Glucagon-Induced Acetylation of Energy-Sensing Factors in Control of Hepatic Metabolism

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Abstract: The liver is the central organ of glycolipid metabolism, which regulates the metabolism of lipids and glucose to maintain energy homeostasis upon alterations of physiological conditions. Researchers formerly focused on the phosphorylation of glucagon in controlling liver metabolism. Noteworthily, emerging evidence has shown glucagon could additionally induce acetylation to control hepatic metabolism in response to different physiological states. Through inducing acetylation of complex metabolic networks, glucagon interacts extensively with various energy-sensing factors in shifting from glucose metabolism to lipid metabolism during prolonged fasting. In addition, glucagon-induced acetylation of different energy-sensing factors is involved in the advancement of nonalcoholic fatty liver disease (NAFLD) to liver cancer. Here, we summarize the latest findings on glucagon to control hepatic metabolism by inducing acetylation of energy-sensing factors. Finally, we summarize and discuss the potential impact of glucagon on the treatment of liver diseases.

Keywords: glucagon; acetylation; deacetylation; energy-sensing factors; hepatic metabolism

1. Introduction

Health problems associated with obesity, type 2 diabetes (T2DM), and nonalcoholic fatty liver disease (NAFLD) are becoming more arresting by the day [1–3]. Abnormal physiological control could destroy metabolic balance and would eventually give rise to these chronic acquired diseases [4,5]. Overnutrition or malnutrition have been revealed to be linked to chronic inflammation and may result in disorders of energy balance in the body [6,7]. As the hub of metabolism, the liver has an abundant blood supply, and its unique morphological structure makes its metabolism extremely active [8]. It is also closely related to various tissues and organs in the metabolism of glucose, lipids, protein, vitamins, and hormones, etc. Consequently, the liver is responsible for maintaining somatic harmony. It does so by precisely controlling the metabolism of glucose and lipids [9]. Hepatic metabolic disorders are strongly linked to the existence of liver diseases. Perpetual obesity and overnutrition inflict inflammation in the liver and invite many metabolic disorders and diseases. These effects eventually contribute to the appearance and metastasis of liver cancer, which is currently the leading cause of death from liver disease [10,11].

A growing body of studies have uncovered that some transcription factors play significant roles in controlling liver energy metabolism. After undergoing post-translational modifications (PTMs), the activity and stability of these transcription factors will be altered, thereby affecting their biological functions in the liver [12]. During the past decades, many researchers have indicated that acetylation has become a critical post-translational modification in cell regulation, particularly by modifying histones and nuclear transcriptional factors. Lysine acetylation is an evolutionarily, highly conserved post-translational modification mechanism. Histone acetylation under the control of lysine
Acetyltransferases (KATs) and histone deacetylases (HDACs), and the dynamic balance of these two activities, is the linchpin in maintaining homeostasis [13,14].

Recent mass spectrometry has unmasked that almost all metabolism enzymes are acetylated, indicating that acetylation has a broad regulatory effect on cellular metabolism. Furthermore, acetylation also participates in various biological processes, such as energy metabolism, signal transduction, and oxidative stress, by altering the protein–protein interactions, protein stability, catalytic activity, and subcellular localization of metabolic enzymes [15,16]. Regulation of metabolic pathways by acetylation is important for the occurrence and development of metabolic-related diseases such as obesity, cardiovascular disease, diabetes, and tumorigenesis [17,18]. Predictably, as a vital metabolic organ, most metabolic processes in the liver are subjected to acetylation, such as glycolipid metabolism and urea cycles. The acetyltransferase and deacetylase enzymes are affected by the nutritional levels, so they can quickly respond to the liver energy balance.

Metabolism of nutrients in the liver is under the control of glucagon and insulin. This is the reason the interaction between insulin and glucagon is able to maintain the body’s energy balance [19]. Glucagon is a polypeptide synthesized and secreted by pancreatic alpha cells. The primary physiological role of glucagon is to fight insulin and induce hepatic glucose production, thereby maintaining glucose balance in the liver. Previous research has demonstrated that most liver metabolic diseases are concomitant with an increase in plasma glucagon concentration [20–23]. Recently, some researchers have shown that glucagon regulates liver metabolism by controlling acetylation of energy-sensing factors. Energy-sensing factors are capable of making the corresponding transformation according to different energy levels of the body to maintain energy balance [24]. For example, in the fasting state, glucagon regulates the expression of forkhead box o1 (FOXO1) and cyclic AMP (cAMP)-response element binding protein (CREB)-regulated transcription coactivator 2 (CRTC2) by inducing acetylation, thereby increasing the expression of gluconeogenesis-related genes to regulate glucose metabolism [25–28]. Glucagon additionally induces the acetylation of sterol regulatory element binding protein-1c (SREBP-1c) and cAMP-responsive element binding protein H (CREBH) to regulate lipid metabolism [29–32]. Additionally, in the pathological state of the liver, glucagon-induced acetylation of energy-sensing factors such as signal transducer and activator of transcription–3 (STAT3) provide a potential treatment strategy for liver disease [33] (Table 1). This review primarily focuses on how glucagon controls hepatic metabolism by altering the acetylation status of energy-sensing factors.
### Table 1. Overview of the regulation of different targets related to hepatic metabolism via glucagon-induced acetylation in different physiological states.

| Physiological/Pathological State | Enzyme | Acetylation/Deacetylation | Targets | Effect | Metabolic Response | Reference |
|----------------------------------|--------|---------------------------|---------|--------|--------------------|-----------|
| Fasting state                    | P300   | Acetylation               | CRTC2   | Stimulatory | Gluconeogenesis↑ | [25,34]  |
|                                  |        |                           | FOXO1   | Stimulatory | Gluconeogenesis↑ | [26,35]  |
| Fasting state                    | Ets-1  | Acetylation               | FOXO1   | Inhibitory | Gluconeogenesis↑ | [36]      |
| Fasting state                    | SIRT6 and GCN5 | Acetylation and Deacetylation | PGC1-α  | Inhibitory | Gluconeogenesis↓ | [37–39]  |
| Prolonged fasting state          |        |                           | GP      | Inhibitory | Gluconeogenesis↓ | [40]     |
| Fasting state                    | SIRT1  | Deacetylation             | CRTC2   | Inhibitory | Gluconeogenesis↑ | [25]      |
|                                  |        |                           | FOXO1   | Stimulatory | Gluconeogenesis↑ | [25]     |
| Fasting state                    | class IIa HDACs | Deacetylation | FOXOs  | Inhibitory | Gluconeogenesis↑ | [41]     |
| Fasting state                    | SIRT5  | Deacetylation             | LCAD    | Stimulatory | FFA oxidation↑  | [42]      |
|                                  |        |                           | /       | Stimulatory | FFA oxidation↑  | [43]      |
| Fasting state                    | SIRT1  | Deacetylation             | PPAR-α  | Stimulatory | FFA oxidation↑  | [44,45]  |
|                                  |        |                           | Foxa2   | Inhibitory | FFA oxidation↑  | [46,47]  |
| Fasting state                    | PCAF   | Acetylation               | CREBH   | Stimulatory | FFA synthesis↓  | [31]     |
| Prolonged fasting state          | SIRT1  | Deacetylation             | CREBH   | Stimulatory | FFA synthesis↓  | [31]     |
| Fasting state                    | SIRT1  | Deacetylation             | SREBP-1c| Inhibitory | FFA synthesis↓  | [29]     |
| Fasting state                    | SIRT3 and SIRT5 | Deacetylation | CPS1 and OTC | Stimulatory | Ureagenesis↑  | [49,50]  |
| NAFLD                            | SIRT1  | Deacetylation             | NF-κB   | Inhibitory | Inflammation↓  | [51]     |
| Hepatic fibrosis                 | SIRT1  | Deacetylation             | STAT3   | Inhibitory | Inflammation↓  | [53,54]  |
| Hepatic fibrosis                 | SIRT1  | Deacetylation             | TGF-β   | Inhibitory | Inflammation↓  | [55,56]  |
| Liver cancer                     | PCAF   | Acetylation               | PGK1    | Stimulatory | Glycolysis↑  | [57]     |
| Liver cancer                     | PCAF   | Acetylation               | PKM2    | Inhibitory | Tumor growth and cell proliferation↑ | [58,59] |
| Liver cancer                     | GCN5   | Acetylation               | PGC-1a  | Inhibitory | Glycolysis↑  | [60]     |
| Liver cancer                     | SIRT1  | Deacetylation             | PGC-1a  | Stimulatory | Glycolysis↑  | [61]     |
| Liver cancer                     | P300   | Acetylation               | FOXO1   | Inhibitory | Glycolysis↑  | [62,63]  |

2. Glucagon-Mediated Glucose Homeostasis in the Liver

As an essential nutrient of the body, glucose is the primary source of energy for many cells and is dependent on blood for transportation. Therefore, maintaining blood glucose balance is significant for ensuring the nutritional supply and normal metabolic activities of various tissues and organs. The liver is the main organ that critically maintains blood glucose balance. It takes up glucose through glycogen production and releases glucose through gluconeogenesis [64]. During fasting or caloric restriction (CR), the liver maintains energy supply by enhancing glycogenolysis and gluconeogenesis [65]. Meanwhile, glucagon stimulates transcription of the gluconeogenesis gene through various ways in the fasting state, one of which is acetylation of energy-sensing factors (Figure 1A).
Figure 1. Glucagon-induced acetylation of energy-sensing factors in control of hepatic glycolipid metabolism. (a) Blue arrow: Glucagon initiates the transcription of downstream G6Pase and PEPCK1 by inducing acetylation of CRTC2 and FOXO1 and reducing acetylation of PGC-1α and GP, which leads to elevating gluconeogenesis.
Red arrow: Glucagon-induced deacetylation of CRTC2 and FOXO have different roles in glucose metabolism. (b) Blue arrow: Glucagon-induced acetylation of CREBH and SREBP-1c inhibit the hepatic lipids synthesis. Red arrow: Glucagon-induced acetylation of PPAR-α and Foxa2 increase fatty acid oxidation. (G6Pase: Glucose-6-phosphatase; CRTC2: CREB regulated transcription coactivator 2; FOXO1: Forkhead box O1; PEPCK1: Phosphoenolpyruvate carboxykinase; GP: Glycogen phosphorylase; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1α; PPAR-α: Peroxisome proliferator-activated receptor-α; SREBP-1c: Sterol regulatory-element-binding protein-1c; CREBH: cAMP-responsive element-binding protein H).

