Influence of AMP-activated protein kinase and calcineurin on metabolic networks in skeletal muscle

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Submitted 28 February 2008; accepted in final form 4 June 2008

Skeletal Muscle Plays a Critical Role in Energy Substrate Homeostasis. Under postprandial conditions, skeletal muscle accounts for about 75% of glucose disposal and is therefore a key tissue involved in whole body glucose homeostasis. The metabolic property of skeletal muscle is also highly malleable and adapts to nutrient availability by altering energy substrate utilization. In healthy lean subjects, skeletal muscle fuel utilization can readily switch from lipid oxidation under fasting conditions (2) to glucose utilization with a concomitant suppression of lipid oxidation under insulin-stimulated conditions (44). The capacity and flexibility of skeletal muscle to utilize and switch between glucose and fatty acids as energy substrates is central in the regulation of whole body energy balance. Given the contribution of skeletal muscle to the total energy consumption, impaired metabolic response of skeletal muscle is closely associated with metabolic diseases, including type 2 diabetes mellitus.

Skeletal Muscle Metabolism and Insulin Resistance

In obese insulin-resistant individuals and people with type 2 diabetes, the flexibility of skeletal muscle in shifting between glucose and lipid oxidation is severely impaired (42, 43). Under fasting conditions, skeletal muscle fatty acid oxidation fails to increase in insulin-resistant individuals, and a higher rate of glucose oxidation is observed compared with insulin-sensitive subjects. Although there is a sharp increase in glucose oxidation under insulin-stimulated conditions in lean insulin-sensitive subjects, such an increase is blunted in insulin-resistant obese and type 2 diabetic subjects, with a lower rate of glucose oxidation observed in diabetic individuals. The failure to turn on fatty acid oxidation by switching energy substrate utilization in insulin-resistant obese and type 2 diabetic subjects may be a key mechanism leading to intramuscular triglyceride accumulation (41). Consistently, impaired expression of genes essential for skeletal muscle lipid metabolism and mitochondrial function in insulin-resistant individuals has also been reported (63, 64). Molecular pathways that regulate skeletal muscle metabolic flexibility may offer novel therapeutic entry points for the treatment of insulin resistance and metabolic disease.

Transcriptional Adaptations of Skeletal Muscle

Glucose and lipids are the main energy substrates in skeletal muscle, and their utilization is coordinated by complex regulatory mechanisms (19, 37). Glucose is the main energy substrate of skeletal muscle under fed conditions. However, sub-
strate metabolism shifts from glucose to lipids under fasting conditions (2) for glucose sparing to other organs, particularly the brain. In skeletal muscle, the change in fuel utilization is regulated at the levels of substrate availability and direct regulation of metabolic enzymes. Under fasting conditions, when plasma glucose and insulin concentrations are low, this leads to an increase in lipolysis and supply of nonesterified fatty acids. Therefore, fatty acids are the main energy substrate for skeletal muscle when insulin-stimulated glucose utilization is greatly diminished (19). Several fatty acid oxidation-derived metabolites also inhibit glycolytic enzyme activity (37). Elevation of acetyl-CoA, for example, suppresses the activity of pyruvate dehydrogenase, and an increase in the citrate level inhibits phosphofructokinase, whereas an accumulation of glucose 6-phosphate would in turn inhibit hexokinase 2 (HK2) (37).

The shift toward lipid utilization in skeletal muscle is also associated with a coordinated increase in the expression of genes essential for lipid metabolism, such as \( Lpl \) (lipoprotein lipase), \( Cpt1 \) (carnitine palmitoyl transferase I), and \( Ucp3 \) (uncoupling protein-3), after an overnight fast (15, 26, 67). Coordinated transcriptional changes in gene expression are also observed after a few days of endurance exercise training (46, 75, 81). During submaximal intense exercise, the contribution of fatty acid oxidation to total energy expenditure is greater in the trained state compared with the untrained state. The larger contribution from fatty acids produces a glucose-sparing effect that results in a slower depletion of intramuscular glycogen stores, which delays the development of exhaustion. The glucose-sparing effect is considered one of the most critical mechanisms by which training increases the capacity to perform prolonged high-intensity exercise (27).

