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Epigenetic Regulation of Hepatic Lipogenesis: Role in Hepatosteatosis and Diabetes

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Hepatosteatosis, which is frequently associated with development of metabolic syndrome and insulin resistance, manifests when triglyceride (TG) input in the liver is greater than TG output, resulting in the excess accumulation of TG. Dysregulation of lipogenesis therefore has the potential to increase lipid accumulation in the liver, leading to insulin resistance and type 2 diabetes. Recently, efforts have been made to examine the epigenetic regulation of metabolism by histone-modifying enzymes that alter chromatin accessibility for activation or repression of transcription. For regulation of lipogenic gene transcription, various known lipogenic transcription factors, such as USF1, ChREBP, and LXR, interact with and recruit specific histone modifiers, directing specificity toward lipogenesis. Alteration or impairment of the functions of these histone modifiers can lead to dysregulation of lipogenesis and thus hepatosteatosis leading to insulin resistance and type 2 diabetes.

Over the last few decades, the prevalence of obesity has increased worldwide due in large part to hypercaloric "Western diets" high in fat and simple sugars (1). Reduced energy expenditure and excess caloric intake result in the accumulation of lipid in the form of triglycerides (TG) in adipose tissue. While some of the fatty acids (FA) come directly from the diet, a large fraction are from de novo lipogenesis in the liver, where FA are synthesized from glucose and subsequently esterified to TG (2).

De novo lipogenesis fluctuates greatly depending on nutritional status. During fasting when nutrient availability is low, de novo FA synthesis in the liver is inhibited markedly. After eating, increased levels of glucose and insulin in circulation lead to a drastic increase in de novo lipogenesis (3). Various enzymes involved in lipogenesis, including fatty acid synthase (FASN), acetyl-CoA carboxylase (ACC), ATP citrate lyase (ACLY), sterol regulatory element binding protein 1c (SREBP-1c), stearoyl-CoA desaturase 1 (SCD1), and mitochondrial glycerol-3-phosphate acyltransferase (mGPAT), are regulated coordinately at the transcriptional level. Transcription factors, including upstream stimulating factor 1 (USF1), SREBP-1c, carbohydrate response element binding protein (ChREBP), and liver X receptor (LXR), have been implicated in the induction of lipogenesis (4). Hepatosteatosis, the excess accumulation of lipid in the liver, is highly correlated with obesity and results from higher TG input than output and is thus highly influenced by de novo lipogenesis. In fact, in patients with nonalcoholic fatty liver disease (NAFLD), ~30% of the TG accumulated in the liver is derived from de novo lipogenesis (5). Hepatosteatosis not only can progress to nonalcoholic steatohepatitis (NASH) and to liver fibrosis/cirrhosis, but can lead to the development of insulin resistance and diabetes.

Recent work in the study of metabolic regulation has begun to investigate the role of epigenetic modifications in the development of metabolic disorders. Epigenetic modifications do not alter the DNA sequence, but include gene activation or silencing through DNA methylation or post-translational modifications of histones that alter DNA packaging and chromatin accessibility. Various enzymes, classified as writers or erasers, work to add or remove epigenetic modifications in order to respond to various environmental cues to affect gene transcription (6). In this review we discuss the relationship between epigenetics and metabolism with an emphasis on lipogenesis, hepatosteatosis, and diabetes. Also discussed are the interplay between gene-specific transcription factors and histone-modifying enzymes as well as the role of intracellular metabolites in modulating their activity in health and disease.

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Coordinate Transcriptional Regulation of Lipogenesis

USF1 plays a key role in the activation of lipogenesis by insulin, as recruitment of USF1 to the −65 E-box on the FASN promoter is required for transcriptional activation. USF1 also binds to the promoter regions of various lipogenic enzymes, such as mGPAT. USF1 functions as a molecular switch responsible for the recruitment of multiple transcription factors and coregulators to lipogenic promoter regions (7–11). In the presence of insulin, USF1 is phosphorylated by DNA-dependent protein kinase (DNA-PK) at S262 and then acetylated by P300/CBP associated factor (P/CAF) at K237 (8). This modified USF1 recruits SREBP to bind its serum response element (SRE). The modified USF1 also recruits BRG1-associated factor 60c (BAF60c), which is phosphorylated at S257 by atypical protein kinase C (aPKC), allowing the formation of the LipoBAF complex at the promoter regions of lipogenic genes for chromatin remodeling and transcription (10). Recently, we found that Mediator complex subunit MED17 is also recruited by USF1 to lipogenic promoters in response to insulin, following its phosphorylation by casein kinase 2 (CK2) at S53, thereby providing a functional link to RNA Pol II and the general transcriptional machinery (11). In this manner, various insulin signaling cascades converge on USF1 to activate transcription of a multitude of lipogenic genes, thereby increasing lipogenesis.

