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Brain-specific microRNA-mediated regulation of metabolic homeostasis in Drosophila melanogaster

To maintain optimal metabolic balance, an organism must coordinate its food intake, fat storage, and appropriate energy mobilization to meet physiological demands and support overall well-being. These metabolic processes require precise regulation to ensure timely responses to environmental and internal cues. Small non-coding microRNAs (miRNAs) are well suited for this role, as they can regulate physiological and adaptive processes that require rapid or localized control of gene expression.

We have identified a novel neural circuit in Drosophila that plays an important role in metabolic homeostasis, mediated by the conserved Central Nervous System (CNS)-specific miRNA miR-1000. We previously identified miR-1000 to be a neuroprotective miRNA by regulating Glutamatergic signaling in the brain (Verma et al., Nature Neuroscience, 2015). In addition to its role in neuroprotection, we recently discovered that miR-1000 also regulates key aspects of metabolism, including body weight, fat storage, survival during nutrient deprivation, and longevity (Verma et al, Genes and Development, 2026). miR-1000 achieves this by repressing the Neuropeptide Like Peptide 1 (Nplp1) gene in the CNS. Loss of miR-1000 and consequent increase in Nplp1 expression result in flies with higher fat storage and extended survival under nutrient-deprived conditions. While the biological function of Nplp1 neuropeptides has been largely unknown, this study highlights their critical role in maintaining metabolic homeostasis in Drosophila. Additionally, we observed that miR-1000 and Nplp1 levels change dynamically during refeeding after starvation, suggesting their involvement in adaptive metabolic responses. miR-1000 regulates triacylglycerol (TAG) synthesis and storage in lipid droplets, supports fat mobilization during starvation, and facilitates its storage upon refeeding. These findings underscore the importance of miR-1000 and Nplp1 in metabolic regulation and provide new insights into the mechanisms of energy balance.

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