Control of Muscle Metabolism by the Mediator Complex

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Exercise represents an energetic challenge to whole-body homeostasis. In skeletal muscle, exercise activates a variety of signaling pathways that culminate in the nucleus to regulate genes involved in metabolism and contractility; however, much remains to be learned about the transcriptional effectors of exercise. Mediator is a multiprotein complex that links signal-dependent transcription factors and other transcriptional regulators with the basal transcriptional machinery, thereby serving as a transcriptional “hub.” In this article, we discuss recent studies highlighting the role of Mediator subunits in metabolic regulation and glucose metabolism, as well as exercise responsiveness. Elucidation of the roles of Mediator subunits in metabolic control has revealed new mechanisms and molecular targets for the modulation of metabolism and metabolic disorders.

Transcriptional control of metabolic pathways in mammals is accomplished by the coordinated action of numerous transcription factors and associated coregulators, which integrate signals from dietary, metabolic, and endocrine pathways to control target gene expression. In recent years, interest has increased in cofactors that bridge proteins and allow DNA-bound transcription factors to activate or repress the transcriptional machinery in response to environmental and energy demands.

Exercise represents an energetic challenge to whole-body homeostasis. To meet this energetic need, acute and adaptive responses take place at the cellular and systemic levels (Bassel-Duby and Olson 2006; Egan and Zierath 2013; Hawley et al. 2014). Conversely, nutritional stresses, such

as long-term excess of caloric intake, generate adaptive responses that function to minimize or compensate for metabolic disruptions (Desvergne et al. 2006; Feige and Auwerx 2007; Cantó and Auwerx 2009; Mouchiroud et al. 2014). This article will focus on the role of the transcriptional regulator, Mediator complex, in the regulation of cellular and systemic metabolic processes.

THE MEDIATOR COMPLEX

The Mediator complex is an evolutionarily conserved multiprotein complex that links signal-dependent transcription factors and other transcriptional regulators with the basal transcriptional machinery, thereby serving as a hub

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Figure 1. Mediator complex transcriptional hub. The Mediator complex regulates transcription by interacting with nuclear receptors, transcription factors (TFs), RNA polymerase II (Pol II), and enhancers.

for transcriptional control (Fig. 1). First discovered in yeast as an essential regulator of activator-induced transcription, the Mediator complex has subsequently been isolated from mammalian cells in active and inactive forms (Flanagan et al. 1991). The core Mediator complex contains 26 subunits and can be divided into four distinct modules named the head, middle, tail, and CDK8 kinase submodule. The latter submodule, which is the focus of this review, contains CDK8 (or its paralog CDK8L), cyclin C, MED12 (or MED12L), and MED13 (or MED13L) subunits (Fig. 2) (Malik and Roeder 2010; Taatjes 2010) and functions as a dissociable inhibitor of the core Mediator complex (Belakavadi and Fondell 2010; Galbraith et al. 2010; Taatjes 2010; Chen and Roeder 2011; Fondell 2013).

Originally, the Mediator-kinase submodule interaction was shown to block Mediator–Pol II binding, which regulates transcription initiation or reinitiation events at the promoter. Therefore, it was believed that the kinase submodule is a regulatory protein complex, which generally exerts negative effects on gene expression in a promoter-specific manner via its association with the Mediator core complex (Fondell et al. 1996). However, recent studies indicate that the kinase submodule can either repress or activate gene transcription, depending on the biological context (Belakavadi and Fondell 2010; Donner et al. 2010; Taatjes 2010). Additionally, the subunit composition of the

Mediator complex can vary, providing an additional layer of regulatory control.

