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Regulatory Mechanism and Application of lncRNAs in Poultry

Zhuanjian Li, Tuanhui Ren, Wenyi Li and Ruili Han

Abstract

Long noncoding RNA (lncRNAs) are transcripts greater than 200 nt in length with decreased coding potential and are widespread in all types of biological organisms. lncRNAs can interact with protein, DNA and RNA, respectively, which may participate in the multilevel regulation of transcriptional, post-transcriptional and epigenetic modifications. It is well known that lncRNA, which length is single-stranded non-coding RNA molecule, plays crucial roles in animal growth, development, cell proliferation and differentiation, and other life activities. In this research, we review the regulation mechanism and current research status of lncRNAs in chicken economic traits and disease, which would contribute to further understanding the regulatory mechanisms and application of lncRNAs in poultry.

Keywords: chicken, long noncoding RNAs, economic traits, regulation mechanism

1. Introduction

In the past half century, poultry industry has made great progress with the research of poultry genetic improvement and feed nutrition. Poultry industry is the fastest growing industry in animal husbandry, and it is also the industry with the highest degree of scale, intensivism and the most complete industrial chain, which plays an important role in the development of the whole animal husbandry economy. Over the past 40 years, the rapid development of poultry breeding, feed and farming has contributed to unprecedented growth in global poultry production and productivity. Poultry production rose from 15 million tonnes in 1970 to 95 million tonnes in 2010, making it the second largest consumer of meat after pork, with egg production rising from 20 million tonnes to 68 million tonnes. There is no doubt that world poultry consumption will continue to rise in the future as the world population increases from nearly 7 billion in 2010 to 7.5 billion in 2020. According to the forecast, by 2020, the world poultry meat production will reach 122.5 million tonnes, egg production will reach 72 million tonnes. Global poultry consumption will grow by 2.5% a year by 2030, and developing countries by 3.4%, far outpacing other meat consumption. However, with the gradual improvement of people's living standards, the demand of consumers for meat and eggs no longer stays on the quantity, and puts forward higher requirements for the sense and flavor of meat and eggs. At present, people expect the prominent contradiction between the improvement of meat and egg quality and the decline of meat and egg quality, which has become a practical problem to be solved urgently in front of the broad masses of poultry breeders. Therefore, the research on egg and meat quality has

become the focus of breeding workers in poultry industry, and the research on meat and egg quality has become one of the hotspots in animal science research.

In recent years, geneticists and breeders have carried out breeding of new poultry varieties (lines) through modern biotechnology, such as molecular breeding and transgenic, focusing on the selection of poultry growth speed and meat and egg quality traits. To some extent, the performance of poultry is improved. However, for a biological trait, it is not only controlled by DNA level genes, but also regulated by mRNA level before and after transcription, and this level of regulation is more comprehensive, systematic and accurate. Long non-coding RNA (lncRNAs) plays an important role in regulating gene expression at the transcriptional level [1–5]. It is traditionally believed that lncRNA does not have the ability to encode proteins. The length of transcripts of RNA is longer than that of 200 nt, which exists widely in a variety of organisms [6]. lncRNA is involved in many levels of regulation such as epigenetic modification [7, 8], transcription and post-transcription [3–5]. But in recent years some studies have found that a small amount of lncRNAs can encode peptides [9–14]. These studies suggest that the coding capabilities of lncRNAs are far more complex than previously thought and need to be further studied and refined.

At present, lncRNA has been found to play a key role in many life processes, such as cell differentiation and proliferation [15, 16], growth and development [17], organogenesis [18], immune response and tumorigenesis [10, 19]. Its discovery opens a new chapter for human understanding of non-coding RNA, and provide a new way of gene regulation in animal cells, as well as complements the more rapid and effective regulation of target mRNA molecules at the level of RNA. Anyway, lncRNA identification and functional annotation provide a new perspective for us to study the molecular mechanism of the formation of important economic traits in poultry.

2. Overview of lncRNA

ENCODE's research shows that about 80% of human genome sequences can be transcribed, while less than 2% of the human genome is used for protein translation, and most of the remaining transcripts are non-coding RNA (ncRNA) [20]. The central principle of molecular biology is that genetic information is transcribed from DNA to RNA, and then translated into proteins by RNA [21]. However, transcriptome sequencing analysis shows that non-coding RNA (ncRNA) is not translated into protein, but through a variety of regulatory mechanisms to change gene expression, such as RNA interference or overexpression can affect gene transcription or translation. According to the fragment size, ncRNA can be classified as short sequence ncRNAs and long sequence ncRNAs [22, 23]. Long non-coding RNA (lncRNA) is generally defined as a class of weak or non-protein coding potential, low species conservation, the length of transcripts longer than 200 nt RNA molecules, widely exist in a variety of organisms [6]. Compared with the widely reported miRNA, lncRNA in small ncRNAs, the functional mechanism analysis is relatively less. Compared with protein-coding genes, lncRNAs has complex species and mechanism of action, lower expression of lncRNAs, space-time and tissue-specific, and low sequence conservation in species. According to different forms, lncRNAs can be divided into several types. lncRNAs has PolyA tail and no PolyA tail. The position in the genome relative to the protein-coding gene can be divided into five types: sense type (the transcript overlaps with the exon of the coding ability gene) and antisense type (the transcript originates from the reversal of the protein-coding gene, antisense), intron type (transcripts derived from intron, intronic) of protein-coding genes, Intergenic noncoding RNA (intronic) and bidirectional (bidirectional) (**Figure 1**) [23].

