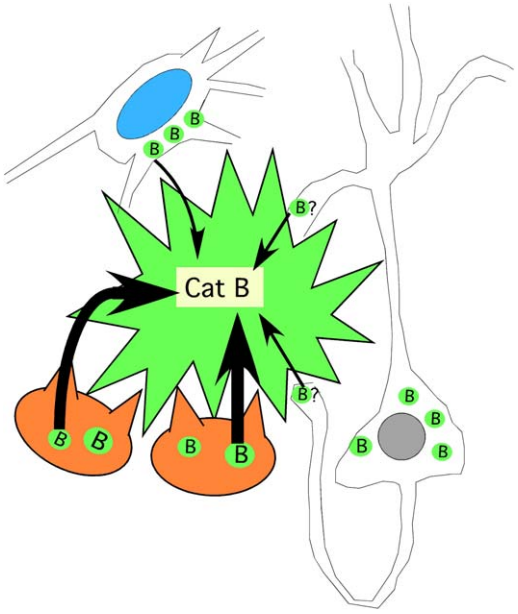

Figure 1. Schematic Diagram Showing the Role of Cathepsin B in Amyloid Clearance

Mueller-Steiner et al. demonstrate that cathepsin B (CatB) can clear fibrillar amyloid-β. CatB can be secreted (arrows) into plaques (green star) and promote the degradation of extracellular amyloid-β. A major potential source of CatB in plaques may be microglia (orange), which secrete avidly in vitro, but other cell types (astrocytes, blue top left) and neurons (gray, right) may also contribute CatB to plaques. The green circles with "B" represent endosomes or lysosomes containing CatB, where it may degrade intracellular Aβ. It is unclear whether CatB secreted from neurons is primarily dendritic or nerve terminal in origin.

to plaques (Simard et al., 2006). However, there is reason to be cautious about overexpression of CatB, which has been reported to contribute to neurotoxic effects of microglia (Gan et al., 2004; Kingham and Pocock, 2001). Of course, there may be other ways to increase intracellular CatB expression with small molecules. Whether or not the new findings lead to CatB-based therapeutics, the evidence for this normal clearance tale for Aβ aggregates is clearly an important new chapter for the AD research field. And with any luck, this will not end as just a Cat in mouse story.

Greg M. Cole[1,2] and Sally A. Frautschy[1,2]
[1]Greater Los Angeles Healthcare System
Veterans Administration Medical Center
Geriatric Research Education Clinical Center
North Hills, California 91343
[2]Departments of Medicine and Neurology
University of California, Los Angeles
Los Angeles, California 90095

Selected Reading

Bard, F., Barbour, R., Cannon, C., Carretto, R., Fox, M., Games, D., Guido, T., Hoenow, K., Hu, K., Johnson-Wood, K., et al. (2003). Proc. Natl. Acad. Sci. USA *100*, 2023–2028.

Billings, L.M., Oddo, S., Green, K.N., McGaugh, J.L., and LaFerla, F.M. (2005). Neuron *45*, 675–688.

Eckman, E.A., and Eckman, C.B. (2005). Biochem. Soc. Trans. *33*, 1101–1105.

Gan, L., Ye, S., Chu, A., Anton, K., Yi, S., Vincent, V.A., von Schack, D., Chin, D., Murray, J., Lohr, S., et al. (2004). J. Biol. Chem. *279*, 5565–5572.

Huang, S.M., Mouri, A., Kokubo, H., Nakajima, R., Suemoto, T., Higuchi, M., Staufenbiel, M., Noda, Y., Yamaguchi, H., Nabeshima, T., et al. (2006). J. Biol. Chem. *281*, 17941–17951.

Kingham, P.J., and Pocock, J.M. (2001). J. Neurochem. *76*, 1475–1484.

Mueller-Steiner, S., Zhou, Y., Arai, H., Sun, B., Roberson, E.D., Chen, J., Wang, X., Yu, G., Esposito, L., Mucke, L., and Gan, L. (2006). Neuron *51*, this issue, 703–714.

Nixon, R.A., and Cataldo, A.M. (2006). J. Alzheimers Dis. *9*, 277–289.

Simard, A.R., Soulet, D., Gowing, G., Julien, J.P., and Rivest, S. (2006). Neuron *49*, 489–502.

Takahashi, R.H., Almeida, C.G., Kearney, P.F., Yu, F., Lin, M.T., Milner, T.A., and Gouras, G.K. (2004). J. Neurosci. *24*, 3592–3599.

Yan, P., Hu, X., Song, H., Yin, K., Bateman, R.J., Cirrito, J.R., Xiao, Q., Hsu, F.F., Turk, J.W., Xu, J., et al. (2006). J. Biol. Chem. *281*, 24566–24574.

