The *C. elegans* "hibernation": surviving cold through ferritin-mediated iron detoxification

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Abstract

Hibernation is a strategy developed by some endotherms in order to survive unfavorable environmental conditions. Hibernating animals lower down their core body temperature and reduce their metabolic rate without any negative consequences for their health. The detailed cellular mechanism/mechanisms underlying entrance or exit to the hibernation state has not been fully determined.

To uncover molecular processes involved in hibernation-like response, we employed a simple model organism that enters a hibernation-like state, the nematode *Caenorhabditis elegans*. Our previous research using this model revealed that nematodes lacking ETS-4 transcription factor exhibited improved cold survival via the upregulation of *ftn-1* mRNA. *ftn-1* encodes an ortholog of mammalian ferritin heavy chain (FTH1). Therefore, the main aim of this study was to determine processes underlying the *C. elegans* ferritin-mediated cold protection during hibernation-like response.

In this dissertation, I confirmed that *ftn-1* mRNA was increased in response to the cold treatment of nematodes lacking ETS-4. Additionally, the *ftn-1* overexpression robustly enhanced wild-type *C. elegans* cold resistance, and slightly increased their total lifespan. Moreover, the ferroxidase activity of FTN-1 was crucial for its function in cold survival improvement. Interestingly, my results suggest that FTN-1 acts as an antioxidant in the protection against reactive oxygen species (ROS) generated by cold exposure. Additionally, I characterized the contribution of two other transcription factors, ELT-2 and HIF-1, in the regulation of *ftn-1* expression in the cold. Moreover, I revealed that FTN-1 induction in response to starvation is mediated by different mechanism than the one used in the cold response. Finally, I showed that two RNA-binding proteins cooperating in *ets-4* mRNA regulation upon normal conditions, RLE-1 and REGE-1, are also involved in *ets-4* mRNA silencing during cold response.

Overall, the results obtained within this dissertation revealed a crucial role of ferritin in cold protection. This knowledge may contribute to the improvement of strategies imitating hibernation state with potential use in e.g. treatment of patients with traumatic brain injury.