domain that is not present in Ras family proteins. The two switch regions are so called because they change dramatically in conformation upon hydrolysis of GTP (*10*). This conformational change reduces the affinity of Ras and Gα for their effectors.

GTP is hydrolyzed by in-line attack of its γ phosphate by a nucleophilic water molecule. There appears to be no enzymic base to abstract a proton from this attacking water molecule, but a glutamine residue (Gln^{61} in Ras and Gln^{204} in $G\alpha_{i1}$) perched at the amino-terminus of switch II is essential for catalysis in both Gα and Ras. Mutations of this residue promote a constitutively active, GTP-bound state and are therefore transforming. Three-dimensional structures of Ras bound to a nonhydrolyzable GTP analog show that the switch II helix is flexible and Gln^{61} poorly ordered (*11*). In Gα, but not in Ras, mutation of a conserved arginine residue in switch I (Arg^{178} in $G\alpha_{i1}$) also impairs GTP hydrolysis. In the transition state for GTP hydrolysis, the γ phosphate is pentacoordinate. The attacking water (or hydroxyl group) and an oxygen atom of the β phosphate leaving group are transaxial ligands. The crystal structures of $G\alpha_{i1}$ and $G\alpha_t$ containing GDP and the square planar AlF_4^- that mimics the trigonal γ phosphate, demonstrate that Glu^{204} and Arg^{178} have distinct roles in stabilizing the transition state for GTP hydrolysis (*12*, *13*). However, both residues must be reoriented in order to stabilize the transition state. This barrier, together with the absence of an enzymic base, may explain the weak catalytic properties of Gα. Ras suffers further in that it lacks a catalytic arginine and cannot itself bind to AlF_4^- (*14*).

When GAP binds to Ras (*4*), it lands on the switches (see the left panel of the figure) and measurably reduces their flexibility. Precisely the same is true of the RGS4·$G\alpha_{i1}$ interaction (right panel) (*15*). RGS4 offers an asparagine residue (Asn^{128}) to stabilize the conformation of Gln^{204}. Likewise, GAP uses a main-chain carbonyl group to orient the corresponding Gln^{61}. Yet GAP goes a step further by inserting Arg^{789} into the active site of Ras, thereby mimicking, almost identically, the position and function of Arg^{178} in $G\alpha_{i1}$ [see figure 5C of (*4*)]. Because this residue is poised to stabilize developing charge on the γ phosphate rather than the leaving group, Ras·GAP most likely stabilizes an associative transition state.

Nevertheless, it is unlikely that the contribution of Arg^{789} accounts for all of the rate acceleration provided by GAP. RGS4 stimulates Gα even though it appears to provide no catalytic residues in the transition state complex (although Asn^{128} may assist catalysis in the ground state). Loss of flexibility in the Ras and Gα switches suggests that GAP and RGS4 stabilize conformations of $G\alpha_{i1}$ and Ras that are most complementary to the transition state. Both Ras and $G\alpha_{i1}$ bind to their stimulatory factors more tightly in the transition state than in the ground state (*6*, *14*). A larger view of catalysis (*16*) might suggest that GAPs and RGS couple the energy of substrate binding to transition state stabilization. How such coupling is achieved might be revealed in future structures of the ground state Ras·GAP complex. In the meantime, the structure at hand unites Ras and its elusive partner, arrested at the moment of catalysis.

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NEUROSCIENCE

How Does the Brain Organize Memories?

Howard Eichenbaum

Cognitive neuroscientists agree that there are multiple forms of memory, each mediated by distinct brain pathways (*1*, *2*). There is not such ready agreement, however, as to the critical distinctions among types of memory and the contributions of specific anatomical structures to each. On page 377 of this issue, Vargha-Khadem *et al.* (*3*) address both of these issues by analyzing the memory deficits in three individuals who had sustained brain lesions very early in life. Their results show that the hippocampus, a structure located within the medial temporal lobe of the brain and long associated with memory function (*4*), is critical for everyday episodic memory (our record of personal events), but is not necessary for semantic memory (our lifetime accumulation of universal factual knowledge). Although the hippocampus has been argued to function in episodic memory before (*5*), these new case studies offer a particularly impressive example that can be attributed to selective focal hippocampal damage early in life.

Striking as the findings are, they are also consistent with the possibility that both types of learning are impaired in these cases. Directly comparing new episodic and semantic learning in the laboratory turns out to be quite difficult, because normal subjects can take advantage of their episodic memory to recall new semantic material. This problem in separating performance of the two types of memory has led some to eschew the episodic-semantic distinction, focusing instead on amnesics' characteristic failure in conscious recollection of both events and facts. Such a deficit in so-called declarative memory is contrasted with fully spared acquisition of biases, skills, and habits expressed unconsciously through changes in performance speed or choice (*6*). Using this account, the seemingly selective deficit in these amnesics' memory for unique episodes, as well as their forgetting of a story or drawing, can be attributed to a partially compromised declarative capacity doing especially poorly on any type of complex material experienced only once.

