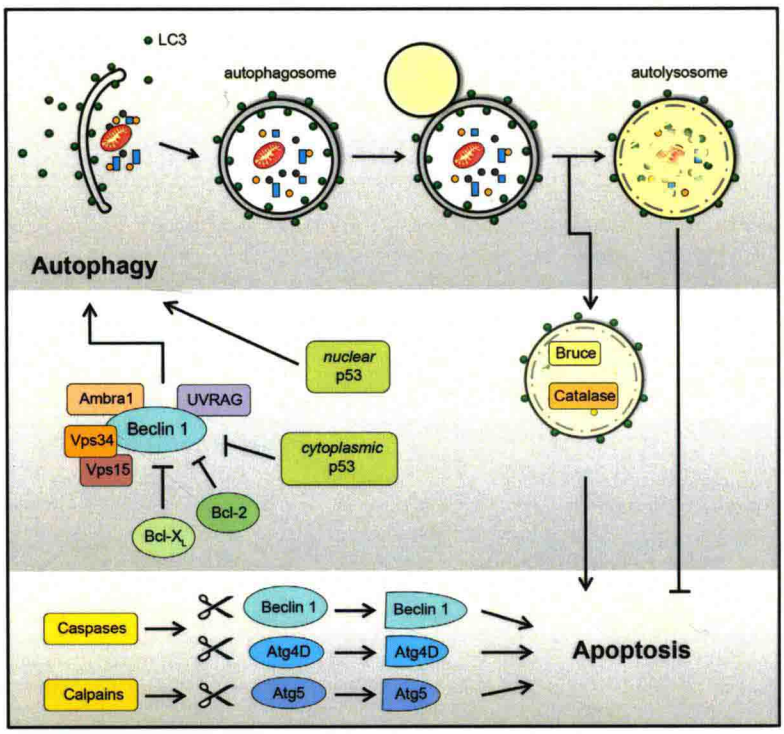
# AUTOPHAGY

## CANCER, OTHER PATHOLOGIES, INFLAMMATION, IMMUNITY, INFECTION, AND AGING

VOLUME 3

EDITED BY

M. A. HAYAT



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*Edited by*

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# AUTOPHAGY

# Dedication

**To**

Julio A. Aguirre-Ghiso, Patrice Codogno, Eduardo Couve, Ana Maria Cuervo, Guido R. Y. De Meyer, Vojo Deretic, Fred J. Dice, William A. Dunn Jr, Eeva-Lisa Eskelinen, Sharon Gorski, Tomotake Kanki, Daniel J. Klionsky, Guido Kroemer, Beth Levine, Noboru Mizushima, Yoshinori Ohsumi, Brinda Ravikumar, David Rubinsztein, Isei Tanida, Sharon A. Tooze, Herbert W. Virgin, Eileen White, Tamotsu Yoshimori, and others.

The men and women involved in the odyssey of deciphering the molecular mechanisms underlying the complexity of the autophagy process that governs our lives.

Life in the Balance, Longevity the Goal
Self-eating, recycling, cash-for-your clunkers:
Trade up to the mitochondrial equivalent Prius.
The road to rejuvenation is paved with destruction
For clearing the rubble precedes reconstruction
But remember that life's circular dance
Depends on opposite forces in balance
Excess destruction, too much biogenesis,
Brings heart failure, cancer or neurodegeneries

*Roberta A. Gottlieb*

# Preface

In order to remain healthy, eukaryotic cells require a constant turnover and replacement of old, damaged, or excess cell components, including cell organelles with new functional components. It is an intracellular pathway for the bulk or selective delivery of cytoplasmic materials to lysosomes in animal cells and to vacuoles in yeast and plant cells for degradation. Autophagy determines the basal turnover of cytoplasm, renovates cells during cell differentiation, recycles old macromolecules for reuse, and mostly protects cells from their own dangerous products and even unwanted visitors. Autophagy has long been recognized as a response to nutrient deprivation to provide energy and anabolic building blocks to maintain energy homeostasis. In addition, autophagy has been shown to function as a mechanism of intracellular pathogen sensing. Defects in autophagy can lead to increased susceptibility to infection and disease. Autophagy not only protects us from cancer, but also against the development of other diseases.

