Regulation of Hepatic Metabolism and Cell Growth by the ATF/CREB Family of Transcription Factors

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The liver is a major metabolic organ that regulates the whole-body metabolic homeostasis and controls hepatocyte proliferation and growth. The ATF/CREB family of transcription factors integrates nutritional and growth signals to the regulation of metabolism and cell growth in the liver, and deregulated ATF/CREB family signaling is implicated in the progression of type 2 diabetes, nonalcoholic fatty liver disease, and cancer. This article focuses on the roles of the ATF/CREB family in the regulation of glucose and lipid metabolism and cell growth and its importance in liver physiology. We also highlight how the disrupted ATF/CREB network contributes to human diseases and discuss the perspectives of therapeutically targeting ATF/CREB members in the clinic.

The liver plays a central role in metabolic homeostasis. Deregulation of glucose and lipid metabolism predisposes to the development of metabolic diseases, such as insulin resistance, type 2 diabetes, and nonalcoholic fatty liver disease (NAFLD), and increases the risk of developing several types of cancers, such as hepatocellular carcinomas (HCC) (1,2). Aberrant signaling regulated by the transcription factor or cofactor in response to nutrients and growth factors plays pivotal roles in the development of these disorders.

The ATF/CREB members are a conserved family of proteins that share a basic-region leucine zipper (bZIP) domain composed of both a DNA-binding basic region and a leucine zipper dimerization motif (3–5). Activating transcription factor (ATF) was first named in 1987 to define a group of proteins that bind to a core sequence "CGTCA" on an adenoviral gene promoter (6). cAMP-responsive element–binding protein (CREB) was defined as a nuclear protein that binds to the cAMP-responsive element (CRE) on the promoter of neuropeptide somatostatin (7). The ATF binding site was later recognized as TGACGT (C/A) (G/A) (8), which is in full accord with the CRE sequence (TGACGTCA) (9). Because of this consistency, these two groups of proteins were collectively known as the ATF/CREB family (3,4). More than 20 proteins named with an ATF/CREB prefix have been identified in mammals. They are divided into subgroups based on their amino acid similarity both inside and outside the bZIP domain (Table 1). Given that proteins among different subgroups do not share more resemblance beside the bZIP domain, they should be considered as distinct proteins, although they have similar confusing names (3). Many of the ATF/CREB proteins are ubiquitously expressed in various cell types. The family proteins form the homodimer or selective heterodimer with each other or with other bZIP proteins and are involved in regulating the expression of genes associated with a wide range of cellular processes in mammalian cells. Extensive researches have established that the ATF/CREB proteins can sense and respond to extracellular fluctuation in nutrient concentration, hormone levels, and energy status and function as transcription factors or cofactors to play critical roles in the regulation of systemic homeostasis in the key metabolic tissues, especially in the liver (Table 1). However, whether and how these proteins are modulated by extracellular signals, and then contribute to the homeostasis of cell metabolism and growth, are not well understood. How chronic overnutrition disrupts these homeostatic mechanisms under physiological conditions, resulting in excess lipid storage in the liver, altered secretion of hepatokines, hyperinsulinemia, and ultimately type 2 diabetes, NAFLD, and HCC, is currently an intense area of research. This review focuses on the discovery of major ATF/CREB proteins in coupling nutritional and growth signals to the regulation of glucose and lipid metabolism and cell growth and proliferation in the liver.

PERSPECTIVES IN DIABETES

Table 1—The localization and function of the ATF/CREB family members

Subgroup	Members	Location	Alternative names	Metabolic and proliferative function
CREB	CREB	Nucleus	ATF-47, CREB1	Gluconeogenesis ↑↓, lipogenesis ↑, hepatocyte damage ↑, fibrosis ↑
	CREM	Nucleus	ICER, CREM-2	Cell proliferation ↑, liver regeneration ↑
	ATF1	Nucleus	TREB36, TCRATF1, ATF-43	Cell proliferation ↑, cell transformation ↑
CRE-BP1	ATF2	Nucleus, mitochondria, cytosol	CRE-BP, TREB, CREB2, HB16	Inflammation ↑, cell proliferation ↑, liver regeneration ↑, HCC ↑
	ATF7	Nucleus	ATFA	Telomere shortening ↑
	CREB5	Nucleus	CREBPα	Metastasis ↑
CREB3	CREB3	Nucleus, ER, Golgi	LZIP, Luman	Apoptosis ↓, metastasis ↑
	CREB3L1	Nucleus, ER	OASIS, OI16	Metastasis ↑↓, tumor invasion ↑
	CREB3L2	Nucleus, ER	BBF2H7	Cell proliferation ↑, cell survival ↑
	CREBH	Nucleus, ER	CREB3L3, CR3L3	Gluconeogenesis ↑, glycogenolysis ↑, insulin sensitivity ↓, de novo lipogenesis ↑, fatty acid elongation ↑, lipolysis ↑, fatty acid oxidation ↑, lipoprotein metabolism ↑, cell proliferation ↓
	CREB4	Nucleus, ER, Golgi	AIBZIP, ATCE1, TISP40, CREB3L4, JAL	Spermatogenesis ↑
ATF3	ATF3	Nucleus	LRF-1, LRG-21, CRG-5	Gluconeogenesis ↓, insulin sensitivity ↓, cell proliferation ↑↓
	JDP-2	Nucleus	JUNDM2	Apoptosis ↓
ATF4	ATF4	Nucleus	CREB2, TXREB	Insulin sensitivity ↓, de novo lipogenesis ↑, FGF21 ↑, cell proliferation ↑
	ATF5	Nucleus, cytosol	ATFx	Cell proliferation ↓, apoptosis ↑
ATF6	ATF6α	Nucleus, ER	ATF6, ACHM7	Gluconeogenesis ↓, insulin sensitivity ↓, de novo lipogenesis ↓, fatty acid oxidation ↑, FGF21 ↑, cell proliferation ↑
	ATF6β	Nucleus, ER	CREBL1, G13, CREB-RP	Cell survival ↑
B-ATF	B-ATF	Nucleus	SFA-2	Cell growth ↓
	B-ATF2	Nucleus	SARI	Cell proliferation ↓
	B-ATF3	Nucleus	JDP-1, DNAJC12	Cell proliferation ↑
CREBZF	CREBZF	Nucleus	ZF, Zhangfei	De novo lipogenesis ↑, liver regeneration ↓, gluconeogenesis ↓

ATF, activating transcription factor; B-ATF, basic leucine zipper ATF-like transcription factor; CREB, cAMP-responsive element–binding protein; CRE-BP1, cAMP-responsive element–binding protein; CREB3L1, cAMP-responsive element–binding protein 3–like 1; CREB3L2, cAMP-responsive element–binding protein 3–like 2; CREBH, cAMP-responsive element–binding protein H; CREBZF, CREB/ATF bZIP transcription factor; CREM, cAMP-responsive element modulator; JDP-2, Jun dimerization protein-2.

