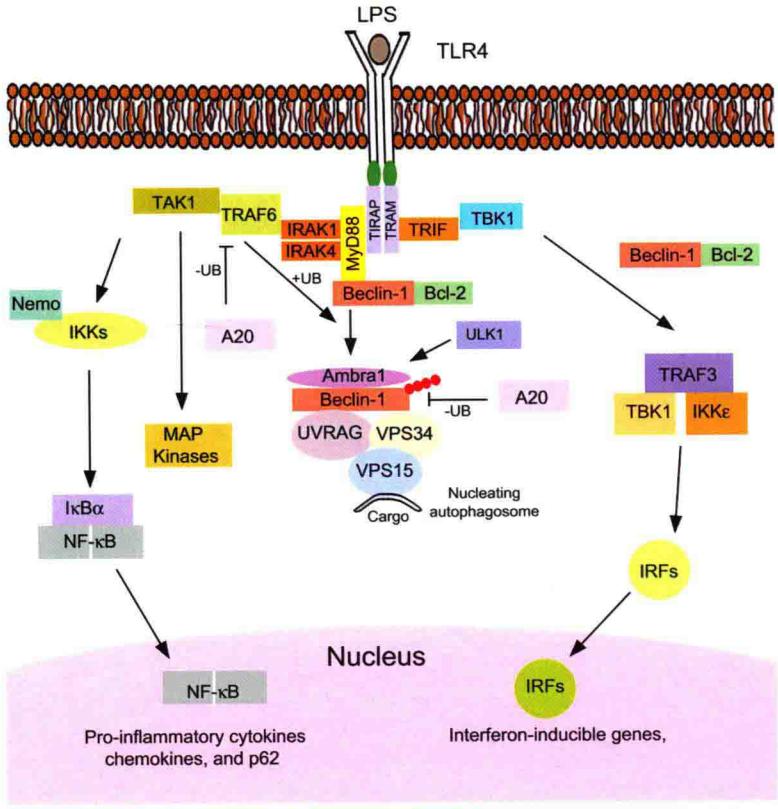
AUTOPHAGY

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

VOLUME 6

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

Autophagy and Cancer

When speaking of cancer, autophagy's good
By culling mitochondria and clearing deadwood
Autophagy limits the radical chain
That breaks DNA and mutates a gene
That makes a cell double, so careless and mean
In order for cells to malignant transform
They lose mitochondria except for a few
Using glycolysis as the source of their fuel
How they achieve mitochondrial decimation
Is nothing more than autophagic elimination

Then one cell is many, an ominous mass
Demanding more glucose, hungry and crass,
Directing formation of artery and vein
'Til capsular fibers give way under strain
Then cancer cells spread so far and so wide
They demand blood vessels the body provide
But until those are patent the tumor cells strive
To rely on autophagy to neatly survive
The hurdles required for metastasis
Until blood flow's established for cancerous bliss.

Blocking autophagy sends them over the brink
And how chloroquine works, we think
But tumors are slowed by statin's effects
Which induce autophagy and tumor cell death
Autophagy's good, autophagy's bad
The confusion's enough to drive us all mad
So study we must, and learn ever more
'Til enlightenment finally opens the door
Oncologists must heed the tumor's agenda
And decide whether autophagy is a friend or foe.

Roberta A. Gottlieb

Foreword

It is with great pleasure that I introduce Volume 6 of the impressive seven-volume series on autophagy edited by M.A. (Eric) Hayat. This volume addresses a number of mechanistic advances in our understanding of the regulation of autophagy, particularly the importance of nutrient availability. Regulatory mechanisms through microRNAs and cross-talk with other protein degradation pathways are presented. Several chapters cover the expanding role of autophagy in host immunity and the ways in which various intracellular pathogens repurpose the pathway for their own benefit. Finally, this volume addresses selective autophagy for degradation of mitochondria and endocytosed gap junctions.