The ultimate goal of research in the field of autophagy is to decipher the molecular mechanisms underlying the exceedingly complex autophagic process, and use them for the development of effective therapy against diseases. This goal becomes urgent considering that the treatments presently available (chemotherapy, radiation, surgery, hormone therapy, and vaccine therapy) for major diseases such as cancer are only modestly successful. During the last two decades, an astonishing advance has been made in the understanding of the molecular mechanisms involved in the degradation of intracellular proteins in yeast vacuoles and the lysosomal compartment in mammalian cells. Advances in genome-scale approaches and computational tools have presented opportunities to explore the broader context in which autophagy is regulated at the systems level.

This is Volume 3 of the four-volume series, *Autophagy: Cancer, Other Pathologies, Inflammation, Immunity, Infection, and Aging*, which will discuss almost all aspects of the autophagy process. The text is divided into four subheadings (Molecular Mechanisms, Role in Disease, Role in Cancer, and Cross-Talk between Autophagy and Apoptosis) for the convenience of the readers.

By bringing together a large number of experts (oncologists, physicians, medical research scientists, and pathologists) in the field of autophagy, it is my hope that substantial progress will be made against terrible diseases inflicting humans. It is difficult for a single author to discuss effectively and comprehensively various aspects of an exceedingly complex process such as autophagy. Another advantage of involving more than one author is to present different points of view on a specific controversial aspect of the role of autophagy in health and disease. I hope these goals will be fulfilled in this and other volumes of the series.

This volume was written by 61 contributors representing 12 countries. I am grateful to them for their promptness in accepting my suggestions. Their practical experience highlights the very high quality of their writings, which should build and further the endeavors

of the readers in this important medical field. I respect and appreciate the hard work and exceptional insight into the autophagy machinery provided by these contributors.

It is my hope that subsequent volumes of the series will join this volume in assisting in the more complete understanding of the complex process of autophagy, and eventually in the development of therapeutic applications. There exists a tremendous, urgent demand by the public and the scientific community to address the treatments of major diseases. In light of existing disease calamity, government funding must give priority to eradicating deadly malignancies over global military superiority.

I am grateful to Dr. Dawood Farahi and Mr. Philip Connelly for recognizing the importance of medical research and publishing through an institution of higher education. I am thankful to my students for their contribution to the preparation of this volume.

*M.A. Hayat*
August 2013

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# Abbreviations and Glossary

| | |
|---|---|
| **1AP** | inhibitor of apoptosis protein |
| **3-MA** | 3-methyladenine, an autophagy inhibitor |
| **3-methyladenine** | an autophagic inhibitor |
| **5-Fu** | 5 fluorouracil |
| **AAP** | protein that mediates selective autophagy |
| **ACF** | aberrant crypt foci |
| **aggrephagy** | degradation of ubiquitinated protein aggregates |
| **aggresome** | inclusion body where misfolded proteins are confined and degraded by autophagy |
| **AIF** | apoptosis–inducing factor |
| **AIM** | Atg8-family interacting motif |
| **Akt** | protein kinase B regulates autophagy |
| **Alfy** | autophagy-linked FYVE protein |
| **ALIS** | aggresome-like induced structures |
| **ALR** | autophagic lysosome reformation. |
| **AMBRA-1** | activating molecule in Beclin 1-regulated autophagy |
| **AMP** | adenosine monophosphate |
| **amphisome** | intermediate compartment formed by fusing an autophagosome with an endosome |
| **AMPK** | adenosine monophosphate-activated protein kinase |
| **APC** | antigen-presenting cells |
| **APG** | autophagy |
| **aPKC** | atypical protein kinase C |
| **APMA** | autophagic macrophage activation |
| **apoptosis** | programmed cell death type 1 |
| **ARD1** | arrest-defective protein 1 |
| **ASK** | apoptosis signal regulating kinase |
| **AT1** | Atg8-interacting protein |
| **ATF5** | activating transcription factor 5 |
| **ATF6** | activating transcription factor 6 |
| **Atg** | autophagy-related gene or protein |
| **Atg1** | serine/threonine protein 1 kinase |
| **Atg2** | protein that functions along with Atg18 |
| **Atg3** | ubiqitin conjugating enzyme analogue |
| **Atg4** | cysteine protease |
| **Atg5** | protein containing ubiquitin folds |

