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Autophagy for the avoidance of degenerative, inflammatory, infectious and neoplastic disease

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Macroautophagy (henceforth referred to as autophagy) is a process conserved from yeast to man for the identification, collection and degradation of cellular components including proteins, lipids and organelles. Basal autophagy serves to maintain protein and organelle quality control and thereby preserves cellular and organismal viability and health. Stress and starvation trigger autophagy where accelerated turnover of cellular components sustains energy homeostasis through cellular self-cannibalization that provides an internal source of building blocks for macromolecular synthesis. Autophagy also prevents the toxic buildup of lipids and damaged proteins and organelles, particularly during stress. In development, autophagy plays a role in differentiation in a tissue-specific manner by facilitating cellular and tissue remodeling through the degradation and removal of cellular material.

It has become clear recently that autophagy dysfunction contributes to or is the cause of many diseases, revealing the novel opportunity for autophagy modulation in therapeutic interventions. Evidence suggests that defective autophagy promotes cancer, neurodegenerative disorders, liver disease, aging, and inflammatory conditions such as Crohn's disease, and compromises host defense against pathogens. This realization has prompted efforts to identify the autophagy machinery, the molecular processes involved, the regulatory pathways, and the means to modulate autophagy in disease settings. This special issue of *Current Opinion on Cell Biology* is devoted to highlighting both the recent advances in the role of autophagy in disease and the remaining important issues that need to be addressed. The intent is to provide fundamental insights into the physiological function and pathological role of autophagy and

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to explore possible therapeutic interventions on autophagy that might ease the suffering from or even eliminate a spectrum of human diseases.

Basic Mechanisms of Autophagy

Fundamental to the process of autophagy is the mechanism of formation of the double membrane vesicles that capture cellular material. This process is fairly well understood in yeast and less so in mammals and involves the autophagy proteins encoded largely by the so-called *atg* genes. The *atg* genes encode protein and lipid kinases, the protease of the Atg4 family, and two ubiquitin-like conjugation systems that are responsible for genesis of autophagosomes. Drs. Klionsky, Mizushima and Levine and colleagues discuss the core autophagy machinery and its regulation in mammals. These papers cover the regulation of the Atg1/Ulk complex by mTOR and the initiation of autophagosome formation as well as the regulation of the Beclin1 complex that controls autophagosome membrane production. Dr. Tooze and colleagues investigate the source of membranes utilized to initiate autophagosome formation, their maturation, and subsequent trafficking of autophagic vesicles through the endocytic compartment to lysosomes.

Autophagy is a tightly regulated process linked to numerous stress-responsive and nutrient sensing signaling pathways. One of the key regulators of autophagy is the phosphoinositol-3 (PI-3) kinase pathway and the mammalian target of rapamycin (mTOR), thereby linking the key anabolic pathway to catabolism. How mTOR interfaces nutrient, growth factor, and energy availability with the autophagy pathway is provided by work in yeast, but also in *Drosophila* as highlighted by Dr. Neufeld and in mammals as discussed by Drs. Efeyan and Sabatini. As the PI-3 kinase pathway is commonly deregulated in cancer, and mTOR inhibitors are in use for cancer therapy, understanding the relationship between mTOR and autophagy is critical for establishing optimal cancer treatments [1].

Stressful stimuli such as hypoxia and induction of the hypoxia-inducible transcription factor HIF-1 also trigger autophagy and a specialized form of autophagy directed at the autophagic elimination of mitochondria [2]. The role of and mechanism by which HIF-1 functions in stress management through autophagy and limiting reactive oxygen species (ROS) is discussed by Drs. Mazure and Pouyssegur. The stress responsive p53 tumor suppressor also influences autophagy directly as discussed by Kroemer and colleagues and indirectly through the regulation of glucose metabolism, which is presented by Cheung and Vousden. Understanding these regulatory events is relevant for the settings of cancer and aging.

Stress also increases the intracellular burden of unfolded proteins and the role of autophagy and also the ubiquitin proteasome system (UPS) is to prevent stress through the degradation of unfolded proteins. Ubiquitin is also used to tag and target proteins to both UPS and autophagy, inhibition of autophagy sensitizes cells to proteasome inhibition [3] and suppresses UPS-mediated degradation [4]. Drs. Lamark and Johansen discuss this important cross talk between these two partly complementary protein degradation pathways. Finally, although in most settings autophagy promotes cellular survival, progressive or excessive autophagy has been proposed to lead to cell death in some situations [5]. Drs. Bailik and Kimchi discuss the role of DAP kinase in the regulation of autophagic cell death.

Role of autophagy in development and disease

Work in model organisms is clarifying the roles for autophagy in development. Autophagy is required for mammalian embryogenesis [6] and for surviving neonatal starvation [7], most likely by sustaining metabolic homeostasis. Moreover, the elimination of organelles through autophagy is indispensable for the final step of erythropoiesis [8], and autophagy is essential for normal lipid metabolism and adipocyte differentiation [9]. In *Drosophila* development,

extensive tissue remodeling is facilitated by autophagy [10]. The use of non-mammalian model organisms is a powerful approach to define the role of autophagy and regulators of the autophagy pathway in development and disease.

