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A comprehensive glossary of autophagy-related molecules and processes

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Abstract

Autophagy is a rapidly expanding field in the sense that our knowledge about the molecular mechanism and its connections to a wide range of physiological processes has increased substantially in the past decade. Similarly, the vocabulary associated with autophagy has grown concomitantly. This fact makes it difficult for readers, even those who work in the field, to keep up with the ever-expanding terminology associated with the various autophagy-related processes. Accordingly, we have developed a comprehensive glossary of autophagy-related terms that is meant to provide a quick reference for researchers who need a brief reminder of the regulatory effects of transcription factors or chemical agents that induce or inhibit autophagy, the function of the autophagy-related proteins, or the role of accessory machinery or structures that are associated with autophagy.

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Introduction

One meaning for the term “comprehensive” is to “cover completely or broadly.” However, the rapid expansion in the field of autophagy is such that this glossary will be out of date as soon as it is published. On the other hand, “comprehensive” can also indicate, “marked by or showing extensive understanding.” If we consider that our knowledge of autophagy has indeed expanded tremendously over the past decade, it may be appropriate to suggest that we have an extensive understanding of this subject. Of course we fully expect that our current understanding will undergo substantial change in the coming months and years, and that even the breadth of our knowledge may amount to little more than the tip of the autophagy iceberg. Nonetheless, it is useful to essentially catalog the information we currently have about autophagy in an easily accessible format.

Accordingly, we present here the first attempt at a comprehensive glossary for autophagy. We have purposely kept the definitions of the included terms relatively short with the intention that the reader can get a quick, rather than an in-depth, understanding of the function or meaning of the relevant word. In addition, we have provided references that generally cite the first use of particular terms, or the first cloning of a gene and description of the corresponding protein, or an appropriate review article, but due to space considerations this list is far from being inclusive. We encourage readers to examine the primary literature for additional details about the process of autophagy and the components described herein.

3-MA (3-methyladenine)

An inhibitor of class I and class III PtdIns 3-kinase, which results in autophagy inhibition due to suppression of class III PtdIns 3-kinase.[1]

ABT737

A BH3 mimetic that competitively disrupts the interaction between Beclin 1 and Bcl-2 or Bcl-X_L, thus inducing macroautophagy.[2]

Aggrephagy

The selective removal of aggregates by macroautophagy.[3]

AIM (Atg8-family Interacting Motif)

This term refers to the WXXL-like sequences found in Atg19, Atg32, NBR1, Nix and p62 that link these proteins to Atg8/LC3. See also WXXL and LIR/LRS.[4]

Alfy (autophagy-linked FYVE protein)

Targets cytosolic protein aggregates for autophagic degradation.[5]

Ambra1 (activating molecule in Beclin 1-regulated autophagy)

A positive regulator of macroautophagy. Ambra1 binds Beclin 1 and modulates its activity.[6]

Amphisome

Intermediate compartment formed by the fusion of an autophagosome with an endosome (this compartment can be considered a type of autophagic vacuole and may be equivalent to a late autophagosome, and as such has a single limiting membrane); this compartment has not yet fused with a lysosome.[7]

AMPK (AMP-activated protein kinase)

A sensor of energy level that is activated by an increase in the AMP/ATP ratio via the LKB1 kinase. Phosphorylates the mTORC1 subunit Raptor to cause induction of macroautophagy. AMPK also activates the TSC1/2 complex. The yeast homologue is Snf1.[8,9]

APMA (autophagic macrophage activation)

A collection of autophagy-related processes in cells of the reticulo-endothelial system. APMA includes (1) convergence of phagocytosis and the autophagic machinery; (2) enhanced microbicidal properties of autolysosomes in comparison to standard phagolysosomes; (3) autophagic modulation of pathogen recognition receptor (PRR) signaling; (4) cooperation between immunity-related GTPases and autophagy or Atg proteins in attacking parasitophorus vacuoles; and (5) enhanced antigen presentation. APMA is thus recognized as a complex outcome of autophagy stimulation in macrophages, representing a unique composite process bringing about a heightened state of immunological activation.[10]

ARD1 (arrest-defective protein 1)

A protein that interacts with and stabilizes TSC2 by acetylation, resulting in repression of mTOR and induction of macroautophagy.[11]

Atg (autophagy-related)

The abbreviation used for most of the components of the protein machinery that are involved in selective and nonselective macroautophagy and in selective microautophagy.[12]

Atg1

A serine/threonine protein kinase that functions in recruitment and release of other Atg proteins from the PAS.[13]

Atg2

A protein that acts along with Atg18 to mediate the retrograde movement of Atg9 away from the PAS.[14,15]

Atg3

A ubiquitin conjugating enzyme (E2) analog that conjugates Atg8/LC3 to phosphatidylethanolamine (PE) after activation of the C-terminal residue by Atg7.[16,17]

Atg4

A cysteine protease that processes Atg8/LC3 by removing the amino acid residue(s) that are located on the C-terminal side of what will become the ultimate glycine. Atg4 also removes PE from Atg8/LC3.[18]

Atg5

A protein containing ubiquitin folds that is part of the Atg12–Atg5-Atg16 complex, which acts in part as an E3 ligase for Atg8/LC3–PE conjugation.[19]

Atg6 (Vps30)

A component of the class III PtdIns 3-kinase complex. Atg6 forms part of two distinct complexes (I and II), which are required for the Atg and Vps pathways, respectively. See also Beclin 1.[20]

