may be relevant for many more proteins, but it has never been recognized as such. Once again, glial cells have evoked important questions.

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Senseless makes sense for spinocerebellar ataxia-1

Vikram Khurana, Tudor A Fulga & Mel B Feany

Why are some neurons selectively targeted for death in neurodegenerative diseases? A recent paper combines genetics in the fruit fly and mouse to uncover mechanisms underlying the vulnerability of Purkinje cells in spinocerebellar ataxia-1.

Neurodegenerative diseases share many features, including a progressive loss of neurons and the formation of proteinaceous aggregates. These similarities have motivated research into common underlying pathogenic processes, including dysfunction of the ubiquitin-proteasome system, impaired axonal transport and oxidative stress. A recent paper in *Cell* by Hiroshi Tsuda and colleagues[1] reminds us that neurodegenerative diseases also have important features that distinguish them from one another, including the selective vulnerability of particular groups of neurons.

The authors focus on a type of spinocerebellar ataxia (SCA). SCAs are debilitating neurodegenerative diseases characterized by progressive gait incoordination and cerebellar atrophy. Tsuda *et al.* delineate a physical and functional interaction between the AXH domain of ataxin-1, a protein of unknown function, and the transcription factor known as Senseless in *Drosophila melanogaster* and Gfi-1 in vertebrates. The authors provide compelling evidence in animal models that this interaction contributes to the progressive demise of Purkinje neurons in SCA-1.

Autosomal-dominant polyglutamine (polyQ) expansion disorders, including Huntington disease and a number of SCAs, are all caused by the expansion of unstable CAG repeat sequences within the coding region of the causative gene[2]. Neurodegeneration accompanies the intraneuronal aggregation of the polyQ-expanded proteins in each disease. The dominant mode of inheritance, together with the recapitulation of disease phenotypes in overexpression but not knockout animal models, suggests a toxic gain-of-function mechanism whereby the expanded polyQ tract confers new molecular functions upon the causative protein. Notably, however, despite ubiquitous expression in the nervous system, only certain neuronal groups are targeted for death in these diseases. Furthermore, differing polyQ repeat lengths are required to initiate neurodegeneration in the different diseases. These differences strongly implicate sequences outside the CAG repeat region in disease pathogenesis.

Tsuda *et al.*[1] have now taken us a significant step closer to understanding the unique features of ataxin-1 that mediate degeneration of Purkinje cells in SCA-1. This disease is caused by a polyglutamine expansion in ataxin-1 and accompanied by nuclear aggregation of this protein in neurons. The authors previously showed that overexpressing human ataxin-1 (hAtx-1) with an expanded polyQ tract in *Drosophila* resulted in neurodegeneration[3]; further, they showed that phosphorylation of Ser776 by the kinase Akt is critical to toxicity by enabling an interaction with 14-3-3 and increasing hAtx-1 stability[4]. Tsuda *et al.*[1] now report that expressing the fly homolog of ataxin-1 (dAtx-1), but not a polyQ repeat alone, recapitulates hAtx-1–induced phenotypes in different fly tissues, albeit with reduced severity. Intriguingly, dAtx-1 does not contain a polyQ domain but shares an AXH (ataxin-1/HBP1) domain with hAtx-1, a domain recently implicated in RNA binding and self-association[5]. The authors further demonstrate that dAtx-1 physically interacts with the transcription factor Senseless (Sens) by means of this domain. An *in vitro* transcriptional assay and a functional analysis in the fly reveal that both Sens activity and protein abundance are downregulated by dAtx-1. Furthermore, expressing hAtx-1 with an expanded polyQ tract reduces Sens levels more potently than dAtx-1, whereas over-expressing the polyQ tract alone, or polyQ-expanded hAtx-1 with the AXH domain deleted, has no effect on Sens levels.

