embryos and germline of non-mammalian (anamniote) vertebrates could contribute to the transgenerational epigenetic

Table 1
Reprogramming of embryonic DNA methylation in human and model animals.

Species	Occurrence of global 5-methylcytosine (5-mC) reprogramming during post-fertilization period	Genomic regions without global mC reprogramming during post-fertilization period	Occurrence of global mC reprogramming in primordial germ cells	Genomic regions without reprogramming in primordial germ cells
Homo sapiens	Occurred	Imprinting control regions, long interspersed nuclear element (Guo et al., 2014; Smith et al., 2014); endogenous retrovirus K transposons (ERVK) (Gkountela et al., 2015; Smith et al., 2014); Exons, 3′ untranslated regions (UTRs), promoters, splice sites, and L1 *Homo sapiens*-specific (L1HS) (Gkountela et al., 2015)	Occurred	Exons, 3′ UTRs, promoters, splice sites, enhancers, gene bodies, CpG islands (CGIs) and repeats, L1HS, long interspersed nuclear element, short interspersed nuclear elements (Alu), and ERVK (Gkountela et al., 2015; Guo et al., 2015; Tang et al., 2015)
Mus musculus	Occurred	Intracisternal A particle (IAP), imprinting control regions (Lane et al., 2015; Smith et al., 2012; Wang et al., 2014), Single-copy germline-expressed genes and somatically expressed genes (Borgel et al., 2010)	Occurred	IAPs, Promoter and non-IAP-related CGIs, ERVK (Guibert et al., 2012; Hackett et al., 2013; Seisenberger et al., 2012; Skvortsova et al., 2018)
Danio rerio	Non-occurred	Global paternal methylome inheritance (Jiang et al., 2013; Potok et al., 2013)	Non-occurred	Retention of paternal epigenetic memory (Skvortsova et al., 2019)

inheritance in humans and domestic animals (Bogdanovic et al., 2011; Hontelez et al., 2015; Iwanami et al., 2020; Jiang et al., 2013; Macleod et al., 1999; Oswald et al., 2000; Potok et al., 2013; Skvortsova et al., 2019; Smith et al., 2012; Veenstra and Wolffe, 2001). Studies on the mechanisms that mediate the paternal transgenerational epigenetic regulation processes have proved that paternal environmental exposures, such as diets (Guo et al., 2020; Lane et al., 2015; Li et al., 2019; Schagdarsurengin et al., 2012; Yang et al., 2020b), environmental pollution (Bautista et al., 2020; Shukla et al., 2019) or toxicants (DeCourten et al., 2020; Zhang et al., 2019), and psychosocial stresses (Blaze and Roth, 2015; Cunningham et al., 2021) could influence the spermatozoa DNA methylation and then the gene expression and behaviors in the offspring.

Except for DNA methylation, the covalent modifications of histones also mediate the parental effects (Campos et al., 2014). It has been confirmed that histone modifications at some loci are certainly transmitted between generations in mammals (Brykczynska et al., 2010; Hammoud et al., 2009; Lismer et al., 2020), fishes (Wang et al., 2016), and worms (Tabuchi et al., 2018). Thus, it is plausible that they could also underlie some paternal effects. Similar to DNA methylation, the inheritance of significantly altered paternal histone modification through sperm is the key to transgenerational inheritance. In mammalian sperm, the majority of nucleosomes are replaced with protamines to facilitate the compaction of the paternal genome (Fang et al., 2019). Nevertheless, a small percentage of nucleosomes and their associated histone post-translational modifications (PTMs) are retained, thereby forming a potential platform for the intergenerational transmission of regulatory states (Stensballe et al., 2013; Alhasan et al., 2020). Recent genome-wide studies revealed the existence of robust inheritance of trimethylation of lysine 4 on histone H3 protein subunit (H3K4me3) and trimethylation of lysine 27 on histone H3 protein subunit (H3K27me3) patterns through oocytes in mice and their role in the regulation of embryonic development (Guo et al., 2020; Vidal et al., 2013; Gray et al., 2017; Örtqvist et al., 2017). In line with these findings, overexpression of human lysine specific demethylase 1 (LSD1) in the developing mouse sperm resulted in the reduction of dimethylation of lysine 4 on histone H3 protein subunit (H3K4me2) at promoters of genes regulating developmental and metabolic processes and was accompanied by deregulation of gene expression in early F1 embryos (Örtqvist et al., 2017). Notably, these changes promoted developmental defects in the offspring and were transmitted across three generations, indicative of transgenerational epigenetic effects. Further in *Caenorhabditis elegans*, an epigenetic memory of germline transcription, mediated histone H3K36 trimethylation (H3K36me3) on active genes and H3K27me3 on repressed genes, is passed from one generation to the next generation and essential for germline viability (Kreher et al., 2018; Tabuchi et al., 2018). These results demonstrate an example of non-environmentally responsive epigenetic inheritance that is critical for normal development and physiology.