Atg7

A ubiquitin activating (E1) enzyme homologue that activates both Atg8/LC3 and Atg12 in an ATP-dependent process.[21,22]

Atg8

A ubiquitin-like protein that is conjugated to PE; involved in cargo recruitment into, and biogenesis of, autophagosomes. Autophagosomal size is regulated by the amount of Atg8. Since Atg8 is selectively enclosed into autophagosomes, its breakdown allows measurement of the autophagic rate. There are several Atg8 homologueues in mammals including LC3, GATE-16 and GABARAP.[23,24]

Atg9

A transmembrane protein that may act as a lipid carrier for expansion of the phagophore. In mammalian cells, mAtg9 localizes to the *trans*-Golgi network and endosomes, whereas in fungi this protein localizes in part to reservoirs that are localized near the mitochondria as well as to the PAS.[25,26]

Atg10

A ubiquitin conjugating (E2) enzyme analog that conjugates Atg12 to Atg5.[27]

Atg11

A fungal scaffold protein that acts in selective types of macroautophagy including the Cvt pathway, mitophagy and pexophagy. Atg11 binds Atg19, PpAtg30 and Atg32 as part of its role in specific cargo recognition. It also binds Atg9 and is needed for its movement to the PAS.[28]

Atg12

A ubiquitin-like protein that modifies an internal lysine of Atg5 by covalently binding via its C-terminal glycine.[19]

Atg13

A component of the Atg1 complex that is needed for Atg1 kinase activity. Atg13 is highly phosphorylated in a PKA- and Tor-dependent manner in rich medium conditions. During starvation-induced macroautophagy in yeast, Atg13 is partially dephosphorylated. In mammalian cells at least Tor and Ulk1/Atg1 phsophorylate Atg13. The decreased phosphorylation of Atg13 that results from Tor inhibition is partly offset by the Ulk1-dependent phosphorylation that occurs upon Ulk1 activation.[29,30]

Atg14

A component of the class III PtdIns 3-kinase complex, which is necessary for it to function in macroautophagy.[20]

Atg15

A vacuolar protein that contains a lipase/esterase active site motif and is needed for the breakdown of autophagic and Cvt bodies within the vacuole lumen.[31,32]

Atg16

A component of the Atg12–Atg5-Atg16 complex. Atg16 dimerizes to form a large complex.[33] There are two mammalian homologueues, Atg16L1 and Atg16L2. The former is one of the risk alleles associated with Crohn disease.[34]

Atg17

A yeast protein that is part of the Atg1 kinase complex. Atg17 is not essential for macroautophagy, but modulates the magnitude of the response; smaller autophagosomes are formed in the absence of Atg17.[35,36]

Atg18

A protein that binds to PtdIns(3)P (and PtdIns(3,5) P_2; but the latter is not known to have a role in autophagy) via its WD40 β-propeller domain. Atg18 functions along with Atg2 in the retrograde movement of Atg9. Atg18 has additional nonautophagic functions, for example, in retrograde transport from the vacuole to the Golgi complex, and in the regulation of PtdIns(3,5)P_2 synthesis; the latter function affects the vacuole's role in osmoregulation.[37]

Atg19

A receptor for the Cvt pathway that binds the propeptide of precursor aminopeptidase I, Atg11 and Atg8. Atg19 is also a receptor for α-mannosidase, another Cvt pathway cargo.[38,39]

Atg20

A PtdIns(3)P binding protein that is part of the Atg1 kinase complex.[40]

Atg21

A PtdIns(3)P binding protein that is a homologue of, and partially redundant with, Atg18.[41]

Atg22

A vacuolar amino acid permease that is required for efflux after autophagic breakdown of proteins.[42,43]

Atg23

A yeast protein that transits with Atg9.[44-46]

Atg24 (Snx4)

A PtdIns(3)P binding protein that is part of the Atg1 kinase complex.[40]

Atg25

A coiled-coil protein required for macropexophagy in *Hansenula polymorpha*.[47]

Atg26

A sterol glucosyltransferase that is required for micro- and macropexophagy in *Pichia pastoris*, but not in *Saccharomyces cerevisiae*.[48,49]

Atg27

An integral membrane protein that is required for the movement of Atg9 to the PAS. The absence of Atg27 results in a reduced number of autophagosomes under autophagy-inducing conditions.[50]

Atg28

A coiled-coil protein involved in micro- and macropexophagy in *Pichia pastoris*.[51]

Atg29

A protein required for efficient nonspecific macroautophagy in fungi. Part of an Atg17-Atg29-Atg31 complex that functions at the PAS for protein recruitment.[52]

Atg30

A protein required for the recognition of peroxisomes during micro- and macropexophagy in *Pichia pastoris*. It binds the peroxin PpPex14 and the selective autophagy adaptor protein PpAtg11.[53]

Atg31

A protein required for nonspecific macroautophagy in fungi. Part of an Atg17-Atg29-Atg31 complex that functions at the PAS for protein recruitment.[54]

Atg32

A mitochondrial outer membrane protein that is required for mitophagy in fungi. Atg32 binds Atg8 and Atg11 preferentially during mitophagy-inducing conditions.[55,56]

Atg33

A mitochondrial outer membrane protein that is required for mitophagy in fungi.[57]

Atg101

An Atg13-binding protein conserved in various eukaryotes but not in *S. cerevisiae*. Forms a stable complex with ULK1/2-Atg13-FIP200 (i.e., not nutrient-dependent), required for macroautophagy and localizes to the phagophore.[58,59]

ATM (ataxia-telangiectasia mutated)