2.1. Glucagon-Induced Acetylation Regulates Hepatic Gluconeogenesis during the Fasting State

During fasting and CR, the liver provides glucose to tissues and organs through glycogenolysis and gluconeogenesis to ensure healthy metabolism of the body [66]. The gluconeogenesis process is regulated by nutrient levels and various hormones [67]. Several transcription factors and coactivators are engaged in this process after being acetylated by glucagon induction. Glucagon promotes dephosphorylation of the Ser89 site of p300 via the cAMP-dependent protein kinase (PKA) pathway, thereby increasing p300 activity [25]. p300 has histone acetyltransferase activity, where it transfers an acetyl group to the lysine residue, which enhances the activity of CRTC2 by acetylating the Lys628 site of CRTC2 [25,68,69]. As the switch protein for blood glucose regulation in humans, CRTC2 is sensitive to hormones and glucose levels, mainly expressed in the liver and kidney [70]. Therefore, glucagon initiates the transcription of downstream glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK1) by acetylating CRTC2 via p300, such that it enhances gluconeogenesis to maintain energy balance [25,34,71]. Additionally, Anne and colleagues showed that mRNA and protein levels of FOXO1 were elevated prominently in mice livers after fasting [25]. FOXO1 can also promote transcription of gluconeogenic enzyme genes such as G6Pase and PEPCK1, which in turn leads to elevating gluconeogenesis [28,68]. Remarkably, silence of coactivator p300 leads to a decrease in mRNA and protein levels of FOXO1. In addition, suppression of histone acetyltransferase activity of p300 prominently reduces mRNA and protein levels of FOXO1 in the liver of fasting mice and fasting blood glucose levels [26,35]. Accordingly, we conclude that glucagon might elevate the FOXO1 gene and CRTC2 expression in the fasting state via p300, and the expression of FOXO1 and CRTC2 would further increase gluconeogenesis. A recent study also revealed that Ets1-mediated acetylation of FOXO1 responds to glucagon signaling to regulate gluconeogenesis in the fasting state [36]. During fasting, glucagon down-regulates the activity of Ets1 via the mitogen-activated protein kinase kinase (MEK) extracellular signal-regulated kinase (ERK) pathway [36,72]. FOXO1 is acetylated by Ets1 and leads to its incapacity of binding to gluconeogenic promoters. Therefore, glucagon inhibits the process of Ets1 acetylation of FOXO1 to increase gluconeogenesis.

A recent finding illustrates that glucagon plays a significant role in control of the process where general control nonrepressed protein 5 (GCN5) acetylates peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) in the fasting state [73,74]. As one regulator of gluconeogenesis, PGC-1α effectively stimulates hepatic gluconeogenesis by increasing the expression of gluconeogenic genes such as PEPCK and G6Pase [37]. GCN5 can acetylate PGC-1α and decrease its activity, such that PGC-1α cannot bind to the promoter of its target gene, which leads to decrease of gluconeogenesis [74]. Surprisingly, as one of the deacetylases, sirtuin 6 (SIRT6) increases PGC-1α acetylation and downgrades hepatic glucose production (HGP). The reason is that SIRT6 increases the degree of acetylation of PGC-1α through the deacetylation and activation of GCN5 [38]. In the fasting state, glucagon down-regulates the expression of SIRT6 by phosphorylation, resulting in inhibition of GCN5 activity [38,39]. Glucagon reduces the degree of acetylation of PGC1-α by restraining GCN5, thereby transmitting the signal of cellular energy status to PGC-1α, accordingly increasing the output of cellular energy by increasing the expression of gluconeogenesis genes. In summary, this finding reveals an interesting phenomenon in which glucagon is able to participate in the acetylation process of the energy-sensing factors PGC-1α by regulating the SIRT6.
Additionally, glucagon lessens glycogen phosphorylase acetylation to promote hepatic glycogen phosphorylase (GP) activity. GP acts as a catalytic rate-limiting enzyme in the glycogenolysis process and plays an essential role in preserving glucose homeostasis [75,76]. Zhang et al. unmasked that the activity of GP was reduced after being modified by acetylation. Afterward, they recorded the acetylation levels of GP expressed in hepatocytes after treatment with glucagon, and the results revealed that GP acetylation was decreased by glucagon induction. Finally, their research unmasked that glucagon induced the decreasing acetylation of GP and led to higher GP activity, resulting in increased production of glucose by glycogenolysis [40]. However, it is unclear which enzymes are involved in this process, and the precise mechanism by which glucagon regulates GP acetylation remains to be elucidated.

2.2. Glucagon-Induced Deacetylation Regulates Hepatic Gluconeogenesis during the Fasting State

Glucagon also regulates glucose balance by inducing deacetylation of energy-sense factors. Sirtuins are a class of NAD$^+$-dependent deacetylases, and their functions are closely related to cellular metabolism [77]. There are seven recognized members of the human sirtuin family, which can interact with p53, FOXO1/PGC-1α, Nuclear factor kappa B (NF-κB), and other proteins to regulate cellular stress response, metabolism, aging, and apoptosis [30]. In the past few decades, research on biological functions of the sirtuin family has made considerable progress. In this progress, sirtuin 1 (SIRT1) was studied wildly in many aspects. SIRT1 deacetylates histones and many important transcription factors to act as an energy-sensing factor in hepatic energy metabolism [78–80]. Lilia et al. provided in vivo evidence that glucagon increases SIRT1 expression through CREB activation in the fasting state. In response to CR, glucagon promotes energy production through PKA-mediated activation of the CREB, and CREB is capable of binding to the SIRT1 promoter to increase its transcription [81].

As mentioned above, glucagon increases the activity of CRTC2 through p300 to increase gluconeogenesis in the fasting state. In fact, short-term fasting can increase CRTC2–p300 interaction in the liver, while long-term fasting destroys it through SIRT1. During prolonged fasting, glucagon impels SIRT1 to deacetylase CRTC2 and promotes CRTC2 ubiquitin-dependent degradation with constitutively photomorphogenic 1 (COP1). Meanwhile, SIRT1-mediated deacetylation increases the activity of FOXO1 to promote expression of the glycogen production program [25]. Additionally, studies have shown that SIRT1 activators reduce gluconeogenesis in insulin-resistant animals. Paradoxically, it also increases the activity of FOXO1, and the increase of FOXO1 will lead to increased gluconeogenesis [82–84]. During this time, upregulation of FOXO1 activity by SIRT1 appears to be critical for maintaining energy balance. Interestingly, activation of CRTC2 by glucagon is abolished by deacetylation of CRTC2 by SIRT1 in prolonged fasting, and SIRT1 has a positive regulatory effect on SIRT6, all of which will inhibit the production of glucose [85–87]. It seems contradictory that SIRT1 can both promote and inhibit gluconeogenesis. In fact, several studies about the function of SIRT1 in the liver metabolism have found that SIRT1 plays a diametrically opposite role hepatic glucose metabolism during different physiological periods. Also, the notion has been put forward that prolonged stimulation of SIRT1 expression might tone down the gluconeogenic program through deacetylation and inhibition of CRTC2, thereby favoring energy-sparing processes such as ketogenesis [25,84,88–90]. This result reflects that glucagon-induced deacetylation through SIRT1 has different regulatory effects on glucose production in different fasting stages.

HDACs, a class of proteases that deacetylate histone, contribute to chromosome structural modification and regulation of gene expression [91]. HDACs regulate the expression of crucial gluconeogenesis enzymes by controlling the activity of the forkhead transcription factor (FOXO) family, thereby regulating gluconeogenesis. For example, HDAC1 induces the expression of hepatocyte nuclear factor 4α (HNF4α), leading to the dephosphorylation of FOXO1 into the nucleus of hepatocytes, which in turn prompts the expression of staple enzymes in the liver and increases glycogenesis. Recent studies have found that class IIa HDACs were also involved in the regulation of FOXO family activity to regulate hepatic gluconeogenesis [41]. In the fasting state, glucagon rapidly dephosphorylates
class IIa HDACs and transfers it from the cytoplasm to the nucleus, thereby recruiting HDAC3 to form a complex and promoting deacetylation of FOXOs. This enhances its transcriptional activity and induces transcription of the key enzymes promoting gluconeogenesis. Additionally, HDACs are also involved in the gluconeogenesis process regulated by signal transducers and STAT3 [33]. The deacetylation of STAT3 by HDACs promotes transcription of STAT3 hepatic glycogenase in the hepatocytes of obese and diabetic patients. Accordingly, HDACs play an essential role in regulating hepatic glucose production.

3. Glucagon-Mediated Lipid Homeostasis in the Liver during the Fasting State

Lipids represent a necessary source of energy, particularly for the purposes of long-term storage. Lipids also protect the internal organs with skin, bones, and muscles, prevent the body temperature from spreading, and help the absorption of fat-soluble vitamins in food. Lipid metabolism is regulated by genetics, neurohumoral fluids, hormones, enzymes, and organs such as the liver. When these factors are abnormal, it brings about lipid metabolism disorders and pathophysiological changes in related organs such as hyperlipoproteinemia, lipid storage disease and its clinical syndrome, obesity, ketoacidosis, fatty liver, and neonatal scleredema [92]. As the central organ of lipid metabolism, the liver responds to nutrient and hormonal signals by regulating fatty acid oxidation and lipogenesis. It can synthesize lipoproteins, which is beneficial to lipid transport, fatty acid oxidation, and ketone body formation [93]. In the fasting state, the sugar supply is insufficient and glucagon secretion is increased, thus altering the acetylation state of the lipid metabolism enzyme, resulting in accelerated fat decomposition and increased ketone body formation (Figure 1B).

3.1. Glucagon-Induced Acetylation Enhances Fatty Acid Oxidation

When glycogen in the liver is depleted, the liver enhances oxidation of fatty acids to maintain the energy supply [94]. Fatty acid oxidation can not only provide a large amount of required energy, it is also the primary pathway for fatty acid decomposition and transformation in the body. The length fatty acid chains needed by the human body are different, and they are transformed by fatty acid oxidation. Therefore, chain fatty acids are turned into a suitable length for metabolism in the body [95]. Based on findings from many researchers, we summarize that glucagon can change the activity of fatty acid metabolism enzymes by acetylation in the liver, which is the most active organ for fatty acid oxidation, thereby enhancing fatty acid oxidation and increasing ketone body production.

For example, glucagon raises the expression of sirtuin 3 (SIRT3) by enhancing the activity of PGC1-α in the fasting state [49,96,97]. SIRT3 is also an important member of the mammalian sirtuin family protein and plays a vital role in controlling metabolic activities [98,99]. Anderson et al. demonstrated that SIRT3 could regulate long-chain acyl-CoA dehydrogenase (LCAD) in the liver of mice through its deacetylation activity, increase LCAD levels, and enhance fatty acid oxidation. Thereby, it would reduce triglycerides and the accumulation of fatty acid oxidation intermediates affecting the metabolic syndrome [42]. LCAD is a crucial mitochondrial fatty acid oxidation enzyme. The defects of LCAD lead to fatty acid oxidation disorders and the accumulation of free fatty acids (FFA). These results suggest that glucagon regulates LCAD by regulating SIRT3 and reduces the accumulation of free fatty acids (FFA). Additionally, Tong et al. found that accumulation of lipids was decreased by SIRT3-mediated motivation of the AMP-activated protein kinase (AMPK) in hepatocytes. The decrease in cellular energy storage results in reduction of the ATP/ADP ratio and an increase in the AMP/ATP ratio, while activation of AMPK promotes ATP synthesis, accordingly decreasing fatty acid synthesis and increasing fatty acid oxidation. This result suggests that glucagon may increase the oxidation of fatty acids through the activation of the SIRT3-AMPK signaling pathway [43]. And we can infer that glucagon-induced acetylation of energy-sensing factors by SIRT3 acts as a metabolic sensor in response to changes in cellular energy status.

