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The role of CREB-H transcription factor in triglyceride metabolism

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Abstract

Purpose of review—CREB-H is a transcription factor that is highly and selectively expressed in liver and small intestine. Here I summarize recent findings on the role of CREB-H in lipid metabolism.

Recent findings—Recent studies have demonstrated that hepatic CREB-H is transcriptionally activated by fasting, and induces lipid metabolism genes, such as Apoa4, Apoa5, and Apoc2 apolipoproteins which exhibit stimulatory effects on lipoprotein lipase (LPL). Consistent with the essential role of LPL in TG clearance, CREB-H deficient mice showed hypertriglyceridemia, associated with defective production of these apolipoproteins and decreased LPL activity. DNA sequencing of the CREB3L3 gene (encoding CREB-H) identified multiple nonsynonymous mutations in CREB3L3 in individuals with extreme hypertriglyceridemia.

Summary—Recent studies uncover a novel function of CREB-H in the regulation of TG metabolism in rodents and humans. In liver and small intestine, CREB-H induces LPL coactivators, Apoa4, Apoa5, and Apoc2 that facilitate TG clearance from plasma.

Keywords

CREB-H; CREB3L3; transcription factor; triglyceride; apolipoprotein

Introduction

Dysregulation of lipid metabolism leading to increased plasma cholesterol and triglyceride (TG) is closely associated with coronary artery disease (CAD), obesity and type 2 diabetes [1]. Transcription factors play central roles in metabolic regulation in mammals by controlling the synthesis of key metabolic proteins in response to nutritional and hormonal cues [2]. Thus, transcription factors such as nuclear hormone receptors have proven to be fruitful drug targets for the treatment of metabolic disorders.

CREB-H was first identified as a liver specific bZIP transcription factor that could bind to CRE (TGACGTCA) [3] and box-B-like elements within the promoters of liver-expressed genes [4, 5]. Later studies revealed that CREB-H is also highly expressed in small intestine [6, 7••]. CREB-H is produced as an ER-localized type II transmembrane glycoprotein that is converted into the mature nuclear form by sequence specific proteases, Site-1 protease (S1P)

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and Site-2 protease (S2P) [8, 9], which also cleave the sterol regulatory element-binding proteins (SREBPs) and activating transcription factor 6 (ATF6) [10, 11] (Figure 1). The upstream signal that activates the proteolytic processing of CERB-H is largely unknown or controversial. On the other hand, several independent studies have demonstrated that CREB-H plays a role in acute phase response (APR) [9]; induces hepcidin, a peptide hormone that controls iron absorption [12]; promotes gluconeogenesis [13••].

Recent several studies have demonstrated that hepatic CREB-H expression is influenced by nutrition, and it is involved in the regulation of glucose and lipid metabolism. In this review, I will discuss the emerging role of CREB-H in nutrient metabolism.

ER transmembrane transcription factors

As a continuous membrane network inside the cell, endoplasmic reticulum (ER) carries out many important functions, such as protein folding and post-translational modifications, lipid synthesis, and detoxification of xenobiotics. It has been demonstrated that biological processes occurring in the ER are transcriptionally regulated via signaling pathways involving proteolytic activation of transcription factors that are anchored in the ER through their transmembrane domains. For example, the synthesis of fatty acids and cholesterol is controlled by SREBP transcription factors as demonstrated by elegant studies led by the Brown and Goldstein group [14, 15]. Disequilibrium of protein folding in the ER leading to an increase of unfolded protein species causes ER stress and triggers a cellular defense mechanism called the unfolded protein response (UPR) [16, 17]. ER stress induces proteolytic cleavage of ATF6α and ATF6β, which play important roles in the UPR by inducing genes involved in protein folding and degradation of misfolded proteins generated in the ER [18]. Based on amino acid sequence homology, additional transcriptional factors have been identified that possess conserved ER transmembrane domains (reviewed in [19, 20•]). These include Luman/CREB3, OASIS/CREB3L1, BBF2H7/CREB3L2, CREB-H/CREB3L3, and CREB4/AIBZIP/CREB3L4 (Figure 1). In vitro studies have demonstrated that these transcription factors require proteolytic cleavage for the activation, similar to SREBP and ATF6 [19, 20]. Several studies demonstrated that ER stress activated these transcription factors at both the transcriptional and post-transcriptional level [9, 19, 21-23], although their roles in the ER stress response and normal animal physiology are not fully understood. However, given their localization to the ER, it is conceivable that signals activating these transcription factors and their functions might be related to the ER functions described above.