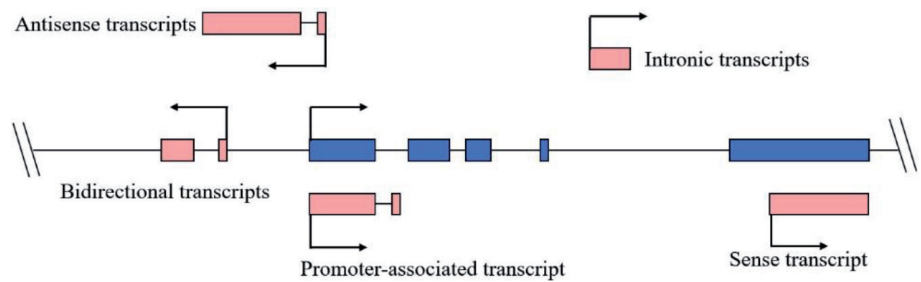


Figure 1.
Classification of lncRNAs based on their genomic regions. Blue and orange are exons encoding RNA and non-coding RNA, respectively [23].

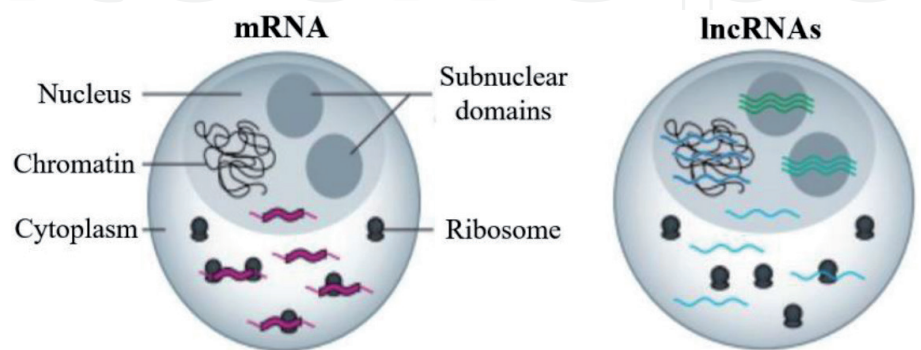


Figure 2.
Subcellular localization of lncRNAs [27, 28].

Most of the annotated lncRNAs are transcribed by polymerase II, so they can be capped, polyadenylated and cut like mRNA [2, 24]. Intergenic noncoding RNA (lincRNA) is transcribed in the intergenic region of the genome, while the natural antisense transcript, NATs is derived from a relative chain of protein-encoded genes. By far, lincRNA is the most abundant category of lncRNAs. Compared with mRNA, lncRNA may contain fewer exons than mRNA and usually have weak splicing and polyadenylation signals [25]. Similar to proteins, the function of lncRNA depends on the cell compartment in which they are located, and its localization information can provide some reference for predicting its function [26]. lncRNAs can be divided into cytoplasm and nuclear lncRNA, according to their cellular localization. Some lncRNAs are located in the nucleus and also exist in the cytoplasm. The different localization of lncRNA may play a different regulatory mechanism. lncRNAs, which exists in the cytoplasm, can bind through the interaction between the double strands of RNA, and then participate in the regulation of mRNA expression and maintain its stability. For example, Linc-MD1 is mainly expressed in the cytoplasm as ceRNA regulates the differentiation of skeletal muscle [17]. If lncRNA is located in the nucleus, it may have the ability to directly bind the target gene to inhibit or activate the target gene expression, and may also be involved in the recruitment of transcription factors or histone modified complex to mediate the regulation of gene expression. For Xist localizes the inactivated X chromosome in the nucleus and affects gene transcription by modifying the chromatin structure (**Figure 2**) [27, 28].

3. Biological functions of lncRNAs

Transcriptional, posttranscriptional and epigenetic modifications of lncRNAs in different cellular environments and biological processes have

regulatory effects on gene expression [24]. A large number of studies have shown that the mechanism of ncRNA, miRNA is through the complementary combination of RNA-RNA [29]. Compared with miRNAs, lncRNAs have longer sequences and more complex spatial structures, so they have more mechanisms and more information [30]. lncRNAs has many different mechanisms, including molecular decoy, molecular scaffold, molecular signal and molecular guide, which can regulate gene expression by cis-action, trans-action and antisense interference [31]. Although many of the functions and mechanisms of lncRNAs are still unclear, some of the mechanisms of lncRNAs that have been studied earlier have been fully elucidated. lncRNA has been reported to be involved in cell differentiation and proliferation, growth and development, and organ formation, immune response and tumorigenesis and other important regulatory processes [32].

3.1 Regulation of lncRNAs at transcription level

Transcriptional regulation is an important part of eukaryotic gene expression regulation, and it is the most important regulation mode of gene expression. lncRNAs can bind regulatory sequences to form DNA-RNA stable triple complexes to inhibit transcription. For example, the upstream promoter of DHFR gene of human dihydrofolate reductase can transcribe an lncRNA, and the transcribed lncRNA can form an lncRNA-DNA complex through the DNA sequence with the promoter, which can inhibit transcription [33]. The widespread transcription of enhancers and promoters indicates the core role of lncRNA in the regulation of gene transcription, and the way lncRNAs regulates transcription exists in a variety of mechanisms [34].

Proximal promoters can be transcribed into transcriptional programs with the function of recruiting RNA binding proteins, such as inhibiting the transcription of cyclin (Dl) in human cell lines [34]. The damage signal of DNA can induce the expression of lncRNA related to Dl gene, and co-regulate the activity of RNA binding protein (TLS). TLS can inhibit the activity of histone acetyltransferase p300 and CREB binding protein so as to inhibit the expression of Dl. Depending on the location, lncRNAs can positively or negatively regulate the expression of adjacent genes. When lncRNA is located near the upstream region of the protein-coding gene, the transcription of lncRNA may affect the binding of the transcript factor to the promoter region of the downstream protein-coding gene, such as the elongation of the transcription of lncRNA SRG1 in yeast, which occupies the downstream SER3 promoter region. Hinders the binding of transcription factors to the SER3 promoter, resulting in SER3 not being transcribed normally [35, 36], lncRNA acts as a coactivator to regulate the activity of transcription factors. In mice, the hyper-conserved distal enhancer of Dlx6 gene transcribes lncRNA Evf2, Evf2 as a coactivator of homologous structural protein DLX2 and forms a complex with DLX2 [22]. lncRNA can also bind directly to transcription factors, promoters or polymerase II of genes, preventing gene promoters from binding with polymerase II to play a regulatory role [36, 37]. lncRNAs regulate transcription through several mechanisms as **Figure 3**.