ATF/CREB Family in Glucose Metabolism

Liver is a pivotal organ that maintains the systemic glucose homeostasis that depends on the coordination of multiple biochemical pathways such as glycogenesis, gluconeogenesis, glycogen synthesis, and glycolysis. The regulatory hormones, including insulin, glucagon, and glucocorticoids (10), control hepatic glucose homeostasis during the fasting and feeding cycle via regulating the expression of genes involved in these pathways. The ATF/CREB family of transcription factors modulates a variety of cellular processes of glucose metabolism, especially in the regulation of gluconeogenesis and insulin sensitivity (Fig. 1).

Gluconeogenesis

Gluconeogenesis is a metabolic pathway that leads to the synthesis of glucose from pyruvate and other noncarbohydrate precursors, such as amino acids, lactate, and glycerol. Gluconeogenesis is activated during prolonged fasting or energy restriction to maintain the homeostasis of circulating glucose levels (11). As a member of the ATF/CREB family, CREB acts as a master regulator for hepatic gluconeogenesis. In response to fasting, CREB is phosphorylated and activated by glucagon-induced cAMP-PKA signaling. CREB activation promotes gluconeogenesis by stimulating the expression of key gluconeogenic enzymes, such as PEPCK and G6Pase (12–14), and the nuclear receptor coactivator PGC-1α (15), which is important for gluconeogenesis. Second, transcriptional activation of CREB is potentiated by dephosphorylation and nuclear translocation of CREB-regulated transcription coactivator 2 (CRTC2) (15). Recent studies show that the activity of CREB is regulated by cryptochromes (Cry) in a circadian
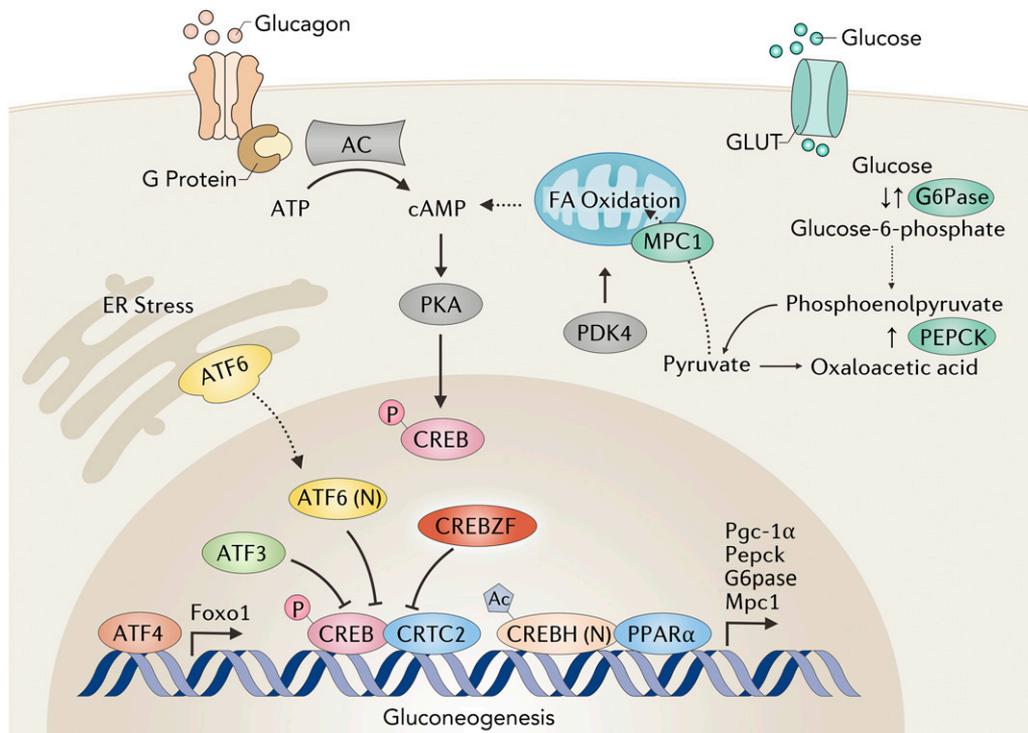
Figure 1—Overview of the role of the ATF/CREB family in the pathway involved in hepatic gluconeogenesis. The ATF/CREB family members play central roles in hepatic gluconeogenesis as transcriptional regulators. Under fasting conditions, elevated circulating glucagon binds G-protein–coupled receptor (GPCR) and stimulates the production of cAMP. CREB is phosphorylated and activated by PKA, which transduces the signal into the nucleus via cooperating with CRTC2. CREB/CRTC2 binds to the CRE motif in the promoter of gluconeogenic enzymes such as G6Pase and PEPCK. Expression levels of PGC-1α and MPC1 are also induced by CREB/CRTC2 complex, leading to enhanced gluconeogenesis. ATF3, ATF6, and CREBZF suppress gluconeogenesis via disrupting the interaction between CREB and CRTC2. CREBH forms a complex with PPARα and promotes glycolysis and gluconeogenesis via binding to a unique sequence distinct from the CREB/CRTC2 binding site. ATF4 regulates gluconeogenesis by promoting the expression of FOXO1, which functions as the transcriptional activator of gluconeogenesis. AC, adenylyl cyclase; CRTC2, CREB-regulated transcription coactivator 2; G6Pase, glucose-6-phosphatase; FA, fatty acid; FOXO1, forkhead box class O 1; MPC1, mitochondrial pyruvate carrier 1; PEPCK, phosphoenolpyruvate carboxykinase; PGC-1α, peroxisome proliferator–activated receptor γ coactivator-1α; PPARα, peroxisome proliferator–activated receptor α.