The inhibitory effect of SIRT1 on gluconeogenesis might be an energy-saving means of the body, which would be reflected in lipid metabolism. With the extension of fasting time, glucose supply
is insufficient and the body turns to lipid metabolism for energy supply. Under prolonged fasting conditions, the energy source is shifted from glucose metabolism to lipid metabolism in response to the insufficient supply of glucose [101]. Undoubtedly, this series of transformations is regulated by glucagon as the primary hormone that maintains energy balance during fasting. With the effect of glucagon, SIRT1 certainly regulates peroxisome proliferator-activated receptor-α (PPAR-α) to control hepatic lipid metabolism. PPAR-α is a nuclear receptor that is primarily located in organs with active lipid metabolisms, such as the liver [102]. The activation of PPAR-α promotes the utilization and catabolism of fatty acids by upregulating genes involved in fatty acid metabolism [103–105]. Therefore, as a lipid-sensing factor, activated PPAR-α modifies gene expression of proteins highly involved in the regulation of fatty acid metabolism, such as adipocyte fatty acid-binding protein (AFABP), fatty acid transporter (FATP), and lipoprotein lipase (LPL) [106–109]. Other research has found that the hepatocyte-specific deletion of SIRT1 undermined the activity of PPAR-α, which decreased fatty acid oxidation and led to development of hepatic steatosis and inflammation [110,111].

Furthermore, Ferdinand et al. revealed that glucagon-induced acetylation of Foxa2 was in control of lipid metabolism in response to fasting conditions [44]. The cofactors p300 and SIRT1, respectively, regulate Foxa2 acetylation and deacetylation at the Lys259 site [44]. During fasting, glucagon inhibits the activity of salt-inducible kinase 2 (SIK2) by activating adenylate cyclase (AC), thereby SIK2 decreases p300 activity [25]. Through this approach, glucagon improves the activity of p300 and further promotes the acetylation of Foxa2. Acetylation of Foxa2 increases the expression of genes involved in β-oxidation, such as carnitine palmitoyltransferase 1A (CPT1A) or medium-chain acyl-CoA dehydrogenase (MCAD) [45,46]. But SIRT1 can inactivate Foxa2 by deacetylation and thereby decrease the activity of Foxa2, which reflects a contradiction of SIRT1 in fatty acid metabolism [44,47]. The reason might be that SIRT1 improves the activity of PPAR-α by inhibiting Foxa2 because PPAR-α and Foxa2 competitively bind to the same promoter [112]. In addition, the concept that fasting increases SIRT1 activity has been oppugned [90,113]. Therefore, it deserves more attention to explore the different functions of SIRT1 and figure out its roles in the same metabolic process, which is helpful to clarify the metabolic mechanism. These results reflect that glucagon maintains the energy supply through different pathways under different nutritional conditions.

3.2. Glucagon-Induced Acetylation Inhibits Lipogenesis in the Liver

Lipogenesis in the liver is significant for the formation of very-low-density lipoprotein (VLDL) and the delivery of energy to other tissues, and this process is tightly regulated by hormones and nutritional status [114]. In the fasting state, because of an elevated glucagon concentration and activation of the intracellular cyclic adenosine monophosphate pathway, the acetylation status of lipid synthesis-related transcription factors is altered, resulting in low levels of de novo lipogenesis (DNL) [115]. In the fasting state, glucagon-mediated p300-CBP-associated factor (PCAF) acetylation and SIRT1 deacetylation pathways are involved in the acetylation of cAMP-responsive element-binding protein H (CREBH) to regulate hepatic lipogenesis [31]. As an energy-sensing factor for hepatic lipid metabolism, CREBH activates the expression of genes involved in the lipogenesis [116]. After glucagon stimulation, CREBH is acetylated by PCAF at the Lys294 site, which is necessary to interact with PPARα [31]. It has also been observed that the interaction of CREBH and PPARα synergistically increases fibroblast growth factor 21 (FGF21), leading to inhibition of lipogenesis in the fasting state [48]. Interestingly, after prolonged fasting, SIRT1 will in turn enhance the interaction of CREBH and PPARα [31]. This is compatible with the conclusion that SIRT1 plays distinct roles in different periods of fasting. In summary, this finding reveals that glucagon induces acetylation of CREBH to modulate lipid homeostasis in a time-dependent way.

In addition, glucagon has a significant regulatory effect on the activity of SREBP-1c through SIRT1-mediated acetylation modification. The transcription factor SREBP-1c works essentially on impacting transcription of hepatic genes such as glucokinase and fatty acid synthase. So, SREBP-1c positively regulates lipid synthesis by affecting the expression of the above genes [117,118]. In the
fasting state, glucagon promotes the expression of SIRT1, and SIRT1 can respectively deacetylate SREBP-1c at Lys-289 and Lys-309. Deacetylation of SREBP-1c by SIRT1 decreases SREBP-1c activity and its association with lipogenic gene promoters [29]. In vivo experiments have also demonstrated that overexpression of SIRT1 reduces the stability of SREBP-1c, resulting in reduced lipid synthesis [119]. Besides, the function of SIRT1 in deacetylating the energy-sensing factor PGC-1α has been proved in fasting [84,120,121]. SIRT1-mediated deacetylation of PGC-1α increases its activity, which decreases lipid synthesis in response to glucagon [122–124]. These results indicate that glucagon precisely controls lipid synthesis by regulating the acetylation status of different energy-sensing factors.

4. Glucagon-Mediated Protein Homeostasis in the Liver

In health, the liver orchestrates the metabolism of proteins and amino acids. After proteins in food are broken down into amino acids (AAs) through the gastrointestinal tract, synthesis and metabolism of proteins in the body are re-executed mainly in the liver. The liver circulates urea to counter toxic ammonia produced in protein metabolism, thereby relieving the toxicity of ammonia. Thus, the urea cycle is the primary way for organisms to discharge nitrogen-containing metabolic waste [125–127]. During prolonged fasting, hepatic gluconeogenesis promotes carbon flux from AAs into central metabolism, when AAs become an important source of energy [127–129]. Under this condition, excessive ammonia is converted into urea to relieve ammonia poisoning [130,131]. As a hormone secreted mainly in the fasting state, glucagon maintains the metabolic balance of the body during CR by stimulating PGC1-α [120,132]. Research has shown that glucagon activates SIRT3 and sirtuin 5 (SIRT5) in the fasting state, which increases the activity of carbamoyl phosphate synthetase 1 (CPS1) and ornithine transcarbamylase (OTC) involved in ureagenesis. In this way, glucagon positively regulates ureagenesis by activating SIRT3 and SIRT5. SIRT3 and SIRT5 provide essential post-translational modification for a number of critical metabolic pathways [133–135]. Recent studies report that SIRT3 and SIRT5 promote ureagenesis in the fasting state [127,136]. During fasting, glucagon secretion stimulates the expression of PGC1-α in hepatocytes and alanine as a nitrogen source for urea production. PGC-1α enhances hepatic ureagenesis via promoting SIRT3 and SIRT5-mediated deacetylation of CPS1 and OTC [49,50]. This mechanism indicates that glucagon-induced acetylation of energy-sensing factors can also maintain metabolic homeostasis through ammonia detoxification during fasting, reflecting the diversity of glucagon biological functions.

5. Glucagon-Mediated Acetylation in Liver Disease

Hepatocytes are target cells of many hepatotoxic substances such as viruses, alcohol metabolites, and bile acids [137–139]. Therefore, the liver is vulnerable to attack by these hepatotoxic substances that contribute to liver metabolic syndrome [140]. It is well established that glucagon brings about elevation in plasma c-AMP and stimulates glycolipid metabolism in the liver. Undoubtedly, impairment of the liver will affect c-AMP biosynthesis, which is encouraged by glucagon, leading to compromised hepatic sensitivity to glucagon [141]. Multiple research studies have proven that metabolic disorders accompany an increase in plasma glucagon concentration [20,142]. We have introduced the critical role of glucagon-induced acetylation in liver metabolism. Further in-depth studies on its regulatory mechanisms and functions will contribute to improving hepatic metabolic diseases including NAFLD, hepatic fibrosis, and cancer.

5.1. Glucagon-Mediated Acetylation in Nonalcoholic Fatty Liver Disease (NAFLD) and Hepatic Fibrosis

Recently, NAFLD has been recognized to be one of the most common liver metabolic diseases in the world. NAFLD is thought to be a manifestation of metabolic syndrome in the liver, involving a series of disorders ranging from steatosis to steatohepatitis, with inflammation, liver damage, hepatocyte ballooning, glucose homeostasis, insulin resistance, and hepatic fibrosis [143–145]. Hepatic fibrosis is a pathological process characterized by the proliferation of extracellular matrix (ECM) after liver injury. Chronic hepatitis is accompanied by the progressive deposit of hepatic fibrosis, which may lead to
cirrhosis. Patients with NAFLD and advanced hepatic fibrosis are at the highest risk for progressing to end-stage liver disease [146–148]. Recent investigations suggested that SIRT1, a critical metabolic regulator, and its enzymatic activity may be regulated by cellular energy, significantly improving disease progression in animal models of NAFLD [149–152]. It has been observed that the liver becomes insensitive to glucagon as a result of hepatic steatosis in NAFLD patients, which further promotes glucagon secretion [141]. However, in this state, the biological effect of glucagon is weakened, and the impact of glucagon on SIRT1 is also impaired, while SIRT1 can inhibit hepatic steatosis and inflammatory responses to hepatic metabolic disorders. Additionally, SIRT1 can reduce the level of oxygen consumption, which is correlative with NAFLD [153,154]. Conversely, hepatocyte-specific knockout of SIRT1 can cause significant hepatic steatosis and aggravate liver inflammatory responses. As a result, SIRT1 can deacetylate and modify STAT3, which will lead to STAT3 phosphorylation and lessen the activity of STAT3 [53,54]. STAT3 can regulate many target genes related to antiviral protection, hepatitis, and liver remodeling, and plays an essential role in liver fibrosis [54,155,156]. Additionally, glucagon can promote SIRT1 inhibition of liver inflammation, and inflammation is the most critical factor leading to the progression of liver fibrosis [157–159]. On the one hand, SIRT1 can down-regulate NF-κB activity and reduce inflammation [51,52]. On the other hand, SIRT1 can participate in fibrosis by regulating the transforming growth factor β (TGF-β) signaling pathway, which is very important in liver fibrosis [55,56]. These findings suggest that SIRT1 not only plays a crucial role in liver lipid metabolism-related diseases, such as NAFLD, but also plays a vital role in the development of liver fibrosis.

