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Mediating Lipid Biosynthesis: Implications for Cardiovascular Disease

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Abstract

Dysregulation of lipid homeostasis is a risk factor for cardiovascular disease (CVD). Thus, understanding the molecular mechanisms of maintaining lipid homeostasis may aid the discovery of novel targets for treating CVD. MED15 and Cyclin-dependent kinase-8 (CDK8) are subunits of the Mediator complex, which contains multiple proteins and functions as a transcriptional cofactor. Mediator can positively or negatively regulate gene expression, depending on the contexts and its associated transcription factors. Recent studies revealed a critical role of MED15 and CDK8 in regulating sterol regulatory element-binding protein (SREBP) transcription factors, which are master activators for genes that are responsible for lipid biosynthesis. Here, we review the function of MED15 and CDK8 in regulating lipid homeostasis and discuss the implications for CVD.

Keywords

MED15; CDK8; SREBP; Transcription; Lipid; Phosphorylation; CVD; Atherosclerosis

Introduction

CVD is the leading cause of death in the developed countries. According to the data from US Center for Disease Control, currently one in every three deaths is from heart disease or stroke in the United States. Most of these deaths are caused by atherosclerosis. Although the molecular mechanisms of such pathological changes remains poorly understood, the major risk factors for atherosclerosis include obesity and its associated diseases, such as type 2 diabetes mellitus (T2DM) (Bornfeldt and Tabas 2011). Because of over-nutrition and sedentary life-styles, obesity is becoming this century's prevalent health issue. One common feature of obesity-associated diseases is dysregulation of lipid homeostasis (Muoio and Newgard 2006). Studies have shown that dysregulation of lipid homeostasis is closely associated with T2DM and CVD (Bornfeldt and Tabas 2011; Muoio and Newgard 2006; Reaven 2011). However, regulation of lipid homeostasis is extremely complicated, and at the molecular level, more genes involved in this process still remain to be discovered.

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Among the known regulators, the SREBP transcription factors critically stimulate the lipid production by activating the transcription of numerous genes encoded for key enzymes in the pathway (Horton et al. 2002; Jeon and Osborne 2012; Osborne and Espenshade 2009). As a result, SREBPs play important roles in the development of metabolic diseases (Jeon and Osborne 2012; Raghow et al. 2008; Shimano 2009).

The control of SREBP activation occurs at multiple steps, including gene transcription, precursor maturation, nuclear protein stability and transcriptional activity (Eberle et al. 2004; Zhao and Yang 2012). Regulation of SREBP precursor maturation through proteolytic processing is a critical step and has been well studied (Horton et al. 2002). In the nucleus, the protein abundance of mature SREBPs is further controlled through proteasome-mediated degradation (Sundqvist et al. 2005). The transcriptional activity of nuclear SREBPs is modulated through recruiting specific transcriptional cofactors, including CBP/p300 (Giandomenico et al. 2003) and the Mediator complexes (Naar et al. 1999; Yang et al. 2006). Interestingly, recruitment of transcriptional cofactors sometimes also affects the protein stability of nuclear SREBPs through post-translational modifications (Giandomenico et al. 2003; Zhao et al. 2012). Such regulatory mechanisms could provide another link between extracellular signals and SREBP activity in the nucleus. In this short review, we will primarily discuss the recent data on regulation of nuclear SREBPs and lipid homeostasis by two Mediator subunits, MED15 and CDK8. These findings may have important implications for CVD.