manner (16,17) and by pyruvate dehydrogenase kinase 4 (PDK4), which increases mitochondria fatty acid oxidation and cytosolic cAMP accumulation (18). Moreover, gluconeogenic effects of CREB/CRTC2 are mediated by stimulating of mitochondrial pyruvate carrier 1 (MPC1), leading to enhanced pyruvate transportation into mitochondria and increased substrates for gluconeogenesis (19). Interestingly, fasting glucose levels and gluconeogenic capacity remain intact in liver-specific CREB knockout mice generated by injection of floxed CREB mice with adeno-associated virus expressing Cre recombinase (20), suggesting that functional redundancy may exist among CREB-related cellular proteins in the regulation of gluconeogenesis.

Notably, other ATF/CREB family members, such as ATF3, ATF6, CREBH, and CREBZF, also play roles in regulating gluconeogenic process. ATF3 acts as a transcriptional repressor to inhibit gluconeogenesis. Transgenic overexpression of ATF3 in the liver represses gluconeogenesis and leads to hypoglycemia in mice fed with chow diet via ATF3-mediated binding of the ATF/CRE site on the

PEPCK gene promoter (21,22). Upon ethanol treatment, ATF3 binds to the cAMP-response element and blocks the recruitment of CREB and CRTC2 to the promoter of gluconeogenic genes, leading to reduced gluconeogenesis (23). Moreover, ATF6, one of the sensors of the unfolded protein response under endoplasmic reticulum (ER) stress, inhibits gluconeogenesis and couples the ER stress signals to glucose metabolism (24,25). Mechanistically, ATF6 binds to CRTC2 and disrupts its association with CREB, leading to repressed transcriptional activity of CREB and reduced gluconeogenesis. As to CREBH, it acts as a positive regulator for hepatic gluconeogenesis and controls glucose metabolism. CREBH deficiency or liver-specific CREBH knockdown leads to reduced fasting glucose levels (26,27). Mechanistically, active nuclear form of CREBH is induced upon fasting, leading to increased transcription of PEPCK and G6Pase via binding to a unique sequence distinct from the CREB/CRTC2 binding site (26,28,29). Moreover, it also acts as a circadian-related transcriptional regulator and plays roles in hepatic glucose metabolism (29). The proteolytic cleavage and acetylation modification

of CREBH are regulated by the circadian clock, and the acetylated nuclear form of CREBH interacts with peroxisome proliferator–activated receptor α (PPARα), leading to increased glycogenolysis and gluconeogenesis (29). Interestingly, adenovirus-mediated overexpression of CREBZF appears to inhibit CREB/CRTC2 complex activity and repress the expression of PGC-1α, PEPCK, and G6Pase, leading to reduced glucose output in mice under fed conditions (30). Together, these studies show that CREB coordinates with other ATF/CREB proteins to control hepatic glucose production and that the ATF/CREB network is critical for gluconeogenesis and maintenance of systemic glucose homeostasis.

Insulin Sensitivity

Much evidence shows critical roles of the ATF/CREB family in the regulation of insulin sensitivity and glucose metabolism. ATF3 appears to exert detrimental effects on insulin signaling, and increases the incidence of type 2 diabetes, although it was shown to inhibit hepatic gluconeogenesis. Knockdown of ATF3 with an in vivo-jetPEI siRNA delivery system ameliorates impaired insulin action and glucose intolerance in Zucker diabetic fatty (ZDF) rats (31). In hepatocytes, ATF3 inhibits the expression of AdipoR2, a key adiponectin receptor with abundant expression in the liver, which may contribute to the development of insulin resistance (32). Moreover, expression levels of ATF3 are increased in livers of diabetic ZDF rats and patients with type 2 diabetes, suggesting that ATF3 may be a biomarker for type 2 diabetes in humans. As to ATF4, it abrogates insulin signaling and leads to insulin resistance and hyperglycemia (33–35). ATF4-deficient mice are protected from age- and high-fat diet (HFD)-induced hyperglycemia, glucose intolerance, and obesity (33). The inhibitory effects of ATF4 on insulin sensitivity are mediated by the transcriptional induction of TRB3, an inhibitor of Akt (34).

In contrast to the inhibitory effects of ATF3 and ATF4 on insulin sensitivity, ATF6 is sufficient to activate insulin-induced phosphorylation of Akt and activation of insulin signaling. ATF6 also acts as an insulin sensitizer via suppressing the protein kinase R-like ER kinase (PERK)–phosphorylated eIF2α–ATF4 branch of the unfolded protein response pathway (34,36). In addition to inducing gluconeogenesis, CREB promotes insulin resistance via ATF3-mediated repression of adiponectin and GLUT4 in adipocytes (37). Chronic activation of the CREB coactivator CRTC2 in the liver is sufficient to promote hepatic insulin resistance and disrupt glucose homeostasis (38). However, these results are contradictory to the findings that macrophage-specific deficiency of CREB causes insulin resistance by repressing polarization of M2 macrophages in visceral white adipose tissue in mice fed with HFD (39). Moreover, previous studies show that CREB mediates the insulin-sensitizing effects of calcium/calmodulin-dependent protein kinase IV (CaMKIV) (40). Therefore, these data suggest that the regulatory role of CREB in hepatic and systemic insulin signaling requires further investigation. Consistent with CREB, CREBH appears to cause insulin resistance. The deficiency of CREBH enhances insulin sensitivity in chow- and HFD-fed mice (27,41). Moreover, adenovirus-mediated CREBH knockdown improves the hepatic insulin sensitivity as evidenced by hyperinsulinemic-euglycemic clamps (26), although this is contradictory to the results showing that adenoviral or transgenic overexpression of CREBH in the liver causes both induction of insulin sensitivity and reduction of systemic glucose levels (42). With these studies taken together, it appears that the ATF/CREB family plays a diverse role in the control of hepatic insulin signaling and systemic glucose homeostasis. Intriguingly, the novel cross talk within the family members, such as CREB-mediated insulin resistance via ATF3, may represent a novel molecular basis underlying deregulated glucose metabolism and hyperglycemia. The understanding of the complex mechanism may provide therapeutic strategies for treating insulin resistance and type 2 diabetes.

