NEURODEGENERATIVE DISEASES

A sticky subject

The accumulation of misfolded proteins in neurons is linked to pathogenesis in many neurodegenerative diseases, yet research directed at identifying mutations in disease-specific proteins that might cause such a build-up has been successful in only a few cases. Findings published in *Nature* now reveal a more general mechanism by which errors in the translation of the genetic code might lead to aberrant protein synthesis, misfolding and, eventually, cell death.

The new insights arose from analysis of a mutant mouse strain, which earned the name sticky (*Sti*) because of its dishevelled fur. *Sti* mice suffer from slow progressive degeneration of cerebellar Purkinje cells, leading to motor defects reminiscent of many neurodegenerative conditions. Ackerman and colleagues therefore set out to determine the genetic defect underlying this neurodegeneration.

The authors pinned down the mutation to the alanyl-tRNA synthetase (*Aars*) gene. AARS recognizes and links, by aminoacylation, the amino acid alanine to appropriate tRNA ($tRNA^{Ala}$) molecules and is crucial for the translation of mRNA transcripts into accurate peptide sequences. The mutation affects the editing domain of AARS, which deacylates $tRNA^{Ala}$ molecules that are mistakenly bound to similarly sized but inappropriate amino acids, such as serine. As would be predicted, the mutation reduced the ability of the enzyme to deacylate serine–$tRNA^{Ala}$ molecules, whereas the capacity to recognize alanine and catalyse appropriate aminoacylation reactions was unaffected.

To investigate the functional consequences of this reduced editing capacity the researchers examined the effects of high serine concentrations on cultured fibroblasts. Cell viability was reduced in mutant fibroblasts, accompanied by the intracellular accumulation of polyubiquitylated proteins indicative of protein misfolding.

In vivo, protein aggregates were observed in the Purkinje cells of *Sti* mice. Positive staining of Purkinje cells for ubiquitin and molecular chaperones, which are involved in the degradation of misfolded proteins, together with the presence of autophagosomes suggested that the cells were attempting to clear the aberrant proteins. An upregulation of molecules associated with endoplasmic reticulum stress provided a clue as to how the misfolded proteins might affect cell viability.

Given the ubiquitous nature of AARS, the restriction of

DEVELOPMENT

Channels show the way

Electrical activity, mediated by a variety of voltage-gated ion channels, guides the development of embryonic neurons. For example, voltage-gated calcium channels are known to regulate several aspects of neuronal differentiation; however, the role of voltage-gated sodium (Nav) channels in developing neurons has remained elusive. Now, Pineda and colleagues describe cell-autonomous and non-cell-autonomous roles for Nav1.6a in the axonal outgrowth of zebrafish motor neurons.

When spinal cord neurons extend axons into the periphery, spontaneous activity is important for axonal outgrowth and pathfinding. A possible role for Nav channels in this process was suggested by the aberrant sprouting of motor nerve terminals and paralysis seen in a mouse mutant lacking functional Nav1.6. In zebrafish, the gene encoding Nav1.6a, *scn8aa*, is expressed early in the developing spinal cord. Taking advantage of a gene knockdown method that has been successfully used in zebrafish — antisense morpholinos, which are stable oligonucleotides that block the translation or splicing of RNA — the authors investigated the specific role and mechanisms of Nav1.6a in spinal cord neuron development.

They detected *scn8aa* transcripts in several populations of spinal neurons, including two classes of motor neuron: the ventrally projecting subtype of primary motor neurons known as CaPs, and a class of dorsally projecting secondary motor neurons (SMNs). Injection of antisense morpholinos at the 1–2 cell stage led to a knockdown of Nav1.6a protein in these neurons and disrupted the outgrowth and axonal pathfinding of discrete groups of motor neurons.

The dorsally projecting SMNs that normally express *scn8aa* showed delayed axonal outgrowth, indicating a cell-autonomous role for Nav1.6a in the axonal development of these neurons. However, no defects were seen in CaPs. Surprisingly though, ventrally projecting SMNs — which do not express *scn8aa* — were affected, with an increase in axon branching and a decrease in synapse formation.

> “These results reveal a function for Nav1.6a in the axonal outgrowth and pathfinding of secondary motor neurons.”

neurodegeneration to cerebellar Purkinje cells seems counterintuitive. Potential explanations proposed by the authors include the possibility that Purkinje cells possess a reduced capacity to degrade such proteins or that other cell types make greater use of compensatory editing enzymes.