5.2. Glucagon-Mediated Acetylation in Tumorigenesis and Hepatocarcinogenesis

Pathological changes in liver metabolism and physiological states will eventually lead to tumorigenesis and liver cancer. Hepatocellular carcinoma (HCC) is one of the end-stage liver diseases, and it has become the third leading cause of cancer mortality worldwide [160]. As a multi-factor, complex disease, the relationship between metabolic abnormalities and HCC has gradually been valued by researchers in recent years. Abnormal glycolipid metabolism is considered a potential risk factor for the development of HCC [161]. Cancer cells preferably generate lactate by the glycolysis pathway, even in aerobic conditions, to meet their demands of rapid growth and proliferation, known as aerobic glycolysis [162]. The main physiological functions of glucagon include the regulation of glycolipid metabolism and the inhibition of glycolysis, so there might be some association between tumorigenesis and HCC. High nuclear acetylation levels have also been observed in cancer cells for the increased activity of acetyltransferase [17,18]. Here, we review and discuss recent advances to elucidate how glucagon-induced acetylation of different energy-sensing factors has different effects on hepatocarcinogenesis and tumor growth.

As mentioned above, glucagon can improve PCAF activity, and mounting evidence has revealed different effects of PCAF on HCC over the last few years. Overexpression of PCAF induces HCC cell apoptosis and autophagy, which is harmful for cancer cell proliferation [163]. In addition, PCAF induces acetylation of the K1323 site of PGK1, which in turn enhances the activity of deacetylase Sirtuin 7 (SIRT7) on K1323 and promotes cancer cell proliferation [57]. Pyruvate kinase M2 (PKM2) is acetylated at the K305 site by PCAF, which in turn leads to degradation of PKM2 [58,59]. PKM2 is expressed in different tissues and organs in which all large amounts of nucleic acids are synthesized, especially in tumor cells. Therefore, a high expression of PKM2 is accompanied by a variety of tumors, and this phenomenon is not caused by PKM2 splicing changes [164]. Ectopic expression of PCAF increases acetylation of PKM2, at K305 and decreases PKM2 activity. A decrease in the activity of PKM2 results in the accumulation of glycolytic intermediates upstream, such as fructose-1, 6-bisphosphate (FBP), and G6Pase [165,166]. So, the function of glycolysis is shifted from producing ATP to accumulating intermediate metabolites, providing raw materials for the synthesis of various biomacromolecules, thereby allowing tumor growth and cell proliferation.
Glucagon-induced acetylation of PGC-1α and FOXO controls the expression of glycolytic genes. GCN5 acetylates PGC-1α and inhibits its transcriptional activity. The deacetylation of PGC-1α by SIRT1 in turn improves its activity, both of which modulate the balance of gluconeogenic and glycolytic genesis in hepatocytes [60,61]. FOXO transcription factors have been implicated in the upregulation of gluconeogenic genes and downregulation of glycolytic genes, playing a crucial role in tumor suppression [167]. Recent studies revealed the crucial role of FOXO acetylation in tumor suppression; activating FOXO will downregulate glycolytic genes. Glucagon-induced acetylation of FOXO by p300 inhibits its transcriptional and biological activities. In this regard, acetylation of FOXO could heighten glycolysis activity and promote cancer cell growth [62,63]. In summary, these findings may reveal that glucagon-induced acetylation of different energy-sensing factors has diverse effects on tumorigenesis and hepatocarcinogenesis, and also provides potential strategies for the treatment of liver cancer.

6. Concluding Discussion and Perspective

In-depth studies on glucagon biology and pharmacology will help to further understand various modes in control of metabolism and provide potential therapeutic strategies for liver metabolic diseases. Researchers are aware that glucagon plays an unparalleled role in hepatic pathophysiology. Therefore, we reviewed glucagon-induced acetylation of energy factors in the control of hepatic metabolism, aiming to provide a treatment reference for liver metabolism diseases.

Acetylation is a type of PTM in the nucleus, cytoplasm, mitochondria, and other organelles. Acetylation of energy-sensing factors is a significant regulator in hepatic metabolism. The number of nutrients in the environment and the changes in the types of nutrients can alter the direction of metabolism and the transformation between various metabolic pathways by affecting glucagon-induced acetylation of energy-sensing factors. Lysine acetylation modification of energy-sensing factors coordinates the interaction of various metabolic pathways well, and plays a fine role in the metabolic network of the organism.

The discovery of glucagon-mediated acetylation of energy-sensing factors in control of liver metabolism opened new avenues of research into the biology and pharmacology of glucagon. Meanwhile, there are several important questions that need to be resolved, which are crucial for assessing whether glucagon-induced acetylation of different energy-sensing factors is a potential strategy for treating liver metabolism diseases:

1. The mechanisms by which glucagon regulates metabolic disorders remain unclear and require more relevant research.
2. It is still poorly understood how acetylation dynamically regulates the metabolic state of different cells and tissues and interacts with specific signaling pathways in response to changes of external environment.
3. Further understanding of the function and regulation of acetyltransferase and deacetylase will help to show how acetylation integrates different metabolic fluxes within cells and coordinates the entire metabolic network to meet the metabolic needs of cells.
4. Metabolic-related diseases have strong individual differences. Physiological and pathological changes in the acetylation state of different energy-sensing factors and their importance in the development of liver metabolism diseases still needs to be studied in depth, which not only contributes to detection and diagnosis of diseases, but also provides ideas for the further development of tissue-specific and metabolic pathway-specific drugs.

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Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| AA           | Amino acids |
| AC           | Adenylate cyclase |
| AFABP        | Adipocyte fatty acid binding protein |
| AMPK         | AMP-activated protein kinase |
| cAMP         | Cyclic AMP |
| CMA          | Chaperone-mediated autophagy |
| COP1         | Constitutively photomorphogenic 1 |
| CPS1         | Carbamoyl phosphate synthetase 1 |
| CPT1A        | Carnitine palmitoyltransferase 1A |
| CR           | Caloric restriction |
| CREB         | cAMP response-element-binding protein |
| CREBH        | cAMP responsive element-binding protein H |
| CRTC2        | CREB regulated transcription coactivator 2 |
| DNL          | De novo lipogenesis |
| ECM          | Extracellular matrix |
| FATP         | Fatty acid transporter |
| FBP          | Fructose-1, 6-bisphosphate |
| FFA          | Free fatty acids |
| FGF21        | Fibroblast growth factor 21 |
| FOXO1        | Forkhead box O1 |
| G6Pase       | Glucose-6-phosphatase |
| GCN5         | General control nonrepressed protein 5 |
| GP           | Glycogen phosphorylase |
| HCC          | Hepatocellular carcinoma |
| HDACs        | Histone deacetylases |
| HGP          | Hepatic glucose production |
| HNF-4α       | Hepatocyte nuclear factor 4α |
| KATs         | Lysine acetyltransferases |
| LCAD         | Long-chain acyl-CoA dehydrogenase |
| LPL          | Lipoprotein lipase |
| LCAT         | Medium-chain acyl-CoA dehydrogenase |
| MEK/ERK      | Mitogen-activated protein kinase kinase-extracellular signal-regulated kinase |
| NAFLD        | Nonalcoholic fatty liver disease |
| NF-κB        | Nuclear factor kappa B |
| OTC          | Ornithine transcarbamylase |
| PCAF         | P300-CBP associated factor |
| PEPCK1       | Phosphoenolpyruvate carboxykinase |
| PGC-1α       | Peroxisome proliferator-activated receptor gamma coactivator 1α |
| PKA          | Protein kinase A |
| PKM2         | Pyruvate kinase M2 |
| PPAR         | Peroxisome proliferator-activated receptor |
| PPAR-α       | Peroxisome proliferators-activated receptor-α |
| PTMs         | Post-translational modifications |
| SIK2         | Salt-inducible kinase 2 |
| SIRT1        | Sirtuin 1 |
| SIRT3        | Sirtuin 3 |
| SIRT5        | Sirtuin 5 |
| SIRT6        | Sirtuin 6 |
| SIRT7        | Sirtuin 7 |
SREBP-1c  Sterol regulatory-element-binding protein-1c  
STAT3  Signal transducer and activator of transcription-3  
T2DM  Type 2 diabetes  
TGF-β  Transforming growth factor β  
VLDL  Very-low-density lipoprotein

References
1. Furukawa, S.; Fujita, T.; Shimabukuro, M.; Iwaki, M.; Yamada, Y.; Nakajima, Y.; Nakayama, O.; Makishima, M.; Matsuda, M.; Shimomura, I. Increased oxidative stress in obesity and its impact on metabolic syndrome. *J. Clin. Investig.* 2017, 114, 1752–1761. [CrossRef] [PubMed]
2. Zinman, B.; Wanner, C.; Lachin, J.M.; Fitchett, D.; Bluhmki, E.; Hantel, S.; Mattheus, M.; Devins, T.; Johansen, O.E.; Woerle, H.J. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N. Engl. J. Med.* 2015, 373, 2117–2128. [CrossRef]
3. Byrne, C.D.; Targher, G. NAFLD: A multisystem disease. *J. Hepatol.* 2015, 62, S47–S64. [CrossRef]
4. Kotas, M.E.; Medzhitov, R. Homeostasis, inflammation, and disease susceptibility. *Cell* 2015, 160, 816–827. [CrossRef] [PubMed]
5. Rhee, C.M.; Ahmadi, S.-F.; Kalantar-Zadeh, K. The dual roles of obesity in chronic kidney disease: A review of the current literature. *Curr. Opin. Nephrol. Hypertens.* 2016, 25, 208. [CrossRef]
6. Jensen, G.L. Malnutrition and inflammation—burning down the house: Inflammation as an adaptive physiologic response versus self-destruction? *Acta Médica de Cuba* 2016, 17, 68526. [CrossRef]
7. Stylianou, E. Epigenetics of chronic inflammatory diseases. *J. Inflamm. Res.* 2019, 12, 1. [CrossRef]
8. Peng, H.; Wisse, E.; Tian, Z. Liver natural killer cells: Subsets and roles in liver immunity. *Cell. Mol. Immunol.* 2016, 13, 328. [CrossRef] [PubMed]
9. Ahmadian, M.; Suh, J.M.; Hah, N.; Liddle, C.; Atkins, A.R.; Downes, M.; Evans, R.M. PPARγ signaling and metabolism: The good, the bad and the future. *Nat. Med.* 2013, 19, 557. [CrossRef]
10. Yoshimoto, S.; Loo, T.M.; Atarashi, K.; Kanda, H.; Sato, S.; Oyadomari, S.; Iwakura, Y.; Oshima, K.; Morita, H.; Hattori, M. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. *Nature* 2013, 499, 97. [CrossRef] [PubMed]
11. Yamashita, T.; Wang, X.W. Cancer stem cells in the development of liver cancer. *J. Clin. Investig.* 2013, 123, 1911–1918. [CrossRef]
12. Pejaver, V.; Hsu, W.L.; Xin, F.; Dunker, A.K.; Uversky, V.N.; Radivojac, P. The structural and functional signatures of proteins that undergo multiple events of post-translational modification. *Protein Sci.* 2014, 23, 1077–1093. [CrossRef]
13. Choudhary, C.; Weinert, B.T.; Nishida, Y.; Verdin, E.; Mann, M. The growing landscape of lysine acetylation links metabolism and cell signalling. *Nat. Rev. Mol. Cell Biol.* 2014, 15, 536. [CrossRef]
14. Jeffers, V.; Sullivan, W.J. Lysine acetylation is widespread on proteins of diverse function and localization in the protozoan parasite Toxoplasma gondii. *Eukaryot. Cell* 2012, 11, 735–742. [CrossRef]
15. Shen, Y.; Wei, W.; Zhou, D.-X. Histone acetylation enzymes coordinate metabolism and gene expression. *Trends Plant Sci.* 2015, 20, 614–621. [CrossRef] [PubMed]
16. Lin, H.; Su, X.; He, B. Protein lysine acylation and cysteine succination by intermediates of energy metabolism. *ACS Chem. Biol.* 2012, 7, 947–960. [CrossRef] [PubMed]
17. Lee, J.V.; Carrer, A.; Shah, S.; Snyder, N.W.; Wei, S.; Venneti, S.; Worth, A.J.; Yuan, Z.-F.; Lim, H.-W.; Liu, S. Akt-dependent metabolic reprogramming regulates tumor cell histone acetylation. *Cell Metab.* 2014, 20, 306–319. [CrossRef] [PubMed]
18. Lin, R.; Tao, R.; Gao, X.; Li, T.; Zhou, X.; Guan, K.-L.; Xiong, Y.; Lei, Q.-Y. Acetylation stabilizes ATP-citrate lyase to promote lipid biosynthesis and tumor growth. *Mol. Cell* 2013, 51, 506–518. [CrossRef] [PubMed]
19. Danai, L.V.; Babic, A.; Rosenthal, M.H.; Dennstedt, E.A.; Muir, A.; Lien, E.C.; Mayers, J.R.; Tai, K.; Lau, A.N.; Jones-Sali, P. Altered exocrine function can drive adipose wasting in early pancreatic cancer. *Nature* 2018, 558, 600. [CrossRef]
20. Unger, R.H.; Cherrington, A.D. Glucagonocentric restructuring of diabetes: A pathophysiologic and therapeutic makeover. *J. Clin. Investig.* 2012, 122, 4–12. [CrossRef]
21. Lee, Y.H.; Wang, M.-Y.; Yu, X.-X.; Unger, R.H. Glucagon is the key factor in the development of diabetes. *Diabetologia* 2016, 59, 1372–1375. [CrossRef]

