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PEOPLE & IDEAS

Elda Grabocka: Stress-buffering comes in granules

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Elda Grabocka investigates the role of stress granules in obesity and cancer.

When one thinks of high school, sharing hallways with students from 80 different countries is not the usual image that springs to mind. This was indeed Elda Grabocka's experience. She grew up in Pogradec, a remote town in Albania—her parents, both physicians, were assigned to this location by the state. Elda won one of the two spots available for Albanian students in a national competition to attend the United World College of the Adriatic in Trieste, Italy, a high school focused on social change that brings together students from around the globe to promote intercultural understanding. Elda still remembers, with a smile on her face, the first glimpse at the laboratories as the senior students were working on their thesis projects: "That was exactly what I wanted to do!" She barely spoke English at the time and had to catch up to the level of her peers, but her perseverance and passion prevailed, and she obtained the International Baccalaureate Diploma (IBD). For the independent study of the IBD program, she submitted a research project in chemistry, which ended up being an important learning and life lesson: "That helped me understand that I was more suited to biology! In hindsight, it was great to have that experience so early; I certainly had no awareness then how essential failing and then learning from your failures is to science, but having a level of comfort with it from the beginning was probably a bonus."

But science was not the only professional option Elda contemplated—her volunteering experience with relief organizations in various refugee camps made her consider a career in public health and humanitarian relief efforts. She finally sought a PhD degree in molecular pharmacology and structural biology in the laboratory of Phil Wedegaertner at Thomas Jefferson University. After studying heterotrimeric G-proteins and how the subcellular localization of their exchange factors regulates function, Elda felt the need to seek greener pastures. She went on to do a postdoc on one of longest-studied oncogenes, RAS—her choice wasn't motivated by the field, but by the mentor, Dafna Bar-Sagi. Elda's admiration for Dafna is notable when she speaks about her time at the New York University Langone Medical Center: "It's remarkable how many novel aspects of RAS biology that have shaped and then re-shaped our thinking about this oncogene have come out of her lab; I felt there was a depth and breadth to her approach to scientific research that if I could learn, I'd be able to see more of the angles, so to speak, ask better questions; she has really expanded my mind in all those aspects." Elda's work focused on the interplay between the mutated forms of RAS and the wild-type isoforms, which she and others have shown is context dependent, with the wild-type isoforms acting as both tumor suppressors and tumor promoters (1). While still in Dafna's laboratory, Elda pursued a more independent scientific interest: the role of stress granules in mutant KRAS cells. In 2016, Elda returned to her alma mater, joining the Department of Cancer Biology at the Sidney Kimmel Cancer Center at Jefferson as an assistant professor, with stress granules in cancer as the focus of her laboratory. We contacted her to learn more about her research journey.

Elda Grabocka. Photo courtesy of Chris Hamilton Photography.

What interested you about stress granules and their connection with obesity and cancer?

I became interested in stress granules and their potential role in cancer early in my postdoc. I read a review by Stephen Elledge's group where they described the "stress phenotype" of cancer as an important player in tumorigenesis. I realized that cancer cells exist mostly in a state of stress—for example, mutated genes, like oncogenic RAS, are potent inducers of many types of cellular stresses. I was working on a RAS ubiquitination project, and one of the candidates for a RAS de-ubiquitinating enzyme we were looking at was implicated in stress granule formation. Little was known about stress granules at the time—they are induced by types of stresses associated with tumors (hypoxia, oxidative stress, osmotic pressure, proteotoxic stress, metabolic stress, etc.), so the question I asked was whether stress granules could function as a stress coping/adaptation mechanism in cancer. Indeed, I found that stress granules are prevalent in tissues from patients with

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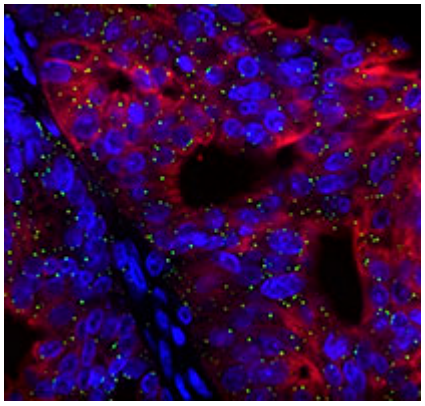

Immunofluorescence staining of pancreatic ductal adenocarcinoma tissue showing cancer cells in red, stress granules in green, and nuclei in blue. Image courtesy of the Grabocka laboratory.

pancreatic cancer and mouse models of pancreatic cancer. Remarkably, not all cancer cells are the same in their capacity to form stress granules—all cells will make stress granules under stress, but KRAS mutant cancer cells have a heightened ability to do so because signaling from mutant KRAS enhances the levels of a critical molecule to stress granule formation, 15-deoxy-prostaglandin J2 (2). This enhanced capacity to make stress granules, in turn, renders KRAS mutant cells more resistant to stress and more dependent on stress granules; inhibition of stress granules leads to increased cell death in KRAS mutant versus KRAS wild-type cancer cells.

