Autophagy in kidney disease and aging: lessons from rodent models

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Autophagy is a highly regulated lysosomal protein degradation pathway that removes protein aggregates and damaged or excess organelles to maintain intracellular homeostasis and cell integrity. Dysregulation of autophagy is involved in the pathogenesis of a variety of metabolic and age-related diseases. Growing evidence suggests that autophagy is implicated in cell injury during renal diseases, both in the tubulointerstitial compartment and in glomeruli. Nevertheless, the impact of autophagy on renal disease progression and aging is still not fully understood. This review summarizes the recent advances in understanding the role of autophagy for kidney disease and aging.

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Autophagy ("self-eating" in Greek) is a highly regulated lysosomal protein degradation pathway that removes protein aggregates and damaged organelles to maintain intracellular homeostasis and cell integrity.[1–3] This process was first described in 1957 by Sam Clark Jr.,[4] but the term *autophagy* was coined by Christian de Duve only in the late 1950s.[5] The autophagy process is well conserved in the evolution from yeast to mammals.[6,7] Characterization of the molecular regulators of autophagy was first described in the 1990s with the identification of autophagy-related genes (ATGs) in autophagy-defective yeast cells,[8,9] Then mammal orthologs and the molecular machinery were identified.[10]

Three types of autophagy have been described to date as follows: macroautophagy, the most studied form and the focus of this review; microautophagy; and chaperone-mediated autophagy. All differ in their mechanisms and functions[11]: microautophagy involves the engulfment of small cytoplasmic cargos within lysosomal membrane invaginations[12] and chaperone-mediated autophagy involves the heat shock cognate protein 70–mediated recruitment of KFERQ motif–bearing proteins to the lysosome,[13,14] whereas macroautophagy is the most prevalent and probably less selective type and is referred to in this review as autophagy.

In this review, we describe the pathway of autophagy and highlight its role in renal physiology, renal aging, and kidney diseases. We will also discuss the potential implication of manipulating autophagy as a potential novel renoprotective therapeutic strategy.

AUTOPHAGY

Functions of autophagy

Autophagy has been demonstrated to be essential for a number of fundamental biological activities,[15] such as the maintenance of cellular homeostasis and cellular stress response, particularly in postmitotic cells. Autophagy participates in recycling of organelles such as mitochondria (mitophagy),[16,17] endoplasmic reticulum (ER), and peroxisomes[7,18–22]; the clearance of polyubiquitinated proteins aggregates[23]; and lipid degradation (lipophagy).[24] Dysregulation of autophagy is involved in the pathogenesis of a variety of metabolic and age-related diseases.[25–31] The major role of

autophagy is to provide metabolic precursors for survival in stress conditions and to serve as a quality control by clearing misfolded proteins and others cellular debris. Interestingly, genetic evidence (i.e., polymorphisms in *ATGs*) indicates that autophagy is implicated in several immune diseases associated with kidney dysfunction, such as systemic lupus erythematosus (autophagy related 5 gene [*ATG5*])[32] and rheumatoid arthritis (the PR domain 1 gene [*PRDM1*]-*ATG5* intergenic region).[33] Furthermore, activation of autophagy at the whole-body level extends the life span of various model organisms, including mice.[28] There is a growing amount of evidence that dysregulation of the autophagic pathway is implicated in the pathogenesis of kidney aging and in several renal diseases such as acute kidney injury (AKI), polycystic kidney disease (PKD), diabetic nephropathy (DN), obstructive nephropathy, focal and segmental glomerulosclerosis (FSGS), and potentially other kidney diseases.[34–37]

Molecular mechanisms of autophagy

Autophagy proceeds through at least five steps. Autophagosomes are initiated by expansion and sealing of a small vesicle made of a double-membrane structure called phagophore or isolation membrane. The origin of the autophagosome membrane may involve different sources, such as lipid droplets, mitochondria, Golgi, ER, plasma membrane, and recycling endosomes.[38,39] The phagophore is generated at a specialized site known as the phagophore assembly site or preautophagosomal structure. Sixteen ATG proteins comprise the conserved core ATG machinery that catalyzes formation of the phagophore and its expansion into autophagosomes in all eukaryotes[40] (Figure 1). The metabolites generated in the lysosomes/vacuoles are subsequently transported in the cytoplasm and recycled. Macroautophagy has recently been shown to achieve some selectivity for lipid droplets, ribosomes, pathogens, surplus reticulum, peroxisomes, enzymes, and proteins aggregates in processes that are called lipophagy, ribophagy, xenophagy, reticulophagy, pexophagy, zymophagy, and aggrephagy, respectively (reviewed and discussed in Birgisdottir *et al.*,[41] Johansen and Lamark,[42] Johansen and Lamark,[43] Mochida *et al.*,[44] Khaminets *et al.*,[45] and Khaminets *et al.*[46]).