22. Marliss, E.B.; Aoki, T.T.; Unger, R.H.; Soeldner, J.S.; Cahill, G.F. Glucagon levels and metabolic effects in fasting man. *J. Clin. Invest.* 1970, 49, 2256–2270. [CrossRef] [PubMed]

23. Jones, B.; Tan, T.; Bloom, S. Mini review: Glucagon in stress and energy homeostasis. *Endocrinology* 2012, 153, 1049–1054. [CrossRef]

24. Buler, M.; Aatsinki, S.-M.; Skoumal, R.; Hakkola, J. Energy sensing factors PGC-1α and SIRT1 modulate PXR expression and function. *Biochem. Pharmacol.* 2011, 82, 2008–2015. [CrossRef] [PubMed]

25. Liu, Y.; Dentin, R.; Chen, D.; Hedrick, S.; Ravnskjæer, K.; Schenk, S.; Milne, J.; Meyers, D.J.; Cole, P.; Yates III, J. A fasting inducible switch modulates gluconeogenesis via activator/coactivator exchange. *Nature* 2008, 456, 269. [CrossRef]

26. Wondisford, A.R.; Xiong, L.; Chang, E.; Meng, S.; Meyers, D.J.; Li, M.; Cole, P.A.; He, L. Control of Foxo1 gene expression by co-activator P300. *J. Biol. Chem.* 2014, 289, 4326–4333. [CrossRef]

27. Wang, Y.; Inoue, H.; Ravnskjaer, K.; Viste, K.; Miller, N.; Liu, Y.; Hedrick, S.; Vera, L.; Montminy, M. Targeted disruption of the CREB coactivator Crtc2 increases insulin sensitivity. *Proc. Natl. Acad. Sci. USA* 2010, 107, 3087–3092. [CrossRef] [PubMed]

28. Oh, K.-J.; Han, H.-S.; Kim, M.-J.; Koo, S.-H. CREB and FoxO1: Two transcription factors for the regulation of hepatic gluconeogenesis. *BMB Rep.* 2013, 46, 567. [CrossRef] [PubMed]

29. Ponugoti, B.; Kim, D.-H.; Xiao, Z.; Smith, Z.; Miao, J.; Zang, M.; Wu, S.-Y.; Chiang, C.-M.; Veenstra, T.D.; Kemper, J.K. SIRT1 deacetylates and inhibits SREBP-1C activity in regulation of hepatic lipid metabolism. *J. Biol. Chem.* 2010, 285, 33959–33970. [CrossRef] [PubMed]

30. Chang, H.-C.; Guarente, L. SIRT1 and other sirtuins in metabolism. *Trends Endocrinol. Metab.* 2014, 25, 138–145. [CrossRef]

31. Kim, H.; Mendez, R.; Chen, X.; Fang, D.; Zhang, K. Lysine acetylation of CREBH regulates fasting-induced hepatic lipid metabolism. *Mol. Cell. Biol.* 2015, 35, 4121–4134. [CrossRef]

32. Qiang, L.; Lin, H.V.; Kim-Muller, J.Y.; Welch, C.L.; Gu, W.; Accili, D. Proatherogenic abnormalities of lipid metabolism in SirT1 transgenic mice are mediated through Creb deacetylation. *Cell Metab.* 2011, 14, 758–767. [CrossRef]

33. Nie, Y.; Erion, D.M.; Yuan, Z.; Dietrich, M.; Shulman, G.I.; Horvath, T.L.; Gao, Q. STAT3 inhibition of gluconeogenesis is downregulated by SirT1. *Nat. Cell Biol.* 2009, 11, 492. [CrossRef] [PubMed]

34. Ravnskjæer, K.; Hogan, M.F.; Lackey, D.; Tora, L.; Dent, S.Y.; Olefsky, J.; Montminy, M. Glucagon regulates gluconeogenesis through KAT2B-and WDR5-mediated epigenetic effects. *J. Clin. Invest.* 2013, 123, 4318–4328. [CrossRef] [PubMed]

35. Qiang, L.; Banks, A.S.; Accili, D. Uncoupling of acetylation from phosphorylation regulates FoxO1 function independent of its subcellular localization. *J. Biol. Chem.* 2010, 285, 27396–27401. [CrossRef] [PubMed]

36. Li, K.; Qu, C.; Sun, P.; Liu, D.-C.; Wu, T.-J.; Wang, K.; Zhou, Y.-C.; Chang, X.-A.; Yin, Y.; Chen, F. Ets1-mediated acetylation of FoxO1 is critical for gluconeogenesis regulation during feed-fast cycles. *Cell Rep.* 2019, 26, 2998–3010. [CrossRef] [PubMed]

37. Shin, J.-H.; Ko, H.S.; Kang, H.; Lee, Y.; Lee, Y.-I.; Pletinkova, O.; Troconso, J.C.; Dawson, V.L.; Dawson, T.M. PARIS (ZN7F46) repression of PGC-1α contributes to neurodegeneration in Parkinson’s disease. *Cell* 2011, 144, 689–702. [CrossRef]

38. Dominy J.E., Jr.; Lee, Y.; Jedrychowski, M.P.; Chim, H.; Jurczak, M.J.; Camporez, J.P.; Ruan, H.-B.; Feldman, J.; Pierce, K.; Mostoslavsky, R. The deacetylase Sirt6 activates the acetyltransferase GCN5 and suppresses hepatic gluconeogenesis. *Mol. Cell* 2012, 48, 900–913. [CrossRef] [PubMed]

39. Gertler, A.A.; Cohen, H.Y. SIRT6, a protein with many faces. *Biogerontology* 2013, 14, 629–639. [CrossRef]

40. Zhang, T.; Wang, S.; Lin, Y.; Xu, W.; Ye, D.; Xiong, Y.; Zhao, S.; Guan, K.-L. Acetylation negatively regulates glycogen phosphorylase by recruiting protein phosphatase 1. *Cell Metab.* 2012, 15, 75–87. [CrossRef]

41. Mihaylova, M.M.; Vasquez, D.S.; Ravnskjæer, K.; Denechaud, P.-D.; Ruth, T.Y.; Alvarez, J.G.; Downes, M.; Evans, R.M.; Montminy, M.; Shaw, R.J. Class IIa histone deacetylases are hormone-activated regulators of FOXO and mammalian glucose homeostasis. *Cell* 2011, 145, 607–621. [CrossRef] [PubMed]

