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Autophagy researchers

Ravi Amaravadi

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Research focus

The role of autophagy inhibition in cancer therapy.

Model system

Cancer cell lines, xenograft mouse models, human clinical trials.

Education and career

1996, BA, biochemistry, Columbia University, New York, NY, USA; advisor: Dr Alexander Tzagaloff. 2000, MD, Johns Hopkins University, Baltimore, MD, USA. 2003, residency, internal medicine, Brigham and Women's Hospital, Harvard University, Boston, MA, USA; advisor: Dr Gary Gilliland. 2006, fellowship, hematology oncology, Brigham and Women's Hospital; advisor: Dr Craig Thompson. 2006–2007, instructor, medicine, University of Pennsylvania, Philadelphia, PA, USA. 2007–present, assistant professor, medicine, University of Pennsylvania.

Why do you study autophagy?

In general, cancer patients have a low rate of response and/or a short duration of response to current therapy. These therapies have some merit because in specific patients they can produce dramatic results. If we understood and developed strategies to overcome resistance mechanisms, many more patients would benefit. Autophagy could be a mechanism that is limiting the effectiveness of a number of therapies that have already gone through the expensive and inefficient path to clinical use. My initial EM studies in growing tumors from my own patients showed a massive number of vesicles, convincing me that autophagy likely plays an important role in human cancers, and further study would be fruitful.

What do you think is a key question in the autophagy field, and where do you think the field is heading?

It is clear that one direction the field is heading towards is identifying effective autophagy modulators as therapeutics for human disease. Some of the key questions in the autophagy field include: what are the druggable nonredundant targets for therapy in the autophagy pathway? How do we select the best drugs? At what point in the disease process is it best to intervene with autophagy modulators? For what diseases and contexts is it best to induce autophagy versus inhibit autophagy? How do we select patients that will respond best to autophagy modulation?

What do you hope to achieve in your scientific career?

To make findings that can help improve the treatment of cancer and other difficult to treat diseases.

Is there a key experiment/finding that stands out in your mind with regard to autophagy?

The discovery of lipidated LC3 gave a molecular handle on prior EM work in the field.

Which paper in your research field represents seminal work on autophagy?

Julian Lum and Craig Thompson's *Cell* paper (2005) demonstrating that growth factor withdrawal in rapidly proliferating cells activated a cytoprotective and reversible autophagy program, was the inspiration for my career. The activation of a survival pathway in apoptosis-defective cells that could be turned on and off by therapeutic interventions and the removal of the intervention was very reminiscent of the natural course of cancer therapy for most patients: response, latency, and recurrence when the therapy was removed. The natural extension of this work was my work, which replicated the findings in a mouse lymphoma model with chemotherapy instead of growth factor withdrawal. This paper opened the door to clinical trials involving hydroxychloroquine (manuscripts in press in *Autophagy*), and spurred the development of Lys05, a novel lysosomal autophagy inhibitor.

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

Jonas Salk, for conducting a 1.8 million-patient clinical trial in children involving a vaccine his team created. The results were spectacular (near complete irradication of polio), and saved many millions more lives. I would spend some time understanding how he motivated his team (including the millions of patients, tens of thousands of volunteers, and Congress) to work so well together.

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

If I could start over I would pursue my same career with more focus. I would not choose a different career. Being an academic physician-scientist in oncology has many privileges from being able to work with cells, model organisms, and humans who are suffering from real disease. Their suffering motivates the research and also provides a perspective that makes me appreciate every moment of my life.

How do you balance clinical care of patients, laboratory research, and clinical trials?

The key is to have excellent teams in each sphere, and open lines of communication between the teams. My patients and research nurses know a lot about autophagy! And my lab knows a lot about taking care of cancer patients.

Personal comments

When I am not working on autophagy or taking care of melanoma patients, I enjoy cooking without recipes. My most unusual vacation was a hike to the Mount Everest base camp. My favorite activity with the members of my lab includes looking at data that has come hot off the presses, and exploring the hundreds of innovative restaurants (last one was a vegan microbrewery) in Philadelphia for our lab celebrations.

Maureen E Murphy

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Research focus

The role of autophagy in cancer.

Model system

Genetically engineered mice, murine, and human cell lines.

Education and career

1987, Rutgers University, BSc, biochemistry. 1993, PhD, University of Pennsylvania School of Medicine, Philadelphia, PA, USA; advisor: Donna L George. 1994–1998, postdoctoral fellow, Princeton University, Princeton, NJ, USA; advisor: Arnold J Levine. 1998–2011, assistant, associate, full professor, Fox Chase Cancer Center, Philadelphia, PA. 2011–present, professor and program leader, Program in Molecular and Cellular Oncogenesis, The Wistar Institute, Philadelphia, PA.

How did you get into the study of autophagy?

