



paralog that partners with cyclin K (5)—promote ptRNA accumulation by increasing the frequency of premature termination (9, 10) rather than acting posttranscriptionally. Mutations in *CDK12* and *CDK13* generate different ptRNA profiles, with *CDK12* mutations preferentially affecting genes involved in an effective DNA damage response (DDR) (9, 10). The consequent reduction in full-length mRNAs encoding DDR factors is thought to underlie defects in homology-directed repair and sensitivity to poly(ADP-ribose) polymerase (PARP) inhibitors—a BRCA-like phenotype—of *CDK12* mutant cancers (11). The findings of Insko *et al.* raise the possibility that ptRNA translation might also contribute to oncogenesis in *CDK12* mutant tumors.

CDK12 and *-13* share ~92% identity in their kinase domains, have similar structures in complexes with cyclin K (5, 12, 13), and are sensitive to the same small-molecule inhibitors (14). Selective inhibition of either CDK caused perturbations of RNAPII elongation, which were more widespread when both kinases were inactivated (15). Therefore, *CDK12* and *-13* are at least partially redundant. The requirement of *CDK13* in nuclear RNA surveillance, as uncovered by Insko *et al.*, may be unique to *CDK13* and specific to *CDK13*–cyclin T1. By associating with multiple cyclins, CDKs involved in cell cycle control acquire different substrate specificities or subcellular localizations (1); this may be an example of such promiscuity by a transcriptional CDK, but whether *CDK13*–cyclin T1 differs from *CDK13*–cyclin K in substrate specificity or functional targeting (e.g., recruitment to chromatin or activity in the nucleoplasm) remains to be tested. It is not necessarily the case, however, that ZC3H14 phosphorylation must occur posttranscriptionally; it might occur during transcript elongation but execute its function after transcription terminates. As drugs targeting transcriptional CDKs advance toward clinical applications, a better understanding of CDK function in posttranscriptional RNA metabolism, in both normal and cancer cells, is needed. ■

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Organization of the ctenophore (*Mnemiopsis leidyi*) nerve net raises questions about the evolution of the animal nervous system.

NEUROSCIENCE

Neurons that connect without synapses

The ctenophore nerve net suggests a complex evolutionary history of the animal nervous system

By Casey Dunn

Long-standing wisdom about the evolution of the animal nervous system posits that all neurons connect to each other with synapses and that the nervous system arose once in evolutionary history and was never lost. But this tidy picture has seen surprising challenges in recent years. On page 293 of this issue, Burkhardt *et al.* (1) provide new information on the structure of the nervous system of ctenophores—marine invertebrates commonly known as comb jellies. These exciting findings further erode this traditional view and help build a fascinating and more complex understanding of nervous system evolution.

All living animals belong to one of five groups. Of these, Porifera (sponges) and Placozoa (small, disc-shaped animals) lack neurons. Ctenophora (comb jellies) and Cnidaria (corals, medusa jellyfish, siphonophores, and others) have nerve nets—nervous systems with neurons arranged into diffuse networks. Bilateria (the group that contains most animal species, including vertebrates, arthropods, and many other invertebrates) includes some animals with a nerve net, but most have a central nervous system.

The traditional explanation for this nervous system diversity is that these organisms represent ancestral steps in the increase of nervous system complexity. In this scenario, sponges diverged first from other animals, before the origin of the nervous system (2), and nervous system complexity increased in a ratchet-like manner in other animals.

It was unexpected, then, when the first Placozoa (3) and Porifera (4) genomes were sequenced and found to contain genes that were previously thought to be specific to nervous system function. A closer look in placozoans found that they have gland cells that secrete neurosecretory components (5). More recently, single-cell expression analyses revealed that some sponge cells communicate through structures that resemble synapses (6). This has made it clear that different nervous system features, such as neuron morphology and neuron signaling molecules, have different distributions across animals.

In parallel, traditional hypotheses about the earliest relationships in the animal phylogeny have been challenged. Some phylogenomic analyses support Porifera as the sister group to all other animals (7). There is growing evidence, however, that Ctenophora is the sister group to all other animals (8, 9). The latter indicates that some nervous system features arose independently in ctenophores or that some nervous system components were lost in

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sponges. This further challenges the historically accepted notion that there has been a simple, stepwise increase in nervous system complexity through the course of animal evolution.

Burkhardt *et al.* provide critical understanding about the structure of the ctenophore nerve net that goes right to the heart of these questions. The authors report that the ctenophore nerve net is unlike the nervous systems of other animals. The difference is particularly relevant to debates at the dawn of neurobiology. In the late 19th century, Golgi proposed that the nervous system is a syncytial continuum, with the neurons directly connected with shared cell membranes and cytoplasm (10). This is known as the reticulate theory of nervous system structure. Ramón y Cajal proposed instead that neurons are distinct cells (11). This is known as the neuronal doctrine, and the discovery of synapses seemed to settle the debate in favor of this view.

