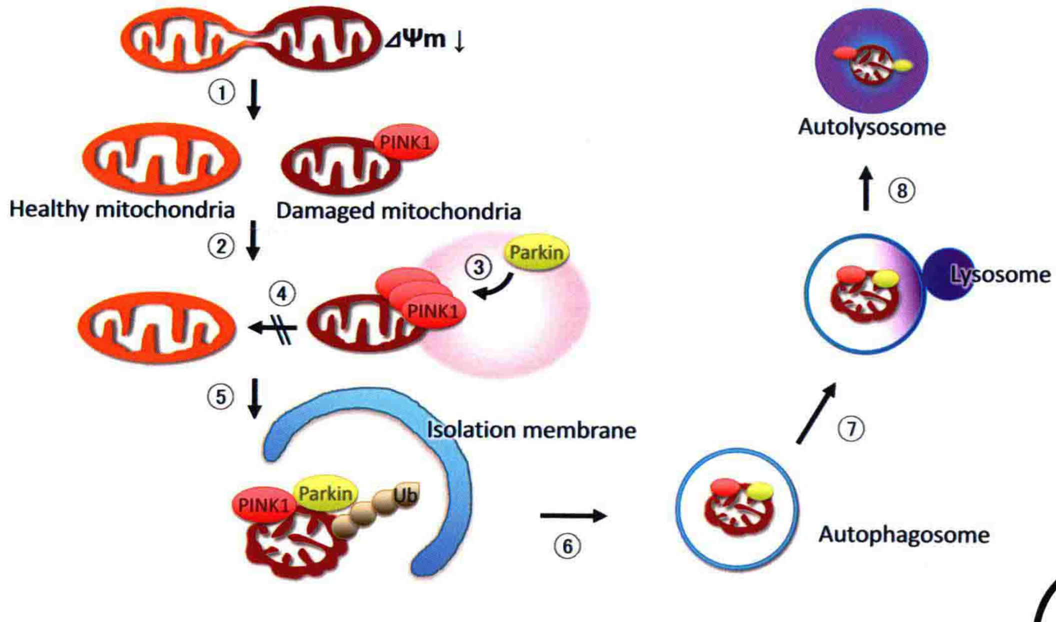
AUTOPHAGY

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

VOLUME 4

EDITED BY

M. A. HAYAT



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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.

Mitophagy and Biogenesis

mTOR and nutrient sensors control
Autophagy processes in all of our cells
Dozens of proteins must play each their role
To enable engulfment of bad organelles.

Those who are young may mistakenly think one
Is safe and immune to the dangers of aging
But if you are lacking in proper PINK1
Mitochondrial fires are already raging.

For insight and knowledge some turn to the fly;
Drosophila's *genes can help us discover*
The causes of aggregates seen in the eye,
And even find drugs to help us recover.

Ubiquitin's role in degeneration
Is to set out red flags on relevant cargo
Marking the junk that needs degradation
At a pace that is presto rather than largo.

Mitochondria fear Parkin known as PARK2
Whose ubiquitin tags on two mitofusins
Determine the fate of one or a slew,
For a lonely short life of network exclusion.

Their fate is ensured by sequestosome 1
Who recruits membranes rich with LC3-II
Autophagosome to lysosome a perfect home run
Cellular housekeeping momentarily through.

But the work isn't over and the job isn't done
Unless Paris is tagged with ubiquitin too
Then repression is lifted from PGC1
So biogenesis starts and mitos renew!

Roberta A. Gottlieb

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

Foreword

It is with great pleasure that I offer a foreword for Volume 4 (Mitophagy), of the Autophagy series edited by M.A. (Eric) Hayat. The series represents a Herculean effort on the part of Professor Hayat. He has recruited an outstanding collection of authors for this volume on mitophagy. Collectively they tell an exciting story of the importance of mitophagy in human pathophysiology.

