Lethal Mitochondrial Cardiomyopathy in a Hypomorphic Med30 Mouse Mutant is Ameliorated by Ketogenic Diet

Krebs et al


The complexity of mitochondrial diseases has made their treatment problematic. However, in a recent study from PNAS in 2011, researchers show how diet may be the key to better understanding and possibly fighting the expression of these diseases.

In their study, Krebs and colleagues report that treatment with a ketogenic diet reduces lethality in a mouse model of mitochondrial cardiomyopathy.1 The cardiomyopathy is caused by a homozygous nonsynonymous A-to-T transversion in Med30, a gene encoding one of the ~30 subunits of the Mediator complex A. The homozygous mutation, which was induced on treatment with N-ethyl-N-nitrosurea, impairs oxidative phosphorylation and mitochondrial integrity leading to premature lethality within 2 to 3 weeks after weaning. Activity of the Mediator complex is required to express RNA-polymerase II-transcribed genes in the presence of gene-specific activators by promoting preinitiation complex assembly.2 As a result of the Med30 mutation, the authors observed a progressive decline in the transcription of genes specifically involved in oxidative phosphorylation and mitochondrial integrity. The transcriptional profile of the left ventricle of the 5 weeks old homozygous mutant mice displayed a considerable reduction in Pparγc1α and Esrra transcripts, which code for PGC1α (peroxisome proliferator-activated receptor-γ coactivator-1α) and ERRα (estrogen-related receptor-α), respectively. PGC1α and ERRα are known transcriptional factors for oxidative metabolism enzymes, including the respiratory chain, mitochondrial antioxidant defenses, and mitochondrial biogenesis (Figure).3 Accordingly, transcripts and activities of a number of PGC1α-ERRα–dependent mitochondrial enzymes were also decreased. The homozygous mutant mice, presumably as a result of the mitochondrial loss of function, developed a postweaning cardiomyopathy and were invariably deceased at 7 weeks of age. A ketogenic diet, known to stimulate downstream targets of PGC1α pathway,4 allowed a significant lifespan extension, supporting an instrumental role of decreased PGC1α activity in this lethal phenotype.

The study starts by identifying the molecular basis of an intriguing disease phenotype in the mouse; shedding new light on the function of the Mediator complex. A detailed description of the heart-related phenotype follows, and a plausible underlying mechanism is suggested. The paper ends by the icing on the cake: a successful attempt to oppose the plausible underlying mechanism is suggested. The paper ends by the icing on the cake: a successful attempt to oppose the

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Figure. The Sirt1/AMPK/PGC1/ERR signaling pathway for mitochondrial biogenesis. This is an oversimplified view of the Sirt1/AMPK/PGC1 signaling pathway showing the targets of various effectors that have been proposed as therapeutic compounds in mitochondrial diseases. The mediator complex and its MED30 subunit are also featured although the mechanism of their interaction with the pathway has yet to be established. Finally, the scheme indicates the potential interactions between PGC1 transcription factor and ketone bodies derived from the diet. AMPK indicates AMP-activated protein kinase; ERR, estrogen receptor related; NRF1 and 2, nuclear respiratory factor 1 and 2; PPARs, peroxisome proliferator-activated receptors; PGC1, PPAR-γ coactivator 1; RXR, retinoid X receptor; SIRT1, Sir2 family (silent mating type information regulation 2 homolog 1); mtTFBs, mitochondrial transcription factors; TFAM, mitochondrial transcription factor A.

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nase, and cytochrome oxidase staining in the heart of the mutant animal. The decrease in respiratory chain activities if expressed per protein rather than corrected for the citrate synthase level would have been possibly even more spectacular than reported, because the expression of citrate synthase (and presumably its activity) is also severely diminished in these mice. The comprehensive assessment of the decrease in gene expression nicely points to the PGC1α signaling pathway as the target of the mutant MED30. Indeed a large set of the known downstream targets of this pathway appear affected in the mutant mouse. The mechanism by which mutant MED30 interferes with the transcriptional activity of PGC1α is not yet established. The authors suggest that the mutant MED30 would perturb the PGC1α-Mediator complex. However, this remains to be verified in future research.

There is no reason to reject the proposal that the course of the postweaning cardiomyopathy in these mice is determined from the considerable decrease in fat intake on shifting from ≈40% fat-rich maternal milk to the 5% fat-enriched regular chow. This explanation is attractive because ketone diet administered after weaning is shown to slow down the progression of the disease. This perfectly fits with postulated role for the change in fat intake in the course of the heart disease; presumably any treatment that would have protected/increased mitochondrial function would have had a similar protective effect. Of major interest is the observation that mitochondrial dysfunction can be counteracted by changing the diet. Mitochondrial diseases encompass a wide range of presentations and mechanisms, with quite variable age of onset and course. This likely reflects the genetic complexity of mitochondrial biology, which requires an excess of 2,000 genes to function properly with numerous interfering epigenetic and environmental factors. We are indeed far from understanding the complexity of mitochondrial diseases, which involve far more than just decreased ATP. As a result, we are still severely limited in our ability to treat or even to slow down the progression of these frequently devastating diseases.6 In this context, any clue to assist in the fight against mitochondrial disease progression is obviously of major interest. Because mitochondrial diseases are essentially metabolic diseases, the idea that these diseases could be countered by diet modulation per se is not new. However we still lack the definite evidence that diet modulation significantly changes the course of disease in humans, presumably because of the difficulties in organizing clinical trials with these rare and variable conditions. In keeping with this, mouse studies allow us to bypass these difficulties, as long as faithful models for mitochondrial diseases are used.7 To date a number of mouse models have been described and several attempts to delay the progression of disease have been reported. Strikingly, among the most promising strategies emerging from these studies are diet modulation8,9 and the use of factors intimately related with diet utilization, ie, the factors acting on the Sirt1/AMPK/PGC1α/PPAR pathway (Figure).10,11 In their study, Krebs and colleagues established a temporal link between worsening of cardiomyopathy and weaning. Remarkably they deduced that changing the diet might be sufficient to significantly slow the progression of heart disease. The authors actually demonstrated the positive effects of ketogenic diet on enzyme activity and life duration. Based on these observations in the MED30 mutant mouse, the reported protective effect of the ketogenic diet might be applicable to mitochondrial dysfunction resulting from other causes.9 The findings also implicate diet as a central actor in the course of mitochondrial diseases and it could explain, in part, the interindividual variability of expression of these diseases.

Disclosures

None.

References

Changing the Diet to Make More Mitochondria and Protect the Heart
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