3.2 Regulation of lncRNAs at post-transcriptional levels

lncRNAs can regulate the post-transcriptional process of mRNA through complementary binding sequences, including the selective variable splicing of mRNA precursors, acting as a sponge to adsorb miRNA, translation regulation, mRNA degradation mediated or maintenance of mRNA stability in **Figure 4** [24, 38].

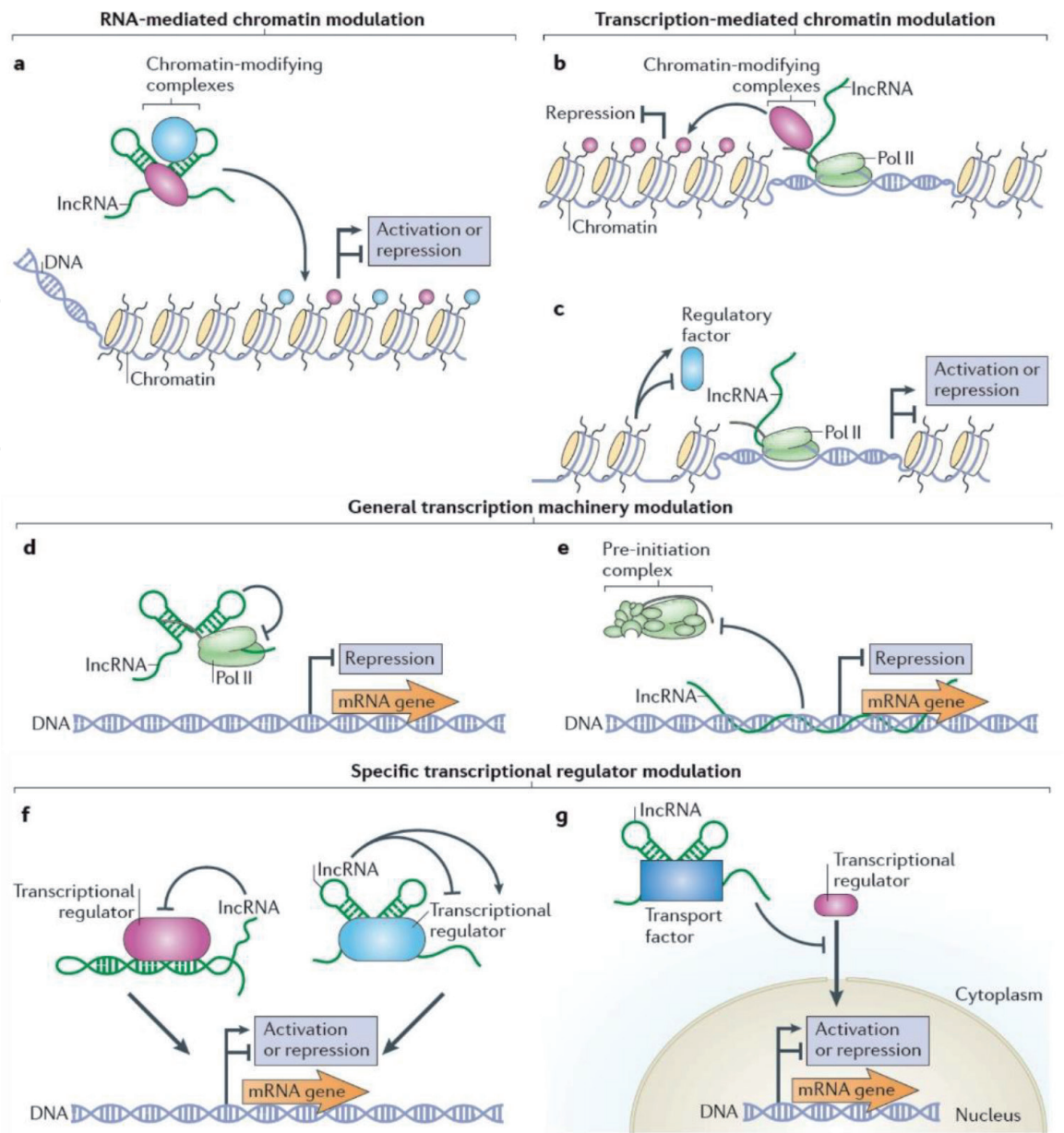


Figure 3. lncRNAs regulate transcription through several mechanisms. (a–c) Long non-coding RNAs (lncRNAs) can modulate chromatin through transcription-independent (part a) and transcription-dependent mechanisms (parts b and c). lncRNAs can modulate both the general transcription machinery (parts d and e) as well as specific regulatory factors (parts f and g). This picture is quoted from [38].

3.2.1 lncRNAs combined with alternative splicing factor to regulate alternative splicing

In previous studies, variable splice of mRNA was mostly reported. For example, the metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is abnormally expressed in cancer, binds SR protein to regulate SR phosphorylation level in normal cells, and then regulate the variable shear of pre-mRNA, MALAT1 can also regulate the distribution of SR in cells, the absence of MALAT1 in cells will lead to the increase of SR protein level, giving priority to the form of dephosphorylation, thus changing the variable splicing mode of pre-mRNA [39]. Antisense lncRNAs can cover mRNA homeotropic elements (cis-elements) through the formation of double strand of RNA, which can directly regulate the variable splice of pre-mRNA. For example, antisense lncRNA Zeb2 (sip1) complements the 5' splicing site of intron 5' in zeb 5'UTR, which is a zinc finger Ebox homeotypic gene, and causes intron retention, which enables Zeb2 to be efficiently expressed and translated [40].

