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REVIEW

SREBP-1c and TFE3, energy transcription factors that regulate hepatic insulin signaling

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Abstract Genes involved in carbohydrate and lipid metabolism are nutritionally regulated at the transcriptional level in a coordinated fashion. SREBP-1c is a bHLH transcription factor that controls lipogenesis and is induced during overnutrition to facilitate the conversion of glucose to fatty acids and triglycerides for the storage of the excess energy. Uncontrolled activation of nuclear SREBP-1c in the liver can cause hepatosteatosis, hypertriglyceridemia, and hepatic insulin resistance due to direct suppression of insulin signaling pathways, precipitating development of metabolic syndrome. Conversely, TFE3 is a novel bHLH transcription factor that strongly activates various insulin signaling molecules, protecting against the development of insulin resistance and the metabolic syndrome. Regulation of IRS-2 is the primary site where TFE3 in synergy with Foxo1, and SREBP-1c converge. Taken together, TFE3/Foxo1 and SREBP-1c reciprocally regulate IRS-2 expression and insulin sensitivity in the liver. This scenario provides a mechanistic explanation for the physiological link between glucose and lipid metabolism such as physiological switching of glycogen synthesis to lipogenesis. In addition, these two transcription factors may ultimately contribute to pathophysiological effects of overnutrition leading to the development of the metabolic syndrome and diabetes. In this review, I will discuss roles of SREBP-1c and TFE3 in homeostasis of energy metabolism and in metabolic disturbances, focusing on hepatic insulin sensitivity.

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Keywords Insulin signaling · Lipogenesis · Metabolic syndrome

Nutritional regulation of hepatic lipogenesis by SREBP-1c

Ingestion of excess energy induces fatty acid synthesis in the liver. Dissection of its molecular mechanism is a pathway to understanding of transcriptional regulation of energy metabolism involving physiology of energy storage and pathophysiology linking to hepatosteatosis, dyslipidemia, metabolic syndrome, and diabetes. The sterol regulatory element-binding protein (SREBP) family is a group of transcription factors that control biosynthesis of lipids and play a pivotal role in the homeostasis of cellular sterol regulation [1]. SREBP-1c is the isoform that controls biosynthesis of fatty acids and triglycerides in the liver [2, 3]. Nuclear SREBP-1c up-regulates gene expression of a group of target lipogenic enzymes such as acetyl CoA carboxylase, fatty acid synthase, long chain fatty acid

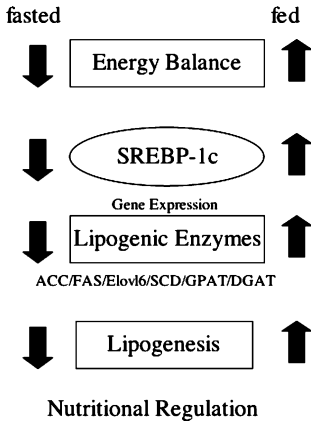

Fig. 1 Nutritional regulation of hepatic lipogenesis controlled by SREBP-1c

elongase (Evolv-6), and stearoyl-CoA desaturase 1 which coordinately are responsible for the conversion of glucose to oleate, the final end-product of de novo fatty acid synthesis in the liver (Fig. 1). The crucial role for SREBP-1c in hepatic lipogenesis was established primarily through animal studies. Overproduction of hepatic nuclear SREBP-1c in transgenic mice caused activation of these lipogenic genes leading to fatty liver, whereas absence of SREBP-1 by targeted gene disruption abolished nutritional regulation of lipogenic enzymes [4–6]. Of physiological relevance, hepatic SREBP-1c is highly regulated by nutritional conditions. Fasting suppresses and refeeding induces SREBP-1c expression [7, 8]. In addition, diets rich in carbohydrates, sugars, or saturated fatty acids are strong inducers, whereas polyunsaturated fatty acids (PUFA) are inhibitors of SREBP-1c (discussed later).

