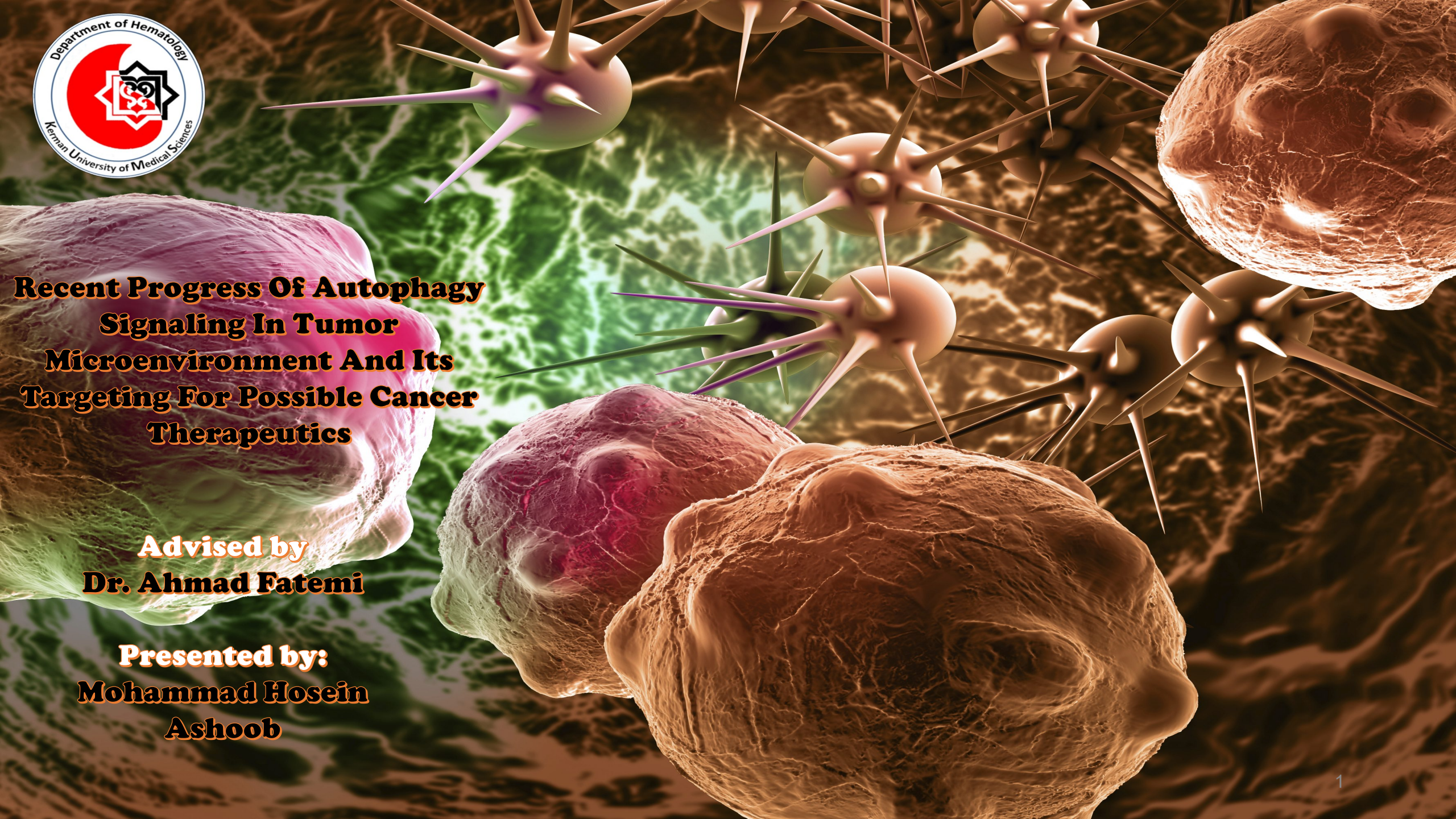

Recent Progress Of Autophagy Signaling In Tumor Microenvironment And Its Targeting For Possible Cancer Therapeutics