Mode of activation of ER transmembrane transcription factors

ER transmembrane transcription factors are synthesized as precursor forms anchored to the ER membrane. In order to be transported to the nucleus to carry out their function as transcription factors, they have to be cleaved by proteases that release the mature N-terminal portion of the protein, in a process called Regulated Intramembrane Proteolysis (RIP), as the protease cleavage site is buried in the lipid bilayer [24]. Components of proteolytic activation and their mode of action were identified and characterized largely by the Goldstein and Brown group, who focused on SREBP activation by sterol [24•]. SREBPs are produced as precursor proteins containing two transmembrane domains, which anchor the protein in the ER complexed with the SREBP cleavage activating protein (SCAP) and ER retention protein called Insig [24]. Low sterol triggers a conformational change of the sterol sensitive SCAP protein that dissociates the SCAP-SREBP complex from Insig [24•]. The SCAP-SREBP complex migrates to the Golgi apparatus, where SREBPs are sequentially cleaved by site 1 (S1P) and site 2 (S2P) proteases to liberate the mature proteins that translocate to the nucleus and act as active transcription factors [24•]. ATF6 is also activated

by sequential cleavage by S1P and S2P, but the signal that triggers the mobilization of ATF6 to Golgi is ER stress instead of sterol concentration [11]. Under normal conditions, ATF6 is tightly associated with an ER chaperone BiP, which is dissociated by ER stress to allow the mobilization of ATF6 to the Golgi [25]. It has been demonstrated that S1P and S2P are also essential for the activation of CREB3L3/Luman [22], OASIS [21], CREB4/CREB3L4 [23], and CREB-H [9].

Regulation of CREB-H expression

CREB-H is highly and selectively expressed in liver and small intestine [6, 7••]. A recent study demonstrated that CREB-H is a downstream target gene of hepatocyte nuclear factor 4α (HNF-4α), which plays a critical role in hepatocyte differentiation and liver function [26]. Ablation of HNF-4α abolished CREB-H mRNA expression in the liver, but not in the small intestine, suggesting an essential role of HNF-4α in hepatic CREB-H expression [6]. An HNF-4α binding site was identified at 3.7 kb upstream of the CREB-H promoter.

Nutritionally, hepatic CREB-H expression is induced under fasting condition and suppressed by refeeding [7••, 13••, 27••], which correlates with plasma glucocorticoids and free fatty acid (FFA) concentrations. Glucocorticoids produced from adrenal gland bind to glucocorticoid receptor (GR), which exerts antagonizing effect of insulin and promotes gluconeogenesis [28]. It is notable that dexamethasone, a synthetic corticosteroid, induced CREB-H transcription [13••]. Lee and colleagues demonstrated that GR induces CREB-H gene transcription by directly binding to the glucocorticoid transcriptional response element (GRE) in the proximal promoter region [13••]. CREB-H gene promoter also contains a peroxisome proliferator responsive element (PPRE) for PPARα transactivation [27••]. PPARα plays a central role in the adaptive response to fasting by regulating genes involved in FA oxidation in peroxisomes and mitochondria [29]. PPARα is activated by increased concentrations of FFA secreted from adipose tissue during fasting, or pharmacologically by synthetic agonists, such as fibrates. It has been demonstrated that FFA induces CREB-H gene transcription in hepatocytes [27••, 30•], presumably by activating PPARα. It remains to be determined if CREB-H mRNA and protein expression is indeed suppressed in PPARα deficient mice. CREB-H expression can be also induced by the endocannabinoid system that is known to be involved in various liver diseases [31•, 32].