The importance of autophagy in host defense represents an exciting emerging field. Autophagy facilitates antigen presentation, participates in thymic development, and shares many regulatory nodes with innate immunity, including cross-talk with Toll-like receptors, reflecting its important role in regulating the immune response. Autophagy is also a participant in the dynamic struggle between intracellular pathogens and the host. While cells often use autophagy to eliminate intracellular pathogens and to activate innate and adaptive immunity, bacterial and viral pathogens have evolved defensive mechanisms, enabling them to subvert autophagy for their own purposes. As mitochondria can be viewed as domesticated intracellular bacteria, it is not surprising that autophagy plays a significant role in their removal.

The state of current knowledge on these important topics is summarized in the chapters of Volume 6, with contributions from experts from around the world. Researchers in immunology and infectious disease will find this volume to be particularly valuable, as well as those interested in selective autophagy and its regulation.

Roberta A. Gottlieb M.D.
Cedars-Sinai Heart Institute

Preface

It is becoming clear that cancer is an exceedingly complex molecular network, consisting of tumor cells at different stages of differentiation and noncancerous cells from the tumor microenvironment, both of which play a role in sustaining cancer progression. The latter cells maintain a proinflammatory environment conducive to cancer progression through induction of angiogenesis and evasion of the innate immune system. Although induction of cancer cell death by apoptosis, autophagy and necroptosis has been the main system exploited as anticancer strategies, an understanding of the role of the alterations in cellular metabolism is necessary for the development of new, more effective anticancer therapies. For example, it is known that cancer cells switch towards aerobic glycolysis from mitochondrial oxidative phosphorylation.

Autophagy, on the other hand, also possesses mechanisms that can promote cancer cell survival and growth of established tumors. Regarding cell survival, tumor cells themselves activate autophagy in response to cellular stress and/or increased metabolic demands related to rapid cell proliferation. Autophagy-related stress tolerance can enable cell survival by maintaining energy production that can lead to tumor growth and therapeutic resistance. Tumors are often subjected to metabolic stress due to insufficient vascularization. Under these circumstances, autophagy is induced and localized to these hypoxic regions where it supports survival of tumors. Aggressive tumors have increased metabolic demands because of their rapid proliferation and growth. Thus, such tumors show augmented dependency on autophagy for their survival.

Defective autophagy causes abnormal mitochondria accumulation and reduced mitochondrial function in starvation, which is associated with reduced energy output. Because mitochondrial function is required for survival during starvation, autophagy supports cell survival. The recycling of intracellular constituents as a result of their degradation serves as an alternative energy source for tumor survival, especially during periods of metabolic stress. In this context, in tumor cells with defective apoptosis, autophagy allows prolonged survival of tumor cells. However, paradoxically, as mentioned above, autophagy is also associated with antitumorigenesis. Autophagy induced by cancer therapy can also be utilized by cancer cells to obtain nutrients for their growth and proliferation. Therefore, such treatments are counterproductive to therapeutic efficacy.

This is the sixth volume of the seven-volume series, *Autophagy: Cancer, Other Pathologies, Inflammation, Immunity, Infection and Aging*. This series discusses in detail almost all aspects of the autophagy machinery in the context of cancer and certain other pathologies. Emphasis is placed on maintaining homeostasis during starvation or stress conditions by balancing the synthesis of cellular components and their degradation by autophagy.

Both autophagy and ubiquitin-proteasome systems degrade damaged and superfluous proteins. Degradation of intracellular

components through these catabolic pathways results in the liberation of basic building blocks required to maintain cellular energy and homeostasis. However, less than or more than optimal protein degradation can result in human pathologies. An attempt is made in this volume to include information on the extent to which various protein degradation pathways interact, collaborate or antagonize one another.

It is known that conditions resulting in cellular stress (e.g., hypoxia, starvation, pathogen entry) activate autophagy, but dysregulation of autophagy at this stage might result in pathological states including cancer. MicroRNAs are non-protein-coding small RNAs that control levels of transcripts and proteins through post-transcriptional mechanisms. Current knowledge of microRNA regulation of autophagy is presented in this volume.