SREBPs are synthesized as membrane-bound proteins and reside on rough endoplasmic reticulum. Like SREBP-1a and SREBP-2, SREBP-1c requires a cleavage process to release the amino-terminal portion of the protein into the nucleus for transactivation of its target genes [9, 10]. Whereas this SREBP-cleavage process is the key regulatory step for cellular sterol regulation mediated by SREBP-2, it is not crucial for the activation of hepatic SREBP-1c. The amount of nuclear SREBP-1c protein, the active form, is highly correlated with SREBP-1c mRNA level [7, 11]. Thus, gene expression of SREBP-1c is the key regulatory step for its activity and ultimately determines hepatic lipogenesis.

Upon analysis of the mouse SREBP-1c gene promoter, we identified multiple systems that contribute to nutritional regulation of SREBP-1c and by extension, lipogenesis. The SREBP-1c promoter contains a sterol regulatory element (SRE), which is a canonical binding site for SREBP. This regulatory an auto-loop could explain the phenomenon of overshooting of lipogenic enzyme synthesis when mice are fed high carbohydrate diets after fasting [12]. Upstream of the SRE, there are two LXR response elements or LXREs [13]. LXR plays a crucial role in cholesterol metabolism as an oxysterol receptor and is now also a dominant regulator of SREBP-1c [13, 14]. Control of energy metabolism can be added to the expanding list of LXR functions [15]. It is likely that LXR is involved in the nutritional regulation of SREBP-1c by fasting/refeeding, although more studies are necessary to characterize the relationship between LXR and SREBP-1c in energy metabolism.

Many nutrients and nutrition-related signals, including insulin and glucagon, regulate SREBP-1c expression in a coordinated fashion as summarized in Fig. 2. Nutrients such as carbohydrates (glucose and fructose), as well as saturated fatty acids, are strong inducers of SREBP-1c [7, 8, 11, 16, 17]. Protein kinase A and AMP kinase, both of which are activated during energy depletion, suppress SREBP-1c [18, 19] (Yamamoto T and Shimano H, unpublished data). Leptin also strongly suppresses SREBP-1c [20]. Conversely, insulin and hyperglycemia elevate SREBP-1c expression [11, 16–18, 21, 22]. Some of PKC signals also could be involved in SRBP-1c activation [23] (Yamamoto T and Shimano H, unpublished data). Nevertheless, the precise molecular mechanism by which these nutritional signals control the SREBP-1c promoter is still an enigma. Unlike the dynamic nutritional regulation of hepatic SREBP-1c that occurs in vivo depending upon nutritional states, this level of control is not fully observed in cultured cells including primary hepatocytes, hampering molecular dissection of this system by in vitro experiments.

Potential involvement of SREBP-1c in metabolic syndrome

Nutritional regulation of SREBP-1c is also involved in the pathogenesis of clinically relevant metabolic dis-

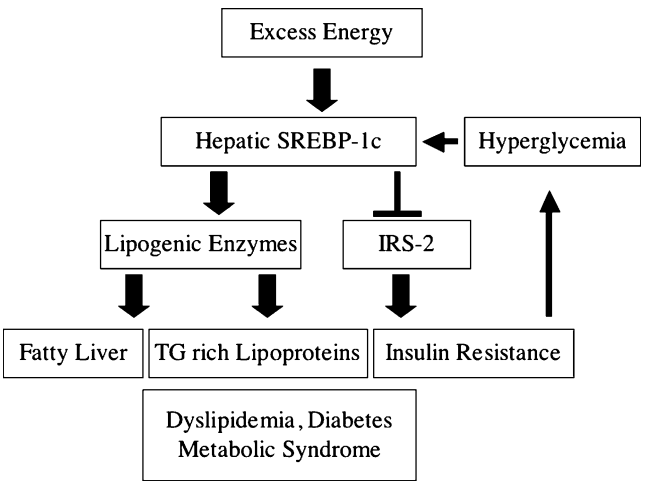

Fig. 2 Nutrients and signals that regulate hepatic SREBP-1c expression. *Note* LXRs and SREBPs known to directly activate SREBP-1c promoter are not indicated here

