PROFILE

Profile of David D. Ginty

Sandeep Ravindran, *Science Writer*

The sense of touch is key to humans' ability to experience the world, but unraveling the neural pathways underpinning this key sense has been a challenge. David D. Ginty has spent more than two decades investigating the development of the somatosensory system and fundamental mechanisms underlying the sense of touch. The Edward R. and Anne G. Lefler professor of neurobiology at Harvard Medical School and an investigator of the Howard Hughes Medical Institute, Ginty has combined a variety of sophisticated genetic tools with physiological, developmental, and behavioral analyses to uncover the peripheral sensory neurons of touch and the central nervous system circuits they engage.

Ginty discovered his love of the natural world at an early age through many childhood hours spent exploring the Connecticut outdoors and catching fish, frogs, and turtles with his older brother, Mark. Ginty's interest in research was kindled during his time synthesizing porphryin ring compounds with his organic chemistry professor, James Thomas at Mount St. Mary's College, Maryland. "That was the first time I realized that one could actually make a living testing, tinkering, brainstorming, and ultimately finding answers to interesting questions," says Ginty.

David D. Ginty. Image courtesy of Harvard Medical School.

However, it was Ginty's experiences with his doctoral advisor, Ed Seidel at East Carolina University, that cemented his desire to spend the rest of his life as an academic scientist. "Ed exuded the joy and satisfaction that comes with scientific discovery," Ginty says. Later, as a postdoctoral fellow with Michael Greenberg at Harvard Medical School, Ginty worked on the mechanisms of action of neuronal growth factors. "Mike is not only a brilliant scientist but also a terrific mentor and role model," he says.

When Ginty started his own laboratory at The Johns Hopkins University, his interest in studying growth factor signaling led him to focus on the peripheral nervous system. Over the course of his career, Ginty has combined a variety of sophisticated genetic tools with anatomical, physiological, developmental, and behavioral analyses to understand the peripheral sensory neurons of touch and the central nervous system circuits they engage. Ginty has discovered many of the mechanisms and signals regulating the activation, growth, and survival of sensory neurons. He has also tracked the functional organization of different sensory neuron types in the skin and their projections to the spinal cord; Ginty describes some of his latest findings in his Inaugural Article (1). For his many discoveries, Ginty was elected to the National Academy of Sciences in 2017. However, back when Ginty was starting his scientific career as a developmental neurobiologist, he had little idea that he would end up studying the sense of touch.

From Growth Factors to Neurons of Touch

Ginty's initial interest was in how growth factors work to promote cellular growth and survival. During his postdoctoral fellowship, he began to study a well-explored growth factor, nerve growth factor (NGF).

NGF targets neurons in the peripheral nervous system, which led Ginty to focus on these neurons as he studied NGF signaling in vitro. When he started his own laboratory at The Johns Hopkins University in 1995, Ginty began to examine growth factor signaling in vivo, initially in simple systems. "Our goal was to study how growth factor signaling events control survival and axonal growth of neurons in vivo, which for NGF are sympathetic neurons and small diameter sensory neurons," he says. Ginty also teamed up with his friend and Johns Hopkins colleague Alex Kolodkin,

This is a Profile of a member of the National Academy of Sciences to accompany the member's Inaugural Article on page 9168 in issue 19 of volume 116.

Published online June 3, 2019.

www.pnas.org/cgi/doi/10.1073/pnas.1908066116

to study how the projections of developing neurons are properly guided to their targets.

Technological advances would dramatically change the way Ginty approached these questions. "Those were early days of using targeted homologous recombination approaches to manipulate the genome in a way that you could actually ask questions about growth factors and guidance cues, gene function, and signal transduction in vivo," says Ginty. "When we started doing that, I was just immediately hooked because it was so powerful seeing in vivo phenotypes."

Ginty spent the next 10 years developing mouse genetic tools and harnessing their power to study the in vivo functions of growth factors and axonal guidance cues and the signaling pathways they control. The principal goal was to understand how neuronal growth factor and axonal guidance cue signals contribute to the development of the peripheral nervous system.