CREB-H is produced as a precursor form that requires proteolytic processing for activation, a process that might be regulated by specific signals. An initial study demonstrated that CREB-H is activated by ER stress, similarly to ATF6 [9]. It was shown that CREB-H processing was induced when cells were treated with ER stress inducers such as tunicamycin, thapsigargin and dithiothreitol, which also proteolytically activated ATF6 [9]. However, following two independent studies failed to observe any induction of CREB-H processing by ER stress inducers [8, 33••]. On the contrary, Chan et al. demonstrated that inhibition of N-linked glycosylation by tunicamycin treatment or by destruction of the glycosylation sites in CREB-H actually suppressed CREB-H processing, suggesting that ER stress is not the major upstream signal for CREB-H activation [33••]. Under normal condition in C57BL/6 mice, processed nuclear CREBH(N) accounts for ~10% of total CREB-H in the liver [7••]. CREB-H is also spontaneously processed in the intestine, generating significant amount of CREB-H(N) detectable by Western blotting. It remains to be determined if CREB-H is spontaneously processed in these organs or its processing is regulated under any physiologically relevant conditions.

The role of CREB-H in hepatic lipid metabolism

DNA microarray analysis of hepatic gene expression profiles in CREB-H knockout mice identified CREB-H target genes in liver [7••, 34••]. Interestingly, gene ontology analysis

revealed that genes involved in lipid metabolic process were significantly down-regulated in CREB-H deficient liver [7••, 34••]. Decreased expression of Apoa4 (apoA-IV), Apoa5 (apoA-V), and Apoc2 (apoC-II) in CREB-H knockout mice was notable. These apolipoprotein mRNAs were induced by fasting in WT, but not in CREB-H deficient mice. ApoA-IV, apoA-V, and apoC-II are known to augment lipoprotein lipase (LPL) activity [35-37]. LPL is bound to the vascular endothelium, and hydrolyzes chylomicron and VLDL-associated TG to facilitate the transport of hydrolyzed fatty acids to peripheral cells [38]. Patients with genetic defects in AOPC2, APOA5 or LPL display high circulating TG levels due to impaired TG clearance [35, 37-39]. Identification of Apoa4, Apoa5 and Apoc2 as CREB-H target genes suggested that CREB-H might be involved in TG catabolism. CREB-H also strongly induces FGF21, a liver expressed hormone that has antidiabetic and TG-lowering effects [40•], and Cidec which encodes a lipid droplet-associated protein [41].

Consistent with the role of CREB-H in the expression of lipid metabolism genes, CREB-H knockout mice showed remarkable TG phenotypes [7••, 34]. Plasma TG levels were dramatically increased in CREB-H knockout mice, due to inefficient LPL-mediated TG clearance. Hepatic TG content was also increased in CREB-H knockout mice under fasting condition [7••]. A recent paper demonstrated that CREB-H knockout mice fed an atherogenic “Paigen” diet developed severe hepatic steatosis, associated with decreased expression of a variety of genes involved in lipogenesis, lipolysis and fatty acid oxidation, suggesting that CREB-H has a crucial role in the maintenance of hepatic TG homeostasis under metabolic stress [34].

