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Autophagy researchers

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Research focus

Defining new roles and mechanisms of autophagy, mainly in Drosophila.

Model system

Drosophila and cultured insect cells.

Education and career

2004, PhD in cell biology, Eötvös University, Budapest, Hungary; advisor: Miklós Sass. 2004–2006, postdoc, University of Minnesota, Minneapolis, MN, USA; advisor: Tom Neufeld. 2006–2009, assistant professor, Eötvös University. 2009–present, research associate professor, Eötvös University.

Why do you study autophagy?

I joined the Sass lab to study autophagy in 1996 when I was an undergraduate in my second year. The lab was starting to work with a new model at that time: Drosophila. I stayed there for my PhD, and I could graduate partly thanks to a Soros fellowship that allowed me to work for 6 months at two excellent Drosophila genetics labs in Szeged. The next big step was joining the renowned Neufeld lab. I was hesitating whether I should change research fields when I was about to return to Europe. I stayed because autophagy was getting really hot, and a job offer came from Budapest at the same time. Soon I managed to obtain funding as well, so I have spent my whole career studying autophagy so far.

What do you think is a key question in the autophagy field?

I think we are still far from understanding all the details of core mechanisms and regulation circuits, and I expect that these will be very important before we can take full advantage of autophagy modulation by drugs for therapy.

Why is the field of autophagy important to you?

I participated in a number of related meetings, starting from the 2002 GRC on lysosomes when autophagy was only a session with five speakers. It was interesting to witness how this field transformed into a hot topic, and the community is still supportive, although it gets more and more competitive all the time. While there are major discoveries and tremendous progress has been made in recent years, plenty of unanswered questions remain. I think we have the test systems, lots of data and new reagents in hand to contribute in useful ways.

What do you hope to achieve in your scientific career?

We carried out a genome-wide RNAi screen for autophagy genes in mosaic animals, and have dozens of very interesting hits. Unfortunately some of these were recently characterized in other systems, removing the "conceptual novelty" from some projects. While we should be able to publish a couple of new stories in the near future, I hope to collaborate more with mammalian cell culture labs to speed up our in vivo research projects. I also plan to slowly move our research focus towards studying the role of autophagy in a developmental context and its regulation by heterotypical cell communication. This way we could take full advantage of using Drosophila instead of cell culture. I think it is difficult to plan for the long-term now, given the current financial situation of our country.

Is teaching a substantial part of your current position? If so, what do you teach? Does it benefit your research, or benefit from your research?

I still teach even though my Wellcome Trust grant now covers my salary, but I only undertake Master's and PhD courses. I have my own cancer biology and transgenic technologies courses, I teach the autophagy half of our apoptosis and autophagy course, and give a few lectures in others. This way I may recruit potential future lab members and get to learn and discuss fields related to our research, which can give new ideas for projects and experiments.

Personal comments

I am pressed for time, as work can take up day and night, and as a group leader I have less time for experiments. Having a Drosophila station with CO_2 and a microscope at home helps a little, though (we have also been working with rats in the past two years in the lab, but my wife would not let me take those home). I spend the time I can spare with my wife and our two small kids. The last thing I read was "The Book of Big Machines," to my son, and we learned how a tunnel-boring machine works. I enjoy sports such as hiking and mountaineering, traveling and playing various games. I trust we will spend more time doing these again as the kids grow.

Rosa Puertollano

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Research focus

Role of lysosomes and autophagy in health and disease.

Model system

Although we mainly work with human cell lines, we have recently started using zebrafish and mice.

Education and career

1999, PhD in biochemistry and molecular biology, Consejo Superior de Investigaciones Científicas, Centro de Biología Molecular, Severo Ochoa, Madrid, Spain; advisor: Miguel Alonso. 1999–2004, postdoctoral fellow, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA; advisor: Juan Bonifacino. 2004–present, principal investigator, Cell Biology and Physiology Center, National Heart, Lung, and Blood Institute, National Institutes of Health.

Why do you study autophagy?

