Research Advances on the Effects and Mechanisms of Methionine on Reproductive Performance in Livestock and Poultry (Postprint)

Authors: Cai Shuang, Ye Qianhong, Zeng Xiangfang

Date: 2018-12-24T00:00:00+00:00

Abstract

Methionine is an essential amino acid for animals and also a functional amino acid. In addition to participating in protein synthesis, it can also regulate cell proliferation and differentiation, fetal growth and development, scavenge free radicals in the body, enhance immunity, and is of great significance to the growth, development, and reproduction of livestock and poultry. This article summarizes the physicochemical properties, in vivo metabolism, placental transport and absorption of methionine, expounds on the effects of methionine on the reproductive performance of livestock and poultry and its underlying mechanisms, and provides a reference for future in-depth research and application of methionine in livestock and poultry production.

Full Text

Research Progress on Effects and Mechanisms of Methionine on Reproductive Performance in Livestock and Poultry

Cai Shuang, Ye Qianhong, Zeng Xiangfang*
(College of Animal Science and Technology, China Agricultural University, Beijing 100193, China)

Abstract: Methionine is an essential amino acid in animals and also functions as a functional amino acid. Beyond its role in protein synthesis, methionine regulates cell proliferation and differentiation, supports fetal growth and development, scavenges free radicals, and enhances immune function, making it critically important for animal growth and reproduction. This review summarizes the physicochemical properties of methionine, its metabolism in vivo, and placental transport and absorption mechanisms. We also elaborate on the effects of methionine on reproductive performance in livestock and poultry and

explore its underlying mechanisms, providing a reference for future research and application of methionine in animal production.

Keywords: methionine; metabolism; absorption; reproductive performance

---

Methionine is a sulfur-containing amino acid and an essential amino acid that limits animal growth and development. It participates in more than 80 biochemical reactions and is known as a "life-sustaining amino acid" [1]. In diets where plant-based protein ingredients serve as the primary protein source, methionine is typically the first limiting amino acid for poultry and ruminants and the second limiting amino acid for swine, making it crucial for livestock growth and development [2].

Methione possesses important physiological functions. First, methionine participates in protein synthesis as the initiating amino acid in this process. Additionally, methionine serves as a methyl donor in the synthesis of phospholipids, DNA, and RNA [3]. In recent years, increasing evidence has demonstrated that methionine can also scavenge free radicals, enhance immune function, and regulate cell proliferation and differentiation, embryo implantation, and fetal growth and development, exerting significant influence on livestock growth and reproductive performance [4-6]. However, current research on methionine' s effects on livestock reproductive performance remains limited, and the specific mechanisms are still unclear. This review summarizes research on methionine' s effects on livestock reproductive performance and analyzes its potential mechanisms, aiming to provide references for future research and application.

1 Physicochemical Properties of Methionine

Methionine, systematically named 2-amino-4-(methylthio)butanoic acid, has a relative molecular mass of 149.21 and the structural formula H3C-CH2-CH2-CH(NH2)-COOH. It is a neutral amino acid that exists as D- and L-isomers with optical activity. D-methionine must be converted to the L-form before it can be absorbed and utilized by the body. Methionine appears as a white powder or flaky crystal with a distinctive odor. It is insoluble in ether but readily soluble in water, dilute alkali, and dilute acid, and slightly soluble in ethanol, with a relative density of 1.340 and a melting point of 281°C [7].

In practical production, industrially synthesized methionine products are widely used to compensate for methionine deficiency in natural feed ingredients. Common industrial methionine products include: (1) DL-methionine and its sodium salt, which appear as light yellow or white powder and flaky crystals; (2) methionine derivatives, mainly including N-hydroxymethionine calcium and liquid hydroxy analogs; (3) DL-methionine hydroxy analog, a brown or dark brown viscous liquid; (4) DL-methionine hydroxy analog calcium salt, light brown granules or powder; and (5) microbially fermented methionine.

2 Methionine Metabolism in the Body

The liver is the primary site of methionine metabolism. While most cells in animals exhibit methionine transmethylation and remethylation activities, transsulfuration occurs only in specific tissues and organs such as the liver, kidneys, intestine, and pancreas [8].