We first got into autophagy in 2008 when studying TP53 and its mitochondrial localization pathway. Olivier Humbey and Julia Pimkina, postdocs in the lab, chose to ask whether the CDKN2A/ARF tumor suppressor caused TP53 to localize to mitochondria, and in doing so were surprised to discover a substantial fraction of CDKN2A trafficked to mitochondria. In working up this angle, they discovered CDKN2A could induce autophagy, in part by interaction with BCL2L1/Bcl-xl. Earlier this year, Anna Budina in the lab showed that full-length CDKN2A induces autophagy, and that the smaller-weight variant of CDKN2A called smARF (small mitochondrial isoform of ARF) instead induces mitophagy, thus clarifying some controversies in the field. Anna also went on to show that tumor-derived mutations in CDKN2A, located within exon 2 of the *CDKN2A* gene, are impaired for CDKN2A-induced autophagy, thus confirming yet again that autophagy is suppressive to tumor initiation.

What do you think are key questions in the autophagy field?

I think we still don't know why tumors mutate autophagy genes. The fact that they almost always mutate only one copy of an autophagy gene suggests that they cannot live without this pathway, yet they go to the trouble of hemizygously mutating genes within the pathway, apparently at their own expense: by doing this, they are dampening down a key survival pathway, and the question is why? It can't simply be to increase reactive oxygen species or mutation rate, as there are many different ways tumors can achieve increased mutation rate. It must be that dampening down autophagy gives them a survival advantage they cannot get any other way. Finding out the nature of this survival advantage will be a key emerging question in autophagy and cancer. Finally, how autophagy contributes to tumor cell metabolism and metastasis are also fields that I predict will blossom in 2014.

What do you hope to achieve in your scientific career?

It is no secret that science can be the most rewarding, but also the toughest, vocation known to humankind. That toughness can make this field of work appear to be a "shark pit." I hope to be known as someone who was a tough but supportive mentor, and who never contributed to the "shark pit" mentality, by showing people that the rewards of science outweigh any difficulty.

Which people in your research field have done seminal work on autophagy?

There are so many great researchers studying autophagy and cancer. Certainly the papers of Beth Levine, Eileen White, and Victor Jin on autophagy as a tumor suppressive mechanism have been key developments in the field. But then those of Craig Thompson, Ravi Amaravadi, and John Cleveland, showing that some tumors require autophagy for survival, are also seminal. The recent paper by Kevin Ryan that some tumors grow better when you inhibit autophagy really shows there is much to understand. Finally, I give Dan Klionsky enormous credit for unifying the field, by creating an outstanding journal with very high standards.

Is teaching a substantial part of your current position? Does it benefit your research, or benefit from your research?

I love teaching, and am benefited enormously by it; the trainees at The Wistar Institute are simply outstanding, and they are always keeping me on my mental toes. Their questions on autophagy and cancer are always insightful and inspiring.

Personal comments

One thing I try very hard to impress upon my lab is that your life should be divided up into "pie pieces": what you label these pieces, and how big each piece is, is up to you. For example in my case, family and work are the biggest pieces, taking up to 2/3 of my "pie," followed by smaller pieces consisting of finance and fitness. It's important in life to pay sufficient attention to each piece, according to its size. But absolutely, positively, one of the pieces should be volunteering. And I think my message has gotten through. My entire lab runs the Susan G Komen race in Philly every year, raising money for breast cancer research. Additionally, several of us run 2 or 3 half marathons each year, again to raise money for causes that concern us. Giving back to your community should absolutely be a piece of everyone's pie. The rest is up to you.

Thierry Soldati

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Research focus

We are focusing on understanding the cellular and molecular mechanisms of mycobacteria virulence and host cell defense strategies.

Model system

The social amoeba *Dictyostelium discoideum*.

Education and career

1987–1990, PhD, Institute of Cell Biology, Swiss Federal Institute of Technology (ETH) Zurich, Switzerland; advisor: Prof Dr J-C Perriard; co-advisors: Prof Dr HM Eppenberger and Prof Dr TE Kreis. 1991–1995, postdoctoral fellow, Department of Biochemistry School of Medicine, Stanford University Medical Center, Stanford, California, USA; advisor: Dr Suzanne R Pfeffer. 1995–2001, group leader, Max-Planck Institute for Medical Research, Heidelberg, Germany. 2001–2004, lecturer, Molecular Cell Biology, Imperial College London, UK. 2004–2011, Maître d'Enseignement et de Recherche, Department of Biochemistry, University of Geneva, Switzerland. 2011–present, associate professor, Department of Biochemistry, University of Geneva.

Why do you study autophagy?

