the preference of superficial pyramidal cells in the rat visual cortex to connect with each other if they receive correlated input from layer 2/3 and layer 4 pyramidal cells[14]. The observed choices of partners would follow from a simple application of Hebb's rule were it not for the additional observation that pairs of pyramidal cells receive correlated input from layer 5 even if they are not connected[14]. On the basis of Yu *et al.*'s[2] findings, the connected pyramidal cells might be cousins whose synapse formation is triggered by Hebbian learning. However, it is improbable that local circuit construction is restricted to family business involving close relatives. Each cortical neuron receives and forms synapses with hundreds of other neurons, and there must be many neurons who are not close relatives that nevertheless form synapses with each other (as suggested by Yu *et al.*'s[2] findings). Thus, the question remains open as to the general reasons for observed biases in the formation of connections.

Yu *et al.*'s[2] study has some obvious limitations. One is that the circuits were only studied until P17, after which major circuit remodeling still occurs. It would be interesting to know what happens at later stages in development and in the adult cortex, where synaptic plasticity continues. It would also be useful to understand if there are morphological differences between siblings and nonsiblings. Preferential connectivity could be influenced by the particular layout of the axonal and dendritic trees of siblings, such that the overlap is increased, leading to an increased probability of connection[15]. A comparison of the branching geometry of siblings and nonsiblings might give some insights into this issue. What is the functional benefit of a higher percentage sibling connection? Siblings consistently connected across cortical layers are likely to provide spatial patterns of correlated neural firing. As with a scaffold, such correlation patterns might be necessary for the subsequent Hebbian sculpting of the full neural circuits during development.

Sperry's[3] original proposal of a cortical network architecture specified by chemospecific markers has been dismissed on the grounds that the number of required markers would exceed the information capacity of the genome[3]. Yu *et al.*'s[2] study breathes new life into a local version of this idea, where only the connections between siblings are specified in this way. However, whether each sibling uses a unique set of marker(s) or a chemospecific gradient across the family tree is established is an open question. The identity of the 'words' and 'syntax' of the secret language of siblings remains a missing piece in the cortical puzzle.

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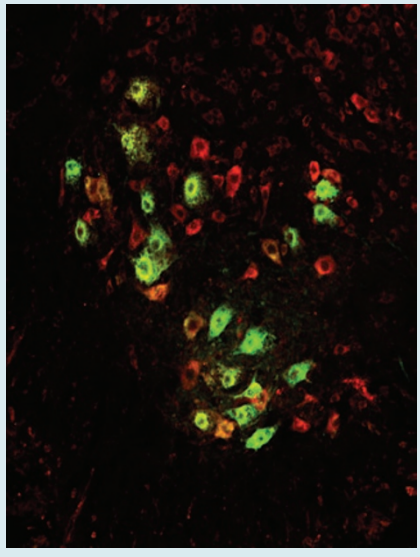
Motoneurons buckling under stress



Amyotrophic lateral sclerosis (ALS) selectively affects motoneurons. This selectivity is seen even for certain familial cases of ALS (fALS) that are caused by mutations in a ubiquitously expressed gene, SOD1, which codes for a superoxide dismutase enzyme that is important for cells' antioxidant defenses. Pico Caroni's laboratory previously found that, in mice expressing the human fALS mutation SOD1^{G93A}, the fast fatigable (FF) motoneurons die early during the course of the disease, whereas the fast fatigue–resistant (FFR) motoneurons survive longer and the slow motoneurons are largely resistant to degeneration.

On pp. 627–636 of this issue, Saxena *et al.* studied gene expression patterns in hopes of understanding why FF motoneurons are particularly prone to degeneration. Because FF, FFR and slow motoneurons selectively innervate particular muscles, the authors were able to separately label FF cells and a mixed FFR/slow population using retrograde tracers. The two sets of neurons were laser-microdissected from wild-type and SOD1^{G93A} transgenic mice at several time points preceding the onset of axonal loss. Microarray analysis revealed the expression of stress indicators in 12-d-old FF motoneurons. At 32 d of age, genes involved in the unfolded protein response (UPR) were strongly upregulated. The UPR preceded the initial loss of peripheral FF axons by about 20 d. Very similar patterns of stress and UPR gene induction, preceding denervation by 20–30 d, were seen in FF motoneurons from two other SOD1 mutant transgenic fALS model mouse lines.

All cells in the SOD1^{G93A} mice express high levels of mutant, misfolding SOD1 protein. Both vulnerable and resistant motoneurons (but not other cells in the spinal cord) similarly accumulated ubiquitinated misfolded protein over time. In the vulnerable FF motoneurons, this accumulation was followed by the induction of UPR genes within a few days. A subgroup of the resistant population upregulated UPR genes approximately 4 weeks later, followed by axon degeneration another 4 weeks after that. The figure here shows a section of lumbar spinal cord from a 55-d-old SOD1^{G93A} mouse. Highly vulnerable motoneurons strongly express the UPR marker phospho-eIF2α (green). Resistant motoneurons at this age also show signs of endoplasmic reticulum stress, indicated by immunostaining for BiP (red), but do not yet express UPR genes.

Although the authors' analysis does not explain why FF motoneurons are so particularly vulnerable to damage by mutant SOD1, this careful longitudinal analysis of gene expression patterns pinpoints what seems to be a watershed mechanism: the induction of the UPR genes. Future work will look into the exact regulation of UPR genes and will hopefully reveal the reason for selective motoneuron vulnerability in ALS.

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