There is strong evidence for a role for autophagy in preventing aging, neurodegeneration, inflammation, cancer, and in promoting host defense against pathogens. It is clear that autophagy is important for the degradation of ubiquitinated, mutated and unfolded proteins and that defects in autophagy and the failure to eliminate these proteins can be toxic and manifest in disease. Deficiency in Atg5 or Atg7 in the brain of mice causes the accumulation of ubiquitinated protein aggregates, neuronal cell death and neurodegeneration [7,11]. Drs. Moreau and Rubinsztein discuss how bulk degradation of aggregation-prone proteins, aging mitochondria, and pathogens by autophagy provides a cytoprotective effect that limits degenerative diseases, aging and infection. Dr. Virgin and colleagues [12] describe how hypomorphic alleles in Atg16L impair autophagy, and disrupt the function of Paneth cells in the small intestine causing an injury response that manifests in Crohn's disease. A similar role for autophagy-mediated protein degradation in limiting inflammation and degenerative liver disease [13], supports a general theme for autophagy as a homeostatic mechanism to preserve cellular and tissue health that limits cell death, inflammation and tissue degeneration.

Another disease linked to defective autophagy and promotion of inflammation is cancer. Allelic loss of the essential autophagy gene *beclin1* predisposes mice to liver and lung tumors and lymphomas and defects in other autophagy genes renders mice or cells derived from them tumorigenic, as discussed in detail by Drs. White, Cleveland and Jung and colleagues. The role of autophagy in cancer may depend on the tissue type, nature of the oncogenic events, and whether tumor initiation, progression, metastasis, or treatment is involved. White and colleagues describe the causal relationship between autophagy defects, ROS, chronic cell death and inflammation, and cancer initiation. Drs. Young and Narita report how autophagy enables the tumor suppression mechanism of oncogene-induced senescence. Drs. Kenific, Thorburn and Debnath discuss how autophagy promotes survival during epithelial cell detachment from extracellular matrix (anoikis) and how this may influence tumor metastasis.

Modulation of the autophagy pathway for cancer treatment and prevention is also discussed by Drs. Cleveland, White, and Giaccia and colleagues. As autophagy is a stress survival pathway, inhibiting autophagy has been proposed to enhance cancer therapy. Alternatively, autophagy stimulation as a means for cancer prevention has been proposed to prevent tissue damage and inflammation, limit tolerance to oncogene activation, or lead to cellular self-consumption and death.

Lastly, autophagy plays an important role in the host defense against pathogens. Deretic and colleagues discuss the ability of autophagy to sanitize the cellular interior by killing intracellular microbes and how successful intracellular pathogens have evolved to protect themselves from autophagy. Autophagy also plays an important role in virtually all cells of the innate and cognate immune systems, at multiple levels, including in specialized antigen-presenting cells.

Collectively, the existing literature suggests that autophagy can play an essential role in the avoidance of degenerative, inflammatory, infectious and neoplastic disease. Indeed, experiments performed in non-mammalian model organisms including yeast, nematodes and flies suggest that autophagy is required for the antiaging effect of caloric restriction or longevity extending pharmacological agents [14].

Key questions going forward

While strolling through these informative chapters, the reader should bare in mind that there remain many unanswered key questions in this emerging field of autophagy and disease. For example, does autophagy mediate the anticancer effects of caloric restriction? Alternatively, does autophagy suppression contribute to obesity-associated disease? Will autophagy promotion suppress aging in humans and if so what is the best way to accomplish this? What is the contribution of autophagy suppression to the phenotype of PI-3 kinase pathway activation in cancer? Can autophagy stimulation delay the onset or ameliorate symptoms of neurodegenerative conditions in susceptible individuals? What about liver disease, cancer, Crohn's disease? Can autophagy inhibition block tumor survival and dormancy to increase efficacy in cancer therapy? What are the best targets in the autophagy pathway for drug discovery: kinases, the ubiquitin conjugating systems, proteases, upstream regulators, or downstream regulators? Can autophagy stimulation promote immune surveillance and pathogen elimination? What are the individual contributions of organelle, protein and lipid turnover failure in autophagy-mediated disease manifestation? How can this be controlled in therapy? What is the role of autophagy-mediated support of metabolism in disease mitigation? How does autophagy prevent the generation of ROS and what role does this play in different disease settings? Will autophagy modulation work therapeutically and for which diseases? Can autophagy be therapeutically up regulated to induce autophagic cell death and if so what would be the mechanism of cellular demise? Is the mechanism of autophagic cell death fundamentally different from known forms of regulated cell death including necroptosis as discussed by Drs. Christofferson and Yuan, which involves a specific set of kinases that "program" the cell for its demise? Can insights from non-mammalian model organisms guide this effort? What controls the selectivity for autophagy substrates? What are the regulatory pathways and complexes that assemble autophagosomes, and their recognition and capture of cellular cargo? How is this cargo delivered to the lysosomal compartment and recycled? What is the interface between autophagy and the vesicle trafficking machinery? How do stress and starvation impact these processes? What are the tissue-specific mechanisms for regulating autophagy?

The fairly recent revelation that autophagy plays a critical role in many different human diseases has dramatically increased interest in the field. Now the challenge is to identify the best means to take advantage of our increasing understanding of the autophagy pathway to improve human health.

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