Studies deciphering Mediator complex regulation are still in early stages. Altered phosphorylation has been suggested as a mechanism for the regulation of Mediator subunits (Miller et al. 2012). Belakavadi and colleagues have shown that phosphorylation of MED1 by extracellular signal-regulated kinase (ERK) leads to enhanced transcription of thyroid hormone receptor (TR)-regulated genes (Belakavadi et al. 2008). MED13/MED13L are also regulated by ubiquitination, which targets these subunits for degradation by SCF-Fbw7 (Davis et al. 2013). It is likely that other posttranslational modifications regulate Mediator subunits, and of particular interest are those generated by metabolic pathways. For example, palmitoylation and/or O-linked β -N-acetylglucosamine (O-GlcNAc) modifications of the Mediator subunits could enhance or inhibit interactions with other transcriptional factors and coactivators or corepressors (Özcan et al. 2010).

Early studies focused primarily on how the Mediator complex conveys signals from transcription factors to the Pol II basal machinery and general transcription factors. These studies supported a “bridge” model, in which the Mediator complex connects transcription factors and Pol II to promote formation of the preinitiation complex (Biddick and Young 2005; Björklund and Gustafsson 2005; Malik and Roeder 2005). However, it soon became apparent that

Figure 2. Mediator complex composition. The Mediator complex consists of the head (gray), middle (blue), and tail (green) domains. The kinase submodule (yellow) reversibly associates with the core complex and regulates Mediator transcriptional activity.

multiple pathways responsible for cell growth, differentiation, and tissue development were coupled to one or more of the 26 subunits of the Mediator complex through transcriptional regulators, suggesting that the Mediator complex acts as a centralized “hub” or “integrator” for transcriptional regulation (Malik and Roeder 2010; Carlsten et al. 2013). An increasing number of studies have revealed new functions for Mediator and also highlighted a role for the Mediator complex in developmental abnormalities, cancer, and metabolic disorders. Thus, it appears that the Mediator complex acts as a master coordinator that regulates multiple aspects of transcription to ensure the precise intensity, pattern, and timing of global gene expression during diverse processes. Here, we describe recent studies of the Mediator complex, with an emphasis on its functions in metabolism.

The roles of different Mediator subunits in metabolic control are summarized in Figure 3 and Table 1. The Mediator complex was initially copurified with nuclear receptors (NRs) and has been found to be crucial for several ligand-dependent NR functions (Fondell et al. 1996). Numerous members of the NR family are sensors of metabolic status that respond to

dietary signals and metabolites, and are responsible for metabolic adaptation at the cell, organ, and whole organismal level (Fig. 3) (Ito and Roeder 2001; Ge et al. 2002, 2008; Huss 2004; Smith and Muscat 2005; Yang et al. 2006; Wang et al. 2009; Chen et al. 2010; Grontved et al. 2010; Krebs et al. 2011; Rana et al. 2011; Grueter et al. 2012; Zhao et al. 2012; Baskin et al. 2014; Chu et al. 2014; Jia et al. 2014, 2016; Lee et al. 2014; Amoasii et al. 2016). Mediator complex subunits have been shown to interact strongly with numerous NRs in a ligand-dependent manner, and to interact with transcription factors to regulate a variety of metabolic processes.

MEDIATOR COMPLEX AND LIPID METABOLISM

One common feature of obesity-associated diseases is dysregulation of lipid metabolism, which impacts numerous processes including adipogenesis and lipogenesis. Key regulators in these processes have been identified, namely, the transcription factors, peroxisome proliferator-activated receptor γ (PPAR γ), and sterol regulatory element-binding proteins (SREBPs) (Horton et al. 2002; Osborne and Espenshade 2009; Jeon and Osborne 2012; Poulsen et al.

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Figure 3. Mediator complex subunits involved in regulation of metabolic processes (highlighted in red).

2012). Recent studies have shown that the Mediator complex is a pivotal cofactor for these transcription factors, suggesting a role of Mediator in lipid metabolism.

