AUTHOR COMMENTARIES - From Special Topics

Autophagy - July 2009
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David Rubinsztein
From the Special Topic of Autophagy

In the Special Topics analysis on autophagy, the paper "Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease," (Ravikumar B, et al., Nat. Genet. *36[6]: 585-95, June 2004) appears on both the list of the 20 most-cited papers in the past decade and the Research Front Map on Autophagy. According to* Essential Science Indicators℠ *from Thomson Reuters, this paper has been cited 335 times from its publication in 2004 to February 28, 2009.*

The leading scientist behind this paper is Professor David Rubinsztein, whose record in the database includes 118 papers, the bulk of which are classified under Molecular Biology & Genetics, cited a total of 4,402 times. Prof. Rubinsztein is currently Professor of Molecular Neurogenetics and Wellcome Trust Senior Fellow in Clinical Science in the Department of Medical Genetics at the University of Cambridge's Cambridge Institute for Medical Research.

In the interview below, ScienceWatch.com *talks with Prof. Rubinsztein about this paper and its impact on the field of autophagy.*

SW: Would you please describe the significance of your paper and why it is highly cited?

Many neurodegenerative diseases, including Huntington's disease, are caused by intraneuronal aggregate-prone proteins. These proteins generally cause disease by gain-of-function mechanisms, thereby acting as "toxins."

Previously, we had shown in cell culture that such aggregate-prone proteins could be cleared from the cytoplasm by autophagy. (Ravikumar B, *et al.*, *Hum. Mol. Genet.* 11[9]:1107-17, 1 May 2002). Autophagy is a process whereby cells form double-layered vesicles that engulf a portion of cytoplasm and deliver these to lysosomes for degradation of their contents.

In this *Nature Genetics* study, we showed that autophagy induction with rapamycin enhanced the removal of a form of mutant huntingtin (which causes Huntington's disease), and thereby reduced its toxicity in transgenic *Drosophila* and mouse models of Huntington's disease.

I think that this study showed proof-of-principle *in vivo* for the possibility that autophagy upregulation may be a therapeutic strategy for Huntington's disease and related conditions.

The study also shows that once the large aggregates form, they sequester and inactivate the mammalian target of rapamycin protein (mTOR). mTOR inactivation is one of the pathways that induces autophagy, and thus this suggested a possible protective consequence of the large aggregates.

"...we need to try to understand how autophagy may be involved in a range of diseases and normal physiological processes..."

SW: How did you become involved in this research, and were there any particular successes or obstacles that stand out?

I had been working on Huntington's disease since 1993 and thought that reducing the levels of the toxic protein was a possible strategy that one could consider. One way of doing this was by enhancing its degradation.

While people were very focused on the ubiquitin-proteasome system in the context of Huntington's disease and related conditions, I became more aware of autophagy as a process and around 2000 thought that we should test it as a clearance pathway for Huntington's disease.

"I am keen to develop and test the strategy of inducing autophagy as a therapy for a range of neurodegenerative diseases."

SW: Where do you see your research and the broader field leading in the future?

I am keen to develop and test the strategy of inducing autophagy as a therapy for a range of neurodegenerative diseases. In conditions like Huntington's disease, one can identify people at risk who carry the mutation, as it is inherited in an autosomal dominant manner and most cases will have a family history. In such cases, there is also the possibility of starting treatment in asymptomatic mutation-positive cases long before disease onset, with the aim of delaying the onset of symptoms. This may require treatment of healthy people for many years. I would like to identify the safest possible ways of inducing autophagy for these purposes.

This will require a better understanding of the signaling pathways regulating autophagy, as well as identification of the possible druggable targets in the autophagy machinery.

SW: What are the implications of your work for this field?

We have helped to develop the idea that autophagy may be a protective process in certain conditions, and that its upregulation may be beneficial.

I think that this supports the idea that we need to try to understand how autophagy may be involved in a range of diseases and normal physiological processes, and there has certainly been impressive progress from many labs in these areas in recent years.

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David Rubinsztein's current most-cited paper in *Essential Science Indicators*, with 335 cites:

Ravikumar B, *et al*., "Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease," *Nat. Genet.* 36(6): 585-95, June 2004. Source: *Essential Science Indicators* from Thomson Reuters.

Additional Information:

View a Emerging Research Front comment from David C. Rubinsztein (Dec. 2008).

KEYWORDS: MTOR, AUTOPHAGY, TOXICITY, POLYGLUTAMINE, FLY MODEL, MOUSE MODEL, HUNTINGTON DISEASE, AGGREGATE-PRONE PROTEINS, RAPAMYCIN, HUNTINGTIN, THERAPEUTIC STRATEGIES, SIGNALLING PATHWAYS, INTRANUCLEAR INCLUSIONS; SYNAPTIC PLASTICITY; CELLULAR GROWTH; TRANSGENIC MICE; DROSOPHILA; MUTATION; PROTEIN; TRANSLATION; NUCLEAR; DEATH.

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