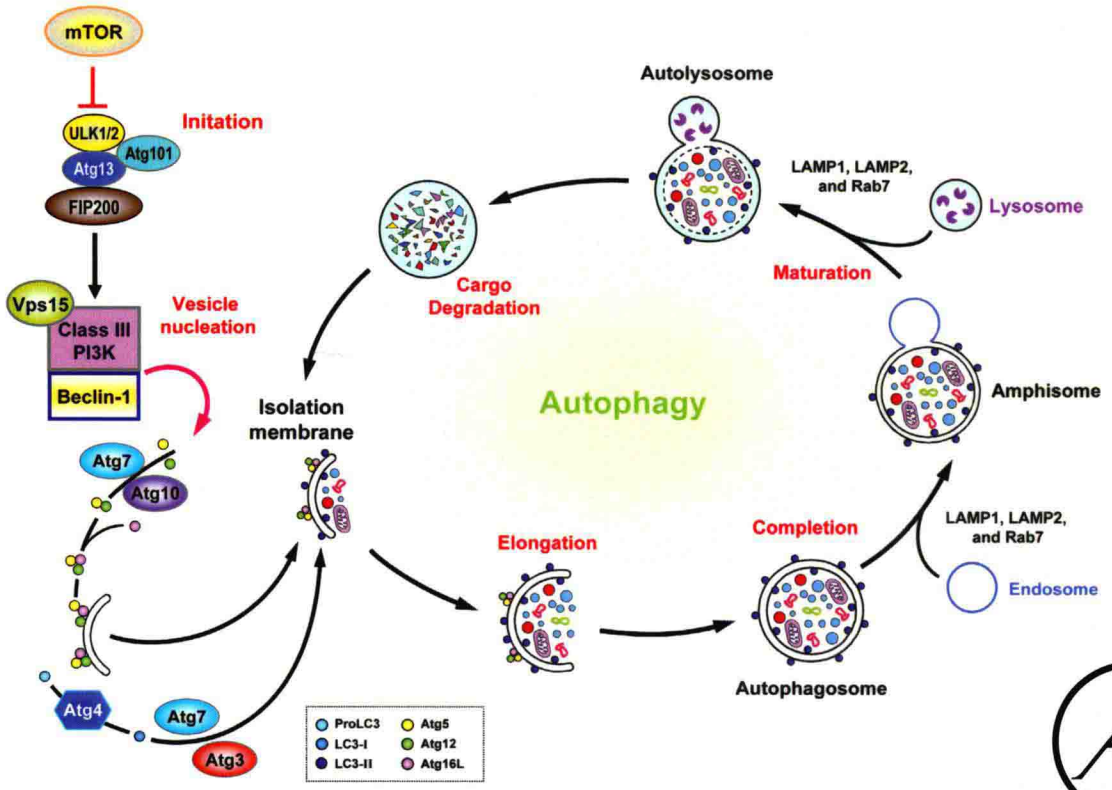
AUTOPHAGY

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

VOLUME 2

EDITED BY

M. A. HAYAT



AUTOPHAGY

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

VOLUME 2

Edited by

M. A. Hayat
Distinguished Professor
Department of Biological Sciences
Kean University
Union, New Jersey

ELSEVIER

AMSTERDAM • BOSTON • HEIDELBERG • LONDON
NEW YORK • OXFORD • PARIS • SAN DIEGO
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO
Academic Press is an imprint of Elsevier

Academic Press is an imprint of Elsevier
525 B Street, Suite 1900, San Diego, CA 92101-4495, USA
32 Jamestown Road, London NW1 7BY, UK
225 Wyman Street, Waltham, MA 02451, USA

Notice
No responsibility is assumed by the publisher for any injury and/or damage to persons, or property as a matter of products liability, negligence or otherwise, or from any use or, operation of any methods, products, instructions or ideas contained in the material herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made.

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-12-405877-4

Typeset by MPS Limited, Chennai, India
www.adi-mps.com

Printed and bound in the United States of America

14 15 16 17 10 9 8 7 6 5 4 3 2 1

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 neurodegeneris

Roberta A. Gottlieb

Preface

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 presently available treatments (chemotherapy, radiation, surgery, and hormone therapy) for major diseases such as cancer are only modestly successful. During the past 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 2 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 (Proteins, Pathogens, Immunity, and General Diseases) for the convenience of the reader. The contents of the volume are summarized below. The introductory chapter contains brief summaries of the large number of autophagic functions, including their roles in disease and health, especially with regard to both oncogenic and tumor-suppressive roles during tumor and cancer development. Autophagy protects us not only from cancer but also the development of other diseases, which are discussed here.