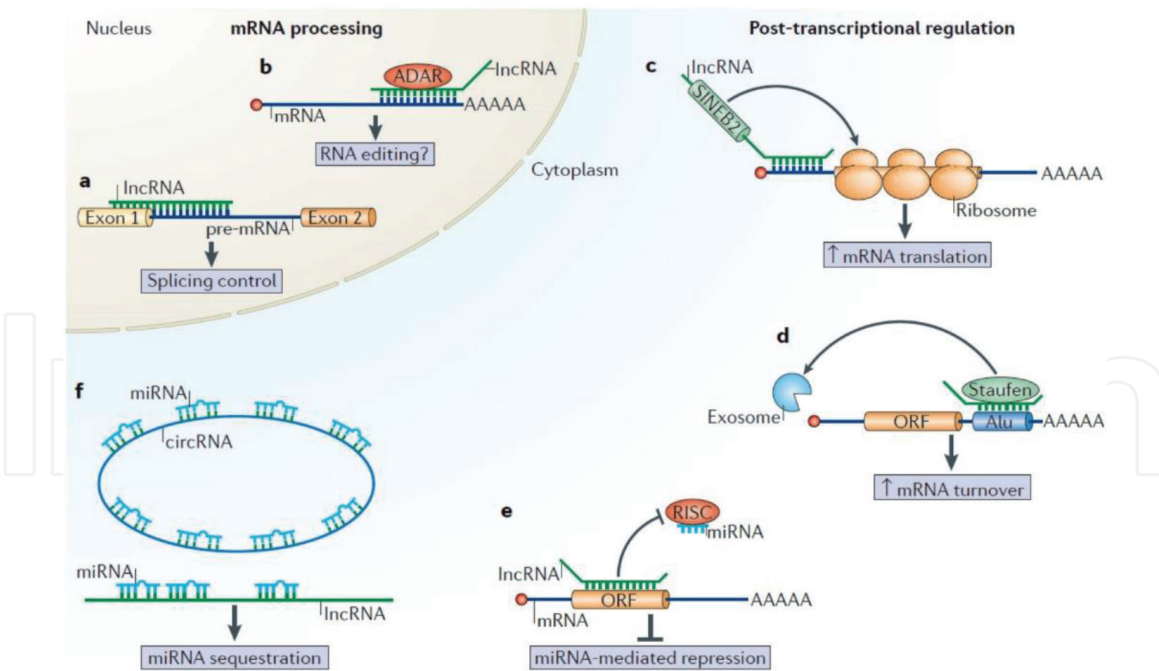


Figure 4. *lncRNAs influence mRNA processing and post-transcriptional regulation. (a and b) Long non-coding RNAs (lncRNAs) can modulate mRNA processing. (c–f) lncRNAs modulate post-transcriptional regulatory events. This picture is quoted from [38].*

3.2.2 lncRNAs participates in the stability of mRNA and regulates translation

Antisense lncRNA can form a protective mechanism of mRNA by binding to 3'UTR sites on mRNA that can be degraded by miRNA. For example, the natural antisense transcripts of beta-amyloid converting enzyme 1 (BACE1) gene, BACE1-AS, can bind to BACE1 mRNA to form a stable RNA double strand, which will block the recognition site of mRNA degradation mediated by miRNA, prevent BACE1 mRNA degradation, and lead to the up-regulation of BACE1 protein product expression [24]. In addition, lncRNAs can regulate the translation of mRNA, when RNA binding protein HuR or Ago2 is absent in cells, the stability of lincRNA-p21 is increased, and lincRNA-p21 binds to target mRNA and inhibits its translation [41].

3.2.3 Complementary binding of lncRNAs and mRNA to mediate their degradation

The abundance of mRNA is an important factor affecting protein yield, which is mainly determined by the degradation rate and transcription quantity. In eukaryotic organisms, there is nonsense-mediated RNA degradation (NMD). RNA-binding protein STAU1 increases protein 1 by binding to NMD factors and recruits it to the 3'UTR of the RNA, which leads to the degradation of the RNA, this is known as the Stau1 mediated mRNA degradation mechanism [42].

3.2.4 lncRNAs act as an adsorption sponge for miRNA

miRNA is an important member of ncRNAs, which does not have a ORF box and has a short sequence of 18–25 nt [38]. For example, lncRNAs are used as molecular decoys for the specific adsorption of miRNA, which indirectly regulates the expression of miRNA target genes. This mode of action is called “sponge effect” of lncRNAs [24]. lncRNAs regulates miRNA by binding to miRNA responsive element MRE, and this competitive binding is mutually regulated. Such as some studies reported that a 3'UTR of lncRNAs contains a certain number of MREs, when the microRNAs are adsorbed by MRE of lncRNAs, they can act indirectly on

the microRNAs through trans or directly on the lncRNAs through cis [43, 44]. In addition, lncRNA can complement the sequence of the target gene and form ceRNA mechanism with miRNA, which can relieve the inhibition of the target gene. In adipocytes, ADNCR can act as an adsorptive sponge of miRNA-204, and then release the inhibition of miRNA-204 on its target gene SIRT1. The expression of SIRT1 increases and binds to the transcription co-inhibitors SMRT and NCoR, which led to the inhibition of adipogenesis [45].

