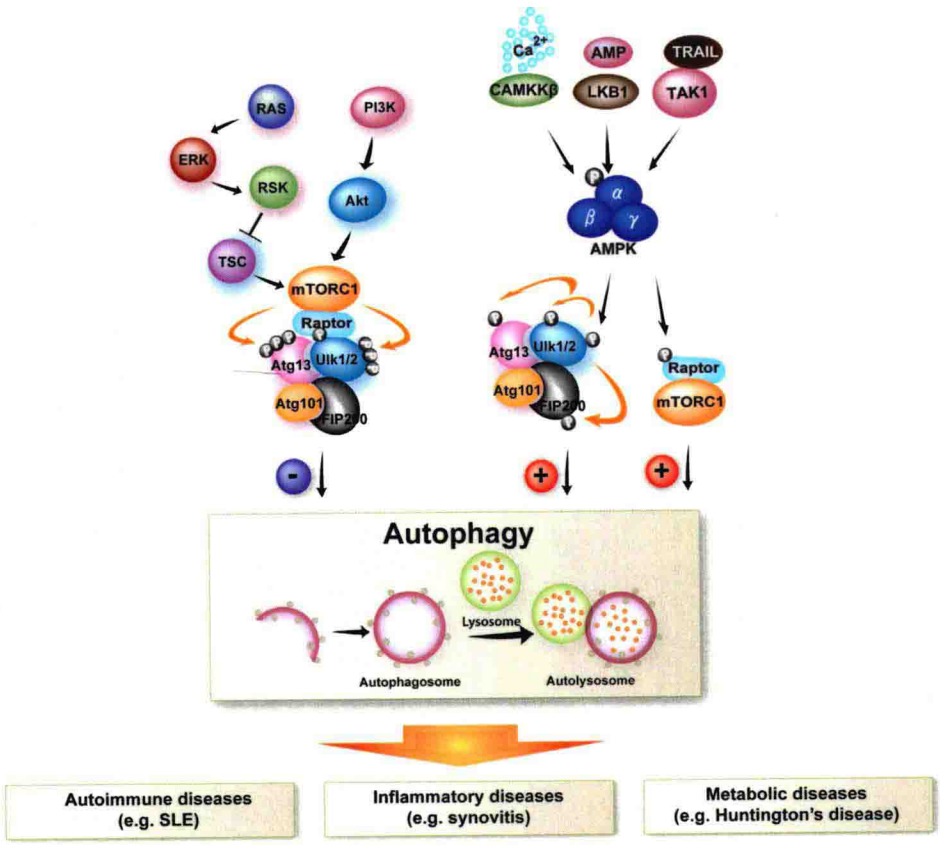
AUTOPHAGY

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

VOLUME 1

EDITED BY

M. A. HAYAT



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Edited by

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Dedication

To

Patrice Codogno, Ana Maria Cuervo, Guido R.Y. De Meyer, Vojo Deretic, Fred J. Dice, William A. Dunn Jr., Eeva-Lisa Eskelinen, Sharon Gorski, 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

The ultimate goal of research in this field 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 protein 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 1, *Autophagy: Cancer, Other Pathologies, Inflammation, Immunity, Infection, and Aging*, of a four-volume series that will discuss almost all aspects of the autophagy process. The text is divided into three subheadings (General Diseases, Cancer, and Tumors) for the convenience of readers. The Introduction to *Autophagy* 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 against the development of other diseases. The role of autophagy in cellular defense against inflammation is also included.

The role of autophagy in the suppression of tumors and in tumor survival is discussed. Induction of autophagic cell death by anticancer agents is presented. On the other hand, some anticancer drugs induce autophagy that protects cells, while autophagy inhibitors sensitize cells to chemotherapy, which then becomes more effective. The importance of autophagy, stem cells, and dormancy in health and disease is also explained. That death-associated protein kinase 1 suppresses tumor growth and metastasis via autophagy and apoptosis is included in this volume. The role of autophagy in the treatment of diabetic cardiomyopathy is explained.

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 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 specific controversial aspects 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 56 contributors representing 11 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 treatment 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
March 2013

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Autophagy and NADPH Oxidase Activity Tends to Regulate Angiogenesis in Pulmonary Artery Endothelial Cells with Pulmonary Hypertension

(incomplete)

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	ubiqitin 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
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 maturations	events occurring post-autophagosome closure followed by delivery of the cargo to lysosomes
autophagosome	double-membrane vesicle that engulfs cytoplasmic contents for delivery to the lysosome
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	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 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
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
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
Hsc70	heat shock cognate protein
Hsp	heat shock protein