Consistent with the increased energy input from fatty acid metabolism, endurance training increases the capacity of skeletal muscle to utilize fatty acids (31, 82, 83). This adaptation is associated with increased expression of genes involved in lipid metabolism, including \( Lpl \) (46, 75), fatty acid transporter \( Cd36 \) (CD36) (11, 46, 81), \( Cpt1 \) (81), and activity of HAD (β-hydroxyacyl-CoA dehydrogenase) (77). Skeletal muscle glycogen synthesis is enhanced following glycogen-depleting exercise as an adaptation to an increased energy demand (9, 22, 70). In corroboration with this observation, the expression of \( Glut4 \) (glucose transporter 4) (49) and \( Hk2 \) (48), two genes that are involved in glucose transport and glycogenesis, is also augmented by exercise training. Collectively, these studies provide molecular evidence for changes in the skeletal muscle transcriptional network in response to increased physiological demands, thereby promoting metabolic flexibility of the tissue to meet changes in substrate utilization.

**AMP-Activated Protein Kinase As a Regulator of Skeletal Muscle Gene Expression**

AMP-activated protein kinase (AMPK) is an important mediator of skeletal muscle energy substrate switching in response to energy deprivation. An important biochemical property of AMPK as a putative mediator of skeletal muscle metabolic adaptations is its capacity to monitor and respond to changes in cellular energy status. AMPK is a heterotrimeric complex composed of a catalytic α- and regulatory β- and γ-subunits (13, 24, 45). AMPK is activated by an increase in the ratio of cellular AMP/ATP concentration and therefore functions as an efficient metabolic sensor. Binding of AMP to the γ-subunit activates AMPK allosterically and promotes the phosphorylation of threonine residue (Thr172) within the activation domain of α-subunit by the tumor suppressor LKB1, an upstream AMPK kinase in skeletal muscle (13, 24, 40).

Earlier studies modeled the energy-deprived state by pharmacological activation of AMPK via long-term in vivo 5-aminoimidazole-4-carboxamide-1-β-d-ribofuranoside (AICAR) treatment (Table 1), which leads to increased skeletal muscle GLUT4 and HK2 protein content (28, 76) and enhanced insulin-stimulated glucose transport (12, 34). AICAR-induced glucose metabolic gene expression appears to require AMPKα2 activity. In skeletal muscle of AMPKα2 knockout mice, the AICAR-driven expression of \( Glut4 \) and \( Hk2 \) was abolished (38).

AMPK exerts a profound effect on skeletal muscle oxidative capacity and mitochondrial biogenesis (Fig. 1). In AMPKγ3-knockout mice, the fasting-induced expression of skeletal muscle lipid oxidative genes is impaired, whereas in transgenic mice overexpressing an activated form of the AMPKγ3 subunit, an upregulation of lipid metabolic and mitochondrial gene expression is observed (50). Activation of AMPK via pharmacological means also increases skeletal muscle mitochondrial proteins (8, 38, 95), and overexpression of a kinase-dead AMPKα2 or deletion of the AMPKα2 isoform abolishes these effects. The advantage of activating AMPK has been highlighted by the findings that transgenic mice overexpressing an activated form of the AMPKγ3 subunit are protected against dietary-induced skeletal muscle insulin resistance (6) and, at the local level in isolated skeletal muscle, display fatigue resistance in response to intense anaerobic exercise (4).

**Transcriptional Effectors of the AMPK Pathway**

The strong association between AMPK activation and induction of metabolic genes and mitochondrial biogenesis indicates that transcriptional effectors are an integral component of the AMPK pathway. The positive effect of AMPK on \( Glut4 \) is supported by evidence showing that AMPK-induced expression of \( Glut4 \) occurs in parallel with an increased expression of the \( Mef2 \) (myocyte enhancer factor 2), a transcription factor interacting with the \( Glut4 \) gene promoter (59). Activation of AMPK response element-binding protein, a transcription factor of the HK2 gene by AMPK via direct phosphorylation by the kinase, has also been reported (79). AMPK activation increased nuclear respiratory factor-1 activity (8) and peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1 (PGC-1) content (95), both of which are critical transcriptional regulators for mitochondrial gene expression (69). Moreover, the AMPK-induced expression of \( Glut4 \) and mitochondrial gene expression requires PGC-1α, and AMPK directly phosphorylates PGC-1α and activates the expression of PGC-1α (35). Whether AMPK cooperates with other transcriptional regulators such as PPARα and -δ, which have also been implicated in the regulation of lipid oxidative gene expression in skeletal muscle, is currently unknown.