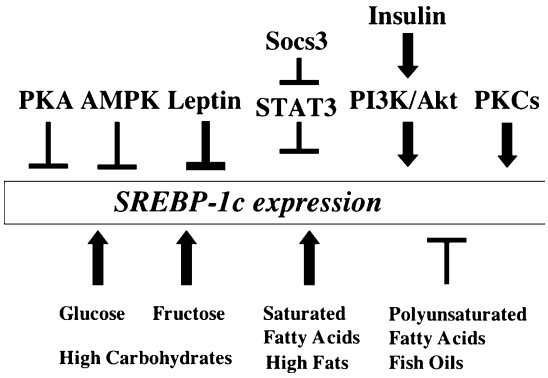

Fig. 3 Contribution of hepatic SREBP-1c to metabolic syndrome

turbances (Fig. 3). Hepatic lipogenesis, which is controlled by SREBP-1c, is linked to production of triglyceride-rich very low-density lipoprotein secreted into circulation as a source of energy for peripheral tissues. Thus, it is conceivable that activation of SREBP-1c can contribute to hyperlipidemia, especially hypertriglyceridemia, which is exacerbated by overnutrition. Experiments in animal provide evidence that overproduction of SREBP-1a and SREBP-1c is associated with hyperlipidemia under conditions in which plasma clearance of apoB-containing lipoproteins is retarded. This has been observed in SREBP-1a transgenic/LDL receptor KO and in ob/ob LDL receptor KO mice [24, 25]. The metabolic syndrome is defined as a cluster of cardiovascular risks such as abdominal obesity, hypertriglyceridemia, low HDL cholesterol level, hypertension, and impaired fasting glucose, all of which enhance atherosclerotic lesion formation. To examine the role of SREBP-1c in the metabolic syndrome, we recently developed a mouse model with SREBP-1c overexpressed in the liver on a background of LDLR deficiency (Takahashi A and Shimano H, unpublished data). These mice exhibited a plasma lipoprotein pattern of increased VLDL triglycerides and decreased HDL cholesterol without changes in LDL cholesterol, a profile similar to that seen in individuals with the metabolic syndrome. These mice develop atherosclerosis, confirming the atherogenicity of the metabolic syndrome-like lipoprotein profiles elicited by overexpression of SREBP-1c. In contrast, SREBP-1 knockout mice have consistently lower triglyceride levels in both plasma and liver than wild-type mice.

SREBP-1c causes hepatic insulin resistance

In addition to the regulation of lipid synthesis, SERBP-1c is involved in the regulation of insulin signaling [26] (Fig. 4). Animal models for obesity and insulin resistance such as ob/ob, db/db, KKAy, IRS-2 knockout mice, and aP2-SREBP-1c transgenic mice often exhibit fatty livers with increased SREBP-1c expression [20, 27]. Among insulin signaling molecules, IRS-1 and -2 play the crucial and complementary roles in hepatic insulin signaling. IRS-1 and -2 exhibit differential regulation and roles. IRS-1 is regulated at the protein level and is reported to be more closely linked to glucose homeostasis such as suppression of gluconeogenic genes, whereas IRS-2 controls lipid metabolism [28]. IRS-2 is unique because it is nutritionally regulated at the transcription level. IRS-2 knockout mice exhibited type 2 diabetes, and repression of IRS-2 was observed in the above insulin resistant mice [29, 30]. Thus, IRS-2 is the major hepatic insulin signal molecule in the long-term regulation. Intriguingly, in various nutritional conditions, expression of IRS-2 and SREBP-1c was consistently reciprocal, which led us to speculate that SREBP-1c should repress IRS-2 expression. Through adenoviral overexpression experiments and promoter analyses, it was found that SREBP directly binds to the promoter of IRS-2 and suppresses IRS-2 expression, leading to impaired insulin sensitivity [26]. Adenoviral overexpression of nuclear SREBP-1c decreased IRS-2 protein and autophosphorylation, accompanied by decreased Akt phosphorylation. Glycogen synthesis, a marker of insulin sensitivity, was suppressed by SREBP-1c, whereas fatty acid synthesis was activated. Thus, SREBP-1c could be a molecular mechanism of lipotoxicity in the liver by causing both insulin resistance and fatty liver. Hepatic insulin resistance could lead to hyperglycemia and further activation of hepatic SREBP-1c, forming a vicious circle of metabolic disturbances (Fig. 3). This scenario could also explain lipotoxicity in pancreatic beta cells, as overexpression of SREBP-1c in insulin-promoter transgenic mice exhibits impaired insulin secretion and decreased beta cell mass [31]. Consistently, SREBP-1 knockout mice show