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Seminars in Cancer Biology

Supports *open access*

18.1
CiteScore

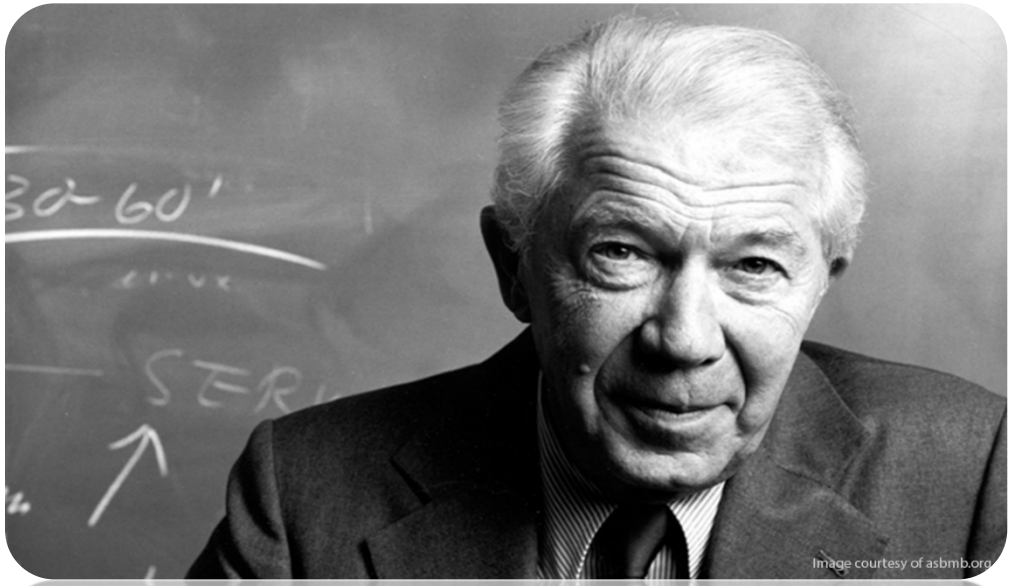
15.707
Impact Factor

About the journal

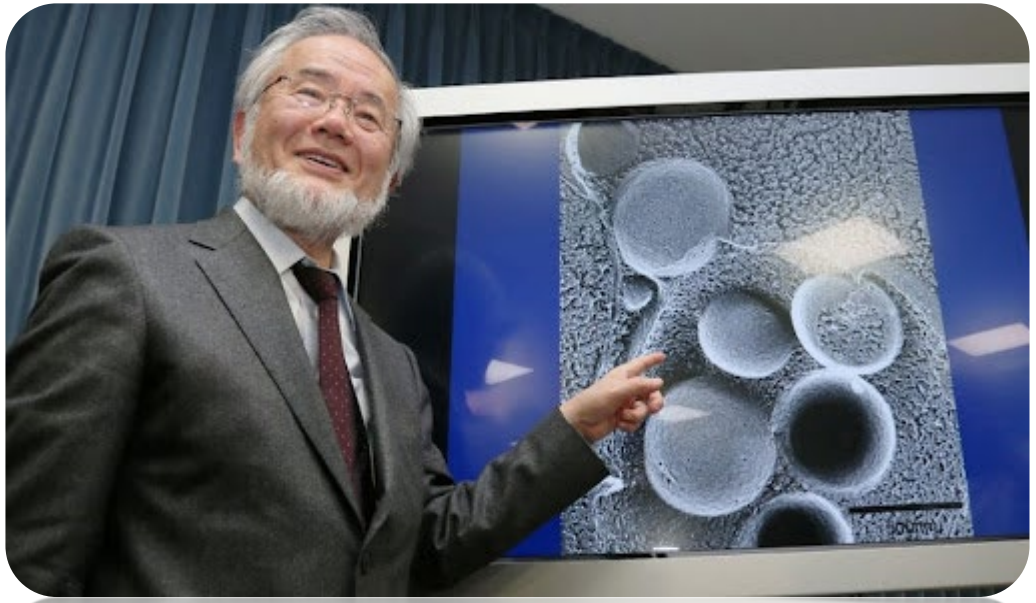
Aims and scope | Editorial board | Abstracting and indexing

Seminars in Cancer Biology is a review journal dedicated to keeping scientists informed of developments in the field of **molecular oncology** on a topic by topic basis. Each issue is thematic in approach, devoted to an important topic of interest to **cancer biologists**, from the underlying genetic and molecular causes of **cellular transformation** and cancer to the molecular basis of potential **therapies**. Every issue is edited by a guest editor or editors, an internationally acknowledged expert(s) in the field, and contains approximately eight to twelve authoritative invited reviews on different aspects of the subject area. The aim of each issue is to provide a coordinated, readable, and lively review of a selected area, published rapidly to ensure currency.