3.3 Regulation mechanism of lncRNAs on epigenetics

3.3.1 lncRNAs and DNA methylation

In mammals, DNA methylation is a key form of epigenetic modification [46]. For example, X chromosome inactivated transcription (Xist) is the earliest discovered lncRNA. Its expression makes a large number of histone methylated, thus causing the X chromosome inactivation. In mammals, lncRNA deactivation can mediate X chromosome inactivation, which is also regulated by other lncRNAs, Tsix and Jpx encoded in the X chromosome inactivation center. Jpx can activate deactivation via cis or trans. Tsix changes the chromatin state through the action of cis, interferes with transcripts and regulates DNA methylation, resulting in silencing of Xist expression [24].

3.3.2 lncRNAs and histone modification

lncRNAs recruit DNA sequences or protein complexes related to chromatin modification to their adjacent genes and regulate adjacent genes via cis or trans. For example, lncRNA HOTMR can promote the trimethylation on lysine 27 of histone 3 by recruiting multiple comb inhibiting complex (PRC2), thereby inhibiting gene expression [47]. It is reported that lncRNA HOTAIR, which can act as a skeleton molecule, participates in epigenetic regulation by changing chromatin state. The 5' and 3' of HOTAIR can bind to different histone modified complexes respectively. Its 5' can bind to PRC2 protein complex, and its 3' can bind to CoREST/LSD1/REST protein complex. The 5' of HOTAIR has demethylation function, while the 3' has the function of promoting methylation, which regulates different methylation forms of different target genome proteins and then regulates gene expression [48]. Overexpression of lncRNA HOTAIR can reposition the PRC2 complex in the whole genome, induce silencing of specific tumor suppressor genes, and promote metastasis of breast cancer [49]. lncRNA ANRIL, which has similar function to HOTAIR, can change chromatin state by recruiting PRC2 and PRC1 complex, decrease the expression of cyclin dependent kinase inhibitor 2A (CDKN2A) gene, enabling cancer cells to proliferate indefinitely [50].

3.3.3 lncRNAs and chromatin remodeling

Chromatin remodeling is mainly involved in the changes of nucleosome translocation, recombination and decreased stability. Nucleosome translocation and recombination can change the affinity between DNA regulatory sequence and transcription factors, and then affect the expression of related genes. lncRNAs can change chromatin structure through epigenetic approach, and can also affect chromatin conformation through direct binding [51–53].

In addition, lncRNAs can also participate in genomic imprinting. Interference with lncRNAs can alter chromatin condensation, suggesting that their binding may make the chromatin spatial structure more stable or facilitate chromatin/nonhistone binding [54]. So there are many other mechanisms in lncRNA that need further analysis.

4. The study of antisense long noncoding RNAs

Natural antisense transcripts, Nats, also called natural antisense RNA, is a complementary transcription product of sense RNA produced in natural organisms, which is transcribed by antisense strand in DNA double strand and processed by RNA polymerase II (RNA polymerase II) [55–59]. NATs can regulate the expression of mRNA and protein at the transcriptional and post-transcriptional levels [60]. The researchers classified NATs transcriptional initiation sites (TSS) as cis NATs (cis-form NATs) and trans NATs (trans-formNATs) [61]. Cis-NATs means that the TSS position of NATs is the same as that of sense chain mRNA, but it is located on antisense chain, and the nucleic acid sequence is completely reverse complementary to the sense chain gene mRNA [62] (**Figure 5a**). Trans-NATs means that NATs TSS is still antisense, corresponding to different exons or introns of the sense chain gene (different from the TSS position of the sense chain mRNA), but the nucleic acid sequence complements partially or completely with the sense chain gene mRNA (**Figure 5a**) [63]. In addition, the transcripts of sense and antisense chains can be divided into bidirectional transcripts and unidirectional transcripts [64]. The transcripts of sense and antisense strands can be divided into bidirectional transcripts and unidirectional transcripts according to whether the transcripts of the sense and antisense strands are derived from the same TSS in different transcriptional directions. In addition, we can refer to the relative position of NATs and sense chain gene mRNA to classify them. (1) Head-to-head overlap (head-head): partial or total reverse complementation of the 5' regions (5'UTR) of sense and antisense transcripts; (2) tail-to-tail overlap (tail-tail): That is, the three untranslated regions