Burkhardt *et al.* used serial block face scanning electron microscopy to make three-dimensional ultrastructural reconstructions of a ctenophore subepithelial nerve net. They observed that this nerve net is not formed by neurons connecting to each other with synapses. Instead, the processes of the neurons are directly fused to each other, forming a syncytial continuum. There are synapses elsewhere, including where the nerve net connects to effector cells, but the subepithelial nerve net itself is not formed with synaptic connections.

The findings of Burkhardt *et al.* suggest that Ramón y Cajal's neuronal doctrine and Golgi's reticulate theory are not universally exclusive hypotheses. Most animals with nervous systems (cnidarians and bilaterians) conform to the neuronal doctrine of separate cells that communicate through synapses. The subepithelial nerve net of this ctenophore species consists of fused neurons, as in Golgi's reticulate theory. It was never a question, then, of whether all animal nervous systems conform to the neuronal doctrine or the reticulate theory but rather of describing which animals conform to which theory.

There is much that remains unknown about the anatomy, physiology, genome biology, and natural history of nonbilaterian animals. This creates the dual illusions that nonbilaterians are simpler than they are (because studies tend to focus on bilaterian traits they lack rather than the many distinctive traits that they have) and that these animals are more similar to each other than they actually are (because superficial similarities are often prioritized over clear differences) (12). Studies such as that of Burkhardt *et al.* are important for dispelling such illusions. For example, ctenophores and cnidarians are

both transparent and squishy (they are “jellyfish” in the broad sense), and both have nerve nets. Historically, they have therefore been placed together in the animal tree of life as Coelenterata. This grouping has been taken as evidence that Ctenophora cannot be a sister group to all other animals. But many animals that live suspended in the open ocean (as many ctenophores and cnidarians do), including some annelids and molluscs, have independently converged in soft transparent bodies, which indicates that so-called jellyfish traits are not good support for Coelenterata (12). This leaves the nerve net as one of the only traits uniting Ctenophora and Cnidaria into the single group Coelenterata. Burkhardt *et al.* show that resemblances of nerve nets between Ctenophora and Cnidaria are also superficial, and they remove some of the last remaining evidence for Coelenterata.

The findings of Burkhardt *et al.* help drive home the point that the gain of the nervous system should not be marked as a singular event in the history of animal evolution. Instead, the evolution of many constituent traits that can together make up a nervous system should be considered, including morphology, molecular inventory, and physiology (13). Some animals may have lost nervous system components, as may be the case in sponges. Sponges are filter feeders, which tend to have reduced nervous systems even within Bilateria. Other animals may have convergently evolved superficially similar nervous system features, such as the nerve nets of ctenophores and cnidarians, when faced with the same functional challenges.

It is exciting that such fundamental observations about animal anatomy, like those described by Burkhardt *et al.*, can still have such big implications for the study of animal evolution. The work of Burkhardt *et al.* shows how much potential lies at the growing intersection of comparative morphology, phylogenetics, physiology, and genomics. Answering the most important open questions about early animal evolution will require the integration of all these diverse approaches and perspectives. ■

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MATERIALS SCIENCE

Fixing the desalination membrane pipeline

Materials discovery alone has not translated into lower-cost water treatment

By Jeffrey R. McCutcheon¹ and Meagan S. Mauter²

Global water scarcity is motivating the expanded treatment of seawater, brackish water, and wastewater. Robust treatment trains typically include semipermeable reverse osmosis (RO) membrane barriers that allow the passage of clean water while retaining the majority (>99%) of salts, dissolved organics, and pathogens. Despite considerable research effort to optimize membrane chemistry, morphology, and module designs for diverse source-water and end-use applications, most treatment trains deploy RO membrane modules that closely resemble those developed for seawater desalination over 50 years ago. The enduring dominance of these traditional RO membranes reveals a broader need within the water treatment community to reassess the innovation pipeline for membranes for desalination and water treatment.

Past breakthroughs in membrane-based processes for desalination and water treatment were enabled by the joint discovery of new materials with desirable separation properties alongside manufacturing tools for processing these materials into membranes at scale. The first set of innovations in the 1960s combined the high-salt-rejecting properties of cellulose acetate with the nonsolvent-induced phase separation manufacturing process (1). Twenty years later, the discovery of aromatic polyamide materials manufactured through interfacial polymerization led to the thin-film composite (TFC) membrane that delivered 10-fold improvements in both water productivity

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Neurons that connect without synapses

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