Dispatches

Septins: Cellular and Functional Barriers of Neuronal Activity

How conserved is sub-cellular compartmentalization across species and does it play a similar role? Here, two studies now demonstrate that buds in yeast and spines in mammalian neurons share many properties and suggest unexpected commonalities between simple and complex organisms.

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Synaptic plasticity is a fundamental property of neuronal cells that relies on the ability of synapses to modulate their activity in response to incoming signal. Postsynaptic spines on dendrites of neurons play a critical role in this property and constitute a cellular sub-compartment that integrates presynaptic and postsynaptic signaling. Each spine is unique in that respect because it can respond to local patterns of activity, individually and independently from neighboring spines. The mechanisms that allow spines to act individually and function separately are not well understood.

Previous studies have suggested that spine morphology plays an important role in determining the amplitude with which spines respond to stimulation via two possible mechanisms [1]. First, spine morphology influences the kinetics with which Ca^{2+} influx spreads along the rest of the spine: spines with a narrow neck maintain a high calcium concentration longer and are therefore more likely to generate an action potential upon stimulation. Second, the size of the spine influences the number of ion channels, receptors and associated proteins contained in the spine and thereby its responsiveness. Spine activity further depends on the relative concentration of various factors that positively or negatively regulate signal transduction. The observation that different spines on the same dendrite can show distinct responses therefore suggests that spines behave as independent subcellular compartments that are insulated from the rest of the cell. Such insulation appears to be a basic requirement for proper neuronal signaling and for functions such as learning and memory. Two papers in a recent issue of *Current Biology* [2,3] provide new insights into the molecular structures that are involved in the control of spine morphogenesis and potentially in their insulation.

In recent years, advanced microscopy techniques have been used to study the lateral mobility of postsynaptic receptors in dendritic membranes and have revealed that receptors move rapidly at the surface of dendritic shafts. However, receptors only traffic slowly between spines and the rest of the dendritic membrane, indicating that the spine neck can limit the exchange of transmembrane proteins between the spine and the dendrite, despite the continuity of the membrane [4,5]. This in turn suggests the presence of a diffusion barrier at the neck of spines and of specific structures in the plasma membrane that restrict the diffusion of soluble factors through the neck. Hence, beyond spine morphology, spine neck organization appears to be a structurally specialized component underlying spine compartmentalization and individualization. Until recently, there was no clear insight into the molecular basis of the functional specialization of spine necks.

It has been recently recognized, however, that compartmentalization in dendritic spines has an unexpected parallel with compartmentalization in a much simpler organism, the baker's yeast *Saccharomyces cerevisiae*. This unicellular organism has evolved a seemingly unique mode of division, whereby one daughter cell emerges from the surface of its mother at each division. This process, known as budding, makes yeast division a fundamentally asymmetric process where the two progenies, mother and bud, are not only different in size but also develop different identities [6], separate transcriptional programs and distinct lifespan potential (reviewed in [7]).

Most remarkably, mother and bud behave differently even before they separate. The bud — the only growing part of the cell — recruits a number of polarity factors to its surface to promote its growth by extending the cell wall and plasma membrane. The bud is also a site for specialized translational activity owing to the presence of polar mRNAs that are actively delivered, using actin cables as tracks [8]. Among these polar mRNAs are those encoding bud-specific transcription factors that are involved in the transcriptional specialization of the daughter cell relative to its mother, after the completion of cytokinesis. Finally, the bud cortex also organizes specialized signaling pathways involved, for example, in the control of mitotic exit. In contrast, the mother cell, which does not grow, is responsible for all transcriptional activity of the cell until cytokinesis.