It is widely accepted that complex traits such as cholesterol and TG levels are determined by multiple genetic factors, such as common DNA sequence polymorphisms, heterozygous rare variants of disease associated genes, and monogenic defects in Mendelian disorders [42•, 43]. The rare variant hypothesis suggests that although rare and only partially penetrant individually, the combined effects of multiple rare variants with moderate to high penetrance increase the risk of common inherited diseases [44•, 45]. Genetic variants in CREB3L3 that produce nonfunctional or hypomorphic CREB-H protein exist in humans, although rare. Remarkably, heterozygous nonsynonymous or insertional mutations in CREB3L3 that produce hypomorphic or nonfunctional CREB-H protein were more common in HTG patients than in the control group [7••, 46•]. The number of HTG carriers of heterozygous *CREB3L3* mutations was comparable to that observed for the established HTG-associated genes *LPL* and *APOA5*. Together with the data from CREB-H deficient mice, these studies demonstrate the crucial function of CREB-H in TG metabolism and the involvement of CREB-H mutations in human hypertriglyceridemia (Figure 2). A replication study using independent cohorts would firmly establish the association between CREB3L3 variants and hypertriglyceridemia.

Role of CREB-H in hepatic gluconeogenesis

As a CREB family transcription factor, CREB-H was shown to bind to cAMP response element (CRE) and transactivate a CRE reporter [5]. Gluconeogenesis genes, such as Phosphoenolpyruvate carboxykinase (PEPCK) and glucose 6 phosphatase (G6P) contain CREs in the promoter that mediate the transcriptional activation of these genes by glucagon [47]. As expected, CREB-H transactivated these CRE containing promoters, and induced PEPCK and G6P mRNAs upon overexpression [13••, 48]. Importantly, silencing of hepatic CREB-H by shRNA suppressed PCPCK and G6P expression, and thus suppressed hepatic glucose production [13]. It would be interesting to determine if gluconeogenesis is also impaired in CREB-H deficient mice.

Role of CREB-H in ER stress response

As discussed above, CREB-H processing appears to be unaffected by ER stress [8], and rather suppressed by tunicamycin treatment that inhibits protein N-linked glycosylation [33••]. Two papers reported that tunicamycin treatment induced hepcidin, a liver-produced hormone that plays a central role in iron homeostasis, and APR genes, such as CRP and SAP, in hepatocytes in CREB-H dependent manners [9, 12•]. Luciferase reporters containing CRP, SAP, or hepcidin gene promoters were induced by cotransfection with constitutively active CREB-H(N). These results suggest that CREB-H plays important roles in APR and iron metabolism, but are puzzling, given that tunicamycin does not activate CREB-H, and warrants re-revaluation under more physiological conditions, other than tunicamycin treatment that might have pleiotropic effects.

Conclusion

Liver and small intestine secrete TG-rich very-low-density lipoprotein (VLDL) and chylomicrons, respectively, to deliver TG to peripheral tissues, such as adipose tissue and muscle. CREB-H is highly expressed in these organs, and activates genes that promote TG catabolism, decreasing plasma TG levels. Markedly elevated plasma TG levels in CREB-H deficient mice, and the presence of nonsynonymous mutations in CREB3L3 only in hypertriglyceridemia patients strongly suggest that CREB-H regulates TG metabolism both in humans and mice. CREB-H appears to be closely related to PPARα, which plays a central role in the adaptive response to fasting in liver by inducing genes involved in FA oxidation and ketogenesis [29]. Both CREB-H and PPARα are activated by fasting and induce common targets such as FGF21 and Cidec. It is possible that CREB-H and PPARα are in the same signaling pathway, one regulating the other. It is also possible that they are independently activated and share only a small subset of common targets. It is of interest to define direct CREB-H target genes by Chromatin immunoprecipitation (ChIP) followed by DNA sequencing (ChIP-Seq), and to investigate the functional relationship between CREB-H and PPARα. Another interesting research area is to interrogate the function of CREB-H in intestine. We do not know if intestinal CREB-H is regulated by any metabolic cues, and if it has any role in TG metabolism in small intestine.

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Key points

- CREB-H is an ER transmembrane transcription factor expressed in liver and small intestine.
- Hepatic CREB-H transcription is induced by glucocorticoid receptor and PPARα that mediate fasting response.
- CREB-H induces apolipoproteins that stimulate LPL activity.
- Plasma TG level is elevated in CREB-H deficient mice, associated with impaired LPL-mediated TG clearance.
- Genetic mutations in CREB3L3 that produce nonfunctional or hypomorphic CREB-H were identified in individuals with extreme hypertriglyceridemia.

