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Review Article

The Epigenetic Modification in Mammals under Heat Stress

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Abstract

Temperature is one of the most important physiological stressors for organisms and Heat Stress (HS) is a global issue, which results in decreased production, growth and fertility. It has been known that epigenetic modifications play extensive and important roles in coping with the heat stress for mammals. Here, we briefly reviewed the latest knowledge about epigenetic modifications in mammals under heat stress, including DNA methylation, RNA methylation, his tone modifications, and micro RNA regulation. This review can provide useful information for understanding the mechanism of epigenetic modification under heat stress as well as references for improving growth and economic benefits in mammals.

Keywords: Heat stress; Epigenetics; Mammals

Introduction

The effects of heat stress

Animals have the ability to compensate external thermal fluctuations to maintain its internal body temperature. Heat Stress (HS) is the sum of non-specific responses of animals to thermal environment, which can lead to the imbalance of internal metabolism and damage to multiple tissues and organs. HS response is a complex molecular process involving the transcription and post-transcriptional regulation of stress-related genes. With the gradual increase of global temperature and the intensification and industrialization level of global animal husbandry, mammals have suffered various pressures, among which the HS caused by environment has induced detrimental effects on the production and reproduction of mammals and tends to be serious. HS exerts adverse influence on oocyte development, fertilization and early embryo formation as well as on the sperm quality of male mammals, especially in the stage of meiosis. It has been reported that HS can lead to shorter estrus cycle and lower estrus rate in cows and dairy goats [1,2].

Types of epigenetic modifications

Epigenetics is a branch of genetics that regulation of gene expression by not involving changing DNA sequences, the concept of which was first proposed in 1942 by Waddington. According the category of modification, epigenetics mainly includes six types including DNA methylation, RNA methylation, and histone covalent modification, non-coding RNAs, chromatin higher order structure, and X chromosome random inactivation. These epigenetic modifications are the response of body to the changes of various environmental stimulation factors. They interact with each other to regulate gene expression, cell differentiation and individual phenotype, which is necessary to maintain the homeostasis of the mammal body.

DNA methylation

DNA methylation is the most abundant epigenetic modification that directly affects the DNA molecule in mammals, and this process is reversible. In eukaryotes, methylation occurs only in cytosine, it involves the addition of a methyl group on carbon 5 position of CPG dinucleotide cytosine catalyzed by DNA methyl transferase (DNMTs), thereby creating 5-methylcytosine (5-mc). These processes are performed by various enzyme families, such as the DNMT enzyme family and the Ten-Eleven Translocation (TET) protein family, which made the importance of studying enzymes regulating DNA methylation status [3]. DNA methylation can be reversed at a certain stage of biological development either in a certain state of cell differentiation. Therefore, it plays an important role in cell differentiation and environmental adaptation in multi-cellular organisms. It is generally acknowledged that the hyper-methylation of promoter regions is related to gene silencing, while the hypo-methylation is associated with gene activation [4,5].

RNA methylation

RNA is an important transmitter and regulator of genetic information which has broad roles in gene expression and regulation. Nucleotide modifications of mRNA include 2'-O-methylation, pseudouridylation, m6A, m5C, m7G, m1A, 5hmC, among which m6A is the most abundant methylation modification in eukaryotic mRNAs and being the focus of research. It has been reported that N6-methyladenosine (m6A) is found in tRNA, rRNA, ncRNA and microRNA, mainly by affecting the binding of mRNA and reading protein, so as to regulate the expression of downstream genes accordingly. Proteins participating in this dynamic modification in mammalian cells including "writer" (Methyltransferase complex), "eraser" (Demethylase), and "reader" (RNA-binding proteins) have been revealed successively. m6A modifications play important roles in several important biological processes, including tissue development, heat shock or DNA damage response, as well as maternal-to-zygotic transition. Recently, a series of advanced technology provide great convenience for comprehensive inspection and further biological function research of mRNA nucleotide modification.