Autophagy (macroautophagy) is strictly regulated and the second messenger Ca^{+2} regulates starvation-induced autophagy. Withdrawal of essential amino acids increases intracellular Ca^{+2}, leading to the activation of adenosine monophosphate-activated protein kinase and the inhibition of the mTORC1, which eventually results in the enhanced formation of autophagosomes. The importance of this signaling pathway and other pathways (AMPK, AKT) within the autophagy signaling network is emphasized in this volume.

Recent discoveries of autophagic receptors that recognize specific cellular cargo have opened a new chapter in the autophagy field. Receptors are indispensable for the initiation and finalization of specific cargo removal by autophagy. For example, BNIP3L/NIX mediates mitochondrial clearance, which is discussed in this volume. It is pointed out that, in the absence of such clearance, accumulation of ROS can severely damage the mitochondrial population within the neuron and ultimately cause apoptosis of the affected neurons. Mitochondrial dysfunction is implicated in Parkinson's disease. Toll-like receptors (TLRs) play critical roles in host defense by recognizing specific molecular patterns from a wide variety of pathogens. In macrophages, TLR signaling induces autophagy, limiting the replication of intracellular pathogens. How TLRs activate autophagosome formation in macrophages and enhance immunity is discussed in this volume.

Autophagy plays an important role during viral and bacterial infection. Autophagy can act either as a part of the immune defense system or as a pro-viral or pro-bacterial mechanism. In other words, although autophagy suppresses the replication of some viruses, it enhances the replication of others. Several examples of the latter viruses are discussed in this volume. For example, *Herpes viridae* family members encode autophagy-regulating proteins, which contribute to the host antiviral defenses, either by enhancing innate immunity or by helping antigen presentation. Herpes viruses have also evolved proteins that are able to inhibit this cellular mechanism. Positive or negative impact of autophagy on viral infection is explained in this volume.

Another example of the role of a virus in inducing autophagy is varicella-zoster virus (VZV); this human herpes virus causes chickenpox. Infected cells show a large number of autophagosomes and an enlarged endoplasmic reticulum (ER) indicating its stress, which is a precursor to autophagy through the inositol requiring enzyme-1 pathway and PERK pathway. Hepatocellular β virus (HBV) also activates the autophagic pathway while avoiding lysosomal, protein degradation.

As in the case of VZV, ER stress also plays a positive role in HBV replication.

The possible effect of autophagy on HBV-induced hepatocarcinogenesis is also included in this volume. *Staphylococcus aureus* pathogen not only induces an autophagic response in the host cell (localizing in LC3 decorated components), but also benefits from that state.

Although inflammatory responses are essential for eradicating intracellular pathogens and tissue repair, they can be detrimental to the host when uncontrolled. Therefore, inflammation needs to be tightly controlled to prevent excessive inflammation and collateral damage. Cytokine IL-1β (produced by microglia in the CNS) is one of the pro-inflammatory mediators. The pivotal role of autophagy in regulating the production and secretion of the IL-1 family members is explained in this volume. Atg6L1, an essential component of autophagy, suppresses pro-inflammatory signaling. Better understanding of the role of the autophagy-lysosomal pathway in the maturation and secretion of IL-1 should provide a new strategy for targeting inflammation in various pathological conditions.

Excess adiposity contributes to the development of obesity-associated metabolic disturbances such as insulin resistance, type 2 diabetes, or metabolic syndrome. It is pointed out that imbalance between ghrelin (a gut-derived hormone) and tumor necrosis factor in states of insulin resistance may contribute to altered apoptosis and autophagy found in the adipose tissue of patients with type 2 diabetes.

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 that inflict 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 various controversial aspects of the role of autophagy in health and disease. I hope these goals will be fulfilled in this and future volumes of this series.

This volume was written by 46 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 role of autophagy in disease 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 and Phillip Connelly 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
July 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	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 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 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 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 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