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Review

Autophagy, polyphenols and healthy ageing

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ABSTRACT

Autophagy is a lysosomal degradation process that evolved as a starvation response in lower eukaryotes and has gained numerous functions in higher organisms. In animals, autophagy works as a central process in cellular quality control by removing waste or excess proteins and organelles. Impaired autophagy and the age-related decline of this pathway favour the pathogenesis of many diseases that occur especially at higher age such as neurodegenerative diseases and cancer. Caloric restriction (CR) promotes longevity and healthy ageing. Currently, the contributing role of autophagy in the context of CR-induced health benefits is being unravelled. Furthermore recent studies imply that the advantages from polyphenol consumption may be also connected to autophagy induction.

In this review, the literature on autophagy regulation by (dietary) polyphenols such as resveratrol, catechin, quercetin, silibinin and curcumin is discussed with a focus on the underlying molecular mechanisms. Special attention is paid to the implications of age-related autophagy decline for diseases and the possibility of dietary countermeasures.

1. Introduction

It is a well-established finding that caloric restriction (CR) prolongs lifespan in various organisms and can even delay onset of late-in-life illnesses (Colman et al., 2009). One of the processes favoured by CR is autophagy, an evolutionarily conserved mechanism of lysosomal proteolysis in eukaryotes. Autophagy is induced as a response to nutrient deprivation and is regulated by a variety of stimuli including drugs and trophic factors. Apart from providing the starving cell with energy from degraded self-components (the word autophagy is Greek for self-eating), autophagy removes otherwise harmful proteins, is important for the oxidative stress response and plays a role in endocrine signalling and the immune response.

Functioning autophagy is vital for the healthy organism, but in older organisms, autophagic activity decreases (Del Roso et al., 2003). This can lead to neurodegeneration, cancer, compromised immune response and possibly favours the genesis of diabetes type II. Considering that malfunctioning autophagy plays such an important role in age-related pathophysiology and that caloric restriction improves health and lifespan, it is not surprising that emerging evidence shows how the beneficial effect of dietary restriction is partly linked to autophagy (Hansen et al., 2008).

There is increasing interest in the potential health effects of (dietary) polyphenols (Egert and Rimbach, 2011; Scalbert and Williamson, 2000). Fruits and vegetables as well as tea are important sources of polyphenols. Epidemiological studies have indicated that the consumption of polyphenol-rich foods may be associated with a lower chronic disease risk.

As the health advantages associated with autophagy can be influenced by dietary factors including polyphenols, studying autophagy in the context of nutrition is of special interest.

2. Autophagy

Degradation in the lysosome is one of the two main pathways of intracellular proteolysis (De Duve et al., 1955), the other being

Abbreviations: AD, Alzheimer's disease; AMP, adenosine monophosphate; AMPK, adenosine monophosphate activated protein kinase; APP, amyloid beta precursor protein; Atg, autophagy (related gene); ATP, adenosine triphosphate; AV, autophagic vacuoles; Aβ, amyloid beta; Bcl-2, B-cell lymphoma 2; Bcl-xl, Bcl-X long; CMA, chaperone mediated autophagy; CR, caloric restriction; DAPK, death-associated protein kinase; EGCG, epigallocatechingallate; Erk, extracellular signal-regulated kinase; FoxO, forkhead box O (transcription factor); HD, Huntington's disease; HMGB1, high-mobility group protein B1; Hsc70, heat shock cognate protein of 70 kDa; Htt, Huntingtin protein; JNK1, c-Jun N-terminal protein kinase; LAMP, lysosome associated membrane protein; LC3, microtubule associated protein 1-light chain 3; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase (MaPK)/extracellular signal-regulated kinase (Erk) kinase; m-TOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; NAD, nicotinamide adenine dinucleotide; NFkappaB, nuclear factor of kappa light polypeptide gene enhancer in B-cells 1; Nrf2, nuclear factor erythroid 2-related factor 2 (transcription factor); PCD, programmed cell death; PD, Parkinson's disease; PE, phosphatidylethanolamine; PI3K, phosphatidylinositol-3-kinase; PINK1, PTEN induced putative kinase 1; PMN, piecemeal microautophagy of the nucleus; PS-1, presenilin 1; PTEN, phosphatase and tensin homolog; Raptor, regulatory associated protein of mTOR; ROS, reactive oxygen species; SAMP8, senescence accelerated mouse prone 8; SQSTM1 (=p62), sequestosome-1; TOR, target of rapamycin; TSC, tuberous sclerosis complex; Ulk1, Unc-51-like kinase 1; Vps, vacuolar protein sorting.