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Histone modification

Histones are not only an important part of the nucleosome, but also play regulatory roles by changing the conformation (loose or condensation state) of chromosomes to affect the binding of transcription factors to DNA, or by affecting the affinity of other transcription factors to gene promoters. The N-terminal of histones undergo a variety of post-translation modifications including methylation, acetylation, phosphorylation, ubiquitination, ADP-ribosylation, sumoylation, etc., among which acetylation and methylation are most comprehensively investigated. A large number of combinations of histone modifications constitute into the "histone code" which made histone covalent modification a more delicate regulation mode of gene expression. Moreover, histone modifications are associated with DNA methylation to orchestrate into more sophisticated regulatory mechanisms.

Chromatin higher order structure

Chromosome forms the ordered three-dimensional spatial structure in the nucleus through hierarchical compression and folding. There are many regulatory elements located on the genome, the target genes of which could be far away from each other in linear arrangement. With the change of chromatin's higher order structure, target genes located on the same or different chromosomes can be approached and regulated by regulatory elements. Chromatin higher order structure can be widely involved in DNA replication, DNA repair, cell division and transcriptional regulation, which make it one of the most important steps in understanding life processes.

Non-coding RNA regulation

Numerous studies have shown that the non-coding RNAs can regulate gene expression at the chromosome level and the genome level. MicroRNA is the most widely studied class of highly conserved small single-stranded non-coding RNAs with the length about 22 nucleotides, which negatively regulates gene expression after transcription and widely involved in almost all physiological processes such as cell proliferation, differentiation, apoptosis and development. More and more evidence indicates that microRNAs play important roles in resisting HS in mammals, such as regulation of Heat Shock Proteins (HSPs) genes, redox genes, immune genes, cell apoptosis genes and relevant metabolic genes.

The Effects of Heat Stress on Epigenetic Modification in Mammals

Gametes and early embryonic development in mammals are accompanied by many important cellular and molecular events [6]. After fertilization genome-wide DNA methylation underwent extensively erasing and reconstruction processes, including zygotic genome activation, cell fate differentiation and X chromosome inactivation [7]. It has been well documented in domestic mammals and mice that exposure to high temperature of early dividing embryoes has disadvantageous effects on the production of cleavage blastocysts or early fetal development. However, the embryo acquired resistance to high temperature when it developed into morula-stage. Heat-induced apoptosis cascade is one of the mechanisms by which embryoes acquire heat resistance. Under this condition, the damaged blastocysts are been removed and the qualified embryo survive through the HS. Environmental factors can promote the transmission of epigenetic information related to disease and phenotypic variation to off springs. As an important environmental factor, there was a closely relationship between HS and the transmission and reprogramming of epigenetic information in early embryonic development of mammals.

Mice and Rats

HS can cause abnormal methylation imprinting in early mice embryoes, leading to the failure of early mice embryo development, and this effect on methylation imprinting seems to be genetically specific [8]. Twice genome-wide processes of DNA methylation removal and reconstruction occur during the development of mouse embryo. The first wave of DNA methylation arises during the gametogenesis stage, and the second wave arises in the period from fertilization to embryo differentiation [9,10]. Zhou et al. [11] demonstrated that under HS, YTHDF2 would bind to the m6A methylation site in the nucleus to prevent the FTO from removing m6A methylation in the 5'UTR region, thereby promoting cap-independent translation initiation of RNA in Mouse Embryonic Fibroblast (MEF). In addition, HS-induced translation initiation of HSP70 is mediated by 5'UTR m6A at a single site in dependent of the 5'end m7G cap. Houston et al. [12] reported that there was a certain stage of heat sensitivity during the second division of spermatogonia. They found that sperm damage was significantly increased when male mice were exposed to high temperature. Choi et al. [13] showed that although long-term mild HS (39°C) did not cause any perturbation during the development into the blastocyst stage, the viability of mice embryoes during pregnancy after embryo transfer were seriously affected. This could be due to the aberrant expression of trophoderm (TE) lineage-specific transcription factor genes including GATA3, TEAD4, CDX2, TCFAP2C, which were responsible for embryonic viability and tropho blast differentiation in the mild-heat-stressed blastocysts. Rao et al. [14] found serious apoptosis of germ cell in mice testis under HS, and they identified 11 differential miRNA sat the early stage of testicular injury, which are involved in a variety of pathways. Yu et al. [15] investigated the expression profiles of miRNA and mRNA in small intestine in rats, and identified 29 differential miRNAs in small intestine of heat-stressed rats. Li et al. [16] demonstrated that miRNA-155 increased the activity of NF-κB signaling pathway by targeting Liver X Receptor α (LXR α) and promoted the expression of immune inflammatory factors in murine bv-236 cells under HS. Findings from Permenter et al. indicated that some miRNA in plasma in conscious rats may serve as biomarkers for organ injury caused by HS, or as potential therapeutic intervention points or drugs to prevent HS injury [17].