In mammals, methionine metabolism proceeds through four main pathways. First, polypeptide and protein synthesis: methionine serves as the initiating amino acid in protein synthesis, binding to tRNA to form methionyl-tRNA, which then synthesizes proteins under mRNA guidance [1]. Second, transmethylation and remethylation: the first step in methionine catabolism involves conversion to S-adenosylmethionine (SAM), a crucial methyl donor that participates in methylation of proteins, DNA, and RNA [3] and regulates gene expression [4], protein localization, and synthesis and metabolism of biomolecules such as phospholipids [5] and neurotransmitters [6]. SAM then transfers its methyl group under the catalysis of various methyltransferases, forming S-adenosylhomocysteine (SAH). SAH is hydrolyzed to release adenosine and becomes homocysteine (Hcy). Hcy can accept methyl groups from betaine or N5-methyltetrahydrofolate to regenerate methionine, completing the methionine cycle [1]. Third, transsulfuration: Hcy condenses with serine under the action of cystathionine -synthase to form cystathionine, which is then metabolized to cysteine by cystathionine -lyase, requiring vitamin B6 as a cofactor. Cysteine can be further incorporated into sulfur-containing proteins and glutathione, or degraded to -ketobutyrate, taurine, and hydrogen sulfide, or converted to sulfate for urinary excretion. Fourth, aminopropyl transfer: SAM undergoes two decarboxylation steps to generate 5' -methylthioadenosine, which transfers aminopropyl groups to spermidine and putrescine to form spermine and spermidine, respectively [1, 9].

3 Methionine Regulates Nutrient Transport and Absorption in the Mammalian Placenta

The fetus obtains nutrients from the mother through the placenta to maintain normal growth and development in utero. Amino acid transport across the placenta represents a crucial pathway for fetal nutrition. Abnormal placental amino acid transport may affect fetal growth and is associated with pregnancy complications such as intrauterine growth restriction [10-11]. Amino acid transport across the placenta is mediated by amino acid transporters, which are heterodimeric protein structures composed of heavy and light chains. During transport, the light chain primarily performs transmembrane transport, while the heavy chain regulates the light chain' s transport activity and directs dimer localization to the cell membrane [11].

As a neutral amino acid, methionine has the largest family of transporter members compared to other amino acids. In placental amino acid transport systems, types A, B0, ASC, G, L, and asc can all transport methionine (Table 1).

During methionine transport across the placenta, Na+-independent L-type and Na+-dependent A-type and ASC-type amino acid transporters play particularly important roles [11].

The L-type transporters include L-type amino acid transporter (LAT) 1, LAT2, LAT3, and LAT4, with LAT1 being the most extensively studied. Human LAT1 protein is expressed in the small intestine, mammary gland, testis, placenta, heart, and brain, with expression levels varying by cell type and tissue location. Notably, LAT1 shows high expression in various hyperplastic tissues and tumor cells [12]. The abundant expression of LAT1 in the placenta is related to fetal nutritional requirements, as many essential amino acids and hormones depend on LAT1 for transport. Studies have shown that LAT1 expression facilitates development from the zygote to blastocyst stage and embryo implantation, and is associated with proliferation, invasion, and migration of placental trophoblast cells [13].

The A-type amino acid transporter was first discovered in Ehrlich ascites carcinoma cells and is encoded by three genes. During pregnancy, the activity of A-type amino acid transporters on the placenta gradually increases, and sodium-coupled neutral amino acid transporter 1 (ATA1) shows higher expression levels than other isoforms on the placenta, suggesting that A-type transporters, particularly ATA1, may transport amino acids crucial for fetal growth [11].

ASC-type transporters are widely distributed in the body and include alanine-serine-cysteine-threonine transporter (ASCT) 1 and ASCT2 isoforms, primarily transporting neutral amino acids without large branched chains, such as alanine, serine, and threonine [14]. Both isoforms are expressed on the placenta and are localized exclusively on the basal membrane of trophoblast cells.

4.1 Effects of Methionine on Poultry Reproductive Performance

Conventional poultry diets contain low levels and utilization rates of methionine, making methionine the first limiting amino acid in poultry diets. Industrially synthesized methionine products are therefore widely used in poultry feed.