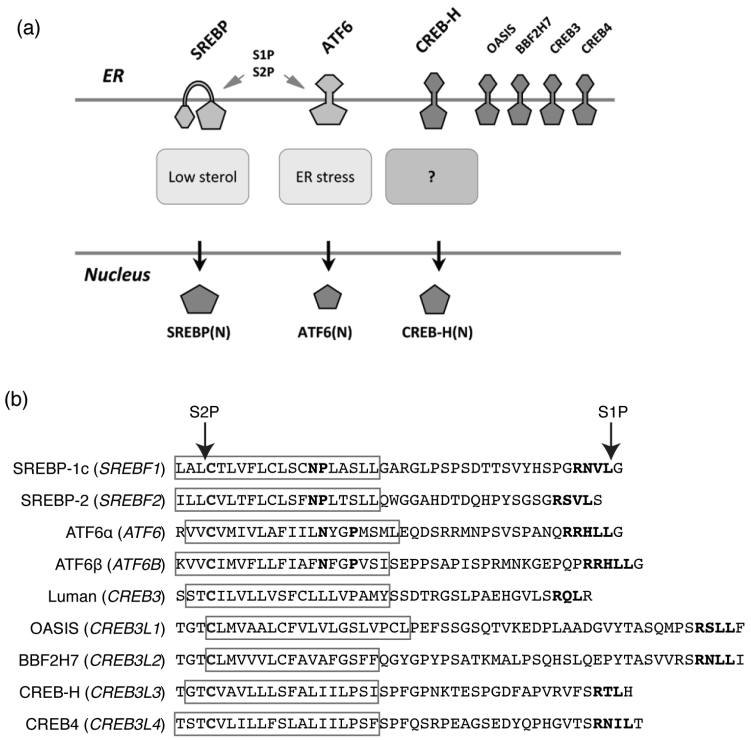

Figure 1. ER transmembrane transcription factors

(a) Activation of ER transmembrane transcription factors by S1P and S2P proteases. Low cellular sterol concentration or ER stress triggers Golgi transport of SREBPs and ATF6, allowing the sequential cleavage by S1P and S2P proteases. (b) Comparison of amino acid sequences of ER transmembrane transcription factors. Boxed regions indicate the predicted transmembrane domains. Amino acid residues critical for the protease cleavage of SREBPs and conserved in other members are marked by bold letters.

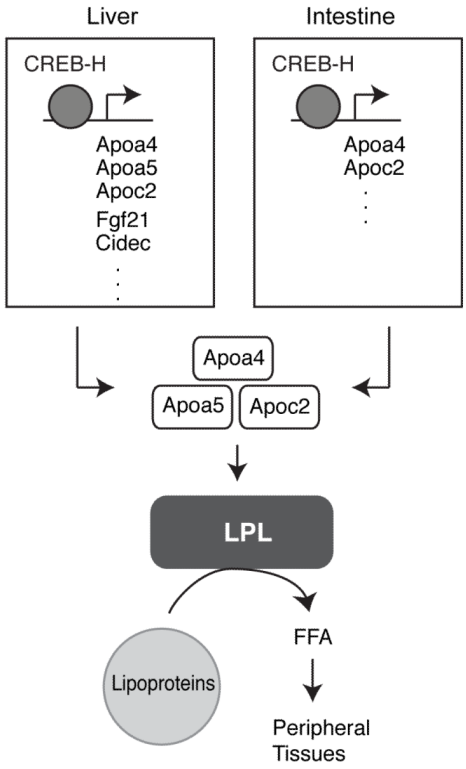

Figure 2. Schematic representation of the role of CREB-H in the regulation of plasma TG levels

In liver and small intestine, CREB-H induces apolipoproteins that facilitates LPL mediated TG clearance from circulation.