This Week in The Journal

Ankyrin-R, Spectrin β3, K_V3.3, and Spinocerebellar Ataxia

Sharon R. Stevens, Meike E. van der Heijden, Yuki Ogawa, Tao Lin, Roy V. Sillitoe, et al.

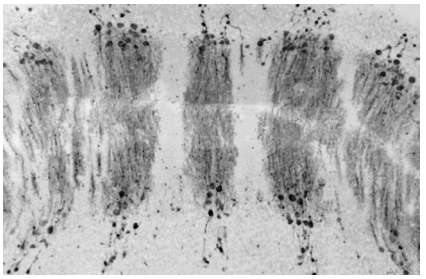
(see pages 2–15)

Illustrations of cells typically show transmembrane proteins sparsely populating a lipid bilayer, with soluble proteins dispersed in the cytoplasm beneath. Missing in these illustrations is the dense network of actin filaments that underlies the plasma membrane and the scaffolding proteins that link transmembrane proteins to this network. These scaffolds are essential, however: they maintain proper subcellular localization of transmembrane proteins, facilitate their interactions with cytoplasmic proteins, and enable adhesion molecules to anchor cells to the extracellular matrix.

One of the best studied scaffolding proteins in neurons is ankyrin-G, which plays crucial roles in the assembly and maintenance of axon initial segments and nodes of Ranvier. Much less is known about the neuronal functions of ankyrin-R (AnkR), which is best known for its role in maintaining the structure or red blood cells. Yet AnkR is expressed at high levels in some neurons, including cerebellar Purkinje cells, and people with hemolytic anemia resulting from AnkR mutations often exhibit cerebellar deficits as well.

To elucidate the role of AnkR in Purkinje cells without disrupting erythrocyte function, Stevens et al. knocked out the encoding gene, *Ank1*, selectively in the nervous system or Purkinje cells. This caused Purkinje cell axons and dendrites to degenerate beginning around 6 months of age, with cell loss apparent by 12 months. Notably, Purkinje cell loss was not uniform across the cerebellum: it was most extensive in the anterior and central zones, and it occurred in a striped pattern reminiscent of previously described stripes of gene expression. In addition, AnkR knockout reduced expression levels of its binding partner β3 spectrin and of K_V3.3 potassium channels, with which AnkR was found to interact, in the cerebellum.

These results indicate that AnkR binds to and helps maintain the expression of K_V3.3 potassium channels and β3 spectrin in cerebellar Purkinje cell somata and is essential for the survival of a subset of these Purkinje cells. Notably, mutations in K_V3.3 and β3 spectrin cause different forms of spinocerebellar ataxia, a disease characterized by loss of Purkinje cells. Therefore, future work should determine whether loss of AnkR causes Purkinje cell loss by disrupting localization of K_V3.3 and/or β3 spectrin and/or by disrupting expression of another, yet-to-be-identified binding partner.



Calbindin staining shows that knocking out AnkR causes a striped pattern of Purkinje cell loss in the cerebellum. See Stevens et al. for details.

Impaired Evidence Accumulation in Dyslexia

Catherine Manning, Cameron D. Hassall, Laurence T. Hunt, Anthony M. Norcia, Eric-Jan Wagenmakers, et al.

(see pages 121–134)

Developmental dyslexia is a common condition involving difficulty in learning to read. The neural bases of this condition continue to be debated, but several studies have shown that people with dyslexia are slower and less accurate than others when performing tasks requiring segregation and integration of elements of complex sensory stimuli. Such deficits can be seen, for example, on tasks requiring people to judge the direction of movement of a subset of coherently moving dots in a field of randomly moving dots. Even this simple task involves multiple neural processes, however. Impairment could stem from deficits in motion perception, difficulty in integrating motion cues from numerous dots, difficulty in ignoring randomly moving dots, or requiring an unusually high level of certainty before indicating a choice.

Fortunately, a cognitive model, called the diffusion model, can be used to tease apart the different neural processes underlying performance on the coherent motion task by using data about people's accuracy and response times across many trials. Manning et al. used this model to analyze the performance of children with and without dyslexia on both the coherent motion task and a variant in which movement information had to be integrated from all dots in the field. This analysis revealed that people with dyslexia had slower "drift rates," indicating slower accumulation of perceptual evidence, in both the coherent motion and the motion integration tasks. Consistent with this, the slope of an EEG component recorded over centroparietal brain regions—a measure previously shown to reflect evidence accumulation—was correlated with drift rate and, in the motion coherence task, it was shallower in children with dyslexia than in control subjects. Finally, evidence for deficits in sensory encoding and motor output was inconclusive, as was evidence about differences in the amount of certainty required to make a decision.

These results suggest that people with dyslexia accumulate and interpret sensory information more slowly than others, and this occurs regardless of whether some of the information needs to be ignored. Notably, however, there was substantial variability within groups, suggesting that not all children with dyslexia have the same deficits. Future work should determine whether and how slowed evidence accumulation relates to reading difficulty.

This Week in The Journal was written by Teresa Esch, Ph.D.

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