SREBPs – Master Regulators of Lipid Biosynthesis

The SREBP transcription factors belong to the basic helix-loop-helix leucine zipper (bHLH-Zip) family (Osborne and Espenshade 2009). Since the discovery by the Brown and Goldstein laboratory (Hua et al. 1993; Wang et al. 1994; Yokoyama et al. 1993), SREBPs have been extensively studied. In mammals, there are three SREBP proteins, SREBP-1a, -1c and -2, encoded by two genes, *srebf1* and *srebf2*. Both SREBP-1a and -1c proteins are originated from the same gene, *srebf1*, by two distinct promoters and alternative splicing (Hua et al. 1995). They differ primarily at the N-terminus, where the trans-activation domain is located. SREBP-1a has a longer amino acid sequence, and thus displays stronger transcriptional activity than SREBP-1c (Shimano et al. 1997). SREBP-1a and -1c also have different expression profiles: SREBP-1a is ubiquitously expressed at a lower level in normal tissues, and is highly expressed in proliferating cells, such as cancer cells (Shimomura et al. 1997), while SREBP-1c in hepatocytes is strongly induced upon food intake at the transcriptional level, primarily by insulin (Ferre and Foulfelle 2007). The third SREBP isoform, SREBP-2, is transcribed from the *srebf2* gene. The target genes of the three SREBP isoforms are also distinct. SREBP-1c mainly activates genes encoding enzymes required in fatty acid and triglyceride biosynthesis, whereas SREBP-2 target genes are involved in the cholesterol pathway (Eberle et al. 2004; Osborne and Espenshade 2009). SREBP-1a is able to activate both pathways in addition to other genes (Eberle et al. 2004; Osborne and Espenshade 2009). The function of SREBPs on fatty acid biosynthesis is highly conserved (Osborne and Espenshade 2009), although lower organisms, such as the popular research models *Drosophila melanogaster* and *C. elegans*, have only one SREBP ortholog and are apparently unable to synthesize cholesterol.

All SREBPs are translated as precursors and located in the endoplasmic reticulum (ER) membrane by forming complexes with Insig (insulin-induced protein -1 or -2) and SREBP cleavage activating protein (SACP) (Osborne and Espenshade 2009). For SREBP-2 in mammalian cells, the presence of sterol stabilizes the SREBP-SCAP-Insig complex and prevents its translocation and modification. Reduction of intracellular sterols stimulates the dissociation of Insig from SREBP-SCAP complex, which is then transported to the Golgi

apparatus where SREBP-2 undergo a two-step proteolytic cleavage by site-1 protease (S1P) and site-2 protease (S2P) (Hua et al. 1993). This maturation process is a critical step in controlling SREBP activation. Upon cleavage, the amino-terminal fragments of SREBP-2 translocate to the nucleus as homo-dimers and bind to the promoters of target genes, including HMG-CoA reductase (HMG-CR) and the low-density lipoprotein receptor (LDLR) (Hua et al. 1993). Similarly, the two SREBP-1 isoforms, SREBP-1a and -1c, are also processed in the Golgi to generate the nuclear forms of SREBP-1 proteins (Wang et al. 1994; Yokoyama et al. 1993). Unlike SREBP-2, the proteolytic maturation process of SREBP-1c is primarily activated by insulin and nutrients (Ferre and Foufelle 2007).

As the master regulators for lipid biosynthesis, SREBPs play important role in obesity, T2DM and CVD (Zhao and Yang 2012). For example, SREBP-1c expression is correlated with insulin resistance and CVD risks in morbid obesity (Mingrone et al. 2003). In animal models, SREBP-1c levels are elevated in the livers of several animal models of insulin resistance (Zhao and Yang 2012), including Zucker obese *fa/fa* rats, *ob/ob* mice, insulin receptor substrate-2 knockout mice, and high-fat diet-induced obese mice. In LDLR-deficient mouse models of atherosclerosis, it has been shown that SREBP-1 determines plasma remnant lipoproteins (Karasawa et al. 2011). As a result, hepatic overexpression of SREBP-1c accelerates atherosclerosis, while knockout of SREBP-1 reduces aortic atheroma formation (Karasawa et al. 2011). These findings support a role of SREBPs in the development of CVD.

