Publication News 115 - 25 March 2023

Unravelling the link between UCHL1 and diabetic sensory neuropathy: insights from Drosophila research

Aims: The aim of this study is to investigate the role of ubiquitin carboxyl-terminal hydrolase L1 (UCHL1) in the pathogenesis of type 2 diabetes and diabetic sensory neuropathy using Drosophila as a model organism.
Methods: A series of biochemical analyses of the hemolymph were conducted to evaluate diabetes-related characteristics in fruit flies with UCHL1 mutations. Sensory deficits in mutant flies were evaluated using a hot plate or an acidic filled plate, by recording the time of their first jumping response. Axonal atrophy and sensory neuron apoptosis were assessed by quantifying sensory axons and leg sensory neurons respectively in UCHL1 KO flies. Inducible knockdown of nervous system UCHL1 in adult flies was achieved using genetic strategies to demonstrate the specific time/location role of UCHL1 in diabetes and diabetic sensory neuropathy associated phenotypes. Both genetic and pharmacological regulation of downstream components of UCHL1 in the insulin signalling pathway were conducted to understand the mechanisms connecting UCH deficiency, sensory nerve-specific insulin resistance, and sensory deficits.
Results: In this study, the authors demonstrated that UCHL1 regulates insulin signalling by acting as a deubiquitinase of insulin receptor substrate (IRS1). Due to its high expression in neurons, particularly sensory neurons, the absence of UCHL1 triggered the degeneration of axons in leg sensory neurons and consequently resulted in diabetic sensory neuropathy in drosophila. Furthermore, they showed that the GSK3B-Snail-CUL1 axis functions as a negative regulator of insulin signalling through IRS1 ubiquitination, a process which is counteracted by UCHL1.
Conclusions: Loss of UCHL1 in Drosophila leads to diabetic sensory neuropathy and insulin resistance, highlighting the role of UCHL1 in these conditions.

Comments. The authors of this well-designed study revealed that the loss of UCHL1 in Drosophila leads to sensory neuropathy like defects and neuron-specific insulin resistance, providing potential new insights into the pathogenesis of diabetic sensory neuropathy. These findings contribute to the understanding of the molecular mechanisms underlying diabetic sensory neuropathy and provide potential targets for therapeutic interventions. The study suggests that inhibitors of the E3 Ligase Cullin 1 (CUL1) neddylation could be a potential therapeutic target for diabetic sensory neuropathy and insulin resistance associated with type 2 diabetes. However, the study primarily focuses on the role of UCHL1 in Drosophila as a model organism, which may not fully represent the complexity of human physiology and disease conditions. The authors are currently in the process of investigating whether their results obtained from Drosophila study are also consistent in rodent models. Overall, while the study provides valuable insights into the role of UCHL1 in diabetic sensory neuropathy and insulin resistance, further research is needed to validate these findings in human settings.

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Reference. Lee D, Yoon E, Ham SJ, Lee K, Jang H, Woo D, Lee DH, Kim S, Choi S, Chung J. Diabetic sensory neuropathy and insulin resistance are induced by loss of UCHL1 in Drosophila. Nat Commun. 2024 Jan 11;15(1):468. doi: 10.1038/s41467-024-44747-9. PMID: 38212312; PMCID: PMC10784524.
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