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PEOPLE & IDEAS

Rushika M. Perera: Lysosomes unveil what cancer cells hide

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Rushika M. Perera studies how pancreatic cancer cells use autophagy and the lysosome to adapt to stress.

Rushika M. Perera was born in Sri Lanka and grew up in Hong Kong and Australia, where her parents emigrated when she was a grade-schooler. She completed a bachelor of science with honors degree at the University of Melbourne and conducted her PhD studies at the same university and the Ludwig Institute for Cancer Research. Rushika did part of her PhD and her postdoctoral training in the United States, first at Yale University and then at the Massachusetts General Hospital in Boston. Having lived in four different countries may have solidified her interest in new cultures and people, but what is clear is that, along the way, she has appreciated how much she can learn from others—mentors, peers, and laboratory members. Her studies explore one of the characteristic features of pancreatic cancer cells—their reliance on autophagy and the lysosome to adapt to stress.

Rushika established her independent laboratory at the University of California, San Francisco, in late 2015. She has been awarded the Günter Blobel Early Career Award from the American Society for Cell Biology (ASCB) this year—definitely an important recognition of her early career trajectory and promising scientific future. We chatted with her to learn more about her current science projects.

When did your interest in science begin?

I was not a student who was good at everything in school. I was terrible at learning languages for example, and struggled in my Italian, French, and Japanese classes (at my high school it was mandatory to study two languages). I was instead more interested and, luckily, good at biology and math. Perhaps that's where it all starts—at the intersection of what interests you and what you are good at. I was fortunate to have great teachers who provided encouragement and positive reinforcement to continue on the biology track. My first experience of "real" science was over a summer when I spent hours cutting frozen sections for a pathology laboratory. Despite being glued to a cryostat for most of the day and not being able to feel my fingers, I was nevertheless in awe of the laboratory environment. The dynamic and unpredictability of daily laboratory life, the team spirit, and the freedom to explore hooked me.

How has your past training in both cancer and cell biology laboratories helped boost your interest in lysosome biology in pancreatic cancer?

I consider myself a cancer cell biologist, having trained in both cancer and cell biology laboratories. At the University of Melbourne and Ludwig Institute, my studies on glioblastoma were focused on identifying unique vulnerabilities that could be exploited therapeutically. At Yale, working jointly with Pietro De Camilli and Derek Toomre, I learned the power of zooming into the cell and visualizing dynamic processes in real time. My interest in endocytosis and trafficking evolved further when I joined the laboratory of Nabeel Bardeesy—an expert in the genetics and biology of pancreatic ductal adenocarcinoma (PDA)—for my postdoctoral studies. In Nabeel's laboratory I had the opportunity to reenter the cancer biology world with a cell biology perspective that helped me to uncover a missing piece of a puzzle. At the time, it was known that trafficking pathways such as autophagy were constitutively activated in PDA. How this occurred was a mystery. I was able to show that a key family of transcription factors—the microphthalmia/transcription factor E (MiT/TFE) family that was shown by Andrea Ballabio to be master regulators of autophagy and lysosome gene expression (1)—were up-regulated and constitutively trafficked into the nucleus to sustain increased autophagy and lysosome biogenesis in PDA (2). From there, a whole new world opened up, along with a plethora of questions relating to how the lysosome

Rushika M. Perera. Photo courtesy of Rushika M. Perera.

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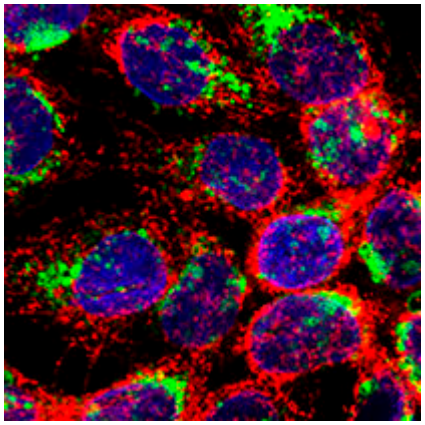

Immunofluorescence image of lysosomes (LAMP1, green) and mitochondria (Tom20, red) in cultured human pancreatic cancer cells. The nucleus is stained with DAPI (blue). Image courtesy of Rushika M. Perera.

