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FIRST PERSON

First person – Gianna Fote

First Person is a series of interviews with the first authors of a selection of papers published in Journal of Cell Science, helping early-career researchers promote themselves alongside their papers. Gianna Fote is first author on 'Isoform-dependent lysosomal degradation and internalization of apolipoprotein E requires autophagy proteins', published in JCS. Gianna conducted the research described in this article while a MD/PhD student in Joan S. Steffan and Leslie M. Thompson's lab at the University of California Irvine School of Medicine, USA, working on the influence of genetic variants on molecular mechanisms of autophagy, and therapeutic modulation of autophagic balance in neurological disease.

Gianna Fote

How would you explain the main findings of your paper in lay terms?

Autophagy is one of the processes that cells use to traffic waste or defective proteins to an acidic organelle called the lysosome for degradation. When autophagy is disrupted, accumulation of waste protein can contribute to neurodegenerative disease, such as Alzheimer's disease. One of the genetic variants associated with Alzheimer's disease is APOE4, a polymorphism of the APOE gene, but it was not previously known exactly how APOE4 is broken down or whether autophagy is involved. We found that both normal APOE3 and the APOE4 variant can be degraded by autophagy, and that APOE4 accumulates quickly within lysosomes. We also found that APOE3 is degraded by several different types of autophagy, including autophagy involving LAMP2A. This finding was surprising because LAMP2A is typically associated with degradation of cytoplasmic proteins, whereas APOE is mostly found in the secretory system. Restoring the balance of the different types of autophagy that degrade APOE may be used in the future to ameliorate disease in people with the APOE4 variant.

Were there any specific challenges associated with this project? If so, how did you overcome them?

One challenge I faced when studying APOE trafficking to the lysosome is that APOE can be expressed and trafficked within the cell and secreted to be taken up by endocytosis in other cells. Thus, APOE that ends up in the lysosome could have originated from within that same cell or from other cells through different pathways. I had to be creative and use pharmacologic inhibition of endocytosis and post-translational modification associated with secretion in order to show that APOE can enter the lysosome directly from within a cell.

When doing the research, did you have a particular result or 'eureka' moment that has stuck with you?

At first, when I was trying to study intracellular trafficking of APOE, I was frustrated that my cells were secreting fluorescent APOE, but eventually I realized that I could use the conditioned medium containing secreted APOE to do some neat studies on the endocytosis of APOE3 and APOE4, and found that endocytosed APOE4 accumulates in enlarged late endosomes and may disrupt mitophagy.

Why did you choose Journal of Cell Science for your paper?

I have always loved reading the beautiful and technically impressive cell biology published in JCS, and I had a wonderful meeting with an editor at an autophagy conference; she was very kind and supportive.

Have you had any significant mentors who have helped you beyond supervision in the lab? How was their guidance special?

Joan Steffan is an incredibly creative scientist and a caring mentor. Her passion for the study of autophagy is contagious and we talked about my experiments daily. She has always had her door open to talk about anything, work or personal. During my time in her lab, I had a concussion, and she was there for me with a home-cooked meal, and when I had acute appendicitis at an MD/PhD conference, she made sure I was ok in the hospital after my surgery. Leslie Thompson is a warm and generous mentor who has always helped me turn my experiments into a compelling story and has connected me with excellent collaborators. She has brought our lab together over happy hours and holiday parties, and has created professional development opportunities for me, including attending conferences, developing my presentation skills, and introducing me to physician scientists and volunteer opportunities. Although not my PI, Jack Reidling is a project scientist who has helped me stay sane and troubleshoot technical difficulties, sometimes at the beach while surfing, the best place to clear my head. I am also grateful to Niki

Gianna Fote's contact details: 1001 Health Sciences Road, University of California Irvine, Irvine, CA 92617, USA.
E-mail: gfote@hs.uci.edu

