Characterizing the roles of ETS-4 transcription factor in fat metabolism

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ABSTRACT

Obesity is a serious health problem affecting people all over the world, therefore it is crucial to understand the mechanisms that regulate fat metabolism. Previous research conducted on *C. elegans* allowed the discovery of the *rege-1*, whose inhibition activated the ETS-4, leading to a reduction in the body fat content. The aim of this thesis was to discover the regulatory axis through which the REGE-1 - ETS-4 influenced fat metabolism in nematodes.

The results from unbiased genetic screening and RNA-Seq data allowed for the selection of potential candidates that could regulate fat accumulation downstream of the REGE-1 - ETS-4 regulatory axis, such as MRP-1 or PEPT-1. However, silencing of genes related to their action, including *sphk-1*, *ltah-1.2*, *pbo-1* or *pbo-4*, resulted only in a partial recovery of the body fat levels in *rege-1* mutants, which may suggest that they regulated fat metabolism in parallel to the REGE -1 - ETS-4 regulatory axis. Moreover, expression of *skn-1* and activation of DAF-16 were enhanced in the *rege-1* mutants, however they were probably responsible for other aspects of physiology, such as oxidative stress response.

Characterization of changes that occured in response to *rege-1* depletion showed a change in the expression of genes associated with lipid metabolism, such as lipid catabolism (*lipl-1* and *lipl-2*), fatty acid desaturation (*fat-5*, *fat-7*) or sphingolipid metabolism (*sptl-1*, *sptl-2*, *hyl-1*, *hyl-2* or *sphk-1*). Simultaneous silencing of *sptl-1* and *sptl-2* in *rege-1* mutants resulted in complete fat recovery, suggesting regulation of fat accumulation via the REGE-1 - ETS-4 regulatory axis. In addition, the *rege-1* mutants were characterized by reduction in the oxygen consumption rate and an increase in the expression of genes related to the oxidative stress response (*sod-4* and *sod-5*). This might suggest disturbance of mitochondrial oxidative phosphorylation and that *rege-1* mutant animals use energy sources other than fatty acids for animal survival. The increase in the *sodh-1* mRNA levels could indicate that carbohydrate metabolism might be enhanced in the *rege-1* mutants.

In conclusion, the fat loss phenotype of the *rege-1* mutants depended on the interaction of multiple signaling pathways that worked in concert with the REGE-1 - ETS-4 regulatory axis, which seemed to modulate fat accumulation predominantly through changes in the sphingolipid metabolism. Given the similarities between nematode REGE-1 and human Regnase-1, finding of potential downstream targets of the REGE-1 – ETS-4 regulatory axis might enable the discovery of potentially novel metabolic pathways that could find an application in the treatment of obesity.