A protein kinase that activates TSC2 via the LKB1-AMPK cascade in response to elevated ROS, resulting in inhibition of mTOR and activation of macroautophagy.[60]

Autolysosome

A degradative compartment formed by the fusion of an autophagosome (or initial autophagic vacuole/AVi) or amphisome with a lysosome (also called degradative autophagic vacuole/AVd or autophagolysosome). Upon completion of degradation this compartment again becomes a lysosome or residual body.[7,61]

Autophagic body

The inner membrane-bound structure of the autophagosome that is released into the vacuolar lumen following fusion of the autophagosome with the vacuole-limiting membrane. In *S. cerevisiae*, autophagic bodies can be stabilized by the addition of the proteinase B inhibitor PMSF to the medium. Visualization of the accumulating autophagic bodies by Nomarski optics is a convenient method to follow macroautophagy.[62]

Autophagosome

A cytosolic membrane-bound compartment denoted by a limiting double membrane (also referred to as initial autophagic vacuole, AVi, or early autophagosome). The early autophagosome contains cytoplasmic inclusions and organelles that are morphologically unchanged because the compartment has not fused with a lysosome and lacks proteolytic enzymes. Although in most cases the term autophagosome refers to a double-membrane vesicle, the late autophagosome has a single membrane (also referred to as an intermediate autophagic vacuole, AVi/d).[7,61]

Autophagy

This term summarizes all processes in which intracellular material is degraded within the lysosome/vacuole and where the macromolecular constituents are recycled.

Autophagy-related (Atg)

The genes and proteins that are generally specific to the process of macroautophagy, including both selective and nonselective mechanisms, and to selective microautophagy.[12]

Bafilomycin A_1

An inhibitor of the vacuolar (V)-type ATPase that alters the pH and membrane potential of acidic compartments, which ultimately results in a block in fusion of autophagosomes with lysosomes, thus preventing the maturation of autophagosomes into autolysosomes.[63,64]

Barkor (Beclin 1-associated autophagy related key regulator)

Also known as Atg14L, the mammalian homologue of yeast Atg14, a component of the class III PtdIns 3-kinase complex.[65]

Bcl-2 family of proteins

There are two general classes of Bcl-2 proteins; anti-apoptotic proteins include Bcl-2, Bcl-X_L, Bcl-w and Mcl-1 that inhibit macroautophagy, and pro-apoptotic BH3-only proteins include BNIP3, Bad, Bik, Noxa, Puma and BimEL that induce macroautophagy. Interaction of Bcl-2 with Beclin 1 prevents the association of the latter with the class III PtdIns 3-kinase.

Beclin 1 (Bcl-2 interacting coiled-coil protein 1)

A mammalian homologue of yeast Atg6/Vps30 that forms part of the class III PtdIns 3-kinase complex involved in activating macroautophagy.[66]

BH3 (Bcl-2 homology 3) domain

A domain that is found in all Bcl-2 family proteins, be they pro-apoptotic or anti-apoptotic. A BH3 domain is also present in Beclin 1 and mediates the interaction with proteins possessing a BH3 receptor domain, namely Bcl-2, Bcl-X_L, Bcl-w and Mcl-1.

BH3-only proteins

A series of proteins that contain a BH3 domain (but not any other Bcl-2 homologue, BH, domains). Several BH3-only proteins (BNIP3, Bad, Bik, Noxa, Puma and BimEL) can competitively disrupt the inhibitory interaction between Bcl-2 and Beclin 1 to allow the latter to act as an allosteric activator of PtdIns 3-kinase and to activate macroautophagy.

Bif-1 (Bax-interacting factor 1)/endophilin B1

A protein that interacts with Beclin 1 via UVRAG and is required for macroautophagy. Bif-1 has a BAR domain, which may be involved in deforming the membrane as part of autophagosome biogenesis.[67]

BNIP3 (Bcl-2/adenovirus E1B 19-kDa interacting protein 3)

A member of the BH3-only subfamily of Bcl-2 family proteins. Originally classified as a pro-apoptotic protein, it is required for the HIF-1-dependent induction of macroautophagy during hypoxia by disrupting the interaction of Beclin 1 with Bcl-2.[68,69]

CaMKKβ (calcium/calmodulin-dependent protein kinase kinase-β)

Activates AMPK in response to an increase in the cytosolic calcium concentration.[70]

CCI-779 (temsirolimus)

A water-soluble rapamycin ester that induces macroautophagy.

CD46

A cell surface glycoprotein that interacts with the scaffold protein GOPC to mediate an immune response to invasive pathogens including *Neisseria* and Group A *Streptococcus*. Interaction of pathogens via the Cyt1 cytosolic tail induces autophagy, which involves GOPC binding to Beclin 1. CD46 is also used as a cellular receptor by several pathogens.[71]

Chaperone-mediated autophagy (CMA)

An autophagic process in mammalian cells by which proteins containing a particular pentapeptide motif related to KFERQ are transported across the lysosomal membrane and degraded.[72,73] The translocation process requires the action of the integral membrane protein LAMP-2A and both cytosolic and lumenal hsc70.[74,75]

Chloroquine

Chloroquine and its derivatives (such as 3-hydroxychloroquine) raise the lysosomal pH and ultimately inhibit the fusion between autophagosomes and lysosomes, thus preventing the maturation of autophagosomes into autolysosomes, and blocking a late step of macroautophagy.[76]

c-Jun

A mammalian transcription factor that inhibits starvation-induced macroautophagy.[77]