Although activation of the AMPK pathway is associated with transcriptional programs that mimic exercise-induced adaptations, AMPK is not necessary for the effects of endurance exercise training. Inhibition of AMPK activity via transgenic
expression of a dominant-negative AMPKα subunit did not repress exercise-induced Glut4 mRNA expression (29). Moreover, genetic ablation of AMPKα2 subunit did not impair training-induced elevation in the protein content of HK2 and GLUT4 as well as mitochondrial enzymes such as HAD and citrate synthase (CS) (38).

**Neural Regulation of Skeletal Muscle Metabolic Properties**

In addition to nutritional cues, motor neuron signaling exerts profound effects on the metabolic properties of skeletal muscle (32, 66). The importance of motor neuron activity in the regulation of the skeletal muscle gene expression program has been highlighted by experiments that involve cross-innervation and electrode-mediated delivery of tonic low-frequency electrical impulses (which mimic the firing pattern of slow muscle fiber motor neurons). Denervated fast glycolytic muscle, when reinnervated with motor neurons of slow oxidative muscle, displayed a fast-to-slow contractile property reprogramming (73).

The neural regulation of skeletal muscle physiology also includes modulation of the energy fuel substrate metabolic networks. When stimulated with chronic low-frequency electrical impulses, the expression of genes essential for skeletal muscle lipid utilization, including Lpl (23), Cd36 (11), Had (78), and Cs (57, 78), is increased. Moreover, genes that are critical for glucose uptake and storage, such as Glut4 and HK2, are increased in skeletal muscle following electrical stimulation (47). Chronic low-frequency stimulation also induces a marked shift of fast-to-slow contractile protein from myosin heavy-chain type 2B to type 1 fibers (53, 87).

Generally, the extent of the adaptive changes that are induced by the increase in neuromuscular activity during exercise training in humans or animals has led to less dramatic changes in gene expression and enzymatic activity compared with that of electrical stimulation. The major adaptations typically involve elevations in enzyme activities of oxidative metabolism, with undetectable or subtle changes (from type 2B to 2A) in myosin heavy-chain conversion. Although electrical stimulation represents an artificial model of neuromuscular activity (66), this model has provided important support for the contribution of neural signals in the control of skeletal muscle metabolic gene program.

**Coupling Neural Activity to Skeletal Muscle Metabolic Program**

Although the central role of motor neuron activity in the regulation of fiber type-specific programs regulating gene expression was established by earlier studies involving cross-innervation and electrical stimulation (66, 85, 86), the mechanisms by which calcium may directly transduce the neural signal to changes in skeletal muscle gene expression remain unclear. Calcineurin is a heterodimeric protein phosphatase that has been proposed to act as a calcium sensor that couples neuronal signals to the activation of the slow fiber-specific gene program (7, 14). The binding of calcium activates calcineurin (18), allowing it to dephosphorylate the nuclear factor

