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# In This Issue

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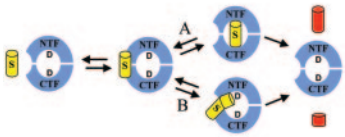
BIOCHEMISTRY

## Elucidating γ-secretase structure and function

Although the essential components of γ-secretase, which is involved in Alzheimer's disease pathology, have previously been identified, a study by Anna Kornilova *et al.* reveals more structural and functional information about this multicomponent intramembrane protease. Using photoaffinity probes designed to mimic a common substrate, the authors determined the location of the initial binding, or docking, site. The authors found that 10-residue helical peptide probes bind at the interface between two presenilin subunits near the enzyme's active site. A peptide probe with three additional residues bound the docking site and interacted with the active site, suggesting that the active and docking sites may be within three residues of each other. In addition, the authors found that some presenilin mutations associated with Alzheimer's disease dramatically altered binding of a transition-state analog photoaffinity probe, probably because of a change in the shape of the active site. These findings reveal the location of initial substrate binding and suggest that the transmembrane substrate gains access to the internal, water-containing active site by passing between the two presenilin subunits.



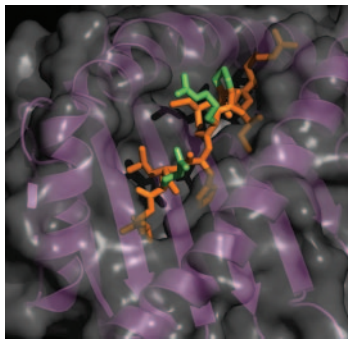

Proposed substrate interactions with γ-secretase.

*"The initial substrate-binding site of γ-secretase is located on presenilin near the active site"* by *Anna Y. Kornilova, Frédéric Bihel, Chittaranjan Das, and Michael S. Wolfe* (see pages 3230–3235)

IMMUNOLOGY

## Fetal-protective MHC protein structure determined

Craig Clements *et al.* report the crystal structure of HLA-G, a nonclassical MHC class I molecule believed to play a role in protecting the fetus from the maternal immune system. The 1.9-Å resolution of HLA-G reveals a number of structural features that may explain unique functional characteristics of this molecule. The authors observed extensive contacts between the HLA-G antigen-binding site and its ligand when HLA-G monomers were complexed with endogenous peptide ligand. This network restricted the identity of peptides that can bind, providing a structural basis for the limited binding capacity of HLA-G. The authors also observed striking differences in the α3 domain of HLA-G compared with classical MHC class I molecules. These differences may account for the high affinity of HLA-G for leukocyte immunoglobulin-like receptor 1 (LIR-1). In addition, HLA-G monomers can join together in a head-to-tail orientation to form homodimers, and this capacity may enhance the affinity of HLA-G to bind immunomodulatory receptors like LIR-1.



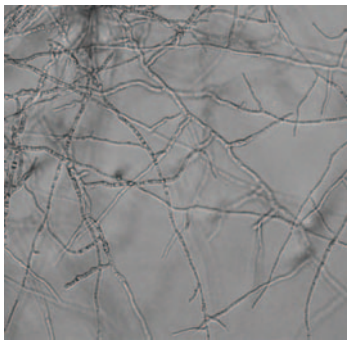
Peptide-binding domain of HLA-G.

*"Crystal structure of HLA-G: A nonclassical MHC class I molecule expressed at the fetal–maternal interface"* by *Craig S. Clements, Lars Kjer-Nielsen, Lyudmila Kostenko, Hilary L. Hoare, Michelle A. Dunstone, Eric Moses, Katy Freed, Andrew G. Brooks, Jamie Rossjohn, and James McCluskey* (see pages 3360–3365)

MICROBIOLOGY

## Proline's antioxidant function in fungus

Changbin Chen and Martin Dickman demonstrate that the amino acid proline can prevent apoptosis in the alfalfa fungal pathogen *Colletotrichum trifolii*. Previous research has shown that mutationally activated oncogenic fungal Ras (DARas) elevates levels of reactive oxygen species (ROS) and causes abnormal fungal growth. The authors studied a *C. trifolii* mutant expressing DARas and found that these fungi reverted to a wild-type phenotype when grown in proline-enriched media. The researchers detected a decrease in ROS levels in DARas fungi when proline was added to the growth media. The researchers monitored markers of apoptosis in the cells, including DNA condensation and fragmentation and phosphatidylserine externalization. All three markers for apoptosis decreased when the mutant fungi were grown with proline. To test proline's ability as a general antioxidant, the authors grew yeast cells in the presence of paraquat, a herbicide that causes lethal levels of ROS. The yeast grown in a proline-enriched media survived, whereas controls did not.



