Chapter 7

# An Overall View of the Regulation of Hepatic Lipid Metabolism in Chicken Revealed by New-Generation Sequencing

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**Abstract**

In chickens, more than 90% of the *de novo* synthesis of fatty acids occurs in the liver; therefore, the liver metabolism has a critical effect on chicken development and egg laying performance. Although the physiological processes of liver lipid metabolism have been studied extensively in chicken, the underlying mechanisms and the roles of noncoding RNAs in the process remain ambiguous. Recently, we investigated the regulatory mechanism of hepatic lipid in chicken by new generation sequencing technology. Our results uncovered many genes, which play crucial roles in mammal lipid metabolism process, might have different biological functions in chicken. Some other genes which might play essential roles in chicken hepatic lipid metabolism were found. In addition, the physiological processes of hepatic lipid metabolism in chicken are regulated by noncoding RNAs, such as miRNAs and lncRNAs.

**Keywords:** lipid metabolism, new generation sequencing, miRNA, lncRNA, chicken

## 1. Introduction

The molecular regulatory mechanisms of the hepatic lipids in domestic chicken had been largely established after being extensively studied (see reviews [1–5]). In recent years, however, with research advances in genomics, epigenomics and related fields such as systematic biology and bioinformatics, and also with the development of advanced techniques such as new generation sequencing and computation programming, our knowledge about gene regulation and interactions has been considerably widened. As a result, the following questions about synthesis, formation and transport of yolk precursors in liver of laying hens remains to be fully elucidated.

First, what enzymes actually catalyze lipids synthesis in laying hen liver? In comparison with mammals, liver is the major site of lipid biosynthesis in the chicken [6–8]. Though most of the chicken genes and their products involved in the hepatic lipid metabolism are highly similar to those in mammals including human, their specialized tasks were considerably different [9–12]. For instance, a recent study on lysophosphatidylglycerol acyltransferase 1 (LPGAT1) indicated that LPGAT1 has a role in lipid synthesis in mice [13]. Our studies revealed, however, LPGAT1 has no significant effect on lipid synthesis with estrogen induction in chicken. In addition, some of the genes related to lipid metabolism had been lost in chicken during evolutionary process [14]. Therefore, the range of genes and their products involved in the hepatic lipid metabolism in laying hen remain to be fully elucidated [8].

Second, how are the very low density lipoprotein (VLDL) particles assembled and secreted in the liver of chicken? In mammals, it was well documented that microsomal triglyceride transfer protein (MTTP) assists in lipoprotein assembly to form very low density lipoprotein [13, 15–19]. The formation of VLDL particles in avian species is tightly regulated by estrogen. However, recent study has proved that upregulation of *MTTP* in the liver is not required for the increased VLDL assembly during egg production in the chicken [20]. Our study on *MTTP* expression levels in livers between pre-laying and egg-laying hens also showed no difference though that the liver *ApoB* and *ApoVLDL II* expression levels and plasma VLDL level were elevated dramatically in laying hen.

Third, how does the estrogen induce lipid synthesis and transfer processes in liver of laying hen regulated by noncoding RNA? It is now well appreciated that a large portion of the eukaryotic genome gives rise to non-protein-coding RNAs (ncRNAs) of various sizes ranging from ∼20 nucleotides to ∼100 kb, which are predicted to play essential roles in a variety of biological processes (see reviews [21–24]). Among ncRNAs, microRNAs (miRNAs) and long ncRNAs (lncRNAs) attracted more researches' attention.

MiRNAs are short, being composed of only 18–25 nucleotides (nt) single-stranded RNAs, which was first described in 1993 [25]. Since then, the view of gene expression regulation has been dramatically altered. MiRNAs are reported to regulate gene expression at the posttranscriptional level through RNA interference (RNAi) pathways [26]. In general, miRNAs interact with mRNAs to perform their functions. It has been argued that one miRNAs can regulate the expression of hundreds of mRNAs, while the expression of one mRNA could be regulated simultaneously by hundreds of miRNAs [27]. In other words, miRNAs can play critical roles through constructing networks of sophisticated regulatory systems in organisms [28]. Currently, many varieties of miRNAs are widely reported in plants, animals and even microbes. Alterations of specific miRNA levels have significant correlation with changes of physiological or pathological functions of divergent origin.