DOI 10.1016/j.neuron.2006.09.005

Inherited Neuropathies: New Genes Don't Fit Old Models

Mutations in *GARS* cause dominantly inherited neuropathies in humans. *GARS* encodes glycyl-tRNA synthetase, the enzyme that couples glycine to its tRNA. In this issue of *Neuron*, Seburn et al. have identified and characterized a mutant mouse with a dominantly inherited axonal neuropathy caused by a *Gars* mutation that is inferred to have a gain of function.

In 1886, Charcot, Marie, and Tooth described patients who are now understood as having a dominantly inherited neuropathy that affects myelinated motor and sensory axons in a length-dependent manner. This disorder is usually called Charcot-Marie-Tooth disease, or simply CMT, and is one of the most common inherited neurological diseases (Lupski and Garcia, 2001; Shy et al., 2005; Wrabetz et al., 2004). Like most kinds of neuropathy, CMT is characterized by progressive dysfunction that is related to the length of the affected axons. The longest sensory and motor axons are affected first and are more affected over time. This progressive, length-dependent dying back of motor and sensory axons produces the classic clinical picture of distally accentuated weakness, atrophy, and sensory loss.

By 1980, a few different kinds of CMT were clinically recognized. The demyelinating form was termed CMT1 and is characterized by slowed nerve conduction velocities and evidence of demyelination and remyelination in nerve biopsies. The neuronal/axonal form was termed CMT2, characterized by relatively normal conduction velocities and axonal loss but not demyelination/remyelination in nerve biopsies. The more severe kinds of demyelinating neuropathy that start in infancy or childhood retained different names (congenital hypomyelinating neuropathy or Dejerine-Sottas neuropathy, respectively), and their relationship to CMT was not understood. The terms hereditary motor neuropathies and

distal spinal muscular atrophy (even the names underscore the uncertainty of whether motor neurons or just their axons are the locus of disease) were used for cases in which motor but not sensory axons are affected in a length-dependent manner. Similarly, the term hereditary sensory neuropathy was given to a group of disorders in which the sensory neurons/axons are disproportionately more affected than are motor neurons/axons.

The molecular basis of these disorders has been increasing illuminated over the last 25 years. Each disorder shows remarkable genetic heterogeneity (www.molgen.ua.ac.be/CMTMutations)—CMT1 (mutations in five different genes), CMT2 (including three kinds of so-called dominant intermediate CMT; 14 different genes), hereditary sensory neuropathy (six), hereditary motor neuropathy (eight), Dejerine-Sottas neuropathy and congenital hypomyelinating neuropathy (five), and recessive demyelinating (nine) and axonal (four) neuropathies. Further, different mutations in the same gene produce different phenotypes. For example, dominant mutations in *MPZ*, the gene that encodes P0, a structural protein of the myelin sheath, produce several distinct phenotypes, usually CMT1, but also CMT2, Dejerine-Sottas neuropathy, and congenital hypomyelinating neuropathy.

This explosion of knowledge is challenging to master but presents opportunities to clinicians and scientists alike. Informed clinicians can provide the precise molecular diagnosis to patients, and the nature of the genetic defect may suggest novel treatments. For example, duplication of the *PMP22* gene (the most common cause of CMT1) probably causes demyelination because three (instead of two) copies of the gene result in modest overexpression of peripheral myelin protein 22 kDa, thereby destabilizing the myelin sheath. Thus, effective therapy might be achieved by modestly decreasing the expression of PMP22 in a variety of ways (Passage et al., 2004; Sereda et al., 2003). For scientists, the genes that cause hereditary neuropathies provide unique insights about which molecules are essential for the proper functioning of myelinated axons. The molecular defects that lead to neuropathy are not limited to those that cause CMT or one of its variants, however, as there are dozens of inherited diseases, including many kinds of hereditary ataxia and spastic paraparesis, in which neuropathy is part of the syndrome.

Because interactions between two different cell types—myelinating Schwann cells and neurons—generate myelinated axons, it could have been anticipated that there are two kinds of CMT. Demyelinating forms arise from abnormalities that are intrinsic to myelinating Schwann cells themselves, and axonal forms are the result of genetic defects that primarily affect neurons and especially their axons. Given their known roles in myelinating Schwann cells and axons, some genes could have been predicted to cause neuropathy because they encode components that are specifically expressed by myelinating Schwann cells (e.g., P0, PMP22, periaxin) or neurons (e.g., neurofilament light subunit). Many of the genes that cause CMT, however, are expressed in multiple cells types (e.g., *Connexin32*, *NDRG1*) or even ubiquitously (e.g., *Mitofusin2*, *RAB7*, *GARS*). Why mutations in these widely expressed genes result in peripheral neuropathy alone and not a more pervasive disorder remains mysterious. The case of *GARS* is particularly perplexing, as glycine tRNA is required by all cells, and *GARS* is the only gene that is known to possess glycyl-tRNA synthetase activity.

