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AMPK-independent variation of sirtuin expression levels is correlated with the reversion of an obesity-like phenotype *Caenorhabditis elegans*.

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Background*: Caenorhabditis elegans* (*C. elegans*) has been recognized as an excellent genetic model for investigating energy homeostasis. Related to lipid metabolism, *C. elegans* stores fat in the form of lipid droplet-like structures in intestinal and epidermal cells. Because *C. elegans* has a transparent body, these fat granules can be visualized directly by staining with Oil-Red.

AMP-activated protein kinase (AMPK) plays a recognized role in energy metabolism. It is considered as a sensor of cellular energy by helping to regulate energy balance and caloric intake. Another key enzyme involved in regulation of energy expenditure is sir2.1 deacetylase (sirtuin, SIRT1 in mammals). The relationship between aak2 (the ortholog of the AMPK α2 catalytic subunit in nematodes) and sir2.1 deacetylase is not yet fully understoodentirely clear.

Objetive: The aim of this study is to determine the role of sirtuins in pathways leading to fat accumulation (obesity) and changes in the nematode life-span, and its interaction with AMPK. The study is also looking for using the results for designing a rapid screening method for sirtuin activators in C. elegans.

Methods: We used N2 wild-type worms and worm mutants which show a phenotype of high level of trygliceride accumulation. After combining the fat-accumulation inducing mutations with deletions in aak2 and sir2.1, we have measured the activation levels of aak2 and sir2.1enzymes at mRNA level by real-time polymerase chain reaction.

Results: We have found that some mutants presented a fat accumulation phenotype that might be directly related with a decrease in expression of lipases fil1 and fil2; while in others is related with a defect in inducing fatty acid β-oxidation. Interestedly, we founded that the decrease of lipases expression was linked to a significant decrease in sir2.1 expression and that the phenotype was independent of AMPK. Furthermore, the treatment with an active agent that decreased fat accumulation, restored both lipases and sir2.1 expression up to almost wild-type levels. In contrast, the phenotype related with changes in the induction of fatty acid β-oxidation was dependent on AMPK.

Conclusion: sir2.1 activation is involved in the cure of an obesity-like phenotype and our experiments suggest about the existence of an AMPK-independent pathway implicated in fat storage and utilization. These results might have important implications in proposing new anti-obesity treatments in humans. We are currently focusing into propose a new model to detect sirtuin activators.