

septins were depleted Orai1 became less uniform with irregular clustering. Following Ca^{2+} store depletion, Orai1 was less able to form discrete puncta. Interestingly, septins do not appear to colocalize with STIM1 and Orai1 in the puncta but instead localize just outside of them in separate clusters [11].

Septins are cytoskeletal proteins capable of forming filamentous structures [13]. Originally discovered as proteins involved in yeast budding, they are now thought to function as membrane sorting or barrier proteins. For example, septins are involved in segregating the constituents of the membranes of dendritic spines from the neurons to which they are attached. Septins also prevent mixing of membrane constituents between apical and basolateral membranes in epithelial secretory cells, and are responsible for maintaining the unique composition of the membranes of cilia. One of the ways that septins regulate membrane composition is by interacting with the key membrane regulatory lipid phosphatidylinositol 4,5-bisphosphate (PIP_2). In accordance with this, Sharma *et al.* [11] found that, when Orai1 accumulates in puncta, PIP_2 is segregated to the periphery; however, when septins are depleted, this segregation of PIP_2 was essentially lost.

Thus, septins clearly have an important function in SOCE: they appear necessary for proper movement of STIM1 to junctional sites where it activates Orai1, and they appear to play a role in modulating Orai1 distribution in the plasma membrane and in clearing PIP_2 from junctional

sites. However, more work will be needed to understand exactly how septins provide these important functions. For example, what is the role of the redistribution of PIP_2 ? Although not entirely clear, from the data it may be suggested that PIP_2 redistribution may contribute to stabilization of the STIM1–Orai1 complexes in puncta. Note that, at more physiological temperatures, STIM1 resides constitutively in the ER–plasma membrane junctions, where it is held by interaction with membrane PIP_2 [14]. Yet, this interaction is not required for the interaction between STIM1 and Orai1. Thus, septins might function by remodeling the lipid composition of the junctional membranes, thereby increasing mobility of STIM1 and facilitating interaction with Orai1.

Sharma *et al.* [11] reasonably speculate that septins may be involved in organizing many other plasma membrane-based signaling mechanisms. This is an exciting possibility and we look forward to the development of the septin story as a newly opened chapter in understanding membrane signaling mechanisms.

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Location Memory: Separate Cortical Coding for Distal and Local Cues

Entorhinal cortex is implicated in coding the location of spatial cues: a new study has found that distinct regions of entorhinal cortex respond differentially to distal *versus* local cues when these cues are rotated in conflict with one another.

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The entorhinal cortex plays an important role in memory function, as demonstrated by impairments of memory for spatial location with lesions

of the entorhinal cortex [1]. Different regions of the entorhinal cortex have been proposed to play a differential role in coding of memory: neurons in the medial entorhinal cortex coding spatial location, and neurons in the

lateral entorhinal cortex coding the identity of local objects [2,3]. These two coding frameworks have not, however, previously been directly contrasted with one another. A recent study by Neunuebel *et al.* [4] directly contrasts the responses of these two regions during manipulations that separately alter the distal cues that drive spatial representations *versus* the local cue representations of items in the environment.

The new study [4] used a well-established experimental design that contrasts the influence of sensory

cues on neuronal responses by a 'double rotation' [5,6]. In this experiment, the firing response of neurons is recorded as a rat runs on a circular track with a standard configuration of cues. This includes distal cues consisting of six salient visual cues placed around the periphery of the track inside of a circular curtain, as well as local cues that differ on each quadrant of the track in terms of visual pattern and somatosensory texture. After recording in the standard condition, recording is made in a separate mismatch session, in which the distal cues have been rotated in one direction and the local cues have been rotated in the opposite direction. The difference in cue rotation varies in magnitude, with the sum of rotations being 45 degrees, 90 degrees, 135 degrees or 180 degrees. This rotation manipulation allows testing of whether individual neurons or populations of neurons preferentially shift their response in the direction of rotation of the distal cues or the local cues.

Neunuebel *et al.* [4] found that neurons of the medial entorhinal cortex predominantly shift the angle of their response depending upon the distal cues in the environment. In contrast, the neurons of the lateral entorhinal cortex predominantly shift their responses with the local cues in the environment. These differences in shifting were observed both for the number of individual neurons that shifted, and the change in the overall correlation of neurons in the two regions. The differential response of the regions was consistent across different rats used in the experiment.

These results provide important support for previous proposals that the medial entorhinal cortex codes spatial context, whereas the lateral entorhinal cortex codes the identity of local objects or items in the environment [2,3]. This provides an important extension of previous studies that suggested differential coding, because those earlier studies involved recordings that separately tested the response of neurons in different regions to different types of stimuli, without putting the stimuli directly in conflict with one another, as in the rotation paradigm of Neunuebel *et al.* [4].

In previous studies, the medial entorhinal cortex was shown to

contain a number of cell types that code spatial dimensions depending predominantly upon distal cues. These cell types include grid cells that respond when a rat visits a regular array of locations [7], head-direction cells that respond to allocentric head direction [8], and boundary-vector cells that respond to the location of barriers to movement [9,10]. In contrast, the same recording techniques applied to lateral entorhinal cortex failed to find these types of neural responses to spatial dimensions [11], rather finding responses that depended upon the presence or recent removal of objects in the environment [12]. The recording of neurons in an experimental manipulation that places local object cues in direct conflict with distal sensory cues provides important support for the presence of two processing streams in lateral *versus* medial entorhinal cortex.