42. Hirschey, M.D.; Shimazu, T.; Goetzman, E.; Jing, E.; Schwer, B.; Lombard, D.B.; Grueter, C.A.; Harris, C.; Biddinger, S.; Ilkayeva, O.R. SIRT3 regulates mitochondrial fatty-acid oxidation by reversible enzyme deacetylation. *Nature* 2010, 464, 121. [CrossRef]
43. Tong, S.; Fan, G.Q.; Xiao, S.D. SIRT3 reduces lipid accumulation via AMPK activation in human hepatic cells. *J. Dig. Dis.* 2010, 11, 55–62.
44. Von Meyenn, F.; Porstmann, T.; Gasser, E.; Selevsek, N.; Schmidt, A.; Aebersold, R.; Stoffel, M. Glucagon-induced acetylation of Foxa2 regulates hepatic lipid metabolism. *Cell Metab.* 2013, 17, 436–447. [CrossRef] [PubMed]
45. Park, J.-M.; Jo, S.-H.; Kim, M.-Y.; Kim, T.-H.; Ahn, Y.-H. Role of transcription factor acetylation in the regulation of metabolic homeostasis. *Protein Cell* 2015, 6, 769–782. [CrossRef] [PubMed]
46. Wolfrum, C.; Asilmaz, E.; Luca, E.; Friedman, J.M.; Stoffel, M. Foxa2 regulates lipid metabolism and ketogenesis in the liver during fasting and in diabetes. *Nature* 2004, 432, 1027. [CrossRef]
47. van Gent, R.; Di Sanza, C.; van den Broek, N.J.; Fleskens, V.; Veenstra, A.; Stout, G.J.; Bresnahan, A.B. SIRT1 mediates FOXA2 breakdown by deacetylation in a nutrient-dependent manner. *PLoS ONE* 2014, 9, e98438. [CrossRef]
48. Kim, H.; Mendez, R.; Zheng, Z.; Chang, L.; Cai, J.; Zhang, R.; Zhang, K. Liver-enriched transcription factor CREBH interacts with peroxisome proliferator-activated receptor α to regulate metabolic hormone FGF21. *Endocrinology* 2014, 155, 804–813. [CrossRef]
49. Buler, M.; Aatsinki, S.-M.; Izzi, V.; Hakkola, J. Metformin reduces hepatic expression of SIRT3, the mitochondrial deacetylase controlling energy metabolism. *PLoS ONE* 2012, 7, e49863. [CrossRef] [PubMed]
50. Buler, M.; Aatsinki, S.-M.; Izzi, V.; Uusimaa, J.; Hakkola, J. SIRT5 is under the control of PGC-1α and AMPK and is involved in regulation of mitochondrial energy metabolism. *FASEB J.* 2014, 28, 3225–3237. [CrossRef]
51. Tian, Y.; Ma, J.; Wang, W.; Zhang, L.; Xu, J.; Wang, K.; Li, D. Resveratrol supplement inhibited the NF-κB inflammation pathway through activating AMPKα-SIRT1 pathway in mice with fatty liver. *Mol. Cell. Biochem.* 2016, 422, 75–84. [CrossRef]
52. Baker, R.G.; Hayden, M.S.; Ghosh, S. NF-κB, inflammation, and metabolic disease. *Cell Metab.* 2011, 13, 11–22. [CrossRef] [PubMed]
53. Bernier, M.; Paul, R.K.; Martin-Montalvo, A.; Scheibye-Knudsen, M.; Song, S.; He, H.-J.; Armour, S.M.; Hubbard, B.P.; Bohr, V.A.; Wang, L. Negative regulation of STAT3 protein-mediated cellular respiration by SIRT1 protein. *J. Biol. Chem.* 2011, 286, 19270–19279. [CrossRef] [PubMed]
54. Hernandez-Gea, V.; Friedman, S.L. Pathogenesis of liver fibrosis. *Annu. Rev. Pathol. Mech. Dis.* 2011, 6, 425–456. [CrossRef] [PubMed]
55. Meng, X.-m.; Nikolic-Paterson, D.J.; Lan, H.Y. TGF-β: The master regulator of fibrosis. *Nat. Rev. Nephrol.* 2016, 12, 325. [CrossRef]
56. Simic, P.; Williams, E.O.; Bell, E.L.; Gong, J.J.; Bonkowski, M.; Guarente, L. SIRT1 suppresses the epithelial-to-mesenchymal transition in cancer metastasis and organ fibrosis. *Cell Rep.* 2013, 3, 1175–1186. [CrossRef]
57. Hu, H.; Zhu, W.; Qin, J.; Chen, M.; Gong, L.; Li, L.; Liu, X.; Tao, Y.; Yin, H.; Zhou, H. Acetylation of PGK1 promotes liver cancer cell proliferation and tumorigenesis. *Hepatology* 2017, 65, 515–528. [CrossRef]
58. Luo, W.; Semenza, G.L. Emerging roles of PKM2 in cell metabolism and cancer progression. *Trends Endocrinol. Metab.* 2012, 23, 560–566. [CrossRef]
59. Macintyre, A.N.; Rathmell, J.C. PKM2 and the tricky balance of growth and energy in cancer. *Mol. Cell* 2011, 42, 713–714. [CrossRef]
60. Luo, X.; Liao, C.; Quan, J.; Cheng, C.; Zhao, X.; Bode, A.M.; Cao, Y. Post-translational regulation of PGC-1α and its implication in cancer metabolism. *Int. J. Cancer* 2019. [CrossRef]
61. Frazzi, R. SIRT1 in Secretory Organ Cancer. *Front. Endocrinol.* 2018, 9. [CrossRef] [PubMed]
62. Carbajo-Pescador, S.; Mauriz, J.; Garcia-Palom, A.; Gonzalez-Gallego, J. FoxO proteins: Regulation and molecular targets in liver cancer. *Curr. Med. Chem.* 2014, 21, 1231–1246. [CrossRef] [PubMed]
63. Hornsveld, M.; Dansen, T.; Derksen, P.; Burgering, B. Re-evaluating the role of FOXOs in cancer. In *Seminars in Cancer Biology*; Elsevier: Amsterdam, The Netherlands, 2018; pp. 90–100.
64. Gonzalez, R.; Perry, R.; Gao, X.; Gaidhu, M.; Cedia, R.; Unniappan, S. Nutrient responsive nesfatin-1 regulates energy balance and induces glucose-stimulated insulin secretion in rats. *Endocrinology* 2011, 152, 3628–3637. [CrossRef] [PubMed]
Barcellos, L.J.G.; Marqueze, A.; Trapp, M.; Quevedo, R.M.; Ferreira, D. The effects of fasting on cortisol, blood glucose and liver and muscle glycogen in adult jundiá Rhamdia quelen. Aquaculture 2010, 300, 231–236. [CrossRef]

Ruan, X.; Li, P.; Cangelosi, A.; Yang, L.; Cao, H. A long non-coding RNA, IncLGR, regulates hepatic glucokinase expression and glycogen storage during fasting. Cell Rep. 2016, 14, 1867–1875. [CrossRef]

Jitrapakdee, S. Transcription factors and coactivators controlling nutrient and hormonal regulation of hepatic gluconeogenesis. Int. J. Biochem. Cell Biol. 2012, 44, 33–45. [CrossRef]

Cheng, Z.; White, M.F. Targeting Forkhead box O1 from the concept to metabolic diseases: Lessons from mouse models. Antioxid. Redox Signal. 2011, 14, 649–661. [CrossRef] [PubMed]

He, L.; Cao, J.; Meng, S.; Ma, A.; Radovick, S.; Wondisford, F.E. Activation of basal gluconeogenesis by coactivator p300 maintains hepatic glycogen storage. Mol. Endocrinol. 2013, 27, 1322–1332. [CrossRef]

Lin, H.V.; Accili, D. Hormonal regulation of hepatic glucose production in health and disease. Cell Metab. 2011, 14, 9–19. [CrossRef]

He, L.; Naik, K.; Meng, S.; Cao, J.; Sidhaye, A.R.; Ma, A.; Radovick, S.; Wondisford, F.E. Transcriptional co-activator p300 maintains basal hepatic gluconeogenesis. J. Biol. Chem. 2012, 287, 32069–32077. [CrossRef]

Jiao, P.; Feng, B.; Li, Y.; He, Q.; Xu, H. Hepatic ERK activity plays a role in energy metabolism. Mol. Cell. Endocrinol. 2013, 375, 157–166. [CrossRef] [PubMed]

Jeninga, E.H.; Schoonjans, K.; Auwerx, J. Reversible acetylation of PGC-1: Connecting energy sensors and effectors to guarantee metabolic flexibility. Oncogene 2010, 29, 4617. [CrossRef] [PubMed]

Dominy, J.E., Jr.; Lee, Y.; Gerhart-Hines, Z.; Puigserver, P. Nutrient-dependent regulation of PGC-1α’s acetylation state and metabolic function through the enzymatic activities of Sirt1/GCN5. Biochim. Biophys. Acta Proteins Proteom. 2010, 1804, 1676–1683. [CrossRef] [PubMed]

Xu, K.; Morgan, K.T.; Gehris, A.T.; Elston, T.C.; Gomez, S.M. A whole-body model for glycogen regulation reveals a critical role for substrate cycling in maintaining blood glucose homeostasis. PLoS Comput. Biol. 2011, 7, e1002272. [CrossRef]

Klover, P.J.; Mooney, R.A. Hepatocytes: Critical for glucose homeostasis. Int. J. Biochem. Cell Biol. 2004, 36, 753–758. [CrossRef]

Wagner, G.R.; Hirschey, M.D. Nonenzymatic protein acylation as a carbon stress regulated by sirtuin deacylases. Mol. Cell 2014, 54, 5–16. [CrossRef]

Cantó, C.; Auwerx, J. Targeting sirtuin 1 to improve metabolism: All you need is NAD+. Pharmacol. Rev. 2012, 64, 166–187. [CrossRef]

Chung, S.; Yao, H.; Caiot, S.; Hwang, J.-w.; Arunachalam, G.; Rahman, I. Regulation of SIRT1 in cellular functions: Role of polyphenols. Arch. Biochem. Biophys. 2010, 501, 79–90. [CrossRef]

Ruderman, N.B.; Julia Xu, X.; Nelson, L.; Cacicedo, J.M.; Saha, A.K.; Lan, F.; Ido, Y. AMPK and SIRT1: A long-standing partnership? Am. J. Physiol. Endocrinol. Metab. 2010, 298, E751–E760. [CrossRef]

Noriega, L.G.; Feige, J.N.; Canto, C.; Yamamoto, H.; Yu, J.; Herman, M.A.; Matakı, C.; Kahn, B.B.; Auwerx, J. CREB and ChREBP oppositely regulate SIRT1 expression in response to energy availability. EMBO Rep. 2011, 12, 1069–1076. [CrossRef]

Milne, J.C.; Lambert, P.D.; Schen, S.; Carney, D.P.; Smith, J.J.; Gagne, D.J.; Jin, L.; Boss, O.; Perni, R.B.; Vu, C.B. Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes. Nature 2007, 450, 712. [CrossRef]

Frescas, D.; Valenti, L.; Accili, D. Nuclear trapping of the forkhead transcription factor FoxO1 via Sirt-dependent deacetylation promotes expression of glucogenetic genes. J. Biol. Chem. 2005, 280, 20589–20595. [CrossRef] [PubMed]

Rodgers, J.T.; Lerin, C.; Haas, W.; Gygi, S.P.; Spiegelman, B.M.; Puigserver, P. Nutrient control of glucose homeostasis through a complex of PGC-1α and SIRT1. Nature 2005, 434, 113. [CrossRef]

Yang, S.J.; Choi, J.M.; Chae, S.W.; Kim, W.J.; Park, S.E.; Rhee, E.J.; Lee, W.Y.; Oh, K.W.; Park, S.W.; Kim, S.W. Activation of peroxisome proliferator-activated receptor gamma by rosiglitazone increases sirt6 expression and ameliorates hepatic steatosis in rats. PLoS ONE 2011, 6, e17057. [CrossRef] [PubMed]