ATF/CREB Family in Lipid Metabolism

The liver is a major site for de novo synthesis and oxidation of fatty acids, which play central roles in maintenance of systemic homeostasis of lipid metabolism. The ATF/CREB family are involved in the regulation of many aspects of lipid metabolism processes (Fig. 2). Intriguingly, many of the ATF/CREB family members are inducible in response to nutrients, hormonal signals, and cellular energy. ATF4 is induced to stimulate excessive lipid accumulation in the liver under high-carbohydrate diet or HFD or injection with glucose or fatty acids (43–47). Upon nutrient overload, translation levels of ATF4 are upregulated by the phosphorylation and activation of PERK and eukaryotic translation initiation factor 2α (eIF2α) of an ER stress pathway (43,48). ATF4 is also induced by eukaryotic initiation factor 6 (eIF6) in response to insulin (49) and by protein tyrosine phosphatase-1B (PTP-1B) (47). Moreover, ATF6 is induced in the liver of mice fed with HFD or administered pharmacological ER stress inducers (50,51), while CREBH is induced by nutrient and hormonal signals, such as fatty acids, insulin, HFD, protein-restriction diet, and starvation (27,52–54). Recently, CREBZF appeared to act as a nutrient sensor in regulating lipid metabolism (55,56). In response to refeeding or insulin treatment, CREBZF is induced via PI3K-Akt signaling in hepatocytes and mouse livers (55). CREBZF is also induced via amino acid response element (AARE)-like sequence under amino acid deprivation, suggesting a potential role in regulating amino acid response (AAR) (56). Together, these studies support nutrient sensing roles of the ATF/CREB family and the existence of the ATF/CREB network for maintenance of hepatic lipid metabolism, especially in the regulation of lipid synthesis, fatty acid oxidation, and lipoprotein metabolism.

Lipid Synthesis

Fatty acids synthesis occurs in the cytosol and is catalyzed by rate-limiting enzyme fatty acid synthase (FAS), where
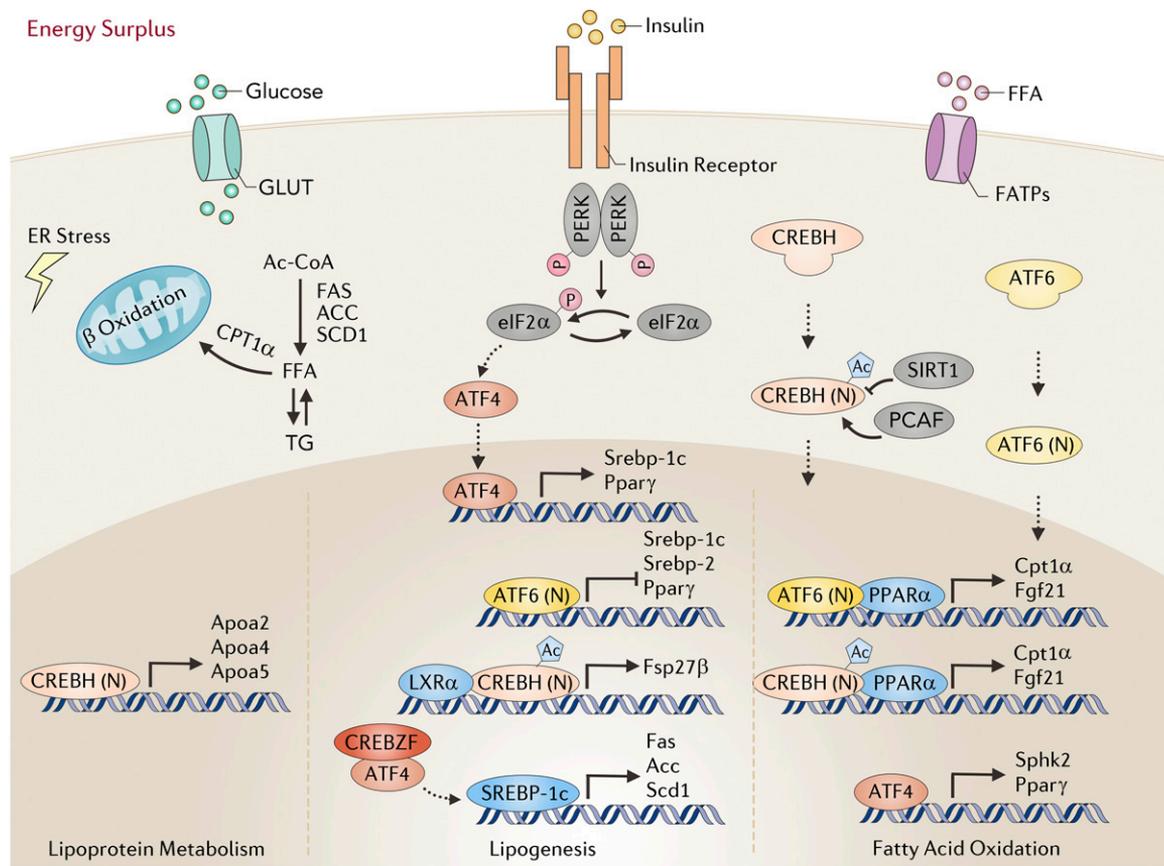
Figure 2—Overview of the role of the ATF/CREB family in the pathway involved in hepatic lipid metabolism. The ATF/CREB family members transduce various nutrient and energy signals into the nucleus and modulate hepatic lipid metabolism via regulating expression of key enzymes and regulators involved in lipogenesis, fatty acid oxidation, and lipoprotein metabolism. ATF4 is activated by the PERK-eIF2α axis of the ER stress response. ATF4 increases lipogenesis via promoting expression of SREBP-1c and PPARγ, the key transcription factors involved in lipid synthesis. ATF4 activates fatty acid oxidation via stimulating the expression of FGF21 and Sphk2. ATF6 is stimulated by nutrient overload and translocates into the nucleus to suppress expression of SREBP-1c, PPARγ, and SREBP-2, which control lipid synthesis. In cooperation with PPARα, ATF6 also elevates fatty acid oxidation by enhancing CPT1α and FGF21. Upon acetylation and activation by PCAF, CREBH associates with LXR to induce expression of Fsp27β, leading to increased hepatic lipid accumulation. CREBH elevates expression of CPT1α and FGF21 to enhance hepatic fatty acid oxidation interacting with PPARα. Moreover, CREBH lowers plasma lipid levels and maintains lipoprotein homeostasis by upregulating expression of Apoa2, Apoa4, and Apoa5. CREBZF couples the insulin signal to promote the cleavage and expression of SREBP-1c via interacting with ATF4, thereby stimulating de novo lipogenesis. Ac-CoA, acetyl-CoA; ACC, acetyl-CoA carboxylase; CPT1α, carnitine palmitoyltransferase 1α; eIF2α, eukaryotic translation initiation factor 2α; FFA, free fatty acid; FGF21, fibroblast growth factor 21; Fsp27β, fat-specific protein 27β; PCAF, p300-CBP–associated factor; PERK, protein kinase R-like ER kinase; PPARα, peroxisome proliferator–activated receptor α; PPARγ, peroxisome proliferator–activated receptor γ; SCD1, stearoyl-CoA desaturase 1; Sphk2, sphingosine kinase; TG, triglyceride.