Research demonstrates that dietary methionine supplementation affects laying performance and egg quality in hens. As dietary methionine levels increased, Jinghong No. 1 laying hens showed significantly improved laying rate and egg production, reduced feed-to-egg ratio, and increased hatchability and healthy chick rate, with maximal egg production and laying rate achieved at a dietary methionine level of 0.43% [15]. Dietary supplementation with 0.35% DL-methionine significantly improved laying rate, reduced feed-to-egg ratio, and enhanced eggshell hardness, eggshell percentage, and eggshell strength in yellow-feathered broiler breeders [16]. Additionally, methionine participates in spermatogenesis; research indicates that a dietary DL-methionine level of 0.19% significantly increased sperm density and viable sperm count in roosters [17]. In Linwu ducks, low dietary DL-methionine levels (0.27%) resulted in higher feed-to-egg ratio and feed intake with lower feed conversion efficiency. As dietary

DL-methionine levels increased (0.32%-0.47%), feed-to-egg ratio and feed intake decreased, improving feed utilization efficiency. The results also showed that dietary DL-methionine levels had no significant effects on yolk color, yolk percentage, eggshell thickness, egg shape index, eggshell percentage, or albumen percentage [18]. Dietary methionine supplementation at 0.25%-0.50% showed no significant effects on egg quality in laying Magang ducks. These findings suggest that methionine' s effects on poultry may vary depending on poultry species, laying cycle stage, and diet composition [19].

4.2 Effects of Methionine on Ruminant Reproductive Performance

Methionine application in ruminants is increasing. To avoid degradation by rumen microorganisms, methionine is typically administered via abomasal infusion, subcutaneous injection, or as rumen-protected methionine.

In Holstein dairy cows fed diets containing 2.4% digestible DL-methionine compared to control diets with 1.9% digestible DL-methionine, significant differences were observed in gene expression of pre-implantation embryos, though whether these differentially expressed genes benefit embryo survival and development requires further investigation [20]. After dietary supplementation with 0.08% digestible DL-methionine, Holstein cows showed significantly lower polymorphonuclear neutrophil ratios compared to controls, suggesting improved uterine health [21]. During in vitro culture of bovine embryos, addition of 10 mmol/L ethionine (a methionine metabolism inhibitor) at the 2-cell stage completely inhibited blastocyst development, while supplementation with 10 mmol/L SAM partially restored blastocyst development [22]. Supplementation with 2 mol/L SAM did not affect blastocyst rate but significantly improved hatching rate [23].

4.3 Effects of Methionine on Porcine Reproductive Performance

Currently, reports on methionine' s effects on porcine reproductive performance are limited. Existing studies indicate that dietary methionine supplementation affects gestating and lactating sows as well as weaned piglets.

Nutritional levels in replacement gilts can influence body weight gain during gestation and subsequent litter performance. Dietary supplementation with 0.12% DL-methionine during the replacement phase significantly increased maternal weight gain during gestation, litter weight, and piglet birth weight, suggesting that methionine may affect anabolic metabolism in late gestation, though the specific mechanisms require further investigation [24]. Within dietary DL-methionine levels of 0.28%-0.48%, increasing methionine levels significantly reduced feed-to-gain ratio and increased average daily gain in weaned piglets, while markedly decreasing serum urea nitrogen content and significantly affecting methionine content in liver but not in muscle [25]. Dietary supplementation with 0.14% DL-methionine significantly increased sulfur-containing amino acids in plasma and fat and protein content in milk of lactating sows, improved feed intake during suckling and post-weaning periods, and enhanced growth perfor-

mance of weaned piglets. Furthermore, the number of goblet cells in the duodenum and ileum of weaned piglets increased significantly, and serum glutathione content rose markedly, thereby improving antioxidant capacity, alleviating intestinal damage from weaning stress, and promoting intestinal mucosal growth and development [26].

5.1 Regulation of DNA Methylation to Promote Embryonic Cell Survival

Methionine and ATP generate SAM under the catalysis of methionine adenosyltransferase. The methyl group from SAM is transferred to the fifth carbon position of cytosine by methyltransferases, forming 5-methylcytosine (5mC). The 5mC protrudes into the major groove of the DNA double helix, interfering with DNA binding to transcription factors [27].