Kanfi, Y.; Peshit, V.; Gil, R.; Naiman, S.; Nahum, L.; Levin, E.; Kronfeld-Schor, N.; Cohen, H.Y. SIRT6 protects against pathological damage caused by diet-induced obesity. Aging Cell 2010, 9, 162–173. [CrossRef] [PubMed]
87. Kim, H.-S.; Xiao, C.; Wang, R.-H.; Lahusen, T.; Xu, X.; Vassilopoulos, A.; Vazquez-Ortiz, G.; Jeong, W.-I.; Park, O.; Ki, S.H. Hepatic-specific disruption of SIRT6 in mice results in fatty liver formation due to enhanced glycolysis and triglyceride synthesis. *Cell Metab.* 2010, 12, 224–236. [CrossRef] [PubMed]
88. Banks, A.S.; Kon, N.; Knight, C.; Matsumoto, M.; Gutiérrez-Juárez, R.; Rossetti, L.; Gu, W.; Accili, D. SIRT1 gain of function increases energy efficiency and prevents diabetes in mice. *Cell Metab.* 2008, 8, 333–341. [CrossRef]
89. Wei, D.; Tao, R.; Zhang, Y.; White, M.F.; Dong, X.C. Feedback regulation of hepatic gluconeogenesis through modulation of SHP/Nr0b2 gene expression by Sirt1 and FoxO1. *Am. J. Physiol. Heart Circ. Physiol.* 2010, 300, E312–E320. [CrossRef] [PubMed]
90. Chen, D.; Bruno, J.; Easlon, E.; Lin, S.-J.; Cheng, H.-L.; Alt, F.W.; Guarente, L. Tissue-specific regulation of SIRT1 by calorie restriction. *Genes Dev.* 2008, 22, 1753–1757. [CrossRef] [PubMed]
91. Seto, E.; Yoshida, M. Erasers of histone acetylation: The histone deacetylase enzymes. *Cold Spring Harb. Perspect. Biol.* 2014, 6, a018713. [CrossRef] [PubMed]
92. Chrast, R.; Saher, G.; Nave, K.-A.; Verheijen, M.H. Lipid metabolism in myelinating glial cells: Lessons from human inherited disorders and mouse models. *J. Lipid Res.* 2011, 52, 419–434. [CrossRef] [PubMed]
93. Rui, L. Energy metabolism in the liver. *Compr. Physiol.* 2010, 5, 177–197. [CrossRef]
94. Houten, S.M.; Wanders, R.J. A general introduction to the biochemistry of mitochondrial fatty acid β-oxidation. *J. Inherit. Metab. Dis.* 2010, 33, 469–477. [CrossRef] [PubMed]
95. Kong, X.; Wang, R.; Xue, Y.; Liu, X.; Zhang, H.; Chen, Y.; Fang, F.; Chang, Y. Sirtuin 3, a new target of PGC-1α, plays an important role in the suppression of ROS and mitochondrial biogenesis. *PLoS ONE* 2010, 5, e11707. [CrossRef] [PubMed]
96. Alkozai, E.M.; Nijsten, M.W.; de Jong, K.P.; Peeters, P.M.; Slooff, M.J.; Porte, R.J.; Lisman, T. Immediate postoperative low platelet count is associated with delayed liver function recovery after partial liver resection. *Ann. Surg.* 2010, 251, 300–306. [CrossRef]
97. Kersten, S. Integrated physiology and systems biology of PPARs. *Perspect. Biol. Med.* 2005, 49, S5. [CrossRef]
98. Ansari, A.; Rahman, M.S.; Saha, S.K.; Saikot, F.K.; Deep, A.; Kim, K.H. Function of the SIRT 3 mitochondrial deacetylase in cellular physiology, cancer, and neurodegenerative disease. *Aging Cell* 2017, 16, 4–16. [CrossRef]
99. Anderson, K.A.; Hirschey, M.D. Mitochondrial protein acetylation regulates metabolism. *Essays Biochem.* 2012, 52, 23–35. [CrossRef]
100. Shinmura, K. Effects of caloric restriction on cardiac oxidative stress and mitochondrial bioenergetics: Potential role of cardiac sirtuins. *Oxidative Med. Cell. Longev.* 2013, 2013, 528935. [CrossRef] [PubMed]
101. Izumida, Y.; Yahagi, N.; Takeuchi, Y.; Nishi, M.; Shikama, A.; Takarada, A.; Masuda, Y.; Kubota, M.; Matsuzaka, T.; Nakagawa, Y. Glycogen shortage during fasting triggers liver-brain-adipose neurocircuitry to facilitate fat utilization. *Nat. Commun.* 2013, 4, 2316. [CrossRef]
102. Purushotham, A.; Schug, T.T.; Xu, Q.; Surapureddi, S.; Guo, X.; Li, X. Hepatocyte-specific deletion of SIRT1 alters fatty acid metabolism and results in hepatic steatosis and inflammation. *Cell Metab.* 2009, 9, 327–338. [CrossRef]
103. Corrales, P.; Vidal-Puig, A.; Medina-Gómez, G. PPARs and metabolic disorders associated with challenged adipose tissue plasticity. *Int. J. Mol. Sci.* 2018, 19, 2124. [CrossRef] [PubMed]
104. Grabacka, M.; Pierzchalska, M.; Dean, M.; Reiss, K. Regulation of ketone body metabolism and the role of PPARα. *Int. J. Mol. Sci.* 2016, 17, 2093. [CrossRef]
105. Kersten, S. Integrated physiology and systems biology of PPARs. *Mol. Metab.* 2014, 3, 354–371. [CrossRef]
106. Zhang, L.; Wu, Y.; Si, P.; Yan, Y.; Xu, H.; Yao, Y. Effects on lipid metabolism and expression of PPARα and FABP of Schizothorax prenanti by oxidized Konjac glucomannan. *Aquac. Int.* 2017, 25, 2007–2025. [CrossRef]
107. Ge, J.; Xiao, C.; Sun, X.-Y.; Yu, J.-Y. Huangkui capsule, an extract from *Abelmoschus manihot* (L.) medic, improves diabetic nephropathy via activating peroxisome proliferator-activated receptor (PPAR)-α/γ and attenuating endoplasmic reticulum stress in rats. *J. Ethnopharmacol.* 2016, 189, 238–249. [CrossRef]
108. Ferri, N.; Corsini, A.; Sirtori, C.; Ruscia, M. PPARα agonists are still on the rise: An update on clinical and experimental findings. *Expert Opin. Investig. Drugs* 2017, 26, 593–602. [CrossRef] [PubMed]
109. Sanchez, M.B.; Miranda-Perez, E.; Verjan, J.C.G.; Barrera, M.d.I.A.F.; Perez-Ramos, J.; Alarcon-Aguilar, F.J. Potential of the chlorogenic acid as multitarget agent: Insulin-secretagogue and PPAR α/γ dual agonist. *Biomed. Pharmacother.* 2017, 94, 169–175. [CrossRef] [PubMed]
110. Holness, M.J.; Caton, P.W.; Sugden, M.C. Acute and long-term nutrient-led modifications of gene expression: Potential role of SIRT1 as a central co-ordinator of short and longer-term programming of tissue function. *Nutrition* **2010**, *26*, 491–501. [CrossRef] [PubMed]

111. You, M.; Jogasuria, A.; Taylor, C.; Wu, J. Sirtuin 1 signaling and alcoholic fatty liver disease. *Hepatobiliary Surg. Nutr.* **2015**, *4*, 88.

112. Wolfrum, C.; Stoffel, M. Coactivation of Foxa2 through Pgc-1β promotes liver fatty acid oxidation and triglyceride/VLDL secretion. *Cell Metab.* **2006**, *3*, 99–110. [CrossRef] [PubMed]

113. Cohen, H.Y.; Miller, C.; Bitterman, K.J.; Wall, N.R.; Hekking, B.; Kessler, B.; Howitz, K.T.; Gorospe, M.; de Cabo, R.; Sinclair, D.A. Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. *Science* **2004**, *305*, 390–392. [CrossRef] [PubMed]

114. Nguyen, P.; Leray, V.; Diez, M.; Serisier, S.; Biloc’h, J.L.; Siliart, B.; Dumon, H. Liver lipid metabolism. *Int. J. Mol. Sci.* **2019**, *20*, 1885.

115. Wang, Y.; Viscarra, J.; Kim, S.-J.; Sul, H.S. Transcriptional regulation of hepatic lipogenesis. *Nat. Rev. Mol. Cell Biol.* **2015**, *16*, 678. [CrossRef] [PubMed]

116. Zhang, C.; Wang, G.; Zheng, Z.; Maddipati, K.R.; Zhang, X.; Dyson, G.; Williams, P.; Duncan, S.A.; Kaufman, R.J.; Zhang, K. Endoplasmic reticulum-tethered transcription factor cAMP responsive element-binding protein, hepatocyte specific, regulates hepatic lipogenesis, fatty acid oxidation, and lipolysis upon metabolic stress in mice. *Hepatology* **2012**, *55*, 1070–1082. [CrossRef] [PubMed]

117. Faget, M.; Guichard, C.; Ferre, P.; Foulfelle, F. Sterol regulatory element binding protein-1c is a major mediator of insulin action on the hepatic expression of glucokinase and lipogenesis-related genes. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 12737–12742. [CrossRef] [PubMed]

118. Dentin, R.; Girard, J.; Postic, C. Carbohydrate responsive element binding protein (ChREBP) and sterol regulatory element binding protein-1c (SREBP-1c): Two key regulators of glucose metabolism and lipid synthesis in liver. *Biochimie* **2007**, *87*, 81–86. [CrossRef] [PubMed]

119. Walker, A.K.; Yang, F.; Jiang, K.; Ji, J.-Y.; Watts, J.L.; Purushotham, A.; Boss, O.; Hirsch, M.L.; Ribich, S.; Smith, J.J. Conserved role of SIRT1 orthologs in fasting-dependent inhibition of the lipid/cholesterol regulator SREBP. *Genes Dev.* **2010**, *24*, 1403–1417. [CrossRef] [PubMed]

120. Lerin, C.; Rodgers, J.T.; Kalume, D.E.; Kim, S.-h.; Pandey, A.; Puigserver, P. GCN5 acetyltransferase complex controls glucose metabolism through transcriptional repression of PGC-1α. *Cell Metab.* **2006**, *3*, 429–438. [CrossRef]

121. Rodgers, J.T.; Puigserver, P. Fasting-dependent glucose and lipid metabolic response through hepatic sirtuin 1. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 12861–12866. [CrossRef]

122. Rodgers, J.T.; Lerin, C.; Gerhart-Hines, Z.; Puigserver, P. Metabolic adaptations through the PGC-1α and SIRT1 pathways. *FEBS Lett.* **2008**, *582*, 46–53. [CrossRef] [PubMed]

123. Baur, J.A.; Pearson, K.J.; Price, N.L.; Jamieson, H.A.; Lerin, C.; Kalra, A.; Prabhu, V.V.; Allard, J.S.; Lopez-Lluch, G.; Lewis, K. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature* **2006**, *444*, 337. [CrossRef]

124. Feige, J.N.; Lagouge, M.; Canto, C.; Strehle, A.; Houten, S.M.; Milne, J.C.; Lambert, P.D.; Mataki, C.; Elliott, P.J.; Auwerx, J. Specific SIRT1 activation mimics low energy levels and protects against diet-induced metabolic disorders by enhancing fat oxidation. *Cell Metab.* **2008**, *8*, 347–358. [CrossRef]

125. Saltiel, A.R. New perspectives into the molecular pathogenesis and treatment of type 2 diabetes. *Cell* **2001**, *104*, 517–529. [CrossRef]

126. Koo, S.-H.; Satoh, H.; Herzig, S.; Lee, C.-H.; Hedrick, S.; Kulkarni, R.; Evans, R.M.; Olefsky, J.; Montminy, M. PGC-1 promotes insulin resistance in liver through PPAR-α-dependent induction of TRB-3. *Nat. Med.* **2004**, *10*, 530. [CrossRef]

127. Nakagawa, T.; Lomb, D.J.; Haigis, M.C.; Guarante, L. SIRT5 Deacetylates carbamoyl phosphate synthetase 1 and regulates the urea cycle. *Cell* **2009**, *137*, 560–570. [CrossRef] [PubMed]

128. Sener, A.; Malaisse, W.J. L-leucine and a nonmetabolized analogue activate pancreatic islet glutamate dehydrogenase. *Nature* **1980**, *288*, 187. [CrossRef]