acetyl-CoA and malonyl-CoA are used as substrates. SREBP-1c is a key transcription factor that controls genes involved in lipid synthesis. ATF4 plays an important role in regulating hepatic lipogenesis. Whole-body ATF4-deficient mice fed with a high-carbohydrate or high-fructose diet are protected from excessive triglycerides accumulation and hepatic steatosis in the liver (44,45). Mechanistically, ATF4 enhances lipogenesis via stimulating SREBP-1c and its downstream lipogenic targets, such as acetyl-CoA carboxylase (ACC), FAS, and stearoyl-CoA desaturase 1 (SCD1) (44,45). As to ATF6, it has been implicated in the suppression of lipogenesis. Whole-body ATF6 knockout mice appear to have reduced expression of lipogenic genes, such as SREBP-1c and PPARγ, and are resistant to HFD-induced hepatic steatosis (57). Mechanistically, ATF6 inhibits

lipogenesis and hepatic lipid accumulation by recruiting the corepressor histone deacetylase 1 (HDAC1) to the ATF6–SREBP-2 complex on sterol regulatory element of lipogenic gene promoter (58). In contrast to the lipogenic lowering effects of ATF6, overexpression of active, nuclear ATF6 appears to increase lipogenesis and hepatic steatosis in the zebrafish with alcohol-induced fatty liver disease (59). Despite this, most evidence supports ATF6's effects in inhibiting lipid synthesis and attenuating hepatic steatosis.

CREBH is involved in the control of lipogenesis. CREBH promotes lipogenesis and hepatic lipid metabolism via interacting with and potentiating lipogenic nuclear receptor liver X receptor α (LXRα) in a circadian manner (60). Adenoviral-mediated overexpression of the constitutively

active CREBH is sufficient to promote lipid droplet enlargement and triglyceride accumulation via inducing fat-specific protein 27b (Fsp27β) in mouse livers (61). It was also reported that CREBH-mediated Fsp27β activation is critical for the development of alcoholic steatohepatitis in mice fed with ethanol and humans with alcoholic steatohepatitis (62). CREB was reported to inhibit lipid synthesis. Knockdown of CREB using adenovirus-mediated overexpression of a dominant-negative CREB leads to increased hepatic expression of lipogenic genes, such as PPARγ, FAS, and ATP citrate lyase (ACLY), in fasted mice (63). Mechanistically, CREB inhibits PPARγ expression via stimulating hairy enhancer of split (HES-1), a transcriptional repressor. Consistently, the CREB-PPARγ signaling mediates beneficial effects of olfactory receptor 43 (Olfr43) on improving hepatic steatosis in mice with diet-induced obesity (64). As to CREBZF, it was reported to promote lipogenesis. In response to refeeding, insulin-induced activation of CREBZF inhibits Insig-2a transcription via interacting with ATF4, allowing SREBP-1 to be processed and activation of fatty acid synthesis. During obesity or nutrient overload, hyperactivation of CREBZF may represent the mechanism of excessive lipogenesis and development of hepatic steatosis in the liver under selective insulin resistance (55). Together, it appears that ATF4, CREBH, and CREBZF stimulate hepatic lipogenesis and lipid accumulation in hepatocytes, whereas ATF6 and CREB have the opposite effect. These findings are particularly interesting, as the ATF/CREB network may provide a means for the hepatocytes to maintain appropriate amounts of fatty acid and therefore control lipid homeostasis in response to nutrient availability.

Fatty Acid Oxidation

Fatty acid β-oxidation is the major pathway for the degradation of fatty acids and is essential for maintaining energy homeostasis, which is highly activated in the liver under the fasted state. The fatty acid acyl-CoA is translocated into the mitochondria by carnitine palmitoyltransferase 1 (CPT1), which provides energy for hepatocytes and ketone bodies as metabolic fuels for other tissues during fasting (65). CREBH promotes fatty acid oxidation by interacting with PPARα (42,52,53,60,66), a key nuclear receptor for increasing fatty acid β-oxidation (67). Lysine 294 acetylation of CREBH by acetyltransferase PCAF is required for the induction of CREBH and PPARα complex activity and reduction of fasting-induced hepatic steatosis, whereas deacetylation by SIRT1 has the opposite effects (68). In support of this, CREBH deficiency causes a potent induction of hepatic steatosis and profound nonalcoholic steatohepatitis (NASH) phenotypes in mice fed with HFD (27). Mechanistically, CREBH induces the hepatokine FGF21 to enhance hepatic fatty acid oxidation by interacting with PPARα (41,42,53,66,69,70). Interestingly, beneficial effects of CREBH on hepatic steatosis are further potentiated by the inhibitory effects of FGF21 on the lipolysis of adipose tissue, leading to reduced triglyceride

mobilization from adipose to the liver (41). Moreover, CREBH deficiency–caused hepatic steatosis and NASH in mice fed with atherogenic HFD have been reversed by recombinant FGF21 protein (53). Together, this evidence suggests that PPARα and FGF21 synergistically mediate beneficial effects of CREBH on fatty acid oxidation and maintain hepatic lipid metabolism.