LncRNAs are RNA polymerase II (RNAPII) transcripts that are longer than 200 nucleotides [29, 30], which may regulate protein-coding gene expression at both the transcriptional and posttranscriptional levels. Transcription regulated by lncRNAs could negatively or positively control protein-coding gene expression either in cis or in trans [31]. Posttranscriptional regulation by lncRNAs could also negatively or positively control protein coding gene expression through competing endogenous RNAs, modulating mRNA stability and transla-

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tion by homologous base pairing, or acting as nuclear retention of mRNAs [32]. A growing number of lncRNAs have recently been described, and their functions are been uncovering.

Therefore, the objective of this chapter is going to give an overview of the molecules regulation of hepatic lipid metabolism in chicken, which was based on the studies performed by using the new generation sequencing technology.

## 2. Genes involved in hepatic lipid metabolism in chicken

Liver as the most important metabolic organ where up to 90% of fatty acids are *de novo* synthesized in chicken [33–35]. It was found that the onset of laying in the poultry is preceded by large increase in the plasma-free fatty acids, lipids and phosphoproteins [36]. We used the pre-laying hens (20-week old) and egg-laying hens (30-week old) of Lushi green-shelled-egg chickens as the experiment model, and the most obvious physiological difference between the two stages is laying egg or not. Three pre-laying hens and three egg-laying hens, which were raised in cages under the same environmental conditions with *ad libitum* to food and water, were slaughtered. Liver tissues were harvested immediately and the RNA from the liver samples was extracted. The new generation sequencing technology was used to establish the gene expression profile [37]. Bioinformatic analysis methods were used to explore the genes involved in hepatic lipid metabolism, and uncover the regulatory mechanism of hepatic lipid metabolism in chicken.

In our research results, compared to pre-laying hen, there were 960 significant differentially expressed (SDE) genes obtained in the liver of egg-laying hen [37]. Among those SDE genes, many ones were enriched in lipid metabolism pathways (**Figure 1**).

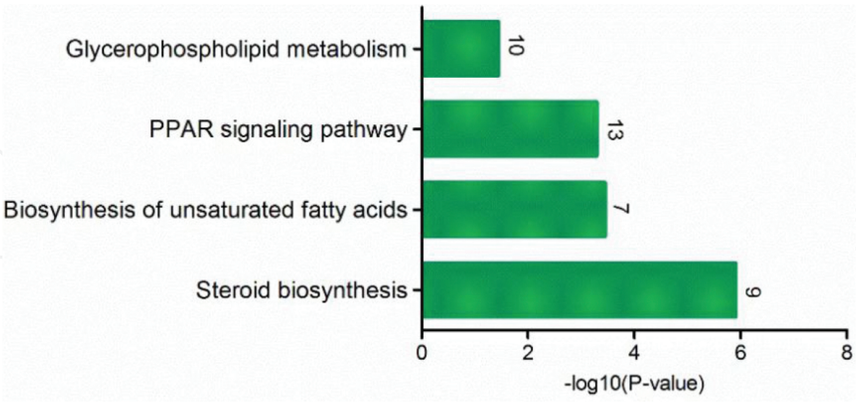


**Figure 1.** The SDE genes significantly enriched in lipid metabolism pathways. Note: The number on each bar means the number of genes enriched in the pathway.

For example, stearoyl-CoA desaturase 1 (SCD-1) is a rate limiting enzyme of monounsaturated fatty acid synthesis in liver and upregulated in egg-laying hens compared with pre-laying hens. Bioinformatic analysis showed it was enriched in the lipogenesis of the peroxisomepro-