Selectivity of autophagy is controlled by autophagy receptors that physically associate with the autophagy compartment by interacting simultaneously with cargo and Atg8- or microtubule-associated protein 1A/1B–light chain 3 (LC3)/γ-aminobutyric acid receptor–associated protein–like

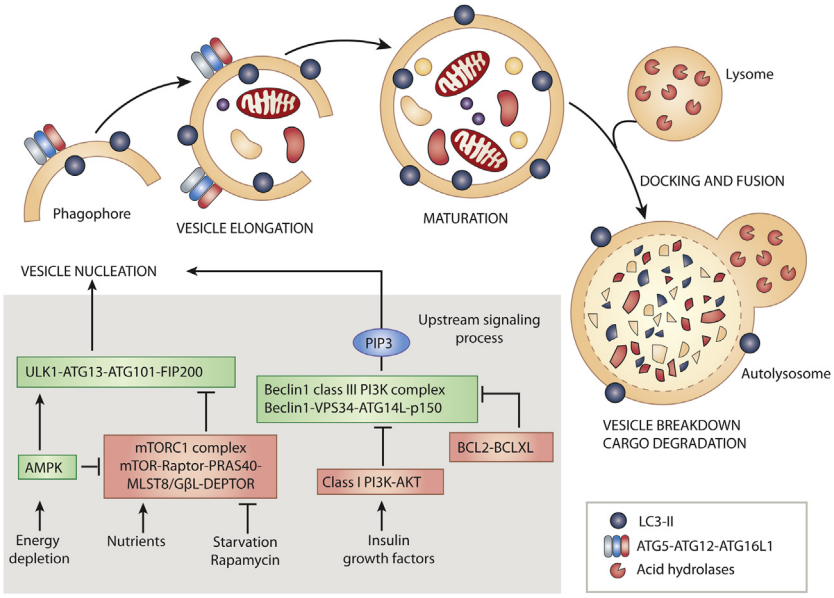

Figure 1 | Autophagy pathway. The autophagic pathway responds to signals from the environment. Nutrients status controls autophagy through the mTOR signaling pathway. The class I PI3K-AKT can also activate the mTORC1 complex in response to insulin and other growth factors, acting as a negative regulator of autophagy. Activation of AMPK in response to low energy status (i) inhibits the mTORC1 complex and (ii) activates the ULK1 complex through ULK1 and ATG13 phosphorylation, thereby acting as a positive regulator of autophagy in response to energy depletion. The BECN1/class III PI3K complex, which is inactivated by Bcl2, and the class I PI3K-AKT complex also regulate autophagy. Upon activation, the Beclin1-VPS34-ATG14L-P150 complex will generate PI3P, which promotes autophagosomal membrane nucleation in coordination with the ULK1-ATG13-ATG101-FIP200 complex. The ATG5-ATG12-ATG16L complex and the LC3-phosphatidylethanolamine system will play roles in cargo recruitment, membrane elongation, and autophagosome maturation. Lysosome fusion to autophagosome to form autolysosome is mediated through SNARE proteins, and lysosomal hydrolases degrade proteins, lipids, and nucleic acids. AKT, protein kinase B; AMPK, adenosine monophosphate–activated protein kinase; ATG, autophagy-related gene; BCL2, B-cell lymphoma 2; BCLXL, B-cell lymphoma–extra large; DEPTOR, DEP domain-containing mTOR-interacting protein; FIP200, FAK family kinase-interacting protein of 200 kDa; LC3, microtubule-associated protein 1 light chain 3; MLST8, target of rapamycin complex subunit LST8; mTOR, mammalian target of rapamycin; mTORC1, mTOR complex 1; PI3K, phosphatidylinositol-3-kinase; PI3P, phosphatidylinositol-3-phosphate; PRAS40, proline-rich v-akt murine thymoma viral oncogene homolog 1 substrate 40 kDa; Raptor, regulatory-associated protein of mTOR; SNARE, soluble NSF attachment protein receptor; ULK1, Unc51-like kinase 1.