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Abstracts

S9 Mitochondria as a Therapeutic Target

9L.1 Stearoyl-CoA desaturase and insulin signaling — What is the molecular switch?

Agnieszka Dobrzyn
Laboratory of Cell Signaling and Metabolic Disorders, Nencki Institute of Experimental Biology, Warsaw, Poland
E-mail: adobrzyn@nencki.gov.pl

Insulin resistance, an impaired biological response to circulating insulin, is a disorder common to most of the obesity-related diseases and, as such, represents an important target of medical research. The precise etiology of impaired insulin action in obese people is still unknown; however, an increasing body of evidence indicates that it may be associated with alterations in intracellular lipid metabolism. Insulin-resistant humans and animals accumulate significant amounts of lipids not only in the adipose tissue, but also in liver, muscle and other peripheral tissues. Storage of even a modest caloric surplus in lean, insulin sensitive tissues leads to insulin resistance. Altered lipid metabolism as seen in the insulin-resistant states largely depends on the aberrant expression of genes encoding key metabolic enzymes. Consequently, several enzymes regulating lipid metabolism have been recently proposed as therapeutic targets. One of these enzymes, stearoyl-CoA desaturase (SCD), appears to be of special significance, because *SCD1* is the major gene target of leptin, which is the central mediator regulating energy homeostasis and a known insulin-sensitizer. Increasing evidence suggests that SCD, the rate limiting enzyme of monounsaturated fatty acid biosynthesis, is an important factor in the pathogenesis of lipid-induced insulin resistance. Mice with a targeted disruption of the *SCD1* gene have improved glucose tolerance compared to wild-type mice, despite lower fasting plasma insulin levels. Increased SCD activity has been found in insulin resistant humans and animals, whereas SCD1 deficiency attenuates both diet- and genetically-induced impairment of insulin action. In skeletal muscle and in brown adipose tissue, basal tyrosine phosphorylation of the IRS1 and IRS2, the association of both IRS1 and IRS2 with the ap85 subunit of phosphatidyl-inositol 3-kinase, the phosphorylation of Akt and membrane GLUT4 translocation are all elevated in $SCD1^{-/-}$ mice compared with wild-type mice. Our recent study showed that deletion of *SCD1* gene protects muscle against lipid-induced insulin resistance. While the precise mechanism of SCD action on insulin signaling remains to be clarified, current findings on SCD point to a very promising novel strategy for the treatment of insulin resistance.

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9L.2 Mitochondrial fatty acid synthesis and respiration

J. Kalervo Hiltunen[1], Kaija J. Autio[1], Melissa S. Schonauer[2], V.A. Samuli Kursu[1], Carol L. Dieckmann[2], Alexander J. Kastaniotis[1]

[1]*Department of Biochemistry and Biocenter Oulu, University of Oulu, Oulu, Finland*
[2]*Department of Biochemistry, University of Arizona, Tucson, Arizona, USA*
E-mail: kalervo.hiltunen@oulu.fi

The dual localization of fatty acid synthesis (FAS) in eukaryotic cells raises the question of why have eukaryotes maintained the FAS in the mitochondria in additions to the "classic" cytoplasmic FAS. The mitochondrial FAS is composed of a discrete set of monofunctional enzymes resembling the bacterial FAS system in contrast to the eukaryotic cytosolic multifunctional complex. Yeast cells deficient in mitochondrial FAS have rudimentary mitochondria and a respiratory deficient phenotype, exhibit loss of spectrally detectable cytochromes, and are defective in mitochondrial RNA processing [3,4]. One task of the mitochondrial FAS is to generate octanoyl-ACP which is used for lipoic acid synthesis. This is apparently also a conserved and essential process in mammals. Lipoic acid is required for the function of several multienzyme complexes involved in the oxidative decarboxylation of α-keto-acids and glycine. The mechanistic details of lipoic acid metabolism are unclear in eukaryotes, despite two well-defined pathways for synthesis and covalent attachment of lipoic acid in prokaryotes. Recently we demonstrated the involvement of four genes in the synthesis and attachment of lipoic acid in *Saccharomyces cerevisiae*. *LIP2* and *LIP5* are required for lipoylation of all three mitochondrial target proteins: Lat1 and Kgd2, the respective E2 subunits of pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, and Gcv3, the H protein of the glycine cleavage enzyme. *LIP3*, which encodes a lipoate-protein ligase homolog, is necessary for lipoylation of Lat1 and Kgd2, and the enzymatic activity of Lip3 is essential for this function. *GCV3*, encoding the H protein target of lipoylation, is itself absolutely required for lipoylation of Lat1 and Kgd2 [5]. Recently pieces of evidence have been emerging which link the mtFAS pathway to disease in mammals. Our recent report on the development of cardiomyopathy in mice overexpressing Etr1 established a possible connection between mtFAS and heart disease [1]. The expression of *17βHSD8,* encoding a subunit in KAR1 [2], has been reported to be repressed in kidney and liver of polycystic kidney disease mouse models.

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