Clg1

A yeast cyclin-like protein that interacts with Pho85 to induce macroautophagy by inhibiting Sic1.[78]

COG (conserved oligomeric Golgi) complex

A cytosolic tethering complex that functions in the fusion of vesicles within the Golgi complex, but also participates in macroautophagy and facilitates the delivery of Atg8 and Atg9 to the PAS.[79]

Cytoplasm to vacuole targeting (Cvt)

A constitutive, biosynthetic pathway in yeast that transports resident hydrolases to the vacuole through a selective macroautophagy-like process.[80]

DAPK (death-associated protein kinase)

A kinase that phosphorylates Thr119 of Beclin 1 to activate it by causing dissociation from Bcl-x_L and Bcl-2, thus activating macroautophagy.[81]

DFCP1 (double FYVE domain-containing protein 1)

A PtdIns(3)P-binding protein that localizes to the omegasome.[82] Knockdown of DFCP1 does not result in an autophagy-defective phenotype.

DOR (diabetes- and obesity-regulated gene)

A mammalian and Drosophila regulatory protein that shuttles between the nucleus and the cytosol; the cytosolic protein interacts with LC3 and GATE-16 and stimulates autophagosome formation.[83]

DRAM (damage-regulated autophagy modulator)

A p53 target that encodes a lysosomal protein that induces macroautophagy.[84]

E2F1

A mammalian transcription factor that upregulates the expression of *LC3*, *ULK1* and *DRAM* directly, and *ATG5* indirectly.[85] E2F1 plays a role during DNA damage-induced macroautophagy.

eIF2α kinase (eukaryotic initiation factor 2α kinase)

There are four mammalian eIF2α kinases that respond to different types of stress. PKR and PERK induce macroautophagy in response to virus infection and ER stress, respectively.[86,87] See also Gcn2, PKR and PERK.

Endosome

The endosomal compartment receives molecules engulfed from the extracellular space. It consists of several discrete subcompartments including the early endosome, sorting endosome (sorts material into late endosomes of the *trans*-Golgi network), and the recycling endosome (recycles material back to the plasma membrane). In mammalian cells, early endosomes fuse with autophagosomes to generate amphisomes.

ERK1/2 (extracellular signal regulated kinase 1/2)

A kinase that phosphorylates and stimulates Gα-interacting protein (GAIP), which is a GTPase activating protein (GAP) for the trimeric G_{i3} protein that activates macroautophagy.[88]

Everolimus (RAD-001)

An mTOR inhibitor similar to rapamycin that induces macroautophagy.

FIP200 (RB1CC1)

A putative mammalian functional counterpart of yeast Atg17. FIP200 is a component of the ULK1 complex.[89]

FKBP12 (FK506-binding protein 12)

An immunophilin that forms a complex with rapamycin and inhibits mTOR.

FoxO3 (forkhead box O transcription factor 3)

Stimulates macroautophagy through transcriptional control of autophagy-related genes.[90,91]

FYCO1 (FYVE and coiled-coil domain containing 1)

A protein that interacts with LC3, PtdIns(3)P and Rab7 to move autophagosomes toward the lysosome through microtubule plus end-directed transport.[92]

GABARAP (gamma-aminobutyric acid receptor-associated protein)

A homologue of LC3.[93,94]

GATE-16 (Golgi-associated ATPase enhancer of 16 kDa)

A homologue of LC3.[93,94]

Gcn2

A mammalian and yeast eIF2α serine/threonine kinase that phosphorylates and activates Gcn4 in response to amino acid depletion, which positively regulates macroautophagy.[86]

Gcn4

A transcriptional activator that controls the synthesis of amino acid biosynthetic genes and positively regulates macroautophagy in response to amino acid depletion.[86]

GOPC (Golgi-associated PDZ and coiled-coil motif-containing protein)

Also known as PIST, FIG, and CAL, interacts with Beclin 1, and the SNARE protein Syntaxin 6. GOPC can induce autophagy via a CD46-Cyt-1-dependent pathway following pathogen invasion.[71]

GSK-3β (glycogen synthase kinase-3β)

A positive regulator of macroautophagy that inhibits mTOR by activating TSC1/2.

HDAC6 (histone deacetylase 6)

A microtubule-associated deacetylase that interacts with ubiquitinated proteins. HDAC6 stimulates autophagosome-lysosome fusion by promoting the remodeling of F actin, promoting the quality control function of macroautophagy.[95-97]

HIF-1 (hypoxia-inducible factor 1)

A dimeric transcription factor in which the α subunit is regulated by oxygen; the hydroxylated protein is degraded by the proteasome. HIF-1-mediated expression of BNIP3 results in the disruption of the Bcl-2-Beclin 1 interaction, thus inducing macroautophagy.[98,99]

hsc70 (heat shock cognate of the Hsp70 family)

This multifunctional cytosolic chaperone is the constitutive member of the hsp70 family of chaperones and participates in targeting of cytosolic proteins to lysosomes for their degradation via chaperone-mediated autophagy (CMA).[100] The cytosolic form of the protein also regulates the dynamics of the CMA receptor, whereas the lumenal form (lys-hsc70) is required for substrate translocation across the membrane.[101]

hsp90 (heat shock protein 90)

Cytosolic chaperone also located in the lumen of the lysosome. The lysosomal form of hsp90 contributes to the stabilization of LAMP-2A during its lateral mobility in the lysosomal membrane.[102]

ICP34.5

A neurovirulence gene product encoded by the herpes simplex virus type 1 (HSV-1) that blocks eIF2α/PKR induction of autophagy.[86] ICP34.5-dependent inhibition of autophagy depends upon its ability to bind to Beclin 1.[103]

