People & Ideas

Elias Spiliotis: Septins set it up

Spiliotis studies the contributions of septins to cellular spatial organization.

When a student anarchist movement shook Greece in the early 1990s, a teenage Elias Spiliotis was marching the streets, protesting alongside his peers. Looking back, he says his antiestablishment sentiment was partly a reaction against the dearth of creative outlets offered by a public school system obsessed with preparing students for stringent national exams. At that time, the biological sciences didn't particularly inspire him; his passions were music, poetry, and art cinema. It wasn't until late in his undergraduate studies that Spiliotis discovered how research could provide the kind of intellectual stimulation and creative pursuits he'd always craved.

Spiliotis found what would become his true research passion while preparing to start his postdoc with James Nelson at Stanford University. That was when he first encountered septins. At the time, little was known about septins beyond the fact that they bound to GTP and were somehow involved in cytokinesis. But by now, Spiliotis and his group have demonstrated that septins are important not only in cell division (1), but also in membrane compartmentalization (2), epithelial polarity (3), and the organization of the cell's microtubule (4) and actin (5) cytoskeletons. Septins also have less obvious but no less important regulatory roles in cells, he told us when we called him recently at his lab at Philadelphia's Drexel University.

> "Somehow the word 'septins' jammed in my head."

UNFAMILIAR TERRITORY

So you didn't have an early affinity for research?

I wasn't like a lot of scientists, who can tell you they loved nature or chemistry or whatever right from the start. I studied biology as a kind of default because I had to choose something to focus on for the national exams, but at that time it was mostly just an abstract interest. I didn't do very well in the national exams, so my family and I decided that I should come to the US for college. That turned out to be a great choice.

I first proposed to study philosophy in college, but my father said to forget about it; no way was he going to pay for that. [*Laughs*] So again I turned to biology, but up until the summer before my senior year at Boston College, I still had doubts about what I wanted to do. The undergraduate labs had not inspired my confidence in my ability to do science, but that summer I worked in a biochemistry lab and was given an actual independent project—not just washing dishes—and I loved it. Having a scientific problem to solve mentally consumed me in an almost obsessive-compulsive way all summer, and I decided to stay in the lab to work on my senior thesis. That was the start of my science career.

Have any of your interests from your teenage years survived to today?

Music has always been very central to my life. I love discovering music and following the music scene. As a teenager, I collected a lot of records and music, and I even hosted a couple of radio shows. As a postdoc I also deejayed and played guitar in an indie band, but I had to give all that up because things were getting really hectic in the next step of my career. There's also the most recent addition to my life, a daughter; I enjoy spending time with her.

How did you first hear of septins?

During my PhD with Michael Edidin, I had been studying MHC class I mobility in the endoplasmic reticulum membrane. When I was trying to figure out which direction I wanted to go as a postdoc, I was most interested in questions of membrane biology and membrane polarity. James Nelson was a major name in both of those fields, so I applied to join his lab.

As things were winding down in graduate school I started preparing for the transition to Nelson's lab by writing some postdoctoral fellowship applications on the project we'd agreed I would work on, which involved vesicle fusion and the exocyst complex. While I was doing my background reading on this, I came across the septins, which I had never heard of before. Somehow the word "septins" jammed in my head. I wondered, "What are they? How come I've never heard of them?"

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Elias Spiliotis

It's funny that this coincided with the 2001 American Society for Cell Biology meeting in DC, which was hosting a special interest group on septins. I decided to go down there and check it out. It was a really small session, and I remember sitting there and thinking, "Oh, my god. Nobody knows what these proteins do."

A month later in the Nelson lab, just to assuage my curiosity, I wrote to my colleague Makoto Kinoshita, who was working in Tim Mitchison's lab and was one of the few people in the country with antibodies to mammalian septins. He very generously sent some of his antibodies to me, and when I used them to visualize septins in interphase cells, I was amazed by what I saw.

A NEW NETWORK

What did you see?

