EMERGING RESEARCH FRONTS - 2008

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David C. Rubinsztein talks with *ScienceWatch.com* and answers a few questions about this month's Emerging Research Front Paper in the field of Pharmacology & Toxicology.

Article: The roles of intracellular protein-degradation pathways in neurodegeneration
Authors: Rubinsztein, DC
Journal: NATURE, 443 (7113): 780-786 OCT 19 2006
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SW: Why do you think your paper is highly cited?

The aim of the paper was to review the current understanding of the importance of protein degradation pathways in neurodegenerative diseases. This has been a rapidly evolving field and the paper provided the opportunity to include a fairly detailed assessment of more recent data implicating autophagy as an important route for the clearance of aggregate-prone proteins that cause many neurodegenerative diseases.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

This was a review which aimed to synthesize and appraise our understanding of the area.

"I have been working on Huntington's disease and related conditions for about 16 years."

SW: Would you summarize the significance of your paper in layman's terms?

Many neurodegenerative diseases, like Parkinson's disease and Huntington's disease, are characterized by the accumulation of specific proteins inside nerve cells in aggregates. Indeed, the relevant proteins show an enhanced propensity to aggregate. Furthermore, many of the aggregate-prone proteins that cause these diseases mediate pathology by a gain-function mechanism—they act as "toxins" to the cells.

While much of the earlier literature was concerned with the factors that influence aggregation specifically, this review considered the importance of pathways that regulate the levels of these "toxins" by influencing their degradation rates—the toxicity of these proteins and the numbers of aggregates that form, correlate with degradation rates. There are now many studies that suggest that impairing the degradation pathways may predispose to neurodegenerative disease, while upregulating specific pathways may be beneficial.

SW: How did you become involved in this research and were any particular problems encountered

along the way?

I have been working on Huntington's disease and related conditions for about 16 years. In 2002, we were the first lab to show that one could enhance the degradation of certain intracytoplasmic aggregate-prone proteins, like mutant huntingtin, by upregulating autophagy in cell culture (Ravikumar B, *et al.*, *Hum. Mol. Genet.* 11:1107-17, 2002). Subsequently, we provided proof-of-principle for this approach in transgenic fly and mouse models of the disease (Ravikumar B, *et al., Nature Genetics* 36: 585-95, 2004). The potential of this approach has led to a rapid expansion in our efforts to understand mammalian autophagy in the context of these diseases.

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

My aim is to develop the safest possible ways to be able to enhance the degradation of intracytoplamic aggregate-prone proteins that cause disease over long periods, as we believe that this would be a rational and potentially plausible therapeutic strategy for a range of neurodegenerative diseases.

SW: Do you foresee any social or political implications for your research?

I would be very happy if we could contribute to helping patients and families with these devastating conditions.

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Keywords: protein degradation pathways in neurodegenerative diseases, aggregate-prone proteins, parkinson's disease, huntington's disease, intracytoplasmic aggregate-prone proteins, mutant huntingtin, upregulating autophagy in cell culture.

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