As with spines, the compartmentalization of the yeast cell into bud and mother proceeds from the specialization of the mother–bud neck, where diffusion barriers for membrane and peripheral membrane proteins assemble, not only in the plasma membrane itself [9,10], but also in more internal membranes, such as the endoplasmic reticulum

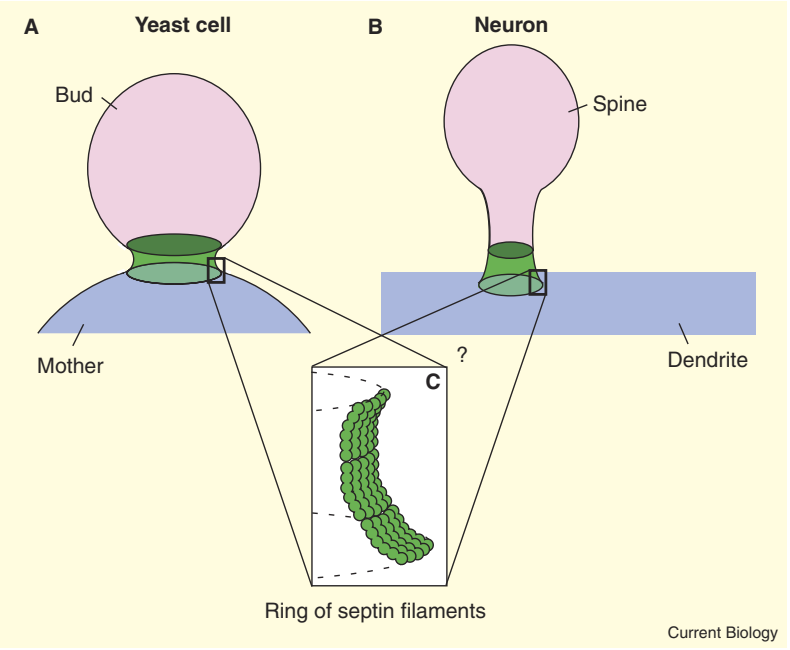

Figure 1. Potential similarity between the yeast bud neck and the neck of dendritic spines.

(A) The yeast bud neck serves as a diffusion barrier to allow the functional differentiation of the bud (pink) from the mother (blue). This barrier function is achieved through the septin-dependent recruitment (green) of specialized factors to the bud neck. (B) In neurons, spines also differentiate from the rest of the dendrite, and Xie *et al.* [2] and Tada *et al.* [3] now demonstrate that septins localize to the necks of spines. (C) Model for the formation of septin rings at the neck of yeast buds and dendritic spines. This model is based on the orientation of the filaments established for yeast [18], and the organization of the septin complexes is based on recently published structural data [19,20].

(ER) [11]. These barriers, which can be easily visualized using photobleaching techniques, similar to those used in neurons, help maintain asymmetries between bud and mother cortices, and hence contribute extensively to the individualization of the bud as it emerges from its mother [10]. Thus, with the exception that no compartmentalization is observed for the cytoplasm of yeast cells, dendritic spines and yeast buds possess a strikingly similar ability to become insulated from the rest of the cell.

Decades of work have provided numerous insights into the molecular mechanisms underlying the specificity of the bud neck (reviewed in [12]). The main players are the septins, a class of membrane-associated GTPases that assemble into multimeric complexes and form higher-order structures such as filaments and sheets of bundled filaments *in vitro* [13] and *in vivo* [14]. These higher-order structures form a septin collar (Figure 1A), comprising a ring of septin filaments tightly associated with the plasma membrane at the bud neck. The septin collar serves as a platform for the recruitment of numerous other molecules to the cortex of the bud neck. This collar is thereby involved in the assembly of diverse cellular machineries, such as exocytic factors required for the specialization of the cell wall at the bud neck, microtubule capture sites for the positioning of the mitotic spindle, signaling cascades involved in the control of anaphase onset, and the cytokinetic machinery that separates bud and mother cells at the end of mitosis [12]. The septin ring and associated kinases are also involved directly in the formation of the diffusion barriers in the plasma membrane, and indirectly in the assembly of the diffusion barrier in the ER membrane at the bud neck.

