

EPENDORF ESSAY WINNER

Deconstructing *C. elegans* Sensory Mechanotransduction

Miriam B. Goodman

As human beings depend greatly on the sensory neurons that govern our sense of touch. If such cells cease to function properly, we may lose the ability to respond to another's touch—say, as a dancer responds to a partner's lead. Additionally, we may be unable to respond to a more painful and potentially damaging event. Reduced touch sensation, or peripheral sensory neuropathy, is especially common in people with diabetes and is a significant contributing factor to lower-extremity amputations (1). Other mechanoreceptor neurons mediate equally vital sensory modalities: proprioception for balance and the control of internal organs, such as the bladder and kidney, and baroreception for homeostatic control of heart rate. Despite the importance of these mechanical senses, however, exactly how sensory cells detect the mechanical energy in a touch, the bend of a limb, or changes in blood vessel diameter remains a mystery.

Although electrical responses to mechanical stimuli were first measured in the 1920s (2, 3), surprisingly little is known about the protein machinery that converts mechanical energy into ionic currents in touch-sensitive neurons, and even less is known about how the individual protein components of this nanomachine operate. Research into the molecular basis of touch transduction lags behind research into other senses because, in many animals, sensory nerves that detect touch are scattered across the body and are deeply embedded in the skin—two properties that complicate traditional biochemical approaches. To circumvent these difficulties, we study touch sensation in the nematode worm *Caenorhabditis elegans*. This is the only animal for which we know the cellular anatomy of the entire nervous system. Compared with tens of thousands cutaneous sensory neurons in mammals, each worm has only six nerve cells that govern touch sensation

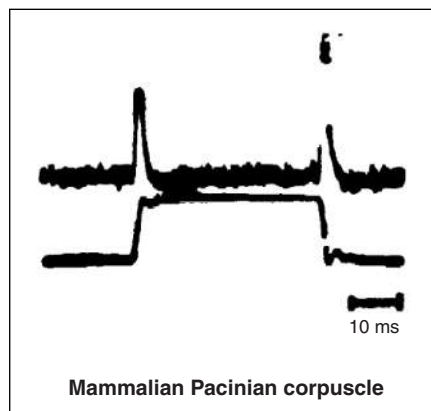
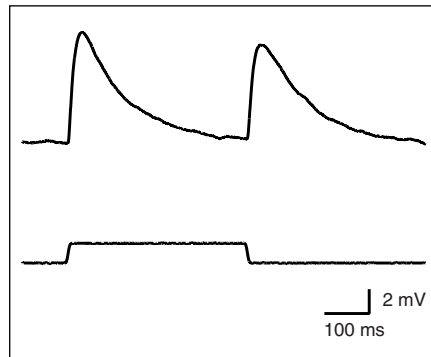
along its body wall (4). Genetic analyses by Martin Chalfie and his colleagues revealed that the worm's sense of touch requires at least 12 specific proteins, encoded by the *mec* or mechanosensory abnormal genes [reviewed in (5)].

To understand how proteins identified by genetic screens contribute to mechanotransduction, my collaborators and I developed methods for *in vivo* recording from identified sensory neu-

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Responding to touch. Comparison of mechanoreceptor potentials in *C. elegans* touch receptor neurons (**top**) and mammalian Pacinian corpuscles (**bottom**). [Data in the bottom panel were adapted from (8)]

rons in *C. elegans* (6) and used these methods to record electrical responses to external force in *C. elegans* touch neurons (7). The initial experiments focused on a pair of neurons that sense gentle touch to the worm's tail. We found that receptor potentials in *C. elegans* touch neurons are reminiscent of the responses of vibration-sensitive Pacinian corpuscles

measured 40 years ago in mammals (8), which suggests that aspects of mechanotransduction may be similar in nematodes and mammals (see the figure). Activation of mechanoreceptor currents (MRCs) in *C. elegans* touch neurons is extremely rapid: Current begins to flow within 1 ms of force applica-

tion. It is the first step in transduction, preceding both membrane depolarization (7) and increases in somatic Ca^{2+} (9). Such latencies are nearly two orders of magnitude faster than those reported for *Drosophila* phototransduction (20 to 100 ms), the current record-holder for a second messenger-mediated G protein signaling cascade (10). Thus, external force might open ion channels directly rather than operating via a separate force receptor.

We are also working to deconstruct the mechanotransduction complex by asking how mutations in *mec* genes alter MRCs *in vivo*. The first mutations we studied eliminate or alter four membrane proteins (MEC-4, MEC-10, MEC-2, and MEC-6), which are believed to form the ion channel at the core of the transduction complex. Consistent with this idea, null mutations in *mec-4*, *mec-2*, and *mec-6* abolish MRCs without affecting other ion currents, which indicates that these proteins are specifically required for the generation of MRCs and are likely to encode subunits of the ion channels that carry MRCs *in vivo*. Additionally, an allele of *mec-10*, which substitutes glutamate for a conserved glycine residue near the second transmembrane domain of MEC-10 (11), reduced but did not eliminate MRCs. This reduction appears to result from altered ion selectivity, as opposed to a genetic deletion of transduction channels. In short, all mutations that diminish touch sensation abolish or alter MRCs *in vivo*. Our findings link the application of external force to the activation of a molecularly defined sensory transduction channel.

