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A role for Glucagon-Like Peptide-1 in the regulation of β-cell autophagy

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ABSTRACT

Autophagy is a highly conserved intracellular recycling pathway that serves to recycle damaged organelles/proteins or superfluous nutrients during times of nutritional stress to provide energy to maintain intracellular homeostasis and sustain core metabolic functions. Under these conditions, autophagy functions as a cell survival mechanism but impairment of this pathway can lead to pro-death stimuli. Due to their role in synthesising and secreting insulin, pancreatic β-cells have a high requirement for robust degradation pathways. Recent research suggests that functional autophagy is required to maintain β-cell survival and function in response to high fat diet suggesting a pro-survival role. However, a role for autophagy has also been implicated in the pathogenesis of type 2 diabetes. Thus, the pro-survival vs pro-death role of autophagy in regulating β-cell mass requires discussion. Emerging evidence suggests that Glucagon-Like Peptide-1 (GLP-1) may exert beneficial effects on glucose homeostasis via autophagy-dependent pathways both in pancreatic β-cells and in other cell types. The aim of the current review is to: i) summarise the literature surrounding β-cell autophagy and its pro-death vs pro-survival role in regulating β-cell mass; ii) review the literature describing the impact of GLP-1 on β-cell autophagy and in other cell types; iii) discuss the potential underlying mechanisms.

1. Introduction

Macroautophagy (hereafter referred to as autophagy) is a highly conserved intracellular recycling pathway which targets cytosolic components for lysosomal degradation. Classically considered an essential mechanism to promote cell survival during nutrient deprivation, recycling of damaged organelles/proteins via autophagy releases nutrients and metabolites for energy production and biosynthesis to maintain cellular function and promote cell survival [1,2]. Under basal conditions when adequate nutrients are available, autophagy is inhibited although some constitutive activity remains to maintain basic cell function, removing unwanted proteins, organelles and foreign matter [3]. Autophagy can also be stimulated in response to nutrient excess to remove toxic aggregates or in response to increased protein synthesis to remove unfolded proteins, again to promote cell survival [1–4]. Thus, autophagy is primarily a cell survival mechanism acting to promote cellular homeostasis [4]. However, when exacerbated for long periods or when deregulated, autophagy can promote cell death. Hence, autophagy has been described as the 'double-edged sword' with the ability to switch from a pro-survival to pro-death role depending on the cellular environment [1–4].

2. Molecular mechanism of autophagy

The degradation of cytosolic components via autophagy involves complex signalling pathways with the interplay of more than 30 autophagy-related (Atg) proteins which are summarised below (Fig. 1). For a comprehensive review of these pathways readers are directed to [1,5,6].

Autophagy is characterised by the formation of autophagosomes which surround and capture cytosolic components destined for recycling and their subsequent fusion with lysosomes to promote degradation and recycling of the contents [1–4]. It can be divided into four main stages: Initiation, Nucleation, Elongation/Completion, and Fusion/Degradation.

Abbreviations: Akt, protein kinase B; Ambra1, Autophagy And Beclin 1 Regulator 1; AMPK, 5′ AMP-activated protein kinase; Atg, autophagy related proteins; CAMKK, Ca^{2+}/calmodulin-dependent protein kinase kinase; DFCP1, double FYVE-containing protein 1; DPP4, dipeptidyl peptidase-4; ER stress, endoplasmic reticulum stress; FIP200, focal adhesion kinase family interacting protein of 200 kDa; FFA, free fatty acids; GFP, green fluorescent protein; GLP-1, glucagon-like peptide 1; HFD, high fat diet; HOPS, homotypic fusion and vacuole protein sorting; IAPP, islet amyloid polypeptide; JNK, c-jun N-terminal kinase; LAMP-2, lysosome-associated membrane glycoprotein-2; LC3, microtubule-associated protein 1 light chain 3 beta; LMP, lysosomal membrane permeabilization; 3-MA, 3-methyladenine; MCOLN1, mucolipin 1; mRFP, monomeric red fluorescent protein; mLST8, mTOR associated protein subunit LST8; mTORC1, mammalian target of rapamycin (mTORC1); PI3P, phosphatidylinositol 3-phosphate; PtdIns3K, class III phosphatidylinositol 3-kinase; Rheb, ras homolog enriched in brain; SNARE, soluble N-ethylmaleimide sensitive factor attachment protein receptor; Tfeb, transcription factor EB; TSC, tuberous sclerosis complex; ULK-1/2, uncoordinated-51-like kinase 1 or 2; UVRAG, UV radiation resistance-associated gene protein; Vsp, vacuolar protein sorting; WIPI, WD repeat domain phosphoinositide-interacting protein-1

