AUTHOR COMMENTARIES - From Special Topics

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Patrice Codogno
From the Special Topic of Autophagy

According to our Special Topics analysis on autophagy, Dr. Patrice Codogno's work ranks at #9 by total papers and at #10 by total cites, based on 39 papers cited a total of 1,994 times. In Essential Science Indicators*SM from Thomson Reuters, Dr. Codogno's record includes 56 papers, the majority of which are classified under Biology & Biochemistry, cited a total of 2,500 times between January 1, 1999 and June 30, 2009.*

Dr. Codogno is a member of INSERM, and works out of the Faculté de Pharmacie of the Université Paris-Sud 11. In the interview below, he talks with ScienceWatch.com *about his research in autophagy.*

SW: Would you tell us a bit about your educational background and research experiences?

I received my Ph.D. in 1984 from the University Pierre et Marie Curie in Paris, France. Soon after being granted tenure at INSERM (National Institute of Health and Medical Research) in 1985, I started studying the role of glycosylation in the intracellular trafficking of proteins.

At the time, little was known about the role of N-glycans in the quality control of proteins and membrane targeting, with the exception of that of mannose 6-phosphate in lysosomal targeting. My current work is centered on the biosynthesis of glycoproteins and extracellular matrix assembly.

SW: What first interested you in autophagy, and is there a specific aspect of autophagy research on which you focus?

While studying the intracellular trafficking of N-linked glycoproteins in human colon cancer cells, my team's studies revealed slight trimming of high-mannose glycans in the complex glycans in undifferentiated cells, but not in differentiated cells. Lysosomal inhibitors and 3-methyladenine, an inhibitor of autophagy, stabilized high-mannose glycoproteins in undifferentiated cells without increasing the appearance of complex-type N-linked glycans.

These results were reported in a *Journal of Biological Chemistry* paper in 1991 (Trugnan G, *et al.,* "The N-glycan processing in HT-29 cells is a function of their state of enterocytic differentiation—evidence for an atypical traffic associated with change in polypeptide stability in undifferentiated HT-29 cells," 266 [31]:20849-55, 5 November 1991), and demonstrated that high-mannose glycoproteins synthesized in the endoplasmic reticulum were diverted to the lysosomal compartment instead of being transported to the Golgi apparatus. These findings were the starting point for our subsequent studies of autophagy.

We soon decided to focus our research on the regulation of autophagy in cancer cells,

because at that time there was still little investigation of the molecular aspect of autophagy and its relationship to tumorigenesis, and not many groups were working in the field (things sure have changed since then!). However, I should point out that I learnt a lot by reading papers by Per O. Seglen, Alfred J. Meijer, E. Knecht, and Glenn Mortimore, who were pioneers in the field.

"These studies show that a pro-apoptotic molecule (ceramide) and an anti-apoptotic molecule (Bcl-2) are also able to regulate autophagy, implying that cross-talk occurs between autophagy and apoptosis."

SW: Your most-cited paper in our analysis is the 2000 *Journal of Biological Chemistry* article, "Distinct classes of phosphatidylinositol 3'-kinases are involved in signaling pathways that control macroautophagy in HT-29 cells," (Petiot A, *et al.,* 275[2]: 992-8, 14 January 2000). Would you talk a little bit about this paper, its findings, and why it is so highly cited?

The germ of this paper was sown when I met Alfred J. Meijer in 1996 at a proteolysis congress in Turku (Finland), where P.O. Seglen had organized the first autophagy symposium...at a conference on proteolysis! 3-methyladenine (3-MA) was routinely used to inhibit the formation of autophagosomes, based on the seminal paper from Seglen's laboratory in 1982. At the meeting, Fred Meijer reported that 3-MA inhibits autophagy by interfering with the activity of phosphatidylinositol 3-kinases. His findings were published a year later in *FEBS Journal* (the former *European Journal of Biochemistry*).

My own team's contribution was to show that the inhibition of autophagy by 3-MA was due to the inhibition of class III PI3K or human Vps34, whereas the inhibition of class I PI3K (which is upstream of mTOR) has a stimulatory effect on autophagy. The role of Vps34 when complexed with the autophagy protein Beclin 1 is an essential step in the formation of the autophagosome, and is highly conserved among eukaryotic cells. Moreover, in mammalian cells, the class-I PI3K signaling pathway plays a major role in inhibiting autophagy.

The modulation of autophagy is now recognized as being an important result of the deregulation of PI3K observed in human diseases, such as cancer. The initial report of the involvement of class-I and class-III PI3K in the regulation of autophagy was therefore an important milestone in the field. Last, but not least, this study marked the beginning of an extremely stimulating and amicable collaboration with Fred Meijer.