Atg5 and Atg7 are essential molecules for inducing autophagy. However, cells lacking these proteins can also form autophagosome/autolysosomes, and carry out autophagy-mediated protein degradation under certain stress conditions. Thus, mammalian macroautophagy (autophagy) can occur via at least two different pathways: the Atg5/Atg7-dependent conventional pathway and the Atg5/Atg7-independent pathway. Lipidation of LC3 does not occur during the latter pathway, and this pathway can compensate for the lack of Atg5-dependent autophagy in embryonic mutant mice. Molecular mechanisms underlying these two pathways are described. Some proteins (e.g., acyl coenzyme A binding protein) are secreted independently of the canonical ER–Golgi pathway. The role of autophagy and the Golgi-associated protein GRASP in the secretion of such proteins is explained.

Atg5 protein expression in T lymphocytes has been implicated in human diseases. For example, high Atg5 expression in peripheral T lymphocytes correlates with multiple sclerosis. For determining the mechanisms responsible for these diseases, the role of Atg5 protein is discussed. This gene is critical for T lymphocyte development, survival, and function. Autophagy is critical for promoting T lymphocyte survival by regulating intracellular organelle homeostasis.

A novel function of autophagy involves the differentiation of monocytes (a type of leukocyte) into macrophages (actively phagocytic cells). The stimuli that promote this

differentiation prevent apoptosis of monocytes. This differentiation is important because macrophages regulate the innate immune response in chronic inflammation. The activation of JNK during monocyte differentiation triggers cell survival by the induction of autophagy.

Lysosomes and their hydrolases (e.g., cathepsin) play a critical role in autophagy and subsequent cancer progression. Inhibition of cathepsins leads to the accumulation of autophagic vacuoles and impairment of the ability of cells to use degraded cell materials to restore homeostasis. The implication is that increased lysosomal biogenesis and proteolytic activity facilitate the promotion of invasive growth. It is known that autophagy is involved in resisting anticancer treatments (chemotherapy, radiotherapy). It is also known that cancer cells with long-term autophagy deficiency can evade the dependence on autophagy in order to survive. Although autophagy regulation is a promising addition to cancer therapy, caution is warranted in using this strategy in clinical practice. It is known that functional inactivation of UV irradiation resistance associated gene (UVRAG) is implicated in cancer. However, recent studies have indicated that this gene is also involved in monitoring endocytic membrane trafficking, maintaining chromosomal stability, and regulating apoptosis during chemotherapy and radiotherapy. Autophagy is required for the ability of UVRAG to suppress tumor progression. These and other functions of this gene are elaborated in this volume.

Primary biliary cirrhosis is an organ-specific autoimmune disease that may lead to liver failure. Autophagy, deregulated autophagy, and cellular senescence are involved in bile duct lesions in this disorder. Accumulation of LC3-positive autophagic vesicles and aggregation of p62 (a marker of deregulated autophagy) are present in damaged small bile ducts in the patients. It is known that acute alcohol consumption induces hepatic steatosis (fatty degeneration) that can evolve into steatohepatitis, which is characterized by necroinflammation and fibrosis. That acute alcohol use elevates CYP2E1, oxidative stress, and activation of JNK, which interact to reduce autophagy, resulting in fatty liver, is pointed out in this volume.

Persistent pulmonary hypertension (PPHN) of the newborn has a high mortality rate. Inadequate pulmonary artery relaxation and decreased blood vessel density in the lungs are the cause of this disorder. A cross-talk between autophagy and NADH oxidase activity in the developing lungs with PPHN plays an important role in regulating angiogenesis.

This volume presents protective and detrimental functions of autophagy in the heart. Although basal levels of autophagy are required for cardiomyocyte survival, dysregulation of autophagy is linked to a change in susceptibility to cell death. Sepsis is one of the leading causes of death worldwide, and is the most common precipitant of organ dysfunction. However, if the septic insult has passed, organs have the potential to regain function. Sepsis represents a hibernating state of the cell to protect it from apoptosis and death. Autophagy plays an essential role in protection against organ injury and prevention of cell death, enabling eventual recovery in survivors. The protective role of autophagy in liver and kidney injury is well known. Obesity (presence of excessive total body fat) contributes to susceptibility to many health disorders, including insulin resistance, hypertension, diabetes, and cardiac anomalies. The autophagy–lysosome pathway is essential for maintaining cardiomyocytes under physiological conditions as well as in metabolic syndrome. Although correlation of obesity and cardiac anomalies is controversial, it is explained here that the autophagic flux is disrupted in the murine heart under obesity. Cardiac autophagy is important in maintaining cardiac homeostasis under obesity.