IKK (IκB kinase)

An activator of the classical NFκB pathway composed of three subunits (IKKα, IKKβ, IKKγ, the latter also called NEMO) that are required for optimal induction of macroautophagy in human and mouse cells.[104]

Immunophagy

A sum of diverse immunological functions of autophagy.[105]

Inositol monophosphatase

An enzyme that regulates the level of myo-inositol 1,4,5 triphosphate (IP_3) levels. Inhibition of inositol monophosphatase stimulates autophagy independently of mTOR.[106]

IP_3R (Inositol 1,4,5-triphosphate receptor)

A Ca^{2+} channel present in the endoplasmic reticulum that controls the steady-state Ca^{2+} level in the ER. IP_3R is activated by IP_3 (inositol 1,4,5-triphosphate), regulated by Bcl-2-like proteins, and acts as an inhibitor of autophagy, forming a multiprotein complex that comprises Bcl-2 and Beclin 1.[106]

IRGM (p47 Immunity-Related GTPase)

Involved in the macroautophagic control of intracellular pathogens.[107]

Isolation membrane

See phagophore.

JNK1 (c-Jun N-terminal kinase 1)

A stress-activated kinase that phosphorylates Bcl-2 at Thr69, Ser70 and Ser87, causing its dissociation from Beclin 1, thus inducing macroautophagy.[108]

Jumpy/MTMR14

A member of the myotubularin family that is a PtdIns 3-phosphatase; knockdown increases macroautophagic activity.[109] Jumpy regulates the interaction of WIPI-1 with the phagophore.

JunB

A mammalian transcription factor that inhibits starvation-induced macroautophagy.[77]

LAMP-2 (lysosome-associated membrane protein type 2)

The second, more abundant, of the single-span lysosomal membrane proteins.[110] Three splice variants of the *lamp2* gene have been described. Knockout of the entire gene results in altered intracellular vesicular trafficking, abnormal lysosomal biogenesis, inefficient autophagosome clearance and alterations in cholesterol metabolism.[111-113]

LAMP-2A (lysosome-associated membrane protein 2A)

One of the spliced variants of the *lamp2* gene that functions as a lysosomal membrane receptor for chaperone-mediated autophagy.[75] LAMP-2A forms multimeric complexes that allow translocation of substrates across the lysosome membrane.[102] Regulation of LAMP-2A is partly achieved by dynamic movement into and out of lipid microdomains in the lysosomal membrane.[101]

LC3 (microtubule-associated protein 1 light chain 3)

A homologue of yeast Atg8, which is frequently used as an autophagosome marker. Cytosolic LC3-I is conjugated to phosphatidylethanolamine to become LC3-II.[114]

Lipophagy

Selective degradation of lipid droplets by lysosomes contributing to lipolysis (breakdown of triglycerides into free fatty acids). In mammals, this selective degradation has been described to occur via macroautophagy (macrolipophagy),[115] whereas in yeast, microlipophagy of cellular lipid stores has also been described.

LIR/LRS (LC3-interacting region/LC3 recognition sequence)

A domain in proteins such as Atg19, Atg32, p62 and NBR1 that interact with Atg8/LC3 (see also AIM and WXXL-motif).[116]

LKB1 (serine/threonine kinase 11)

A kinase that is upstream of, and activates, AMPK.[117]

LY294002

An inhibitor of PtdIns 3-kinases; it inhibits macroautophagy.[118]

Lysosome

A degradative organelle in higher eukaryotes that compartmentalizes a range of hydrolytic enzymes and maintains a highly acidic pH.

Macroautophagy

An autophagic process involving the formation of a double- or multiple-membrane cytosolic vesicle of non-lysosomal/vacuolar origin.

MAP1LC3 (Microtubule-associated protein 1 light chain 3)

See LC3.

MDC (Monodansylcadaverine)

A lysosomotropic autofluo-rescent compound that accumulates in acidic compartments, and labels (but is not specific for) autophagosomes.[119,120]

Microautophagy

An autophagic process involving direct uptake of cytosol, inclusions (e.g., glycogen) and organelles (e.g., ribosomes, peroxisomes) at the lysosome/vacuole by protrusion, invagination or septation of the sequestering organelle membrane.

Mitophagy

The selective degradation of mitochondria; can occur by a micro- or macroautophagic process.[121]

MTMR3 (myotubularin-related phosphatase 3)

This protein localizes to the phagophore and negatively regulates macroautophagy (see Jumpy/MTMR14).[122]

mTOR (mammalian target of rapamycin)

the mammalian orthologue of TOR.

Multivesicular body (MVB)

An endosome containing multiple 50–80 nm vesicles that are derived from invagination of the limiting membrane. Under some conditions the MVB contains hydrolytic enzymes in which case it may be considered to be a lysosome or autolysosome with ongoing microautophagy.

Multivesicular body (MVB) sorting pathway

A process in which proteins are sequestered into vesicles within the endosome through the invagination of the limiting membrane. This process is usually, but not always, dependent upon ubiquitin tags on the cargo and serves as one means of delivering integral membrane proteins destined for degradation into the vacuole lumen. ESCRT (endosomal sorting complex required for transport) complexes are required for the formation of MVB.