Early in evolution, eukaryotic cells harnessed mitochondria to capture their efficient energy production from oxidative phosphorylation, but it was equally necessary to establish a mechanism for eliminating them when things went awry. Mitophagy is the elegant pathway for selective autophagic removal of dysfunctional mitochondria, and studies in yeast have and continue to shed light on this complex process. This volume presents the most current understanding of the proteins and pathways involved in mitophagy, including chapters on the selective damage sensors Nix and Bnip3, which respond to mitochondrial reactive oxygen species; PINK1/Parkin, which respond to mitochondrial depolarization; Atg32, which is regulated by phosphorylation; and FUNDC1, which eliminates mitochondria under hypoxic conditions, where they are superfluous and potentially dangerous to the cell. Nine chapters provide an in-depth treatment of the molecular mechanisms involved in mitophagy initiation and execution.

Mitochondrial ATP production is essential to meet the energy requirements of heart and brain. However, the long-lived cells that make up these organs are most vulnerable to the cumulative effects of damaged mitochondria, and as a result rely heavily on mitophagy to maintain optimal organelle function. Ineffective mitophagy manifests in disease affecting these organs before other tissues. Volume 4 includes four chapters on the role of mitophagy in Parkinson disease, cardiac aging, and skeletal muscle atrophy that clearly illustrate the importance of efficient and tightly regulated mitophagy.

Readers will appreciate this comprehensive and up-to-date collection of reviews by many of the scientists who continue to shape the field of mitophagy in human disease. I invite you to delve into this exciting volume, which will doubtless serve as a valuable and contemporary reference.

Roberta A. Gottlieb

Foreword

Intracellular protein turnover was established in the 1940s; before that time, intracellular proteins were considered stable constituents. Christian De Duve discovered lysosomes in the 1950s, and the first electron microscopic images of mitochondria inside lysosomes were published in the late 1950s. The importance of this finding was not fully understood at that time, but now we know that these early micrographs illustrated autophagosomes containing mitochondria. The crucial contribution of lysosomes to the intracellular turnover was finally recognized in the 1970s. Finally, the role of autophagy in the constant recycling of intracellular constituents and organelles was demonstrated in the 1990s, after the discovery of the genes and proteins that regulate autophagy, which has made it possible to monitor and manipulate the autophagic process and to generate knockout and transgenic animal models. This progress is well demonstrated by the fact that in one of the seminal books on intracellular protein degradation, *Lysosomes: Their Role in Protein Degradation* edited by Hans Glaumann and F. John Ballard and published by Academic Press in 1987, the word "autophagy" is mentioned in the title of only two of the twenty chapters. The first book was published in 2003 by Landes Bioscience/Eurekah.com. The first journal devoted to autophagy, also called *Autophagy*, was established in 2005. Since that time, the number of scientific papers and books on autophagy has grown exponentially; also the present book series contributes to the exponential growth. Since the slow start after the discovery of the first autophagosomes by electron microscopy in the 1950s, autophagy finally receives the attention it deserves.

For a long time, autophagy was considered to be nonselective and cytoplasmic constituents and organelles were thought to become randomly sequestered into autophagosomes for the delivery to lysosomes for degradation. Selective autophagy was first discovered in yeast cells, which have several well-known routes for the selective autophagy of different organelles and proteins. The existence of the first molecular mechanisms and the crucial roles of selective autophagy in mammalian cells were in fact an indication of selective removal of aggregate-prone proteins and damaged organelles, including mitochondria, especially in postmitotic cells such as neurons and muscle cells. This volume concentrates on mitophagy, the selective autophagy of mitochondria. Both molecular mechanisms and roles in diseases are addressed by experts in the field.

The field of autophagy still has many unanswered questions to address, and the topic is attracting an increasing number of scientists from different disciplines. This book will be welcomed by the newcomers as a concise overview of the current knowledge on mitophagy. In addition, this volume will also offer the more experienced scientists working on other aspects of autophagy an excellent way to update their knowledge on mitophagy.