Background and History

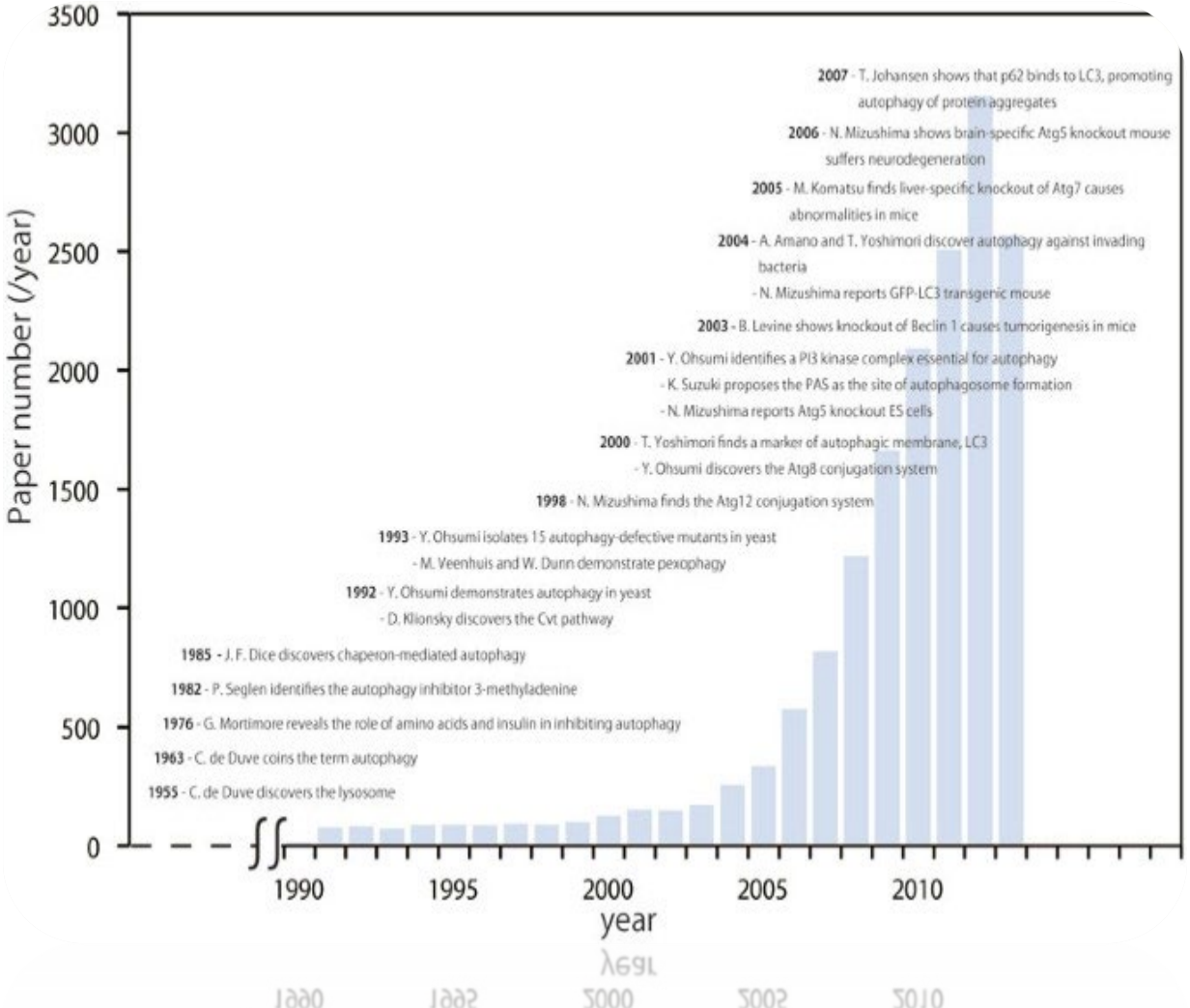


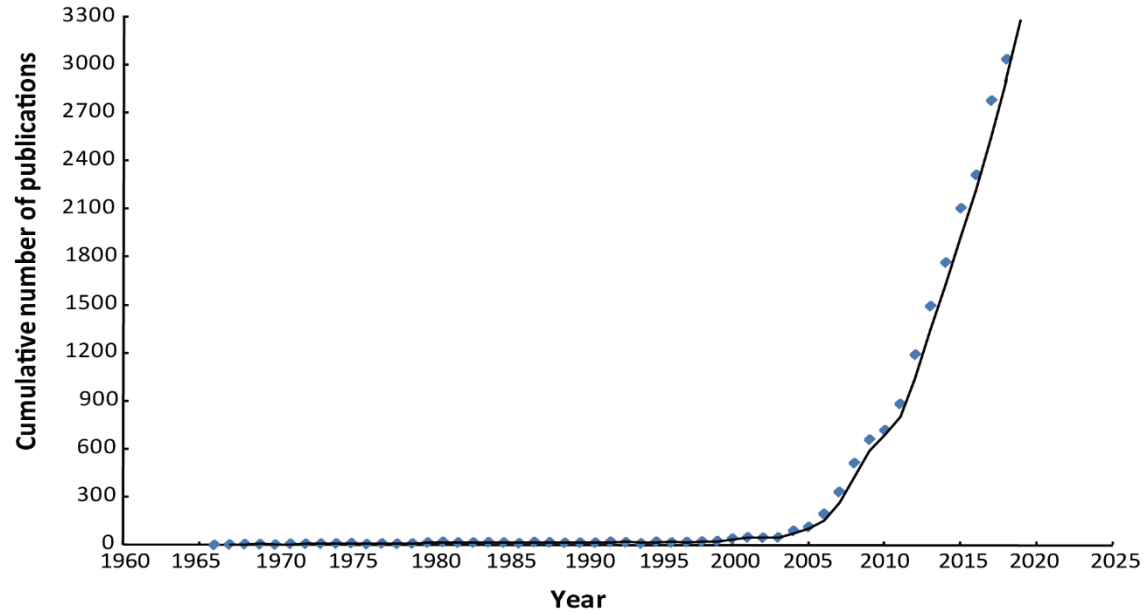
The term "autophagy" was first coined by Nobel Laureate Christian de Duve in 1963



In 2016, Yoshinori Ohsumi was awarded the Nobel