We are fascinated by the recently discovered role of autophagy/xenophagy in the defense of host cells against intracellular pathogens. For years, the major aim of my group has been to understand the integration, and the cooperation of signaling, cytoskeleton, and membrane trafficking in phagocytosis and its relevance to host-pathogen interactions. To this end, we mainly use the social amoeba *Dictyostelium* as a surrogate for the study of phagocytes of the innate immune system. Along the way, we made major contributions to the unraveling of cellular and molecular mechanisms of cell motility, membrane trafficking, and phagosome maturation. Crucially, we established *Dictyostelium* as a model host to study infection and dissemination of pathogenic *Mycobacterium marinum*. This system recapitulates the major hallmarks of a human infection by *M. tuberculosis*. In addition, we discovered that both *M. marinum* and *M. tuberculosis* can escape from their vacuole into the cytosol, and are then ejected from the cell through a structure we named the ejectosome. Recently, we expanded our repertoire of expertise to the establishment and validation of the *Dictyostelium–M. marinum* system for medium-throughput screening of anti-infective compounds.

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

In fact, we are convinced that there are many facets to the various flavors of "autophagies" and are struggling to decipher the causality chain between the damage and the recruitment of the machinery. The more we advance in our research on the resistance mechanisms of *Dictyostelium* against vacuolar and cytosolic *M. marinum*, and in particular the response to the damages

inflicted by the bacterium to the mycobacteria-containing compartment, the more we (re)discover the complexity of autophagy. For example, we want to understand the exact requirements in terms of autophagy factors involved in the re-engulfment of cytosolic bacteria.

Personal comments

What is truly important for me besides research and teaching is the crucial balance of work and family. As a husband of a molecular parasitologist and father of 4, I have strived to keep everything functional and everybody happy while we were hopping around the world to follow the job market. I hope to be able to transmit my general optimism and faith in hard work to the younger generation of researchers in my lab and the students I teach.

Cécile Vindis

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Research focus

Cellular and molecular mechanisms involved in the cell survival and death balance during atherogenesis.

Model system

Human and murine vascular cells, mouse models of atherosclerosis, and human atherosclerotic plaques.

Education and career

2000, PhD, Molecular and Cellular Pharmacology, University of Toulouse, France; advisors: Dr Claudie Cambon and Pr Angelo Parini. 2000–2003, postdoctoral fellow, Department of Nephrology and Clinical Research, University of Bern, Switzerland; advisor: Pr Uyen Huynh-Do. 2003–2005, postdoctoral fellow, INSERM Unit 466, Atherosclerosis and Cellular Regulations, Toulouse; advisor: Pr Robert Salvayre. 2005–present senior researcher, Institut for Cardiovascular and Metabolic Diseases, INSERM, in Dr Anne Nègre-Salvayre's group, Toulouse.

Why do you study autophagy?

Before I entered the autophagy field 4 years ago, my research was focusing on the signaling pathways that control apoptosis triggered by oxidized lipoproteins in vascular cells. We described the involvement of a calcium-dependent mitochondrial apoptotic pathway, and later we realized that this apoptotic pathway was more complex since survival and adaptive pathways were concomitantly activated in cells following death signals. Indeed, the demonstration of ER stress activation both in human atherosclerotic lesions and in vascular cells stimulated with oxidized lipids shed light on the key role of adaptive responses in sensing cellular stress.

My autophagy "déclic" came from the review of Marja Jäättelä on the connections between ER stress, autophagy, and calcium, which convinced me to study autophagy in my model. Two years later we published a paper in *Cell Death and Differentiation* showing that the autophagy process contributes to phosphatidylserine exposure which allows the generation of engulfment signals required for the phagocytic removal of vascular dying cells exposed to oxidized lipoproteins. Our findings make sense with regard to atherogenesis since during lesion development the efferocytosis of apoptotic cells becomes deficient and then contributes to plaque instability and rupture. Now, dissecting signaling pathways controlling autophagy during atherosclerotic plaque development became one of my major focuses of interest.

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

An important issue in the field is the interplay between autophagy and cell death in health and pathological states and whether autophagy modulation could be efficient to treat diseases. In addition, the discovery of a selective autophagy process such as lipophagy, xenophagy, or mitophagy raises exciting questions for scientists and enlarges the investigation fields of autophagy.

What do you hope to achieve in your scientific career?

As I am at the "middle" of my scientific career, it's difficult to answer, but one of my goals is to develop more translational aspects of my research. I also hope to keep my motivation and fighting spirit to train young researchers and to work on ambitious projects; we must keep in mind that scientific research requires time and tranquility, and that curiosity is a locomotive at least as powerful as the societal needs.

Is there a key experiment in your own work that stands out in your mind with regard to autophagy?

With my colleague Audrey Swiader, we are currently working on the role of mitophagy as a key mechanism against cell death in vessel walls during atherogenesis. We are very impressed by all the work from Richard Youle's lab and we hope soon to be getting live cell microscopy images of mitophagy from vascular cells.

Personal comments

As I am married to a chemist scientist, it's sometimes difficult to find equilibrium in the work-life balance. We are very active parents with our 2 daughters and we try to dedicate our free time to traveling, practicing sports, and watching a good movie with them. I am also very fond of running and mountain biking—for me it's one of the best ways to clear the mind. We enjoy living in Toulouse in the west-south of France, as this place has great advantages: quick access to the Pyrenees Mountains, the Atlantic Ocean, and the Mediterranean Sea.