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PEOPLE & IDEAS

# Mahak Sharma: Weaving through traffic

Nicole Infarinato

**Sharma investigates vesicular trafficking to lysosomes and how pathogens hijack the endolysosomal system during infection.**

In Mahak Sharma's childhood home there was a medical laboratory on the ground floor. Her parents were both physicians in a small town outside of New Delhi, India, and growing up in the heart of their practice provided an early window into the scientific world and its endless possibilities. Sharma recalls watching intently as technicians prepared microscope slides and ran diagnostic tests for patients. Throughout her young life, her interest in biology continued to develop, leading her to pursue a PhD at the University of Nebraska Medical Center in the laboratory of Steve Caplan. As a postdoc with Michael Brenner at Harvard Medical School, Mahak was able to marry her experience in membrane trafficking with immunology. Now an independent investigator at the Indian Institute of Science Education and Research Mohali (IISER Mohali), Mahak studies the mechanisms that regulate membrane trafficking to late endosomes and lysosomes in the context of healthy and pathogen-infected cells.

We reached out to Sharma to learn more about her academic career and current research projects.

**When did your interest in science begin?**

My interest in science developed early in childhood, being a passive observer to the discussion my parents would have on medicine, the human body, health, etc. Both of my parents, but especially my mother, would use active learning to demonstrate many concepts to us, whether it was studying the architecture of plant leaves and their relationship to their ecological niches, watching different organisms under the microscope, or understanding organ function by observing the structure of the eye or lungs from a goat. I remember that my parents purchased the book *Biology* by Campbell on their first trip to the United States, and my sister and I would spend hours seeing the computer animations from the CD version. It was amazing to see the biological concepts in action, and it made learning so much fun.

"I am intrigued by the recent observations that not all lysosomes are the same."

**Where and with whom have you studied?**

Like other teenagers, I was confused and did not have a strong inclination toward a particular career when I finished high school. I knew that I wanted to be associated with science but did not have an idea of how to go about it. An opportunity struck when I came across the undergraduate program in biotechnology at Guru Gobind Singh Indraprastha University (Delhi, India). In retrospect, I think I had little idea of what I would do after completing this degree. In spite of these uncertainties, I did thoroughly enjoy the courses that were taught, in particular, how many of the scientific discoveries were made in the field of cell and molecular biology and developmental biology. This ultimately led me to choose the path of PhD and start on my journey of making discoveries. I wanted to do research outside India, as my extremely limited exposure to research laboratories in India was not very enticing and I wanted to explore new places. For my PhD, I chose to join the laboratory of Steve Caplan at the University of Nebraska Medical Center, Omaha, NE. Steve and Naava, who was a coinvestigator in the laboratory and Steve's spouse, were excellent mentors and primarily responsible for shaping my thinking toward a career in academic research. When hunting for a postdoc laboratory, I wanted to combine my knowledge of membrane trafficking/cell biology with another field, and so I joined the laboratory of Michael Brenner at Harvard Medical School who was studying receptor trafficking in immune cells. I am glad to have experienced the competitive work culture and cutting edge science that was being pursued in the department at Harvard. I do want to mention here that at each of these distinct stages of my career, it took me significant time to develop confidence in my abilities and start enjoying the journey.

Mahak Sharma. Image courtesy of Mahak Sharma.

**What interested you about your current area of study?**

My current area of research is to understand the mechanisms regulating vesicular transport to lysosomes and how intracellular pathogens target the endolysosomal machinery of the host cell to survive and replicate inside their vacuolar niches.

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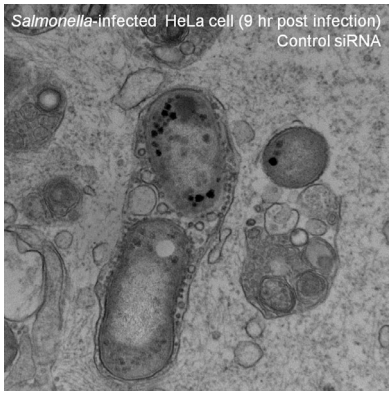


*Salmonella*-containing vacuole (SCV) and *Salmonella*-induced tubules interact with the host endolysosomes by recruiting the HOPS complex. Image courtesy of Maria Ericsson (EM facility, Harvard Medical School).