NBR1 (neighbor of BRCA1 gene 1)

A selective substrate of macroautophagy with structural similarity to p62. Functions as an adaptor that binds ubiquitinated proteins and LC3 to allow the degradation of the former by macroautophagy.[116]

NDP52 (nuclear dot protein 52 kDa)

An adaptor that binds to the bacterial ubiquitin coat and Atg8/LC3 to target invasive bacteria including *Salmonella enterica* serovar Typhimurium and *Streptococcus pyogenes* for autophagosomal sequestration.[123]

NFκB (nuclear factor kappa-light chain-enhancer of activated B cells)

Activates mTOR to inhibit macroautophagy.[124]

NH_4Cl (ammonium chloride)

A weak base that is protonated in acidic compartments and neutralizes them.

NIX (BNIP3L/BNIP3α)

A Bcl-2-related protein that is required for selective mitochondrial clearance (mitophagy) during erythroid differentiation.[125]

Nod (nucleotide-binding oligomerization domain)

An intracellular peptidoglycan (or pattern recognition) receptor that senses bacteria and induces macroautophagy, involving ATG16L1 recruitment to the plasma membrane during bacterial cell invasion.[126]

Omegasome

DFCP1-containing structures located at the ER that are involved in autophagosome formation.[82]

p27 ($p27^{Kip1}$)

A cyclin-dependent kinase inhibitor that is phosphorylated and stabilized by an AMPK-dependent process and stimulates macroautophagy.[117]

p38α (mitogen-activated protein kinase isoform p38α)

A signaling component that negatively regulates the interaction of mAtg9 and p38IP, and thus inhibits macroautophagy. The yeast homologue is Hog1.

p38IP (p38α interacting protein/family with sequence similarity 48A (FAM48A))

A protein that interacts with the C-terminal domain of mAtg9; this interaction is negatively regulated by p38α.[127]

p53

A tumor suppressor. Nuclear p53 activates autophagy, at least in part, by stimulating AMPK and DRAM. Cytoplasmic p53 inhibits autophagy.[128]

p62 (sequestosome 1/SQSTM1)

A selective substrate of macroautophagy, that functions as an adaptor protein that links ubiquitinated proteins to LC3. p62 accumulates in cells when macroautophagy is inhibited. p62 interaction with LC3 requires a WXXL or a LIR motif analogous to the interaction of Atg8 with Atg19.[129]

Parkin

An E3 ubiquitin ligase (mutated in autosomal recessive forms of Parkinson disease) that is recruited from the cytosol to mitochondria with low membrane potential to induce mitophagy.[130]

PAS (phagophore assembly site)

Also referred to as the preautophagosomal structure. A perivacuolar compartment or location that is the proposed nucleation site for sequestering vesicles (e.g., autophagosomes and Cvt vesicles) used in macroautophagy-like processes in fungi. The PAS may supply membranes during the formation of the sequestering vesicles or may be an organizing center where most of the macroautophagic machinery resides at least transiently. The PAS or its equivalent is yet to be defined in mammalian cells.[131,132]

Pcl1

A yeast cyclin that activates Pho85 to stimulate macroautophagy by inhibiting Sic1.[78]

Pcl5

A yeast cyclin that activates Pho85 to inhibit macroautophagy through degradation of Gcn4.[78]

PDK1 (phosphoinositide-dependent protein kinase 1)

An activator of PKB. Recruited to the plasma membrane and activated by PtdIns(3,4,5)P_3 which is generated by the class I PtdIns 3-kinase.

PERK (PKR-like ER Kinase)

A mammalian eIF2α kinase that may induce macroautophagy in response to ER stress.[87]

Pexophagy

A selective type of autophagy involving the sequestration and degradation of peroxisomes; can occur by a micro- or macroautophagic process (micro- or macropexophagy).[133]

Phagophore

Membrane cisterna that is involved in an initial event during formation of the autophagosome. Also referred to as the “isolation membrane,” the phagophore is the initial sequestering compartment of macroautophagy.[134]

Pho80

A yeast cyclin that activates Pho85 to inhibit macroautophagy in response to high phosphate levels.[78]

Pho85

A multifunctional cyclin-dependent kinase that interacts with at least 10 different cyclins or cyclin-like proteins to regulate the cell cycle and responses to nutrient levels. Pho85 acts to negatively and positively regulate macroautophagy, depending on its binding to specific cyclins.[78] See also Clg1, Pcl1, Pcl5, Pho80 and Sic1.

Phosphatidylinositol (PtdIns) 3-kinase

A family of enzymes that adds a phosphate group to the 3′ hydroxyl on the inositol ring of phosphoinositides. The class III PtdIns 3-kinases (see Vps34; also referred to as PI3KC3) are stimulatory for macroautophagy, whereas class I enzymes are inhibitory. So far, nothing is known about the involvement of the class II enzymes in autophagy.

Piecemeal microautophagy of the nucleus (PMN/micronucleophagy)

A process in which portions of the yeast nuclear membrane and nucleoplasm are invaginated into the vacuole, scissioned off from the remaining nuclear envelope and degraded within the vacuole lumen.[135,136]

PINK1 (PTEN-induced kinase 1/PARK6)

A mitochondrial protein (mutated in autosomal recessive forms of Parkinson disease) that spans the outer mitochondrial membrane with its kinase domain in the cytosol; it interacts with and recruits Parkin to mitochondria to facilitate mitophagy of mitochondria that have lost their normal transmembrane potential.[137]

PKA (protein kinase A)

A serine/threonine kinase that negatively regulates macroautophagy in yeast.

PKB (protein kinase B) or Akt

A serine/threonine kinase that negatively regulates macroautophagy.

