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Research Paper

Oxidative stress and autophagy: Crucial modulators of kidney injury

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ABSTRACT

Both acute kidney injury (AKI) and chronic kidney disease (CKD) that lead to diminished kidney function are interdependent risk factors for increased mortality. If untreated over time, end stage renal disease (ESRD) is an inevitable outcome. Acute and chronic kidney diseases occur partly due to imbalance between the molecular mechanisms that govern oxidative stress, inflammation, autophagy and cell death. Oxidative stress refers to the cumulative effects of highly reactive oxidizing molecules that cause cellular damage. Autophagy removes damaged organelles, protein aggregates and pathogens by recruiting these substrates into double membrane vesicles called autophagosomes which subsequently fuse with lysosomes. Mounting evidence suggests that both oxidative stress and autophagy are significantly involved in kidney health and disease. However, very little is known about the signaling processes that link them. This review is focused on understanding the role of oxidative stress and autophagy in kidney diseases. In this review, we also discuss the potential relationships between oxidative stress and autophagy that may enable the development of better therapeutic intervention to halt the progression of kidney disease and promote its repair and resolution.

Introduction

Kidneys are remarkable organs because they perform several functions essential for healthy living such as regulation of body fluids and blood pressure, waste products excretion, and production of red blood cells. Human kidneys receive approximately 25% of cardiac output and consume 7% of daily energy expenditure to support their diverse functions. Kidney diseases pose a worldwide health problem and lead to significant morbidity and mortality amongst adults, especially older adults. In a recent National Health interview survey, out of 234,921 adults aged 18 and over, 3882 (approximately 2%) adults reported that in the past 12 months they had been diagnosed with kidney disease. Kidney diseases are mainly classified into two types, either acute kidney injury (AKI) or chronic kidney disease (CKD). AKI is characterized by sudden and sometimes fatal loss of kidney function resulting in the accumulation of end products of nitrogen metabolism (urea) and creatinine, or decreased urine output, or both [1]. The number of hospital stays associated with AKI has increased from 3942 in 1996 to 23,052 in 2008 [2]. Reduction in kidney function over a period of time results in chronic kidney disease. CKD is characterized by a glomerular filtration rate below 60 mls per minute for more than 3 months or urine albumin-to-creatinine ratio over 30 mg of albumin for each gram of creatinine. According to the Center for Disease Control and Prevention "1 in 10 American adults, more than 20 million individuals, have some level of chronic kidney disease" [2]. The prevalence of CKD is increasing most rapidly in adults 60 years old and above, with the incidence of CKD increasing most rapidly in individuals of age 65 and above [2]. Both AKI and CKD are closely interconnected syndromes and each disease serves as a risk factor for the other [3].

Autophagy: the basics

Autophagy is a highly dynamic multi-step biological process that involves breakdown and recycling of intracellular components and serves as a pro-survival mechanism amongst all eukaryotes ranging from yeasts to plants to mammals. This process occurs constitutively at a basal level and acts as a housekeeping mechanism to remove damaged or long-lived macromolecules or

Abbreviations: AKI, acute kidney injury; Atg, autophagy-related protein; CKD, chronic kidney disease; CLP, cecal ligation and puncture; CMA, chaperone mediated autophagy; DN, diabetic nephropathy; ESRD, end stage renal disease; FSGS, focal segmental glomerulosclerosis; I/R, ischemia–reperfusion; LAMP, lysosomal-associated membrane protein; LC3, microtubule-associated protein 1 light chain 3; LPS, lipopolysaccharide; NADPH, nicotinamide adenine dinucleotide phosphate; NOX, NADPH oxidase; RNS, reactive nitrogen species; ROS, reactive oxygen species; TGF-β1, transforming growth factor-beta 1; UUO, unilateral ureteral obstruction

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organelles. However, the implication that autophagy may be linked to a plethora of human diseases has led to intense interest in the autophagy field over the past decade. In the year 1963, Christian de Duve was the first to coin the term “autophagy” for the observation of organelle degradation within lysosomes [4]. Nearly after 30 years, the scientific world has begun to elucidate the molecular events of autophagy. Autophagy is categorized into three types: macroautophagy, microautophagy and chaperone mediated autophagy (CMA). Macroautophagy (hereafter referred as autophagy) refers to an evolutionarily-conserved lysosomal-mediated intracellular degradation pathway that is activated in response to diverse stressful conditions [5]. In microautophagy, cytosolic components are directly assimilated into the surface membrane of the lysosome or late endosome through invagination. In contrast, CMA targets only single proteins in which KFERQ-motif bearing proteins are identified by a cytosolic chaperone heat shock cognate (hsc70) that delivers them to the surface of the lysosomes for internalization through multimerization of the CMA receptor protein and lysosomal-associated membrane protein (LAMP)-2A.

Molecular aspects of autophagy

Autophagy proceeds through a series of biochemical reactions catalyzed by a core set of proteins termed autophagy-related proteins (Atg). The mechanism of autophagy is best understood in the context of nutrient starvation. To date, nearly 36 Atg proteins have been identified in yeast, and many of their mammalian homologs have also been identified [6,7].