prize in physiology for his contributions to explain the basis of the genetic mechanism of autophagy

Background and History





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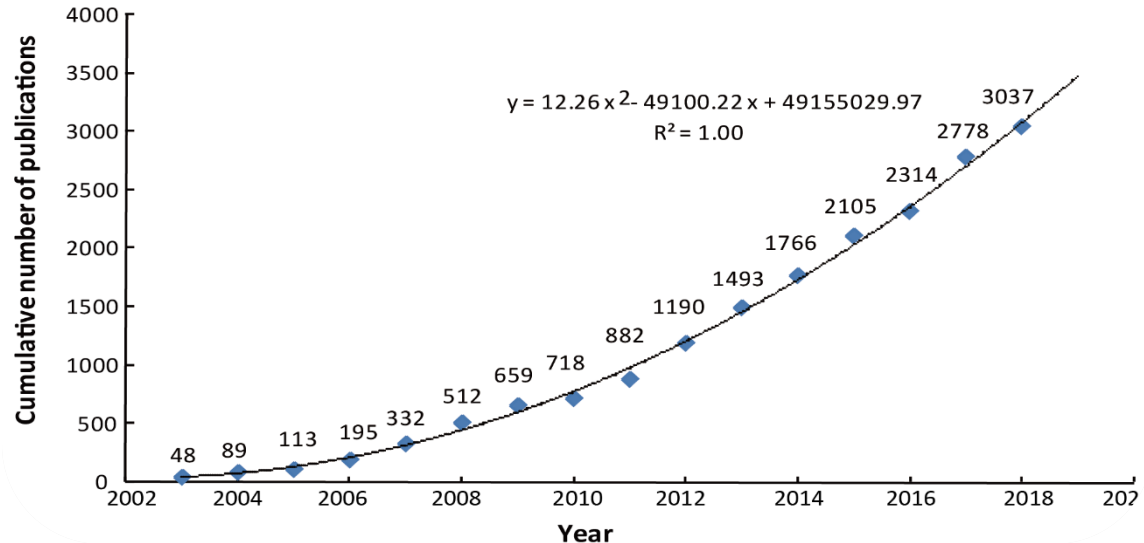


What is Autophagy?