Recognizing this interpretive stand-off, Vargha-Khadem *et al.* turned to nonconventional tests modeled after measures that in animals distinguish the memory functions of the hippocampus itself from that of the immediately surrounding parahippocampal cortical region (see the figure). Monkeys and rats with selective hippocampal damage do surprisingly well at stimulus recognition and stimulus association learning, but have severe deficits after parahippocampal damage (*7*). Likewise, the individuals with hippocampal lesions showed intact recognition memory in similar tests with words and faces, and even normal learning of verbal or face associations, as contrasted with the reports of more extensive impairment in these measures in a patient with identified

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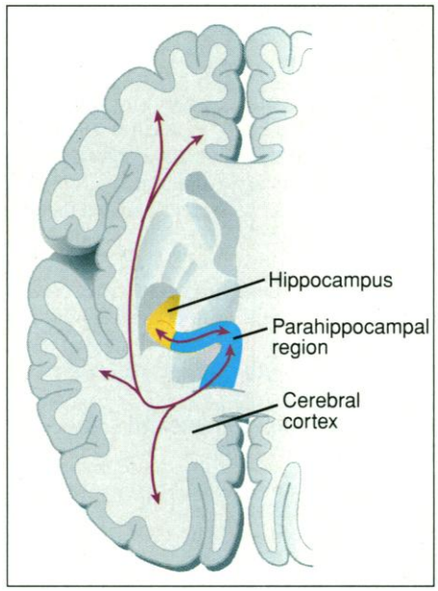
damage in both the hippocampus and parahippocampal region (*4*, *8*). Animals with selective hippocampal damage are impaired in memory for spatial location or spatial context (*9*), a deficit similar to that of the individuals described by Vargha-Khadem in associating an object with the place where it was seen, as well as a face with its voice. These parallels led Vargha-Khadem *et al.* to suggest an anatomically feasible model of complementary memory functions in which representations formed in the cerebral cortex are bound together into semantic associations by the parahippocampal region, and then further processed by the hippocampus to add the contextually rich episodic or spatial information (see the figure).

More detailed neurobiological observations offer another perspective and a degree of reconciliation between the episodic and declarative accounts. One source of data comes from neuropsychological studies showing that the hippocampal deficit observed in animals requires a deeper explanation than attribution to a (spatial) contextual factor (*10*). Thus, when animals with selective hippocampal damage acquire stimulus associations, they fail on novel queries in which the stimuli are only indirectly related through other stimulus elements (*11*). Drawing an even closer parallel with the human studies, animals with hippocampal damage seem to acquire a complex "semantic" structure involving an orderly hierarchy of stimuli. But the nature of their knowledge structure, or access to it, is abnormal in that these animals lack the flexibility of expression that supports inferences between stimulus elements that are only indirectly related within the hierarchy (*12*). A similar dissociation can be observed between their successful, albeit gradual, place learning contrasted with failure when challenged to navigate to the place by a novel route or when previous experiences can interfere with new place learning (*13*). Both rigidity of access and sensitivity to interference are hallmarks of human amnesics' difficulty in conscious recollection, suggesting a connection between hippocampal function in declarative memory and in flexibility of memory expression across species (*5*, *14*).

Complementary evidence from studies on neural activity in the hippocampal area provides further clues about the distinct memory functions of the hippocampus and parahippocampal region. In a recent functional magnetic resonance imaging study, a part of the hippocampus was maximally activated when human subjects indirectly accessed the memory of a word cued by a picture of the corresponding object, whereas the parahippocampal region was maximally activated during simple differentiation and encoding of novel pictures for later recognition (*15*). Similarly, single-cell recordings in both rats and monkeys have shown that cortical areas, including those in the parahippocampal region, encode specific memory cues and can sustain and regenerate these item-specific representations (*16*). By contrast, the activity of hippocampal neurons reflects myriad combinations of items or abstract relations between stimuli, as observed in so-called place cells, whose activity reflects the position of a rat with respect to the configuration of spatial cues (*17*), and in cells whose activity reflects configurations of nonspatial cues and actions (*18*), including



The human brain: wired for memory. Widespread regions of the cerebral cortex, the repositories of highly specific representations, are bidirectionally connected to the parahippocampal region. Interactions among these areas could underlie memories of some associations between cortical representations without hippocampal involvement. The parahippocampal region is then bidirectionally connected with the hippocampus, which can provide an additional influence on memory processing by the preceding areas.

combinations of faces and gender or emotional expression in humans (*19*). In addition, a potentially telling property of hippocampal cells is their propensity to dramatically change representations, even across highly similar situations that vary only in the task contingencies or subtle variations in the stimuli (*20*). These findings have led to the suggestion that the hippocampus seeks to differentiate potentially ambiguous patterns and, at the same time, to capture the relevant contingencies in each of them.