The execution of autophagy involves five major steps (Fig. 1). 1. The formation of the isolation membrane or phagophore 2. Elongation of the phagophore and cargo recruitment 3. Closure of the mature autophagosome 4. Fusion between autophagosome and lysosome 5. Termination or degradation of the autolysosome. The process of autophagy begins with the formation of an isolation membrane or phagophore membrane. The phagophore assembly site (PAS) requires the recruitment of a core set of Atg proteins and several phosphorylation events (Fig. 1). This process is initiated by the activation of the Unc-51-like kinase-1 (ULK1)-Atg13-FIP200 complex upon stimulation with metabolic sensors, for example ATP depletion. At the molecular level, activation of the 5′-adenosine monophosphate-regulated protein kinase (AMPK) phosphorylates ULK1/2, which in turn phosphorylates Atg13 and FIP200 [8]. Recent studies suggest that AMPK-dependent ULK1 phosphorylation regulates the trafficking of mAtg9, a transmembrane protein responsible for membrane vesicle delivery to the PAS [9]. A key report has identified Atg1, Atg2 and Atg9 as Atg1 kinase substrates *in vivo*. Furthermore, a recent report also demonstrated that Atg1 directly phosphorylates Atg9 essential for the autophagosome formation, and added this ULK1/Atg1 signaling mechanism to the pathway of autophagy [10]. The ULK1/Atg1 kinase complex, the class III PI3-kinase Beclin1 complex and PI3P effectors and their related proteins are important for the autophagosome initiation step. A molecular link between ULK1 and the regulation of the Beclin1 complex through direct phosphorylation of Vps34 has recently been described [11,12].

Two ubiquitin-like conjugation systems Atg5-12 and the microtubule-associated protein 1 light chain 3 (LC3)/Atg8 catalyze the elongation of the phagophore membrane. Ubiquitin-like protein Atg5 conjugates with Atg12 with the help of E1-like enzyme Atg7 and E2-like enzyme Atg10 respectively. LC3/Atg8 is processed by Atg4 to generate the cytosolic LC3-I, which then conjugated to phosphatidylethanolamine (PE) in a reaction that requires Atg7 and the E2-like enzyme Atg3 respectively. LC3-II remains incorporated in the autophagosomal membrane until the autophagosome-lysosome fusion step. During the late stages of autophagy, LC3B-II associated with the outer autophagosomal membrane is recycled by Atg4B, whereas LC3B-II at the inner membrane is degraded by lysosomal activity [13]. Termination is the least well-studied step of autophagy, but some evidence suggests that mTOR activity is reactivated after a prolonged period of stress and hence may regulate the termination step [14]. Further investigations are required to elucidate the molecular events regulating the termination process of autophagy.

Selective autophagy/mitophagy

Mitophagy is involved in the selective removal of dysfunctional mitochondria using the autophagy machinery. To date, two types of mitophagy pathways have been described. Activated PINK1 translocates Parkin from the cytoplasm to defective mitochondria followed by polyubiquitination of mitochondrial substrates, which

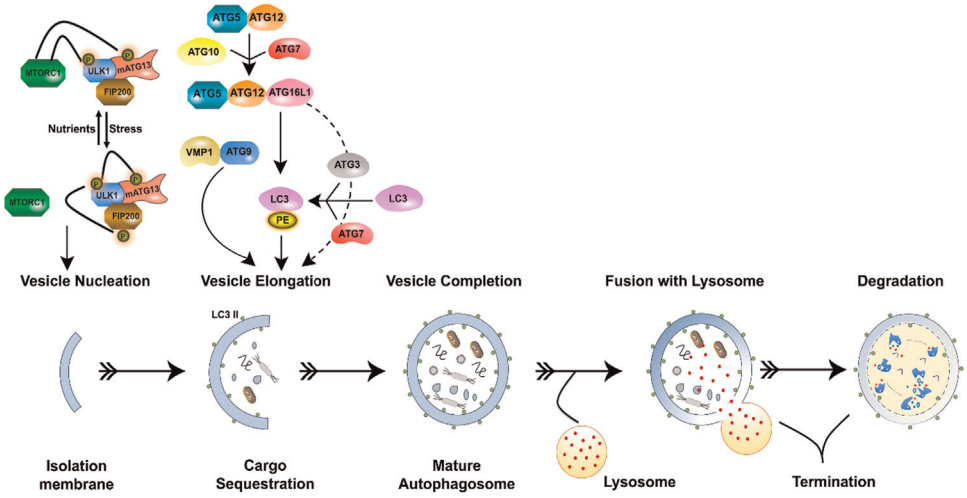

Fig. 1. Schematic depiction illustrating the molecular machinery of autophagy with the major autophagy-related proteins in the autophagy signaling pathway. Molecular components that include the ULK1/2-mAtg13-FIP200 complex are necessary for the induction of the autophagy pathway. Under a nutrient-rich environment, mTORC1 phosphorylates ULK1/2 and mAtg13 and leads to association and subsequent inhibition. During stress or starvation, mTORC1 dephosphorylates ULK1/2 and leads to the phosphorylation of FIP200, resulting in downstream activation of the autophagy pathway. E1-like ATG7 and E2-like ATG3 enzymes mediate the lipidation of ubiquitin-like enzyme LC3 with phosphatidylethanolamine (PE) to form LC3-PE. ATG5-ATG12-ATG16L1 complex and VMP1-ATG9 and LC3-PE systems function in cargo sequestration.