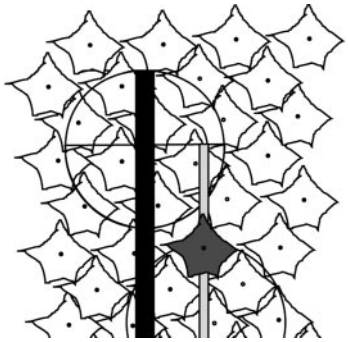
Proline's antioxidant function in fungus.

*"Proline suppresses apoptosis in the fungal pathogen* Colletotrichum trifolii*" by Changbin Chen and Martin B. Dickman* (see pages 3459–3464)

NEUROSCIENCE

## Visual sensitivity and responses of single neurons

Psychophysical sensitivity in certain visual tests may be explained equally well by either pooling information from a group of neurons or by using the information of an appropriately chosen single neuron, Ying Zhang and Clay Reid report. The link between sensory perception and the responses of single cells in the nervous system has posed an unresolved issue in neuroscience. To investigate further, the authors measured the responses of individual cells in the cat lateral geniculate nucleus, an area of the brain associated with vision, in tests of vernier acuity, which measures the ability to visually detect small offsets in vertical bars. The authors found that, if the stimulus could fall anywhere in a single neuron's receptive field, the neuron had a resolution two times worse than previously reported vernier thresholds. For the psychophysical thresholds to be accounted for by the responses of a single cell, the bar stimulus had to fall in a particular area: the quarter of the cell's receptive field that gave the most information about the position of the lines. Alternatively, the absolute psychophysical threshold for vernier acuity could be explained by pooling the responses of a few neurons in an area on the same side of the bar stimulus.



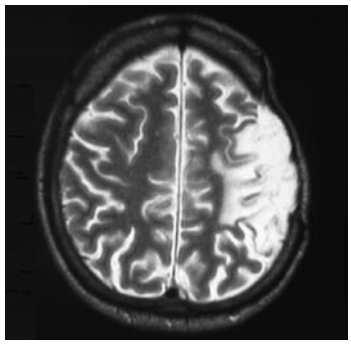
Visual stimulus-based neuron selection.

*"Single-neuron responses and neuronal decisions in a vernier task" by Ying Zhang and R. Clay Reid* (see pages 3507–3512)

PSYCHOLOGY

## Math cognition without language

The human ability for recursive symbolic reasoning, such as in addition and subtraction, may be independent of the machinery for language, researchers suggest. The extent to which language enables other higher cognitive functions is a central question in cognitive neuroscience. Some researchers have suggested that humans solve mathematical expressions by first translating them into language and then drawing on symbolic reasoning machinery that is specialized for language. To explore this mechanism, Rosemary Varley *et al.* examined language and arithmetic abilities in three males with large left hemisphere perisylvian lesions. The participants suffered from severe agrammatic aphasia and could not distinguish between simple, reversible sentences such as "the lion killed the man" and "the man killed the lion." However, the subjects were largely able to evaluate analogous mathematical expressions such as $59 - 13$ and $13 - 59$. Furthermore, the men were sensitive to the embedded structure of bracketed numerical expressions and could solve problems such as $12/(3 - 1)$. The results give experimental evidence against the claim that language is necessary for mathematics. Instead, the authors suggest that numeric reasoning may be able to tap directly into a common cognitive mechanism underlying both language and mathematics or that, in the mature state, the two domains are entirely independent of each other.



Agrammatic math processing.

*"Agrammatic but numerate" by Rosemary A. Varley, Nicolai J. C. Klessinger, Charles A. J. Romanowski, and Michael Siegal* (see pages 3519–3524)