The work establishing this dependence was in vitro, so the primary goal when I started my laboratory was to determine their relevance in tumorigenesis, which led me to explore their connection to obesity and cancer for several reasons. First, obesity is a major predisposing factor for several cancers, including pancreatic and colon, which are prevalent KRAS-driven cancers for which treatment options are limited. Second, obesity is a complex pathology which likely impacts the pathobiology, the therapy response, and even the evolution of cancers that arise in this setting. Given that cell stress and inflammation are key features in obesity, this would make the ideal background to study the contribution of stress granules in tumorigenesis. I think this pre-existing stress [obesity] might necessitate the engagement of stress adaptive mechanisms from the early stages of tumorigenesis and may also lead to a high dependence on these processes.

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

It's a very exciting time to be working on stress granules! The field has grown significantly over the past 10 yr or so, especially with the renewed interest in phase separation. As organelles that form via phase separation when a cell is under stress, stress granules are perhaps one of the best examples of phase separation in vivo and a great platform to understand its relevance. The recent advances in defining the composition, as well as key molecular drivers and their functional domains in stress granule assembly, have been of great benefit. We are now better positioned to define the stress granule–specific functions in health and disease. Because stress granules are induced by various types of stresses, they could function as a pan-stress adaptation mechanism in cancer. This is a very appealing angle, as if we can solve how stress granules enable stress adaptation, which is a major focus of my laboratory, we could have better anti-cancer therapies.

The composition of stress granules, comprising hundreds of proteins and mRNAs involved in several aspects of cell biology, prompted me to ask whether cytoprotection under stress is their main and/or only function. What other cellular processes stress granules regulate, whether these vary with the type of stress, and how such processes are integrated into the stress response of cancer cells are burning questions we are currently working on, as the answers will advance our understanding of the role of stress granules in cancer. The "chronic stress" of cancer is heterogenous in both spatial and temporal terms, as well as in the type of stress and intensity. I am also very curious to see if and how heterogeneity in stress stimuli impact the composition of stress granules and the processes they regulate, and how this may affect tumor evolution. Also, cancer cells are not the only cells in the tumor that make stress granules. As a matter of fact, we reported that KRAS mutant cells can stimulate stress granule formation in a paracrine manner. An ongoing project in the laboratory that I'm very excited about is focused on understanding the contribution of stress granules to the pro-tumorigenic microenvironment.

Out for a paddle. Photo courtesy of Elda Grabocka.

What kind of approach do you bring to your work?

My approach is very hypothesis and observation driven; the latter in the sense that it can often be that initial spark that inspires an idea, draws connections, and looks for context and meaning. I also find that sometimes the answer to my next question or the question I don't know to ask yet is hidden right in front of my eyes, so paying careful attention to the data is key. It is also where objective and critical evaluation of experimental results starts. There's one line that's firmly ingrained in my mind from my postdoctoral training, which is "Science is self-correcting." It's a note of caution that if you don't pay attention and see only what you want to see, it will still eventually prove you wrong, and you'd have wasted a lot of time in the process. So I try to minimize that waste as much as possible—unavoidable entirely, having a favorite hypothesis is part of the scientific thinking process, but crucial to remember to follow the data and not just convince yourself.

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

I'm still quite early in my career to start listing accomplishments. I feel privileged to do the work I do; I essentially get funded to pursue ideas that I find interesting. So I have a hard time with this question because it has a hint of pride, and when you start adding pride to privilege, as a junior principal investigator especially, it gets a bit too self-serving. I hope that the work we are doing

stands the test of time and leads to or helps lead to a meaningful impact on patients' lives—that would be a great accomplishment.

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

The past two years of COVID have certainly been a different reality, and a constantly shifting one at that. From a career perspective, so much of a scientific career happens at the bench: experiments happen at the bench, we train at the bench, animal work is long and requires multiple dedicated essential personnel and facilities, so inevitably, remote work, or shift work, limited occupancy, and the shortages we are now seeing in the supply chain have been a major challenge for everyone. I do think junior laboratories like mine experience that a bit harder. The bandwidth to absorb these challenges is much smaller if you're just starting out, or if you've had a laboratory for a couple of years and are just ramping up. I must say though that it has made for stronger teamwork in the laboratory, and we've had to be really focused and efficient—so there's an upside!

Any tips for a successful research career?

Hard to say, because certainly it means different things to different people. The only tip I would give perhaps is to define what that means, what that success looks like for oneself, and be true to that. I expect how each one defines it also changes with time and experience, but I do think it's very important to identify what success means as early as possible and let that be what you measure your efforts against. It's easy to get distracted, overwhelmed, or even disheartened otherwise. My own definition is quite simple: success is doing what I love to do, working toward answering a meaningful scientific question, and enabling/supporting my trainees to reach their potential—keeping that in mind has been very important and helpful.

References

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