Moreover, the blood-testis barrier, which is tightly controlled, is also known to be permeable to a range of biologically active molecules, including numerous proteins and a rich assemblage of coding and non-coding RNAs (Ryan and Kuzawa, 2020; Schagdarsurengin et al., 2012). Both coding and noncoding RNAs circulate ubiquitously in the body as "exosomes". As tiny lipid vesicles, the exosomes could be secreted from most cell and tissue types (Li et al., 2014). These RNA-containing exosomes are abundant in the blood, lymph tissues, cerebrospinal fluid, breast milk, and semen, and can pass through the blood-testis barrier (Hu et al., 2014; Zhang et al., 2012). Herein, the non-coding RNAs, including Piwi-interacting RNA (piRNAs), microRNAs (miRNAs), transfer RNA-derived small RNAs (tsRNAs), and long non-coding RNAs (lncRNAs),

could also contribute to the paternal trans-epigenetic process (Casier et al., 2019; Ord et al., 2020; Yan, 2014). Notably, small non-coding RNAs (sncRNAs), tsRNAs, piRNAs, and miRNAs are emerging as possible mediators of environmental information transmission through sperm in mammals (Chen et al., 2016a; Dupont et al., 2019; Ord et al., 2020; Rodgers et al., 2013, 2015; Sarker et al., 2019; Yan, 2014). In several cases, a zygotic injection of total sperm miRNA (Chen et al., 2016b; Sarker et al., 2019; Wu et al., 2019a), sncRNA fractions, or specific sncRNAs (Klastrup et al., 2019; Ord et al., 2020; Zhang et al., 2018), and tsRNAs (Chen et al., 2016a) could partially or fully recapitulate the paternally acquired phenotypes. Further, the spermatozoal sncRNAs sequencing results have suggested the transgenerational epigenetic roles of piRNAs and lncRNAs in regulating the offspring metabolism or phenotype changes (Kimura et al., 2020; Ord et al., 2020).

Recently, the roles of gut microbiota in transgenerational "epigenetics" have been proposed. A recent study has proved that the gut microbiome is environmentally contingent but its heritability is universal (Grieneisen et al., 2021). For instance, the changes of maternal microbiota could influence the metabolic phenotype (Kimura et al., 2020), programing (Jašarević and Bale, 2019), behavior (Liu et al., 2021), and immune responses in the offspring (Nyangahu et al., 2018). Further, the epigenetic inheritance induced by microbiota alteration could also be related to the changed microbiota production abundance, such as the increased short-chain fatty acids (SCFAs) (Li, 2018c; Remely et al., 2014). Notably, the inheritance of the gut microbiota from the maternal vaginal and meconium microbiota or even maternal intestinal microbiota have also been widely suggested (He et al., 2020; Kimura et al., 2020; Li, 2018c; Liu et al., 2021; Mortensen et al., 2021; Myles et al., 2013). Two studies on the transgenerational roles of paternal microbiota suggested that a paternal pre-conceptional unhealthy diet predisposed the offspring to the alterations of intestinal microbiota, liver function, and immune responses in the offspring (Laxminarayan et al., 2016; Nguyen et al., 2020). These researches suggested the potential inheritance effects of paternal microbiota on offspring phenotypes and microbiota, although the link between the epigenetic modifications and intestinal microbiota has not been fully established. Overall, the paternal transgenerational regulatory roles in offspring microbiota need more attention. It is worth mentioning that these epigenetic mechanisms are not working along, and may work synergistically or concomitantly to regulate the offspring's gene expression and phenotypes.

Overall, the epigenetics modification that includes DNA methylation, Histone modification, non-coding RNAs expression, as well as the gut microbiota inheritance could all contribute to the transgenerational epigenetic inheritance process that may be affected by the paternal nutrients' supplementation.