Since graduate school, I have been fascinated with how proteins deform the intracellular membranes into tubules and vesicles and how organelles such as Golgi or lysosomes position in the cell and communicate with other intracellular compartments. I was also fascinated by the discoveries of how intracellular pathogens would mimic or manipulate the host proteins to build their replicative niches. During my postdoc, research on lysosomes was emerging to reveal many surprises, including their role as a metabolic sensor and how nutrient availability regulates lysosome biogenesis. As I was transitioning from a postdoc to an independent investigator, I found my previous research experience to be suitable for asking questions on the functioning of the vesicle fusion machinery at the lysosome and involvement of the host endocytic regulatory proteins in the growth and survival of intracellular pathogens.

**What are you currently working on? What is up next for you?**

My laboratory is studying how small GTP-binding proteins of the Rab and Arf-like families and their effectors that reside on late endosomes and lysosomes regulate cargo trafficking toward lysosomes and lysosome positioning in mammalian cells (1, 2). We are also addressing whether this host vesicle fusion machinery could be targeted by intracellular pathogens for their growth and survival within the pathogen-containing vacuole. For instance, we have found that *Salmonella* secretes a bacterial effector protein in host cells that recruits the vesicle fusion machinery of the host lysosome to the *Salmonella*-containingvacuole. This enables the pathogen to acquire membrane and nutrients from the host endocytic compartments (3). I am intrigued by the recent observations that not all lysosomes are the same, and there might be differences in pH and surface and luminal content of lysosomes residing in the cell periphery and near the nucleus. As part of future work, we want to know how this heterogeneity in lysosomes arises and whether pathogens are using this heterogeneity to their benefit by selectively interacting with the nondegradative lysosome-like storage compartments.

**What did you learn during your training that prepared you for being a group leader?**

During my PhD, I took the opportunity to develop my project by formulating a hypothesis and then designing experiments to test these ideas. This academic freedom as a PhD student and later success in publishing these ideas were very helpful in building my motivation toward a career in academic research. As a PhD student, Steve encouraged me to write fellowship/grant proposals that not only contributed to my CV, but also turned out to be extremely helpful when I was writing my first grant as an independent investigator. My postdoc with Michael Brenner was relatively short (less than two years), but being at Harvard, the mecca of scientific research, turned out to be an important milestone in my career. It made me part of an extraordinarily talented and motivated group of people who were doing cutting-edge research, which was both challenging and stimulating at the same time. Lab meetings and floor presentations were crucial learning experiences to present and defend my research ideas. Michael was never threatened by competition from other groups and believed in the open sharing of ideas and resources. I have always tried to follow his example in my research and have also immensely benefited from the open sharing culture of my peers.

I had always dreamed of returning to India after completing my training and so I was delighted to accept a job offer at one of the new institutes of academic excellence in the country, IISERs, that aims to combine undergraduate research and teaching. However, I had never done any serious research work in India before I left for the USA. Thus, when I started my independent career, not only did I have to learn basic aspects like how to order research consumables and equipment for the laboratory but also elements of laboratory designing—what material should be used for sink construction, how to design a clean room, etc. Over the years, I have adjusted to the pace of work in India and also feel happy to have contributed to mentoring enthusiastic young minds of the country. I do not think that there is some golden formula for success in research. But what has worked for me at distinct stages of my academic career was to communicate my research to a broad scientific audience effectively. I also believe in taking regular breaks from the lab to travel and enjoy other aspects of life, and these moments of "not doing real work" keep me going.

1. Khatter, D., et al. 2015. *J. Cell Sci.* 128:1746–1761. https://doi.org/10.1242/jcs.162651
2. Marwaha, R., et al. 2017. *J. Cell Biol.* 216:1051–1070. https://doi.org/10.1083/jcb.201607085
3. Sindhwani, A., et al. 2017. *PLoS Pathog.* 13:e1006700. https://doi.org/10.1371/journal.ppat.1006700

Mahak, her spouse Amit Tuli, and mother Manju Sharma on a trip to Coorg, India. Image courtesy of a staff member at Tamara Resort, Coorg.