Comparative metabolomics reveals the gene function of kat-1 in C. elegans

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In the model organism *Caenorhabditis elegans* mutation of the mitochondrial 3-ketoacyl-CoA thiolase (*kat-1*) has been reported to affect lifespan [1]. Although *kat-1* has been assumed to be implicated in mitochondrial β-oxidation of fatty acids, its precise function has remained enigmatic. Comparative analysis of the *C. elegans* wildtype (N2) and *kat-1* mutant exometabolomes revealed some yet unidentified compounds (see Figure 1).

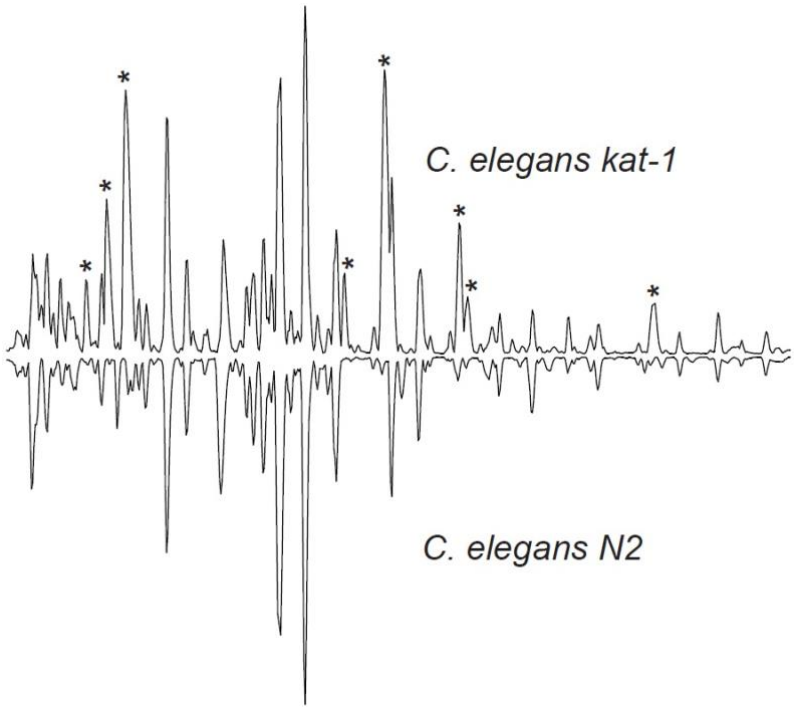

Figure 1: Comparative metabolomics of exometabolomes of a *kat-1* mutant (above) and a *N2* control (below). The markers indicate some of the metabolic changes found in the HPLC-MS traces of the exometabolome.

Large scale cultivation, followed by fractionation, and NMR spectroscopy enabled the identification of several modular tiglyl-glucosides. Their upregulation in *kat-1* suggested a potential function in branched chain amino acid metabolism. Feeding experiments with the *C. elegans kat-1* mutant using L-[U-$^{13}C_5$]-valine, L- [U-$^{13}C_6$,^{14}N]-leucine, and L-[U-$^{13}C_6$,^{14}N]-isoleucine enriched *E. coli Δile Δleu Δval* highlighted diverse metabolites derived from the catabolism of L-isoleucine that are strongly upregulated in the *kat-1* mutant. Taken together, these results indicate that *kat-1* functions as a mitochondrial 2-methylacetoacetyl-CoA thiolase. Consequently, *C. elegans kat-1* might represent a suitable model system to study mitochondrial acetoacetyl-CoA thiolase (T2) deficiency, a rare disease in humans [2].

[1] A. Berdichevsky, S. Nedelcu, K. Boulias, N. A. Bishop, L. Guarente, H. R. Horvitz, Proceedings of the National Academy of Sciences of the United States of America, **2010**, 107, 18927-18932.
[2] E. Abdelkreem, R. K. Harijan, S. Yamaguchi, R. K. Wierenga, T. Fukao, Human Mutation, **2019**, 40, 1641-1663.