SW: Earlier this year, your group published another paper in that same journal, "Role of JNK1-dependent Bcl-2 phosphorylation in ceramide-induced macroautophagy," (Pattingre S, *et al., Journal of Biological Chemistry* 284[5]: 2719-28, 30 January 2009). Could you tell our readers something about this paper?

This work follows on from our initial report published in 2004 in the *Journal of Biological Chemistry* on the role of ceramide as an autophagy stimulator (Scarlatti F, *et al*., "Ceramide-mediated macroautophagy involves inhibition of protein kinase B and up-regulation of beclin 1," 279[18]: 18384-91, 30 April 2004).

In our most recent study, we demonstrate that ceramide activates the class-III PI3K complex and so stimulates autophagy. This stimulation is due to a ceramide-dependent phosphorylation of Bcl-2 by JNK1. The phosphorylation of Bcl-2 abolishes its inhibitory effect on autophagy by abolishing its interaction with Beclin 1 in the class-III PI3K complex. This mechanism is identical to that observed during the induction of autophagy by starvation reported by Beth Levine and her team (Wei *et al*. 2008 *Mol. Cell*).

Interestingly, Edinger and co-workers have reported that ceramide induces starvation in cells by blocking amino acid transport. It therefore makes sense to suggest that ceramide and amino acids use overlapping regulation systems to control autophagy. These studies show that a pro-apoptotic molecule (ceramide) and an anti-apoptotic molecule (Bcl-2) are also able to regulate autophagy, implying that cross-talk occurs between autophagy and apoptosis.

SW: How has our knowledge of autophagy changed over the past decade?

Enormously! It may be interesting here to compare autophagy and apoptosis. A major breakthrough in apoptosis was the discovery of apoptosis genes in *C. elegans* in the mid-1980s (although the term had first been introduced in the early 1970s). The breakthrough in autophagy was the discovery of ATG genes in yeast, which were first reported by Ohsumi and co-workers in 1993 (the term autophagy had been coined in the early 1960s).

"The modulation of autophagy is now recognized as being an important result of the deregulation of PI3K observed in human diseases, such as cancer."

Subsequently, it was demonstrated that ATG5 and Atg6 (beclin 1) were conserved in mammalian cells. Now we know that most of the Atgs involved in the formation of autophagosomes are conserved in mammalian cells. The development of mouse models has revealed the importance of stress-induced autophagy and basal autophagy in tissue homeostasis and survival. Moreover, having identified the role of autophagy in several human diseases is likely to give rise to new approaches to treating neurodegenerative disease and cancer.

Two fascinating aspects of autophagy are the discovery of its function in innate and acquired immunity, and, of course, its function as an anti-ageing mechanism. Another interesting point is the fact that autophagy is considered to be a non-selective mechanism—I am speaking here of macroautophagy, although it is now clear that in many situations autophagy is selective towards cell structures, proteins, and lipids. One may wonder whether unselective autophagy should in fact be regarded as an exception rather than the rule.

One major challenge that remains is to determine the origin of the isolation membrane or "phagophore" (a term coined by P. Seglen 20 years ago) that forms the autophagosomes. Undoubtedly, we can expect huge progress to be made in this "Quest for autophagy" issue in the near future.

SW: Where would you like to take your research on autophagy in the next decade?

I am now interested in non-canonical forms of autophagy, by which I mean forms of autophagy that do not use the whole set of Atg proteins to form an autophagosome (18 in fact). Once again the story overlaps with that of apoptosis, where morphology can involve several different molecular elements. The discovery of non-canonical forms of autophagy points to plasticity in the way autophagosomes are formed, and also in differences in cell functions. Moreover, these forms of autophagy highlight the importance of using an unrestricted panel of methods to measure autophagy. This may also lead to a refining of the definition of macroautophagy.

Another interesting emerging field is that of the role of Atg proteins independently of autophagy. Investigating these issues could be a way to escape to the fringes of mainstream research, and away from areas that have now become rather "crowded" and very competitive.

SW: What would you say the "take-home message" about your work should be?

I came into the field of autophagy by serendipity, at a time when autophagy was not very fashionable in cell biology. It is fascinating for a scientist to be involved in the development of a new field of research (even if one only contributes a small brick to the wall), and even if it is sometimes viewed as a research backwater by many people. We can hope that times have changed, and autophagy is now an interesting challenge with possible applications in many human diseases. So, my take-home message is, "Go for it—just do it!"

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Patrice Codogno's current most-cited paper in *Essential Science Indicators*, with 323 cites:

Petiot A, *et al.*, "Distinct classes of phosphatidylinositol 3'-kinases are involved in signaling pathways that control macroautophagy in HT-29 cells," *J. Biol. Chem.* 275(2): 992-8, 14 January 2000. Source: *Essential Science Indicators* from Thomson Reuters.

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