Eeva-Liisa Eskelinen

Preface

This is the fourth volume of the series discussing almost all aspects of the autophagy machinery. This volume presents detailed information on the role of mitophagy in health and disease. The most important function of mitochondria is to supply a large amount of energy required for normal cellular activities. This organelle is also involved in a large number of other essential cellular functions, including thermogenesis, iron-sulfur cluster biogenesis, biosynthesis of heme and certain lipids and amino acids, autophagy, apoptosis, immune response, cell death, cellular homeostasis and metabolism, differentiation, aging, and the production of reactive oxygen species (ROS). Therefore, the maintenance of a healthy pool of mitochondria is vital for normal cellular physiology and survival. On the other hand, mitochondrial dysfunction can have severe consequences including aging and pathogenesis of neurodegenerative diseases. In this respect, Parkinson's disease, skeletal muscle atrophy, and cardiovascular disease are discussed here. Various steps involved in mitophagy are detailed, and molecular mechanisms underlying this autophagic machinery are reviewed both in yeast and metazoa. Inclusion of information on autophagy including mitophagy in yeast in this volume is relevant and important because studies of yeast have clarified the fundamental principles of autophagy, which serve as a guide for studies of autophagy in metazoans. Almost all aspects of yeast mitophagy, including proteins involved, generation of reactive oxygen species (ROS), and various mechanisms of mitochondrial quality control, are discussed in detail.

As mentioned above, maintaining a healthy and functional population of mitochondria is critically important for all eukaryotic cells. Several quality control systems exist within mitochondria, and an important link between mitochondria maintenance and macroautophagy (mitophagy) has been established. Mitophagy is one of the primary mechanisms for mitochondrial quality control and serves to selectively eliminate dysfunctional or excess mitochondria via an autophagic process that is tightly regulated. The failure to maintain adequate mitophagy leads to accumulation of dysfunctional mitochondria within cells, resulting in cellular dysfunction. Diseases associated with impaired mitophagy include neurodegenerative diseases, myopathies, obesity, and diabetes, most of which are discussed in this volume. The recent advances in our understanding of mitophagy will provide essential insights into the pathogenesis of a variety of mitochondria dysfunction-related diseases.

Several reviews presenting the current understanding of the molecular mechanisms of autophagy involved in cancer, neurodegeneration, aging, infection, and inflammation are included in this volume. At the molecular level, a large group of proteins has been identified in various model organisms which mediate the association of damaged or dysfunctional mitochondria with the autophagic machinery. Four mammalian mitochondrial proteins (tags) (Nix, PINK1, Bnip3, and FUNDC1) are discussed; also the role of Atg32 protein in yeast is explained. PINK1 (encoded by the *PARK6* gene) and Parkin (encoded by the *PARK2* gene) proteins have provided the most important insight into the mechanism of autophagy in mammalian cells.

PINK1/Parkin mutants (*Drosophila*) show severe developmental abnormalities associated with mitochondrial dysfunction. In humans, mutations of PINK1 or Parkin are responsible for most cases of early-onset Parkinson's disease. In healthy mitochondria, PINK1 is imported into mitochondrial inner membrane where it is subsequently degraded by PARL, but in mitochondria with disrupted membrane potential, it is retained on the mitochondrial outer membrane where it recruits Parkin from the cytosol. Once recruited, Parkin initiates mitophagy to eliminate dysfunctional mitochondria. The molecular events involved in PINK1/Parkin promotion of mitophagy are detailed in two chapters.

The role of transmembrane protein Atg32 in autophagy is explained in this volume. Phosphorylated Atg32 is an important mitochondrial tag located in the mitochondrial outer membrane. Phosphorylation of Atg32 is required for recruiting the scaffold protein Atg11, resulting in targeting mitochondria for degradation. Independent of Atg11 binding, Atg8 is recruited to Atg32. Atg8 is essential for autophagosome assembly. Atg11 is also required for other types of autophagies. In fact, the formation of a tripartite (Atg32/Atg11/Atg8) initiator complex is common. Casein kinase 2 is essential for the activation of Atg32.

Another example discussed in this volume is the critical role of Nix and related Bnip3 in mitochondrial autophagy. Nix is located in the mitochondrial outer membrane. The transmembrane domain, but not the BH3 domain of Nix, is essential for its activity. Nix is not required for autophagosome formation, but is essential for sequestration of mitochondria into autophagosomes. Nix plays a vital role in the maturation of the reticulocyte to erythrocyte, during which mitochondria are eliminated by mitophagy.