Initially, numerous studies focused on MED1, a middle module subunit, which serves as an anchor for the interaction between Mediator and NRs (Ito et al. 1999). Mice with MED1 gene deletion die during embryogenesis and display abnormalities in placental, cardiac, hepatic, and bone marrow development. Mouse embryonic fibroblasts (MEFs) derived from MED1-knockout embryos showed defects in the expression of PPAR γ -target genes, suggesting a role of MED1 in adipogenesis. Accordingly, liver-specific knockout of MED1 in mice revealed its role in ligand-dependent activation of PPAR α target genes, which are key players in fatty acid oxidation. Liver-specific knockout of MED1 also inhibited high-fat diet (HFD)-induced fatty liver, which was reported to be caused by the inactivation of PPAR γ (Ge et al. 2002; Jia et al. 2004).

Other submodules of the Mediator complex, such as the tail submodule, have been implicated in different aspects of metabolism. For example, MED14 has been shown to directly interact with PPAR γ and to be required for

the transcriptional activity of PPAR γ . Studies using 3T3-L1 cells showed that MED14 knock-down represses adipogenesis. MEFs lacking MED23 revealed a role of MED23 in insulin-induced adipogenesis in vitro (Wang et al. 2009). Liver-specific deletion of MED23 improved glucose and lipid metabolism, as well as enhanced insulin responsiveness to prevent diet-induced obesity (Chu et al. 2014). In *Caenorhabditis elegans*, MED15 was shown to be required for SREBP-target-gene transcription in lipid biosynthesis (Yang et al. 2006). Taken together, these findings show that middle (MED1) and tail (MED14, MED15, MED24, and MED25) submodules of the Mediator complex regulate lipid metabolism by multiple mechanisms and in a gene-specific and context-specific manner.

The MED30 subunit, part of the head submodule, regulates PPAR coactivator 1 α (PGC-1 α)-mediated expression of metabolic genes. Mice with a missense mutation in MED30 showed pleiotropic changes in transcription of cardiac genes required for oxidative phosphorylation and mitochondrial integrity, suggesting the involvement of MED30 in induction of a metabolic program for oxidative phosphorylation and fatty acid oxidation (Krebs et al. 2011).

Table 1. Mediator complex subunits involved in regulation of metabolic processes

Module	Subunit	Model and tissue	Metabolic process	References
Tail	MED14	3T3-L1 cells knockdown	Adipogenesis	Grontved et al. 2010
Tail	MED15	<i>Caenorhabditis elegans</i>	Cholesterol and lipid homeostasis	Yang et al. 2006
Tail	MED23	Mouse embryonic fibroblasts derived from complete knockout	Adipogenesis	Wang et al. 2009
Tail	MED23	Mouse liver-specific knockout	Gluconeogenesis and cholesterol synthesis	Chu et al. 2014
Tail	MED25	Human liver	Xenobiotic and lipid metabolism	Rana et al. 2011
Middle	MED1	Mouse embryonic fibroblasts derived from complete knockout	Adipogenesis	Ge et al. 2002
Middle	MED1	Mouse skeletal muscle knockout	Enhanced insulin sensitivity and glucose tolerance on HFD	Chen et al. 2010
Middle	MED1	Mouse cardiac muscle knockout	Cardiomyopathy and heart failure associated with mitochondrial damage, increased apoptosis, and interstitial fibrosis	Jia et al. 2016
Middle	MED1	Mouse liver knockout	Reduced hepatic steatosis on HFD	Jia et al. 2014
Head	MED30	Mouse cardiac muscle knockout	Mitochondrial dysfunction in heart and heart failure associated with dysregulation of metabolic program for oxidative phosphorylation and fatty acid oxidation	Krebs et al. 2011
Kinase	MED12	<i>Drosophila</i> heart and skeletal muscle	Increased susceptibility to obesity	Lee et al. 2014
Kinase	MED13	<i>Drosophila</i> heart and skeletal muscle	Increased susceptibility to obesity	Lee et al. 2014
Kinase	MED13	Mouse cardiac muscle transgenic and knockout	Med13 deletion increased susceptibility to obesity; Med13 overexpression enhanced lipid metabolism, insulin sensitivity, and decreased susceptibility to obesity	Grueter et al. 2012; Baskin et al. 2014
Kinase	MED13	Mouse skeletal muscle knockout	Enhanced glucose tolerance, disposal, glycogen storage, enhances insulin sensitivity, and prevention of fatty liver in HFD condition	Amoasii et al. 2016
Kinase	CDK8	<i>C. elegans</i>	Lipid homeostasis	Zhao et al. 2012

HFD, High-fat diet.