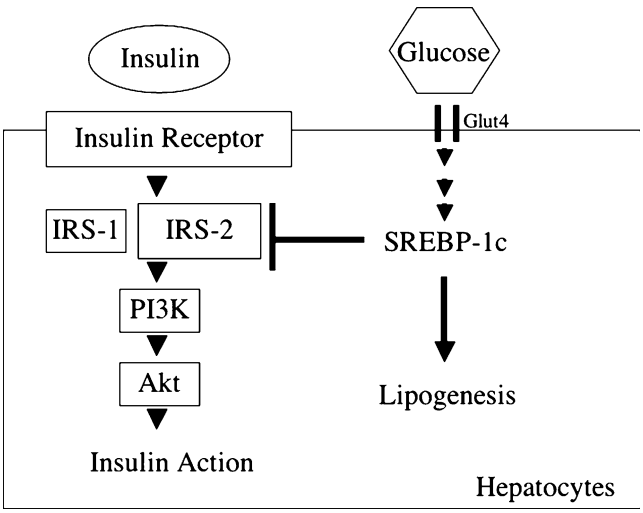

Fig. 4 SREBP-1c and insulin signaling in hepatocytes

higher IRS-2 expression in both liver and beta cells. However, it should also be noticed that these unfavorable lipotoxic effects of SREBP-1c are a dark side of this important lipid transcription factor in the case of chronic activation. In a short term, overexpression of nuclear SREBP-1 consumes glucose for lipogenesis, suppresses PEPCK [32], and could lower blood glucose [33]. Hepatic glucose and lipid metabolism involves many transcription factors and co-factors in a cross-talk network in complex manners and needs to be carefully estimated [3, 34].

Control of SREBP-1c by fatty acids

It is becoming increasingly clear that a link between pro-inflammatory signals and metabolic disturbances exists. Fatty acids are thought to be inducers of pro-inflammatory signaling cascades, and in the context of cellular stress, this pro-inflammatory state may contribute to the development of insulin resistance. SREBP-1c is highly induced by saturated fatty acids in both hepatocytes and isolated islets. This regulation of SREBP-1c by saturated fatty acids may be linked to their ability to promote inflammation. For example, induction of hepatic SREBP-1c by saturated fatty acids is mediated through PGC-1β [35], and pro-inflammatory signals such as STAT3 and SOCS3 are also involved in SREBP-1c regulation [36]. In contrast to saturated fatty acids, polyunsaturated fatty acids (PUFA) suppress SREBP-1c through multiple mechanisms. PUFAs repress SREBP-1c transcription, enhance degradation of its mRNA, and inhibit SREBP-1c cleavage for nuclear translocation [37–39]. When ob/ob mice were administered with PUFAs such as EPA or fish oil in the diet, the nuclear form of SREBP-1c, and subsequently, hepatic triglyceride content, was significantly decreased. The contribution of hepatic SREBP-1c to fatty liver was also shown by amelioration in ob/ob/SREBP-1 KO double mutant mice [40]. In addition to improvement of fatty liver, PUFA administration decreased both plasma insulin and glucose levels, improving insulin resistance [41]. This effect could be at least partially explained by the suppression of hepatic SREBP-1c. The precise molecular mechanism by which PUFAs inhibit the cleavage of SREBP-1 but not SREBP-2 is yet to be clarified, but will be crucial to understanding the differential regulation of SREBP-1 and -2 activation.

Discovery of TFE3 as a potent enhancer of insulin signaling

As mentioned above, SREBP-1c is likely to play an important role as an upstream regulator of lipogenesis, and when overexpressed, it contributes to metabolic disturbances related to lipotoxicity, including hyperlipidemia and insulin resistance. Based upon this knowledge, we sought to discover new factors that could have insulin signaling enhancing effects by playing a reciprocal role to SREBP-1c. E-boxes are consensus *cis*-elements for bHLH proteins and are often found to play a role in the nutritional regulation of metabolic genes. Thus, we adopted an expression strategy that utilized a carbohydrate response element including an E-box found in spot 14 gene. By screening an expression library from SREBP-1 KO mice, two clones that activated a reporter luciferase gene fused to this E-box containing *cis*-element were selected and identified as TFE3 and TFEB [42].