As an independent investigator, I started working on lysosomal storage disorders (LSDs), in particular mucolipidosis type IV (MLIV) that is caused by mutations in the lysosomal calcium channel mucolipin 1 (MCOLN1). It soon became clear that when lysosomes do not work properly, the whole autophagic process is impaired. We think that MCOLN1 is directly implicated in the fusion between autophagosomes and lysosomes. Cells obtained from MLIV patients or MCOLN1 knockout mice show a dramatic accumulation of autophagosomes, ubiquitinated aggregates, and abnormal mitochondria. In fact, several groups have reported defective autophagy in many different LSDs.

The levels of MCOLN1 are regulated by the transcription factor EB (TFEB), a master regulator for the expression of autophagic and lysosomal genes. Overexpression of TFEB leads to increased autophagy, increased lysosomal biogenesis and increased lysosomal degradation. We recently found that the activation of TFEB is regulated by MTOR. It is well known that under nutrient-rich conditions, MTOR blocks autophagy by inhibiting the ULK1/2 complex. We found that MTOR also phosphorylates TFEB and causes its retention in the cytosol. Since active MTOR resides on the lysosomal membrane and proper MTOR-dependent phosphorylation of TFEB requires recruitment of TFEB to this compartment, our work, as well as the work from other labs, reveals a very important role for lysosomes in autophagy regulation and cellular homeostasis.

If you could start over and choose a different career, what would it be?

In high school and college I always enjoyed quantum mechanics and the idea that at a subatomic level things are governed by a different set of "rules." I think I would enjoy anything that implies discovering new things, from exploring unknown places (can you make a career out of this?) to creating new tastes through molecular cuisine.

Where do you think the field is heading?

In my opinion it will be very important to fully understand the role of autophagy, not just for the general homeostasis of the cell, but in more specialized processes such as the immune response and development. The impact of autophagy in cancer progression and neurodegeneration, as well as the characterization of selective autophagy, are also topics of high interest.

Personal comments

I am married to a scientist and we have a very fun three-year old son so there is not much free time. I do love to travel and read, mainly contemporary Spanish authors like Javier Marias and Antonio Munoz-Molina.

Shigeomi Shimizu

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Research focus

Physiological and pathological roles of autophagy and cell death.

Model system

Mice, mammalian cells and *Saccharomyces cerevisiae*.

Education and career

1983-1994, surgeon, Osaka University Medical School, Osaka, Japan. 1994, PhD, Osaka University Medical School; advisor: Kunio Tagawa. 1994-2000, assistant professor, Osaka University Graduate School of Medicine, Osaka; advisor: Dr. Yoshihide Tsujimoto. 2000-2006, associate professor, Osaka University Graduate School of Medicine; advisor: Dr. Yoshihide Tsujimoto. 2006–present, professor, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan.

Why do you study autophagy?

I previously studied the molecular mechanisms of apoptosis, particularly the roles of BCL2

and BCL2L1 (Nature 1994, 1999; Cell 2003). While I was studying DNA damage-induced cell death in *BAX BAK1* DKO cells, I discovered the induction of autophagy-mediated cell death. Subsequently, while studying autophagic cell death, we happened to discover ATG5-independent alternative macroautophagy. I am now interested in the molecular mechanisms and the physiological and pathological roles of both autophagic cell death and alternative macroautophagy.

What do you think is a key question in the autophagy field?

Determining the physiological and pathological roles of autophagy.

Why is the field of autophagy important to you?

I would like to elucidate the principal mechanisms involved in tissue homeostasis. Autophagy and cell death are the most crucial cellular functions for regulating homeostasis.

If you could start over and choose a different career, what would it be?

I was a surgeon for 10 years. I performed gastric, intestinal and liver resection surgery. When I was a surgeon, the major focus of my research was elucidation of the mechanisms of ischemia-reperfusion injury in liver transplantation. Through this experience, I knew the pleasure of research and decided to go from surgery to research.

Is teaching a substantial part of your current position? If so, what do you teach?

My teaching activities include a course in biochemistry and cell biology for post-graduate students. Most of my lectures focus on mitochondrial bioenergetics and cell death.

Personal comments

I love attending classical music concerts and opera. My favorite composers are J.S. Bach, G. Verdi, and R. Wagner. I also like to listen to contemporary classical music such as H.W. Henze and P. Boulez. In Tokyo, we have a good opera house.