5. The use of antibiotics on the health, metabolism, and development of offspring

Aforementioned, the environmental factors could induce transgenerational epigenetic regulation in both humans and animals. Among them, antimicrobial reagents, antibiotics, in particular, have been a mainstay of modern medicine and animal feeding for the past eight decades (Laxminarayan et al., 2016; Lees et al., 2021). However, the side effects, such as the development of antibiotic resistance and drug residues in animal products have been widely reported (Cheng et al., 2014; Lees et al., 2021; Marshall and Levy, 2011). Specifically, the increasing use of antibiotics at sub-therapeutic concentrations for growth promotion and disease prevention (for example, as a substitute for hygiene) is placing substantial selection pressure on the evolution of resistance to antibiotics (Iwu et al., 2020). The worldwide antimicrobial

consumption in farming animals is projected to rise from 63,151 tons in 2010 to 105,596 tons in 2030, placing great selection pressure on resistant bacteria (Manikandan et al., 2020). The unregulated use of antibiotics in animal feeding could further pollute water and soils with the discharge of animal manures (Zhu et al., 2013), which could, in turn, lead to more resistant pathogens and then influence human health. Indeed, the antibiotic residues in animal products, water, and soils could further increase the risk of human antibiotic exposure.

The use of antibiotics could also influence an animal's evolution by epigenetic modification. Recently, several studies have reported that the use of antibiotics during pregnancy could increase the risk of the development of asthma in offspring childhood (Alhasan et al., 2020; Stensballe et al., 2013). Meanwhile, exposure to antibiotics during pregnancy, but not in infantile age, is associated with an increased risk of very early onset inflammatory bowel disease regardless of gastroenteritis (Örtqvist et al., 2019). The changes in the intestinal microbiota and methylation of the imprinting genes are assumed to be the reasons for the increased risk from antibiotics exposure during pregnancy (Gray et al., 2017; Vidal et al., 2013). As for the transgenerational effects on the occurrence of childhood asthma in the offspring, both paternal antibiotics and maternal antibiotics exposures showed a similar effect (Loewen et al., 2018; Örtqvist et al., 2017). Even so, the potential transgenerational epigenetic mechanisms of paternal and maternal antibiotics exposures, especially the potential interaction between inheritable microbiota alteration and epigenetic modifications, have not been investigated yet, and are worth further study.

