People & Ideas

Senthil Muthuswamy: A new road map for cancer

Senthil Muthuswamy uses 3D cell culture to explore the influence of cell polarity on oncogenic transformation.

Senthil Muthuswamy has traveled far from the small town in southern India where he grew up: all the way to ground zero in the fight against cancer. His work is laying a path toward a new understanding of the role of cell polarity in tumorigenesis (1, 2).

Senthil's journey to his new stomping grounds started at an agricultural school in India. It took him through his PhD with William Muller at McMaster University in Hamilton, Canada, studying the role of the receptor tyrosine kinase ErbB2 in breast cancer (3). He next took a postdoctoral position with Michael Gilman at ARAID Pharmaceuticals (4). At ARAID, Senthil met Joan Brugge and soon started a postdoc with her, moving to Harvard Medical School where he developed a three-dimensional cell culture system that would launch the rest of his career (5).

Today, Muthuswamy is happy with where he finds himself, directing research programs at two laboratory groups—one at Cold Spring Harbor Laboratory, New York, and another at the Ontario Cancer Institute in Toronto, Canada, where he has recently moved. We tracked him down at his Canadian office to talk about the ground he's covered so far, and what he sees on the road ahead.

> "Cancer is a disease of tissue structure and shape, not just of cells."

CAMPUS LIFE

Where did you grow up?

I was born in the southern part of India, in a small town called Rasipuram. My father was a professor, a soil chemist, at agricultural research stations in Tamil Nadu, a state in southern India.

Was that your inspiration for pursuing a career in science?

It's not very common in America or Canada, but in India, the universities provide on-campus housing for professors, so my family actually lived on the campus where my dad worked. He would take me into his laboratory a lot, so I really grew up around science. As a kid, I always wanted to do something related to science, but I was particularly interested in medicine, in part because I was inspired by one of my uncles, who is a pediatrician.

Also I should say that in India when I was growing up, there was this sort of mantra taught to all the kids that you had to aim for a professional college in engineering, medicine, or agriculture. Nowadays of course everyone wants to do computer science. But back then if you didn't do well in your secondary school exams and make it into one of these professional schools, then you were no longer going to be successful in your life.

And where did you end up?

As it turned out, I went to an agricultural school called Tamil Nadu Agricultural University. I was very keen on genetics, so after my undergraduate studies there, I went on to an advanced institute in New Delhi to do a master's thesis. I studied the genetics of cooking qualities in different basmati rice strains!

JUMP ACROSS THE POND

Studying rice is very different from what you're working on now! How did that come about?

Yes, from there to breast cancer was a big jump! I eventually decided to switch to mammalian biology because, although I liked plants, I was interested in the molecular aspects of things—genetics, molecular and cell biology, and so on. At the time, these approaches were far more advanced in mammalian systems than in plants. Also, government funding for research was not great in India, so there was no incentive to do in-depth science.

Senthil Muthuswamy

Things are changing now and there is a great deal of importance given to basic research, but back then everything was focused on applied research.

I started applying to a lot of graduate programs, and the one at McMaster University was attractive because it came with a Canadian International Development Agency scholarship that provided full funding, including a travel allowance. Coming from India, where I was planning to support myself, that was a huge boost. So I said, "Okay, I'm going there."

Was that a big transition for you?

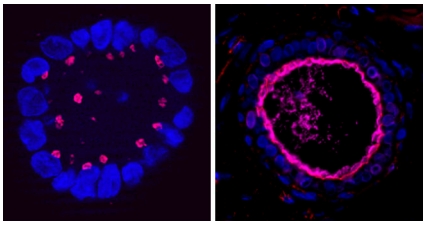
Oh, absolutely. To start with, the weather was freezing in Canada compared with India, and there were mountains of snow. That was a huge shock. And also culturally… I felt intimidated by the openness of the society. In India, you're not supposed to openly disagree with people because it's not polite. Here you are supposed to disagree with your mentor or professor if there is a need for it. That was surprising, and it took a while to adjust, but I eventually adapted. I tell my students and postdoctoral fellows now, that they should never hesitate to raise questions and have a healthy debate. It is a great way to learn.