<table>
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<tr>
<th>Study/Model</th>
<th>Brief Description of Findings</th>
<th>Gene Function/Program</th>
<th>Ref. No(s.)</th>
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<tbody>
<tr>
<td>Long-term AICAR treatment</td>
<td>Increased protein content of GLUT4 and HK2. Effects abolished in AMPKα2 knockout mice. Impaired fasting-induced mRNA expression of Lpl, Cd36, and Cpt1.</td>
<td>Glucose uptake, utilization, and storage. Lipid uptake and oxidation.</td>
<td>28, 38, 76</td>
</tr>
<tr>
<td>Genetic ablation of AMPKγ3 subunit</td>
<td>Enhanced expression of Cd36 and cytochrome c.</td>
<td>Lipid uptake and oxidation.</td>
<td>50</td>
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<tr>
<td>AMPKγ3 (R225Q) transgenic mice</td>
<td>Reduced Pgc1α mRNA expression and decreased mitochondrial protein content of cytochrome c, Cox1, CS, and HAD.</td>
<td>Transcriptional regulator. Mitochondrial biogenesis and substrate oxidation.</td>
<td>38, 39</td>
</tr>
<tr>
<td>Genetic ablation of AMPKα2 subunit</td>
<td>Increased nuclear content of MEF2 protein in rat skeletal muscle. Elevated protein content of MEF2 in L6 myotube.</td>
<td>Transcriptional regulator.</td>
<td>30, 59</td>
</tr>
<tr>
<td>Rat skeletal muscle and myotubes after AICAR treatment</td>
<td>Increase in NRF-1 activity, Alas mRNA expression, and cytochrome c content.</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Activation of rat skeletal muscle AMPK with chronic GPA treatment</td>
<td>Abolished GPA-induced expression of skeletal muscle Pgc1α mRNA expression in kinase-dead mice. Abrogated GPA-induced Alas mRNA expression and cytochrome c content in kinase-dead mice.</td>
<td>Mitochondrial biogenesis and substrate oxidation.</td>
<td>95</td>
</tr>
<tr>
<td>Chronic low-frequency electrical stimulation</td>
<td>Increased expression of Glut4, Hk2, Lpl, Cd36, Had, and Cs.</td>
<td>Glucose uptake, utilization, and storage. Lipid uptake and oxidation.</td>
<td>11, 23, 57, 78</td>
</tr>
<tr>
<td>Transgenic overexpression of activated calcineurin</td>
<td>Enhanced expression of Lpl, Cd36, Cpt1, Had, and Cs and Pdk4 mRNA. Elevated protein content of mitochondrial oxidative enzymes and PPARα, PPARδ, and PGC-1α. Reduced expression of Pfk, Aldo, and Gapdh.</td>
<td>Lipid uptake and oxidation. Mitochondrial biogenesis. Transcriptional regulators. Glycolysis.</td>
<td>51</td>
</tr>
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Calcineurin Signaling in Skeletal Muscle Metabolism

Although several lines of evidence support calcineurin as an activator of the slow fiber program, much work has focused primarily on contractile property conversion (7), with less emphasis on metabolic properties as a marker for skeletal muscle remodeling. If remodeling of skeletal muscle to express slower and more energy-efficient contractile proteins is to cope with the physiological demand, such as prolonging recurrent activity, a compatible metabolic reprogramming is likely to be elicited to meet the energy cost.

Calcineurin exerts profound effects on the metabolic properties of skeletal muscle (Fig. 1). In transgenic mice that overexpress an activated form of calcineurin in fast-twitch muscle, protein content of insulin receptor, Akt and GLUT4 are increased concomitantly with elevated insulin-stimulated glucose uptake (71). The enhancement in insulin sensitivity occurs independently from changes in insulin-stimulated phosphorylation of insulin receptor and glycogen synthase kinase-3, as well as phosphotidylinositol 3-kinase activity (71), suggesting that changes in gene expression programs play a role. These transgenic mice were also protected against high-fat diet-induced skeletal muscle insulin resistance and glucose intolerance (71). Apart from insulin action and glucose metabolism, overexpression of activated calcineurin in skeletal muscle increases lipid oxidation (51, 71). The increased oxidative capacity is supported by a strong coordinated expression of lipid metabolic genes, including Lpl, Cd36, Cpt, and Had, as well as mitochondrial genes (51). In support of the increased lipid oxidative gene expression, activation of calcineurin in skeletal muscle increased protein content of transcription regulators, including PGC-1α, PPARα, and PPARδ (51). Such an increase in lipid oxidation led to marked enhancement in glycogen synthesis concomitant with decreased glucose utilization in fast-twitch muscle (51, 71), providing further support for a glucose-sparing effect. Conversely, inhibition of calcineurin by treatment of cyclosporine...
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A in rats led to a decreased proportion of slow myosin heavy chain and an increase in activities of metabolic enzymes, including cytosolic creatine kinase and lactate dehydrogenase, that are expressed predominantly in fast-twitch fibers (10). The possibility of nonspecific dephosphorylation or inhibition of other targets is a major caveat in transgenic overexpression and pharmacological inhibition of calcineurin. However, genetic ablation of calcineurin Aα and calcineurin Aβ resulted in a drastic reduction in the mitochondrial oxidative capacity of skeletal muscle as assessed by NADH-tetrazolium staining (61). Collectively, these observations provided evidence that calcineurin regulates the metabolic network of skeletal muscle.

