Nothing 'pseudo' about them: Drilling down into the function of pseudophosphatases

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Shantá D. Hinton placed an early-career bet on the study of pseudophosphatases, a class of enzymes that were long thought to be intracellular layabouts. Her lab and others are revealing intriguing disease-related functionalities of pseudophosphatases. Credit: Stephen Salpukas

Shantá D. Hinton, in the good, old pre-COVID days, delivered what is possibly the world's first scientific lecture on proteins to incorporate a call-and-response format.

Hinton, an associate professor in William & Mary's Department of Biology, had the audience at the university's 2017 Tack Faculty Lecture

calling out "kinases!" and "phosphatases!" It was her introduction to the biochemical assembly of enzymes known as phosphatases to a largely lay audience.

Her lab was a pioneer in the study of a group of enzymes known as pseudophosphatases, particularly one known as MK-STYX. Pseudophosphatases were long considered a research dead-end, but Hinton and a handful of other labs discovered that there was nothing pseudo about these proteins.

"I'm still preaching the gospel of MK-STYX," she said in a recent interview. "I will continue that until the day I die. But I am looking forward to adding more pseudophosphatases to my research program."

The gospel of MK-STYX is spreading. Her lab's work on the protein is supported by funding from both the National Institutes of Health and the National Science Foundation. Hinton is the author of "Pseudophosphatase MK-STYX: the atypical member of the MAP kinase phosphatases," which was featured prominently in *The FEBS Journal*, a publication of the Federation of European Biochemical Societies.

The *FEBS Journal* piece is a review article, in essence an overview of investigations, discoveries and prospects of pseudophosphatases, MK-STYK in particular. Hinton explains that she first became interested in MK-STYX when she was a Ph.D. student at Howard University. She kept seeing intriguing papers on pseudophosphatases during her postdoc and early career years.

A phosphatase's job is to attach to a phosphate group in a protein, then delete it. The action changes the protein's functionality. For years, the common perception was that pseudophosphatases were the lazy brothers-in-law within the cellular world: they would grab on, and hold on, to the

phosphate group. But they wouldn't finish the job of deletion.

Hinton said labs such as Jack Dixon's at UC San Diego were publishing evidence that pseudophosphatases weren't so very pseudo after all. And then, another paper came out that said an MK-STYX variant was implicated in the development of Ewing sarcoma, a pediatric cancer. Hinton's lab began drilling down into what MK-STYX actually does.

"We began to put the functionality of MK-STYX on the map," she said. "My lab gave the scientific community phenotypes to look at MK-STYX and one of those phenotypes is that it can induce neurites."

Neurites, Hinton explained, are the first stages in the development of neurons, those specialized cells that communicate with other cells through connections known as synapses. She added that another contribution of her lab was to discover MK-STYX's role in the cell's stress response pathway, as it tends to decrease the number and size of stress granules.

"When cells become stressed by any number of environmental factors, they have a protection mechanism, which is stress granules," she said. "However, if the activity of the stress granules becomes prolonged, it could lead to neurological disorders."

The discovery of those two functions of MK-STYX opened doors of research possibilities for Hinton's lab. They can proceed to more detailed structural studies.

"And it's great timing, because now we have the funding to look at both projects," she said.

Thanks to Hinton and a few other researchers, pseudophosphatases are no longer seen as a dead end. MK-STYX and its variant STYXL1 are

being investigated by some high-throughput research labs for connections to diseases ranging from arthritis to diabetes, and even cancer and neurodegenerative disorders.

Hinton's lab in William & Mary's Integrated Science Center has traditionally been staffed largely with undergraduates. Now, she has three master's students and the NSF funding has allowed her to hire Lynn Zavada as a lab technician. She said her lab continues to be productive during COVID times.

"The situation is challenging," she said. "But my department has been very gracious. If we write certain protocols and complete certain forms, we can be in the lab. We've been in the lab since August."

Hinton acknowledges that things were "very slow" in the spring and early summer, when she had limited access to the lab. She pointed out that her work, like that of many biologists, is heavily "wet bench," which means they need to be in the lab to work. She took advantage of the slow March to July period by sharpening her own computational skills as well as those of her students.

"I went back and addressed evolutionary questions and other aspects that require a computational approach," Hinton said. "I gave a couple of students those types of projects, too. Hopefully, with the next year—or really less—we'll be publishing from that aspect."

She picked undergrads who are majoring in computer science or CAMS—computational & applied mathematics and statistics—for the computational projects. She meets with them weekly.

"And I force myself to learn things," she said. "So that I can communicate with them and tell them what I want. It also helps me for when I communicate with other labs that have more-computational

approaches."

Hinton expanded her renewed interest in the computational side of biochemistry by creating a graduate-level bioinformatics class. The class meets in-person every Wednesday. Each student selects a gene or protein of interest to work on together. It's a learning experience for the professor as well as the students, she says.

"It's active learning. We're learning together," she said. "We have to struggle through this, because we don't want to sit at home. I didn't think that I would teach this course permanently, but after seeing how well it's gone, maybe I will."

More information: Shantá D. Hinton. Pseudophosphatase MK-STYX: the atypical member of the MAP kinase phosphatases, *The FEBS Journal* (2020). DOI: 10.1111/febs.15426

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