In this issue of *Neuron*, Seburn et al. (Seburn et al., 2006) report their studies of *Nmf249* mice, which were identified at the Jackson Laboratory owing to their dominantly inherited phenotype of progressive neuromuscular dysfunction that begins by 3 weeks of age. These workers mapped the gene to a 1.9 mb region on chromosome 6 that contains the murine ortholog of *GARS*. Sequencing the *Gars* gene revealed a mutation that is predicted to replace Pro with LysTyr at 278. Although this Pro residue is phylogenically conserved, this mutation does not affect the activity of glycyl-tRNA synthetase in a biochemical assay.

Seburn et al. (2006) thoroughly document an age-related decrease in the number of large myelinated motor and sensory axons in $Gars^{Nmf249/+}$ mice. The loss of myelinated axons is length dependent, as myelinated motor axons are lost in distal nerves but not in the ventral roots, and there is a length- and time-dependent decrease in motor innervation of distal versus proximal muscles. The findings that most of the axonal loss occurs by 1 month of age and that mice that survive this period can be long lived have an uncanny similarity to clinical descriptions of some kinds of CMT. These pathological alterations are presumed to be the basis for physiological abnormalities in the $Gars^{Nmf249/+}$ mice—reduced amplitudes of muscle compound action potentials and a surprisingly large reduction in sciatic nerve conduction velocity in the absence of demyelination or remyelination. These results demonstrate that $Gars^{Nmf249/+}$ mice are a genetically authentic animal model of CMT caused by dominant *GARS* mutations.

The availability of mice with another *Gars* allele (*XM256*) that is predicted to cause loss of function enabled Seburn et al. (2006) to evaluate further the effects of the *NMF249* allele. Unlike $Gars^{Nmf249/+}$ mice, $Gars^{XM256/+}$ mice do not develop neuropathy, further evidence that the dominant effect of the *NMF249* allele is not the result of haplotype insufficiency. Like $Gars^{Nmf249/Nmf249}$ and $Gars^{XM256/XM256}$ mice, $Gars^{Nmf249/XM256}$ mice are embryonic lethal; the failure of a null allele (*XM256*) to complement a dominant allele (*NMF249*) indicates that the wild-type protein compensates or competes with the mutant protein in a pathogenic gain of function. Variability of this dominant effect may be the biological basis for why some *GARS* mutations do not appear to affect myelinated sensory axons and hence cause a motor neuropathy.

These results support the hypothesis that the phenotype of $Gars^{Nmf249/+}$ mice is caused by a novel pathogenic function of the mutant glycyl-tRNA synthetase. The mechanism is unknown, and possibilities include noncanonical functions of glycyl-tRNA synthetase, as these have been documented for other tRNA synthetases. One presumes that the molecular mechanisms of human and mouse glycyl-tRNA synthetase mutants may relate to how dominant mutations in *YARS* (which encodes tyrosyl-tRNA synthetase) cause a different kind of CMT (Jordanova et al., 2006).

As the authors point out, there are interesting similarities between the $Gars^{Nmf249/+}$ model of CMT4D and mouse models of amyotrophic lateral sclerosis (ALS)

caused by dominant *SOD1* mutations. Like *Gars*$^{Nmf249/+}$ mice, mice expressing dominant human SOD1 mutants develop a length-dependent motor neuropathy that was not anticipated from clinical investigations. Because of the difficulties in distinguishing neuropathies from neuronopathies in humans, careful evaluation of animal models may reveal that axonal degeneration is the primary defect in a number of neurodegenerative diseases. Although many of these diseases are defined clinically owing to the particular populations of affected neurons, axonal disease may be a final common pathway that links them (Roy et al., 2005). A steady supply of new genetic causes of neuropathy and informative animal models will facilitate our understanding of the causes and treatments of neuropathy, both inherited and acquired, and perhaps even more complex disorders.

Steven S. Scherer[1]
[1] William N. Kelley Professor
Department of Neurology
464 Stemmler Hall
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania 19104

Selected Reading

Jordanova, A., Irobi, J., Thomas, F.P., VanDijck, P., Meerschaert, K., Dewil, M., Dierick, I., Jacobs, A., DeVriendt, E., Guergueltcheva, V., et al. (2006). Nat. Genet. *38*, 197–202.

Lupski, J.R., and Garcia, C.A. (2001). In The Metabolic & Molecular Basis of Inherited Disease, C.R. Scriver, A.L. Beaudet, W.S. Sly, D. Valle, B. Childs, and K.W. Kinzler, eds. (New York: McGraw-Hill), pp. 5759–5788.