PKCδ (protein kinase Cδ)

PKCδ regulates JNK activation. PKCδ also activates NADPH oxidases, which are required for antibacterial macroautophagy.

PKR (dsRNA-dependent protein kinase R)

A mammalian eIF2α kinase that induces macroautophagy in response to viral infection.[138]

PGRP (peptidoglycan-recognition protein)

A cytosolic Drosophila protein that induces autophagy in response to invasive *Listeria monocytogenes*.[139]

Programmed cell death (PCD)

Regulated self-destruction of a cell. Type I is associated with apoptosis and is marked by cytoskeletal breakdown and condensation of cytoplasm and chromatin followed by fragmentation. Type II is associated with macroautophagy and is characterized by the presence of autophagic vacuoles (autophagosomes) that sequester organelles. Type III is marked by the absence of nuclear condensation and a necrotic morphology with swelling of cytoplasmic organelles (oncosis).

PTEN

A 3′ phosphoinositide phosphatase that dephosphorylates PtdIns(3,4,5)P_3, thereby inhibiting PDK1 and PKB activity.

RAD001 (Everolimus)

An orally administered derivative of rapamycin.

Rag (Ras-related GTPase)

A GTPase that activates TORC1 in response to amino acids.[140]

Rapamycin

TOR (TOR complex 1) inhibitor, which induces autophagy. TOR complex 2 is much less sensitive to inhibition by rapamycin.

Residual body

A lysosome that contains indigestible material.[141]

Resveratrol

An allosteric activator of Sirtuin 1 that induces macroautophagy.[142]

Reticulophagy

The selective degradation of endoplasmic reticulum by a macroautophagy-like process.[143]

Rheb

A small GTP-binding protein that activates TOR when it is in the GTP-bound form.[144]

Ribophagy

The selective degradation of ribosomes by macroautophagy.[145]

Rim15

A yeast kinase that regulates transcription factors in response to nutrients. Rim15 positively regulates macroautophagy and is negatively regulated by several upstream kinases including Tor, PKA, Sch9 and Pho85.[78,146]

Rubicon (RUN domain and cysteine-rich domain containing, Beclin 1-interacting)

Rubicon is part of a PtdIns 3-kinase complex (Rubicon-UVRAG-Beclin 1-hVps34-p150) that localizes to the late endosome/lysosome and inhibits macroautophagy.[147,148]

Sch9

A kinase that functions in parallel with PKA to negatively regulate macroautophagy. Sch9 appears to function in parallel with TOR, but is also downstream of the TOR kinase.[146]

SEPA-1 (suppressor of ecoptic P granule in autophagy mutants-1)

A *C. elegans* protein that is involved in the selective degradation of P granules through macroautophagy.[149]

Sestrin 2

A protein encoded by a p53 target-induced gene that inhibits mTORC1 and induces macroautophagy, also acting as an AMPK activator.

Sic1

A yeast cyclin-dependent kinase inhibitor that blocks the activity of Cdc28-Clb kinase complexes to control entry into the S phase of the cell cycle. Sic1 is a negative regulator of macroautophagy that inhibits Rim15.[78]

Sirolimus

An immunosuppressant more commonly referred to as rapamycin.

Sirtuin 1

A protein deacetylase that is activated by caloric restriction and that can induce macroautophagy.[150]

Spermidine

A natural polyamine that induces macroautophagy through the inhibition of histone acetylases.[151]

Sphingolipids

Sphingolipids are a major class of lipids. Some metabolites including ceramide, sphingosine and sphingosine 1-phosphate are bioactive signaling molecules. Ceramide and sphingosine 1-phosphate are positive regulators of macroautophagy.[152,153]

TAK1 (transforming growth factor-β-activating kinase 1)

Required for TRAIL-induced activation of AMPK. Required for optimal macroautophagy induction by multiple stimuli.[154]

TGFβ (transforming growth factor-β)

A cytokine that activates autophagy through the Smad and JNK pathways. TGFβ induces the expression of several *ATG* genes including *BECN1.*

TLR (Toll-like receptor)

A family of receptors that induces autophagy following binding to a corresponding pathogen-associated molecular pattern (PAMP).

TM9SF1

A protein with nine transmembrane domains that induces autophagy when overexpressed.[155]

TMEM

TMEM74 and TMEM166 are integral membrane proteins that induce autophagy when overexpressed.[156,157]

TOR (target of rapamycin)

A protein kinase that negatively regulates macroautophagy. Present in two complexes, TORC1 and TORC2. TORC1 is particularly sensitive to inhibition by rapamycin. TORC1 regulates macroautophagy in part through Tap42-PP2A, and also by phosphorylating Atg13 and Atg1.

TORC1 (TOR Complex I)

A rapamycin-sensitive protein complex of TOR that includes Tor1/Tor2 (mTOR), Kog1 (Raptor), Lst8 (mLST8), Rhb1 (Rheb) and Tco89.[158] mTORC1 also includes DEPTOR.[159] In mammalian cells, sensitivity to rapamycin is conferred by Raptor. TORC1 directly regulates macroautophagy.

TORC2 (TOR Complex II)

A relatively rapamycin-insensitive protein complex of TOR that includes Tor2 (mTOR), Avo1 (SIN1), Avo2, Avo3 (Rictor), Bit2, Bit61, Lst8 (mLST8) and Tsc11; mTORC2 also includes DEPTOR, FKBP38, PRAS40 and Protor-1.[158-160] The main difference relative to TORC1 is the replacement of Raptor by Rictor. TORC2 is primarily involved with regulation of the cytoskeleton.