Pigs

Hao et al. [18] showed that the changes in global DNA methylation profile in pig genome were related to long-term thermal stress. Some differentially methylated genes may affect muscle development and meat quality. Itami et al. [19] proved that short-term HS induced the promotion of mitochondrial degradation and biogenesis through Sirtuin1 (SIRT1) activation, thereby improving mitochondrial function and the ability of oocyte developing into blastocysts. In addition, findings from Li et al. [20] suggested that melatonin may be involved in regulating of porcine oocyte maturation *in vitro* under HS by participating in the acetylation modification of histone through deacetylase SIRT1. Heng et al. [21] demonstrated that m6A RNA methylation played an important role in fat deposition of piglets from sows subjected to HS from day 85 of gestation to day 21 of lactation. Another investigation indicated that the long-term HS induced 58 differential miRNA in porcine long issimus dorsi muscle were significantly enriched in glucose metabolism cytoskeleton structure function and stress response [22].

Cattles

The dynamic changes of DNA methylation are to be specific dependent upon gender and cell lineage during pre implantation development of the bovine embryo; the methylation is lower for female embryoes than male embryoes at the blastocyst stage and is lower for the Inner Cell Mass (ICM) than Trophoderm (TE). In particular, global methylation declines to a nadir at the 6 to 8 cell stage and increases thereafter. Changes in expression of DNMT3B may be responsible for developmental changes in DNA methylation [23]. Rahman et al. [24] reported that sperm cells at the spermatogenic and meiotic stages are more susceptible to HS, showing the subtle changes in sperm head shape and the lack of chromatin protamination. In the process of forming zygote in vitro, compared with normal control, spermatozoa produced by heat-stressed cattles with altered chromatin condensation changed the methylation and demethylation procedures leading to a significant decrease in the fertilization rate and abnormal zygote development [25]. De Barros et al. [26] found that early bovine embryoes are extremely susceptible to heat shock at the 2 or 4-cell stage, this apoptosis arrest at cell phase 2 is due to high levels of DNA methylation and deacetylation that block the action of pro-apoptotic factors, whereas embryo >8 cells can activate the apoptosis cascade reaction as an adaptive response to HS. Directly exposure to heat shock will change the expression pattern of parental imprinting genes, leading to recombination of microtubules and microfilaments. It also increases the production of Reactive Oxygen Species (ROS) and the rate of DNA fragmentation and apoptosis, as well as reduces Mitochondrial Membrane Potential (MMP). During the heat induced resistance, cells that exposed to mild heat stimulation synthesizing heat shock proteins entitling cells resistance to more severe heat shock. But the ability of early embryoes to produce heat shock responses remains controversial given that the expression of HSPA1A gene expression did not increase in early embryoes exposed to severe or moderate heat treatment prior to the activation of the main embryo genome [27].