The glucose responsive transcription factor ChREBP is a major regulator of hepatic lipogenesis and works with USF1 in the activation of lipogenic gene transcription. ChREBP heterodimerizes with Max-like factor X (MlX) to bind to the carbohydrate response element (ChoRE) found on target genes (12). Much like USF1, ChREBP is post-translationally modified depending on the metabolic status of the cell. ChREBP is acetylated by p300 at K672 for activation when glucose level is high (13) and phosphorylated by protein kinase A (PKA) at S196/S626/T666 for inhibition during starved conditions (14). These modifications have striking effects on ChREBP DNA binding activity and thus work to regulate ChREBP recruitment to its target genes. Recently, peroxisome proliferator-activated receptor γ coactivator 1-β (PGC-1β) was also found to interact with ChREBP at promoters of lipogenic genes liver pyruvate kinase (L-PK) and ACC in response to high glucose (15). Moreover, ablation of PGC-1β impaired lipogenic response to high glucose in isolated hepatocytes (15).

LXRs are responsive to both insulin and metabolites and function in the transcriptional regulation of lipogenesis. LXR forms heterodimers with retinoid X receptor (RXR) and binds to LXR response elements (LXRE) in the promoters of target genes upon their activation by their metabolite ligands, oxysterols (16). The ability of LXR to increase lipogenesis is derived from its upregulation of SREBP-1c (17), another key transcription factor that binds to SREs within promoters of lipogenic genes to increase their transcription. LXRs are more widely known as master regulators of cholesterol metabolism, as they regulate genes involved in cholesterol biosynthesis and transport (18). LXREs are found in the promoters of several lipogenic genes, and LXR has been reported to regulate lipogenic gene transcription directly through binding to promoter regions as well as indirectly through increasing SREBP-1c transcription (19). LXRs have been reported to be β-linked *N*-acetylglucosamine (*O*-GlcNAc) modified in response to refeeding and high levels of glucose, and this modification increases its activity resulting in higher levels of transcription of its target genes (20).

Interplay Between Histone Modifiers and Transcription Factors in Regulating Lipogenesis

There are a wide assortment of histone-modifying enzymes that have been identified that work to either add or remove specific modifications to histones to alter chromatin organization. These enzymes are classified into different classes depending on their function, such as lysine acyltransferase (KAT), lysine deacetylase (KDAC), histone methyl transferase (HMT), and histone demethylase (HDM), as well as their cofactor requirement. They are organized further into families depending on their substrate specificity and domain architecture. Moreover, within individual histone modifier families, there can be a multitude of enzymes with different functions, such as the JmjC domain-containing family of histone demethylases with ∼30 members in humans (21,22). Even so, these enzymes may maintain some degree of specificity toward the biological functions that they regulate. This specificity is achieved in part through their interactions with cell- and gene-specific transcription factors that recruit them to certain promoters and regulatory regions for the regulation of chromatin organization.

USF1

Both insulin and glucose have been shown to activate lipogenic genes in the liver through USF1, SREBP, LXR, and ChREBP (4). However, the histone modifications necessary for the alteration of the chromatin landscape at lipogenic promoters to allow for USF1 function have not been fully investigated. USF1 must be posttranslationally modified in order to recruit the necessary cofactors for chromatin remodeling and transcriptional activation of lipogenic genes in response to insulin. Interestingly, we found that USF1 is bound to lipogenic promoter regions during both fasting and refeeding, and so USF1 may potentially function as a pioneer factor, a transcription factor that can bind to unmodified or repressed chromatin (8). Indeed, USF1 has been found to be one of the few transcription factors that can bind chromatin lacking activating marks such as acetylation (23). Thus, posttranslational modification of USF1 in response to specific signaling pathways is critical for its role in the recruitment of histone modifiers and chromatin remodelers as well as other transcription factors and coregulators for lipogenic gene transcription. We recently identified an interaction between USF1 and Jumonji domain-containing 1C (JMJD1C), an H3K9 histone demethylase, and found this interaction to