Torin1

A selective ATP-competitive mTOR inhibitor that directly inhibits both TORC1 and TORC2.[161]

TP53INP2 (tumor protein 53-induced nuclear protein 2)

Interacts with VMP1 and is needed for the recruitment of Beclin 1 and LC3 to autophagosomes. Translocates from the nucleus to autophagosomes during autophagy induction and binds VMP1 and LC3 directly.[162]

TRAIL (tumor necrosis factor-related apoptosis-inducing ligand)

Induces autophagy by activating AMPK, thus inhibiting mTORC1 during lumen formation.

TRAPPIII (Transport Protein Particle III)

A guanine nucleotide exchange factor for Ypt1 that functions in macroautophagy in yeast.[163] TRAPPIII is composed of Bet3, Bet5, Trs20, Trs23, Trs31, Trs33 and a unique subunit, Trs85.

TSC1/2 (tuberous sclerosis complex 1/2)

A stable heterodimer (composed of hamartin and tuberin) inhibited by PKB/Akt and ERK1/2 (phosphorylation causes dissociation of the dimer), and activated by AMPK. TSC1/2 acts as a GAP for Rheb, thus inhibiting TOR.

Ubiquilins (UBQLNs)

Adaptor proteins that deliver ubiquitinated substrates to the proteasome. Ubiquilins may aid in the incorporation of protein aggregates into autophagosomes, and also promote the maturation of autophagosomes at the stage of fusion with lysosomes.[164]

Ubiquitin

A 76-kDa protein that is conjugated to lysine residues. Ubiquitin is traditionally considered part of the ubiquitin-proteasome system and tags proteins for degradation; however, ubiquitin is also linked to various types of autophagy including aggrephagy (see p62 and NBR1).

ULK family (Unc51-like kinase)

Homologue of yeast Atg1. In mammalian cells consists of five members, ULK1, ULK2, ULK3, ULK4, STK36/fused (ULK5). ULK1 and ULK2 are required for macroautophagy, and ULK3 for oncogene-induced senescence.[165-167]

UVRAG (UV irradiation resistance-associated gene)

A Vps38 homologue that can be part of the class III PtdIns 3-kinase complex. UVRAG functions in several ways to regulate macroautophagy: 1) It disrupts Beclin 1 dimer formation and forms a heterodimer that activates macroautophagy; 2) it binds to Bif-1 to allow activation of class III PtdIns 3-kinase to stimulate macroautophagy; 3) it interacts with the class C Vps/HOPS proteins involved in fusion of autophagosomes or amphisomes with the lysosome; 4) it competes with Atg14L for binding to Beclin 1, thus directing the class III PtdIns 3-kinase to function in the maturation step of macroautophagy.[168]

Vacuole

The yeast equivalent of the lysosome; this organelle also carries out storage and osmoregulatory functions.

Vacuole import and degradation (Vid)

A degradative pathway in yeast in which a specific protein(s) is sequestered into small single-membrane cytosolic vesicles that fuse with the vacuole allowing the contents to be degraded in the lumen. This process has been characterized for the catabolite-induced degradation of the gluconeogenic enzyme fructose-1,6-bisphosphatase in the presence of glucose, and sequestration is thought to involve translocation into the completed vesicle. An alternate pathway for degradation of fructose-1,6-bisphosphatase by the ubiquitin-proteasome system has also been described.[169]

VMP1 (vacuole membrane protein 1)

A membrane protein that localizes to the plasma membrane or the ER. Interacts with Beclin 1 and is required for macroautophagy.[170,171]

Vps34

The class III PtdIns 3-kinase that generates PtdIns(3) P, which is required for macroautophagy. In yeast, Vps34 is present in two complexes. Complex I consisting of Vps34, Vps15, Vps30/Atg6 and Atg14 is essential for macroautophagy. Complex II composed of Vps34, Vps15, Vps30/Atg6 and Vps38 acts in the vacuolar protein sorting (Vps) pathway. In mammalian cells there are at least three PtdIns 3-kinase complexes that include Vps34, Vps15, Atg14L and Beclin 1, and combinations of UVRAG, Ambra1 and/or Rubicon.

Vps38

A component of the class III PtdIns 3-kinase complex II, which directs it to function in the vacuolar protein sorting (Vps) pathway.

WIPI (WD repeat domain, phosphoinositide interacting)

The WIPI proteins are putative mammalian homologues of yeast Atg18 and Atg21. There are four WIPI proteins in mammalian cells. WIPI1/WIPI49 localizes with LC3 and PtdIns(3)P.[172]

Wortmannin

An inhibitor of PtdIns 3-kinases; it inhibits macroautophagy.[118]

WXXL motif

An amino acid sequence present in proteins that allows an interaction with Atg8/LC3; the consensus is W/YXXL/I. Also see AIM and LIR/LRS.[173]

XBP1

A component of the endoplasmic reticulum stress response that activates macroautophagy. The Xbp1 yeast orthologue is Hac1.[174]

Xenophagy

Cell-autonomous innate immunity defense, whereby cells eliminate intracellular pathogens by capture into autophagosomes with subsequent killing.[175]

Xestospongin B

An antagonist of the IP_3R (inositol 1,4,5-tris-phosphate receptor) that dissociates the inhibitory interaction between IP_3R and Beclin 1 and induces macroautophagy.[176]

Ypt1

A yeast Rab GTPase that functions in macroautophagy.[163] Ypt1 is needed for correct localization of Atg8 to the PAS. See also TRAPPIII.

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