EDITORIAL

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# Focusing on Autophagy

**Autophagy targets portions of cytoplasm, damaged organelles and proteins for lysosomal degradation and has crucial roles in development and disease. This issue presents a series of specially commissioned articles that highlight recent developments and emerging themes in this area.**

Fifty years ago, researchers were puzzled by observations of cytoplasmic material being engulfed within double-membrane vesicles and subsequently degraded. These vesicles were shown to contain fragments of mitochondria and endoplasmic reticulum as well as lysosomal enzymes. In a conference on lysosomes in 1963, Christian de Duve appropriately coined the term autophagy — literally, eating one's self — to describe this phenomenon. But why would a cell digest itself?

Starvation conditions were later shown to enhance the formation of such vesicles, whereas amino acids, the end products of this degradative process, inhibit their formation. So, it appeared that autophagy may be a strategy that had evolved to allow cell survival in low-nutrient conditions. It is now clear that this function represents only the tip of the iceberg. Autophagy has been demonstrated to be relevant for processes as diverse as neurodegeneration, immune function, cancer, ageing and development.

Although the double-membrane vesicles, now called autophagosomes, were thought to be a physiologically relevant entity, the field was stalled for a long time, owing to the lack of markers to follow these vesicles. As late as the 1990s, issues ranging from the signals that regulate autophagy, to the mechanisms that drive the biogenesis of autophagosomes and their subsequent fusion with lysosomes, remained poorly understood. Many researchers working in areas outside autophagy, such as signalling, membrane trafficking, and ubiquitin-related processes, as well as researchers interested in various aspects of physiology, were therefore drawn to this field. Combined with the development of conceptual and technical advances, this has meant that not only have the number of published papers mentioning autophagy increased by approximately tenfold in the past decade, but the number, size and diversity of meetings in the area has also rapidly expanded.

In this issue of *Nature Cell Biology*, we are pleased to present five specially commissioned articles written by leading experts that focus on the mechanistic and functional aspects of autophagy. We hope that this will be an informative introduction to this exciting area for the non-expert and an update on recent research and concepts for the 'aficionado'.

In a Review, Zhifen Yang and Daniel Klionsky present the evolution of the field into the current molecular era. As in many other fields, yeast genetics provided researchers with an initial handle on the molecules involved in the machinery that controls various aspects of autophagy. This was soon followed by the identification of their homologues in other systems, including mammals. The article also discusses molecular, genetic and cell biological approaches that have combined to greatly enhance current mechanistic understanding of autophagy and its implications for various physiological contexts.

Armed with the knowledge of molecules involved in autophagosome formation, researchers could now tackle a pressing question raised since the discovery of the double membrane vesicles and currently, one of the most debated issues in the field: where does the autophagosomal membrane come from? Rapid progress has been made in the past five years to resolve this mystery, thanks to improved electron-microscopy techniques and the use of fluorescently labelled proteins to monitor autophagosome formation in real time. In a Perspective article, Sharon Tooze and Tamotsu Yoshimori present the latest consensus on this matter, suggesting that the membrane source of autophagosomes may vary in response to different cues.

Autophagy was originally viewed as a bulk degradation process. However, certain pathogens, aggregated proteins, damaged mitochondria and even ribosomes can be selectively degraded by autophagy. This inevitably raises the question of how autophagy substrates are selected. Ubiquitylation is a well-established signal for selective degradation by the proteasome and it is also important for sorting proteins into compartments of the endosomal–lysosomal pathway. Because p62, one of the adaptors involved in directing substrates for autophagic degradation, has a ubiquitin-binding domain, researchers focused on ubiquitin as a sorting signal in autophagy. In a Perspective article, Claudine Kraft, Kay Hofmann and Mathias Peter explore the role of ubiquitin for selecting cargo in autophagy and present recent data on the crosstalk between proteasome and autophagy-mediated degradation.

Two articles examine the physiological relevance of autophagy. Noboru Mizushima and Beth Levine discuss how the loss of function analysis of autophagy genes (Atg) in mice has revealed the many roles of the autophagy pathway in mammalian differentiation and development. For example, as a survival pathway providing nutrients to cells, autophagy is essential for the oocyte to embryo transition as well as for neonates to survive the first few hours after birth. Tissue-specific knockouts of Atg genes have also revealed an essential role for autophagy in cell differentiation. The review also highlights the importance of autophagy in maintaining homeostasis in terminally differentiated cells. Finally, a Commentary by Frank Madeo, Nektarios Tavernakis and Guido Kroemer discuss the intriguing evidence suggesting that autophagy can promote organismal longevity.

This collection of articles is not meant to provide comprehensive coverage of the field but rather to draw attention to topical and emerging issues. We would like to thank our contributors and reviewers, without whom this Focus would have not been possible. The Focus articles are hosted at a dedicated website (http://www.nature.com/ncb/webfocus/autophagy/index.html), which also includes a library of selected articles on autophagy from a range of Nature Publishing Group titles. We hope you enjoy reading these pieces and as always, your feedback is welcome.