These new results provide important information on the nature of input to the hippocampal formation. In particular, the hippocampus contains place cells that respond on the basis of spatial location [13]. These place cells could be driven by the neurons in medial entorhinal cortex responding to spatial dimensions such as grid cells [14] or boundary vector cells [15]. However, place cells have also been shown to shift their response based on the position of a specific sensory cue [16,17], suggesting an important role of object representations from lateral entorhinal cortex. In previous studies, the responses of place cells in hippocampal regions CA3 and CA1 were tested during the double rotation manipulation on a circular track [6,18]. Neurons in CA1 showed mixed responses to either distal cues or local cues, consistent with differential input from lateral *versus* medial entorhinal cortex [18]; however, region CA3 neurons seemed to follow local cues more consistently, possibly due to attractor dynamics mediated by recurrent excitatory connections in region CA3 [18]. The demonstration of differential responses in lateral and medial entorhinal cortex [4] provides an important perspective on the nature of input to the hippocampal formation.

Understanding the separate coding of information in the entorhinal cortex is particularly important to understanding

the integration of memory for objects with memory for spatial locations that is essential to associating the 'what' and 'where' of episodic memory [2,3,19]. Along with evidence for coding of time intervals by neurons in the hippocampal formation [20], this provides a framework for understanding how separate processing streams may converge on the hippocampus to form an association between individual items or events and the location and time of these events within an episodic memory [19].

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Dendrite Plasticity: Branching Out for Greener Pastures

Environmental stress triggers substantial alterations in animal physiology and, in some cases, brain structure. Using the nematode *Caenorhabditis elegans*, a new study reports that unfavorable conditions lead to dramatic dendrite remodeling in neurons that mediate an adaptive dispersal behavior.

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Animals utilize an impressive array of strategies for coping with stressful environmental conditions. If food is in short supply, some suppress their metabolism and hibernate, while others migrate in search of new habitat. These physiological and behavioral adjustments are generally orchestrated by the endocrine system and are often accompanied by significant modifications of the nervous system [1,2]. For example, the brain of the hibernating arctic ground squirrel displays a global reduction in the size of neuron cell bodies, dendrite length and complexities, and spine densities, which all revert to normal within a few hours of recovery from torpor [3,4]. In this issue of *Current Biology*, Schroeder *et al.* [5] report an equally dynamic stress-induced remodeling event in a genetic model organism. When the ability to reach sexual maturation is compromised by limited food availability or high population densities, *Caenorhabditis elegans* select an alternative developmental life stage termed dauer, adapting their behavior and morphology until conditions improve [6]. By observing this transition at the cellular level, Schroeder and colleagues discovered that *C. elegans* rapidly and reversibly remodel a subset of their sensory neurons during dauer via a process that involves the function of a furin homologue, KPC-1 [5].

As *C. elegans* transition to dauer, IL2 sensory neurons elaborate their simple

unbranched dendrites into a complex branched network of processes within hours [5] (Figure 1). When conditions improve and the animal decides to resume normal development, this morphology largely reverts to the basal state. Using the power of *C. elegans* genetics, Schroeder *et al.* [5] determined that *kpc-1*, a furin-like member of the proprotein convertase family, is induced during dauer formation and is required for the expansion of IL2 dendrites. Because multidendritic sensory neurons that normally display complex branched morphologies also require *kpc-1*, this phenotype likely represents a defect in dendrite branch elaboration rather than compromised inductive signaling. Two transcription factors — UNC-86 and DAF-19 — were also identified as the regulators of IL2 remodeling during dauer formation, providing another avenue for deciphering the molecular biology underlying this process [5].

Dendrite remodeling in IL2 neurons presents an attractive cellular system for understanding how neurites grow and degenerate in response to extrinsic signals. The rapid expansion of IL2 arbors in response to dauer demands the biogenesis and recruitment of considerable cellular resources, in addition to the remodeling of the cytoskeleton. Similarly, the retraction and degeneration of the IL2 dendrite upon exiting dauer also presents an interesting cell-biological challenge. Is the loss of the dendrite due to the removal of signals needed for its maintenance or, alternatively, to the activation of specialized machinery

involved in dendritic pruning? Will the molecular machinery underlying dendrite remodeling be conserved across phylogeny? The elaborate dendrite morphology of dauer IL2 neurons resembles that of the dendrite arborization (da) neurons in the *Drosophila* peripheral nervous system, whose dendritic arbors undergo developmental pruning and subsequent regrowth [7,8]. These and future model systems will undoubtedly continue to inform our understanding of how neurons reorganize in health and disease.

For what purpose does IL2 remodel during dauer? Because the local environment may perpetually remain unfavorable, dauer larvae extend themselves vertically at the surface of the soil in an attempt to hitchhike on passing insects traveling to more favorable locations — a dispersal behavior termed nictation [9,10]. The cellular and molecular basis underlying nictation is of considerable interest to neurobiologists because it represents a reversible behavior in a genetically accessible model organism. Lee *et al.* [9] have previously proposed that IL2 is required for perceiving the environmental cues that initiate nictation behavior. In the new work, Schroeder *et al.* [5] demonstrate that *kpc-1* mutants require KPC-1 expression specifically in IL2 neurons to display wild-type nictation. Therefore, the morphological remodeling of IL2 is correlatively associated with the emergence of an adaptive behavior. However, similar to other studies that report an association between structural changes and a behavioral phenotype, we must beware the ever-present caveat; *kpc-1* likely affects multiple aspects of neuronal function besides the regulation of dendrite morphology. Indeed, the authors also observed that the morphology of the IL2 axon is altered during dauer, a phenotype less accessible to gross