The author is in the Department of Molecular and Cellular Physiology, Stanford University School of Medicine, Stanford, CA 94305, USA. E-mail: mbgoodman@stanford.edu

In addition to analyzing electrical responses to external force *in vivo*, we have taken the first steps toward reconstructing this ion channel complex in *Xenopus* oocytes. So far, we have bypassed the need for mechanical gating by studying a constitutively active mutant channel (the “d” form). Coexpression of MEC-4d and MEC-10d produces a constitutively active current that, like native MRCs (7), is carried by Na⁺ and blocked by amiloride (12). By contrast with native MRCs, however, neither MEC-2 nor MEC-6 was required to produce detectable channel activity in oocytes (12, 13). Both accessory proteins increased activity of expressed MEC-4d/10d channels at least tenfold without inducing a detectable increase in surface expression of either MEC-4 or MEC-10 (12, 13), which suggests that MEC-2 and MEC-6 increase single-channel conductance or open probability. Preliminary studies of single MEC-4d/10d channels suggest that neither MEC-2 nor MEC-6 significantly increases single-channel conductance, however (14). Additional studies of both expressed and native channels are needed to clarify the function of these accessory proteins in mechanotransduction.

By demonstrating that native MRCs require intact copies of *mec-4*, *mec-10*, *mec-2*, and *mec-6*, we show that each of these four genes is required for the first step in mechanotransduction—namely, activation of sensory mechanotransduction channels. Such channels may be directly gated by mechanical energy, because MRCs can be detected within 1 ms of stimulation. Because both *C. elegans* touch receptor neurons and mammalian Pacinian corpuscles respond preferentially to changes in force (7, 8), we speculate that DEG/ENaC channels could be sensory mechanotransduction channels in nonciliated mechanoreceptor neurons in nematodes and mammals alike. These initial studies raise new questions, such as: How do touch receptor neurons detect changes in force while remaining insensitive to continuous force application? How is force transferred from the worm’s cuticle to transduction channels? What determines sensitivity? A better understanding of the answer to this last question could lead to improved diagnosis and treatment of sensory neuropathy.

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 15. The research described here is the happy result of excellent collaborations with scientists at the University of Oregon, Columbia University, and Stanford University. It would not have been possible except by working jointly. I thank all of you. Research in my lab is supported by fellowships from the Alfred P. Sloan Foundation, the Donald B. and Delia E. Baxter Foundation, and a grant from the National Institute of Neurological Disorders and Stroke.

2004 Grand Prize Winner

Dr. Miriam B. Goodman grew up in Lexington, Massachusetts, and Bethesda, Maryland. As a high school student, she worked in research labs at the National Institutes of Health where she wrote scientific software. She earned a bachelor’s degree in Biochemistry from Brown University in 1986. As a graduate student in neurobiology at the University of Chicago, she analyzed voltage-dependent ion channels that tune vertebrate hair cells. After being awarded her Ph.D. in 1995, she pursued postdoctoral work in *C. elegans* neurophysiology and genetics at the University of Oregon and Columbia University. Currently, Dr. Goodman is an Assistant Professor of Molecular and Cellular Physiology at Stanford University. Work in her laboratory focuses on delineating the molecular events that give rise to the sense of touch. Outside the laboratory, Dr. Goodman enjoys cooking with friends, hiking, rock-climbing, and going to the movies. Though currently sidelined, Dr. Goodman has also played soccer since age 8.



Finalists



Kang Shen, for his essay “Synaptic Matchmakers: Molecular Mechanisms of Synaptic Specificity.” Dr. Shen was born and raised in Wuhan, China. He studied clinical medicine at Tongji Medical University of China. After graduating in 1994, he joined the graduate program at Duke University, where he studied the spatial and temporal control of CaMKII localization in hippocampal neurons in the laboratory of Dr. Tobias Meyer. After receiving his Ph.D. in 1999, he pursued postdoctoral work in Dr. Cornelia Bargmann’s lab at the University of California, San Francisco, where he addressed the question of synaptic specificity, using *C. elegans* as a model system. Dr. Shen started his own lab at Stanford University in 2003, focusing on understanding molecular mechanisms of synaptic target specificity. Outside of the laboratory, Dr. Shen enjoys a variety of sports and outdoor activities.

Qin Shen, for her essay “Preventing Aging in Neural Stem Cells: Regulating Asymmetric Versus Symmetric Cell Divisions.” Dr. Shen was born and grew up in China. She earned her Bachelor’s degree in Pharmacology from Shanghai Medical University in 1991. In 1996, she entered the graduate program in Neuroscience at Albany Medical College, New York, under the guidance of Dr. Sally Temple, who specializes in neural stem cell development. Her Ph.D. project, completed in 2001, focused on asymmetric cell division and the generation of cell diversity in the embryonic murine cerebral cortex. She is now a postdoctoral fellow in Dr. Temple’s laboratory working on mechanisms regulating neural stem cell self-renewal and cell fate choices, including interactions between neural stem cells and endothelial niche cells. The mother of a toddler, Dr. Shen also carves out a little time for gardening and reading.



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