Selective Autophagy in Age-Associated Pathologies

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Selective autophagy degrades a plethora of autophagic cargo, which is targeted upon specific cellular insults. Defective mitochondria (mitophagy), protein aggregates (aggrephagy) or pathogenic bacteria (xenophagy) are selective autophagy triggers. Atg8 proteins interact and recruit selective autophagic receptors, which contain LIR (LC3-interacting) motifs (W/F/Y-X-X-L/I/V), with upstream negatively charged residues for higher affinity interactions, as well as, post-translational modifications, such as phosphorylation.

age-related disease aging aggrephagy mitophagy neurodegeneration nucleophagy pexophagy rapamycin selective autophagy

1. Introduction

Cellular garbage disposal is critical for recycling defective cell constituents, such as proteins and organelles, towards the maintenance of cellular homeostasis. One of the main degradative molecule pathways is autophagy, which is a physiological catabolic process shared by all eukaryotes. Derived from the Greek words ‘auto’ meaning self, and ‘phagy’, meaning eating, autophagy, it was initially considered to be a bulk degradation process, while now its highly selective nature is increasingly appreciated. This self-digestive mechanism relieves the cell from proteotoxic, genotoxic, oxidative and nutrient stress [1]. It is accomplished in an intricate stepwise manner, which leads to clearance of damaged cell constituents, in the degradative organelle, the lysosome. Failure to complete this procedure has been implicated in many age-related diseases. Three main types of autophagy have been characterized in detail: macro-autophagy, henceforth referred to as autophagy, which invariably entails the formation of a double membrane vesicle that fuses with the lysosome; micro-autophagy, where there is direct interaction between the autophagic substrate and the lytic organelle, and chaperone-mediated autophagy (CMA), where autophagic substrates are targeted by chaperones and guided to specific receptors on the lysosome, for degradation.

2. General Autophagy

Autophagy involves three main, consecutive steps: initiation, elongation and autophagosomal/lysosomal fusion. Although basal autophagy occurs at different levels, depending on the tissue, particular stimuli, such as, protein aggregation, DNA damage, reactive oxygen species (ROS), and nutrient deprivation activate or upregulate the autophagic response [2]. Initially, early autophagic structures form, at the pre-autophagosomal site (PAS), where

there is nucleation of the initiation membrane, forming the 'moon-shaped' phagophore. Expansion of the phagophore leads to PI(3)P-rich omegasome formation, which when sealed, forms the double membrane vesicle, the autophagosome. Although the endoplasmic reticulum is the main site for autophagosome formation, ER-mitochondria/plasma membranes contact sites, the plasma membrane itself, the Golgi complex, and recycling endosomes have emerged as autophagosomal biogenesis sites [3][4].

The ULK1 (Unc-51-like kinase 1) and PIKC3-C1 signaling complexes are activated during autophagic induction [5]. Physiologically, phosphorylated ULK1 and ATG13 are inactive and bound to mTORC1 (master cell growth regulator). During amino acid starvation, ULK1 is dephosphorylated and released from mTORC1, which in turn activates ATG13 and FIP200 [6]. Moreover, TFEB is disinhibited upon starvation to upregulate autophagy genes, as well as, lysosomal and lipid catabolism [7]. Next, phagophore expansion involves ATG8 family proteins, which are cleaved by the ATG4 protease at their C-terminus, and then lipidated. Activation of lipidated ATG8s is performed by ATG7 with the aid of ATG5-ATG12. This activity is localized at the phagophore by ATG16L, ultimately leading to phagophore expansion. However, the requirement for ATG8 lipidation for autophagosome assembly has been recently challenged [8].

During autophagosome maturation, the autophagosomal membrane is targeted to the lysosomal membrane by ATGs, the cytoskeleton, mainly microtubule-related kinesins, and the fusion machinery. The fusion machinery comprises SNAREs, both on the autophagosomal, syntaxin 17 (STX17), synaptosomal-associated protein (SNAP29) and lysosomal membrane (VAMP8), with the aid of the homotypic fusion and protein sorting (HOPS) complex, for membrane tethering during fusion [9][10].

3. Selective Autophagy

Selective autophagy degrades a plethora of autophagic cargo, which is targeted upon specific cellular insults. Defective mitochondria (mitophagy), protein aggregates (aggrephagy) or pathogenic bacteria (xenophagy) are selective autophagy triggers. Atg8 proteins interact and recruit selective autophagic receptors, which contain LIR (LC3-interacting) motifs (W/F/Y-X-X-L/I/V), with upstream negatively charged residues for higher affinity interactions, as well as, post-translational modifications, such as phosphorylation [11]. These receptors are recruited upon induction of selective autophagy, which is, in turn, directed to specific autophagic substrates by other tags, such as K27-linked mono-or K63 poly-ubiquitination events. Autophagic receptors such as p62, NBR1 (a neighbor of BRCA1 gene 1), OPTN1 (optineurin) contain both LIR and UBA binding motifs [12]. ULK1 controls selective autophagy independently of mTOR. Recent evidence suggests that ULK1 interaction with huntingtin is required for activation. Subsequently, huntingtin aids the LC3-p62-autophagic cargo interaction [13][14].

4. Conclusions

Extensive research has revealed the direct association of selective autophagy defects and age-related disease. Initially thought to be non-selective, autophagy was considered to be a highly promising therapeutic target.

Diseases associated with physiological aging such as neurodegeneration and metabolic disorders are the outcome of genetic inhibition of selective autophagy, which also declines physiologically during aging. Experimental evidence is increasingly showing the significance of autophagic degradation in maintaining organismal homeostasis, particularly in highly specialized tissues such as the nervous system. The intricacy and crosstalk of these selective autophagic pathways raises the challenge of combinatorial drug treatment.

Selective autophagic induction by genetic intervention or chemical compound administration is currently being investigated in multiple diseases as potential therapeutic approach, although no drug has reached the clinic yet. Indeed, clinical studies concerning druggable autophagy targets, remains limited. This highlights the complexity and intricacies of selective autophagic pathways, which in humans, cannot be easily targeted due to context-dependence and extensive crosstalk with other functional networks. Thus, initial optimism has subsided, with research now focusing on specific compounds that could target specific aspects of selective autophagy. An important objective of the collective efforts of the research community and pharmaceutical companies is to achieve targeting selective autophagy mediators, while not affecting other cellular processes. This would be an imperative step, minimizing adverse consequences to organismal physiology, towards clinical trials in human patients.

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