DNA methylation/demethylation is closely related to mammalian embryonic development. The early embryonic development stage represents one of the most dramatic periods of DNA methylation level changes [28]. During mammalian development, a large-scale DNA methylation reprogramming process occurs from fertilization to early embryo implantation [29]. After fertilization, the oocyte undergoes genome-wide DNA demethylation, followed by DNA remethylation at a specific developmental stage (mostly at the morula or blastocyst stage; in mice at the blastocyst stage, and in cattle at the 8-16 cell stage [30]). DNA methylation affects early embryonic growth and development by regulating gene expression, particularly of imprinted genes. Post-fertilization DNA methylation changes play a decisive role in mammalian early embryonic development [31].

5.2 Metabolic Production of Polyamines to Promote Embryo Implantation

SAM also participates in polyamine formation through aminopropyl transfer. Polyamines play important roles in regulating protein synthesis, gene expression, cell signal transduction, angiogenesis, cell proliferation and differentiation, embryonic development, and placental growth [32-33]. Additionally, polyamines can scavenge reactive oxygen species, protecting DNA, lipids, and proteins from oxidative damage [34].

Research has found that during the embryo implantation period, polyamines are synthesized in large quantities, and expression of genes related to polyamine synthesis increases to achieve uterine decidualization, facilitating successful blastocyst implantation [35]. Endometrial decidualization is characterized by proliferation and differentiation of endometrial stromal cells, which gradually transform into decidual stromal cells. As embryos implant and trophoblast cells invade, the degree of decidualization plays a crucial regulatory role in maintaining normal pregnancy, embryo implantation, and placenta formation [36]. Polyamines may function by regulating steroid hormone production and stimulating ornithine decarboxylase (ODC) expression, thereby influencing placental, embryonic, and

fetal growth and development [37].

5.3 Improving Embryonic Development Environment and Reducing Oxidative Stress Damage

Oxidative stress represents a primary cause of embryonic damage during development [38]. Methionine' s antioxidant effects are primarily achieved through the glutathione pathway and redox cycling.

Methionine serves as a precursor for reduced glutathione synthesis. Reduced glutathione participates in important redox reactions and is essential for maintaining internal environmental stability [39]. Additionally, reduced glutathione can transform harmful substances through glutathione S-transferase and glutathione peroxidase, further scavenging free radicals [40].

Methionine redox cycling plays an important role in clearing toxic substances. Reactive oxygen species in animals can react with disulfide bonds in methionine residues to form methionine sulfoxide (MetO), which can be reduced back to methionine by methionine sulfoxide reductase [41-42]. This interchange between methionine and its derivatives provides an effective pathway for clearing harmful substances and ensures the biological activity of relevant proteins.

5.4 Promotion of Embryonic Neural Tube Closure

Neural tube defects (NTDs), the second most common birth defect after congenital heart disease, seriously threaten human health and population quality. Failure of neural tube closure during weeks 3-4 of pregnancy leads to a series of central nervous system disorders including anencephaly, craniorachischisis, myelomeningocele, and encephalocele [43].

When rat embryos were cultured in fetal bovine serum medium, they exhibited abnormal body curvature, anophthalmia, and encephalocele. Methionine supplementation improved these early embryonic abnormalities [44-45], while other nutrients such as cysteine and folic acid did not show these effects [46]. However, other studies have shown that folic acid supplementation during early pregnancy can improve pregnancy outcomes and reduce NTDs by 25%-30%, though the specific mechanism remains unclear [47-48]. Methionine supplementation in culture medium facilitated neural tube closure in mouse embryos and improved both developmental and morphological indices, suggesting that methionine deficiency may be a potential cause of NTDs [49].

5.5 Promotion of Early Embryonic Cell Proliferation and Improvement of Blastocyst Quality

During early pregnancy, fertilized eggs must proliferate rapidly to develop into qualified blastocysts for successful uterine implantation and subsequent normal fetal development. Research has found that methionine consumption exceeds that of other essential amino acids during rapid cell proliferation [50]. Mouse

blastocysts highly express betaine-homocysteine methyltransferase; knockout of this gene causes delayed blastocyst development and significantly reduced inner cell mass cell numbers, while methionine supplementation can ameliorate this developmental delay, demonstrating methionine' s critical role in embryonic development [51]. Supplementation with free methionine can promote proliferation of bovine mammary epithelial cells, with the strongest effect observed at 48 hours [52]; the percentage of mammary epithelial cells in S and G2 phases increased significantly, while the percentage in G0-G1 phase decreased markedly [53].