6. Nutritional regulation of paternal transgenerational epigenetics focuses on the growth and immune function of animals

The main reason for using antibiotics in domestic animals is to inhibit pathogenic bacteria and to regulate immune functions in the gut, so the growth performance can be improved. This approach could also be replaced with applying those nutrients that have transgenerational epigenetic effects on immune function and the regulation of metabolic processes. Yet, a large number of in vitro studies have shown that some macronutrients such as fat and protein, and some micronutrients including vitamins could be involved in epigenetic regulation. These dietary nutrients could regulate immune and development processes in four epigenetic regulatory ways (Fig. 1). Firstly, some nutrients can act as methyl or acetyl donors, or act as the conferment of methylation and acetylation-related enzymes that participate in the DNA methylation and histone modification of the genes involved in the growth and immunity (Fig. 1A and B). For instance, folic acid, choline, betaine, and methionine contribute to the one-carbon metabolism that is directly involved in DNA methylation or histone regulation, which plays the roles in the regulation of gene expression of lipid and glucose metabolism, immune function, and nucleic acid metabolism (Friso et al., 2017; Mentch et al., 2015; Shyh-Chang et al., 2013) (Fig. 1A). Sinclair et al. (2007) reported that the restriction of the folate, methionine and another one-carbon metabolism related metabolites during pregnancy could reduce the methylation level of CpG island in the offspring genome, which
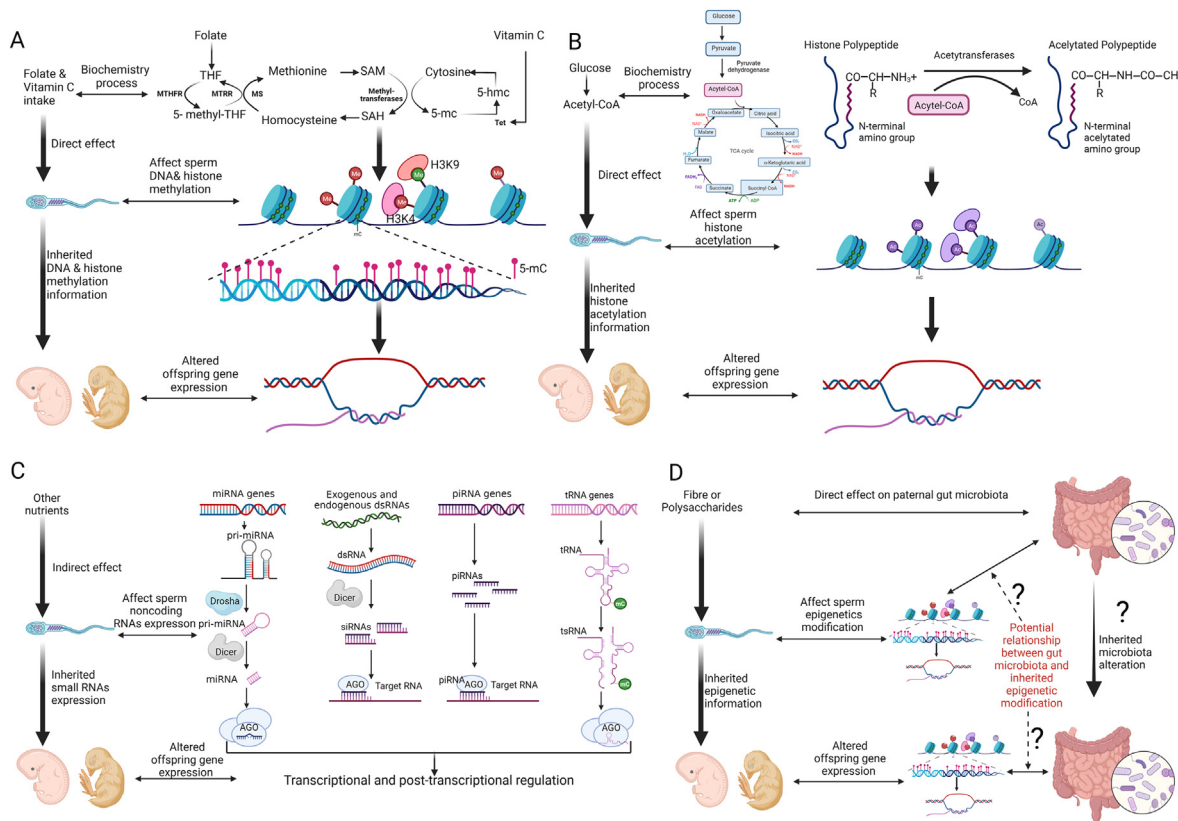
Fig. 1. The potential epigenetic mechanisms reveal how paternal nutrient supplementation affected offspring gene expression. (A) Methyl donor foods or demethylation related foods that affect the DNA methylation and demethylation process. (B) Foods that affect the histone acetylation process. (C) Foods that were not directly involved in the epigenetics process. (D) Foods that may affect the gut microbiota. AGO = argonaute protein; dsRNA = double-stranded RNA; H3K4 = lysine 4 on histone H3 protein subunit; H3K9 = lysine 9 on histone H3 protein subunit; Tet = ten-eleven translocation enzyme; THF = tetrahydrogen folic acid; SAM = S-adenosylmethionine; SAH = S-adenosyl-L-homocysteine; 5-hmC = 5-hydroxymethylcytosine; 5-mC = 5-methylcytosine.

could lead to preterm delivery and abnormal development of the offspring; Timely folate supplementation could reverse these effects by altering the genomic DNA methylation (Sinclair et al., 2007). Another study in chicken demonstrated that paternal folate supplementation could have trans-generational regulation on the lipid and glucose metabolism in broiler offspring, where the energy utilization was improved by increasing gluconeogenesis and glycolysis while reducing lipid catabolism (Wu et al., 2019a). Furthermore, the sperm DNA methylation was involved in the methionine synthase reductase (Mtrr) mutation-induced offspring abnormal development (Padmanabhan et al., 2013). In addition, vitamin B_6, vitamin B_{12}, alpha-ketoglutarate, Fe^{2+}, vitamin C (ascorbic acid), and Zn^{2+} all act as the cofactors to these enzymes that are involved in the one-carbon metabolism or directly serve as the coenzyme of DNA methyltransferase (DNMT), Tet, and histone deacetylase (HDAC) enzymes. These nutrients could also influence DNA methylation or histone methylation process and then regulate the metabolism and development process of the offspring (Anand and Marmorstein, 2007; Friso et al., 2017; Szarc vel Szic et al., 2010; Teperino et al., 2010; Young et al., 2015). Except for the methyl donors, nutrients functioning as acetyl donors can affect histone acetylation through the gene expression process (Fig. 1B). Briefly, the metabolism of glucose, lipids, and proteins are all involved in acetyl-coenzyme A (Acetyl-CoA), which serves as the main donor of acetyl moiety. Thus, these nutrients could be associated with the regulation of offspring immune function and growth through histone acetylation modification (Wellen et al., 2009).