The study proceeds with a logical series of experiments relating the findings in *Drosophila* to a mouse model system, thus strengthening the relevance of AXH domain interactions to the human disease. The authors show that hAtx-1 binds to the vertebrate homolog of Sens, Gfi-1, also through its AXH domain. Importantly, Gfi-1 is maximally expressed in the nervous system within the Purkinje neurons of the cerebellum, one group of neurons that selectively degenerate in SCA-1. In mammalian cells, as in flies, Gfi-1 levels are downregulated by hAtx-1, an effect that is post-translational and depends on the ubiquitin-proteasome system. Significantly, these findings are recapitulated in a mouse model of SCA- 1, where expression of polyQ-expanded hAtx-1 in Purkinje cells leads to an early decrease in the abundance of Gfi-1, preceding Purkinje cell loss and ataxia. Furthermore, removing a single copy of *Gfi1* enhances the neurodegeneration phenotype in this model. In a final elegant proof-of-principle experiment, the authors show that a progressive loss of Purkinje neurons accompanies ataxia in *Gfi1* knockout mice, thus demonstrating that decreased Gfi-1 is sufficient to cause Purkinje cell loss.

These findings are important at multiple levels. Most directly, they suggest that the interaction between the AXH domain of hAtx-1 and Gfi-1 is important for mediating neurodegeneration and that this is potentially a therapeutic target. However, although the authors show that reducing Gfi-1 levels results in an enhancement of hAtx-1–induced neurodegeneration, establishing whether ectopic expression of Sens or Gfi-1 rescues neurodegeneration in flies or mice, respectively, would further strengthen the case for Gfi-1 stabilization as a potential treatment. Beyond

The authors are at the Department of Pathology at Brigham and Women's Hospital and Harvard Medical School, 77 Louis Pasteur Ave., Boston, Massachusetts 02115, USA.
e-mail: mel_feany@hms.harvard.edu

the direct therapeutic implications, however, this study provides critical evidence implicating sequences outside the polyQ region in the selectivity of neurodegeneration in polyQ disorders. Future studies might explore whether the hAtx-1–Gfi1-1 interaction mediates neurodegeneration in other cell populations vulnerable in SCA1, including the inferior olivary nucleus or spinocerebellar tracts, or whether other interactions are involved. In this regard it would be interesting to determine if, in addition to Purkinje neurons, these populations are also vulnerable in Gfi-1–null mice.

The methodology used by Tsuda *et al.*[1] also deserves attention. Whereas several models of autosomal-dominant neurodegenerative diseases have been made by transgenic overexpression of causative human genes in *Drosophila*[6], the present study adopts the normal fly protein as a starting point. The observation that expression of an expanded polyQ tract alone does not phenocopy certain phenotypes shared by dAtx-1 and hAtx-1–polyQ leads the authors to infer the existence of functionally important sequences outside the polyQ region. Flies certainly provide an ideal system to make such comparisons. Further, by recapitulating the biochemical and functional interactions in the mouse model system, the study supports the utility of *Drosophila* in modeling human diseases. Indeed, there are fly homologs for proteins, such as tau, that are involved in other neurodegenerative diseases, raising the possibility that such an approach might be fruitful for these diseases also.

How do we place the present findings in the context of what is known about the pathogenesis of SCA-1 and related disorders? PolyQ expansion clearly initiates the disease process. The model proposed in this study would implicate this expansion in the stabilization of hAtx-1, abnormally potentiating the AXH domain–Gfi-1 interaction. Neurotoxicity would follow from proteasomal degradation of Gfi-1 and transcriptional dysregulation (**Fig. 1**). Here, toxic gain-of-function is caused, not by the protein attaining an entirely aberrant function, but rather from the abnormal activation of a physiological pathway. In contrast, many previous studies have concentrated on abnormal interactions mediated by the polyQ tracts themselves. Because the nuclear localization of causative proteins is essential for neurotoxicity[7], these studies have focused on abnormal effects on transcription, either directly or through sequestration of transcription factors[8]. For example, the polyQ tract of hAtx-1 binds to the nuclear protein PQBP-1 in a manner dependent on polyQ tract length[9]. A resultant complex forming between hAtx-1, PQBP-1 and RNA polymerase II led to a decrease in basal transcription. Intriguingly, PQBP-1 is enriched in the cerebellum, and a polyQ-dependent interaction could therefore contribute to selective neuronal vulnerability in SCA-1 (ref. 10). Other groups have provided data supporting different toxic gain-of-function mechanisms in polyQ-associated diseases, including disruption of axonal transport and downregulation of survival pathways[11]. Wild-type ataxin-3 suppresses degeneration in multiple polyQ models in flies by proteasomal activation, implying not only that common mechanisms might operate in different polyQ-associated diseases, but that loss-of-function mechanisms might also be involved[12].