In contrast to ATF4's effects on inducing lipogenesis, ATF4 appears to increase the production of FGF21 and exert beneficial effects on increasing of fatty acid oxidation and lowering of lipid storage in the hepatocytes (71–75). ATF4 binds to the AARE motif of the FGF21 promoter via a PERK-eIF2α pathway in mice under HFD or ER stress induced by obesity or ER stressors. Activation of ATF4 through constitutive phosphorylation of eIF2α that is induced by liver-specific deletion of eIF2α phosphatase CReP is sufficient to increase FGF21 expression in mice with diet-induced obesity, leading to the reduction of liver triglyceride and improvement of hepatic steatosis (74). In addition, ATF4 increases fatty acid oxidation by upregulating the expression of sphingosine kinase (Sphk2) in diet-induced mice (76). Given the stimulatory effects of ATF4 on lipid synthesis, the relative contribution of ATF4 on hepatic lipid metabolism may be controlled by the precise pathophysiological context, which may be determined by the net effects of ATF4 on anabolism lipogenesis and catabolic fatty acid oxidation. ATF6 was reported to be an important regulator for hepatic fatty acid oxidation (77). Mechanistically, ATF6 physically interacts with PPARα and enhances the transcriptional activity of PPARα. Overexpression of the dominant-negative form of ATF6 (dnATF6) or siRNA-mediated knockdown of ATF6 decreases the transcriptional activity of the PPARα/RXR complex and inhibits oxygen consumption rates in hepatocytes (77). Therefore, ATF6-mediated activation of PPARα may represent an alternative avenue to improvement of liver function and treatment of hepatic steatosis in obesity.

In addition to the regulation of lipogenesis and fatty acid oxidation, CREBH and ATF6 also regulate lipoprotein metabolism. Lipoprotein lipase (LPL) is a key enzyme involved with hydrolysis of the triacylglycerol component of circulating chylomicrons and VLDLs and thereby removal of triglycerides from the blood. CREBH lowers plasma lipid levels by regulating LPL activity. CREBH-deficient mice display hypertriglyceridemia phenotypes, which is due to a reduction of LPL coactivators, such as ApoC2, ApoA4, and ApoA5, as well as an induction of LPL inhibitor ApoC3 (78). CREBH directly induces the transcription of ApoA4 via CREBH binding sites on the ApoA4 gene promoter, resulting in increased hydrolysis of VLDL-triglyceride and reduced triglyceride in circulation (54,79,80). Importantly, it was reported that several CREBH gene mutations encoding nonfunctional CREBH proteins were identified in patients with hypertriglyceridemia, suggesting potential roles of CREBH mutation in the development of dyslipidemia (78). Moreover, ATF6 improves lipid homeostasis by regulating lipoprotein

synthesis and transport. ATF6α deficiency causes destabilized apolipoprotein B-100, leading to decreased VLDL formation and excessive lipid accumulation in ER stress inducers–treated mouse livers (81). Consistently, ATF6α deficiency causes reduced expression of genes related to lipoprotein synthesis and transport in mice (82). These studies demonstrate that CREBH and ATF6 improve hepatic steatosis and control lipid metabolism by regulating lipoprotein metabolism.

Of other regulatory mechanisms, CREB appears to improve hepatic lipid metabolism and liver function via stimulating Bnip3-induced mitophagy, which leads to a reduction of mitochondrial-dependent cell death and protection against hepatic steatosis, fibrosis, and NAFLD (83). In contrast to the beneficial effects on improving lipid metabolism, CREB was reported to promote hepatic fibrosis via activating TGFβ1 in hepatic stellate cells (84). Lentivirus-mediated CREB overexpression promotes fibrogenesis in rat livers under carbon tetrachloride (CCl$_4$) treatment. Further study is needed to determine the causal effects of CREB on fibrosis and NASH with use of tissue-specific CREB knockout mice. Moreover, CREBZF may regulate hepatic fatty acid and cholesterol metabolism via inhibiting the transcriptional activity of nuclear receptors, such as glucocorticoid receptor (GR), constitutive androstane receptor (CAR), and hepatocyte nuclear factor 4 (HNF4) (85). Given that inhibition of GR activity by liver-specific knockout of GR or deficiency of GR's activator FKBP52 leads to hepatic steatosis in mice fed with chow diet or HFD (86,87), inhibition of GR and other nuclear receptors may underscore the potential role of CREBZF in the development of deregulated lipid metabolism and NAFLD (55). Although the elucidation of underlying mechanisms is still underway, current findings suggest that the ATF/CREB network plays a critical role in the regulation of lipid metabolism.

ATF/CREB Family in Cell Growth and Cancer
In addition to glucose and lipid metabolism, the ATF/CREB family members are involved in regulating hepatocyte growth and proliferation in response to multiple external stimuli (Fig. 3). Intriguingly, numerous ATF/CREB proteins are increased by AAR, a pathway in mammalian cells designed to respond to amino acid deficiency and control the synthesis and turnover of mRNA and protein (88). As a key regulator of amino acid metabolism, ATF4 is induced by AAR via amino acid sensor GCN2-mediated phosphorylation of eIF2α (89–92), and thereby the upregulation of ATF4 promotes cell survival through activating the expression of mitochondrial PEPCK (PEPCK-M) (90). In addition, ATF4 promotes cell proliferation by inducing the enzymes required for serine synthesis and maintenance of mTORC1 activity (91), a master regulator of cell growth and metabolism in response to numerous cues such as growth factors and amino acids (93). Consistently, hypothalamic ATF4 enhances mTORC1 activity and increases the susceptibility to insulin resistance (94). ATF4 also