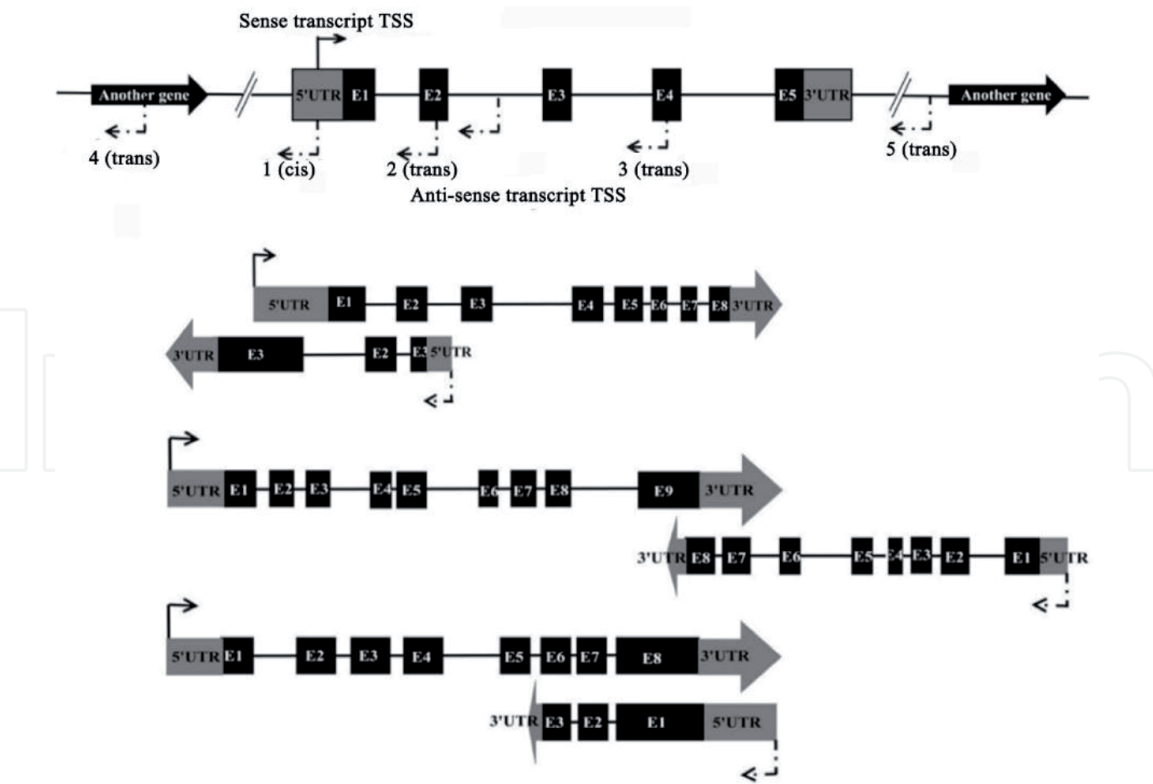


Figure 5. The classification of NATs. ■ is denoted as an exon, ➡ denotes transcripts of other genes adjacent to the gene, ↑ is expressed as a transcript of the sense chain. TSS, ↯ is the TSS of antisense strand transcript. (a) The transcriptional initiation sites are different according to the antisense chain transcripts. Among them, 1 is cis-NATs, 2–5 is the trans-NATs transcribed by TSS in different position; (b) head-to-head overlap (head-head), drawing with DHRS4, AS1DHRS4 as template [59]; (c) tail-to-tail overlap (tail-tail): Drawing with WDR83, DHPS as template [60]; (d) complete overlap, drawing with GHR-S, GHR-AS as template [61].

of sense and antisense chain transcripts, partially or completely reverse complementary; (3) complete overlap: that is, the sequences of the two transcripts are completely reverse complementary (**Figure 5b–d**).

Most of the NATs discovered so far are long-chain non-coding RNAs, which play a variety of important biological functions by regulating the expression of the corresponding justice chain protein-coding genes and has attracted more and more attention. Current studies have shown that there are three main mechanisms of NATs: first, antisense RNA and sense RNA form double-stranded RNA, through complementary regions of the sequence to regulate the stability and translation of RNA; For example, human Wrap53 regulates p53 in this way and plays a role in tumorigenesis [65]. Second, antisense RNA regulates sense RNA through epigenetic modifications, thereby participating in biological processes. For example, p15AS can regulate the expression of p15 gene and promote the proliferation of mouse embryonic stem cells by changing the methylation status of H3K4 (Histone 3 methylated at lysine 4) and H3K9 (Histone 3 methylated at lysine 9) in the promoter region of p15 gene [66]. Similarly, mouse BDNF-AS affects the proliferation of nerve cells and the development of nervous system by changing the modified state of H3K27me3 (the trimethylation on lysine 27 of histone 3) in the promoter region of BDNF [67]. Thirdly, antisense RNA protects and transports sense RNA, such as PTENpg1 antisense RNA, which transports PTENpg1 from the nucleus to the outside of the nucleus by forming a double strand with the mRNA of PTENpg1, thus avoiding the degradation of PTENpg1 and making PTENpg1 play a further role in the fine cytoplasm [68].

5. Regulation of muscle development by lncRNAs in poultry

The muscle content of animals is mainly determined by the total number of muscle fibers, muscle fiber length and muscle fiber size. Muscle content is also affected by different muscle fiber types [69, 70]. In general, chickens and mammals do not increase the amount of muscle fibers around a week before and after birth [71]. The formation of animal muscles depends mainly on the differentiation and proliferation of muscle cells in embryonic, while the growth of muscles is mainly dependent on the hypertrophy of pre-formed muscle cells in postnatal. In the study of chicken muscle development, the first systematic identification of lncRNAs using RNA-Seq to sample the transcriptome, the results identified 281 new intergenic lncRNAs in the chicken genome, these lncRNAs in general are less conserved than coding genes [72].

In recent years, there are some reports about the lncRNA regulated muscle development in chickens [73]. lncRNA pouMU1 was most abundant in the leg muscle and breast muscle tissue, and low or no expression in other tissues. The relative 1 day pouMU1 expression levels were significantly higher than the 6 and 16 weeks in breast muscle. Two mutations of g. 1198A>G and g. 1238-1239del/insGA combination in pouMU1 showed significant associations with leg muscle fiber width and leg muscle fiber roundness, and highly significant associations with leg muscle fiber girth and BW0. These results suggest that the pouMU1 gene may play an important role in early stage muscle development in chickens [32]. lncRNA-Six generated a micropeptide of about 7.26 kDa was found to play an important role in the lncRNA-Six1 cis activity. Based on qPCR, the lncRNA-Six1 and Six1 mRNA were highly expressed in chicken breast muscle. Overexpression of lncRNA-Six1 promoted the mRNA and protein expression level of the Six1 gene, while knockdown of lncRNA-Six1 inhibited Six1 expression. lncRNA-Six1 overexpression promoted cell proliferation and induced cell division. Conversely, its loss of function inhibited

cell proliferation and reduced cell viability. Overexpression or knockdown of Six1 promoted or inhibited, respectively, the expression levels of muscle-growth-related genes, such as MYOG, MYHC, MYOD, IGF1R, and INSR. The results demonstrate that lncRNA-Six1 carries out cis-acting regulation of the protein-encoding Six1 gene, and encodes a micropeptide to activate Six1 gene, thus promoting cell proliferation and being involved in chicken muscle growth [74]. Taken together, these findings will contribute to further understanding the regulatory mechanisms of lncRNAs in chicken muscle development.