**Calcineurin and Exercise-Induced Skeletal Muscle Adaptations**

In humans, exercise-induced skeletal muscle PGC-1α (20, 56, 68) or mitochondrial (20) gene expression is associated with activation of calcineurin (20, 56, 68). Inhibition of calcineurin activity in mice by cyclosporine treatment blunts the exercise-induced activation of skeletal muscle MEF (93), supporting a role of calcineurin in exercise-induced transcriptional adaptations. Activation of MEF is also observed in human skeletal muscle after a single acute bout of exercise, as evidenced by an increase in MEF nuclear abundance and binding capacity (54, 94). However, most studies involving human subjects in general have provided evidence that the major adaptations of skeletal muscle to endurance exercise include increases in oxidative enzyme activities and less dramatic effects on the skeletal muscle fiber type transformation (65).

Transgenic mice expressing activated calcineurin have increased glycogen synthesis, lipid oxidation, and mitochondrial biogenesis (51, 71). Inhibition of calcineurin activity by overexpression of a protein inhibitor of calcineurin, regulator of calcineurin 1 (also known as modulatory calcineurin-interacting protein-1), results in loss of type I fibers without alterations in the oxidative capacity or mitochondrial content in skeletal muscle (58). The precise role of calcineurin in the regulation of skeletal muscle contractile and metabolic adaptations to exercise or motor neuron activity remains to be determined.

**Table 2. Evidence for a skeletal muscle fiber type dependence of AMPK signaling**

<table>
<thead>
<tr>
<th>Study/Model</th>
<th>Brief Description of Findings</th>
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</tr>
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<tbody>
<tr>
<td>Rat fast- and slow-twitch skeletal muscles</td>
<td>AICAR-induced activation of AMPK in fast- and slow-twitch muscles but stimulated glucose uptake only in fast-twitch muscle.</td>
<td>1, 90, 91</td>
</tr>
<tr>
<td>Mouse and rat white skeletal muscle</td>
<td>Selective expression of AMPKγ3 subunit in white skeletal muscle.</td>
<td>52</td>
</tr>
<tr>
<td>AMPKγ3-knockout mice (Ppkγ3^{−/−})</td>
<td>Abolished AICAR-induced glucose uptake, impaired glycogen synthesis, and gene expression.</td>
<td>5, 6, 50</td>
</tr>
<tr>
<td>Calcineurin-induced fast-to-slow twitch skeletal muscle remodeling (MCK-CnA* mice)</td>
<td>Impaired AICAR-induced glucose uptake associated with decreased AMPKγ3 subunit expression. Unaltered contraction-induced glucose uptake despite lower AMPK activation.</td>
<td>72</td>
</tr>
<tr>
<td>Rat soleus muscles with high glycogen content</td>
<td>Unaltered contraction-induced glucose uptake without AMPK activation. Enhanced glucose uptake and Glut4 expression limited to fast glycolytic muscles, undetectable response in slow oxidative muscles.</td>
<td>16, 12</td>
</tr>
<tr>
<td>Chronic AICAR treatment in rats</td>
<td>AICAR-induced gene expression observed in white but not red gastrocnemius muscle. Ablation of AMPKα2 abolished effects in white gastrocnemius muscle.</td>
<td>38</td>
</tr>
<tr>
<td>Chronic AICAR treatment in mouse</td>
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MCK-CnA*, muscle-specific transgenic mice of activated calcineurin A.

**Fiber Type Dependence of AMPK Signaling in Skeletal Muscle**

Although AMPK is expressed ubiquitously in multiple tissues, the regulatory γ3 subunit is the predominant isoform expressed specifically in fast glycolytic muscle (52). In contrast, the expression of the γ1 and -2 subunits display wide tissue distribution. On the basis of immunoprecipitation experiments, the γ3 subunit appears to associate predominantly with the α2 and B2 subunits (52). The selective association of these subunits is of particular interest because genetic knockout of either α2 or γ3 subunits abolished AICAR-induced glucose uptake, suggesting a central role of the α2β2γ3 heterotrimer in mediating the AICAR effect.