The Mediator Complexes – Integrative Regulators of Gene Transcription

Initiation of specific gene transcription requires dynamically regulation by DNA-binding transcription factors and the basal transcription machinery, which contains the RNA polymerase II (Pol-II) and general transcription factors (TFIIA, TFIIB, TFIID, TFIIIE, TFIIF and TFIIH) (Gill 2001; Woychik and Hampsey 2002). In eukaryotic cells, numerous transcriptional cofactors provide additional layers of regulation on gene expression. One such cofactor is the evolutionally conserved Mediator complex, which interacts with both specific transcription factors and Pol-II (Malik and Roeder 2010; Taatjes 2010). Recent data suggest that in addition to the roles in initiation of transcription, Mediator is also involved in later steps of gene expression including elongation, termination and pre-mRNA processing (Conaway and Conaway 2013).

Mediator was initially purified from yeast as a multi-subunit complex required for Pol-II-dependent transcription (Flanagan et al. 1991; Kelleher et al. 1990; Kim et al. 1994). Similar complexes were later purified from human cells as key cofactors for a number of transcription factors, including SREBPs and nuclear hormone receptors (NRs) (Malik and Roeder 2010). There are more than 30 distinct subunits in mammalian Mediator and most of them are conserved among various species, including yeast, *C. elegans*, *Drosophila*, human, mouse and plants (Malik and Roeder 2010). Biochemical analyses have identified at least two distinct Mediator complexes: a small one consisting of ~20 peptides that stimulates transcription of Pol-II-dependent genes *in vitro*, and a large one with four additional subunits that are CDK8, Cyclin C (CycC), MED12, and MED13 (Taatjes et al. 2002). Current data suggest the CDK8-containing large Mediator can either repress or activate gene transcription (Conaway and Conaway 2013; Malik and Roeder 2010; Taatjes 2010). Since Mediator interacts with Pol-II, it is conceivable that Mediator can globally regulate Pol-II-dependent gene expression. However, current data suggest that some subunits display specific biological functions, although those subunits as components of the Mediator can also be recruited broadly to genes subject to other modes of regulation (Malik and Roeder 2010). This is likely due to the following reasons: 1) Not all transcription factors can recruit Mediator (Yang et al. 2006); 2) Not all Mediator-interacting transcription factors are

expressed or active in a given cell, therefore, Mediator displays context-dependent functions; and 3) Transcription factors recruit Mediator through a direct interaction with only one, or a few in some cases, subunit. For example, NRs, such as thyroid hormone receptors, peroxisome proliferator-activated receptors and estrogen receptors, interact with the MED1 subunit through its LXXLL motif in a ligand-dependent fashion (Yuan et al. 1998). Numerous studies from different groups have demonstrated that MED1 is required for NR-mediated functions in tissue culture and *in vivo*. Thus, MED1 is specifically involved in the NR pathways.