6. Regulation of lipid metabolism by lncRNAs in poultry

Abdominal fat is an important carcass trait of chickens. In the last decades, the overemphasis on selection for rapid growth rate leads to excessive fat accumulation in chickens, and excess fat deposition results in reduced feed conversion ratio and carcass yield [75]. The previous report indicated that lncRNAs can regulate adipogenesis and other processes associated with metabolic tissue in cattle and pig [45, 76]. However, little is known about the lncRNAs regulation mechanism during preadipocyte differentiation in the chicken. In recent studies, a total 3095 differentially expressed genes were obtained by pairwise comparison of preadipocytes at different times. The differentially expressed genes were involved in glycerolipid metabolism, and the mTOR signaling, PPAR signaling, and MAPK signaling pathways in chickens [75]. 2193 lncRNA genes were predicted in the chicken liver and adipose tissue by RNA-Seq, among which 1670 were stable expressed in the liver and/or adipose tissue, and which were divided into 177 intragenic and 1493 intergenic lncRNAs located between and within protein-coding genes, respectively. And the study observed similar structural traits between chickens and mammals, have significant synteny conservation but without sequence conservation. In addition, lncDHCR24, a novel lncRNA candidate involved in lipid metabolism, which is very high relevance with the DHCR24 gene that encodes a key enzyme of cholesterol biosynthesis [75]. In a second study, using RNA-seq sequencing, 4698 differentially expressed lncRNAs were obtained by pairwise comparisons of samples collected from preadipocytes at days 0, 2, 4, and 6 of differentiation, and 7 lncRNAs genes were differentially expressed in the entire differentiation process intramuscular preadipocytes, implying their importance in the intramuscular preadipocytes in Jinghai Yellow chicken [77].

7. Regulation of poultry reproduction by lncRNAs (sperm, egg production)

In the study of human disease and model animal reproduction, lncRNA plays an indispensable role is involved in early embryonic germ cell formation, early embryo implantation and development, and related the regulation of hormones [78–80]. lncLER gene is significantly highly expression in the liver tissue of Lushi chicken. The expression of lncLER was upregulated in the chicken liver and liver primary cells of chicken embryos by the estrogen treatment. The study indicated that the expression of lncLER is regulated by estrogen, and lncLER may play an important role in liver fat metabolism and yolk precursor synthesis in Lushi chicken [81]. Sperm motility is the most important indicator in evaluating roosters' fecundity. lncRNA play epigenetic roles in reproduction. In previous study, RNA sequencing was employed to analysis the testis transcriptome of 3 Beijing-you roosters of high sperm motility and 3 with low sperm motility. In total, 2597 lncRNAs were identified in the chicken testis, including 124 differentially

expressed lncRNAs. In addition, 544 mRNAs of differential expression were founded in the study. LOC428510 is the target gene of lncRNA MSTRG. 4081 by predict of software. LOC428510 and DNAH5 gene have similar structure, DNAH5 is an important motor protein of sperm movement, and mutation of DNAH5 may cause the sperm immobility. Meanwhile, the LOC428510 and lncRNA MSTRG. 4081 have co-expression characteristics by qPCR. These results suggested that MSTRG. 4081 and LOC428510 may be involved in the regulation of sperm motility in roosters [82]. MHM is a Z sex chromosome-linked locus adjacent to the DMRT1 gene, is methylated and transcriptionally silent in male chicken cells, but is hypomethylated and transcribed into a lncRNA in female chicken cells. In males, MHM mis-expression impairs gonadal expression of the testis DMRT1 gene and causes an increase in male-biased embryo mortality [83].

8. The role of lncRNAs in disease resistance breeding of poultry

Most evidence suggest that lncRNA plays a key role in the human disease, such as growth and metastasis of tumor cell [84]. There are also a few reports on lncRNA in disease research of poultry.

Gallid herpesvirus 2 (GaHV-2) is an oncogenic alpha-herpesvirus of chickens, previously known as Marek's disease virus (MDV-1) in chicken [85]. The RNA-specific adenosine deaminase (ADAR1) belongs to the ADAR family of proteins, which play a key role in innate immunity to viral infections. The ERL lncRNA, a new viral lncRNA, which is expressed during all phases of infection, and this lncRNA is a natural anti-sense transcript. This study showed that mdv1-miRM4-5p is the most strongly expressed miRNA of the mdv1-mir-M9-M4 cluster encoded by the anti-sense strand of the ERL lncRNA, promoted the overexpression of ADAR1 by downregulating the suppressor of cytokine signaling 1 [86].

Hyperpigmentation results in aberrant immune cell development in Silky Fowl, while, whether the melanocytes regulated B-cell proliferation in the bursa of Fabricius or not is unclear. The bursa of Fabricius development was relatively slower in Silky Fowl than in White Leghorn. Identified 4848 differentially expressed genes, 326 lncRNAs, and 67 microRNAs by the transcriptome analyses in the bursa of Fabricius of Silky Fowl. The annotation of the predicted targets indicate that differentially expressed lncRNAs were mainly associated with cell proliferation pathways, such as WNT, MAPK, JAK-STAT, and Notch signaling pathways. The lncRNAs and microRNAs can regulate the JAK2, STAT3, and IL-15 genes by predict in chicken. Thus, B-cell development in the bursa of Fabricius of Silky Fowl might be regulated and affected by lncRNA [87]. Avian leukosis virus (ALV) can causes substantial economic losses from increased mortality and decreased performance of chicken. Avian leukosis virus subgroup J (ALV-J) is harm the largest in the six subgroups of ALVs. Specific Pathogen-Free female chickens were infected with ALV-J or maintained as non-injected controls. Then, spleen samples were collected at 40 days and sequenced. There are differentially expressed 17 lncRNAs, 7 miRNAs and 864 genes has been identified in infected and non-infected birds. The mRNA with miRNA, lncRNA and virus genes identified key elements within the complex networks utilized during ALV response by co-expression network analysis [88]. In a second study, using high throughput transcriptome sequencing of HD11 and CEF cells infected with ALV-J, in total of 4804 novel lncRNAs were identified, including intergenic lncRNAs, antisense lncRNAs and intron lncRNAs. The results suggested that NONGGAT001975.2, NONGGAT005832.2 and NONGGAT009792.2 may be associated with immune response regulation by qRT-PCR analyses in vivo, and could function as novel biomarkers for ALV-J infection [89]. Se, as an essential micronutrient, plays a pivotal