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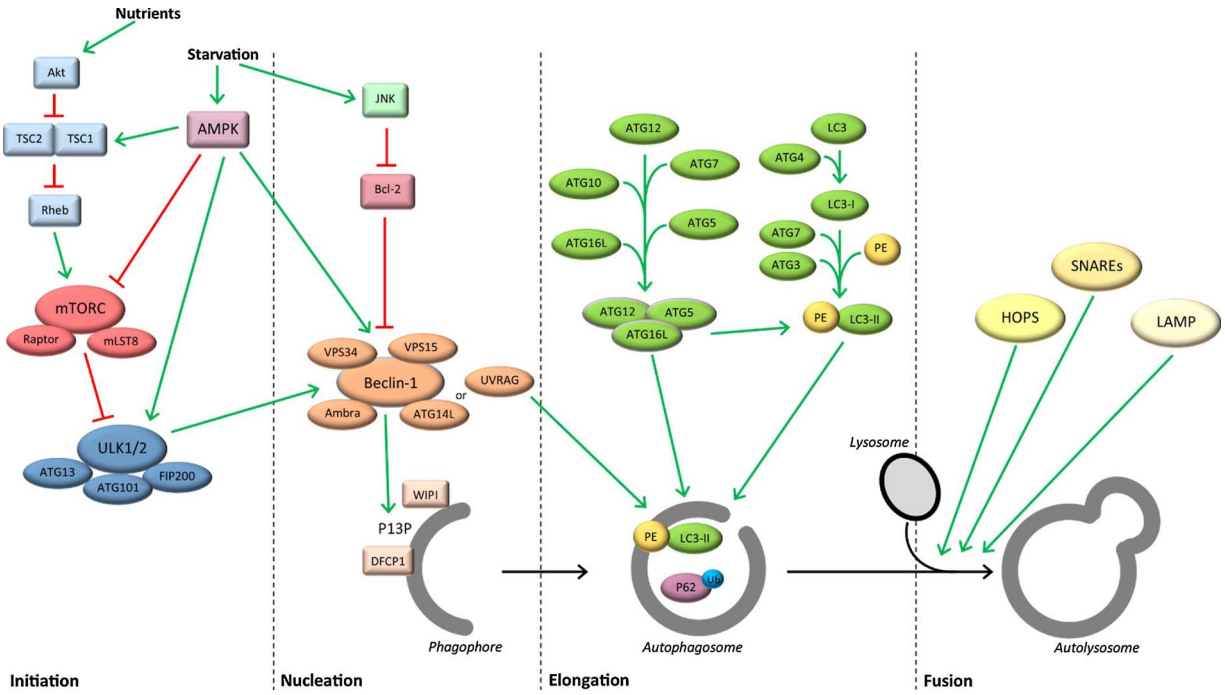