This study highlights the importance of editing during protein translation, showing that loss of this function can lead to the synthesis of misfolded proteins. As such defects might arise spontaneously or through inherited mutations, this mechanism might contribute to numerous neurodegenerative conditions. Moreover, therapeutics that boost endogenous editing activity might slow the progress of neurodegeneration.

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ORIGINAL RESEARCH PAPER Lee, J. W. *et al.* Editing-defective tRNA synthetase causes protein misfolding and neurodegeneration. *Nature* 13 Aug 2006 (doi:10.1038/nature05096)

This indicates an additional non-cell-autonomous role for Nav1.6a in motor neuron development.

Supporting this, a mosaic analysis, in which single cells were injected with morpholino and a lineage tracer, showed that when the Nav1.6a morpholino was present just in ventrally projecting SMNs, their axons developed normally; however, when the Nav1.6a morpholino was present in even just a few other neurons, but absent in ventrally projecting SMNs, some defects were seen.

These results reveal a function for Nav1.6a in the axonal outgrowth and pathfinding of SMNs. It will be interesting to determine the mechanisms by which neurons containing this channel affect the development of others without it, and the importance of other voltage-gated ion channels in the development of neuronal populations throughout the brain.

Daniel McGowan

ORIGINAL RESEARCH PAPER Pineda, R. H. *et al.* Knockdown of $Na_v1.6a$ Na^+ channel affects zebrafish motoneuron development. *Development* **133**, 3827–3836 (2006)

PSYCHIATRIC DISORDERS

ProTREKtion against depression

Serotonergic neurotransmission is involved in both the pathophysiology of depression and the effects of antidepressants such as selective serotonin reuptake inhibitors (SSRIs), but the underlying molecular mechanisms are poorly understood. Writing in *Nature Neuroscience*, Lazdunski and colleagues show that knockout of the potassium channel TREK1, which is regulated by serotonin and also inhibited by some SSRIs, has antidepressant effects, and so could be a potential target for novel antidepressants.

> As elimination of TREK1 induces an antidepressant-like phenotype, novel TREK1 blockers could have antidepressant effects.

Several lines of evidence point to a role for TREK1 in serotonin function. TREK1 is a two-pore domain potassium ion channel and a member of a distinct class of ion channels involved in setting the resting potential and regulating the overall excitability of individual neurons. The TREK1 ion channel is regulated by G-coupled receptors including several types of serotonin receptor, is homologous with other ion channels controlled by serotonin and is expressed in areas of the brain believed to mediate cognitive aspects of depression.

To explore the function of TREK1, the authors studied TREK1-deficient mice in a battery of behavioural models that have been shown to be useful in predicting the antidepressant activity of drugs. In all the models, mice lacking TREK1 were more resistant to developing symptoms linked to depression than were wild-type mice. Moreover, the behaviour of TREK1-deficient mice closely resembled that of wild-type mice that had been treated with SSRIs.

Electrophysiological tests of serotonin-responsive neurons in the brain showed that, compared with wild-type neurons, the neurons of TREK1-deficient mice had an increased level of activation, as if they had been chronically treated with an antidepressant. Consistent with the involvement of serotonin, depletion of the neurotransmitter using a combination of agents to block its synthesis, reuptake and recycling reversed the depression-resistant phenotype of TREK1-deficient mice.

Mice lacking the related potassium ion channel TRAAK did not show an antidepressant phenotype in animal models, displayed normal serotonin transmission and remained sensitive to treatment with antidepressants, suggesting that the effects observed following TREK1 deletion are not a general property of this class of ion channel.

As elimination of TREK1 induces an antidepressant-like phenotype, novel TREK1 blockers could have antidepressant effects. Indeed, fluoxetine and other SSRIs partially inhibit TREK1 at brain concentrations that are comparable with those achieved following clinical dosing in humans, suggesting that the action of these drugs might be mediated in part through TREK1. The role of TREK1 in processes such as neuroprotection raises concerns about potential side effects, but it might offer an opportunity to develop drugs that are efficacious in the considerable proportion of patients who are unresponsive to current therapies.

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ORIGINAL RESEARCH PAPER Heurteaux, C. *et al.* Deletion of the background potassium channel TREK-1 results in a depression-resistant phenotype. *Nature Neuroscience* 13 August 2006 (doi:10.1038/nn1749)
FURTHER READING Kennard, L. E. *et al.* Inhibition of the human two-pore domain potassium channel, TREK-1, by fluoxetine and its metabolite norfluoxetine. *Br. J. Pharmacol.* **144**, 821–829 (2005) | Wong, M.-L. & Licinio, J. From monoamines to genomic targets: a paradigm shift for drug discovery in depression. *Nature Rev. Drug Discov.* **3**, 136–151 (2004)