Recently, several subunits of the kinase submodule have been implicated in the control of lipid metabolism. Specifically, it was revealed in *C. elegans* that the CDK8 subunit of the Mediator complex inhibits lipid biosynthesis by promoting nuclear SREBP-1a/1c protein degradation.

Studies in our laboratory identified MED13, a component of the kinase submodule, as a regulator of systemic metabolism (Grueter et al.

2012; Baskin et al. 2014). Overexpression of MED13, specifically in the heart, led to a striking metabolic phenotype in which mice were resistant to obesity and maintained insulin sensitivity when placed on an HFD (Grueter et al. 2012). In contrast, mice with cardiac-specific deletion of MED13 had increased susceptibility to obesity and diabetes (Grueter et al. 2012). These studies showed that MED13 regulates

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metabolic gene expression in the heart, specifically decreasing expression of fatty acid metabolism genes. Taken together, these findings imply that in addition to being members of the regulatory kinase submodule, MED13 and CDK8, might have additional functions and participate in regulation of metabolic mechanisms.

GLUCOSE METABOLISM

Whole-body energy balance and glucose homeostasis rely on “metabolic flexibility” of skeletal muscle, liver, adipose tissue, heart, and pancreas. A constant glucose supply is mandatory for the brain and red blood cells to maintain normal function. Skeletal muscle is the major site of glucose disposal under insulin-stimulated conditions and, therefore, has a critical role in glycemic control and metabolic homeostasis. Skeletal muscle constitutes 40% of total body mass in mammals and accounts for 30% of the resting metabolic rate in healthy adult humans (DeFronzo et al. 1981; Zurlo et al. 1990). Additionally, skeletal muscle is the largest glycogen storage organ. Remarkably, a single bout of acute exercise improves whole-body insulin sensitivity (Mikines et al. 1988; Koopman et al. 2005). Moreover, exercise increases skeletal muscle glucose uptake through an insulin-independent pathway, indicating that muscle contraction directly impacts glucose homeostasis (Lee et al. 1995). Conversely, in diabetic states related to insulin resistance in skeletal muscle, the translocation of intracellular GLUT4 to the sarcolemma is impaired but the expression of GLUT4 is not significantly reduced (Garvey et al. 1992).

Most mammalian cells import glucose by a process of facilitative diffusion mediated by members of the Glut (SLC2A) family of membrane transport proteins. GLUT4 was identified as the key glucose transporter isoform responsible for insulin- and contraction-stimulated glucose transport in skeletal muscle (Birnbaum 1989; Charron et al. 1989; James et al. 1989). Overexpression of GLUT4 in skeletal muscle is associated with enhanced glucose disposal and insulin action (Treadway et al. 1994; Hansen et al. 1995; Ren et al. 1995; Tsao et al. 1996).

These findings have raised interest in the regulation of skeletal muscle GLUT4 expression and in therapeutic strategies to increase GLUT4 expression in various metabolic disorders characterized by skeletal muscle insulin resistance.

REGULATION OF SKELETAL MUSCLE GLUT4 EXPRESSION

Analysis of the human *GLUT4* promoter identified two highly conserved regions: (1) the region distal to the transcription initiation site, referred to as domain 1, which binds GLUT4 enhancer factor (GEF), and (2) the MEF2 domain, the proximal region containing a binding site for the myocyte enhancer factor 2 (MEF2) family of transcription factors (Oshel et al. 2000). These two regulatory regions of the *GLUT4* promoter are important but not sufficient for complete GLUT4 expression (Thai et al. 1998; Oshel et al. 2000). Additionally, cell culture studies showed that, although GEF and MEF2A individually do not activate *GLUT4* promoter activity, their coexpression enhances GLUT4 promoter activity (Fig. 4) (Knight et al. 2003).