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|---|---|
| **Atg6** | component of the class III PtdIns 3-kinase complex |
| **Atg7** | ubiquitin activating enzyme homologue |
| **Atg8** | ubiquitin-like protein |
| **Atg9** | transmembrane protein |
| **Atg10** | ubiquitin conjugating enzyme analogue |
| **Atg11** | fungal scaffold protein |
| **Atg12** | ubiquitin-like protein |
| **Atg13** | component of the Atg1 complex |
| **Atg14** | component of the class III PtdIns 3-kinase complex |
| **Atg15** | vacuolar protein |
| **Atg16** | component of the Atg12-Atg5-Atg16 |
| **Atg17** | yeast protein |
| **Atg18** | protein that binds to PtdIns |
| **Atg19** | receptor for the Cvt pathway |
| **Atg20** | PtdIns P binding protein |
| **Atg21** | PtdIns P binding protein |
| **Atg22** | vacuolar amino acid permease |
| **Atg23** | yeast protein |
| **Atg24** | PtdIns binding protein |
| **Atg25** | coiled-coil protein |
| **Atg26** | sterol glucosyltransferase |
| **Atg27** | integral membrane protein |
| **Atg28** | coiled-coil protein |
| **Atg29** | protein in fungi |
| **Atg30** | protein required for recognizing peroxisomes |
| **Atg31** | protein in fungi |
| **Atg32** | mitochondrial outer membrane protein |
| **Atg33** | mitochondrial outer membrane protein |
| **Atg101** | Atg13-binding protein |
| **ATM** | ataxia-telangiectasia mutated protein |
| **autolysosome protein** | lysosomal associated membrane protein 2 |
| **autolysosome** | formed by fusion of the autophagosome and lysosome, degrading the engulfed cell components |
| **autophagic body** | the inner membrane-bound structure of the autophogosome |
| **autophagic flux** | the rate of cargo delivery to lysosomes through autophagy |
| **autophagosome** | double-membrane vesicle that engulfs cytoplasmic contents for delivery to the lysosome |
| **autophagosome maturations** | events occurring post-autophagosome closure followed by delivery of the cargo to lysosomes |
| **autophagy** | programmed cell death type 2 |
| **AV** | autophagic vacuole |
| **axonopathy** | degradation of axons in neurodegeneration |
| **BAD** | Bcl-2 associated death promoter protein |
| **Bafilomycin** | inhibitor of the vacular-type ATPase |
| **Bafilomycin A1(Baf-A1)** | an autophagy inhibitor |
| **BAG** | Bcl-2-associated athanogene |

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|---|---|
| **BAG3** | Bcl2-associated athanogene 3 |
| **BAK** | Bcl-2 antagonist/killer |
| **Barkor** | Beclin 1-associated autophagy-related key regulator |
| **BATS** | Barkor/Atg14(L) autophagosome targeting sequence |
| **BAX** | Bcl-2-associated X protein |
| **Bcl-2** | B cell lymphoma-2 |
| **Beclin 1** | mammalian homologue of yeast Atg6, activating macroautophagy |
| **Beclin 1** | Bcl-2-interacting protein 1 |
| **BH3** | Bcl-2 homology domain-3 |
| **BH3-only proteins** | induce macroautopagy |
| **BHMT** | betaine homocysteine methyltransferase protein found in the mammalian autophagosome (metabolic enzyme) |
| **BID** | BH3-interacting domain death agonist |
| **Bif-1 protein** | interacts with Beclin 1, required for macroautophagy |
| **Bim** | Bcl-2 interacting mediator |
| **BNIP** | pro-apoptotic protein |
| **BNIP3 protein** | required for the HIF-1-dependent induction of macroautophagy |
| **bortezomib** | selective proteasome inhibitor |
| **CaMKKβ protein** | activates AMPK at increased cytosolic calcium concentration |
| **CaMK** | calcium/calmodulin-dependent protein kinase |
| **CASA** | chaperone-assisted selective autophagy |
| **caspase** | cysteine aspartic acid specific protease |
| **CCI-779** | rapamycin ester that induces macroautophagy |
| **CD46 glycoprotein** | mediates an immune response to invasive pathogens |
| **chloroquine** | an autophagy inhibitor which inhibits fusion between autophagosomes and lysosomes |
| **c-Jun** | mammalian transcription factor that inhibits starvation-induced macroautophagy |
| **Clg 1** | a yeast cyclin-like protein that induces macroautophagy |
| **CMA** | chaperone-mediated autophagy |
| **COG** | functions in the fusion of vesicles within the Golgi complex |
| **COP1** | coat protein complex1 |
| **CP** | 20S core particle |
| **CRD** | cysteine-rich domain |
| **CSC** | cancer stem cell |
| **CTGF** | connective tissue growth factor |
| **Cvt** | cytoplasm-to-vacuole targeting |
| **DAMP** | damage-associated molecular pattern molecule/danger-associated molecular pattern molecule |
| **DAP1** | death-associated Protien 1 |
| **DAPK** | death-associated protein kinase |
| **DAPK1** | death-associated protein kinase 1 |
| **DDR** | DNA damage response |
| **DEPTOR** | DEP domain containing mTOR-interacting protein |
| **DFCP1** | a PtdIns (3) P-binding protein |