be required to increase chromatin accessibility for transcriptional activation of lipogenic genes, including FASN, ACC, ACLY, and SREBP-1c, as knockdown and liver-specific knockout (KO) of JMJD1C resulted in impaired lipogenic gene induction and reduced lipogenesis. Thus, through its interaction with USF1, JMJD1C activates lipogenesis by demethylating H3K9 in response to insulin/refeeding to create a chromatin environment permissive to transcription. Additionally, we found that JMJD1C is phosphorylated by mammalian target of rapamycin (mTOR) at T505 for its recruitment to USF1 at lipogenic promoters; therefore, it is possible that derangements in mTOR signaling, as are seen in obesity and insulin resistance (24), may lead to improper activation of JMJD1C. Furthermore, we found that ablation of JMJD1C in the liver protects against high-carbohydrate diet–induced hepatosteatosis and insulin resistance, and genome-wide association studies have identified single nucleotide polymorphisms within JMJD1C that are associated with development of type 2 diabetes (25), thus providing further evidence of the involvement of JMJD1C in development of metabolic diseases.

ChREBP

Recent work by Bricambert et al. (26) observed an interaction between ChREBP and the H3K9 demethylase plant homeodomain finger protein 2 (Phf2). By ChIP-seq, Phf2 peaks were found to overlap with ChREBP peaks in specific processes, including lipid metabolism, and ChIP-qPCR found that ChREBP and Phf2 colocalized at ACLY, FASN, and SCD1 promoters. Furthermore, the interaction was found to be necessary for transcriptional activation of ChREBP target genes, as silencing of Phf2 decreased lipogenic gene expression and rates of lipogenesis. Phf2 binds to trimethylated H3K4 histone tails and thus needs promoters that are poised for transcriptional activation to exert its demethylase activity (26). However, Phf2 also requires ChREBP for binding to its target promoters, as silencing of ChREBP drastically impairs recruitment of Phf2 to lipogenic genes such as L-PK and SCD1. Thus, through the interaction with ChREBP, Phf2 can regulate the chromatin landscape to permit transcription upon refeeding. Phf2 was implicated in nonalcoholic fatty liver disease (NAFLD) through the activation of the SCD1 promoter. However, despite the onset of hepatosteatosis in mice, Phf2 overexpression appeared to protect the liver from fibrogenesis and oxidative stress. Even with increased hepatic lipid accumulation, Phf2-overexpressing mice showed improved glucose and insulin tolerance and decreased proinflammatory gene expression compared with controls (26). The authors suggest that Phf2 increases SCD1 activity enhancing the ratio of monounsaturated fatty acids (MUFA) to saturated fatty acids (SFA), granting protection from lipotoxicity and oxidative stress, thereby protecting against insulin resistance.

LXR and SREBP-1c

LXR has been shown to interact with H3K4 methyltransferases mixed-lineage leukemia protein 3/4 (MLL3/44), through the adaptor protein activating signal cointegrator 2 (ASC-2), which is known to associate with multiple nuclear receptors as a transcriptional coactivator (27). Ablation of MLL3 in mice decreased expression of lipogenic genes FASN and SREBP-1c in the liver (27). Furthermore, treatment with LXR agonist T1317 increased recruitment of both MLL3 and MLL4 to LXR, and these effects were not observed in ASC-2 null cells, demonstrating the requirement for both LXR and ASC-2 for recruitment of MLL3/MLL4 for the activation of lipogenesis (27). LXR is also reported to interact with KDAC Sirt1, through the adaptor protein menin (Men1) (28). This interaction, however, serves to antagonize lipogenesis, as Sirt1 blocks the interaction between LXR and its coactivators (29). Interestingly, Sirt1 also interacts with SREBP-1c in order to deacetylate and inactivate it (30), further inhibiting lipogenesis. Furthermore, SREBPs have been reported to interact with cAMP response element binding protein (CBP) (31), which functions as a KAT, and thus likely work to promote activation of lipogenic gene transcription.