Taking these studies together, a picture emerges of both the common mechanisms in polyQ expansion disorders that could be mediated by the polyQ tracts themselves and the distinct effects that could be attributable to non–polyQ-encoding sequences. In keeping with this idea, transcriptional profiling and microarray studies reveal both common and distinct changes in different polyQ animal models[13]. A clear challenge for future studies is to try and integrate the multiple pathways downstream of polyQ expansion into a cohesive picture. For example, in SCA-1, do the implicated transcription factors function as a network influencing common downstream processes? Gfi-1, for example, downregulates proapoptotic genes[14]. Is it possible that downregulation of Gfi-1 by hAtx-1 leads to neuronal apoptosis? Could dysregulation of other transcription factors converge on apoptosis also? To guide investigations into events downstream of transcriptional dysregulation, it would clearly be useful to define the molecular pathways mediating cell death in these diseases, whether apoptotic or non-apoptotic. At present, the mechanisms of cell death in SCA-1 remain unclear, with neurodegeneration in the SCA-1 mouse seeming to be p53 dependent but not classically apoptotic[15].

In summary, Tsuda *et al.* present us with an important and thought-provoking study that provides hope for targeted SCA-1 therapies in the future. Establishing the direct relevance of a physiological protein interaction to disease pathogenesis has implications extending beyond SCA-1 and polyQ disorders to other neurodegenerative diseases for which toxic gain-of-function mechanisms have been proposed, including familial Alzheimer and Parkinson diseases. For mice and fruit flies, the message is loud and clear: resolving the similarities and differences among related neurodegenerative diseases should guarantee employment for many generations to come.

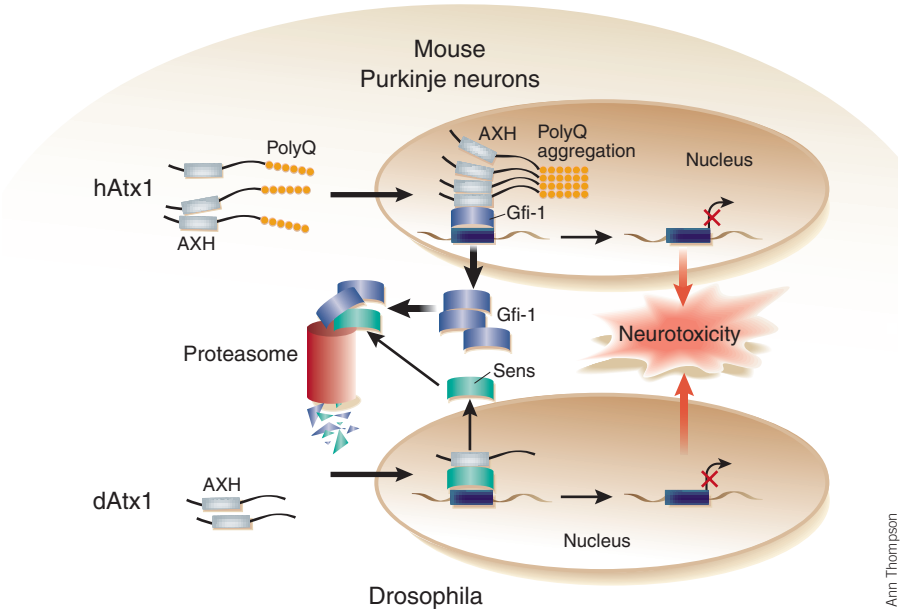

Figure 1 Tsuda *et al.* demonstrate homologous pathways that mediate ataxin-1–induced neurodegeneration in mouse and *Drosophila* models of SCA-1. In *Drosophila*, dAtx-1 (which lacks polyQ repeats) binds, through its AXH domain, to the transcription factor Senseless and targets it for proteasomal degradation. A homologous interaction, potentiated by abnormal polyQ expansion and aggregation, occurs between hAtx-1 and Gfi-1 in mouse Purkinje neurons. The resultant transcriptional dysregulation mediates neurotoxicity in both model systems. Direct dysregulation of transcription by polyQ-expanded repeats may also make an important contribution to neurotoxicity[9].

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How the brain recovers following damage

Yalçin Abdullaev & Michael I Posner

Individuals with neglect fail to process stimuli on the left. A new paper uses functional imaging to show that a restricted lesion, usually caused by a stroke, may influence the network of areas associated with attention shifts.