Fig. 1. Schematic outlining the main molecular mechanisms and signalling pathways regulating autophagy. Under fed conditions, nutrients, growth factors and insulin inhibit autophagy though the activation of mTORC1 via the class I phosphatidylinositol 3-kinase (PI3K)/AKT/TSC/Rheb pathway. Activation of mTORC1 causes its binding to ULK-1 or 2, preventing autophagy. During starvation, AMPK is activated which initiates autophagy by i) activation of TSC1/2 leading to inactivation of mTORC1 which dissociates from ULK-1/2; ii) direct inactivation of mTORC1; iii) direct activation of ULK-1/2. ULK-1/2 is localised to a complex comprised of ULK-1/2, Atg13, Atg101 and FIP200 and its activation marks the initiation of autophagy. The activated ULK-1/2 complex in turn activates the PtdIns3K complex consisting of Beclin1, Vsp15, Vsp34, Atg14L and Ambra1. The activated PtdIns3K complex translocates to the phagophore assembly site (PAS) where it generates PI3P to recruit PI3P binding proteins such as DFCP1 and WIPI2b to PIP3 enriched regions, proteins essential for phagophore formation. Beclin1 can also be activated directly by AMPK and also via the JNK pathway via disruption of the anti-autophagic Bcl-2-Beclin1 complex. The elongation of autophagosomes is dependent on two ubiquitin-like degradation systems, Atg16L1-Atg5-Atg12 and phosphatidylethanolamine (PE)-LC3. Conjugation of Atg proteins to form the Atg-16L1-Atg5-Atg12 complex in the presence of additional Atg proteins mediates LC3-PE formation and its localisation to the expanding phagophore membrane. These processes mediate phagophore elongation to form the autophagosome. In addition to this, replacement of Atg14L with UVRAG in the PtdIns3K complex further promotes autophagosome formation. Fusion of the closed autophagosome with lysosomes to form the autolysosome is dependent on the lipid composition of their membranes and also several proteins including the HOPS complex, the autophagosomal-specific SNARE named syntaxin 17 and LAMP-2 although the precise mechanisms are yet to be identified.

i) *Initiation*: This stage is dependent on the activation state of Uncoordinated (Unc)-51-like kinase 1 or 2 (ULK-1/2) which is regulated by mammalian target of rapamycin (mTORC1) and 5′ AMP-activated protein kinase (AMPK). Starvation causes activation of ULK-1/2 via the activation of AMPK either through inactivation of mTORC1 or directly [7,8]. Under these conditions, autophagy is initiated.
ii) *Nucleation*: Activation of ULK-1/2 in turn activates the class III phosphatidylinositol 3-kinase (PtdIns3K) complex consisting of Beclin 1, Vsp15, Vsp34, Atg14L and Ambra1, which is critical for formation of the phagophore via the localisation of phosphatidylinositol 3-phosphate (PI3P) and subsequent recruitment of key proteins [9,10].
iii) *Elongation/Completion*: Once formed, the phagophore is elongated to generate the autophagosome which encaptures the cargo targeted for degradation. This stage is dependent on two ubiquitin-like degradation systems Atg16L1-Atg5-Atg12 and phosphatidylethanolamine (PE)-LC3, in addition to the PtdIns3K complex to mediate localisation of key proteins such as LC3-PE to the expanding phagophore membrane [9,11–13].
iv) *Fusion/Degradation*: Fusion of the closed autophagosome with lysosomes to form the autolysosome is dependent on several proteins including homotypic fusion and vacuole protein sorting (HOPS) complex, syntaxin 17 and lysosome-associated membrane glycoprotein-2 (LAMP-2). Following fusion, lysosomal enzymes are activated resulting in degradation of the contents to generate nutrients and metabolites which can be used as building blocks to promote cell survival [13–15].

The pathway outlined above assumes continuous flux through the pathway whereby the contents marked for degradation meet their end. However, if flux through the pathway is blocked due to loss of fusion between autophagosomes and lysosomes, this impairment in autophagic signalling can contribute to cell death either via autophagic cell death or by stimulation of other cell death pathways [4,16]. Whether the impairment in flux occurs due to alterations in autophagosomal/lysosomal structures or to changes in signalling varies depending on the stimuli and cell type, and in many instances the underlying cause remains unknown.

3. Technical approaches for monitoring of autophagy

To understand how autophagy is regulated, one must first understand how it's highly dynamic nature is evaluated. Comprehensive guidelines have been published [17] and the commonly used accepted measures are outlined below.

i) *LC3 lipidation* – Lipidation of LC3-I to LC3-II is easily identified as distinct bands via western blotting and is regarded as a marker of increased autophagosomal content. However, an increase in LC3 II can result from both increased autophagy but also due to decreased autophagosomal clearance. Assessing LC3 I–II conversion in the absence or presence of lysosomal inhibitors (such as chloroquine or bafilomycin A1) provides some detail on flux [18,19].
ii) *GFP-LC3 localisation to autophagosomes* – Localisation of exogenously expressed GFP-LC3 to autophagosomes can be detected by a punctate pattern using fluorescence microscopy. Detail on flux can be provided using lysosomal inhibitors [19,20].