TFE3 is a bHLH protein that has been studied in its relation to immunology and cancer. TFE3 binds to enhancer of the immunoglobulin gene [43] and contributes to TGF-β-mediated PAI-1 gene induction through interaction with Smad proteins [44]. TFE3 is expressed ubiquitously, including energy-organs such as liver and adipose tissue. However, the role of TFE3 in metabolism had not been investigated. To obtain a global blueprint of the metabolic function of TFE3, liver samples from mice infected with adenovirus encoding TFE3 (Ad-TFE3) were subjected to DNA microarray analyses. Intriguingly, genes upregulated by TFE3 include IRS2, Akt1, Insig1, and HKII, all of which are involved in insulin signaling (Table 1). Transactivation of IRS2, HKII, and Insig1 by TFE3 was reconfirmed in primary hepatocytes in which TFE3 was overexpressed. Increased IRS-2 protein was associated with enhancement of phosphorylation of Akt, GSK3, and ERK with concomitant activation of glycogen synthesis, an indication of enhanced insulin signaling.

In vivo action of TFE-3

Consistent with enhanced insulin action in hepatocytes, after infection into normal mice, Ad-TFE3 exhibited a potent glucose-lowering action by similar activation of hepatic insulin-signaling molecules.

Next, we explored potential therapeutic effects of TFE3 on murine models of insulin resistance and diabetes. Ad-TFE3 injection caused marked amelioration of diabetes in KK and db/db mice. Both high glucose and insulin levels were decreased by TFE3 overexpression. In addition to overexpression experiments, knockdown of TFE3 in the liver caused suppression of IRS2 and emergence of insulin resistance, implicating TFE3 in physiological regulation of insulin sensitivity. Both TFE3 and IRS-2 are concomitantly repressed in the livers of insulin resistant ob/ob mice and up-regulated in streptozocin-treated mice. The coordinated regulation of TFE3 and IRS-2 in physiological and pathophysiological livers supported TFE3 regulation of IRS-2.

Table 1 Expression of metabolic genes in the murine livers after infection of adenoviral TFE3 as compared to control (adenoviral GFP) in a fasted or refed state

	Fasted		Refed	
	GFP	TFE3A	GFP	TFE3
Insulin signaling				
Insulin receptor	1.00	0.85	1.08	1.15
IRS-1	1.00	0.47	0.76	0.58
IRS-2	1.00	6.50	3.00	5.50
Akt1	1.00	1.74	0.74	1.97
Akt2	1.00	1.18	1.04	1.06
GSK3	1.00	1.08	0.92	1.58
Foxo1	1.00	1.30	0.57	1.13
CD45	1.00	0.24	1.16	0.30
Insig-1	1.00	3.61	2.43	4.79
IGF-I	1.00	1.37	1.24	0.94
Glucose metabolism				
PEPCK	1.00	0.77	0.02	0.92
G6Pase	1.00	0.73	1.79	0.66
HNF4	1.00	1.24	0.83	0.66
PGC-1α	1.00	3.21	0.43	2.21
PGC-1β	1.00	1.83	0.58	1.04
HKII	1.00	2.53	1.12	8.94
Lipid metabolism				
SREBP-1	1.00	1.19	3.92	0.81
FAS	1.00	0.83	20.5	0.97
SCD-1	1.00	0.97	3.10	0.52
LXRα	1.00	0.36	0.80	0.23

Values are expressed as relative expression level based upon Affimetrix gene chip analysis vs AdGFP in a fasted state.