The inhibition of miRNA-24 expression under high temperature reduced the incidence of mammary epithelial cell apoptosis, and promoted the growth and development of milk cow cells [28]. Cai et al. demonstrated that miRNA-216b inhibited HS-induced cell apoptosis by targeting Fas in bovine mammary epithelial cells [29]. The up-regulated miRNA-19a and miRNA-19b participated in the regulation of HS through the regulation of target gene HSP family [30]. Down-regulation of miRNA-181a can reduce HS damage of Peripheral Blood Mononuclear Cells (PBMCs) in Holstein cows [31]. Li et al. [32] identified 27 significantly differentially expressed miRNA in breast tissues under HS by deep RNA sequencing among which 7 candidate miRNA were related to the regulation of WNT, GF-beta, MAPK, Notch and JAK-STAT pathways, indicating these differentially expressed miRNA may act as dominant regulators during HS. Vanselow et al. [33] found that exposure to acute pre-ovulatory HS of lactating cows affected granulosa cell-specific gene expression profiles in dominant follicles among which expression of miRNA-2480 was significantly up-regulated.

Sheep

Few studies have been performed on the epigenetic modification of HS in sheep and goats to date. Di Giacomo et al. [34] showed that acting as a methyl donor, dietary betaine supplementation may improvement the physiological responses of ewes and lambs during HS. Succu et al. [35] demonstrated that melatonin at high concentration may exert some degree of toxic activity on pre implantation ovine embryoes, although melatonin at optimal concentration has been shown to be beneficial for in vitro embryo development after vitrification and warming. Salces-Ortiz et al. [36] revealed that the differences in the transcriptional activity of the HSP90AA1 gene which response to HS are caused by the presence of a cytosine insertion and a C to G trans version at the promoter region, then epigenetic marks at the promoter and along the gene body establishing an allele-specific methylation of the rs397514116 mutation in DNA. HS can cause the reduction in DNA integrity in rams but scrotal heating appears to have few effects on sperm surface protein PH-20 expression and distribution on ejaculated sperm [37]. For female, HS caused an aberrant chromatin configuration in the matured oocyte and heat shock had an adverse effect on embryo quality and reduced ICM number [38]. Recent findings from Lu et al. [39] demonstrated that differences in the level of m6A and the expression of m6A-related enzymes in the liver of sheep were observed after HS, indicating that m6A is involved in the regulation of HS in sheep.

Wild mammals

Epigenetic studies of HS on wild mammalian species are rare. Wey rich et al. [40] demonstrated that paternal exposure to a temporally limited increased ambient temperature led to an immediate and heritable epigenetic response that may even be transmitted to the F2 generation. The methylation level of heat-induced rapid compensatory immediate response in fathers was partly reversely transferred to the next generation as heritable epigenetic modifications. Further investigation demonstrated that STAT3 gene expression was significantly reduced, which indicated a close link between CPG-methylation and expression levels for this gene. This illustrates the presence of a paternal Trans generational epigenetic effect [41]. These studies extend our understanding of the paternal epigenetic response to HS.

Conclusion and Perspective

The evolution of mammalian species have always been impacted and accompanied by dynamic environment. In the context of globally rising temperatures, epigenetic mechanisms may become increasingly relevant for the survival of mammalian species. Due to the close relationship between mothers and off springs, as well as epigenetic reprogramming in blastocysts, most of the present studies mainly focus on maternal epigenetic response and transmission of environmental experiences. But paternal epigenetic effects of heterogeneous wild mammals have been widely neglected. Therefore, it is of evolutionary importance to understand the transmission of epigenetic effects by wild males in changing environments, which helps to improve the fitness of their off springs. With the development of advanced detecting technologies and analytic tools including high-throughput sequencing, CRISPR-based epigenetic editing tools and structural analysis techniques, dynamic profiles of these epigenetic modifications can be obtained at higher resolution level, thus facilitating the interpretation of physiological process and the regulation mechanism under HS in mammals.

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