MEF2A and MEF2D proteins bind to the *GLUT4* promoter (Thai et al. 1998). Furthermore, the MEF2A–MEF2D heterodimer has been implicated in hormonal regulation of the *GLUT4* gene (Mora and Pessin 2000). Together, these studies showed that both domain 1 and the MEF2 domain, and their associated binding factors, are necessary for full GLUT4 expression in skeletal muscle.

Multiple studies have shown that additional transcription factors interact with MEF2 to influence skeletal muscle GLUT4 expression. Santalucía et al. (2001) showed that MyoD and the TR function cooperatively with MEF2 to modulate GLUT4 expression. In addition, the Krüppel-like factor KLF15 specifically interacts with MEF2A and acts in synergy to activate the GLUT4 promoter (Gray et al. 2002). The transcriptional PGC-1 α plays a key role in the regulation of mitochondrial biogenesis but has also been shown to bind and activate MEF2C and, thus, control GLUT4 expression in myocytes (Michael et al. 2001; Wu et al. 2001). MEF2 activity is repressed by direct association

Figure 4. Regulatory sequences in the *Glut4* promoter and the factors that bind to them in skeletal muscle. Exercise increases the binding of GLUT4 enhancer factor (GEF) and an MEF2A/D heterodimer to the indicated binding domains in the *Glut4* promoter. Krüppel-like factor (KLF)-15, MyoD, NURR1, and thyroid hormone receptor (TR) α 1 also bind the *Glut4* promoter. NRE, NURR1 response element; TRE, thyroid hormone response element.

with class II histone deacetylases (HDACs) (McKinsey et al. 2000). HDACs control the balance of acetylation and deacetylation of key residues on histone proteins associated with chromatin. Acetylation of these residues affects the access of transcription factors to promoter regions and transcriptional activation. Several signal-dependent upstream kinases, including calcium/calmodulin-dependent protein kinase (CaMK) and AMP-activated protein kinase (AMPK), stimulate MEF2-dependent gene expression by phosphorylating class II HDACs and promoting their export from the nucleus. Caffeine treatment increases GLUT4 expression via activation of CaMK phosphorylation of HDAC5/HDAC4 and the activation of MEF2A and MEF2D (Ojuka et al. 2012). AMPK, on AICAR activation, phosphorylates HDAC5 kinase and consequently regulates *GLUT4* expression (Ojuka et al. 2002, 2012; McGee et al. 2008). These studies revealed upstream factors that regulate the activity of MEF2 by its association with HDACs. Additionally, these studies reveal the dynamic effect of upstream regulators in the control of *GLUT4* expression in response to different treatments and signals.

Additionally, the serine/threonine phosphatase calcineurin influences GLUT4 expression via its effects on MEF2. Calcineurin can activate MEF2 either directly via dephosphorylation or indirectly via nuclear factor of activated T cells (NFATs) dephosphorylation (Wu et al. 2001). Skeletal muscle GLUT4 levels are increased in transgenic mice overexpressing activated calcineurin (Ryder et al. 2003). Murgia et al. (2009) assessed the collaboration between these various signaling pathways using a genetic approach involving mice that expressed a ki-

nase-dead form of AMPK, in combination with transfection of plasmids expressing specific peptide inhibitors of the CaMKII and calcineurin signaling pathways.

Degradation of GLUT4 by calpain-2 and overexpression of an endogenous calpain inhibitor, calpastatin, has also been shown to increase GLUT4 levels in skeletal muscle (Otani et al. 2004). In summary, these studies report the finely tuned regulation of GLUT4 expression that starts by the positioning of the DNA-binding site elements in the GLUT4 promoter and by the interactions among transcription factors, kinases, and phosphatases.