mediates the effects of mTORC1 on inducing purine synthesis upon growth signals via stimulating methylenetetrahydrofolate dehydrogenase 2 (MTHFD2) (95). Therefore, mTORC1-dependent ATF4 activation might provide a positive feedback loop that further promotes cell growth. As to ATF3, it is transcriptionally induced by ATF4 in response to amino acid deprivation (96), suggesting a potential role of ATF3 in regulating cell growth. ATF3 is also induced by mitogenic signals such as the epidermal growth factor (EGF) and hepatocyte growth factor (HGF). The activation of ATF3 binds to the AP-1 motif of the cyclin D1 gene promoter, leading to increased transcription of cyclin D1 and hepatocyte DNA synthesis and proliferation (97). However, it is also reported that ATF3 promotes apoptosis, arrests cell cycle, and inhibits Ras-mediated tumorigenesis (98). Given the contradictory observations, the effects of ATF3 on cell proliferation need further investigation. Moreover, ATF2 is induced by the AAR pathway–activated JNK activation, which is independent of the ATF4 pathway (99). Activation of ATF2 promotes cell proliferation and may contribute to HCC (100,101). The effects of ATF2 on cell proliferation are further supported by the observations showing increased hepatocyte regeneration by ATF2. It was reported that ATF2 is directly activated by MKK7, JNK-1, and glutathione transferases P1/P2 (GSTP1/2), which promotes cell cycle gene expression and hepatocyte proliferation (102–104). Furthermore, ATF2 is phosphorylated by MKKs-activated p38 MAP kinases (MAPK) to promote cell survival and growth. In contrast, activation of c-Jun/ATF2 inhibits the phosphorylation of p38 by stimulating MAPK phosphatases, which provides a negative-feedback mechanism to suppress hyperactivation of p38 activity and aberrant cell survival and growth (105).

Uncontrolled activation of cell growth and proliferation leads to tumorigenesis. In HCC tissues, expression levels of ATF6 are elevated and are correlated with histological grading of HCC (106). Overexpression of ATF6α in human lung fibroblast (HLF) cells, a human HCC cell line, causes an induction of 18 genes that are highly expressed in HCC tissues (107), suggesting a potential role of ATF6 in the pathogenesis of HCC (106,107). In contrast, the liver-enriched CREBH functions as a growth suppressor to inhibit cell proliferation. Overexpression of CREBH inhibits S-phase entry and blocks cell cycle progression in HepG2 cells, leading to repressed hepatocyte growth and proliferation (108). Importantly, expression levels of CREBH are lower in human HCC tissues compared with adjacent noncancerous liver tissues (108). These results suggest that CREBH functions as an inhibitor for hepatocyte growth and proliferation and that loss of CREBH activity might contribute to the initiation and/or progression of HCC. Intriguingly, as another member of the ATF/CREB family, CREB3, sharing highly conserved domains with CREBH (109,110), is also involved in the metastasis of tumor cells. Mechanistically, CREB3 promotes the transcription of CXC motif receptor 4 (CXCR4) through binding to the CRE element in the promoter of
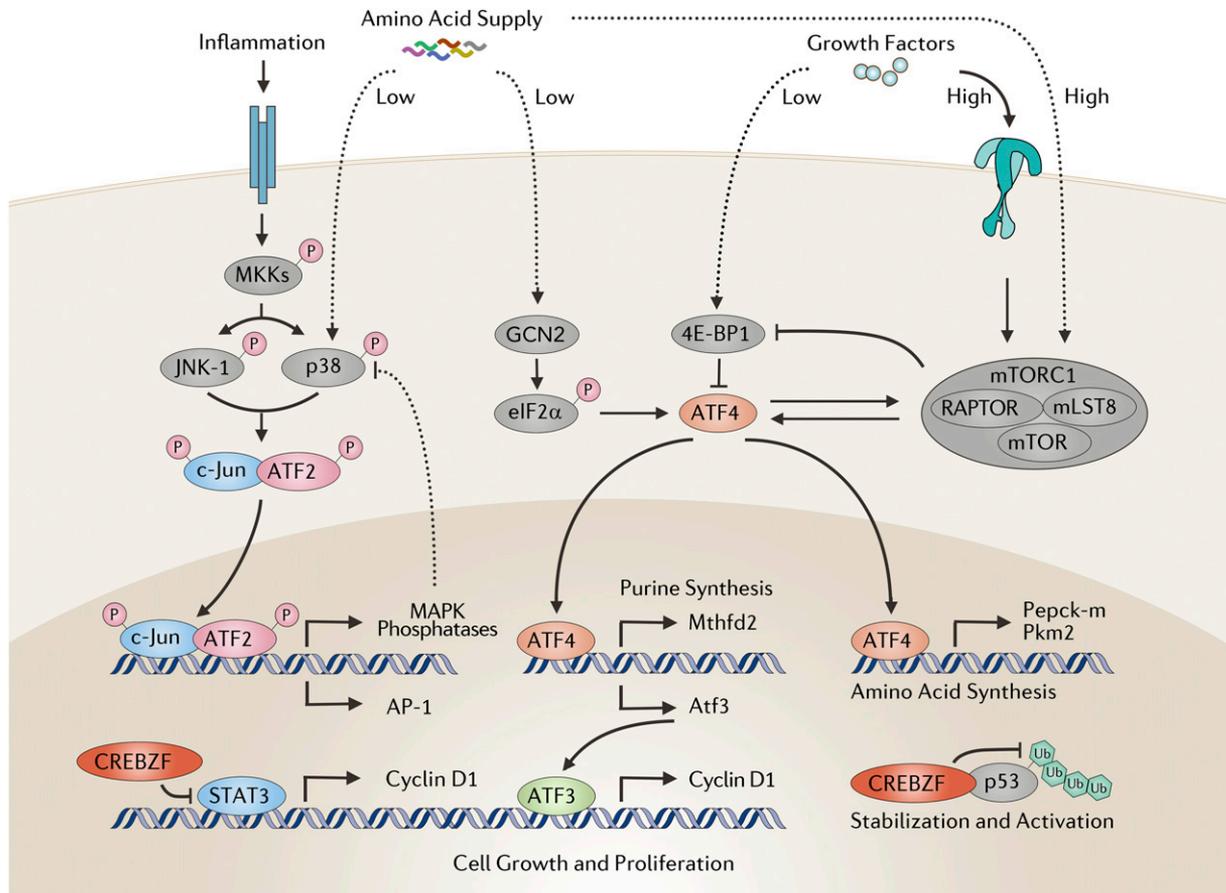
Figure 3—Regulation of cell proliferation and growth by the ATF/CREB family of transcription factors. In response to growth factors (such as insulin) and amino acids, ATF4 is activated by the activation of mTORC1 complex or by AAR via amino acid sensor GCN2-mediated phosphorylation of eIF2α. The upregulation of ATF4 promotes purine synthesis and cell survival through stimulating MTHFD2, and PEPCK-M and PKM2, respectively. Conversely, ATF4 activity is inhibited by eukaryotic translation initiation factor 4E-BP1 as a consequence of low growth factors. Moreover, dimerization and activation of c-Jun and ATF2 are triggered by AAR or inflammatory signals, which promote cell proliferation and may contribute to HCC. ATF3 is transcriptionally induced by ATF4. ATF3 enhances the expression of cyclin D1 via binding to the AP-1 motif of the cyclin D1 gene promoter, leading to increased hepatocyte DNA synthesis and proliferation. Intriguingly, CREBZF inhibits cell growth and proliferation via the repression of the dimerization and transcriptional activity of STAT3 as well as the stabilization and activation of p53. GCN2, general control nonderepressible 2; 4E-BP1, 4E-binding protein; JNK, c-Jun N-terminal kinase; mLST8, mammalian lethal with Sec13 protein 8; MTHFD2, methylenetetrahydrofolate dehydrogenase 2; mTORC1, mammalian target of rapamycin complex 1; PEPCK-M, mitochondrial phosphoenolpyruvate carboxykinase; PKM2, pyruvate kinase isozyme type M2; RAPTOR, regulatory associated protein of mTOR 1.