After right-hemisphere stroke, some people see objects in their world as having no left side (**Fig. 1**). In the acute stage immediately following the stroke, such individuals with 'spatial neglect' may fail to orient to people approaching from their left, to recognize their left arm as their own and to eat from the left side of their plate. How can a stroke to a local area of the brain be associated with such a mysterious array of symptoms?

In this issue, Corbetta *et al.*[1] report that the activity of an interconnected network of dorsal, ventral parietal and frontal areas may be influenced by comparatively restricted lesions of the ventral right hemisphere. The dorsal network includes the superior parietal lobe and the frontal eye fields, and the ventral network involves the temporal parietal junction and the ventral lateral prefrontal cortex[1]. In normal people, imaging studies show that this interconnected network is important for shifts of spatial attention[2].

The authors tracked the recovery of this network in individuals with neglect through successive functional magnetic resonance imaging (fMRI) scans taken while the patients performed a task. In an fMRI scanner, participants were instructed to direct their gaze to the center of the screen in front of them. An arrow appeared at this central point, directing the subjects to attend to either the left or the right side of the screen, without moving their eyes. Participants were then asked to press a button when they detected a target. The target appeared on the side indicated by the arrow most of the time, but occasionally it appeared on the other, unattended side. Normal participants have longer reaction times when the target appears on the side opposite to where they are directing their attention[3]. People with neglect show particularly long reaction times in response to targets on the left side when they are first cued to attend to the right[4]. In the acute stage immediately after the stroke, they may miss such targets completely, and even after many years they have a large deficit in reaction time[3].

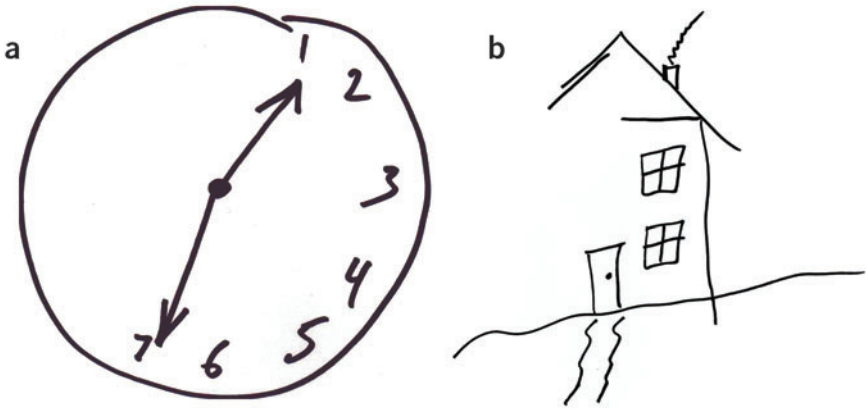

Figure 1 Sample drawings by individuals with spatial neglect. (**a**,**b**) The pictures demonstrate how they ignore their left visual field in trying to make simple line drawings of a clock (**a**) or a house (**b**).

The Corbetta *et al.* study[1] found a dramatic alteration in the pattern of activation in the parietal-frontal network four weeks after the stroke (the acute stage), even though the individual nodes showed no evidence of structural damage. Seven months later (in the chronic stage), the participants had considerably improved in their ability to orient and detect stimuli on the left. Functionally, the most striking change was that the dorsal right parietal lobe, which was not activated at all during the acute phase, was now strongly activated in the chronic phase. This was in contrast with an actual reduction of activity in similar areas in the left hemisphere. Therefore, the dorsal parietal area, which is critical for voluntary shifts of attention in normal people[2], was the only brain area that showed increased activity on the lesioned side from the acute to the chronic stage. This was accompanied by reduced activity in the non-lesioned hemisphere. This effect is likely to be responsible for the observed reduction in rightward bias from the acute to the chronic stage.

How do these parietal findings relate to what is found in visually specific areas of the cortex? Several studies[5] indicate that the source of attention effects (manifested as increased activity in visual cortex during stimulus detection) lies in parietal areas. The results of Corbetta *et al.*[1] show that activity in the left visual cortex is reduced in the chronic phase as compared to the acute phase, whereas right hemisphere visual cortex activation is increased. These findings mirror those in the parietal lobe.

Individuals recovering from neglect also

Yalçin Abdullaev and Michael I. Posner are in the Department of Psychology, University of Oregon, Eugene, Oregon 97403, USA.
e-mail: mposner@darkwing.uoregon.edu