IN BRIEF

NEURODEGENERATIVE DISEASE

Antisense therapy for prion disease

Raymond, G. J et al. *JCI Insight* **4**, e131175 (2019)

To date, no treatment is available for transmissible spongiform encephalopathies (TSEs), a group of fatal neurodegenerative diseases caused by a conformational change of the cellular prion protein (PrP) in the central nervous system of humans and other mammals. Previous work has shown that PrP depletion in mice is protective against prion disease, leading researchers to investigate the potential of PrP-lowering therapies. However, limitations such as poor tolerability of drug delivery by osmotic pumps have hindered the development of RNA interference therapy. By showing that intracerebroventricular bolus injection of antisense oligonucleotides (ASO)s complementary to *Prnp* mRNA could extend the survival of prion-infected mice, a study brings new hope for ASO therapy for prion disease. *ALB*

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ANIMAL BEHAVIOR

Mitochondria linked to stress response

Misiewicz, Z et al. *PLoS Genet*. **15**, e1008358 (2019)

Little is known about the pathways underlying individual differences in stress responses. Using the chronic social defeat stress (CSDS) model to develop anxiety in male mice, a team of investigators applied a multi-omics approach to compare the molecular signatures of two inbred strains, the stress-resilient C57BL/6NCrl (B6) and the stress-susceptible DBA/2NCrl (D2). Their analysis revealed that CSDS induces changes in the expression of mitochondrial-related genes and proteins in blood cells and in the nucleus of the stria terminalis, a brain region that has been associated with anxiety; the pattern of differential expression was opposite in the B6 and D2 mouse strains. These findings suggest that mitochondrial-related pathways control stress responses and could be targeted to treat anxiety disorders. *ALB*

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NEURODEGENERATIVE DISEASE

Glycolysis in Parkinson's disease

Cai, R et al. *J. Clin. Invest*. **129**, 4539–4549 (2019)

Parkinson's disease (PD) is a common neurodegenerative disease with no cure. Several mechanisms, including metabolic dysfunction, have been proposed to contribute to neuron death in PD. The observation that energy deficits and reduced ATP levels are common features of PD led investigators to hypothesize that increasing glycolysis might be a therapeutic option to slow the neurodegeneration associated with PD. They administered terazosin (TZ) a drug that binds and activates phosphoglycerate kinase 1 (PGK1) — the first ATP-generating enzyme in glycolysis — to genetic and toxin-induced PD models in mice, rats and flies, and showed that TZ increased brain ATP levels and slowed neuron loss. These findings suggest that PGK1 and glycolysis could be targeted to slow PD progression. *ALB*

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NEUROSCIENCE

Active forgetting in the fly

Gao, Y. et al *Proc. Natl Acad. Sci. USA* https://doi.org/10.1073/pnas.1903763116 (2019)

The process of forgetting is not always passive; it can be more intentional, involving an orchestrated erasure of memories. Previous studies in *Drosophila* have shown that Rac1 and Cdc42, two Rho GTPases that coordinate actin remodeling, mediate the forgetting of labile (anesthesia-sensitive memory) and consolidated (anesthesia-resistant memory) memories, respectively. Now, a study using multiple transgenic flies reveals that the effects of Rac1 and Cdc42 in mushroom body neurons are mediated by two different actin-polymerization pathways. These findings increase our understanding of the molecular mechanisms that link forgetting to actin remodeling and might contribute to the development of new drugs to treat human brain disorders that alter active forgetting mechanisms. *ALB*

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