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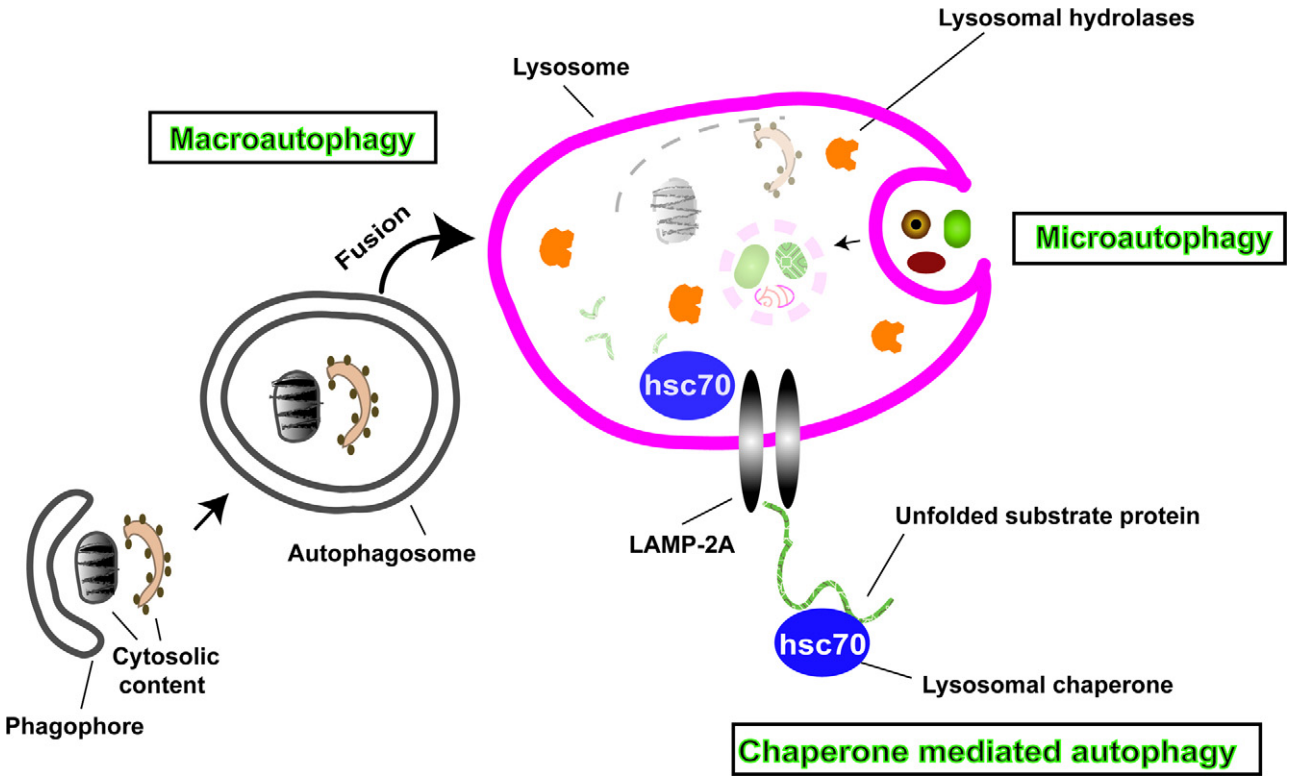