Methionine may promote cell proliferation through its metabolite hydrogen sulfide. Recent studies have shown that colon cancer cells overexpress cystathionine- -synthase, producing more hydrogen sulfide. Hydrogen sulfide can maintain bioenergetics required for cancer cell growth, angiogenesis, and vasodilation. Addition of 0.1-3.0 mmol/L SAM to cell culture medium significantly increased hydrogen sulfide concentration, and cell proliferation rate increased with methionine levels in the short term, though 3 mmol/L SAM inhibited cell proliferation [53].

6 Summary

Methionine is an important functional amino acid that plays vital roles in protein anabolism, regulation of DNA methylation, synthesis of polyamines and glutathione, promotion of embryonic neural tube closure, and early embryonic cell proliferation, exerting significant influence on livestock and poultry reproductive performance. Its application in animal production is increasing. However, systematic and in-depth research is still needed on the molecular mechanisms through which methionine improves reproductive performance and its interactions with other nutrients.

References

[1] Hu Chengjun, Jiang Qingyan, Kong Xiangfeng. Research progress on methionine metabolism and physiological functions in livestock and poultry [J]. Feed Industry, 2016, 37(15): 23-27.
[2] Zhu Zhongsheng, Li Lümu. Research progress on methionine [J]. Feed Review, 2015(7): 11-17.
[3] XU J, SINCLAIR K D. One-carbon metabolism and epigenetic regulation of embryo development [J]. Reproduction Fertility and Development, 2015, 27(4): 667-676.
[4] MIRANDA T B, JONES P A. DNA methylation: The nuts and bolts of repression [J]. Journal of Cellular Physiology, 2007, 213(2): 384-390.
[5] WINTER-VANN A M, KAMEN B A, BERGO M O, et al. Targeting Ras signaling through inhibition of carboxyl methylation: an unexpected property of methotrexate [J]. Proceedings of the National Academy of Sciences of the United States of America, 2003, 100(11): 6529-6534.

[6] STEAD L M, AU K P, JACOBS R L, et al. Methylation demand and homocysteine metabolism: effects of dietary provision of creatine and guanidinoacetate [J]. American Journal of Physiology-Endocrinology and Metabolism, 2001, 281(5): E1095-E1100.
[7] Qiao Detang. Research progress on animal methionine nutrition [J]. Shandong Journal of Animal Science and Veterinary Medicine, 2007, 28(4): 57-58.
[8] FINKELSTEIN J D. Methionine metabolism in mammals [J]. The Journal of Nutritional Biochemistry, 1990, 1(5): 228-237.
[9] MATO J M, MARTÍNEZ-CHANTAR M L, LU S C. Methionine metabolism and liver disease [J]. The Annual Review of Nutrition, 2008, 28(1): 273-293.
[10] Shi Changyou, Wang Wence, Geng Meimei, et al. Effects of different dietary protein levels on CAT1 mRNA expression of amino acid transporter in finishing pigs [J]. Chinese Journal of Animal Nutrition, 2008, 20(6): 692-698.
[11] Chen Yunping, Lü Chunmei, Zhu Hui. Research progress on placental amino acid transporters [J]. Maternal and Child Health Care of China, 2013, 28(26): 4416-4418.
[12] HOWIE G J, SLOBODA D M, KAMAL T, et al. Maternal nutritional history predicts obesity in adult offspring independent of postnatal diet [J]. The Journal of Physiology, 2009, 587(4): 905-915.
[13] DESFORGES M, MYNETT K J, JONES R L, et al. The SNAT4 isoform of the system A amino acid transporter is functional in human placental microvillous plasma membrane [J]. The Journal of Physiology, 2009, 587(1): 61-72.
[14] Ma Jing, Tan Yi, Tan Dongmei, et al. Effect of amino acid transporter LAT1 on early placenta establishment in mice [J]. Acta Laboratorium Animalis Scientia Sinica, 2015, 23(3): 256-260.
[15] Fu Guoqiang, Ji Cheng, Ma Qiugang. Effects of dietary methionine and lysine levels on production and reproductive performance of Jinghong laying hens during peak laying period [J]. Chinese Abstracts of Animal Husbandry and Veterinary Medicine, 2013, 49(9): 52.
[16] XIAO X, WANG Y X, LIU W L, et al. Effects of different methionine sources on production and reproduction performance, egg quality and serum biochemical indices of broiler breeders [J]. Asian-Australasian Journal of Animal Sciences, 2017, 30(6): 828-833.
[17] Dai Guojun, Wang Zhiyue, Wu Zhaolin, et al. Effects of different protein sources on semen collection volume and quality in roosters [J]. Chinese Journal of Animal Science, 2000, 36(4): 32-33.
[18] Huang Xuan, Li Chuang, He Ping, et al. Study on methionine requirement of Linwu ducks during peak laying period [J]. Chinese Journal of Animal Nutrition, 2015, 27(4): 1110-1116.
[19] Ruan Dong, Lin Yingcai, Zhang Hanxing, et al. Effects of methionine level on laying performance, egg quality and ovarian morphology of laying Magang ducks [J]. Chinese Journal of Animal Science, 2012, 48(7): 34-38.
[20] PEÑAGARICANO F, SOUZA A H, CARVALHO P D, et al. Effect of maternal methionine supplementation transcriptome bovine preimplantation embryos [J]. PLoS One, 2008, 8(8): e72302.

