
Credit: Tetra Images/Getty

The authors next sought to determine the neural circuit innervating iBAT using retrograde viral tracing, in which nodes of a circuit close to the infection point are labelled at earlier time points than more distal nodes. The authors found that DRN^{VGAT} neurons were labelled at later time points than the raphe pallidus (RPa), suggesting that this area lies downstream of DRN^{VGAT} neurons. Further experiments showed that DRN^{VGAT} neurons send descending projections to the RPa, which in turn projects indirectly to iBAT. Photoactivation of DRN^{VGAT} neurons projecting to the RPa reduced iBAT temperature, confirming a role for this pathway in thermoregulation.

The tracing experiments also showed that DRN^{VGAT} neurons project to forebrain areas known to play a role in the regulation of energy balance, including the bed nucleus of stria terminalis, dorsomedial hypothalamus and medial preoptic area. Optical activation of DRN^{VGAT} axon terminals in these areas each led to a decrease in iBAT temperature. Overall, these findings suggest that the DRN is an important node in central circuits that regulate thermoregulation and energy balance.

Sian Lewis

ORIGINAL ARTICLE Schneeberger, M. et al. Regulation of energy expenditure by brainstem GABA neurons. *Cell* https://doi.org/10.1016/j.cell.2019.05.048 (2019)

whole transcriptome analysis of gene expression in peripheral neutrophils and macrophages of transgenic mice lacking TREM1 (TREM1$^{-/-}$ mice), and found an increase in the expression of genes involved in 'protective' responses, such as antioxidant defence, the clearance of cellular debris and anti-inflammatory signalling.

These findings suggested that approaches that limit TREM1 induction in peripheral myeloid cells could have beneficial effects after cerebral ischaemia. Indeed, the authors showed that TREM1$^{-/-}$ mice, as well as mice treated with a decoy peptide that blocks TREM1 signalling at the time of MCAo, exhibited an improvement in neurological scores, better survival rates and reduced infarct volume. The peptide also reduced the infiltration of peripheral myeloid cells to the ischaemic brain and increased their expression of the anti-inflammatory receptor TREM2. To mimic a more therapeutically realistic scenario, the authors examined the effects of four doses of the peptide administered between 4.5 and 48 hours after MCAo. Even with this slightly delayed start to the treatment, the mice showed improved neurological scores and motor performance 7 days after the ischaemic event.

Which factors stimulate TREM1 induction and initiate the immune response to MCAo? It is known that cerebral ischaemia can disrupt sympathetic input to the intestine, increasing gut permeability. Here, the authors showed that the induction of TREM1 expression in peripheral myeloid cells was inhibited when changes in gut permeability after MCAo were blocked, suggesting that exposure to immunogenic factors present in the intestine could contribute to the induction of peripheral TREM1.

This study thus provides evidence that TREM1 induction in peripheral myeloid cells amplifies the secondary damage that follows cerebral ischaemia and points to this pathway as a potential target for future therapeutic investigation.

Katherine Whalley

ORIGINAL ARTICLE Liu, Q. et al. Peripheral TREM1 responses to brain and intestinal immunogens amplify stroke severity. *Nat. Immunol.* https://doi.org/10.1038/s41590-019-0421-2 (2019)

IN BRIEF

NEURAL CIRCUITS

Putting the brakes on feeding

The effects of obesity on the lateral hypothalamic area (LHA; a highly conserved brain region that mediates feeding behaviour) have been unclear to date. In this study, a combination of high-throughput single-cell RNA sequencing and longitudinal in vivo two-photon calcium imaging revealed that, in mice, glutamatergic neurons in the LHA act as a brake on feeding and supresses further food intake. Notably, the activity of these neurons is affected by diet-induced obesity, promoting further overeating.

ORIGINAL ARTICLE Rossi, M. A. et al. Obesity remodels activity and transcriptional state of a lateral hypothalamic brake on feeding. *Science* **364**, 1271–1274 (2019)

NEURODEGENERATIVE DISEASE

Crosstalk in Alzheimer disease

The genes encoding the microglial receptors CD33 and TREM2 have been associated with Alzheimer disease (AD) in GWASs. Here, the authors investigated crosstalk between these two receptors. Knockout of *Cd33* alone decreased amyloid-β (Aβ) pathology and improved cognition in the 5xFAD mouse model of AD, effects that were abrogated by additional *Trem2* knockout. As Aβ pathology and neurodegeneration were exacerbated in *Trem2*$^{-/-}$ 5xFAD mice, the authors conclude that TREM2 acts downstream of CD33, and that inhibiting CD33 and/or increasing the activity of TREM2 could represent novel therapeutic approaches.

ORIGINAL ARTICLE Griciuc, A. et al. TREM2 acts downstream of CD33 in modulating microglial pathology in Alzheimer's disease. *Neuron* https://doi.org/10.1016/j.neuron.2019.06.010 (2019)

SLEEP

Sleep like a … fish

Sleep has been described in all branches of the animal kingdom, but slow-wave sleep (SWS) and paradoxical or rapid eye movement (REM) sleep have only been described in mammals, birds and reptiles. Cellular-resolution polysomnography in zebrafish revealed two major sleep signatures — termed slow bursting sleep and propagating wave sleep — that share features of SWS and REM sleep. The authors also found that melanin-concentrating hormone signalling (which is involved in mammalian sleep) regulates propagating wave sleep and the overall amount of sleep in zebrafish. These findings suggest that common neural sleep signatures might be present across all vertebrates.

ORIGINAL ARTICLE Leung, L. C. et al. Neural signatures of sleep in zebrafish. *Nature* **571**, 198–201 (2019)

NEURODEGENERATIVE DISEASE

Repressing mutant proteins

Huntington disease (HD) is caused by a CAG trinucleotide expansion in the huntingtin gene (*HTT*), which codes for the pathologic mutant HTT (mHTT) protein. Here, the authors engineered zinc finger protein transcription factors (ZFP-TFs) to target the CAG repeat and selectively repress levels of mHTT. In patient-derived fibroblasts and neurons, ZFP-TFs selectively repressed >99% of HD-causing alleles while preserving expression of >86% of normal alleles. This allele selective approach is essential as normal HTT is thought to have an important role in brain function.

ORIGINAL ARTICLE Zeitler, B. et al. Allele-selective transcriptional repression of mutant *HTT* for the treatment of Huntington's disease. *Nat. Med.* **25**, 1131–1142 (2019)