"Many years into that, we realized that for the developing sensory nervous system, we were studying development of a very heterogeneous population of neurons," says Ginty. For example, there are seven or more different subtypes of peripheral sensory neurons that respond to mechanical stimulation of the skin. Each of them responds in a different way and in response to different stimuli. "Some are slowly adapting to indentation of the skin, some are rapidly adapting, and they have different conduction velocities, so their electrical impulses propagate from the skin into the spinal cord in different patterns and at different speeds," says Ginty.

The heterogeneity prompted Ginty to move from a generalized approach to a focus on specific sensory neuron subtypes. "There must be unique signals and cues controlling development of the range of sensory neuron subtypes because each one ends up being morphologically and physiologically different," he says. "We would also like to know what features of these neurons give rise to their unique response properties."

Labeling Sensory Neuron Subtypes

Slightly more than a decade ago, Wenqin Luo, a postdoctoral fellow in Ginty's laboratory, found that she was able to use genetic tools to label one subtype of somatosensory neuron. Around the same time, it was becoming clear that the growth factor receptors Ginty had spent many years studying are expressed in different populations of sensory neurons, and many of the genetic tools his laboratory had generated enabled unprecedented insights into sensory neuron subtypes.

"That early work made us realize that we could use existing and new genetic tools to gain access to each of the principal sensory neuron subtypes, allowing for focused examination of each one's developmental pathways, morphological and physiological properties, and functions," says Ginty. "That was a turning point for us."

Over the last 12 years, Ginty's laboratory has identified genes that are uniquely expressed in sensory neuron and spinal cord neuron subtypes. "We can use homologous recombination, or more recently CRISPR-Cas9, to harness specific patterns of expression of genes for driving expression of reporter proteins and actuators in sensory neuron and spinal cord neuron subtypes," says Ginty.

Ginty and his colleagues have used gene-targeting strategies to label sensory neurons and spinal cord neurons with different fluorescent proteins to visualize them and see what their projections look like. Visualizing specific neuron subtypes also allowed the researchers to record their electrical activity. "That allows to us understand what they're responding to when we tickle the skin in a particular way," says Ginty. He has also expressed proteins, such as channelrhodopsin, in specific sensory neuron subtypes. "If you express channelrhodopsin through genetic means in just one sensory neuron subtype and shine light on the skin, then you can see what kind of physiological response or behavioral response is evoked just by activating that one subtype," he says. "That is enormously powerful."

Ginty and his colleagues could now ask questions about a specific sensory neuron subtype, such as what kind of endings it forms in the skin and in the spinal cord. "Each one forms a different type of ending in the skin, and the ending structures provide clues as to why that neuron responds to mechanical stimuli the way it does," says Ginty. "It became immediately obvious that having these genetic tools provided tremendous new opportunities for revealing the secrets of the functional organization of the adult somatosensory system."

Ginty's work has greatly improved our understanding of the mechanisms of touch perception and of the features underlying the physiological differences between different sensory neuron subtypes (2–5). It has also elucidated some of the higher-order complexity of touch perception, which enables the sensing of complex features of mechanical stimuli, such as the direction and speed of movement across the skin.

"We're starting to understand how the central nervous system receives this complex information emanating from the skin that we imagine as being propagated like a symphony, with different levels and patterns of activity of each of the seven or so touch neurons," says Ginty. "We want to know how the central nervous system interprets these different ensembles of activity that are carried by these sensory neurons, the primary instruments of touch, if you will, that innervate the skin."

Studying Nerve Endings and Development

In his Inaugural Article (1), Ginty and his colleagues probed the functional organization of different sensory neuron subtypes. In particular, they looked at the five light touch-sensitive neurons that project into hairy skin, which comprises most of the skin on the body. By labeling each of the neurons of a particular class in either red, green, or yellow, the researchers could look at the skin and identify where the different color endings were relative to each other, and

whether they overlapped. They could also follow the projection in the other direction to see whether neurons with adjacent endings in the skin also had adjacent endings in the spinal cord.

"In a nutshell, what this study shows is that most classes of mechanosensory neuron endings in the skin are tiled, which ensures complete coverage of the periphery in a nonoverlapping manner," says Ginty. "This pattern was known to exist for invertebrate mechanosensory neurons but not for mammalian mechanosensory neurons, and for those that have peripheral projections adjacent to one another in the skin, their central projections were found to be immediately adjacent in the spinal cord," Ginty says. That's despite the fact that their cell bodies can be randomly positioned in the ganglia, or even be present in different ganglia.