liferator-activated receptor (*PPAR*) signaling pathway, and the mRNA expression and activity of *SCD-1* have been shown to be triggered by insulin to promote fat synthesis [38]. Interestingly, a very recent study demonstrated that B-cell translocation gene 1 (*BTG1*) overexpression inhibited the expression of *SCD-1* gene and altered hepatic lipid metabolism by decreased triglyceride accumulation in human [39]. However, our data showed that *BTG1* expression level also significantly increased when the *SCD-1* gene expression level elevated in egg-laying hens. It suggests that expression of *SCD-1* gene is regulated in different ways in chicken. The *FABP1* and *FABP3*, which are involved in hepatic fatty acid oxidation [40, 41], intracellular fatty acid transport [42], storage and export, as well as in cholesterol and phospholipid metabolism [43–45], were both significantly upregulated in the liver of egg-laying hens compared with pre-laying hens. They may promote lipid metabolism through the PPAR signaling pathway to meet the requirements of laying eggs. Some transcriptional factors such as sterol regulatory element binding protein (*SREBP-1)* and fatty acid synthase (*FASN*) genes were found to be elevated coordinately in egg-laying chicken liver that could synthesize fatty acids *de novo* [46]. Meanwhile, some novel genes and alternative splicing isoforms were also found to be differentially expressed and predicted to be relevant with lipid associated processes [37].

In the *de novo* fatty acids synthesis process, some key genes reported to be important in regulating lipid metabolism in mammals, but do not play the same roles in chicken (**Figure 2**). It is well documented that the triacylglycerol (TG) is postulated to synthesize through two biosynthetic pathways in liver. One is called glycerophosphate pathway, the other is monoacylglycerol pathway [47]. In the glycerophosphate pathway, TG is synthesized from the small precursor molecule glycerol-3-phosphate (G3P) and through the precursor phosphatidic acid (PA). The sequential reactions of acyl-CoA: G3P acyltransferase (GPAT) and acyl-CoA: 1-acyl-G3P acyltransferase (AGPAT) are involved in the incorporation of fatty acids into the glycerol backbone of phospholipids [47]. Glycerol-3-phosphate acyltransferase mitochondrial (GPAM) is an enzyme that plays a central role in *de novo* lipogenesis. The diacylglycerols (DG) is generated by PA dephosphorylation [48], and this process can be influenced by lipins [48, 49], which define a family of Mg2+-dependent PA3 phosphatase enzymes with key roles in lipid metabolism [50]. Lipins have different expression patterns in different species, only one lipin in fungi, flies and worms [51], and three lipins including lipin1, 2 and 3 in mammals [52]. The DG can also be synthesized from monoacylglycerol (MG) catalyzed by Acyl-CoA:monoacylglycerol acyltransferase (MOGAT) family including MOGT1, MOGT2 and MOGT3 in mammals. In addition, LPGAT1 involves in triacylglycerol synthesis and secretion in liver [53] and promotes hepatic lipogenesis in mice [54]. In our study, compared to pre-laying hens, the expression levels *GPAM, AGPAT2, AGPAT3, lipin1* and *lipin2* genes were significantly upregulated in egg-laying hens. It suggested that these enzymes may play key roles in TG biosynthesis in the liver of chicken. However, some of the enzyme genes such as *GPAT2, AGPAT4, AGPAT5* and *AGPAT6* showed no changes in their expression levels, and some genes such as *AGPAT9, MOGAT1* and *LPGAT1* even exhibited down-regulated expression patterns. The other enzyme family members, which existed in mammals, were not detected in our animal model. Clearly, genes related to specific functions in regulating fatty acid synthesis are significantly different between mammals and avian species.

