NEW HOT PAPERS - 2009

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Beth Levine & Guido Kroemer talk with *ScienceWatch.com* and answer a few questions about this month's New Hot Paper in the field of Molecular Biology & Genetics.

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Article Title: Autophagy in the pathogenesis of disease
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SW: Why do you think your paper is highly cited?

Autophagy is an important emerging topic in biomedical research. Autophagy (literally "self-eating") consists in the sequestration of portions of a cell's cytoplasm within a specific organelle, termed the autophagosome, which subsequently delivers its contents to the lysosome for degradation.

Recently, basic cell biologists and disease-oriented researchers have teamed up to discover the immense importance of autophagy in normal physiological processes and aging as well as in the pathogenesis of multiple diseases, including cancer, neurodegenerative disorders, infectious diseases, and inflammatory bowel disorders such as Crohn's disease. This rapidly growing appreciation of the implications of autophagy (and the deregulation of autophagy) in human diseases is a major reason why our paper is highly cited.

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

Our review article provides a state-of-the-art synthesis of knowledge on the role of autophagy deregulation in human disease. When a cell is stressed or damaged, it often responds by activating the autophagic machinery. Autophagy allows the cell to mobilize its energy resources and to survive in conditions of reduced nutrient or oxygen supply. Autophagy is also involved in the removal of superfluous or damaged proteins or organelles—for instance, uncoupled or permeabilized mitochondria—and hence, has an important role in the maintenance of cellular homeostasis.

Autophagy is also essential for the maintenance of genomic stability. As a result, disabled autophagy can lead to malignant transformation and participate in tumor progression. Reduced autophagy can also accelerate degenerative processes in the heart, liver, muscle, and brain, and the stimulation of autophagy can retard organismal aging and postpone the manifestations of neurodegenerative diseases.

Defective autophagy can also compromise the ability of the host to fight infections and control inflammatory responses, which may explain the recently described genetic association between a polymorphism in an autophagy protein and susceptibility to Crohn's disease. So, in this article, we emphasize the likely contribution of deregulated autophagy to a variety of major diseases.

Coauthor
Guido Kroemer

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

Autophagy has been regarded by many investigators as a mode of cellular self-destruction. In our paper, we emphasize the contribution of autophagy to the maintenance of cellular and organismal health. If insufficient autophagy is indeed involved in the development of major human diseases, including age-associated degenerative processes, its pharmacological induction may have a therapeutic effect. There are also specific circumstances in which inhibition of autophagy may constitute a therapeutic goal, and this is also discussed in our paper.

SW: How did you become involved in this research, and were there any problems along the way?

In the '90s, Beth Levine discovered a protein, named Beclin 1, that physically interacts with Bcl-2, one of the major regulators of apoptosis. This protein turned out to be a tumor suppressor protein and to be required for autophagy, thus providing the first example how defective autophagy may be pathogenic. Dr. Levine also first defined a role for autophagy genes in fighting viral infections and in preventing aging. Since then, she has explored the mechanisms by which Beclin 1 contributes to autophagy regulation and she is studying the pathophysiological implications of deregulated autophagy in a variety of important medical diseases.

"Our review article provides a state-of-the-art synthesis of knowledge on the role of autophagy deregulation in human disease."

Guido Kroemer challenged the idea that autophagy would constitute a modality of programmed cell death starting in 2005, when he published that inhibition of autophagy can accelerate the apoptotic demise of stressed cells *in vitro*. Since then, he has been interested in the crosstalk between apoptosis and autophagy in molecular terms. This has turned out to be a fascinating and complex area of research, with wide implications for various diseases.

SW: Where do you see your research leading in the future? Do you foresee any social or political implications for your research?

Perhaps, along with cell division, cell differentiation, and cell death, autophagy is one of the most fundamental phenomena in cell biology. However, the molecular comprehension of autophagy is still in its infancy. We anticipate that a more detailed comprehension of the autophagic process and its complex regulation will facilitate its therapeutic manipulation. Given the broad impact of autophagy on major, socioeconomically relevant diseases, including cancer, neurodegeneration, and global infectious diseases, we believe that therapeutic measures designed to correct disease- or age-related autophagic defects might have a major impact on public health.

At present, the only known strategy to induce autophagy without major side effects is fasting, and caloric restriction indeed prolongs the longevity of animals through the induction of autophagy. Therefore, it will be interesting to invent strategies to induce autophagy in such a way that the discomfort of caloric restriction is avoided, while stimulating autophagy in a manner that will conserve its beneficial actions on human health.

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Read an Interview with Guido Kroemer, named in the top 20 list of highly cited scientists in the special topic of Apoptosis.

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