Parkinson's disease is pathologically characterized by the presence of cytoplasmic inclusions such as Lewy bodies. The formation of these bodies is related to protein degradation systems (ubiquitin–proteasome and autophagy–lysosome). An alteration of these systems results in neurodegeneration and formation of these bodies. The autophagic process is impaired through alteration of the autophagosomal components in Lewy body disease.

Huntington's disorder is a fatal hereditary disease caused by an expansion of polyglutamine secretion in the huntingtin protein. The hallmark of this disease is accumulation of this mutant protein, especially of its N-terminal fragments. No effective treatment for these patients is available, despite enormous efforts. The best approach is to decrease the intracellular levels of this mutant protein without affecting the normal levels of the proteins.

Infectious diseases are a major health problem, especially in developing countries. Approximately 1400 agents of infectious diseases have been identified. An important function of autophagy is defense of the host cell against the pathogen. The host cell reacts to pathogen entry and induces autophagy. For example, CD36 is a widely expressed transmembrane protein that is recognized by several human pathogens (e.g., measles virus, streptococcus) which use this surface protein as the entry receptor. Following pathogen entry, autophagy degrades the pathogen by targeting bacteria to autophagosomes. Autophagy, similarly, can control *Mycobacterium tuberculosis* and *Listeria monocytogenes* infection. It is explained that CD46-mediated autophagy is involved in the degradation of pathogens.

Intracellular parasitic protists are known to manipulate host cell autophagy to establish or maintain infection within a host. Several different parasitic protists (e.g., *Toxoplasma*) are discussed in this volume, especially functions of autophagy proteins in these parasites. Tuberculosis is the major threat for humans, and understanding the strategies employed by *Mycobacterium tuberculosis* to evade cell defense is a challenge. Virulent bacteria unregulate interleukin-6 that interferes with IFN-γ-induced signals, resulting in the inhibition of autophagy formation. Interleukin-6 lowers the Atg 12–Atg5 complex, which leads to inhibition of autophagosome biogenesis rather than autophagolysosome formation. On the other hand, autophagy and apoptosis of the host cell combat this invading pathogen.

Helicobacter pylori is a major cause of gastric pathologies, including peptic ulcer disease and gastric cancer. Infection involves modulation of the host environment by bacterial virulence factors (vacuolating A), which facilitates the formation of an intracellular survival niche in gastric cells, increasing the disease severity. This factor triggers autophagy that can decrease levels of vacuolating A and limit bacterial survival. However, prolonged exposure to this factor disrupts autophagy by disarming the pathway of the degradative enzyme cathepsin D.

Although alveolar macrophages present defense of the lung against infection by pathogens, *Mycobacterium tuberculosis* can proliferate in these macrophages by inhibiting phagolysosome biogenesis. Host defense mechanisms use autophagy to control the proliferation of intracellular pathogens. Intracellular pathogen invasion triggers autophagy induction. For example, alveolar macrophages also present defense of the lung against infection by pathogens, including *Mycobacterium tuberculosis*. On the other hand, several types of intracellular bacteria evade the elimination induced by the autophagic process. It is explained that inhibition of Cronin-1a (an actin-binding protein) facilitates the formation of autophagosomes around bacterial phagosomes. In other words, this protein inhibits autophagosome formation to this bacterium, allowing bacterial survival in alveolar macrophages.

Autophagy is recognized as an innate mechanism that degrades intracellular pathogens into autolysosomes. However, some types of viruses can evade, subvert, or exploit the autophagy to promote their growth, establish infection, and increase their pathogenicity; hepatitis C virus is a member of this group of viruses. The status of unfolded protein response and autophagy signaling on the regulation of innate immunity and hepatitis C virus replication are discussed. Some enveloped viruses induce autophagy through membrane fusion at the entry step of their life cycle. This fusion occurs between the virus membrane of the infected cell and the membrane of the uninfected target cell, triggering the autophagy in CD4 T lymphocytes that leads to their apoptosis responsible for the development of AIDS. This mechanism of killing specially the uninfected T lymphocytes through membrane fusion is explained in this volume.