Passage, E., Norreel, J.C., Noack-Fraissignes, P., Sanguedolce, V., Pizant, J., Thirion, X., Robaglia-Schlupp, A., Pellissier, J.F., and Fontes, M. (2004). Nat. Med. *10*, 396–401.

Roy, S., Zhang, B., Lee, V.M.Y., and Trojanowski, J.Q. (2005). Acta Neuropathol. (Berl.) *109*, 5–13.

Seburn, K.L., Nangle, L.A., Cox, G.A., Schimmel, P., and Burgess, R.W. (2006). Neuron *51*, this issue, 715–726.

Sereda, M.W., Horste, G.M.Z., Suter, U., Uzma, N., and Nave, K.A. (2003). Nat. Med. *9*, 1533–1537.

Shy, M.E., Lupski, J.R., Chance, P.F., Klein, C.J., and Dyck, P.J. (2005). In Peripheral Neuropathy, P.J. Dyck and P.K. Thomas, eds. (Philadelphia: Saunders), pp. 1623–1658.

Wrabetz, L., Feltri, M.L., Kleopa, K.A., and Scherer, S.S. (2004). In Myelin Biology and Disorders, R.A. Lazzarini, ed. (San Diego: Elsevier), pp. 905–951.

DOI 10.1016/j.neuron.2006.09.008

Nervous Rac: DOCK7 Regulation of Axon Formation

Microtubules play an important role in neuronal polarity. In this issue of *Neuron*, Watabe-Uchida et al. link a novel Rac-mediated pathway that regulates microtubule dynamics to axon formation.

Polarization of most vertebrate neurons begins with the specification of one neurite as the axon while other neurites subsequently develop into dendrites. Although the molecular mechanisms that determine how a neuron specifies an axon and dendrites remain poorly understood, it has become clear that the establishment and maintenance of neuronal polarity depends upon the microtubule network. Many signaling cascades influence microtubule dynamics in the developing axon. Targets of these signaling pathways include microtubule motor proteins (Wiggin et al., 2005) as well as structural microtubule-associated proteins (MAPs) (Dehmelt and Halpain, 2004). When the function of these molecules is perturbed, neuronal polarity is disrupted. This type of disruption often results in neurons with multiple axons, multiple dendrites, or many long neurites that lack axonal or dendritic characteristics (Arimura and Kaibuchi, 2005; Wiggin et al., 2005). The signaling pathways upstream of the MAPs, however, are not well delineated.

In this issue of *Neuron*, studies from the Van Aelst (Watabe-Uchida et al., 2006) group provide new insights into a signaling pathway upstream of a specific MAP that is mediated by a novel Rac-activating protein, DOCK7. In other cell types, Rac has been shown to influence the microtubule cytoskeleton (Wittmann et al., 2004). However, little is known about its effect on microtubule dynamics in neurons. Rac has been implicated in the regulation of neuronal polarity. Perturbation of Rac preferentially affects the outgrowth of axons but not dendrites in vivo (Luo et al., 1996). The Par-6/Par-3/aPKC polarity complex, which functions in axon specification, may directly influence Rac activation by regulating Rac-GEFs (guanine nucleotide exchange factors) (Nishimura et al., 2005). It is not known whether these Rac-associated signaling pathways eventually influence the microtubule cytoskeleton, and if so, through which MAPs.

The report by Watabe-Uchida et al. identifies a novel Rac GTPase activator, DOCK7, that plays a crucial role in axon formation. A member of the DOCK180-related superfamily, DOCK7 is an unconventional GEF, directly associating with Rac through its DHR2 domain. Although DOCK180-related family members have been shown to be regulators of polarization in different cell types (Meller et al., 2005), DOCK7 is the first member found to play a critical role in the early stages of axon formation in hippocampal neurons. Watabe-Uchida et al. observe that DOCK7 is concentrated in a single neurite after immature neurites have formed. DOCK7 is then selectively localized to the axon that forms. This observation suggests that DOCK7 is involved in the initial specification of the axon. Overexpression of DOCK7 disrupts polarity by promoting multiple axon formation; knockdown of DOCK7 expression blocks the development of polarity, preventing the formation of an axon. The investigators determine that regulation of Rac activity by DOCK7 seems to be important in its ability to promote axon formation.

It is interesting to note that other Rac-specific GEFs, Tiam1 and STEF, have also been implicated in axon formation. The implication suggests that the spatial and temporal activity of Rac is important in axon specification (Kunda et al., 2001; Nishimura et al., 2005). If neurons have Tiam1 and STEF, why do they need DOCK7? Perhaps different extracellular stimuli determine the type of GEFs that activate Rac. Alternatively, these different GEFs may affect different downstream effector molecules that Rac binds to and activates. It will be