MED15 Regulation of SREBP Transcriptional Activity

Previously termed as ARC105 or PCQAP in literature, the MED15 subunit of Mediator is conserved from yeast (Gal11 as the ortholog of MED15) to mammals and plants. Current data support an important role of MED15 in regulating lipid homeostasis (Yang et al. 2006) and multi-drug resistance (Thakur et al. 2008). Human Mediator can directly interact with the transactivation domain (TAD) of SREBP-1a (Naar et al. 1999). In chromatin-based *in vitro* transcription assays using the LDLR promoter, Mediator is required for SREBP-1a-dependent gene expression (Naar et al. 1999). To search for the SREBP-1a-interacting surface in Mediator using biochemical pull-down followed by mass spectrometry analysis, we found that SREBP-1a-TAD interacts with MED15 (Yang et al. 2006). In fact, the TADs of SREBP-1c and SREBP-2 also interact with MED15 (Yang et al. 2006). Further biochemical analysis mapped the SREBP-interaction domain to the N-terminus of MED15, which has a structure similar to the KIX domains in CBP, and SREBPs interact with MED15 through the third helix of MED15-KIX domain (Yang et al. 2006). A synthetic peptide corresponding to the MED15-KIX third helix efficiently inhibited both the recruitment of Mediator to SREBP-1a-TAD and SREBP-1a-dependent transcription *in vitro*, suggesting that in Mediator, the MED15-KIX domain is the functional docking surface for SREBPs (Yang et al. 2006). Interestingly, the MED15-KIX domain is highly selective in binding to transcription factors. Unlike the CBP-KIX domain, which interacts several transcription factors including SREBPs, c-Myb and CREB, the MED15-KIX domain interacts only with SREBPs (Yang et al. 2006). Functionally, MED15 knockdown by siRNA or shRNA resulted in a decrease in SREBP-target gene expression in mammalian cells (such as fatty acid synthase, FAS) and *C. elegans* (Yang et al. 2006). Multiple lines of evidence suggest that the major target genes of MED15 ortholog MDT-15 in *C. elegans* are stearyl-CoA desaturases, which are regulated at the transcriptional level by SBP-1 (the *C. elegans* ortholog of SREBP) (Yang et al. 2006). As a result, MDT-15 knockdown in *C. elegans* decreased oleate production, which subsequently led to a decrease of lipid accumulation, resulting in a phenotype similar to that in fasted *C. elegans* (Yang et al. 2006). The phenotypes of MDT-15 knockdown were nearly identical to those of SBP-1 knockdown, suggesting that MED15 and SREBP functions in the same pathways, and importantly, supplementation with oleic acid could specifically rescue most of the phenotypes caused by MDT-15 knockdown, suggesting that the observed phenotypes were due to decreased production of oleic acid (Yang et al. 2006). Thus, MED15 is required for SREBP-mediated gene expression and plays an important role in controlling lipid biosynthesis.

CDK8 Regulation of Nuclear SREBP Protein Stability

It has been shown that phosphorylation of nuclear SREBPs within a conserved domain controls the protein stability (Bengoechea-Alonso and Ericsson 2009; Sundqvist et al. 2005). GSK-3, which functions downstream of the insulin signaling, was reported to be responsible for the phosphorylation of SREBPs at several conserved sites, including Threonine-426 of SREBP-1a (corresponding to Threonine-402 in SREBP-1c) (Bengoechea-Alonso and Ericsson 2009; Sundqvist et al. 2005). Phosphorylation at the Threonine-426

residue has been shown to facilitate SREBP-1a binding to the E3 ligase, SCF^{Fbw7b}, thus controlling its ubiquitination and subsequent degradation (Sundqvist et al. 2005). Interestingly, the poly-ubiquitination sites of lysine residues in SREBPs are also regulated by acetylation (Giandomenico et al. 2003) and deacetylation (Walker et al. 2010). CBP/p300-stimulated acetylation blocks poly-ubiquitination and thus proteasome-mediated degradation of SREBPs (Giandomenico et al. 2003). Conversely, the NAD⁺-dependent protein deacetylase SIRT1 can deacetylate SREBPs, increasing the availability of ubiquitination sites in SREBPs and thus decreasing SREBP protein stability and target-gene expression (Walker et al. 2010).

Recently, we have identified a novel mechanism for the CDK8 subunit of Mediator in regulating lipid biosynthesis by controlling nuclear SREBP protein stability (Zhao et al. 2012). CDK8 and its regulatory subunit CycC are highly conserved in model organisms and human. In our studies with *Drosophila*, we initially observed an “obese” phenotype with a significant increase of triglycerides in CDK8 or CycC -null larvae (Zhao et al. 2012). Although the “obese” phenotype could be due to either accelerated lipid biosynthesis or decreased fatty acid oxidation, or both, microarray analysis revealed a specific up-regulation of SREBP-target genes in CDK8 and CycC-null larvae (Zhao et al. 2012), suggesting that the increased triglyceride accumulation was primarily due to the elevation of biosynthesis. CDK8 regulation of SREBP-target gene expression is conserved in mammalian cells, as knockdown of CDK8 or CycC using shRNA increased expression of genes, such as FAS, and caused triglyceride accumulation in hepatocytes (Zhao et al. 2012). More importantly, CDK8 knockdown in mouse liver *in vivo* caused a fatty liver-like phenotype along with an increase of SREBP-target gene expression and *de novo* lipogenesis (Zhao et al. 2012). Interestingly, CDK8 knockdown in mouse liver also caused a dramatic elevation of triglycerides in plasma (Zhao et al. 2012), suggesting a critical role of hepatic CDK8 in controlling blood lipid levels. Multiple lines of *in vitro* and *in vivo* data demonstrate that CDK8 is a key negative regulator for SREBP-dependent lipid biosynthesis.