Autophagy is a well-regulated, orderly process to break down and recycle various cellular components.
A type of self-renewal method focusing on removing older structures so that the new ones can take their place..

Autophagy Prevents Cancer

Autophagy plays an important role in preventing the onset and early growth of cancer cells. It is has been known to suppress several processes leading to cancer, such as DNA damage, chronic inflammation, and genome instability.

Autophagy Enhances Muscle Performance

As you exercise, you are put stress on your cells. As this happens, energy use increases and the cell components get worn out at a faster rate. Autophagy makes sure to balance energy use within a cell.

Autophagy Prevents Neurodegenerative Diseases

Stimulating autophagy can help protect your brain by properly removing misfolded proteins inside neurons that cause cell death in your brain and loss of mental capacity.

Autophagy Regulates Inflammation

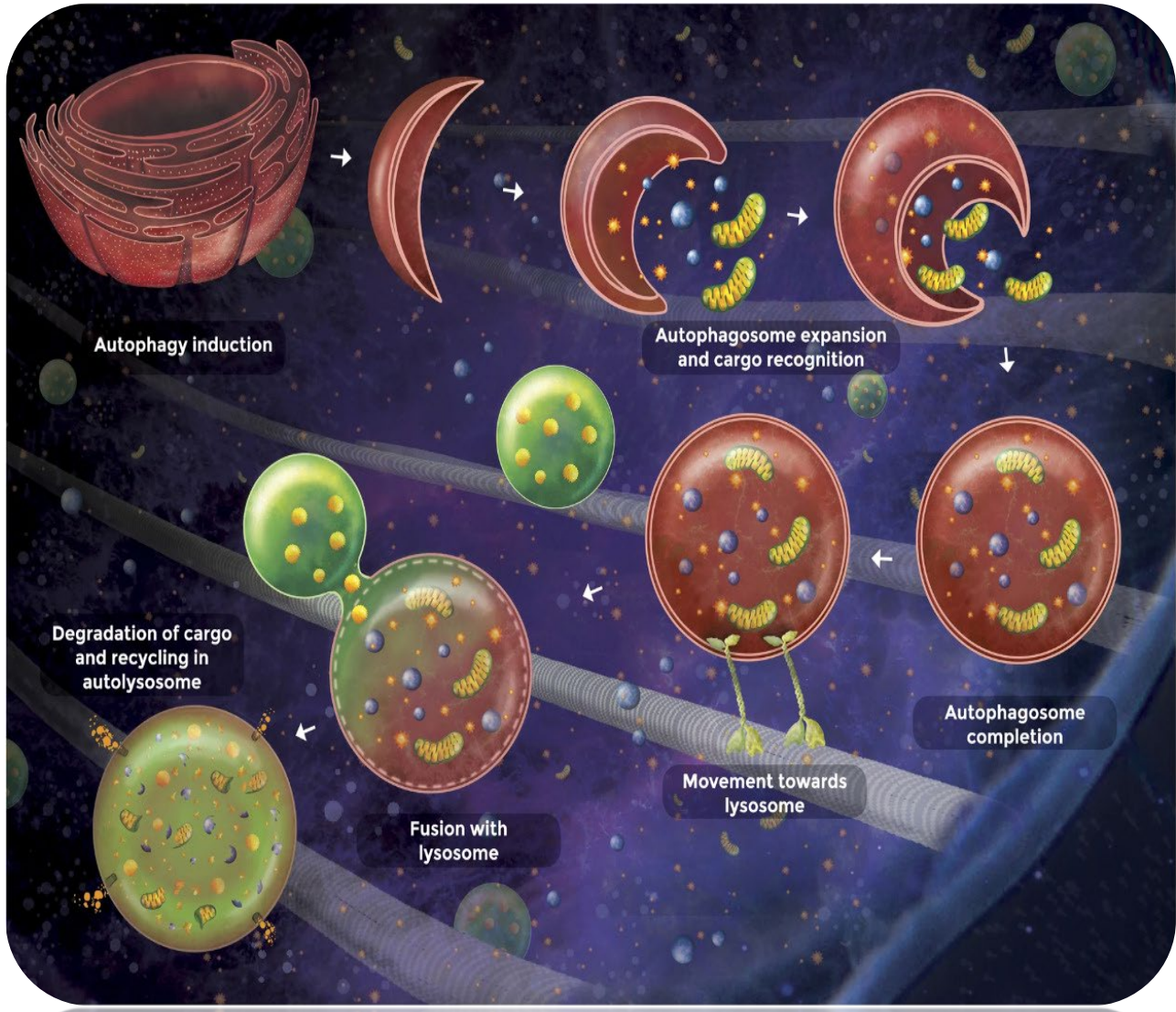
Autophagy can help decrease inflammation within your body. It also gets rid of any pro-immune response molecules from the body to lower down the level of inflammation.