[21] IKEDA S, SUGIMOTO M, KUME S. Importance of methionine metabolism in morula-to-blastocyst transition in bovine preimplantation embryos [J]. Journal of Reproduction and Development, 2012, 58(1): 91-97.
[22] SAADI H S, GAGNÉ D, FOURNIER É, et al. Responses of bovine early embryos to S-adenosyl methionine supplementation in culture [J]. Epigenomics, 2016, 8(8): 1039-1060.
[23] Jian Yongjun, Liu Guoqing, Zhao Lihong, et al. Effects of dietary methionine to lysine ratio on growth and reproductive performance of replacement gilts [J]. Chinese Journal of Animal Science, 2016, 52(9): 32-36.
[24] Lin Yingcai, Jiang Zongyong, Yu Deqian, et al. Study on digestible methionine, threonine, and tryptophan requirement parameters for ultra-early weaned piglets [J]. Chinese Journal of Animal Nutrition, 2001, 13(3): 30-39.
[25] Li Hao. Effects of dietary methionine source and level on growth and intestinal development of suckling-weaned piglets [D]. Master' s Thesis. Ya' an: Sichuan Agricultural University, 2013: 67-78.
[26] NAICHE L A, HARRELSON Z, KELLY R G, et al. T-box genes in vertebrate development [J]. Annual Review of Genetics, 2005, 39(1): 219-239.
[27] Su Wenlong, Li Lu, Cao Hui, et al. DNA methylation/demethylation and in vitro development of mammalian embryos [J]. Chinese Journal of Animal Science, 2015, 51(9): 68-71.
[28] REIK W. Stability and flexibility of epigenetic gene regulation in mammalian development [J]. Nature, 2007, 447(7143): 425-432.
[29] DEAN W, SANTOS F, STOJKOVIC M, et al. Conservation of methylation reprogramming in mammalian development: aberrant reprogramming in cloned embryos [J]. Proceedings of National Academy of Sciences of the United States of America, 2001, 98(24): 13734-13738.
[30] SILVA A R R E, ADENOT P, DANIEL N, et al. Dynamics of DNA methylation levels in maternal and paternal rabbit genomes after fertilization [J]. Epigenetics, 2011, 6(8): 987-993.
[31] ZENG X, WANG F, FAN X, et al. Dietary arginine supplementation during early pregnancy enhances embryonic survival in rats [J]. Journal of Nutrition, 2008, 138(8): 1421-1425.
[32] Huang Zhenru, Cai Meiqin. Role of arginine in early human growth and development [J]. Journal of Shanghai Jiao Tong University: Medical Science, 2016, 36(3): 451-454.
[33] Tan Minjie, Kong Xiangfeng, Liu Qingyou, et al. Polyamines and conceptus development in mammals [J]. Chinese Journal of Animal Nutrition, 2015, 27(1): 43-48.
[34] ZHAO Y C, CHI Y J, YU Y S, et al. Polyamines essential embryo implantation: expression and function of polyamine-related genes in mouse uterus during peri-implantation period [J]. Endocrinology, 2008, 149(5): 2325-2332.
[35] RAMATHAL C Y, BAGCHI I C, TAYLOR R N, et al. Endometrial decidualization: of mice and men [J]. Seminars in Reproductive Medicine, 2010, 28(1): 17-26.
[36] BAZER F W, SONG G, KIM J, et al. Mechanistic mammalian target of rapamycin (MTOR) cell signaling: effects of select nutrients and secreted