Perera laboratory wearing purple in honor of Pancreatic Cancer Awareness Month (November). Photo courtesy of Rushika M. Perera.

contributes to cancer progression. Marja Jäättelä had pioneered much of the early studies on lysosomes in cancer, and I was inspired by her work. At a 2015 EMBO meeting on autophagy we met for the first time, and after listening to Marja, Andrea, and many other leaders in the field talk about a new renaissance in lysosome biology, I knew there was still much to learn about this fascinating organelle.

What are you currently working on and what is up next for you?

When I started my laboratory in 2015, I was first interested in tackling what seemed to be a fairly simple question at the time: How different are PDA lysosomes relative to lysosomes in normal cells? The advent of new techniques to rapidly purify organelles that were amenable to mass spectrometry-based proteomics allowed us to tackle this question. These early studies in my laboratory have taught us a lot about the unique features of cancer lysosomes and the dynamic and diverse ways in which the lysosome promotes cancer cell growth. Currently we are delving deeper into how cancer cells use the autophagy–lysosome pathway and crosstalk between metabolic organelles to adapt to a range of intracellular and extracellular stressors, as well as further understanding how the MiT/TFE factors are regulated in cancer cells. We've also generated new genetically engineered mouse models of PDA that allow us to purify intact lysosomes at different stages of disease progression. Our goal is to uncover unique vulnerabilities of PDA that can be targeted to halt disease progression and metastasis.

What kind of approach do you bring to your work?

I think it's important to "go deep" and unravel as much of the puzzle as possible. This usually means committing to a given problem—e.g., in my case, I have been studying pancreatic cancer biology for over a decade—but also be willing to take steps outside of your field in order to follow where the science takes you—e.g., our foray into cancer immunology (3) was daunting at first but has opened up a new and exciting direction for my laboratory.

What have you learned from your mentors that helped you prepare to become a group leader? Is there anything you were unprepared for?

My former mentors were great examples, and I have adopted several of their scientific and practical philosophies that I thought were important to embody as a group leader—from having laboratory meetings early in the week and unanimous consensus when selecting new laboratory members to being thoughtful about the scientific questions we pursue and establishing a scientific identity. The most valuable advice I have received were to lead by example, have realistic expectations and communicate these effectively, and to remember that we are always learning. I also feel very fortunate to have incredible colleagues who are great sources of honest, candid advice. During the first years as a junior principal investigator, my laboratory neighbor and faculty mentor Zena Werb was a great influence. We spoke almost daily for 5 yr. Zena was an invaluable source of sound, practical advice and encouragement, and I will forever be grateful for her mentorship and kind spirit.

I was somewhat unprepared for all the mistakes I was to make (and still make)! When starting out, it feels like every misstep is a major setback. By talking about this openly, I've realized that missteps are instead valuable opportunities to reflect, learn, and implement new strategies.

What has been the biggest accomplishment in your career so far? And your biggest challenge?

Recruiting and progressively building a wonderful team is a major accomplishment for me. I recently graduated my second PhD student and feel a great sense of joy and pride seeing a trainee blossom into a confident, skilled, and rigorous scientist.

A challenge: the unpredictability of science. There are many exciting and important scientific questions to pursue, and having to choose can be hard. What was

initially an "easy" or "safe" project may turn out to be far more complicated, and usually is. More often than not, feasibility, interest, impact, and funding all play a role in getting a study off the ground, and sometimes these factors don't all align at the same time. The hope is that persistence is rewarded in due time!

You have been awarded the Günter Blobel Early Career Award by the ASCB this year—congratulations! What does this award mean to you?

It is an incredible honor to be selected as the Günter Blobel Early Career Awardee. As a cancer cell biologist, I am very grateful that ASCB sees the value of applying cell biological studies to understanding disease processes. Günter Blobel captured this concept when he said, "The tremendous acquisition of basic knowledge will allow a much more rational treatment of cancer, viral infection, degenerative disease, and mental disease."

References

1. Sardiello, M., et al. 2009. *Science.* https://doi.org/10.1126/science.1174447
2. Perera, R.M., et al. 2015. *Nature.* https://doi.org/10.1038/nature14587
3. Yamamoto, K., et al. 2020. *Nature.* https://doi.org/10.1038/s41586-020-2229-5