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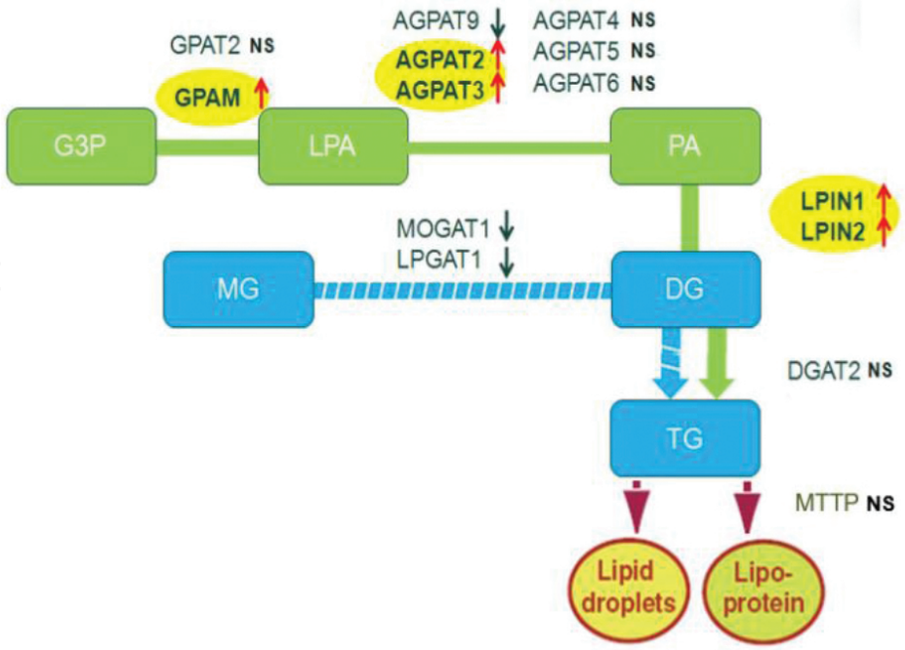


**Figure 2.** Expression pattern of key genes involved in chicken lipid metabolism. Note: NS means gene not significant differentially expressed in our RNA-seq results; up-arrow means gene up-regulated, down-arrow means down-regulated.

The final step in the *de novo* synthesis of TG is catalyzed by acyl-CoA: diacylglycerol acyltransferase (DGAT) enzymes, including DGAT1 and DGAT2 [55]. Overexpression of human *DGAT1* in McA-RH7777 cells can result in increasing the synthesis, accumulation and secretion of TG and VLDL [56]. Due to majority of the TG destined for secretion by liver is synthesized by *DGAT2* [57], expression of *DGAT2* in McA-RH7777 cells is positively related with the secretion of TG and apoB [56, 57]. However, the *DGAT1* gene was not expressed in chicken liver, and the expression level of *DGAT2* was not changed between the pre- and egg-laying hens. Another member of DGAT family, *SOAT1* (sterol O-acyltransferase 1) even was down-regulated. It implied that there must be some other gene(s) involved in the process. Interestingly, a novel gene designated *DGAT2-like* gene, which possesses essential domains as does *DGAT2*, was identified and found to be significantly upregulated in egg-laying hens. This result suggests that *DGAT2-like* may play the role catalyzing TG formation in the liver of chicken as *DGAT2* does in mammals.

The MTTP assists in lipoprotein assembly to form low density lipoprotein [54, 58–62], and highly related with VLDL assembly and lipoprotein particle secretion [63, 64]. However, a previous study demonstrated that the upregulation of *MTTP* in liver was not required for increasing VLDL assembly during the laying period in chicken [20]. Same to the above result, our study also indicated that the *MTTP* was not significant differentially expressed in the liver of egg-laying hens in comparison to pre-laying hens. It implies that *MTTP–like* does not act the role as it does in mammals. As we expected, a novel gene-designated *MTTP-like*, which contains all the essential domains and motifs as *MTTP* does, was found to be significantly upregulated in egg-laying hens. Estrogen induction studies both *in vivo* and *in vitro* further revealed

that the *MTTP-like* expression was regulated by estrogen in a dose dependent manner in liver of chicken. Although most the current findings appear to be consistent with the conservation of lipid metabolism in chicken and mammal, species-specific differences should be considered when comparing chicken with mammalian systems. The chicken liver transcriptome reported here could greatly broaden our understanding of the regulation and network of gene expression related to liver lipid metabolism in chicken at different physiological stages.