Except for these nutrients, some other metabolites that are not directly involved in the epigenetics process can also exhibit a transgenerational epigenetic regulatory effect (Fig. 1C). For instance, the paternal astragalus polysaccharide supplementation to broilers affected the offspring's immune functions, including enhancing spleen immunity and modulating the transgenerational endotoxin tolerance-like function in the jejunum, which are associated with the fight against pathogen infections (Li et al., 2018a, 2018b). Vitamin A is involved in the trans-generational effect on the offspring's immune function, such as the increase of intestinal Peyer's patches numbers (van de Pavert et al., 2014). Notably, the time window is crucial for these nutrients to implement the transgenerational influence on the offspring metabolism and immune function, for example, during the spermatogonia stem cell formation and the spermatogenesis periods (Bogdanovic et al., 2011; Hackett and Surani, 2013; Hontelez et al., 2015; Jiang et al., 2013; Macleod et al., 1999; Oswald et al., 2000; Potok et al., 2013; Sanford et al., 1987; Smith et al., 2012; Trasler, 2009; Veenstra and Wolffe, 2001). Folate is involved in the DNA methylation process in broilers, and a folate supplementation could affect the spermatozoal miRNA and lncRNA expression profiles and regulate the offspring's metabolism (Wu et al., 2019a). Paternal lipid supplementation affected the sperm's tsRNA expression and induced an alteration of the glucose metabolism and increases insulin resistance in the offspring (Yan, 2014). These researches suggest that the aforementioned nutrients could play a transgenerational epigenetic regulation role without directly taking part in the epigenetic modification process.

It has been reported that the parental microbiota can modulate offspring's development, body mass, and fecundity in a polyphagous fruit fly (Nguyen et al., 2020). A recent study proved that paternal exposure to inorganic arsenic altered the intestinal microbiome which was involved in the trans-generationally regulatory effects on the offspring lipid metabolism (Gong et al., 2021). The gut microbiome heritability is universal, and the inheritance of the gut microbiome could link with the inheritable genomic and

even epigenetic information (Grieneisen et al., 2021). In other words, the above epigenetic modification alterations such as inheritable small RNAs, DNA methylations, and Histone modifications information could further influence the gut microbiota colonization, which could, in turn, induce the heritable gut microbiota (Fig. 1D). Further, considering the sperms and seminal fluid contain microbiota (Baud et al., 2019; Javurek et al., 2017), it may also be possible a change in paternal microbiota that could influence the offspring microbiota or directly interact with the epigenetic modification. Polysaccharides, probiotics, and prebiotics all affect the microbiota, so their potential effects on the offspring microbiota or epigenetics modification need further studies.

To understand the paternal nutritional effects on the offspring metabolism, immune, and growth performance in domestic animals, more researches have been conducted. In a three-generation study in pigs, the F0 generation boars were fed a diet supplemented with methylating micronutrients, and the F2 generation had lower fat percentage and increased shoulder muscle percentage compared with un-supplementation control; The significant differences in hepatics DNA methylation were noted in the F0 and F2 generations (Braunschweig et al., 2012). In a chicken model, paternal folate supplementation to broilers altered spermatozoal miRNAs and lncRNAs, leading to the transgenerational effects on the lipid and glucose metabolism in the offspring (Wu et al., 2019a). A paternal dietary methionine supplementation to chicken improved the carcass traits and meat quality in their progeny (Elsharkawy et al., 2021). A paternal dietary Astragalus polysaccharide supplementation to broilers affected the sperm DNA methylome and induced transgenerational endotoxin tolerance-like effect in the jejunum mucosa and spleen in the offspring, enhancing their ability to reduce inflection caused by pathogen infection (Li et al., 2018a, 2018b). Furthermore, epigenetic modifications in the sperm of cattle were associated with environmental changes (Rahman et al., 2014; Wu and Sirard, 2020). A recent study with cattle suggested that the paternal genome and epigenome could impact the gestation length potentially through regulation of embryonic development (Fang et al., 2019). Although these studies suggest that paternal nutrition improvement may regulate offspring development and metabolism, limited studies have been conducted so far to determine the effect of nutrition on the epigenetic maturity of male gametes in cows, cattle, and lambs, and its consequence on subsequent offspring.