**DISC** death-inducing signaling complex
**DMV** double-membrane vesicle
**DOR** diabetes-and obesity-regulated gene
**DRAM** damage-regulated autophagy modulator
**DRAM-1** damage-regulated autophagy modulator 1 induces autophagy in a p53-dependent manner.
**DRC** desmin-related cardiomyopathy
**DRiP** defective ribosomal protein
**DRP1** dynamin related protein 1
**DUB** deubiquitinases that accumulate proteins into aggresomes
**E2F1** a mammalian transcription factor
**efferocytosis** phagocytosis of apoptotic cells
**EGFR** epidermal growth factor receptor
**EIF2α** eukaryotic initiation factor 2 alpha kinase
**endosomes** early compartments fuse with autophagosomes to generate amphisomes
**ERAA** endoplasmic reticulum-activated autophagy
**ERAD** endoplasmic reticulum-associated degradation pathway
**ERK** extracellular signal regulated kinase
**ERK1/2** extracellular signal regulated kinase 1/2
**ERT** enzyme replacement therapy
**ESCRT** endosomal sorting complex required for transport
**everolimus** mTOR inhibitor
**FADD** Fas-associated death domain
**FKBP12** FK506-binding protein 12
**FoxO3** Forkhead box O transcription factor 3
**FYCO1** FYVE and coiled domain containing 1
**GAA** acid α-glucosidase
**GABARAP** gamma-aminobutyric acid receptor-associated protein
**GAS** group A streptococcus
**GATE-16** Golgi-associated ATPase enhancer of 16 kDa
**GFP** green fluorescent protein
**glycophagy** degradation of glycogen particles
**GPCR** G protein-coupled receptor
**GSK-3β** glycogen synthase kinase 3 beta regulates macroautophagy
**GST-BHMT** BHMT fusion protein used to assay macroautophagy in mammalian cells
**HAV** heavy autophagic vacuole
**HCQ** hydroxychloroquine
**HCV** hepatitis C virus
**HDAC** histone deacetylase
**HDAC6** histone deacetylase 6
**HIF** hypoxia-inducible factor
**HIF1** hypoxia-inducible factor 1
**HMGB1** high mobility group box 1