Autophagy Reduces the Effects of Aging

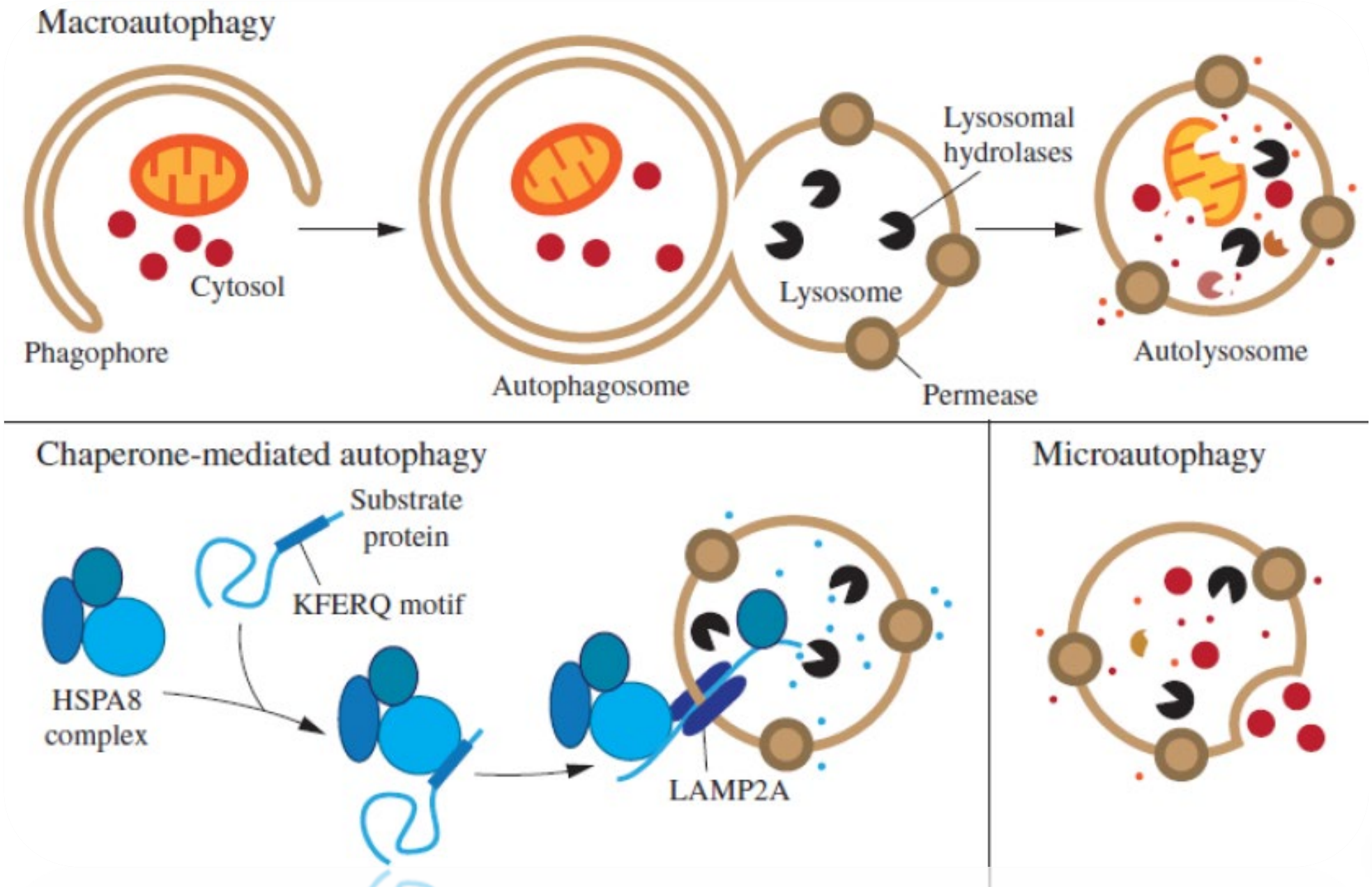
Autophagy along with intermittent fasting boosts the production of Human Growth Hormone (HGH). HGH is largely associated with an increased healthy muscle growth but also provides powerful anti-aging benefits.