Text and Interview by Caitlin Sedwick
csedwick@gmail.com

What about your scientific adaptations?
I didn't know anything about mammalian biology, so I had to learn the basics. I took all the standard courses: biochemistry and molecular cell biology. I also took pathology. The pathology classes were an eye-opening experience, because they immediately taught me that cancer is a disease of tissue structure and shape, not just of cells. This meshed with my research at the time: In the Muller laboratory everyone was making mouse models for breast cancer. We'd take different oncogenes and express them in a mammary gland and see what kind of tumors you'd get. We knew that those oncogenes seemed to do very similar things when you transform cells in tissue culture, yet each oncogene gave rise to a different histopathologically distinct tumor. Nobody understood why.

MIND THE GAP

The distinct effects of oncogenes really seemed to capture you.
When I went to Joan Brugge's laboratory to do my postdoctoral work, we looked at ways to study why these different oncogenes create distinct kinds of tumors in animals. We were inspired by Mina Bissell's work on three-dimensional cell culture and decided to study cancer and transformation in a 3D context. Joan and Mina started collaborating, and I did a few experiments using ErbB2 and other molecules that I had been studying in my PhD. We found that when we put different oncogenes—for example, EGF receptor, cyclin D1, or ErbB2—into cells and grew the cells on a flat plastic dish, you couldn't tell them apart by looking at them. But, we would see completely different and obvious phenotypes when the cells were grown in 3D culture. While we already knew the role of uncontrolled proliferation in cancer, this system clearly told us that there is also something else going on.



Human mammary epithelial cells grown in 3D culture (left) form structures resembling breast tissue (right).

And what is that something else?
Well, this is a difficult problem, and one I took with me to my own laboratory at Cold Spring Harbor Laboratory. We had lots of ideas about it that didn't really pan out. Our first big insight came when we started looking at the impact of some of these oncogenes on cell polarity. We found that active ErbB2 not only provokes cell proliferation, but also disrupts apical–basal polarity when it is overexpressed in epithelia. But, the pathways by which ErbB2 influences cell polarity and proliferation are entirely separable. That led us to ask: What is the effect of simply disrupting polarity pathways? We investigated a polarity protein called Scribble and found that when cell polarity is defective, you get disorganized growth, but not overproliferation, in 3D culture. However, when you combine Scribble defects with a proliferation driver—for example, oncogenes like c-myc or human papillomavirus E7—you get an ErbB2-like situation.

This observation required an eye for detail.
I like to look at the details, maybe because of my hobby, photography. I get inspired by looking at things. In photography and in cell biology, the important stuff is all in the details and what perspective you take to look at a given situation.

Muthuswamy's photo, "Summer Ice."

Do you think this might be a common progression in cancer?
Yes. If you think about it, cells divide a lot in response to physiological conditions and cues. For example, remodeling colonic epithelium or expanding ductal epithelium in the breast are tissues with high cell proliferation rates. However, as long as cell–cell interactions are being recognized and the cell polarity machinery is intact, cells are able to form a restricted pattern of 3D structural morphogenesis to maintain tissue organization.

Cells can sense the mechanical tensions that tell them they've grown enough and should stop growing. But if a cell is unable to normally polarize and organize its growth, it is no longer constrained by these signals because it's not sensing them. So, any sort of genetic or epigenetic event that interferes with genes and pathways that regulate polarization and morphogenesis will lead to a loss of tissue structure. The way we see it, this creates a permissive environment for other events to happen that push a cell into uncontrolled proliferation and unorganized growth. Loss of tissue organization is a recipe for disaster in the long run.

> "In cell biology, the important stuff is all in the details and what perspective you take to look at a given situation."

We're very excited because these ideas allow us to think about the cancer cell in a different way, one that will allow us to find ways to treat cancer early.

1. Zhan, L., et al. 2008. *Cell.* 135:865–878.
2. Aranda, V., et al. 2006. *Nat. Cell Biol.* 8:1235–1245.
3. Muthuswamy, S.K., et al. 1994. *Mol. Cell. Biol.* 14:735–743.
4. Muthuswamy, S.K., et al. 1999. *Mol. Cell. Biol.* 19:6845–6857.
5. Muthuswamy, S.K., et al. 2001. *Nat. Cell Biol.* 3:785–792.