Activation of IRS-2 promoter by TFE3

Human IRS-2 promoter analysis (reporter and gel shift assays) revealed that TFE3 binds to an E-box in the middle of the SREBP binding site and next to a Foxo binding site. In transfection studies, co-expression of TFE3 and Foxo1 synergistically activated the IRS2 promoter. As expected from the synergistic activation of IRS-2 promoter, Foxo1/TFE3 physically interact as shown by co-immunoprecipitation. Further analysis of Insig-1 and HKII promoters confirmed that HKII and Insig-1 are also direct target genes of TFE3. Physical in vivo binding of these factors to IRS-2 promoter was confirmed by ChIP assays. SREBP binds to the IRS-2 promoter in competition with Foxo1/TFE3 and leads to insulin resistance. As summarized in Fig. 5, TFE3/Foxo1 and SREBP-1c dictate nutritional regulation of IRS-2 expression and insulin sensitivity in the liver. In a fasted state with low plasma insulin levels, TFE3 and Foxo1 bind to the IRS2 promoter and trans-activate IRS2 expression, presumably through recruiting the co-activator, PGC-1α [26]. High expression of IRS2 assures efficient insulin signaling preparing for the next meal with its concomitant rise in insulin. In a re-fed condition or insulin-resistance states, active SREBP-1c accumulates in the nucleus, occupies and suppresses the IRS-2 promoter, and leads to hepatic insulin resistance. Collectively, SREBP-1c, Foxo1, and TFE3 control insulin sensitivity by regulating IRS-2 expression.

Various metabolic impacts of TFE3 overexpression

It is noteworthy that TFE3 markedly improved plasma glucose levels even in STZ-treated diabetic mice, a model of type 1 diabetes characterized by insulin depletion. This effect implicates that in addition to increasing levels of insulin signaling molecules, TFE3 also activates insulin signaling through a novel mechanism other than increases in IRS-2/Akt. TFE3 overexpression experiments in rat primary hepatocytes demonstrated that phosphorylation of IRS-2 and Akt was observed only in the presence of insulin, whereas phosphorylation of GSK3β and ERK was induced by TFE3 even in the absence of insulin. The precise molecular mechanism by which insulin signaling molecules were selectively hyperphosphorylated by TFE3 in the absence of insulin is currently unknown. It is conceivable that in addition to activation of HKII, this unique feature can account for the glucose-lowering effect of TFE3 in STZ-treated mice.

In addition to glucose/insulin metabolism, TFE3 has a profound effect on lipid metabolism. Hepatic triglyceride and cholesterol content as well as plasma triglycerides were diminished in Ad-TFE3-treated mice. This is likely

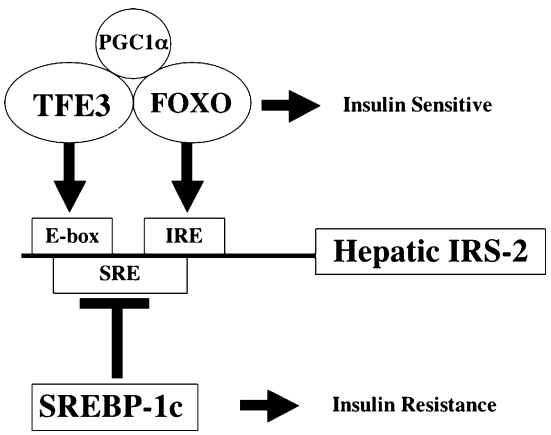

Fig. 5 Regulation of IRS-2 and insulin sensitivity by TFE3/Foxo1 and SREBP-1c TFE3/Foxo1 and SREBP-1c compete for binding to their overlapped binding site in the IRS-2 promoter. TFE3/Foxo1 activate IRS-2 expression in a fasted or insulin-depleted state. SREBP-1c accumulates in overnutrition and represses IRS-2 expression. When these three factors are co-localized in the nucleus, as observed in an insulin-resistant state, SREBP dominates over TFE3/Foxo1 for binding to the IRS-2 promoter, and insulin resistance persists

due to the activation of Insig-1 by TFE3. Insig-1 retains SREBP/SCAP at rough ER, prevents their travel to golgi, and thus, functions as an inhibitor of SREBPs. AdTFE3 activated Insig-1 and abolished accumulation of nuclear SREBP-1c protein and lipogenesis.