MEDIATOR CONTROL OF GLUT4 EXPRESSION AND GLUCOSE METABOLISM

We showed that MED13, a subunit of the CDK8 kinase submodule regulates the expression of *GLUT4* and other genes involved in glucose uptake and glycogen storage. Skeletal muscle-specific deletion of MED13-enhanced muscle glucose uptake and resistance to hepatic steatosis as a result of diversion of energy away from the liver and uptake into skeletal muscle under conditions of caloric excess (Amoasii et al. 2016). Among a collection of genes up-regulated in skeletal muscle was the orphan NR *NR4A2*, also known as *NURR1*. Moreover, this study revealed that NURR1 protein binds and activates the *GLUT4* promoter by acting in synergy with MEF2. MED13 represses the ability of NURR1 and MEF2 to cooperatively control the *Glut4* promoter. MED13 represses both the expression and the activity of NURR1 by regulating *Nurr1* gene expression and also through direct interaction with the NURR1 protein. Taken together,

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these findings revealed a novel pathway coordinated by MED13 in the regulation of the *Glut4* gene and other metabolic genes.

Additional studies suggested the involvement of MED1 in regulation of glucose metabolism, because skeletal muscle-specific MED1 knockout mice show enhanced insulin sensitivity, improved glucose tolerance, and resistance to HFD-induced obesity. The majority of up-regulated genes in MED1-deficient skeletal muscle were involved in metabolic pathways, including PEPCK, C/EBP α , and PPAR γ , which have been strongly implicated in energy metabolism, indicating a role for MED1 in energy and glucose metabolism (Chen et al. 2010). Intriguingly, cardiac deletion of MED1 generated the opposite effect on skeletal muscle, because it led to down-regulation of *HK2*, *GK*, and *Glut4* genes, which are involved in glucose metabolism (Jia et al. 2016). MED1-deficient hearts displayed mitochondrial damage, increased apoptosis, and interstitial fibrosis. Global gene expression analysis revealed that loss of MED1 in the heart down-regulates >200 genes, including genes that are critical for calcium signaling, cardiac muscle contraction, and PPAR-regulated energy metabolism. Many genes essential for oxidative phosphorylation and proper mitochondrial function, such as genes coding for the succinate dehydrogenase subunits of the mitochondrial complex II, were also down-regulated in MED1-deficient hearts.

Interestingly, overexpression of MED13 in the heart impacts global metabolism and enhances lipid oxidation, and mitochondrial activity in WAT, BAT, and liver (Grueter et al. 2012; Baskin et al. 2014). In contrast, MED13 in skeletal muscle was revealed as a suppressor of glucose metabolism under conditions of HFD-induced insulin resistance. These observations suggest opposing metabolic functions of MED13 in cardiac and skeletal muscle tissues. Similarly, skeletal muscle deletion of MED1 enhanced glucose metabolism and cardiac deletion of MED1 caused repression of glucose metabolic genes and additional physiological abnormalities.

These findings show an important new function of the Mediator complex subunits in

the regulation of glucose metabolism and highlight the importance of interorgan communication for maintenance of whole body energy homeostasis. Additionally, these results showed that the Mediator complex performs customized, tissue-specific functions in metabolic regulation involving cardiac and skeletal muscle.

REGULATION OF GLUT4 EXPRESSION AND GLUCOSE METABOLISM BY EXERCISE

One striking physiological characteristic of skeletal muscle is the capacity to rapidly modulate the rate of energy production, blood flow, and substrate use in response to exercise. Exercise induces several physiological signals such as mechanical contraction, calcium flux changes, and ADP:ATP ratio variations that in turn activate different signaling pathways (Fig. 5). The activation of these signal transduction pathways culminates in the nucleus to modulate the expression of *GLUT4* and other metabolic genes.