These observations begin to fill in the mechanistic details of the model shown in the figure (*21*). Functionally specific cortical representations converge onto the parahippocampal region, which might support a binding of simultaneously experienced contiguities through feedback onto the cortex. When the items are in the same modality or are closely contiguous, this could lead to an overly rigid binding of the items, making them inaccessible when the elements are later separated (for example, we meet someone in a conference but can't recognize the person later on the street outside). The physiological data, as well as computational models (*22*), suggest that the hippocampus is suited to promote more flexible associations by recognizing relations among items and differentiating overlapping patterns (separating where one sees the person from the places and times of the events). This could contribute to the encoding of each unique episode, as well as relating the context-free information into semantic knowledge. The data from animals with amnesia, as well as computational modeling, indicate that the hippocampus may also interleave patterns within the memory network so as to provide access to the whole knowledge structure from any point. Within this scheme, episodic and declarative memory are not alternative types of memory, but rather are two powerful benefits of the networking of cortical memories supported by the hippocampus.

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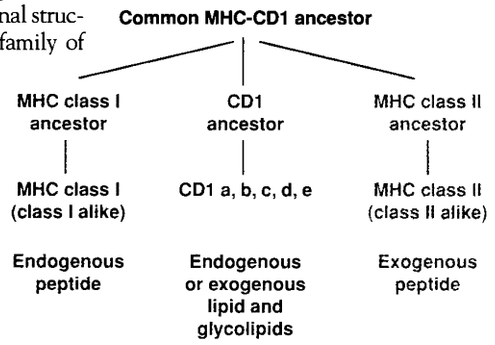
UPDATE: IMMUNOLOGY

Antigen Presentation: A Balanced Diet

Michael Brenner and Steven Porcelli

For much of the past decade, immunologists studying how the immune system recognizes foreign molecules have focused on the molecular mechanisms by which T cells recognize peptide antigens. A series of landmark crystallographic studies have revealed how peptide antigens are displayed on the surface of cells. Amino acid side chains of the peptide are anchored into specific pockets in the peptide binding grooves of the major histocompatibility complex (MHC) class I and class II membrane proteins. This determines which peptides can bind MHC, and thus which peptides have the potential to be recognized by T cell receptors. However, several remarkable findings suggest that an important part of the story has not yet been told. On page 339 of this issue, Zeng *et al.* present the three-dimensional structure of murine CD1d1, a representative of a family of conserved mammalian proteins that are distant cousins of MHC molecules (*1*) (see figure). This structure reinforces the view that CD1 proteins bind and present antigen in a way that offers T cells a fundamentally different look at the antigenic universe, one that includes lipids and glycolipids.



The CD1 genes are located on a different chromosome than the MHC and encode five isoforms (CD1a through e) in human and two homologs of CD1d in mice. These are nonpolymorphic proteins with barely 30% homology to MHC class I or II molecules (*2*, *3*). Despite this marked divergence from MHC structure, a role for CD1 in antigen presentation was shown by the finding that CD1b expression on antigen-presenting cells was required for the responses of certain T cell clones to *Mycobacterium tuberculosis* (*4*). Further studies in this system led to the surprising finding that the mycobacterial antigens recognized by CD1-restricted T cells are not peptides, but instead are lipids (mycolic acids) and glycolipids (lipoarabinomannan and phosphatidylinsositol mannosides) found in the cell walls of these bacteria (*5*, *6*). How could such antigens be presented? Has the immune system evolved a third family of antigen-presenting molecules capable of binding nonpeptide lipid antigens?

The structure described by Zeng *et al.* suggests that this is indeed the case. Although the overall structure of murine CD1d1 is strikingly like that of an MHC class I molecule, the region corresponding to the peptide binding groove of MHC molecules is significantly larger. Narrow at its opening, the CD1 groove descends into a deep cavity lined almost entirely by nonpolar or hydrophobic amino acid side chains. The multiple distinct pockets (generally six or more) for anchoring peptide antigen side chains seen in all MHC binding grooves seem to coalesce in the CD1 structure into just two large pockets. The cluster of tyrosines that contribute to the hydrogen bonding network that anchors the NH_2-terminus of peptides in MHC class I molecules is eliminated in the CD1 structure, and the large CD1 groove has less capacity for hydrogen bonding than any other antigen-presenting molecule yet examined.

The size and topography of the CD1 cavity weigh heavily against its being able to bind peptides after the manner of MHC molecules. Instead, the CD1 cavity appears ideally suited to bind markedly hydrophobic ligands, such as the lipid and glycolipid bacterial antigens that are presented to human CD1-restricted T cells. The mouse CD1 crystal structure contains a poorly defined, unbranched density within the pockets of the deep hydrophobic groove. Although the nature of this density has yet to be clarified, its unbranched structure suggests that it is not a peptide, and it may in fact represent a bound acyl chain. Given the data on antigen specificity of CD1-restricted T cells and the structure described by Zeng *et al.* (*1*), one might hypothesize that the lipid tails of microbial antigens like mycolic acids and lipoarabinomannan anchor in the hydrophobic cavity of CD1, leaving the hydrophilic glycan and oxygen-containing groups protruding out and accessible for interactions with T cell receptors. The putative CD1 antigen binding cavity begins to provide a molecular explanation for the immune system's balanced diet of antigens.

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