Despite the limited information available, it is clear that interactions between lipogenic transcription factors and histone modifiers play a key role in the regulation of hepatic lipogenic gene transcription. Additionally, there appears to be some redundancy in function as both JMJD1C and Phf2 exhibit H3K9me1/2 demethylase activity. Interestingly, since Phf2, which interacts with ChREBP, requires trimethylated H3K4 histone tails to carry out its demethylase activity (26), it is likely that the recruitment of H3K4 methyl transferases MLL3 and MLL4 to lipogenic genes by LXR must occur first. Similarly, since neither ChREBP nor LXR has been reported to bind repressed chromatin, it is likely that both would require USF1 to bind lipogenic promoters first to recruit histone modifiers, such as JMJD1C, and chromatin remodelers to create a chromatin landscape permissive to their binding and subsequent activation of transcription (Fig. 1). Thus, there exists a complex interplay between various signaling pathways that activate gene-specific transcription factors and the histone modifiers that serve as coregulators.

Metabolites and Histone Modifiers That Affect Lipogenesis and Thus Hepatosteatosis

Each of the histone modifier classes depend on different metabolites as cofactors or cosubstrates for posttranslational modifications of histones. KATs depend on acetyl-CoA to transfer the acetyl group to lysine residues, whereas sirtuin (SIRT) KDACs depend on NAD^+ to remove the acetyl group. HMTs depend on *S*-adenosyl methionine (SAM) to transfer a methyl group, whereas JmjC domain-containing demethylases depend on α-ketoglutarate (αKG) to remove the methyl group. The very first histone demethylase discovered, lysine-specific demethylase 1 (LSD1), is distinct from the JmjC domain-containing demethylases in that it depends on FAD for its demethylase activity (32). Thus, the intracellular metabolite availability at specific cell

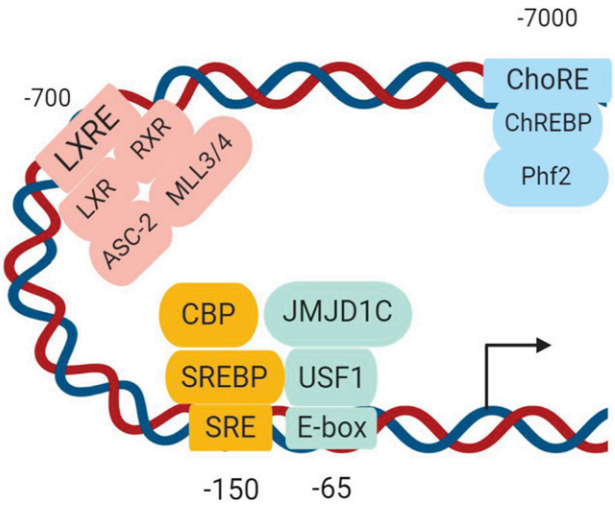

Figure 1—Schematic of the FASN promoter showing position of E-box, SRE, LXRE, and ChoRE and respective lipogenic transcription factors bound by histone modifiers reported to increase lipogenesis.

compartments has the potential to drastically alter the activity of histone modifiers and subsequently alter the organization of chromatin.

αKG and JmjC Domain-Containing Demethylases

αKG is an important intermediate in the tricarboxylic acid (TCA) cycle that can be used as a substrate in many anabolic processes. It is generated by the oxidation of isocitrate and can also be derived from glutamine through its conversion to glutamate and subsequently to αKG. αKG levels fluctuate depending on the metabolic status of the cell (33), and levels of hepatic αKG have been reported to decrease during fasting (34). Histone demethylation by the JmjC domain-containing family of demethylases is coupled to decarboxylation of αKG, and thus changes in the cellular concentration of αKG can have profound effects on demethylase activity and histone methylation (22).

There are ~30 members of the Jmj domain-containing demethylase family, and multiple members have been implicated in the regulation of metabolism, either directly or indirectly, through their demethylase activity. As mentioned above, JMJD1C, a member of the KDM3 family of JmjC domain-containing demethylases, has been implicated in metabolic regulation through its interaction with USF1 for the activation of lipogenesis. JMJD1C preferentially demethylates H3K9me2, a repressive mark, upon insulin stimulation or feeding to increase chromatin accessibility for lipogenic gene transcription. JmjC domain-containing lysine demethylase 2A (JHDM2A) also belongs to the KDM3 family and preferentially demethylates mono- and di-methyl H3K9 at target promoters to open chromatin and activate transcription (35). JHDM2A-deficient mice develop obesity by 8 weeks of age, exhibit increased plasma TG, and become insulin and glucose intolerant (35), demonstrating the clear involvement of this demethylase in lipid metabolism.

