This Week in The Journal

● Cellular/Molecular

acj6 *Splice Variants Regulate Different Genes*

Lei Bai and John R. Carlson

(see pages 5028–5036)

Drosophila olfactory neurons (ORNs) are classified by how they respond to a panel of odors, which in turn is determined by which olfactory receptor(s) they express. The maxillary palp, one of two olfactory organs in *Drosophila*, contain six classes of ORNs, and specific pairs of these innervate each of three kinds of sensory hairs (sensilla). Each ORN expresses one or two olfactory receptor genes, and which gene(s) it expresses is determined by a combination of transcription factors, including Acj6. When Acj6 is inactivated, some ORNs express no olfactory receptor and others express an inappropriate receptor. Bai and Carlson report that 13 alternatively spliced variants of *acj6* are expressed in olfactory organs, and expression of any single variant partially rescues the *acj6*-null phenotype. Different splice forms rescue different ORNs, however, and each produces some ORNs with abnormal responses, indicating that the variants differentially regulate receptor genes. Thus, alternative splicing adds extra complexity to the regulation of receptor gene expression.

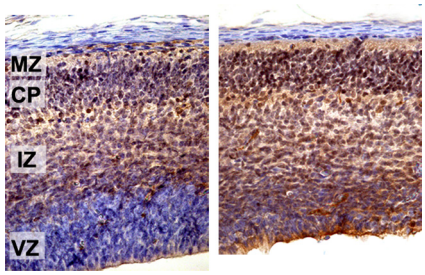
▲ Development/Plasticity/Repair

ADAM10 Helps Notch Prevent Premature Differentiation

Ellen Jorissen, Johannes Prox, Christian Bernreuther, Silvio Weber, Ralf Schwanbeck, *et al.*

(see pages 4833–4844)

Neuronal differentiation is shaped by environmental cues that vary in concentration over development, so different types of neurons develop at different times. Premature differentiation—which precludes mitosis and thus depletes the progenitor pool—leads to an overabundance of early-born neuronal types at the expense of later-born types. Premature differentiation is prevented in part by production of Notch ligands by neural precursors: the ligands bind to Notch receptors on adjacent cells, leading to expression of transcriptional repressors that downregulate proneural genes in those cells. Cleavage of ligand-bound Notch receptors by A disintegrin and metalloprotease (ADAM10) is required for ligand-activated Notch signaling. Jorissen et al. knocked out ADAM10 selectively in mouse CNS neural progenitor cells, and thus reduced Notch cleavage and expression of downstream transcriptional repressors. Consequently, precursors differentiated prematurely and the pool of neural progenitors was partially depleted. As a result, cortical layering was disorganized and fewer neurons were present than in controls.



Compared to wild-type mice (left), more newborn neurons (brown) are present at embryonic day 15.5 in the ventricular zone (VZ) of mice lacking ADAM10 (right). See the article by Jorissen et al. for details.

■ Behavioral/Systems/Cognitive

Within-Session Extinction Does Not Predict between-Session Extinction

Wolfgang Plendl and Carsten T. Wotjak

(see pages 4990–4998)

Conditioned fear responses (e.g., freezing) elicited by pairing an innocuous cue (e.g., a tone) with an aversive stimulus (e.g., a shock) are subsequently extinguished if the tone is repeatedly presented without the shock. Extinction likely results from new learning about the relationship between the cue and stimulus rather than by erasure of the original association. Therefore, one might predict that reduced freezing during extinction training would necessarily precede reduced freezing in subsequent tests. But Plendl and Wotjak suggest that reduced freezing during extinction training is neither necessary nor sufficient to produce reduced freezing on subsequent days. Presentation of either several brief tones or one continuous tone on the day after fear conditioning extinguished freezing during that session; but on the next day, mice exposed to brief tones froze significantly less than those that received one. Furthermore, if extinction training occurred 40 days after conditioning, neither tone protocol reduced freezing that day; nonetheless, on day 41, mice exposed to multiple tones froze less.

♦ Neurobiology of Disease

Most Features of AD Occur in Absence of Aβ Plaques

Takami Tomiyama, Shogo Matsuyama, Hiroyuki Iso, Tomohiro Umeda, Hiroshi Takuma, *et al.*

(see pages 4845–4856)

Much evidence suggests that the synaptic dysfunction underlying cognitive decline in Alzheimer's disease (AD) is caused by soluble oligomers of β-amyloid (Aβ); but the role of Aβ deposits (plaques) in AD remains uncertain. Tomiyama et al. recently identified a mutation in the human amyloid precursor protein that causes AD without plaques. They have now generated transgenic mice that express this mutation. Like human patients, mice never developed Aβ plaques. Nonetheless, insoluble Aβ oligomers accumulated intraneuronally in brains of mutant mice starting at 8 months. At this time, mutant mice had reduced levels of synaptophysin, paired-pulse facilitation, and long-term potentiation, and they exhibited impaired spatial memory compared to wild-type mice. As mutant mice aged, abnormal tau phosphorylation and staining for markers of activated glia increased, and by 24 months, the mice had significantly fewer hippocampal neurons than controls. Therefore, these features of AD can occur in the absence of plaques.