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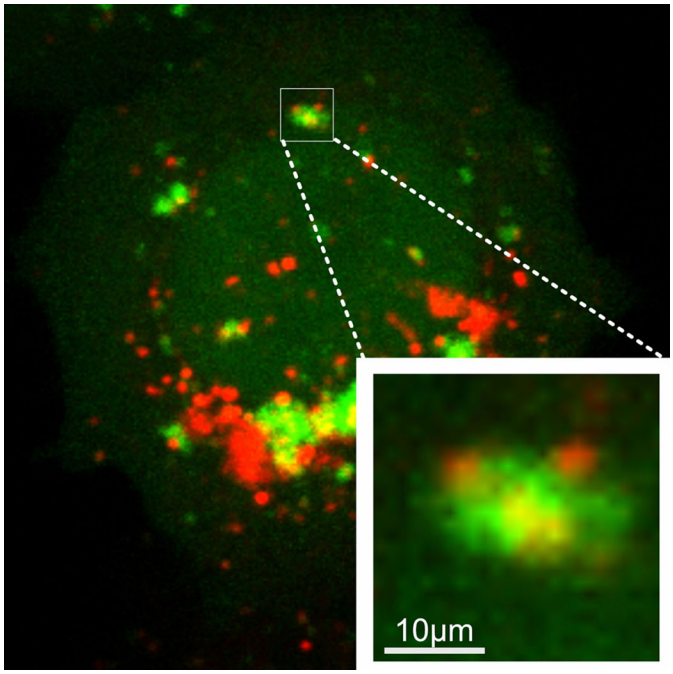

A three-dimensional *Z*-stack of HeLa cells transiently expressing APOE3–mCherry and GFP–LC3A demonstrates colocalization and complete envelopment of APOE3 in LC3A-positive vesicles.

Geller, a hard-working and gifted lab assistant now bound for graduate school, who has contributed tremendously to all of my projects, and outside the lab is one of my closest friends. I hope we will continue to work together throughout our careers! Finally, Lorna Carlin's philanthropic support of this work and my growth as a scientist have been very meaningful to me; I am in awe of her kindness and inquisitive spirit.

What motivated you to pursue a career in science, and what have been the most interesting moments on the path that led you to where you are now?

I began research in high school, studying the life cycle of *Aplysia californica*, a large sea slug native to the area where I grew up, that I had observed in the wild. As I read up about these interesting creatures, I was surprised and excited to discover that they are a pivotal model organism for the study of learning and memory. I have always had a passion for exploring the natural world, whether I'm searching for slugs in tide pools or culturing a new cell line; science is the ultimate intellectual adventure. Neurological disease is at medicine's frontier; we have some exciting new therapies just around the corner. I feel privileged to be mapping the mechanisms of these diseases through basic science to pave the way for new treatments.

Who are your role models in science? Why?

My PIs Joan Steffan and Leslie Thompson are both brilliant and have an incredible collaboration; they have worked together closely for many years and perfectly complement each others' strengths. They are a tough act to follow, but I hope to emulate their collegiality and excellent mentorship in my scientific career. As an MD/PhD student, I have also sought mentorship from many physician scientists who have helped me envision how an active clinical practice can inspire my research efforts.

What's next for you?

After defending my PhD, I returned to medical school, and I will be applying for research-focused residencies next year. I hope to continue studying autophagy in neurodegenerative disease in my future, and explore how tissue samples obtained during neurosurgery can inform our understanding of autophagic balance in neurological disease.

Tell us something interesting about yourself that wouldn't be on your CV

I played competitive water polo in college and graduate school, and still hold my high school's record for most career assists, which I think shows that I'm a team player. I sustained a concussion at practice during graduate school, and have been helping with research on head impacts in water polo ever since.

Reference

Fote, G. M., Geller, N. R., Efstathiou, N. E., Hendricks, N., Vavvas, D. G., Reidling, J. C., Thompson, L. M. and Steffan, J. S. (2022). Isoform-dependent lysosomal degradation and internalization of apolipoprotein E requires autophagy proteins. *J. Cell Sci.* **135**, jcs258687. doi:10.1242/jcs.258687