In skeletal muscle of rats treated chronically with AICAR, the enhancement in glucose uptake and Glut4 expression was limited to fast glycolytic muscles, including extensor digitorum longus and white gastrocnemius, and was undetected in slow oxidative muscles such as soleus and red gastrocnemius (12). A later study provided consistent evidence that AICAR-driven mitochondrial gene expression is restricted to white gastrocnemius muscle, with no observable effects in the red gastrocnemius muscle (38). The lack of an AICAR response in terms of glucose uptake is also observed in rat soleus muscle (90). Thus, although the role of AMPK in skeletal muscle metabolism is apparent, the effect of the AMPK signaling pathway appears to be dependent on muscle fiber type (Table 2).

Given the restrictive expression of the AMPKγ3 subunit in fast glycolytic muscle, the role of the γ3 subunit in mediating fiber-type specific AMPK metabolic responses deserves special consideration. Calcineurin-induced fast-to-slow twitch muscle remodeling (55) suppresses AICAR-induced glucose uptake in extensor digitorum longus muscles from transgenic mice expressing an activated calcineurin (72). The impaired AICAR response is associated with a decrease in the expression of the AMPKγ3 subunit, a critical subunit required for AICAR-stimulated glucose uptake (6). The impaired AICAR-induced glucose uptake in skeletal muscle is not associated with any observable decrease in AICAR-induced phosphorylation of the AMPKα subunit (72). Thus, AMPKγ3 subunit expression may be altered by calcineurin-induced fast-to-slow twitch muscle reprogramming, which in turn alters AMPK-mediated meta-
bolic responses. Further studies are needed to provide new insights into whether other fiber type-specific AMPK-induced metabolic adaptations are regulated by AMPKγ3 subunit.

Conclusions and Future Perspectives

Various genetic mouse models have provided new concepts for the role of AMPK and calcineurin in the regulation of skeletal muscle metabolic and gene regulatory events. The flexibility of skeletal muscle lipid and glucose metabolic gene programming is tightly regulated by AMPK and calcineurin through the recruitment of various critical transcription regulators. The results are clinically relevant and pertinent to human muscle metabolism. Reduction in lipid oxidative gene expression (62) and impaired lipid oxidation is thought to cause intramuscular triglyceride accumulation in type 2 diabetes (41). Activation of AMPK or calcineurin to overcome skeletal muscle metabolic inflexibility may offer novel therapeutic entry points for the treatment of insulin resistance and metabolic diseases. The pharmaceutical benefit of activating AMPK has been supported by the findings that transgenic mice of the AMPKγ3 subunit is protected against diet-induced insulin resistance by sustaining fatty acid oxidation and decreasing accumulation of intramuscular triglyceride (6). Similarly, the increased lipid oxidative capacity of activated calcineurin transgenic mice resulted in improved insulin responsiveness and protection against the development of diet-induced skeletal muscle insulin resistance and glucose intolerance (71). Activation of calcineurin or AMPK may lead to possible unfavorable side effects in other tissues such as the heart. Activation of calcineurin in the heart induced detrimental cardiac hypertrophy and hypertrophic gene programs (84). A naturally occurring mutation in human AMPKγ2 subunit activates AMPK and causes cardiac hypertrophy and electrophysiological abnormalities, including Wolf-Parkinson-White syndrome (3, 21, 74). Further investigations in the tissue-specific AMPK and calcineurin pathways, as well as cross-talk with other signaling cascades, may reveal novel molecular candidates to restrict the pharmacological action in skeletal muscle. Additional skeletal muscle drug targeting may also be achieved with advancements in pharmacokinetics and drug delivery. The AMPK and calcineurin pathways are critical for skeletal muscle metabolic flexibility and may offer novel therapeutic entry points and preventive strategies for metabolic diseases.

GRANTS

We are supported by funding obtained from the European Foundation for the Study of Diabetes, Swedish Research Council, Swedish Diabetes Association, Strategic Research Foundation, Knut and Alice Wallenberg Foundation, and Commission of the European Communities (contract no. LSHM-CT-2004-005272 EXGENESIS and contract no. LSHM-CT-2004-512013 EUGENE2).

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