## 3. Regulation of hepatic lipid metabolism by ncRNAs in chicken

Lipid synthesis and transfer are dynamic and complex processes, which can be steered by various regulatory factors. During the egg-laying period, the estrogen level of hens goes up significantly and promotes the liver to synthesize egg yolk precursors. It was reported that estrogen can dramatically stimulate hepatic synthesis of apoB [65] and induce the *de novo* synthesis of the reproduction-specific apolipoprotein and apoVLDL-II in poultry by enhancing the accumulation of the mRNAs [66]. Our findings are consistent with previous reports that apoB and apoVLDL-II were significantly increased in the liver of egg-laying chicken compared with pre-laying hens (**Figure 3**). The increase in expression levels of *apoB, apoVLDL-II* and many other genes are supposed to be induced by estrogen. However, some upregulated genes such as sirtuin isoforms (*Sirt 1-7*) in egg-laying hens seems to be regulated by other factors instead of estrogen, because the expression levels of these genes in chicken liver tended to be decreased when chicken or chicken embryonic hepatic cells were treat with estrogen (unpublished data, related article is under reviewing).

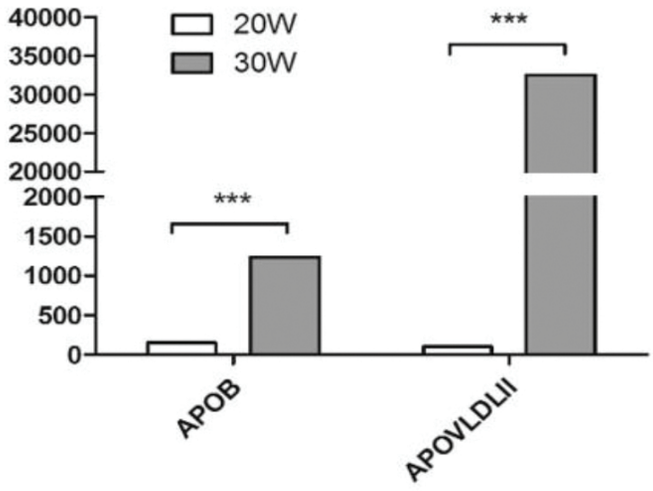


**Figure 3.** The expression of genes in 20- and 30-week-old hens.

MiRNA as a kind of posttranscriptional regulatory factor are reported to serve as important roles in lipid metabolism. It was identified that both gga-miR-148a and miR-122 are highly abundant miRNA in chicken hepatocytes [67] and in porcine liver [68]. A liver-specific miR-122 with high expression abundance in mammalian liver could modulate the hepatic fatty acids

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and cholesterol synthesis through repressing the expression of genes involved in cholesterol biosynthesis [69, 70]. MiR-33 involves in liver metabolism by regulating cholesterol efflux and high density lipoprotein metabolism by targeting the ATP-binding cassette subfamily A member 1 and ATP-binding cassette subfamily G member 1 [71]. These implied that some miRNAs may also involve in regulating chicken hepatic lipid metabolism through binding their target genes.

Considering the obvious difference of physiological activities between pre- and egg-laying stages, the pre- and egg-laying hens experiment model used in RNA-seq research [37] was used to investigate the critical miRNAs that may regulate the lipid metabolism. Bioinformatic analysis methods were used to explore the differentially expressed miRNAs involved in hepatic lipid metabolism and uncover the regulation ways of hepatic lipid metabolism in chicken [72]. Our results showed that majority of the target genes of down-regulated miRNAs significantly enriched in lipid metabolism-related processes, and enzyme activity, iron, vitamin binding molecular function (**Figure 4**). It is consistent with the event that eggs are rich in essential amino acids and fatty acids, as well as of some minerals and vitamins [73]. Our results suggest that the differentially expressed miRNAs may participate in chicken hepatic lipid metabolism through acting with their target genes.