Now Xie *et al.* [2] and Tada *et al.* [3] have reported the identification and the first functional characterization of a septin complex at the neck of spines and at dendritic branch points in mammalian hippocampal neurons (Figure 1B). Their studies clearly establish that this septin complex, comprising Sept5, Sept7, and Sept11, is required for spine maturation and proper spine morphogenesis. The data also suggest that Sept2 and Sept6, the localization of which is not yet clear, are involved in spine morphogenesis. These new findings in mammalian cells make it tempting to speculate that the molecular mechanisms underlying the compartmentalization of yeast buds and dendritic spines share similar components. This parallel is supported by the fact that septins are strongly conserved across species [15]. The new studies further lead to a generalized concept suggesting the existence of diffusion barriers formed by similar septin assemblies in different species.

Refined structural analyses will be required in the future to determine the degree of similarity of septin rings across species and confirm their universality. Moreover, molecular analyses of septin functions will also be needed to address the role of septins in different cellular compartments and cellular systems, such as in presynaptic versus postsynaptic processes in neurons. The diversity and multiplicity of septins will make these analyses complex but should provide better understanding of the functions of each individual septin. For instance, in neuronal cells, the restricted localization of specific septins at the neck of spines makes them likely to be involved in the trafficking of extra-synaptic neurotransmitter receptors — recognized to be critical regulators of neuronal activity — into the spine. Clarifying the involvement of these specific septins is therefore important. Finally, the implication of septins in various diseases, such as neurological disorders, neuropathy or neoplasia [16,17], calls for thorough *in vivo* investigations, which, in the future, may provide new perspectives for the treatment of these diseases.

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Cilia Biology: Stop Overeating Now!

Knocking out primary cilia of adult mouse tissues or a specific subset of cilia from POMC-expressing neurons in the brain initiates uncontrolled eating. This behavior leads to obesity and kidney disease.

Peter Satir

For almost fifty years, it has been known that many mammalian cell types, including neurons, possess a single cilium, which is generally missing the central microtubule pair and the dynein arms essential for ciliary motility. These non-motile, so-called 9+0 cilia were named 'primary cilia'. With considerable hubris, some cell biologists dismissed the primary cilia as vestigial. In recent years, however, these organelles have been implicated as sensory antennae — comparable to the 9+0 cilia found in sensory organs, such as the human eye or insect ears. From studies of the single celled alga *Chlamydomonas*, we have learned that virtually all cilia, including primary and sensory organ cilia, are built by a process called 'intraflagellar transport' (IFT) [1]. When one of the transport proteins, e.g. IFT88, or one of the transport motors, such as Kif3a, is missing, the cilia are not assembled and sensory signaling fails. The result is a syndrome of phenotypes caused by the failure of ciliary signaling, most probably because the membrane receptors or channels necessary for signaling cannot be properly placed in the ciliary membrane [2]. Mice lacking IFT88, the *Tg737* gene product, were developed as a model for a form of polycystic kidney disease, but they also have eye, pancreas and liver disease, and they usually die before birth [3,4]. When neuronal cilia are missing in mice, the hedgehog signaling pathway is affected, the nervous system does not develop properly and the result is also embryonic or neonatal lethality [5].

To overcome this early lethality, Davenport *et al.* [6], writing in a recent issue of *Current Biology*, studied the effect of knocking out primary cilia specifically in adult mice after development is complete. They accomplish this by using an inducible system to disrupt *Tg737* or Kif3a-based intraflagellar transport, either generally or in specific tissues. This double pronged attack makes it likely that effects on pathways outside of ciliogenesis are not counfounding the observed effects. Surprisingly, when cilia were missing from all adult tissues, the devastating abnormalities and lethality seen after embryonic loss of cilia did not occur, and severe polycystic kidneys only developed a year after induction. A similar delay in cystic kidney disease development has been reported recently [7] after adult-specific knock-out of polycystin 1, a major ciliary signaling molecule in the disease. This effect may be due to a greatly reduced rate of cell division and a different pattern of gene expression [7]. Changes in cell proliferation rate may relegate the