By bringing together a large number of experts (oncologists, neurosurgeons, physicians, research scientists, and pathologists) in the field of autophagy, it is my hope that substantial progress will be made against the 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 65 contributors representing 10 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 and urgent demand by the public and the scientific community to address to treatments of major diseases. In the light of existing disease calamities, 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
April 2013

Contributors

Satoko Arakawa Department of Pathological Cell Biology, Medical Research Institute, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo

Mohammad Aslam Khan Division of Cell Biology and Immunology, Institute of Microbial Technology, Chandigarh 1600036, India

Peter O. Bauer Department of Neuroscience, May Clinic, 4500 San Pablo Road, Jacksonville, Florida, USA

Riccardo Bernasconi Institute for Research in Biomedicine, Protein Folding and Quality Control, CH-6500 Bellinzona, Switzerland

Sébastien Besteiro UMR5235, Université de Montpellier 2, Place Eugene Bataillon, Batiment 24, Montpellier Cedex 5, France

Martine Biard-Piechaczyk Centre d'études d'agents Pathogénes et Biotechnologies pour la Santé, CNRS UMR5236, UM1/UM2, 1919 Route de mende, 34293 Montpellier Cedex 5, France

Ana M. Botero University of Pittsburgh, School of Medicine, NW653 MUH, 3459 Fifth Avenue, Pittsburgh, Pennsylvania 15213, USA

Arthur I. Cederbaum Department of Pharmacology and Systems Therapeutics, Mount Sinai School of Medicine, Box 1603, One Gustave L. Lewy Place, New York 10029, New York, USA

Steve S.-L. Chen Institute of Biomedical Sciences, Academia Sinica, 128, Section 2, Yen-Chiu-Yuan Road, Taipei 11529, Taiwan, Republic of China

Xi Chen Children's Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

Swati Choksi Center for Cancer Research, National Cancer Institute, Building 37, Room 1130, Bethesda, Maryland 20892, USA

Robert Clarke Department of Oncology, Breast Cancer Program, Lombardi Comprehensive Cancer Center, Georgetown University, 3970 Reservoir Road, NW, Washington DC, USA

Anna-Mart Engelbrecht Stellenbosch University – South Africa, Department of Physiological Sciences, Mike de Vries Building, 7600 Stellenbosch, South Africa

Daniel A. Escobar Department of Surgery, University of Pittsburgh, School of Medicine, NW653 MUH, 3459 Fifth Avenue, Pittsburgh, Pennsylvania 15213, USA

Lucile Espert Centre d'études d'agents Pathogénes et Biotechnologies pour la Santé, CNRS UMR5236, UM1/UM2, 1919 Route de mende, 34293 Montpellier Cedex 5, France

Hernando Gomez Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213, USA

M.A. Hayat Department of Biological Sciences, Kean University, 100 Morris Avenue, Union, New Jersey 07083, USA

Ming-Xiao He Department of Immunology, Duke University Medical Center, Durham, North Carolina 27710, USA

Shanshan He Department of Molecular Microbiology and Immunology, University of Southern California, Keck School of Medicine, Room 5514, MC NRT 9605, 1450 Biggy Street, Los Angeles, California, USA

You-Wen He Department of Immunology, Box 3010, Duke University Medical Center, Durham, North Carolina 27710, USA

Toshinobu Horii Department of Infectious Diseases, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku Hamamatsu, Japan

Fuyuhiko Inagaki Department of Structural Biology, Faculty of Advanced Life Science, Hokkaido University, Kita-ku, Sapporo 001-0021, Japan

Mohammad Ishaq Division of Cell Biology and Immunology, Institute of Microbial Technology, Chandigarh 1600036, India

Nicola L. Jones Division of GI/Hepatology/Nutrition, SickKids, 555 University Ave, Toronto, Ontario M45G 1 X8, Canada

Pierre-Emmanuel Joubert Unité Immunobiologie des Cellules Dendritiques, Paris, France

Po-Yuan Ke Institute of Biomedical Science, Academia Sinica, Taipei 11529, Taiwan, Republic of China; Department of Biochemistry and Molecular Biology, College of Medicine, Chang Gung University, Taoyuan 33371, Taiwan, Republic of China

Peter K. Kim Cell Biology Program, The Hospital for Sick Children, Department of Biochemistry, University of Toronto, 555 University Avenue, Toronto, Ontario M5G 1 X 8, Canada

Vladimir Kirkin Oncology Platform, Merck Serono, Merck KGaA, Darmstadt, Germany

Yukio Koide Department of Infectious Diseases, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku Hamamatsu, Japan

Rajesh Kumar-Dutta Division of Cell Biology and Immunology, Institute of Microbial Technology, Chandigarh 1600036, India

Kelsey B. Law Cell Biology Program, The Hospital for Sick Children, Department of Biochemistry, University of Toronto 555 University Ave, Toronto, Ontario M5G 1X8, Canada