Fig. 1. Different types of autophagy. Macroautophagy refers to the sequestration of cytosolic contents such as bulk cytoplasm, organelles or invading microbes by a unique double-membrane which expands from the phagophore and closes to become a vesicle called autophagosome. This autophagosome eventually fuses with the lysosome, thereby acquiring hydrolases and forming an autolysosome in which the inner membrane of the autophagosome and its contents are degraded. In a process termed microautophagy the lysosome membrane forms invaginations in which small portions of cytoplasm with cytosolic components are sequestered directly by the lysosome. In the case of chaperone-mediated autophagy (CMA), proteins are selectively unfolded and translocated through the lysosome membrane by the cytosolic and lysosomal chaperone hsc70, and the lysosomal membrane receptor LAMP-2A (lysosome-associated membrane protein type 2A).
Modified from Mizushima et al. (2008).

the proteasome system. Whilst the proteasome is more important for short-lived molecules, degradation of proteins with longer half-lives tends to take place in the lysosome (Jung et al., 2009). Molecules arrive at the lysosome through endocytosis, phagocytosis or autophagy. In yeast, autophagic degradation emerged as a survival mechanism in order to recycle cell components during limited nutrient supply. However, autophagic proteolysis has gained functions in higher eukaryotes as it also degrades molecules, cellular aggregates, microorganisms and entire organelles that would otherwise harm the cell, and it therefore seems to operate as a type of quality control in the cell. This is why autophagy plays a role in tumourigenesis and immunity and protects neurons and cardiomyocytes (Mizushima et al., 2008).

2.1. Macroautophagy

There are various types of autophagy that differ in how the to-be-degraded cargo is delivered into the lysosome (see Fig. 1). Macroautophagy is the most investigated type of autophagy and often simply referred to as autophagy. Whilst cells show basal levels of macroautophagy, further regulation of autophagy depends on amino acid and energy levels, growth factors and nutrient supplies. Consequently, the classic macroautophagy pathway acts downstream of a central kinase involved in sensing all these parameters, the mammalian target of rapamycin (m-TOR). In its protein complex mTORC1, this Ser/Thr kinase suppresses the autophagic machinery which is why the inhibitor of mTOR, rapamycin, induces macroautophagy. Upon induction of macroautophagy, vesicles with double or multiple membranes engulf portions of cytoplasm containing soluble proteins or other intracellular compounds ranging from proteinaceous aggregates and lipid deposits to whole organelles or pathogens (Cuervo and Macian, 2012). The sequestration of cytosolic components can be unselective or, as for example in the case of mitophagy, specifically target mitochondria (Kanki and Klionsky, 2008) (see Table 1). The vesicles enclosing the to-be degraded content are called autophagosomes and fuse with lysosomes to form autolysosomes in which the degradation takes place. Autophagosomes arise from their precursor, the phagophore, which is also called the isolation membrane. The origin of this precursor remains unclear with the endoplasmatic reticulum, the Golgi-apparatus and the cell membrane being discussed as possible sources (Hailey et al., 2010; Hayashi-Nishino et al., 2009; van der Vaart et al., 2010).

2.1.1. Molecular mechanisms of (macro)autophagy

As far as molecular mechanisms are concerned, 35 autophagy-related genes (Atgs) have been discovered in yeast so far and many of them have homologues in mammals. These Atgs are mostly situated downstream of the central macroautophagy regulator mTORC1 and the majority of them play a role in autophagosome formation and growth (Yang and Klionsky, 2010).

Upstream mTOR, as a sensor of energy levels in the cell, the AMP-activated protein kinase (AMPK) is induced upon caloric restriction. When ATP levels drop, AMPK can induce autophagy via a negative mTORC1 regulator, the tuberous sclerosis complex 1/2 (TSC1/2). Another signalling pathway that regulates mTORC1 positively (and as a consequence autophagy negatively) is induced via the class