Maria Ines Vaccaro

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Research focus

The molecular mechanisms involved in VMP1-mediated mammalian autophagy and its role in the cellular response to complex diseases, such as pancreatitis, pancreatic cancer and diabetes.

Model system

Cell lines, transgenic mice and human tissue.

Education and career

1984, PhD, biochemistry, School of Pharmacy and Biochemistry, University of Buenos Aires, Buenos Aires, Argentina; advisor: Omar H. Pivetta, MD. 1985–1990, postdoctoral fellow, University Clinical Medicine Hospital, University of Buenos Aires, Buenos Aires, Argentina; advisor: Osvaldo M. Tiscornia, MD, PhD. 1990–present, member, National Council for Scientific Research (2012–present, principal researcher). 2005, Master in Medical Education, National University of Tucuman, San Miguel de Tucumán, Argentina. 2000–2007, visiting scientist, INSERM, Marseille, France (annual 1-month stay), and assistant professor, Human Physiology, School of Medicine, University of Buenos Aires. 2007–2010, associate professor, Human Physiology, University of Buenos Aires. 2009, fellow of the American Gastroenterological Association Institute (AGAF). 2009–present, professor and chair, Human Pathophysiology, School of Pharmacy and Biochemistry, University of Buenos Aires.

Why do you study autophagy?

Autophagy represents a turning point in my research career. I was studying changes in the protein expression of the pancreatic acinar cell under the acute phase response when I had the opportunity to participate in a collaborative international project searching for new genes activated during acute pancreatitis. Among several other genes found, there is one, named Vmp1 (vacuole membrane protein 1), that encodes a transmembrane protein, whose expression induces cytosolic vesicle formation. Using in situ hybridization of its mRNA and immunohistochemistry, my lab demonstrated that VMP1 is highly expressed in acinar cells during acute pancreatitis and it correlates with pancreatitis-induced autophagic vesicles. Since acute pancreatitis was defined as pancreas self-digestion and autophagic features were described as an early cellular event, I hypothesized that VMP1 expression triggers autophagy. From then on, my research group experienced an important shift and entered into the "autophagy world." We characterized VMP1 as a transmembrane protein of the autophagosome that has no known homolog in yeast. We discovered that VMP1 expression triggers autophagy even under nutrient-replete conditions. VMP1 expression acts as a switch for autophagy and is essential for autophagosome formation in mammalian cells. We found that VMP1 directly interacts with BECN1, being a new player in the mammalian autophagy BECN1-PtdIns3K complex. Searching for

the role of autophagy in acute pancreatitis, we found that VMP1 mediates a sophisticated cell defense mechanism interacting with USP9X. We identified a novel selective form of autophagy, zymophagy, which degrades activated zymogen granules as a protective response to acute pancreatitis. Now, I am devoted to autophagy, its molecular mechanisms and its functions, and I am extremely grateful to belong to the community of autophagy researchers.

Why is the field of autophagy important to you?

I am particularly interested in autophagy acting as a cell response to complex diseases such as pancreatitis, pancreatic cancer and diabetes. In my view, the knowledge of the molecular mechanisms involved in the autophagic

processes, in response to injury, will help us to design more effective therapeutic strategies against disease.

If you could meet any scientist, currently living or from the past, who would it be and why?

I would meet George Palade. He characterized the zymogen granules and discovered the intracellular processing of proteins for export using electron microscopy, and the pancreatic acinar cell was his experimental model.

Is teaching a substantial part of your current position?

As chair and professor of human pathophysiology at the School of Pharmacy and Biochemistry, teaching undergraduate and postgraduate students represents a substantial part of my time. Teaching activities and students definitely benefit from professors' research. Also, some students become enthusiastic about research. Therefore, I enjoy very much giving lectures for young people hoping many of them will achieve great goals.

Personal comments

Besides my teaching and research activity, I am married to Carlos Chiesa. He is a biochemist and works on quality assurance for the pharmaceutical industry, he is an expert in good manufacturing practices and sometimes he helps me with GLP aspects in my lab. We have two great kids. Paula is an outstanding medical doctor, and Lucas is an electronic engineer working on robotics. Finally, I love music (especially Beethoven sonatas and Puccini operas) and I am always planning to return to my piano lessons. Someday I will.