129. Haigis, M.C.; Mostoslavsky, R.; Haigis, K.M.; Fahie, K.; Christodoulou, D.C.; Murphy, A.J.; Valenzuela, D.M.; Yancopoulos, G.D.; Karow, M.; Blander, G. SIRT4 inhibits glutamate dehydrogenase and opposes the effects of calorie restriction in pancreatic β cells. *Cell* **2006**, *126*, 941–954. [CrossRef]
130. Meijer, A.J.; Lamers, W.H.; Chamuleau, R. Nitrogen metabolism and ornithine cycle function. *Physiol. Rev.* 1990, 70, 701–748. [CrossRef] [PubMed]

131. Morris Jr, S.M. Regulation of enzymes of the urea cycle and arginine metabolism. *Annu. Rev. Nutr.* 2002, 22, 87–105. [CrossRef] [PubMed]

132. Allister, E.M.; Robson-Doucette, C.A.; Prentice, K.J.; Hardy, A.B.; Sultan, S.; Gaisano, H.Y.; Kong, D.; Gilon, P.; Herrera, P.L.; Lowell, B.B. UCP2 regulates the glucone response to fasting and starvation. *Diabetes* 2013, 62, 1623–1633. [CrossRef] [PubMed]

133. Hallows, W.C.; Yu, W.; Smith, B.C.; Devires, M.K.; Ellinger, J.J.; Someya, S.; Shortreed, M.R.; Prolla, T.; Markley, J.L.; Smith, L.M. Sirt3 promotes the urea cycle and fatty acid oxidation during dietary restriction. *Mol. Cell* 2011, 41, 139–149. [CrossRef] [PubMed]

134. Nakagawa, T.; Guarente, L. Urea cycle regulation by mitochondrial sirtuin, SIRT5. *Aging* 2009, 1, 578. [CrossRef]

135. Ogura, M.; Nakamura, Y.; Tanaka, D.; Zhuang, X.; Fujita, Y.; Obara, A.; Hamaasaki, A.; Hosokawa, M.; Inagaki, N. Overexpression of SIRT5 confirms its involvement in deacetylation and activation of carbamoyl phosphate synthetase I. *Biochem. Biophys. Res. Commun.* 2010, 393, 73–78. [CrossRef] [PubMed]

136. Newman, J.C.; He, W.; Verdin, E. Mitochondrial protein acylation and intermediary metabolism: Regulation by sirtuins and implications for metabolic disease. *J. Biol. Chem.* 2012, 287, 42436–42443. [CrossRef] [PubMed]

137. Malhi, H.; Guicciardi, M.E.; Gores, G.J. Hepatocyte death: A clear and present danger. *Physiol. Rev.* 2010, 90, 1165–1194. [CrossRef] [PubMed]

138. Godoy, P.; Hewitt, N.J.; Albrecht, U.; Andersen, M.E.; Ansari, N.; Bhattacharya, S.; Bode, J.G.; Bolleyn, J.; Borner, C.; Boettger, J. Recent advances in 2D and 3D in vitro systems using primary hepatocytes, alternative hepatocyte sources and non-parenchymal liver cells and their use in investigating mechanisms of hepatotoxicity, cell signaling and ADME. *Arch. Toxicol.* 2013, 87, 1315–1530. [CrossRef]

139. Shin, S.M.; Yang, J.H.; Ki, S.H. Role of the Nrf2-ARE pathway in liver diseases. *Oxidative Med. Cell. Longev.* 2013. [CrossRef]

140. Li, S.; Tan, H.-Y.; Wang, N.; Zhang, Z.-J.; Lao, L.; Wong, C.-W.; Feng, Y. The role of oxidative stress and antioxidants in liver diseases. *Int. J. Mol. Sci.* 2015, 16, 26087–26124. [CrossRef] [PubMed]

141. Suppli, M.P.; Lund, A.; Bagger, J.I.; Vilsbøll, T.; Knop, F.K. Involvement of steatosis-induced glucagon resistance in hyperglucagonaemia. *Med. Hypotheses* 2016, 86, 100–103. [CrossRef] [PubMed]

142. Unger, R.; Orci, L. The essential role of glucagon in the pathogenesis of diabetes mellitus. *Lancet* 1975, 305, 14–16. [CrossRef]

143. Pirola, C.J.; Gianotti, T.F.; Castaño, G.O.; Mallardi, P.; San Martino, J.; Ledesma, M.M.G.L.; Flichman, D.; Mirshahi, F.; Sanyal, A.J.; Sookoian, S. Circulating microRNA signature in non-alcoholic fatty liver disease: From serum non-coding RNAs to liver histology and disease pathogenesis. *Gut* 2015, 64, 800–812. [CrossRef] [PubMed]

144. Stefan, N.; Häring, H.-U.; Cusi, K. Non-alcoholic fatty liver disease: Causes, diagnosis, cardiometabolic consequences, and treatment strategies. *Lancet Diabetes Endocrinol.* 2018, 7, 313–324. [CrossRef]

145. Prat, L.I.; Tsochatzis, E.A. The effect of antidiabetic medications on non-alcoholic fatty liver disease (NAFLD). *Hormones* 2018, 17, 219–229. [CrossRef]

146. Nasr, P.; Ignatova, S.; Kechagias, S.; Ekstedt, M. Natural history of nonalcoholic fatty liver disease: A prospective follow-up study with serial biopsies. *Hepatol. Commun.* 2018, 2, 199–210. [CrossRef] [PubMed]

147. Calzadilla Bertot, L.; Adams, L. The natural course of non-alcoholic fatty liver disease. *Int. J. Mol. Sci.* 2016, 17, 774. [CrossRef]

148. Rinella, M.E.; Sanyal, A.J. Management of NAFLD: A stage-based approach. *Nat. Rev. Gastroenterol. Hepatol.* 2016, 13, 196. [CrossRef]

149. Ren, T.; Huang, C.; Cheng, M. Dietary blueberry and bifidobacteria attenuate nonalcoholic fatty liver disease in rats by affecting SIRT1-mediated signaling pathway. *Oxidative Med. Cell. Longev.* 2014, 2014, 469059. [CrossRef]

150. Colak, Y.; Yesil, A.; Mutlu, H.H.; Cakiliki, O.T.; Ulasoglu, C.; Senates, E.; Takir, M.; Kostek, O.; Yılmaz, Y.; Yılmaz Enc, F. A potential treatment of non-alcoholic fatty liver disease with SIRT1 activators. *J. Gastrointestin Liver Dis.* 2014, 23, 311–319. [PubMed]
151. Sodhi, K.; Puri, N.; Favero, G.; Stevens, S.; Meadows, C.; Abraham, N.G.; Rezzani, R.; Ansinelli, H.; Lebovics, E.; Shapiro, J.I. Fructose mediated non-alcoholic fatty liver is attenuated by HO-1-SIRT1 module in murine hepatocytes and mice fed a high fructose diet. *PLoS ONE* 2015, 10, e0128648. [CrossRef]  
152. Yao, H.; Tao, X.; Xu, L.; Qi, Y.; Yin, L.; Han, X.; Xu, Y.; Zheng, L.; Peng, J. Dioscin alleviates non-alcoholic fatty liver disease through adjusting lipid metabolism via SIRT1/AMPK signaling pathway. *Pharmacol. Res.* 2018, 131, 51–60. [CrossRef] [PubMed]  
153. Scheibye-Knudsen, M.; Mitchell, S.J.; Fang, E.F.; Iyama, T.; Ward, T.; Wang, J.; Dunn, C.A.; Singh, N.; Veith, S.; Hasan-Olive, M.M. A high-fat diet and NAD+ activate Sirt1 to rescue premature aging in cockayne syndrome. *Cell Metab.* 2014, 20, 840–855. [CrossRef] [PubMed]  
154. Li, Y.; Wong, K.; Giles, A.; Jiang, J.; Lee, J.W.; Adams, A.C.; Kharitonenkov, A.; Yang, Q.; Gao, B.; Guarente, L. Hepatic SIRT1 attenuates hepatic steatosis and controls energy balance in mice by inducing fibroblast growth factor 21. *Gastroenterology* 2014, 146, 539–549. [CrossRef]  
155. He, G.; Karin, M. NF-κB and STAT3–key players in liver inflammation and cancer. *Cell Res.* 2011, 21, 159. [CrossRef]  
156. Wu, W.-Y.; Li, J.; Wu, Z.-S.; Zhang, C.-L.; Meng, X.-L. STAT3 activation in monocytes accelerates liver cancer progression. *BMC Cancer* 2011, 11, 506. [CrossRef]  
157. Andrade, J.M.O.; Paraíso, A.F.; de Oliveira, M.V.M.; Martins, A.M.E.; Neto, J.F.; Guimarães, A.L.S.; de Paula, A.M.; Qureshi, M.; Santos, S.H.S. Resveratrol attenuates hepatic steatosis in high-fat fed mice by decreasing lipogenesis and inflammation. *Nutrition* 2014, 30, 915–919. [CrossRef]  
158. Xie, J.; Zhang, X.; Zhang, L. Negative regulation of inflammation by SIRT1. *Pharmacol. Res.* 2013, 67, 60–67. [CrossRef] [PubMed]  
159. Castro, R.E.; Ferreira, D.M.; Afonso, M.B.; Borralho, P.M.; Machado, M.V.; Cortez-Pinto, H.; Rodrigues, C.M. miR-34a/SIRT1/p53 is suppressed by ursodeoxycholic acid in the rat liver and activated by disease severity in human non-alcoholic fatty liver disease. *J. Hepatol.* 2013, 58, 119–125. [CrossRef]  
160. Welzel, T.M.; Graubard, B.I.; Zeuzem, S.; El-Serag, H.B.; Davila, J.A.; McGlynn, K.A. Metabolic syndrome increases the risk of primary liver cancer in the United States: A study in the SEER-Medicare database. *Hepatology* 2011, 54, 463–471. [CrossRef] [PubMed]  
161. Jinjuvadia, R.; Patel, S.; Liangpunsakul, S. The association between metabolic syndrome and hepatocellular carcinoma: Systemic review and meta-analysis. *J. Clin. Gastroenterol.* 2014, 48, 172–177. [CrossRef] [PubMed]  
162. Hitosugi, T.; Chen, J. Post-translational modifications and the Warburg effect. *Oncogene* 2014, 33, 4279. [CrossRef] [PubMed]  
163. Jia, Y.-L.; Xu, M.; Dou, C.-W.; Liu, Z.-K.; Xue, Y.-M.; Yao, B.-W.; Ding, L.-L.; Tu, K.-S.; Zheng, X.; Liu, Q.-G. P300/CBP-associated factor (PCAF) inhibits the growth of hepatocellular carcinoma by promoting cell autophagy. *Cell Death Dis.* 2016, 7, e2400. [CrossRef] [PubMed]  
164. Wong, N.; Ojo, D.; Yan, J.; Tang, D. PKM2 contributes to cancer metabolism. *Cancer Lett.* 2015, 356, 184–191. [CrossRef] [PubMed]  
165. Xiong, X.; Tao, R.; DePinho, R.A.; Dong, X.C. Deletion of hepatic FoxO1/FoxO3/FoxO4 genes in mice significantly impacts on glucose metabolism through downregulation of gluconeogenesis and upregulation of glycolysis. *PLoS ONE* 2013, 8, e74340. [CrossRef] [PubMed]  
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