Enhances Cellular Energy

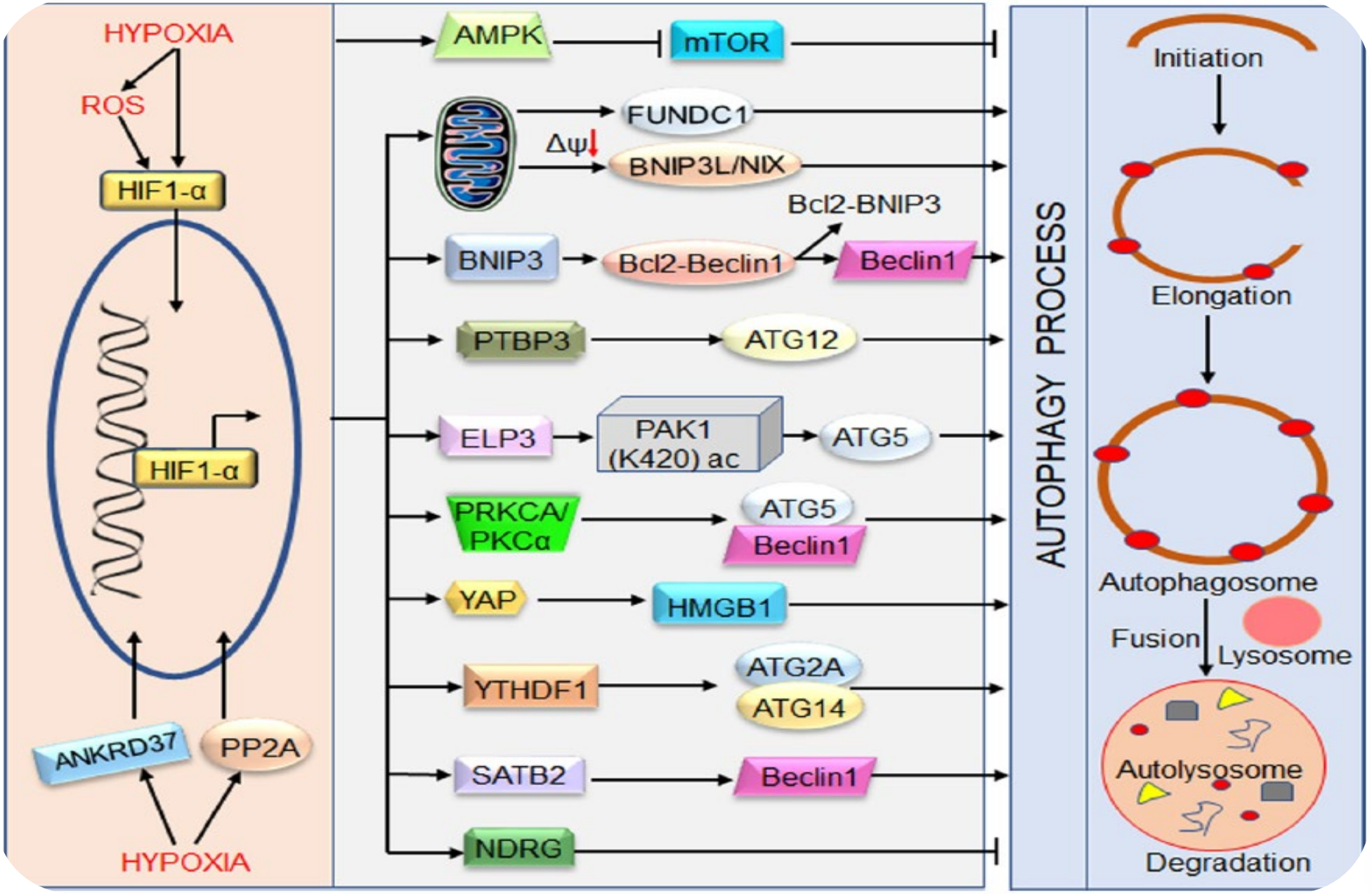
The mitochondria undergo an autophagy process called "mitophagy" that favors the development of new and stronger mitochondria that can produce more cellular energy.



