the C-terminal arm and a further cysteine of DsrC in close proximity are involved in reduction of sulfite to sulfide. However, the exact reaction mechanism has remained unresolved (*9*–*11*).

Santos *et al.* now use an array of elegant biochemical, genetic, and physiological in vitro and in vivo experiments, in combination with mass spectrometry, to show that the DsrC protein is a co-substrate for sulfite reduction by DsrAB. They reveal that a sulfite-derived, zero-valent sulfur bridges the two conserved cysteine residues of the DsrC protein during sulfite reduction. In the first step of trisulfide synthesis, the coupled siroheme–[4Fe-4S] catalytic site of DsrAB receives two electrons from a reductant of unknown identity. Sulfite then binds to siroheme and gets reduced to an S(1+) intermediate; the latter leaves the iron coordination sphere and finally ends on DsrC, forming a protein-based trisulfide (see the figure, middle panel).

Deletion of the gene encoding DsrC is lethal for the microorganisms; hence, DsrC is vital for catalysis and energy conservation. The trisulfide is presumably reduced at a membrane-bound complex and sulfide is liberated as a product. In this way, the reduction of sulfite in the cytoplasm can be efficiently coupled to energy conservation at the membrane.

The discovery of the trisulfide in DsrC as the product of sulfite reduction represents major progress in understanding microbial sulfur conversion. It redefines the in vivo redox chemistry of DsrAB and links the energy-providing redox reactions to the generation of a chemiosmotic gradient. This finding moves the sulfate reducers a bit closer to the methanogens, underscoring the similarities of anaerobic respiration among these organisms and pointing to their common ancient origin. Researchers should now have a closer look at the membrane protein complexes involved. Knowing the stoichiometry of ions translocated across the membrane per electron transferred will be crucial for understanding the bioenergetics of DSR. Moreover, the electron donors for DsrAB and for the other enzymes of DSR have not yet been identified. ■

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NEUROSCIENCE

Opting in or out of the network

Does learning commit neurons that are predisposed to recruitment to a memory network?

By **K. C. Martin**[1] *and* **E. M. Schuman**[2]

Plasticity, a general feature of all nervous systems, is essential for the survival of organisms, allowing them to respond and adapt to their environment through the processes of learning and memory. Even relatively simple forms of learning, such as habituation (a reduction in responsiveness to stimuli that have no immediate consequences) or sensitization (an increase in overall responsiveness following an arousing stimulus), involve changes in neural gene transcription and protein translation, and the modification of neuronal connections (synapses) and neural networks (*1*). In a recent study, Hill *et al.* (*2*) examined the mechanisms that underlie the sensitization of a swimming response in the marine mollusk *Tritonia*. The authors propose that memories are stored as an expansion in the number of neurons in networks that underlie behavior, presumably to enhance responsiveness to other potential stimuli in the environment. But is this simply too simple a model?

> ***"...'nonsynaptic' mechanisms ...occur together with synaptic changes in... learning..."***

Hill *et al.* made use of a voltage-sensitive dye that allowed them to monitor, simultaneously, the activity of ~66 neurons in the pedal ganglion, the neurons that control *Tritonia*'s escape swim response (*2, 3*). For many rhythmic motor behaviors like swimming, the neural activity that drives and sustains these behaviors involves central pattern-generating circuits and "bursting"—clusters of action potentials elicited with a relatively high frequency—that entrain and drive downstream neurons in the network. Following a sensitizing stimulus (shock to the pedal nerve), the onset latency for the *Tritonia* swim motor program is reduced, indicating that the system exhibits sensitization (*4, 5*). Hill *et al.* examined the contribution of individual neurons to this program before, during, and after sensitization. The authors built upon earlier identification of neurons within the pedal ganglion that contribute to the swim motor program with different propensities to burst—reliable bursters, variable bursters, and nonbursters (*3*). By monitoring the activity of each class of neuron, they observed that after sensitization, an increased number of neurons exhibited reliable bursting behavior due to the conversion of some neurons from variable or nonbursting to reliable bursting phenotypes (see the figure). Dissipation of sensitization was accompanied by a return to the original network size. Remarkably, however, the constituent neurons in each class of the network (reliable bursters, variable bursters and nonbursters) following loss of sensitization were different from those observed before sensitization, indicating that the swim motor program is encoded by a dynamic network rather than by a fixed network of specific neurons.

To identify the cellular mechanisms that drive the reorganization observed during sensitization, Hill *et al.* focused on neurons containing the neurotransmitter serotonin that constitute part of the swim central pattern generator (*6*). Not only did stimulation of these neurons decrease the latency of the swim motor program (consistent with sensitization), but application of serotonin to the pedal ganglion decreased latency and increased the number of reliable burster neurons in the swim motor program network. As such, activation of a small number of serotonergic neurons was sufficient to implant a "false sensitization memory" in the system.