CXCR4, leading to increased migration of MDA-MB-231 metastatic breast cancer cells (111). CREM is upregulated in human and mouse HCC cells and may function as an oncogene candidate in the pathogenesis of HCC (112). The effects of CREM on cell growth and proliferation are further supported by the observations showing increased liver regeneration in CREM-deficient mice after hepatectomy (108,113,114). As to CREBZF, it functions as an inhibitor of cell growth. Overexpressing CREBZF causes a potent stabilization and activation of the tumor suppressor p53, leading to the inhibition of cell growth inhibition (115), whereas knockdown of CREBZF results in a reduction of p53 and induction of cell cycle progression (116). Moreover, the inhibitory role of CREBZF in hepatocyte proliferation and liver regeneration has been revealed (117). Hepatocyte-specific CREBZF deficiency

stimulates the expression of the cyclin gene family, promotes cell cycle progression, and enhances liver regeneration after partial hepatectomy or in response to CCl4 treatment. Mechanistically, CREBZF potently associates with the linker domain of STAT3 and represses its dimerization and transcriptional activity (117). Taken together, the ATF/CREB family of transcription factors is vital in maintaining liver function and physiology, and aberrant regulation of these signaling might lead to human cancers including HCC. Targeting these molecules may provide potential therapies for HCC tumorigenesis and progression.

Conclusions and Future Perspectives
Studies from the last decades have identified pleotropic functions of the ATF/CREB protein family in regulating

metabolism and cell growth. These findings have markedly enhanced our understanding of the pathogenesis of type 2 diabetes, NAFLD, and cancer and identification of new targets for prevention and treatment of these diseases. Although many ATF/CREB family proteins have overlapping functions in metabolism, they play nonredundant roles in response to nutrient, hormone, and energy availability. Upon activation, they function as transcription factors or cofactors to control metabolic homeostasis via the formation of complexes with other cellular proteins. Further transcriptomic and proteomic analyses are needed to further delineate the biology and mechanism of the ATF/CREB family proteins under various physiological and pathological conditions.

Intriguingly, preclinical studies show that the ATF/CREB family might represent therapeutics for treating some types of cancer. CREB inhibitor 666-15 is sufficient to inhibit cancer cell growth in the MDA-MB-468 xenograft model (118). Melatonin acts as an ATF6 inhibitor to promote the apoptosis of hepatoma cells and may be a potential candidate for the treatment of HCC (119). Moreover, ATF3 and ATF4 are hyperactivated in the liver of NAFLD and NASH patients (31,120), and several CREBH gene mutations were identified in patients with hypertriglyceridemia (78). Given that the activities of the family members are dysregulated in diabetes, fatty liver disease, and tumors, therapeutic approaches such as ATF/CREB inhibitors or agonists may offer an exciting new avenue for treating these diseases.

Nevertheless, many questions remain to be answered. Although the ATF/CREB family integrates wide ranges of intracellular and extracellular signals, such as glucose, free fatty acids, growth factors, and steroid hormones, how the integrated signals and cross talk are regulated among the family members independently or cooperating with other nuclear factors or cofactors is not well understood. The physiological relevance of ATF/CREB signaling pathways requires further investigation in animal models. The biology of ATF/CREB proteins and the mechanism of actions should be studied with use of various tissue-specific knockout mice. Whether and how does the ATF/CREB signaling play roles in coupling the alteration of glucose or lipid metabolism to the development of uncontrolled cell growth and tumorigenesis?

Given the broad spectrum of gene expression patterns, the ATF/CREB family members also function in other key metabolic tissues, such as adipose tissue, skeleton muscle, immunocytes, and nervous system. Future studies into understanding the mechanisms of action of ATF/CREB proteins in these tissues are important for unlocking their full pathophysiological potential in the control of whole-body metabolic homeostasis. Together, the ATF/CREB family is critical for a variety of signaling pathways that are important for human health. Further illumination of their biological function and the underlying mechanism, and translation of the basic research findings into new therapeutics, will certainly be the focus of research for years to come.

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