"As a developmental biologist, that just blows my mind," says Ginty.

Returning to his roots in developmental biology, Ginty is studying the origin of the topographic organization of the central nervous system. He hypothesizes that sensory neurons that have their terminals immediately adjacent to each other in the skin are likely to fire action potentials in synchrony. "One idea is that somehow coactivation contributes to the central alignment of the terminals in the spinal cord," he says. "That's one of the burning questions we have that I hope, over the next year or two, is going to be answered," says Ginty.

Ginty's work has also led him to uncover some interesting findings about the role of touch in autism. Animal models of autism experience tactile overreactivity, in which an innocuous tactile stimulus causes a hyperreactive response. Using genetic tools, Ginty and his colleagues analyzed autism-related genes in the somatosensory pathway of a mouse model of autism to elucidate the basis of touch overreactivity.

To their surprise, they found that knocking out autism-related genes in the peripheral somatosensory system alone was sufficient to produce not just tactile overreactivity but also deficits in social interaction. "The animals are very sensitive to light touch and they also display anxiety-like behaviors when the autism-related genes were deleted exclusively in the peripheral somatosensory system," says Ginty.

"What's also really fascinating about it is the deficits in tactile reactivity have to occur developmentally in order for them to cause the anxiety-like behavior or social interaction behavior," says Ginty. If the researchers deleted the genes in adult animals, they were still overreactive to touch but did not display anxiety-like behavior.

"There's something about normal developmental touch processing that's required for preventing this anxiety-like behavior in adulthood," says Ginty. "My former postdoc, Lauren Orefice, and I been thinking about ways of translating this work to devise therapeutic approaches to reduce tactile reactivity, and hope to move our findings into the clinic at some point to treat sensory overreactivity in children with autism."

Unexpected Complexity

Ginty's work has revealed that the neural encoding of touch is a lot more complex than researchers previously thought. One of Ginty's major revelations has been that a lot of this complexity exists even at the subcortical level of the nervous system. "A longstanding view has been that the sensory neurons that innervate the skin carry their signals up through linear pathways all the way to the brain, and it's a range of clever circuits within the cortex that give rise to complex feature representation of the outside world," he says. "I think one of the main things that we've learned is that a tremendous amount of processing and integration of these mechanosensory signals conveyed by different mechanosensory neuron subtypes occurs at the earliest stages of the somatosensory system, in the spinal cord and within the brain stem," says Ginty.

To better understand the complexity of the subcortical components of the somatosensory system, Ginty's laboratory is starting to study how different sensory neuron subtypes form, how gene expression during development may underpin their different physiological properties, and the logic of synaptic arrangements of sensory neuron inputs to the spinal cord. Ginty and his colleagues are also exploring the developmental basis of connectivity with the spinal cord, which establishes the circuits that give rise to higher-order feature representation.

"These are all enormously fascinating and complex questions," says Ginty. "The great thing is, now we have a range of new, powerful tools and technologies, and so the amount of understanding that we're going to gain over the next 10 years will be simply breathtaking."

1 E. D. Kuehn, S. Meltzer, V. E. Abraira, C. Y. Ho, D. D. Ginty, Tiling and somatotopic alignment of mammalian low-threshold mechanoreceptors. *Proc. Natl. Acad. Sci. U.S.A.* **116**, 9168–9177 (2019).

2 L. Li *et al.*, The functional organization of cutaneous low-threshold mechanosensory neurons. *Cell* **147**, 1615–1627 (2011).

3 M. Rutlin *et al.*, The cellular and molecular basis of direction selectivity of Aδ-LTMRs. *Cell* **159**, 1640–1651 (2014).

4 L. Bai *et al.*, Genetic identification of an expansive mechanoreceptor sensitive to skinstroking. *Cell* **163**, 1783–1795 (2015).

5 L. L. Orefice *et al.*, Peripheral mechanosensory neuron dysfunction underlies tactile and behavioral deficits in mouse models of ASDs. *Cell* **166**, 299–313 (2016).