Acetyl-CoA and Histone Acetyltransferases

Acetyl-CoA is a central metabolite in the TCA cycle and is an important intermediate in the synthesis of other macromolecules. Acetyl-CoA is derived primarily from the breakdown of carbohydrates through glycolysis and FA through β-oxidation, and thus the levels of acetyl-CoA in the cell fluctuate depending on the metabolic state of the cell (36). Levels of hepatic acetyl-CoA have been reported to be higher in obese rats, owing to higher levels of lipolysis from white adipose tissue (WAT) (37). This was shown through the inhibition of lipolysis in WAT, with atglistatin, as well as the inhibition of FA oxidation in liver, with etomoxir, both of which decreased hepatic acetyl-CoA concentrations (37). Elevated levels of hepatic acetyl-CoA were maintained even in the fasted state and were thought to contribute to the deregulation of hepatic glucose production, a key feature of type 2 diabetes (37). Moreover, it has been reported that increased levels of acetyl-CoA are sufficient to increase acetylation of H3K9 and H4K8 globally in liver (13) as well as H3K9, H3K27, and H3K56 specifically at lipogenic promoters FASN and ACC in HepG2 cells to increase rates of FA and fat synthesis (38). Therefore, increased acetyl-CoA has the capacity to increase histone acetylation, which is compounded in disease states such as obesity, and can lead to the development of diabetes potentially through deregulation of hepatic glucose production and lipogenesis.

Hyperacetylation of H3K9 and H4K8 by p300/CBP has been implicated in regulating chromatin accessibility for the transcriptional activation of lipogenic genes (L-PK, FASN, ACC, and ACLY) in cultured cells (13). Wan et al. (39) found that occupancy of p300 at promoter regions of lipogenic genes resulted in higher expression of lipogenic genes and higher FA production. Similarly, Henry et al. (40) report that increased acetyl-CoA levels result in increased activity of KAT p300. Overactivity of p300 is seen in livers of mice maintained on high-fat diet (HFD) as well as in aged mice. Jin et al. (41) showed that mice on HFD had enhanced occupancy of p300 at lipogenic promoters diglyceride acyltransferase (DGAT)1 and 2 and that this resulted in increased acetylation of H3K9. Both the HFD-fed mice and aged mice showed increased accumulation of lipid in the liver and development of hepatosteatosis, which was blocked by overexpressing dominant negative p300. Additionally, Jin et al. showed that this dysfunction was also observed in humans with fatty liver disease, as hepatocytes from NAFLD patients had significantly higher levels of p300/CBP and DGAT2 (41). Moreover, PGC-1β that interacts with ChREBP may be required to recruit KATs to lipogenic promoters since its ablation resulted in decreased H3 acetylation (15). Histone acetylation plays a key role in the dysregulation of lipogenesis that results in the development of hepatosteatosis, and it would appear that excess lipid in the diet exacerbates this by promoting p300 function.

NAD^+ and Histone Deacetylases

Histone deacetylases are divided among the classic Zn^{2+}-dependent KDACs and the NAD^+-dependent SIRT KDACs

(42). NAD^+ is a necessary cofactor in various metabolic processes and has been reported to increase substantially in the liver during fasting (43), potentially through activity of the SIRT class of KDAC enzymes. In addition to its inhibitory interactions with LXR and SREBP-1c, SIRT1 has been reported to downregulate hepatic lipid metabolism directly by deacetylating histone H3 on target gene promoters (28). Another member of the SIRT family, SIRT6, has also been shown to regulate hepatic lipid metabolism through its deacetylase activity. Hepatic SIRT6 mRNA and protein levels increase drastically upon 18-h fasting and decrease upon refeeding (44). In addition, SIRT6 activity is reported to be regulated by FA, with up to 35-fold increase in catalytic activity at physiological concentrations (45), and thus increased lipolysis during fasting may result in a feed-forward loop for SIRT6 activity to quickly inhibit lipogenesis. Liver-specific SIRT6 KO mice showed increased liver TG accumulation and reduced insulin tolerance along with increased lipogenic gene expression (44). Furthermore, these liver-specific SIRT6 KO mice showed increased global H3K9 acetylation as well as increased H3K9 acetylation at promoter regions of lipogenic genes, FAS, ACC1, and SCD1, whereas SIRT6 overexpression decreased H3K9 acetylation. SIRT6 protein levels were shown to decrease ~50% in human fatty liver samples compared with normal liver, suggesting that SIRT6 may play a role in the development of hepatosteatosis (44). In fasting, SIRT1 and SIRT6 appear to work in an inhibitory manner to repress lipogenesis, and thus dysregulation of their activity results in the onset of hepatosteatosis and insulin resistance, which may potentially progress to diabetes.