In summary, those nutrients could directly take roles in the epigenetic process, or chronically affect the gene expression pathways and spermatozoal epigenetic markers such as non-coding RNAs or DNA methylation, therefore, showing transgenerational effects on the immune and growth performance of the offspring. There could be a possibility to use these nutrients as substitutes for antibiotics in animal production.

7. Opportunity of reducing the antibiotics used in animal feeding when considering the paternal transgenerational nutritional epigenetic effects

The transgenerational epigenetic inheritance induced by paternal nutrition supplementation has been widely suggested in human offspring health and disease regulation (Dimofski et al., 2021). In comparison, limited study has been performed to study the paternal nutritional effects on offspring metabolism and growth. Through those above discussions in this review, we hope the paternal transgenerational nutritional epigenetic effects to reduce the use of antibiotics in animal feeding could raise more attention. Since we want to find suitable nutrients which could

exhibit paternal transgenerational effects on offspring health, metabolism, and growth, I do believe 3 aspects of research are worthy of further study. Firstly, the paternal transgenerational effects of antibiotics, as well as the banning of antibiotics in domestic animals, can be studied when considering the epigenetic modification changes and gene expression changes, as well as the gut microbiota changes that related to their health, metabolism, and growth performance. Secondly, more research should be performed to study the differential paternal transgenerational epigenetic mechanism between those nutrients that could take part in the epigenetics modification process, and those nutrients could only chronically affect the gene expression pathways and spermatozoal epigenetic markers such as non-coding RNAs or DNA methylation (Wu et al., 2019a; Li et al., 2018a, 2018b). Notably, more researches focused on the potential paternal transgenerational epigenetic effects and mechanisms of these antibiotics-replacement nutrients, that could exhibit the immune regulation or growth-promoting effects, are derived more attention and needed further research. Herein, the potential antibiotics replacement nutrients which may have paternal transgenerational effects can be selected. Last but not the least, further good quality data are needed to define the real effect dose of those antibiotics' replacement nutrients in different feeding conditions so that we can finally welcome the coming of antibiotics-free animal feeding century.

8. Conclusion

A stable gene expression pattern, that includes the significantly increased metabolic function and decreased immune and anti-stress functions, has been built via genetic selection and the use of AGPs. In order to maintain the growth performance and health of domestic animals when the AGPs were banned, the paternal nutritional epigenetic effects, which includes the formation and inheritance of spermatozoal DNA methylation, histone modification, chromatin degeneration, and non-coding RNAs differential expression, may contribute to improve the immune and anti-stress functions, enhance intestinal health, maintain high digestion, absorption, and metabolic functions. Hence, further research and application of transgenerational epigenetic regulation theory in the animal production process will solve the problems left by genetic breeding from the direction of gene epigenetic modification and expression regulation. These effects might become a novel method to maintain or enhance animals' growth and health. Based on the analysis of the epigenetic mechanism of inheritance and the epigenetic regulation by nutrition, we believed that paternal nutritional manipulation on epigenetic modification of those genes relating to the metabolism and immunity could improve the growth performance and immune function in livestock and poultry. By further identifying the underlying transgenerational epigenetic mechanism, the appropriate nutritional requirements of breeder animals should be reconsidered.

Author contributions

Xinyi Li: writing-original draft, writing-review & editing, conceptualization, visualization, supervision. **Mengya Wang:** writing-review & editing, conceptualization, visualization. **Shimin Liu:** writing-review & editing, conceptualization. **Xiaodong Chen:** conceptualization, visualization. **Yu Qiao:** conceptualization. **Xiaojun Yang:** conceptualization, writing-review & editing, funding acquisition. **Junhu Yao:** conceptualization, writing-review & editing, funding acquisition. **Shengru Wu:** writing-original draft, conceptualization, writing-review & editing, visualization, funding acquisition, supervision.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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