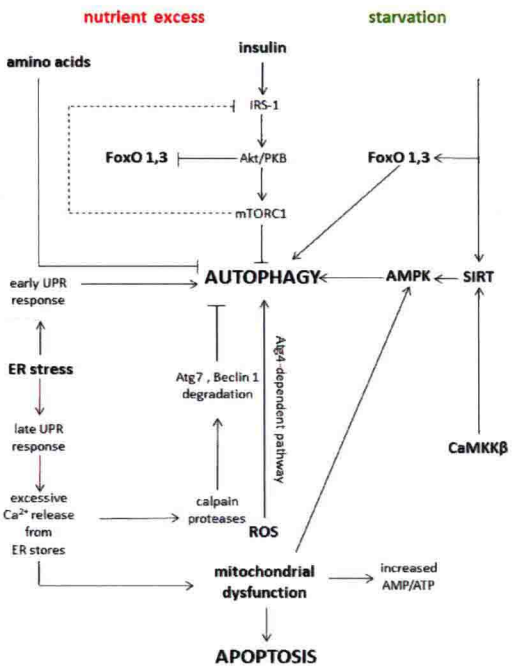
AUTOPHAGY

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

VOLUME 5

EDITED BY

M. A. HAYAT



MAIN MECHANISMS INVOLVED IN THE REGULATION OF AUTOPHAGY

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

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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-Liisa 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 foe or a friend-a.

Roberta A. Gottlieb

Foreword

I have the pleasure of introducing Volume 5 of the impressive seven-volume series on autophagy edited by M.A. (Eric) Hayat. This volume examines the role of autophagy in some of the most important human diseases, and represents the state of knowledge of leading experts in their fields. The excitement over the importance of autophagy in human disease is well-justified, and the reader is encouraged to peruse the chapters of this volume to gain a deeper understanding of its myriad roles.

The leading causes of death are heart disease and cancer, and both are exacerbated by the comorbid constellation of obesity, insulin resistance, and type 2 diabetes. Autophagy plays a critical role in cellular homeostasis to prevent tumorigenesis, ameliorate ischemic injury, and delay neurodegeneration. As autophagy is suppressed in the setting of obesity and diabetes, it is not surprising, then, that the epidemic of obesity is paralleled by a rise in cancer and age-related diseases of the heart and brain. This volume assembles a comprehensive discussion of the importance of autophagy in these disorders.

Detailed molecular studies of cancer reveal that at the stage of tumor initiation, autophagy plays a preventive role by eliminating damaged mitochondria that generate excessive free radicals responsible for DNA damage. A cell that acquires a DNA mutation that unleashes proliferation will undergo clonal expansion. The rapidly growing population of cells will accumulate additional DNA mutations which may confer metastatic potential and drug resistance. A key event is the transition from mitochondrial oxidative phosphorylation to glycolysis, a process that may be assisted by autophagy. Autophagy can also enable tumor cells to survive nutrient-limited conditions, e.g., at the hypoxic core of a solid tumor or in primary or metastatic tumors before angiogenesis is established to deliver nutrients to the expanding mass of cells. Autophagy enables tumor cells to survive treatments directed at eliminating the blood supply (anti-angiogenic therapies). However, induction of autophagy in other tumor cell types can trigger cell death. Thus, manipulation of autophagy in cancer cells may represent a novel avenue for therapy.

Impaired autophagy leads to accumulation of damaged mitochondria with reduced energy output and excessive free radical production. Autophagy of mitochondria has been shown to be important for cellular homeostasis in a variety of settings, including insulin secretion by pancreatic beta cells, cardiac function, atherosclerosis, and organ tolerance to ischemic stress. Autophagic elimination of intracellular aggregates is also essential for prevention of neurodegenerative diseases. This homeostatic process is particularly important for tissues comprised of long-lived cells such as the heart and brain.

This volume will be of interest to researchers interested in the disease implications of autophagy and to clinicians dealing with these conditions who find they need to understand autophagy in order to tailor their therapies.

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, called *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; 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 first molecular mechanisms and 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.

The field of autophagy still has many unanswered questions to address, and the topic is attracting an increasing number of scientists from different disciplines.

Eeva-Liisa Eskelinen

Preface

Presently, global cancer cases have reached 14 million annually, a marked rise from 12.7 million in 2008. The number of deaths due to cancer in the same period has also increased from 7.6 million to 8.2 million. It is predicted that the annual number of cancer cases may rise to more than 19 million by the year 2025. The rising burden of cancer is mainly due to a shift in lifestyles in the developing countries to those of the populations in the industrialized countries. This increase is related to a rise in smoking (lung cancer), obesity, living longer, lack of exercise, and increased stress. Smoking causes 1.8 million deaths annually, accounting for approximately 13% of total cancer deaths. Breast cancer deaths are now the most common cancer deaths in women, both in the less developed countries and in the industrialized countries. Apparently, an increase in breast cancer deaths in the former countries is partly due to limited availability of clinical advances in cancer diagnosis and treatment. For many years the impairment of proliferation and viability of the most differentiated cancer cells has been extensively studied, but this approach has been less successful in the understanding and prevention of cancer relapse.

The failure of even cancer-targeted drugs can be explained by assuming that a single tumor can be composed of many different types of cancer cells, necessitating the determination of the diversity within a tumor and the need of different treatments. In other words, a cancerous tumor is not homogeneous. It is possible that cancerous cells continue to mutate, become more aggressive, move around, and resist therapeutic drugs. The implication is that a cancer patient may have multiple subtypes of a cancer. The initial mutation is common to all cancer cells in a tumor, but subsequently cancer diversifies. Consequently, a single drug is unable to kill all the mutated cells. The drug might slow the disease, but it will not stop it.

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 an anticancer strategy, 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 can 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 anti-tumorigenesis. 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 fifth 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.

This volume presents specifically the antitumor and protumor roles of autophagy, as well as the therapeutic inhibition of autophagy in cancer. The role of autophagy in the cellular homeostatic response to gene mutations, the link between autophagy and ErbB receptor tyrosine kinases, and the role of ErbB-directed cancer therapies are discussed. A discussion of the pro-oncogenic changes that render cancer cells more susceptible to lysosomal-associated death pathways is presented and followed by a thoughtful exposition of the complex interplay between autophagy and apoptosis as the determinant of cell fate under normal physiologic and pathologic conditions. In tumor cells with defective apoptosis, autophagy allows prolonged survival of tumor cells. However, paradoxically, autophagy is also associated with anti-tumorigenesis. Autophagy induced by cancer therapy can also benefit certain types of cancer cells to obtain nutrients for their growth and proliferation. Therefore, it is important to understand the specific role of autophagy in a given tumor in order to select the most appropriate therapy.

This volume presents the duality of autophagy's effects in various cardiovascular, metabolic, and neurodegenerative disorders. The role of autophagy in insulin resistance and type 2 diabetes and its participation in atherosclerosis are discussed. The role of autophagy in atrial fibrillation is explained. The importance of autophagy in mitigating ischemic injury during organ transplantation is elucidated for islet transplantation and renal transplantation. Two final chapters elaborate the role of autophagy in the neurodegenerative processes in Alzheimer's disease and Parkinson's disease.

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 the 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 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 48 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 tremendously urgent demand by the public for 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
April, 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