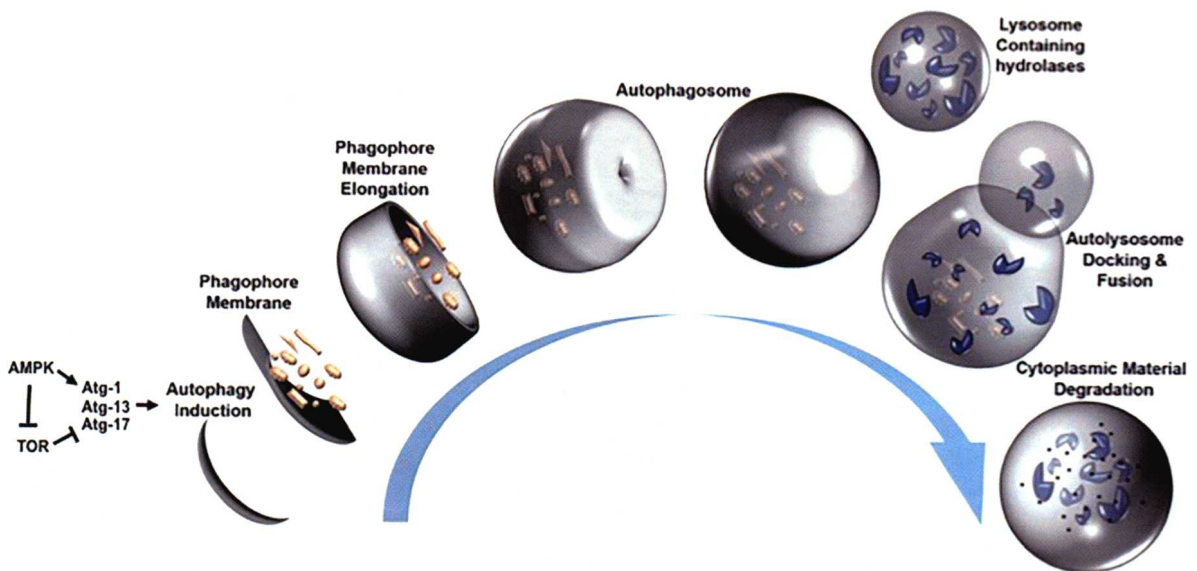


AUTOPHAGY

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

VOLUME 11

EDITED BY
M. A. HAYAT



Schematic representation of classical autophagy process, showing AMPK and TOR kinases targeting a serine-threonine kinase complex containing Atg1, Atg13, and Atg17, and regulating autophagy induction from beginning (production of isolation membrane, phagophore) to end (degradation of cytosolic components, autophagosome fusion with lysosome).



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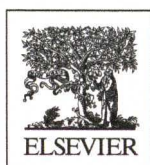
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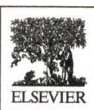
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AUTOPHAGY

Dedication

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,
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Miki Tsukada, 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.

Dedication

In gratitude to:

Philip Connelly and Kimberly Fraone
for their generosity and help

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 inflammation.

Autophagy's a way to share information
From macrophages by antigen presentation
To lymphocytes of each denomination
When properly goaded, MHC-IIs 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