Ben Loos Stellenbosch University – South Africa, Department of Physiological Sciences, Mike de Vries Building, 7600 Stellenbosch, South Africa

Chengyu Liang Department of Molecular Microbiology and Immunology, University of Southern California, Los Angeles, California 90033, USA

Zhenggang Liu Center for Cancer Research, National Cancer Institute, Building 37, Room 1130, Bethesda, Maryland 20892, USA

Sekhar Majumdar Division of Cell Biology and Immunology, Institute of Microbial Technology, Chandigarh 1600036, India

Ravi Manjithaya Molecular Biology and Genetics Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Jakkur, Bangalore, India

Maurizio Molinari Institute for Research in Biomedicine, Protein Folding and Quality Control, CH-6500 Bellinzona, Switzerland, Ecole Polytechnique Fédéralede Lausanne, School of Life Sciences, CH-1015 Lausanne, Switzerland

Fumiaki Mori Department of Neuropathology, Institute of Brain Science, Hirosaki University Graduate School of Medicine, 5 Zaifu-cho, Hirosaki, Japan

Yasuni Nakanuma Department of Human Pathology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan

Yuya Nishida Department of Pathological Cell Biology, Medical Research Institute, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo, Japan

Julia Noack Institute for Research in Biomedicine, Protein Folding and Quality Control, CH-6500 Bellinzona, Switzerland

Nobuo N. Noda Institute of Microbial Chemistry, 3-14-23, Kamiosaki, Shinagawa-ku Tokyo, 141-0021 Japan

Nobuyuki Nukina Laboratory for Structural Neuropathology, Riken Brain Science Institute, Waki-shi, Saitama, Japan

Jun Ren School of Pharmacy, University of Wyoming College of Health Sciences, Laramie, Wyoming, USA

Vladimir Rogov Institute of Biophysical Chemistry and Center for Biomolecular Magnetic Resonance, Goethe University, Frankfurt am Main, Germany

Motoko Sasaki Department of Human Pathology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan

Jessica L. Schwartz-Roberts Lombradi Comprehensive Cancer Center, Georgetown University, Research Building, W401, 3970 Reservoir Road, NW, Washington DC, USA

Shintaro Seto Department of Infectious Diseases, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku Hamamatsu, Japan

Gaurav Sharma Division of Cell Biology and Immunology, Institute of Microbial Technology, Chandigarh 1600036, India

Kapil Sharma Division of Cell Biology and Immunology, Institute of Microbial Technology, Chandigarh 1600036, India

Shigeomi Shimizu Department of Pathological Cell Biology, Medical Research Institute, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo

Sunaina Singh Molecular Biology and Genetics Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Jakkur, Bangalore, India

Balindiwe Sishi Stellenbosch University – South Africa, Department of Physiological Sciences, Mike de Vries Building, 7600 Stellenbosch, South Africa

Kunikazu Tanji Department of Neuropathology, Institute of Brain Science, Hirosaki University Graduate School of Medicine, 5 Zaifu-cho, Hirosaki, Japan

Ru-Jeng Teng Division of Neonatology, Department of Pediatrics, Medical College of Wisconsin, Wauwatosa, Wisconsin, USA

Kunio Tsujimura Department of Infectious Diseases, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku Hamamatsu, Japan

Koichi Wakabayashi Department of Neuropathology, Institute of Brain Science, Hirosaki University Graduate School of Medicine, 5 Zaifu-cho, Hirosaki, Japan

Ying Wan Biomedical Analysis Center, The Third Military Medical University, Chongqing, China

Ted C.H. Wu Departments of Pediatrics and Physiology, University of Toronto, Toronto Cell Biology Program, Sick Kids, Toronto, Canada

Xihui Xu School of Pharmacy, University of Wyoming College of Health Sciences, Laramie, Wyoming, USA

Hirofumi Yamaguchi Department of Pathological Cell Biology, Medical Research Institute, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo

Xiao-Ming Yin Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, Indiana

Tatsushi Yoshida Department of Pathological Cell Biology, Medical Research Institute, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo

Yan Zhang Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, USA

Brian S. Zuckerbraun Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

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
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	ubiquitin conjugating enzyme analogue
Atg4	cysteine protease
Atg5	protein containing ubiquitin folds
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 complex
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 autophagosome
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 vacuolar-type ATPase
Bafilomycin A1(BAF-A1)	an autophagy inhibitor
BAG	Bcl-2-associated athanogene
BAG3	Bcl-2-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 macroautophagy
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 complex 1
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 protein 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-coil 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
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
HR-PCD	hypersensitive response programmed cell death