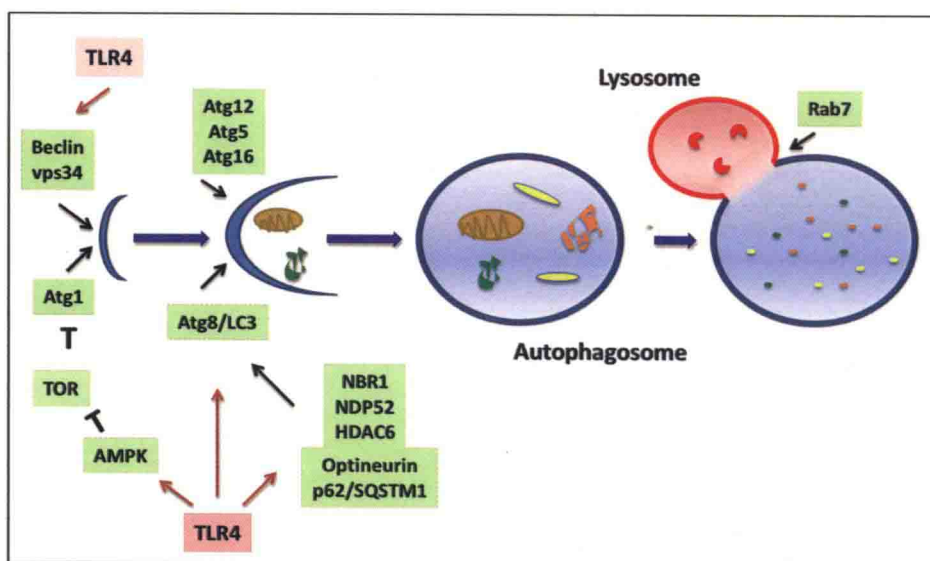


# AUTOPHAGY

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

VOLUME 12

EDITED BY  
M. A. HAYAT



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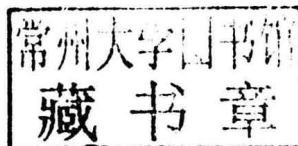
*Edited by*

M. A. HAYAT

*Distinguished Professor,*

*Kean University,*

*Union, NJ, United States*



ACADEMIC PRESS

An imprint of Elsevier

Academic Press is an imprint of Elsevier  
125 London Wall, London EC2Y 5AS, United Kingdom  
525 B Street, Suite 1800, San Diego, CA 92101-4495, United States  
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States  
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

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### 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: 978-0-12-812146-7

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*Publisher:* Sara Tenney  
*Acquisition Editor:* Linda Versteeg-Buschman  
*Editorial Project Manager:* Kathy Padilla  
*Production Project Manager:* Julia Haynes  
*Cover Designer:* Greg Harris

Typeset by MPS Limited, Chennai, India

# AUTOPHAGY

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# Dedication

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To:

Julio A. Aguirre-Ghiso, Patrice Codogno, Eduardo Couve, Ana M. Cuervo,  
Guido R.Y. De Meyer, Vojo Deretic, Fred J. Dice, William A. Dunn Jr., Nicolas Dupont,  
Eeva-Lisa Eskelinen, Sharon Gorski, Roberta A. Gottlieb, Tanya M. Harding, Xuejun Jiang,  
Tomotake Kanki, Vladimir Kirkin, Daniel J. Klionsky, Massaki Komatsu, Guido Kroemer,  
Beth Levine, Noboru Mizushima, Nobuo N. Noda, Yoshinori Ohsumi, Brinda Ravikumar,  
Fulvio Reggiori, David Rubinsztein, Isei Tanida, Michael Thumm, Sharon A. Tooze,  
Miki Tsukada, Herbert W. Virgin, Eileen White, Tamotsu Yoshimori, Claudine Kraft, 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.

# Dedication

---

In gratitude to:

Philip Connelly

# Knowing Autophagy

---

There is debate and stress  
About what is the best  
Autophagy test.  
You can delve inside  
This or Klionsky's Guide  
To help you decide.  
This volume is thick  
But the reading is quick  
So you'll know every trick.

Cells that are stressed  
Will do their best  
To clean up the mess.  
Many cell types agree  
That the best strategy  
Is macroautophagy.  
It doesn't always suffice  
And in cancer-prone mice  
One had better think twice.  
Before you're aware  
Of a need for DNA repair  
Praise be, autophagy's there.

*Roberta A. Gottlieb*

# 10 Lines of Autophagy for Volume 10

---

Autophagy is needed before you're born  
To ensure successful embryogenesis

And at every turn along the way  
Autophagy's there to prevent apoptosis.