phosphoprotein 1 on development of mammalian conceptuses [J]. Molecular and Cellular Endocrinology, 2012, 354(1/2): 22-33.
[37] GASPARRINI B, SAYOUD H, NEGLIA G, et al. Glutathione synthesis during in vitro maturation buffalo (Bubalus bubalis) oocytes: effects cysteamine embryo development [J]. Theriogenology, 2003, 60(5): 943-952.
[38] DRAZIC A, WINTER J. The physiological reversible methionine oxidation [J]. Biochimica Biophysica (BBA)-Proteins Proteomics, 2014, 1844(8): 1367-1382.
[39] HOSHI T, HEINEMANN S. Regulation of cell function by methionine oxidation and reduction [J]. Journal of Physiology, 2001, 531(1): 1-11.
[40] Lin Xiajing, Jiang Shouqun. Effects of amino acids on poultry immune function and its regulatory mechanisms [J]. China Poultry, 2014, 36(11): 39-43.
[41] Cheng Chuanfeng. Effects of methionine level on growth performance and immune function of piglets [D]. Master' s Thesis. Changchun: Jilin Agricultural University, 2012: 67-78.
[42] Bao Rui, Wu Jianxin. Progress in molecular genetics of human neural tube defects [J]. Chinese Journal of Birth Health & Heredity, 2009, 17(5): 1-4.
[43] COELHO C N, WEBER J A, KLEIN N W, et al. Whole rat embryos require methionine for neural closure cultured serum [J]. The Journal Nutrition, 1989, 119(11): 1716-1725.
[44] COELHO C N, KLEIN N W. Methionine and neural tube closure in cultured rat embryos: morphological and biochemical analyses [J]. Teratology, 1990, 42(4): 437-451.
[45] ESSIEN F B, WANNBERG S L. Methionine but not folinic acid or vitamin B-12 alters the frequency neural defects in Axd mutant mice [J]. The Journal Nutrition, 1993, 123(1): 27-34.
[46] BHARGAVA S, TYAGI S C. Nutriepigenetic regulation by folate–homocysteine–methionine axis: a review [J]. Molecular and Cellular Biochemistry, 2014, 387(1/2): 55-61.
[47] KALHAN S C, BIER D M. Protein and amino acid metabolism in the human newborn [J]. The Annual Review of Nutrition, 2008, 28(1): 389-410.
[48] Cheng Junping, Shi Deshun, Lu Fenghua, et al. Effects of amino acids on in vitro development of mammalian embryos [J]. Sichuan Animal & Veterinary Sciences, 2006, 33(2): 27-28.
[49] LEE H J, JEDRYCHOWSKI M P, VINAYAGAM A, et al. Proteomic and metabolomic characterization of a mammalian cellular transition from quiescence to proliferation [J]. Cell Reports, 2017, 20(3): 721-736.
[50] LEE M B, KOOISTRA M, ZHANG B H, et al. Betaine homocysteine methyltransferase is active in the mouse blastocyst and promotes inner cell mass development [J]. Journal of Biological Chemistry, 2012, 287(39): 33094-33103.
[51] Li Xiyan, Wang Jiayi, Wei Hongyang, et al. Effects of lysine and methionine on proliferation of bovine mammary epithelial cells cultured in vitro detected by MTT assay [J]. Biotechnology Bulletin, 2010(3): 143-148.
[52] Yu Cuiping. Regulation of 14-3-3 on milk protein synthesis and cell proliferation in bovine mammary epithelial cells [D]. PhD Thesis. Harbin: Northeast Agricultural University, 2015: 67-78.

[53] MÓDIS K, COLETTA C, ASIMAKOPOULOU A, et al. Effect of S-adenosyl-l-methionine (SAM), an allosteric activator of cystathionine- -synthase (CBS) on colorectal cancer cell proliferation and bioenergetics in vitro [J]. Nitric Oxide, 2014, 41: 146-156.

Note: Figure translations are in progress. See original paper for figures.