The findings of Hill *et al.* add to a rich history of discoveries about the mechanisms of learning and memory in invertebrate "simple systems." Although these systems contain a relatively small number of neurons, they undergo multiple and robust forms of learning. Two features contribute to the experimental tractability of these simple systems: The neurons are often identifiable from animal to animal; and isolated preparations of these neurons undergo forms of plasticity that mirror learning in the animal. These features facilitate the delineation of circuits underlying

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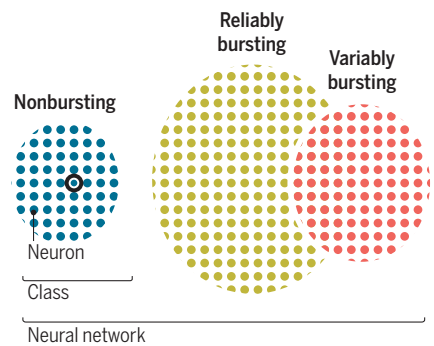
Sensitization and shuffling. The 66 neurons recorded in *Tritonia*'s pedal ganglion that control the swim motor program are present in three different classes. During sensitization to a stimulus and memory formation, neurons presumably predisposed to recruitment move into the reliably bursting class. After loss of sensitization, the number of neurons in each class returns to the naïve state, but the constituent neurons are different.



behavioral modification, and become even more powerful when combined, as by Hill *et al.*, with the use of voltage-sensitive dyes to monitor, simultaneously, the activity of many neurons in a circuit.

The conclusion from Hill *et al.* is that neurons are predisposed to join a given network, and that learning, acting via neuromodulation, commits these predisposed neurons to the network. This relatively "simple" idea is contrasted with the prevailing view that memories are stored as activity-dependent changes in synaptic strength and number, or synaptic plasticity. However, just as simple systems generate complex behaviors from a small number of neurons and circuits, they also do so using multiple mechanisms. Although studies in the marine mollusk *Aplysia californica* have emphasized the importance of changes in synaptic strength and number in mediating learning, including sensitization (*7*), other studies in *Aplysia* and the related mollusk *Hermissenda* have identified "nonsynaptic" mechanisms, including changes in excitability that occur together with synaptic changes in both nonassociative and associative forms of learning (*8, 9*). A remarkable set of studies on a central pattern generator in another invertebrate "simple system," the crustacean stomatogastric ganglion, has revealed tremendous functional variability in neuronal networks, emerging from activity-dependent changes in synaptic strength and excitability (*10*). The findings of Hill *et al.* are indeed reminiscent of the work on the lobster, which established that neurons switch allegiance from one motor pattern to another under neuromodulatory control (*11*). This indicated that the same circuit elements can be recombined in numerous ways, to generate behavioral flexibility.

Hill *et al.*'s framework of synaptic plasticity opposed to network expansion, and of changes in synaptic strength opposed to alterations in neuronal excitability, is simply too simple. The authors do not explore the mechanisms by which the bursting profile of the individual neurons within the network are altered. Changes in bursting behavior could be elicited by changes in intrinsic ionic conductances, but also could be mediated by alterations in excitatory and/or inhibitory transmission in the network. Indeed, the two mechanisms often co-occur (*10*). For example, the usual line-up of ion channels that alter excitability in neuronal processes can also change the properties of axon terminal depolarization and repolarization, resulting in changes in the kinetics and amount of neurotransmitter released. Thus, it's more likely that both mechanisms, and not any single mechanism, are operative, a conclusion often reached in arguments about mechanism in neurobiology. ■

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SYNTHETIC BIOLOGY

Designer cells finely tuned for therapy

Cells are engineered for on-demand control of psoriasis

By **Jeremy Di Domizio** *and* **Michel Gilliet**

The use of disease-specific molecular markers to select the appropriate treatment and dosing regimen is at the essence of precision medicine and represents a major research initiative for the years to come (*1*). A recent study by Schukur *et al.* (*2*) provides a major conceptual advance in this arena, particularly in the treatment of chronic inflammatory diseases. The study shows that synthetic biology can be used to generate cells that selectively respond to a combination of cytokine signals, providing therapeutic output that is disease-specific and related to disease activity. The findings hold great promise for treating psoriasis and other chronic-relapsing inflammatory diseases, including Crohn's disease and rheumatoid arthritis.

Psoriasis is a chronic-relapsing T cell–mediated inflammatory disease of the skin characterized by scaly red plaques that can cover large surfaces of the human body (*3–5*). These plaques are triggered by aberrantly activated dendritic cells that produce the cytokines tumor necrosis factor (TNF) and interleukin-23 (IL-23). These cytokines favor the generation of T helper cell 17 (T_H17) cells, which release the proinflammatory cytokines IL-17 and IL-22 that contribute to disease pathogenesis. The elucidation of immune pathways in psoriasis has led to the development of biologics that target and inhibit these pathogenic cytokines. Blockade of TNF, IL-23p40, and IL-17 by biologics is currently part of the strategic arsenal to treat moderate to severe psoriasis, but it has limitations. Dosing regimens are typically continued for long periods of time regardless of clinical activity of the disease. Because the targeted cytokines are also involved in antimicrobial defense, these standard dosing regimens result in

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