role in various biological activities and Se deficiency induces disease of nutritional muscular dystrophy and exudative diathesis in chickens. A recent report showed that the increased expressions of IL-1 β , IL-6, IL-8, and CCL4, and the decreased expressions of SCD, PPAR α , PPAR β and PPAR γ by silencing of ALDBGALG 0000005049 in chicken myoblasts. In addition, increased expressions of IL-1 β , IL-6, IL-8, and CCL4 and inflammatory cell infiltration in microstructure of chicken muscles treated with Se deficiency were observed. This study revealed that downregulation of ALDBGALG0000005049 caused inflammation by regulating stearyl-CoA desaturase in chicken muscle resulted from Se deficiency [90].

9. Study on antisense lncRNAs in poultry

Numerous studies have demonstrated that about 20% of the genes are capable of producing antisense transcripts (NATs) in the human cell transcriptome, and more than 70% of the transcription units in the mouse genome may produce NATs [25, 91]. Compared with human and mouse, the research of NATs is relatively lagging in chicken.

The programmed cell death 2 (Pcd2) gene was assessed as a member of a highly conserved synteny on mouse chromosome 17. The identified Tbp-alternative Pcd2-antisense transcripts maybe to play some regulatory role in gene expression, compared to the protein-coding function of the Tbp mRNA. The antisense transcripts are mostly localized in the nucleus and transcribed at a level sufficient to interfere with the transcription of the Pcd2 gene. The conservation of Pcd2/Tbp sense/antisense overlap in the mouse and chicken also point out their biological relevance. Moreover, the results suggest that at least some of the cDNAs identified in the sequencing projects labeled as noncoding RNAs are in fact incomplete alternative cDNAs of neighboring protein-coding genes. The conservation of alternative transcription of the Pcd2 gene have different the biological importance in mouse, human and chicken [92]. Growth hormone receptor (GHR) play pivotal roles in human and animal growth. The mutation of GHR gene could lead to human laron type dwarfism and sex-linked dwarf chicken. A previous study identified an endogenously expressed long non-coding NAT, GHR-AS, which overlapped with the GHR mRNA (GHR-S) by a tail to tail manner. qRT-PCR analyses indicated that GHR-AS were highly expressed in chicken liver, and displayed increasing with the development of chicken from E10 to 3 w of age. Interfering GHR-AS could lead to GHR-S decreasing, accompanied with increasing of the H3K9me2, an inactive gene indicator, in the GHR-S promoter regions in LMH cells. RNase A protection experiment showed that GHR-AS and GHR-S can form double strand RNAs at the last exon of GHR gene in vivo and in vitro. Meanwhile, the expression levels of GHR-S and GHR-AS can be affected by DNA methylation. Compared the dwarfs with the normal chicken, the negative correlation trends were indicated between the GHR-S promoter methylation status and the GHR-AS expression levels. These results showed that GHR gene possessed NAT, and the results presented here further highlight the fine and complicated regulating mechanism of GHR gene in chicken development [57].

10. Conclusions

With the development of life sciences, the lower cost of RNA-Seq has become more and more popular in ncRNA research. In recent years, a large number of RNA-seqs have also been performed in livestock animals. The researcher used RNA-Seq data facilitates the analysis of the regulatory mechanisms of lncRNA in specific tissues, organs and cells. The study of lncRNAs fills the gap in the molecular

mechanism of life activities in organisms. lncRNA can play the functions of signal molecules, scaffold molecules, decoy molecules and guiding molecules. And lncRNAs participate in multiple levels regulation of epigenetic, transcriptional and post-transcriptional modifications.

At the present, there are few reports on lncRNA in chicken breeding. Compared with experimental animals, the lncRNA research of chicken are relatively backward, and any reports mainly focuses on the discovery and characteristic analysis of lncRNA in chickens. lncRNAs becomes one of research focuses in life sciences field and increasing lncRNAs has identified in human and mouse. However, there are many problems with the study of lncRNA related to poultry. lncRNA is not highly conserved among species compared with miRNA and mRNA, and it is difficult to learn from each other in species, there are few tools for studying advanced structures, and it is difficult to analyze the real-time dynamic changes of lncRNA in cells. In order to improve economic traits and accelerate breeding of chicken, the researchers could through the establishment of RNA libraries, the use of high-throughput sequencing technology and bioinformatics analysis methods to predict the sequence and structural characteristics of lncRNA, found many new lncRNAs; the candidate lncRNA was verified and determine its expression difference by Northern Blot and PCR technology. The functions of lncRNA were studied by in situ hybridization, overexpression, interference, qPCR, and in vivo experiments; and RNA pull down, RNA-RIP, ChIRP-seq and dual luciferase reporter systems were used to the mechanism of lncRNA. Optimization of these techniques can accelerate the study of chicken-related lncRNAs and dig out more functions. However, how to systematically and specifically study the function of lncRNAs in important economic traits of poultry, is a problem that researchers need to solve in recent years.

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Conflict of interest

The authors declare that they have no conflict of interest.

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