IN BRIEF

DEVELOPMENT

Timing of CNS cell generation: a programmed sequence of neuron and glial cell production from isolated murine cortical stem cells.

Qian, X. *et al. Neuron* 28, 69–80 (2000)

The first lineage analysis of a vertebrate neural stem cell. Qian *et al.* studied individual cortical stem cells in culture and determined the fate of their descendants using long-term video microscopy. They observed that neurogenesis preceded gliogenesis. Initially, stem cells divide asymmetrically and produce a neuroblast and another stem cell. Later, the stem cells lose the potential to produce neuroblasts and enter into a proliferative state able to generate glia.

SYNAPTIC PLASTICITY

Learning-induced LTP in neocortex.

Rioult-Pedotti, M. -S. *et al. Science* 290, 533–536 (2000)

Previous attempts to interfere with learning by saturating synaptic efficacy have not yielded conclusive results. Rioult-Pedotti *et al.* used the converse strategy and found that motor learning interferes with subsequent induction of long-term potentiation (LTP) in the motor cortex, consistent with the idea that LTP is involved in learning. In addition, they observed that training does not shift the upper limit of LTP magnitude, indicating that synapses may normally operate within a constant range of efficacy.

ION CHANNELS

Mechanisms for activation and antagonism of an AMPA-sensitive glutamate receptor: crystal structures of the GluR2 ligand binding core.

Armstrong, N. & Gouaux, E. *Neuron* 28, 165–181 (2000)

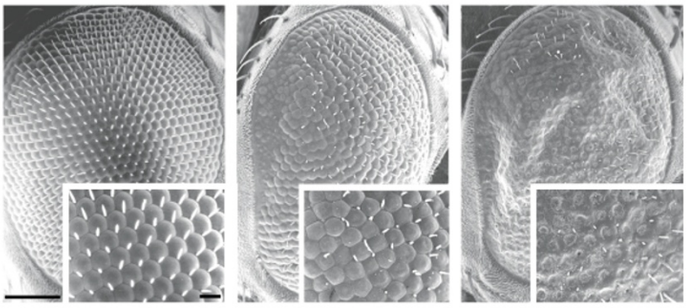
The authors solved the crystal structure of the GluR2 ligand-binding core in the free state and in the presence of various ligands. The binding of a full agonist induced a larger degree of domain closure than a partial agoinst. An antagonist, in turn, caused minimal closure of the core. These findings indicate that the level of channel activation may depend directly on the extent of domain closure. In addition, the binding domain packed as a dimer in the crystals, indicating that GluR2 may assemble as a dimer of dimers.

DEVELOPMENT

Pax6 activity in the lens primordium is required for lens formation and for the correct placement of a single retina in the eye.

Ashery-Padan, R. *et al. Genes Dev.* 14, 2701–2711 (2000)

The transcription factor Pax6 is crucial for eye formation. To dissociate the role of this factor on the development of the different eye components, the authors generated mice lacking *Pax6* exclusively in the lens surface ectoderm. Although lens induction occurred in these mice, its further development was arrested. Notably, the absence of lens led to the formation of several independent retinas, pointing to a direct role of the lens in controlling retinal development.



The expression of ataxin-1 causes cell death in the *Drosphila* eye. Wild-type eye, left; eye expressing wild-type ataxin-1, middle; eye expressing mutant ataxin-1, right. Adapted, with permission, from *Nature* **408**, 101–106 (2000) © Macmillan Magazines Ltd.

NEURODEGENERATION

Down the ataxin-1 track

Spinocerebellar ataxia type 1 (SCA1) is a neurodegenerative disorder caused by the expansion of a glutamine tract in the protein ataxin-1. As with other polyglutamine disorders, the involvement of the mutant protein in pathogenesis is beyond doubt. What is much less clear, however, is the mechanism by which the polyglutamine tract expansion leads to neuronal death. Although aggregation of ataxin-1 seems to be an initial step, the events downstream of aggregation are unknown, curtailing our chances to develop strategies to prevent cell death. Now, Fernandez-Funez *et al.* have taken an initial look at the factors capable of modifying ataxin-1-induced neurodegeneration by creating transgenic flies that express the human version of the mutant, full-length protein.

The expression of mutant *ataxin-1* in the eye or in the ventral nerve cord of transgenic flies caused progressive cell degeneration and was accompanied by the presence of cellular inclusions analogous to those found in SCA1. This observation allowed the authors to conduct a genetic screen to identify genes capable of suppressing or enhancing the phenotype of the mutant flies. Among the genes they identified, some belonged to pathways already implicated in polyglutamine-induced neurodegeneration, such as the ubiquitin and the protein-folding pathways, further highlighting the strength of the approach.

More importantly, the screen led Fernandez-Funez *et al.* to find genes from pathways not previously known to participate in cell death, which could actually suppress the ataxin-1-induced phenotype. One of these genes caused the overproduction of glutathione-*S*-transferase, an enzyme involved in the cellular response to oxidative stress. A second gene was associated with the overexpression of a protein analogous to known components of the nuclear pore, an intriguing finding considering the nuclear accumulation of ataxin-1 aggregates. A third suppressor gene encoded a transcriptional cofactor and, in fact, the screen revealed some other transcriptional cofactors that have the opposite effect and actually exacerbate the phenotype. This indicates that alterations in RNA processing may be involved in the degenerative process.

The unexpected observation that wild-type ataxin-1, which is innocuous in humans, caused mild degeneration in transgenic flies could be related to the protein levels found in the cells of the different organisms. Alternatively, this unexpected effect could be the manifestation of differences between fly and human in the cellular context in which ataxin-1 is expressed. Although these putative differences would need to be characterized to define the potential of this new animal model, the identification of new downstream pathways involved in neurodegeneration opens the door to developing treatments not against the disease trigger, but aimed to lessen the cytotoxic effects of the pathology and slow the decline caused by the polyglutamine disorders.

Juan Carlos López

References and links

ORIGINAL RESEARCH PAPER Fernandez-Funez, P. *et al.* Identification of the genes that modify ataxin-1-induced neurodegeneration. *Nature* **408**, 101–106 (2000)
FURTHER READING Gusella, J. F. & MacDonald, M. E. Molecular genetics: uncovering polyglutamine triggers in neurodegenerative disease. *Nature Rev. Neurosci.* **1**, 109–115 (2000)