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|---|---|
| **HR-PCD** | hypersensitive response programmed cell death |
| **Hsc70** | heat shock cognate protein |
| **HSP** | heat shock protein |
| **Hsp90** | heat shock protein 90 |
| **HspB8** | heat shock cognate protein beta-8 |
| **Htraz** | high temperature requirement factor Az is a pro-apoptotic protein |
| **I13P** | phosphatidylinositol |
| **IAP** | inhibitor of apoptosis protein |
| **IKK** | inhibitor of nuclear factor κB |
| **IL3** | interleukin-3 |
| **IM** | isolation membrane |
| **inflammasome** | an intracellular protein complex that activates caspase-1 |
| **IRF** | interferon regulatory factor |
| **IRGM** | immunity-associated GTPase family M |
| **IRS** | insulin receptor substrate |
| **JNK/SAPK** | c-Jun N-terminal kinase/stress-activated protein kinase |
| **KRAS** | an oncogene that induces autophagy in cancer cells |
| **LAMP** | lysosome-associated membrane protein |
| **LAMP1** | lysosome marker, lysosome-associated membrane protein 1 |
| **LAMP2** | lysosomal-associated membrane protein 2 |
| **LAMP-2A** | lysosomal-associated membrane protein 2A |
| **LAP** | LC3-associated phagocytosis |
| **LAV** | light autophagic vacole |
| **LC3 (MAP1LC3B)** | autophagosome marker microtubule-associated protein 1 light chain 3B |
| **LC3** | microtubule-associated protein light chain 3 |
| **LET** | linear energy transfer |
| **lipophagy** | selective delivery of lipid droplets for lysosomal degradation |
| **LIR** | LC3 interacting region |
| **LKB** | liver kinase B |
| **LSD** | lysosomal storage disorder |
| **lysosomotropic agent** | compound that accumulates preferentially in lysosomes |
| **macroautophagy** | autophagy |
| **macrolipophagy** | regulation of lipid metabolism by autophagy |
| **MALS** | macroautophagy–lysosome system |
| **MAPK** | mitogen-activated protein kinase |
| **MARF** | mitofusion mitochondrial assembly regulatory factor |
| **MCU** | mitochondrial calcium uptake uniporter pore |
| **MDC** | monodansylcadaverine to measure autophagic flux *in vivo* |
| **MEF** | mouse embryonic fibroblast |
| **MFN2** | mitofusin 2, a mitochondrial outer membrane protein involved in fusion/fission to promote mitochondrial segregation and elimination |
| **MHC** | major histocompatibility complex |

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|---|---|
| **MHC-II** | major histocompatibility complex class II |
| **MiCa** | mitochondrial inner membrane calcium channel |
| **micropexophagy or macropexophagy** | peroxisome degradation by autophagic machinery |
| **MIPA** | micropexophagy-specific membrane apparatus |
| **mitofusion** | mitochondrial fusion-promoting factor |
| **mitophagy** | degradation of dysfunctional mitochondria |
| **MOM** | mitochondrial outer membrane |
| **MPS** | mucopolysaccharide |
| **MPT** | mitochondrial permeability transition |
| **mPTP** | mitochondrial permeability transition pore |
| **MSD** | multiple sulfatase deficiency |
| **MTCO2** | mitochondrial marker |
| **MTOC** | microtubule organizing center |
| **mTOR** | mammalian target of rapamycin, which inhibits autophagy and functions as a sensor for cellular energy and amino acid levels |
| **mTORc1** | mammalian target of rapamycin complex 1 |
| **MTP** | mitochondrial transmembrane potential |
| **MTS** | mitochondrial targeting sequence |
| **MVB** | multivesicular body |
| **NBR1** | neighbor of BRCA1 gene 1 |
| **NDP52** | nuclear dot protein 52 kDa |
| **NEC-1** | necrostatin-1 |
| **necroptosis** | a form of programmed cell death by activating autophagy-dependent necrosis |
| **Nix** | a member of the Bcl-2 family required for mitophagy |
| **NLR** | NOD-like receptor |
| **NOD** | nucleotide-binding oligomerization domain |
| **NOS** | nitric oxide synthase |
| **NOX** | NADPH oxidase |
| **Nrf2** | nuclear factor 2 |
| **OCR** | oxygen consumption rate |
| **Omegasome** | PI(3)P-enriched subdomain of the ER involved in autophagosome formation |
| **OMM** | outer mitochondrial membrane |
| **OPA1** | mitafusin 1 is required to promote mitochondrial fusion |
| **Ox-LDL** | oxidized low density lipoprotein is a major inducer of ROS, inflammation, and injury to endothelial cells |
| **p62** | an autophagy substrate |
| **p62/SQSTM1** | sequestosome 1 |
| **PAMP** | pathogen-associated molecular pattern molecule |
| **PAS** | pre-autophagosomal structure |
| **PB1 domain** | Phox and Bem1 domain |
| **PCD** | programmed cell death |
| **PDI** | protein disulfide isomerase |
| **PE** | phosphatidylethanolamine |