During acute exercise in humans, muscle contractions activate mitogen-activated protein kinase (MAPK) subfamilies, such as p38 MAPK. The level of p38 MAPK activation is

Figure 5. Schematic of the major signaling pathways involved transmitting of exercise effect on glucose metabolism. AMPK, AMP-activated protein kinase; HDAC, histone deacetylase; MAPK, mitogen-activated protein kinase; PGC-1, peroxisome proliferator-activated receptor coactivator 1.

dependent on exercise intensity (Yu et al. 2004; Coffey 2005). In response to exercise, p38 MAPK stimulates upstream transcriptional activators of the *PGC-1 α* gene, such as ATF2 and MEF2, which coincides with an increase in *PGC-1 α* expression, GLUT4 expression, and glucose metabolism (Akimoto et al. 2005; Wright et al. 2007; Egan et al. 2010).

Alterations in the ratios of AMP and ATP levels induced by exercise lead to activation of AMPK, which is a serine/threonine kinase that controls metabolism through phosphorylation of metabolic enzymes and via transcriptional regulation of *PGC-1 α* (Carling and Hardie 1989; Bergeron et al. 2001; Jäger et al. 2007). AMPK activation is regulated allosterically by cellular energy deficit, which is reflected by increases in the AMP/ATP and phosphocreatine-to-creatine (PCr/Cr) ratios (Kahn et al. 2005). Increased cellular AMP/ATP ratio caused by intense exercise and cellular stresses that deplete ATP (such as glucose deprivation or oxidative stress) activates AMPK (Green et al. 1992; Kahn et al. 2005). In skeletal muscle, acute AMPK activation suppresses glycogen and protein synthesis, but promotes glucose transport (Carling and Hardie 1989; Merrill et al. 1997; Bolster et al. 2002). Persistent AMPK activation adjusts metabolic gene expression and induces mitochondrial biogenesis, partly via AMPK-induced variation of the DNA-binding activity of transcription factors, including NRF-1, MEF2, and HDACs (Bergeron et al. 2001; McGee et al. 2008). Thus, AMPK activation acts to conserve ATP by inhibiting biosynthetic pathways and anabolic pathways and by stimulating catabolic pathways to restore cellular energy stores (Kahn et al. 2005).

Variations in calcium flux on exercise modulate CaMKs that influence glucose transport and skeletal muscle plasticity (Wu et al. 2002; Wright et al. 2004). Transcription factors, such as CREB, MEF2, and HDACs, are CaMK targets implicated in the regulation of skeletal muscle gene expression. Liu et al. (2005) have shown that the activation of CaMKII leads to phosphorylation and nuclear exclusion of HDAC4, which relieves repression of MEF2. This model couples contraction-induced calcium signaling

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to an increased rate of transcription of MEF2 target genes, such as *PGC-1 α* and *GLUT4* (Chin 2010). Taken together, these pathways synergize to promote muscle adaptation to energy production and substrate use in response to different exercise intensity.

MEDIATOR CONTROL AND EXERCISE-RESPONSIVE FACTORS

MED13 was shown to repress the expression and activity of NURR1 through regulation of *Nurr1* gene expression and also by direct interaction with the NURR1 protein. NURR1 belongs to the NR4A NR family that consists of three members (NR4A1/Nur77, NR4A2/Nurr1, and NR4A3/NOR-1). Expression of NR4A genes is inducible by a range of metabolites (Roche et al. 1999), exercise (Mahoney et al. 2005; Catoire et al. 2012), and environmental stimuli (Kanzleiter et al. 2005, 2009) such as adrenoceptor agonists (Chao et al. 2007; Pearen et al. 2008; Myers et al. 2009), glucose (Susi et al. 1998), insulin (Wu et al. 2007), and others (Fu et al. 2007). Expression of NR4A family members has been reported to decline in obese mice on HFD, suggesting that conditions of insulin resistance suppress expression of NR4A genes (Fu et al. 2007). Remarkably, gene expression analysis from human muscle biopsies revealed that NURR1 was one of the most up-regulated genes in muscle after intensive exercise (Catoire et al. 2012). However, the functions of NURR1 in skeletal muscle and its impact on systemic metabolism have not been fully characterized. The regulation of NURR1 by MED13 in skeletal muscle suggests a potential function of MED13 and NURR1 in exercise-induced pathways.