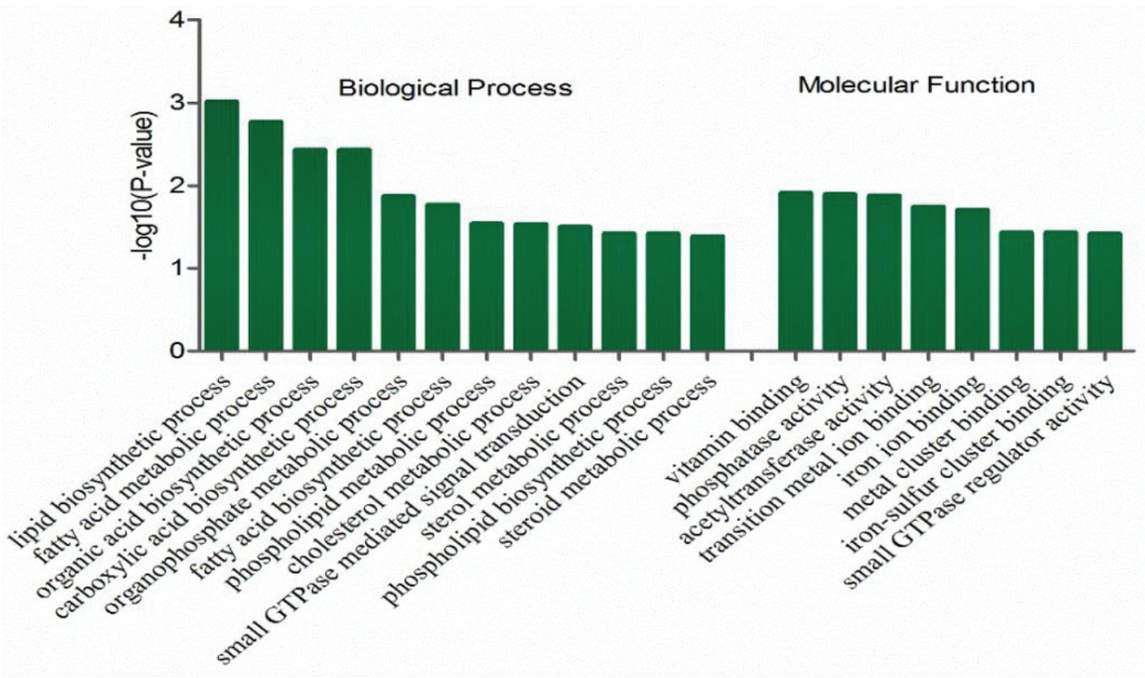


**Figure 4.** The significantly enriched and lipid-related GO terms of the target genes of the down-regulated miRNAs.

LncRNA is a class of pervasive genes involved in a variety of biological functions. Increasing researches present some lncRNAs are contributed to liver relevant metabolisms, including lipid metabolism. LncLGRAs, the transcriptional regulation factor of hepatic glucokinase (*GCK*) gene, can inhibit the expression of *GCK* and reduce hepatic glycogen content in mice during fasting [74]. It is reported that, whether enhanced the expression of lncRNA MALAT1

*in vivo* or *in vitro*, it can activate the nuclear *SREBP1c* expression and induce the intracellular lipid accumulation in mouse hepatocytes [75], while the lncRNAs that may take part in chicken hepatic lipid metabolism are unknown. Therefore, to gain insight into the underlying roles of lncRNAs serving as the hepatic lipid metabolism regulatory molecules, a lncRNA-Seq has be conducted to the livers of pre- and egg-laying hens to detect the lncRNAs.

## 4. Future perspectives

As well known, both lncRNAs and miRNAs serve as the endogenously expressed regulators of gene expression [76]. Recent researches have showed that the aberrant expression of lncRNAs and transcription factors can result in the miRNAs disorder. A study has demonstrated that a highly upregulated liver cancer lncRNA could serve as an endogenous sponge, which can down-regulate a series of miRNAs activities [77]. Due to the long size of lncRNAs, it regulate miRNA abundance via binding and sequestering them, working as the so-called miRNAs sponges, thus regulating the expression of target mRNAs [78, 79]. Given the complex modulation network among mRNAs [37], miRNAs [72] and lncRNAs, it will be great interest for us to combine these data sets to explore the possible regulation mechanisms among lncRNA, mRNA and miRNA. Our results will be a valuable resource for further elucidating the regulatory mechanism of chicken hepatic lipid metabolism and may also provide reference for understanding the molecular mechanisms in other poultry and mammalian species.

It has to be mentioned that the regulation of hepatic lipid metabolism in chicken described in this chapter is based on comparative studies between pre- and egg-laying hens, in which estrogen is supposed to be the main factor influencing lipid metabolism. In fact, many other factors such as feed additives and photogenic compounds may also play important roles in the lipid metabolism process, while the regulatory mechanism that genes involved in may not be the same as the present results [80–82].

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