The classical KDACs do not appear to share regulation by metabolites like the SIRT KDACs and instead are recruited to target genes through their interactions with repressive complexes nucleosome remodeling deacetylase (NuRD), repressor element-1 silencing transcription factor (CoREST), or nuclear receptor corepressor/silencing mediator for retinoid or thyroid-hormone receptor (NCoR/SMRT) (46). KDAC3 has been reported to localize to lipogenic promoter regions to inhibit lipogenesis, and depletion of KDAC3 leads to upregulation of genes involved in lipid synthesis in liver concomitantly with increased liver TG (47,48). Removal of KDAC3 had no effect on H3K9 acetylation but increased acetylation of H4K5, H4K8, and H4K12 globally and at specific genomic regions corresponding to KDAC3 target genes, such as acetyl-CoA carboxylase β (Acacb) (48). More recently, deacetylation of H3K9 and H3K27 at lipogenic promoters by KDAC1 and KDAC2, through their interaction with snail family transcriptional repressor 1 (Snail1), was shown to decrease induction of lipogenic genes and result in suppression of lipogenesis (49). Thus, deletion of Snail1 in liver caused TG accumulation, resulting in NAFLD, while overexpression decreased liver TG and protected from NAFLD (49). These effects as well as those of other histone modifiers are summarized in Table 1.

Table 1—Histone modifiers implicated in the development of metabolic diseases

Histone modifiers	Associated disease	Reference
JMJD1C	Hepatosteatosis Insulin resistance Type 2 diabetes	Viscarra et al. (50) Kim et al. (25)
Phf2	NAFLD	Bricambert et al. (26)
JHDM2A	Obesity Insulin resistance	Inagaki et al. (35)
p300	Hepatosteatosis NAFLD	Wan et al. (39)
Sirt1 (downregulation)	Hepatosteatosis	Kim et al. (44)
Sirt6 (downregulation)	Hepatosteatosis Insulin resistance	Kim et al. (44)
Snail1 (downregulation)	NAFLD	Liu et al. (49)

Concluding Remarks

A great deal of work has focused on assessing the specific function of histone modifications and the role of cellular metabolites in regulating activity of histone modifiers. Transcriptional regulation of lipogenesis is a complex process involving the integration of various signaling cascades involving many transcription factors and coregulators. The epigenetic regulation of this process has only recently begun to be examined, but much progress is being made toward developing a comprehensive understanding of the various histone modifiers involved.

Because dysregulation of lipogenesis can lead to hepatosteatosis and insulin resistance, identifying potential targets for treatment is of utmost importance. Many current therapeutic options for hepatosteatosis work to inhibit the function of various enzymes involved in lipogenesis. Future therapeutics may benefit from targeting histone modifiers directly to modulate their activity and decrease transcription of lipogenic genes. More work needs to be done to characterize the interactions between histone modifiers and lipogenic transcription factors to assess their specificity and determine their suitability as targets for therapeutic intervention. ChIP-seq coupled with assay for transposase accessible chromatin (ATAC-seq) may help to better define the function of these histone modifiers and their interactions with lipogenic transcription factors. Moreover, as there appears to be some redundancy in the class of histone modifiers reported to regulate lipogenesis, careful assessment of their function may help to determine the order of events that take place for proper chromatin reorganization and transcriptional activation. Overall, while the epigenetic regulation of lipogenesis through reversible histone modification adds a layer of complexity to an already complex process, it also provides potential targets for the development of therapeutics against hepatosteatosis, insulin resistance, and diabetes.

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