Additionally, in vitro studies showed that MED1 mediates the activation of the NR4A family member, NR4A3/NOR-1, and NR4A1/Nur77 (Wansa and Muscat 2005). Overexpression of NOR-1 in skeletal muscle also caused enhanced oxidative metabolism, increased glycogen storage, increased endurance, and reduced adiposity (Pearen et al. 2012). However, the MED1 and NOR-1 regulatory link has not been established in vivo in skeletal muscle.

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In summary, these studies identify signaling pathways that respond to exercise in skeletal muscle. Recent findings implicate the Mediator complex in upstream regulation of exercise-induced NRs and transcription factors, such as NURR1 and MEF2.

CONCLUDING REMARKS AND FUTURE DIRECTIONS

Mediator Customized Tissue Function and Composition

A fundamentally important feature of the Mediator complex is that its subunit composition can change with respect to tissue specificity and biological process. However, little is known about how subunit exchange is regulated, and this remains an area of great interest and importance. Additionally, distinct Mediator subunits are recruited by different transcription factors, leading to gene-specific physiological effects, including regulation of lipid metabolism and energy homeostasis. Additional studies have also suggested dual, opposing functions for another Mediator complex subunit, MED23, in regulating cytoskeletal and adipogenic gene programs (Yin et al. 2012). MED13 was shown to perform customized tissue-specific functions in metabolic regulation of cardiac and skeletal muscle. Further investigation of other Mediator components in muscle tissue can potentially reveal novel molecules and pathways that regulate metabolism. The interaction between Mediator subunits, tissue-specific transcription factors, NRs, coregulators, and other factors may explain the systemic effects of tissue-specific manipulation of ubiquitous Mediator components. Based on the studies we reviewed here, it is evident that the Mediator complex is an important regulator of metabolism and plays a significant role in striated muscle. We suspect that modulation of other Mediator components in muscle will likely affect systemic metabolism.

Mediator Complex Regulation in Metabolism

Phosphorylation and ubiquitination of the Mediator subunits have been implicated in the

regulation of the Mediator complex. However, little is known regarding metabolically induced signals and posttranslational modification of Mediator activity. We suggest that metabolically induced posttranslational modification and regulation of the Mediator complex are intimately tied to the metabolic demand of specific tissues and vary in high-fat conditions or exercise. We speculate that Mediator complex subunits are highly responsive to nutritional and energy demands to rapidly modulate the transcriptional gene network in response to whole body demands.

Mediator Complex and Glucose Metabolism

Extensive studies of Glut4 and glucose metabolism regulation have been reported over the past several years. Moreover, new pathways that regulate glucose homeostasis have been identified. However, the mechanism of action and regulatory signals of the novel key players NURR1, MEF2, and MED13 have not been fully clarified. Understanding the new pathways involved in the governance of skeletal muscle glucose metabolism and exploring their mechanistic underpinnings is critical for developing strategies to improve systemic metabolism. Future studies should focus on how the Mediator complex and novel factors regulate glucose metabolism in striated muscle in response to various physiological stimuli such as exercise and metabolic and nutrient stress (e.g., fasting or different diets).

Future Directions

Our understanding of the molecular function of the Mediator complex has been greatly expanded in recent years. However, many questions remain. For example, what is the exact mechanism by which Mediator coordinates multiple transcription factors and cofactors? How is the dynamic composition and configuration of Mediator regulated in different conditions, cells, and tissues? What are the signals and modifications that activate the Mediator complex subunits in HFD conditions and exercise? Among the many uncertainties, it is apparent that the

identification of new aspects of the Mediator complex is inevitable.

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