This Week in The Journal

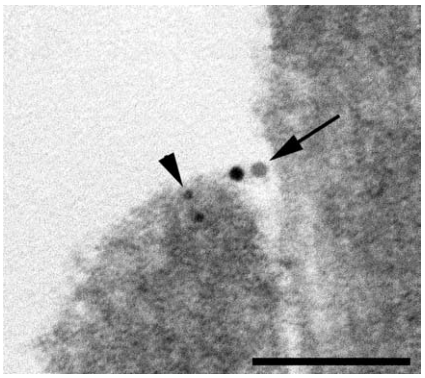
● Cellular/Molecular

Will the Real Tip-Link Antigen Please Stand Up

Zubair M. Ahmed, Richard Goodyear, Saima Riazuddin, Ayala Lagziel, P. Kevin Legan, Martine Behra, Shawn M. Burgess, Kathryn S. Lilley, Edward R. Wilcox, Sheikh Riazuddin, Andrew J. Griffith, Gregory I. Frolenkov, Inna A. Belyantseva, Guy P. Richardson, and Thomas B. Friedman

(see pages 7022–7034)

The tip link sits at the business end of a hair cell, linking the top of a shorter stereocilia on the hair bundle to its taller neighbor and thus presumably gating the mechanosensitive channels. This week, Ahmed et al. set out to identify the protein previously known as the tip-link antigen (TLA). Using mass spectrometric analysis of TLA, the authors identified TLA as protocadherin-15. The isoforms of protocadherin-15 had distinct C-terminal domains (CD1, CD2, and CD3). The distribution of two of the isoforms suggested that they are part of the tip-link complex, probably serving as anchoring elements rather than the central strand. Protocadherin-15-CD3 immunoreactivity was found at the basal end where the tip link attaches to the shorter stereocilia, and CD1 immunoreactivity was found at the distal end where the tip link attaches to the taller sterocilium. Calcium chelation, known to remove tip links and abolish mechanotransduction, also caused loss of CD3 immunoreactivity.



The image shows double immunogold labeling for protocadherin-15 (5 nm particles; arrowhead) and the tip-link antigen (10 nm particles; arrow) in the tip-link region between two stereocilia. Scale bar, 100 nm. See the article by Ahmed et al. for details.

▲ Development/Plasticity/Repair

Interneuronal Migration Sans Reelin

Ramón Pla, Víctor Borrell, Nuria Flames, and Oscar Marín

(see pages 6924 – 6934)

This week, Pla et al. argue that interneurons, unlike cortical projection neurons, migrate to their cortex locations without Reelin, the secreted product of Cajal-Retzius cells. Cortical interneurons originate in the median ganglionic eminence (MGE), migrate tangentially to cortex, and then radially to their final laminar position. The authors report that mice lacking Dab1, the intracellular adaptor protein necessary for Reelin signaling, had impaired laminar distribution, but the tangential migration was normal. To study the laminar migration, the authors used microtransplantation to graft embryonic day 12.5 (E12.5) or E15 interneurons into the MGE of E12 or E15 hosts. The resulting lamination depended on the age of the grafted interneurons and to a lesser extent the age of the host, seemingly incompatible with direct Reelin signaling. Grafts of Dab1 $^{-/-}$ neurons into wild-type hosts also displayed normal lamination. Because interneurons reach their final position after projection neurons, the authors suggest that they are guided by cues from the projection neurons rather than Reelin.

■ Behavioral/Systems/Cognitive

Bimanual Motor Learning

Paul M. Bays and Daniel M. Wolpert

(see pages 7121–7126)

Bays and Wolpert examined our ability to predict and oppose external forces in order to maintain limb or body position. They chose a bimanual task in which a force was applied to the left hand based on the velocity of the right hand. Subjects learned to predict and oppose the force to keep the left hand steady. This task dissociates the representation of the motion that determined the force from the representation of the force itself. After practice reduced the errors in left-hand position, the authors made life complicated by altering the joint configuration of the right or left arm. Interesting, the learned transformation from movement to force involved different coordinate systems for the two hands. The right-hand movement was represented as "extrinsic" coordinates, related to the hand velocity, whereas the force generated in the left hand was represented as "intrinsic" coordinates related to expected joint torques.

♦ Neurobiology of Disease

CHIP-Less Mice Accumulate Tau

Chad A. Dickey, Mei Yue, Wen-Lang Lin, Dennis W. Dickson, Judith H. Dunmore, Wing C. Lee, Cynthia Zehr, Gemma West, Songsong Cao, Amber M. K. Clark, Guy A. Caldwell, Kim A. Caldwell, Christopher Eckman, Cam Patterson, Michael Hutton, and Leonard Petrucelli

(see pages 6985– 6996)

The accumulation of the microtubule-associated protein tau is associated with several neurodegenerative diseases, and in the case of FTDP-17 (frontotemporal dementia with parkinsonism-linked to chromosome 17), tau mutations are sufficient to produce neurodegeneration. This week, Dickey et al. focused on the role of the cochaperone and ubiquitin ligase CHIP (C terminus of the Hsc70-interacting protein) in degradation of phosphorylated tau. In CHIP $^{-/-}$ mice, about half of the knock-out mice showed motor deficits and small size. These symptomatic knock-out mice had elevated tau levels and thus were used for the experiments. In these mice, there was an accumulation of non-aggregated, ubiquitin-negative, hyperphosphorylated tau. Overexpression of mutant human tau (P301L) caused accumulation of phospho-tau but was not sufficient to produce aggregates or "pre-tangle" structures. Thus, the authors suggest that polyubiquitination of tau by CHIP contributes to insoluble tau aggregates and is part of an adaptive neuronal response.