A two-edged sword is autophagy's role  
In cancer survival and chemoresistance

Yet tumor suppression also depends upon  
Autophagy's help to lower cell malignance.

Clear thinking is needed to know when and how  
To invoke autophagy for lifelong gain

Autophagy prevents mental deterioration,  
By slowing degeneration in the aging brain.

Eating too much is a global problem  
Autophagy's suppressed and we store debris

Autophagy helps to clear the fat  
From brain and heart and coronary artery.

So let us fast and pay homage  
To a transient organelle, the autophagosome

Whose greatness is revealed in chapter and verse  
Of Volume 10, this noble tome!

*Roberta A. Gottlieb*



# 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 foe or a friend?

*Roberta A. Gottlieb*

# Some Thoughts on Autophagy and Immunity

---

A bacterium squirmed into a cell  
Thinking "This home will serve me well"  
The cell objected quite forcefully  
Encasing the bug in LC3  
Saying "I'm not your home,  
You're imprisoned in my autophagosome!"  
The bug merely shrugged and secreted a factor  
Poking holes in the shell, releasing the actor  
Who by now had multiplied so many times  
They were all ready to commit more devious crimes.

Autophagy's a way to lock those critters away  
But bugs evolve too, and have learned what to do  
To turn host defense to their convenience.  
So mark my words and mark them well  
If you want to be a clever cell  
Turn autophagy up to kill pathogen C, D, or E  
But keep it turned down for bugs A, B, and D.  
How to do that?  
Eating no meat and eating no fat  
Will turn up the autophagy thermostat.  
But sugar and fat and protein too  
Will slow it down as good as glue.  
Remember a rich diet keeps autophagy quiet  
Skip brunch and sup to turn autophagy up.

Trouble comes as the number one,  
If it's interleukin-1....Beta, that is.  
Relief comes as the number three  
LC3....B, that is.  
Letters and numbers, numbers and letters  
Stop getting dumber and learn from your betters.  
Autophagy works to prevent calamity  
By turning down inflammitty.

Autophagy's a way to share information  
From macrophages by antigen presentation  
To lymphocytes of each denomination  
When properly goaded, MHC-II's are loaded  
With tasty bites of foreign peptides.  
Endosome to lysosome  
Bits of the stranger are made known  
To help program immunity,  
Thanks be to you, autophagy!

*Roberta A. Gottlieb*

# Autophagy: Friend or Foe?

---

Be careful when hugging Atg5  
It can help you get dead or be live.  
When Atg12's covalently bound  
Autophagy's up and death can't be found.  
But if protease scissors free the BH3  
Fragment of Atg5, soon you will see  
Death and destruction, known as  
Programmed cell death or apoptosis.

Beclin 1 is capricious too,  
Hitching itself to Bcl-2.  
In this way it deflects  
Bcl-2's survival effects.  
But helped by VPS34  
It forms a phagophore:  
Autophagy goes well  
And rescues the cell.

*Roberta A. Gottlieb*

# Autophagy: If and When

---

Like a foreign body embedded in scar  
Membrane shrouds the mitochondrion  
Lest it activate the inflammasome  
And trigger release of IL-1.

Of course we need an antidote  
To avoid the damage from mitos gone bad  
Enter the savior—mitophagy,  
Rescuing the cell like Sir Galahad.

Another case where autophagy's good  
Is in the aging, sludgy brain  
Where it serves to clear proteinaceous crud:  
Autophagy to the rescue, once again.

The bleakest core of a malignant mass  
Like a hypoxic inner circle of Hell  
Is where autophagy plays a darker role  
To aid in the survival of cancer cells.

Do we want to trigger autophagy?  
We need to know how, where, and when.  
Read this book of cellular wizardry  
And then you'll know: It all depends!

*Roberta A. Gottlieb*

# What Happened When Autophagy Didn't

---

A mito decayed and leaked DNA  
Plus cytochrome *c* and 8-oxo-dG  
The inflammasome blew  
And the apoptosome too  
And the cell had a very bad day.

*Roberta A. Gottlieb*



# Sugar Isn't Always Sweet

---

When your heart is worn and skips a beat  
Membranes keep it in or out  
And insulin gives a special route

Glut transporters form a pore  
Bringing sugar in the open door  
Too much is bad-too little, too:  
Cells need the proper fuel.

Inside the cell sugar's stored  
Glycogen the sweetest hoard.  
Two enzymes live to break it down:  
A neutral enzyme can be found

In cytosol where granules roam,  
But in the acidic lysosome  
Another waits on bended knee  
To play its role in glycophagy.

Excess carbs are bad: this much is clear.  
So consider maltose when quaffing beer!

*Roberta A. Gottlieb*