How does CDK8 regulate SREBP-target gene expression? Biochemical analyses reveal that SREBP-1c can be directly phosphorylated by CDK8 at the conserved Threonine-402 residue (T402) *in vitro* and in cultured mammalian cells (Zhao et al. 2012). As a result, CDK8 promotes poly-ubiquitination and subsequent degradation of nuclear SREBP-1c without affecting the level of mRNA or precursor of SREBP-1c (Zhao et al. 2012). Therefore, the mechanism of CDK8 regulating SREBP functions is primarily through the phosphorylation-initiated control of nuclear SREBP-1 protein stability. Although both CDK8 and GSK-3 can phosphorylate T402 of SREBP-1c (or T426 of SREBP-1a), it is common that the same threonine or serine residue of a protein can be targeted by multiple kinases. However, it is currently unclear whether there is a relationship between CDK8 and GSK-3-mediated regulation of SREBP-1c.

Interestingly, CDK8 and CycC protein levels are negatively regulated by food intake in mouse liver and by insulin in hepatocyte cultures (Zhao et al. 2012). Thus, a new model is proposed: Insulin stimulates *de novo* lipogenesis by down-regulating CDK8 and CycC proteins, which normally inhibit *de novo* lipogenesis through promoting nuclear SREBP-1c degradation (Zhao et al. 2012). This new mechanism of insulin-induced lipogenesis is in addition to the well-documented function of insulin in stimulating SREBP-1c at the mRNA level. Our recent findings demonstrate a physiological role of CDK8 in regulating fatty acid biosynthesis.

Conclusions and Future Perspectives

In addition to the well-known regulation of SREBP transcription, particularly for SREBP-1c, and maturation by proteolytic processing, recent data suggest an important role of nuclear SREBP regulation in lipid biosynthesis. In the nucleus, SREBPs can be regulated at the levels of transcriptional activity, protein stability and DNA-binding affinity. MED15 is required for the transcriptional activity of SREBPs by providing a docking surface to recruit Mediator and activate target gene transcription. In addition, SREBP-1a and -1c are novel substrates of the large Mediator –specific subunit CDK8. Phosphorylation of SREBP-1 by CDK8 controls the abundance of nuclear SREBPs and subsequent biological function in lipid biosynthesis. Since the protein level of CDK8 is also regulated by environmental factors, such as nutrient and insulin, CDK8 is a novel molecular link between extracellular signals and nuclear SREBPs. Due to the notorious association of lipids with atherosclerosis, MED15 and CDK8 regulation of *de novo* lipogenesis may have significant implications for CVD. In fact, CDK8 knockdown in mouse models causes not only fatty liver but also hypertriglycemia, a risk factor for CVD. However, the following important questions remain open. 1). What is the physiological and patho-physiological significance of MED15 regulation on SREBPs in mammals? 2). Is CDK8-CycC regulation of SREBPs in the context of Mediator? 3). How are the CDK8 and CycC levels controlled by nutrients and insulin? 4). Are MED15, CDK8 and CycC involved in the formation of atherosclerosis in animal models? 5). Clinically, are there any mutations or changes of expression of MED15, CDK8, CycC or any other subunits of Mediator in patients with CVD? Addressing these questions will help to determine whether Mediator subunits are novel targets with therapeutic potentials for fighting human diseases, such as obesity, T2DM and CVD.

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