FUNDC1 is a less known protein located in the mitochondrial outer membrane, with structural similarity to Atg32. Hypoxia induces FUNDC1-dependent mitophagy. Mitochondrial fragmentation accompanies FUNDC1-dependent mitophagy. The role of FUNDC1-dependent mitophagy in hypoxic cancer cells is discussed here.

An interesting example of the role of mitophagy is in mammalian reproduction. Mitophagy occurs physiologically during the removal of sperm mitochondria from egg cells upon fertilization; this process is called allophagy. One possible explanation for such selective mitophagy is that paternal mitochondria are heavily damaged by ROS prior to fertilization, and need to be removed to prevent potentially deleterious effects in the next generation.

It is known that the relentless loss of dopaminergic neurons in the midbrain causes Parkinson's disease. Mitochondrial and lysosomal functions decrease with age and, therefore, both are implicated in aging and age-related disorders such as Parkinson's disease. That impaired mitochondrial function is a predominant feature of this disease is explained in this volume. Two specific processes, mitochondrial fission and mitophagy, involved in this disease are described; the former occurs as an early step during neurodegeneration.

As indicated previously, two Parkinson's disease-associated genes, *PINK1* and *Parkin*, are involved in the maintenance of healthy mitochondria. The pivotal role played by Parkin in maintaining dopaminergic neuronal survival is underscored here, and its dysfunction represents a cause of Parkinson's disease. Parkin in cooperation with PINK1 specifically recognizes damaged mitochondria, isolates them from the mitochondrial network, and eliminates them through the ubiquitin-proteasome and mitophagy pathways. It is emphasized that PINK1 and Parkin protein identify and segregate damaged mitochondria for degradation by mitophagy via ubiquitination of several mitochondrial proteins including mitofusins. Mutations of *PARK2* gene (encoding the ubiquitin ligase Parkin) cause not only familial parkinsonism but also a sporadic form of this disease. As stated before, Parkin is a key regulator of mitochondrial quality control. However, presently the model of Parkin-mediated mitophagy is being debated, which is updated in this volume. The understanding of the molecular mechanisms of PINK1 and Parkin-mediated mitochondrial regulation is also reviewed here.

Intrinsic aging of the cardiovascular system, in addition to chronic exposure to cardiovascular risk factors, is inevitable. This results in the development of cardiovascular disease later in life. It is pointed out that the impairment in mitochondrial function arising from failure of mitochondrial quality control is a major contributing factor to heart senescence. It is also pointed out that damaged mitochondria produce increased amounts of ROS, resulting in oxidative damage to cardiomyocyte components.

Loss of muscle mass and function results mostly from accelerated protein degradation by the ubiquitin-proteasome system and autophagy-lysosome systems. The signaling mechanism underlying the increased protein degradation during muscle atrophy from a genetic perspective is explained here. The importance of mitophagy during skeletal muscle atrophy is pointed out.

The text is divided into three subheadings (General Applications, Molecular Mechanisms, and Role in Disease) 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 mitophagy, it is my hope that substantial progress will be made against terrible diseases afflicting humans. It is difficult for a single author to discuss effectively and comprehensively various aspects of an exceedingly complex process such as mitophagy. Another advantage of involving more than one author is to present different points of view on various controversial aspects of the role of mitophagy in health and disease. I hope these goals will be fulfilled in this and future volumes of this series.

This volume was written by 39 contributors representing 9 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 mitophagy machinery provided by these contributors.

It is my hope that subsequent volumes of this 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 develop better treatments for major diseases. In the light of the human impact of these untreated diseases, government funding must give priority to researching cures over global military superiority.

I am grateful to Dr. Dawood Farahi, Phillip Connelly, and Dr. Veysel Yucetepe for recognizing the importance of medical research and publishing through an institution of higher education. I am thankful to my students for their contributions to the final preparation of this volume.

M. A. Hayat
February 2014

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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	a.k.a. 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

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 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

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 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