I saw this gorgeous network of filaments. It wasn't anything like microtubules or actin in terms of its density, and it had a unique spatial arrangement with a few

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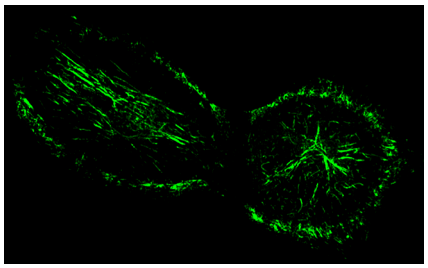

IMAGE COURTESY OF JONATHAN BOWEN

Spiliotis was amazed by a network of septin filaments, which resembles that of no other cytoskeletal element.

long filaments in the perinuclear area and shorter ones along the periphery of the cell. I didn't have to do much at that point to convince James to let me pursue my interest in these proteins and make them the focus of my work. He was very supportive.

The obvious question was, what do septins do? Well, this was in the early 2000s when the first commercially available synthesis of siRNA appeared, and James suggested I try making siRNAs against septins and see what kind of phenotypes came out. So I did, and the main phenotype was an arrest in mitosis. From there we figured out that septins assisted with the capture of kinetochores by spindle microtubules during metaphase.

Septins are important for many processes besides mitosis…

Different septins show structural diversity at their N and C termini, and also have different abilities to hydrolyze GTP. Septins also form hetero-oligomeric or heteropolymeric structures with other septins, whose stability may be governed by GTP hydrolysis. Septin polymers are likely to perform specific functions depending on which septins are present, and what other proteins they interact with.

In mammalian systems, there are 13 septin genes, and several have multiple isoforms. That kind of expansion isn't seen in other species, so from an evolutionary standpoint, it had to be driven by a need to perform unique functions in various contexts.

The idea now is that septins either form scaffolds upon which other proteins can assemble, or—in the context of membranes—they form higher order structures that could act as diffusion barriers. For example, I've collaborated with the Nelson lab on a paper concerning the discovery that septins form a diffusion barrier around the primary cilia of epithelial cells. In my lab now we have projects about the role of septins in membrane processes such as abscission and macropinocytosis. But to me, the most interesting aspect of septins is that they're able to interface with the cytoskeleton and membranes at specific sites within the cell.

BRIDGING AND REGULATING

Tell me about your work on septins' interactions with the microtubule cytoskeleton.

One of our major findings is that the septin-9 N terminus, which is very long and unique among septins, contains repeat motifs very similar to those used by microtubule-associated proteins to bind and bundle microtubules. We showed that these motifs, through their basic residues, could associate with the acidic tails of β-tubulin within microtubules. But, we also found they could interact with one another, and we think these homophilic interactions could allow septin-9 to bridge or bundle microtubules together.

> "Septins may mediate crosstalk… between the actin and microtubule cytoskeletons."

An interesting aspect of that work is that it turns out that septin-9 is the only known gene linked to a rare neuropathy called hereditary neuralgic amyotrophy. This disease often involves alterations such as expansion or mutation of the motifs we found within the N terminus of septin-9. We showed that a disease-associated mutation in one of those motifs affects the microtubule bundling function of septin-9.

What about other cytoskeletal systems?

Septin-9 also crosslinks actin filaments. This is interesting because it suggests septins may mediate crosstalk or bridging between the actin and microtubule cytoskeletons. Of course, this is not the only protein that's been described to interact with both the actin and microtubule cytoskeletons, but this is definitely something we'll be looking at more closely in the future.

Our overarching hypothesis is that septins are a regulatory module that affects spatial organization in cells. We've long known that septins interact with different subsets of microtubules, which brings the question of how septins might affect cargo transport along those microtubules. We recently got some exciting results on differential regulation of motor movement by microtubule-associated septins. That's kind of a holy grail for us.

Are there other burning questions in the septin field that you'd like to see answered?

Absolutely! Right now we know a lot of the processes septins are involved in but very little about how their assembly, disassembly, and localization is controlled. Having more advances on that side of the field would help integrate our knowledge of the function of these proteins.

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Cleo Spiliotis poses for a rock-star selfie with dada.