Furthermore, TFE3 also activates protein synthesis. Ad-TFE3-injected mice demonstrated increased hepatic phosphorylation of p70S6kinase and S6, proteins involved in protein translation. Consistent with the activation of these molecules, serum proteins including albumin were elevated. Ad-TFE3 infection caused enlargement of liver with a hypertrophic change in hepatocytes, which could be a reflection of increased protein synthesis.

Collectively, these data demonstrate that TFE3 has a significant impact on metabolic gene regulation, including increased insulin signaling, increased glycogen synthesis, decreased lipogenesis, and increased protein synthesis (Fig. 6). The unique and remarkable feature of this new metabolic transcription factor is that a single transcription factor has such a deep impact on various metabolic pathways in a coordinated fashion. Enhancement of insulin signaling and hypoglycemic effect, inhibition of lipogenesis, and activation of protein synthesis are all favorable for the prevention of metabolic syndrome and diabetes. The more precise mechanism by which TFE3 controls each of these pathways will require further investigation.

Clinical perspective of energy transcription factors as targets of metabolic diseases

Risk factors such as obesity, insulin resistance, hypertriglyceridemia, and hypertension contribute to the metabolic syndrome. Individually and cumulatively, these factors promote the development of diabetes and cardiovascular disease. Efficient control of each of these factors is required for the prevention of life-threatening events.

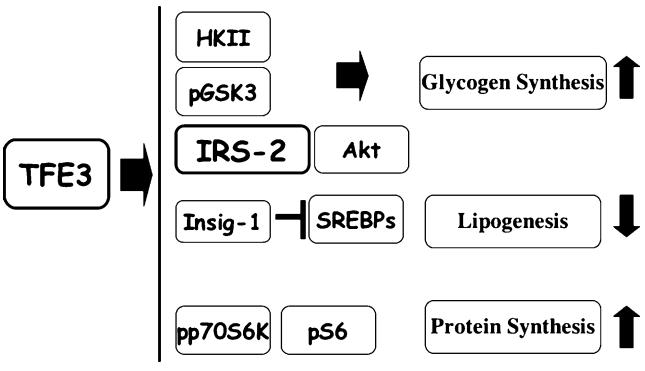

Fig. 6 Various actions of TFE3 on hepatic metabolism

Because insulin resistance is one of the central features of the metabolic syndrome, intervention focused at the underlying pathology for this factor would be more efficient and cause less adverse effects than using multiple drugs for each of the other risks alone. In this respect, modification of energy transcription factors is a reasonable approach. Agonists for PPARs such as fibrates and thiazolidinediones are already clinically used for the improvement of both lipid and glucose metabolism through insulin sensitization. HMGCoA reductase inhibitors (statins) are used most widely for the prevention of atherosclerotic disease. The plasma cholesterol lowering action of statins is mediated through activation of the SREBP-2/LDL receptor pathway. These pieces of well-known clinical evidence demonstrate that energy transcription factors are important targets of metabolic diseases. Meanwhile, cross-talk network of energy transcription factors is complex, and sometimes, drug development that targeted this system might encounter unexpected outcome [3]. For instance, SREBP-2 activation is beneficial in reducing plasma lipid levels because of the up-regulation of LDL receptors; however, activation of endogenous cholesterol synthesis could be harmful to pancreatic beta cells (Ishikawa M and Shimano H, a manuscript in preparation). LXR agonists activate cholesterol efflux in macrophages in atherosclerosis and have been thought to be promising as a future anti-atherosclerosis drug [45]. However, LXR activation in liver directly induces SREBP-1c and phospholipid transfer protein leading to fatty liver and hypertriglyceridemia, implicating double-edged efficacy [46]. To obtain favorable outcomes, it is crucial to modify transcription factors in a targeted manner in specific tissue with the correct intensity as already noticed in the concept of selective estrogen receptor modulators. Based upon our findings, suppression of SREBP-1c and activation of TFE3 in the liver are a favorable strategy to improve insulin resistance for the prevention of diabetes and cardiovascular risks. But their roles in other tissues, especially adipose tissues and skeletal muscle, require further investigation. Roles of these factors in vascular wall are also important issues to be investigated. To seek for the way of TFE3 activation, it is important to clarify physiological mode of regulation of this versatile factor especially at the protein level. These future investigations should also help to understand cross-talk network of energy transcription factors.

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