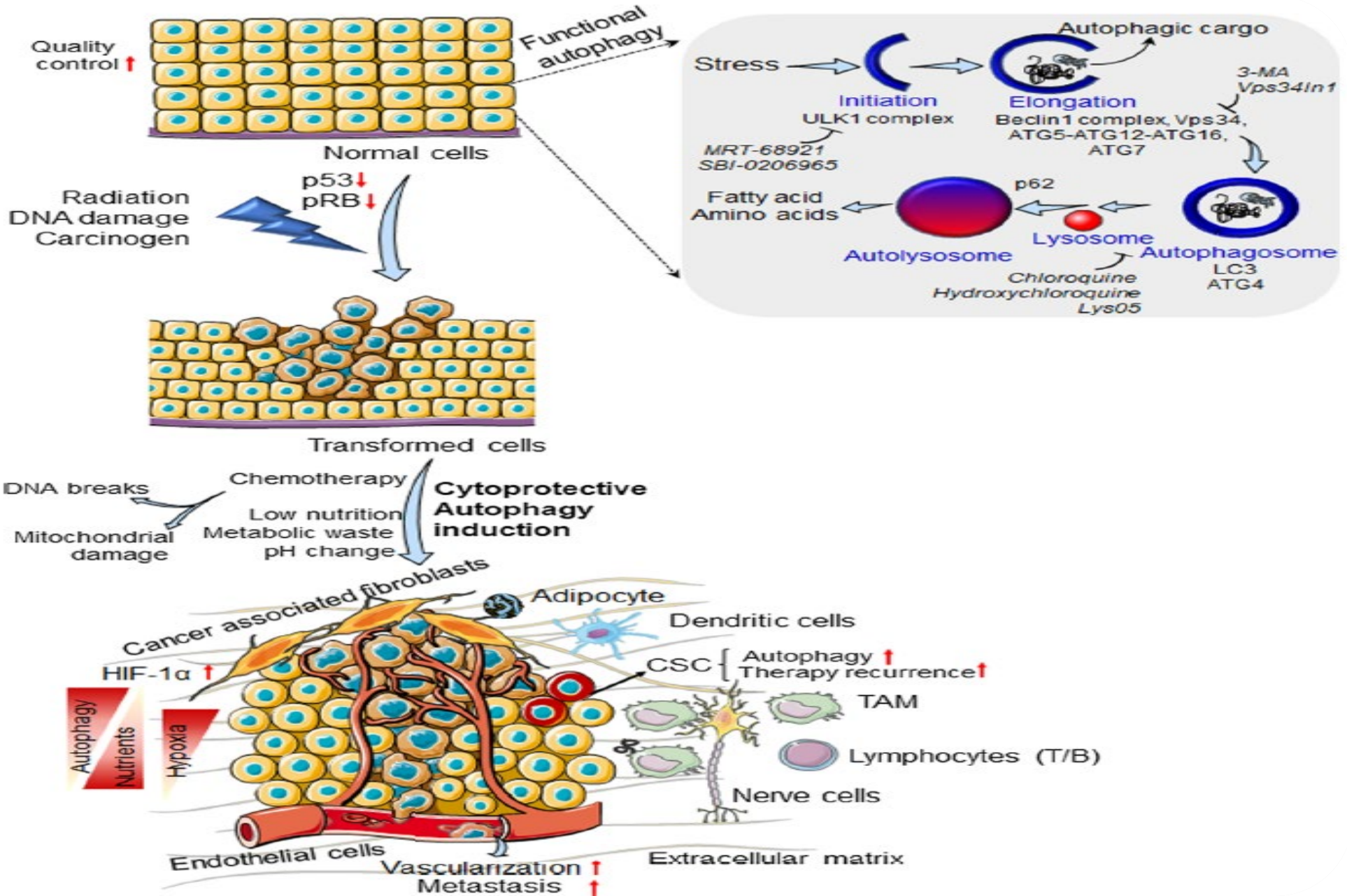
Three types of autophagy in mammalian cells



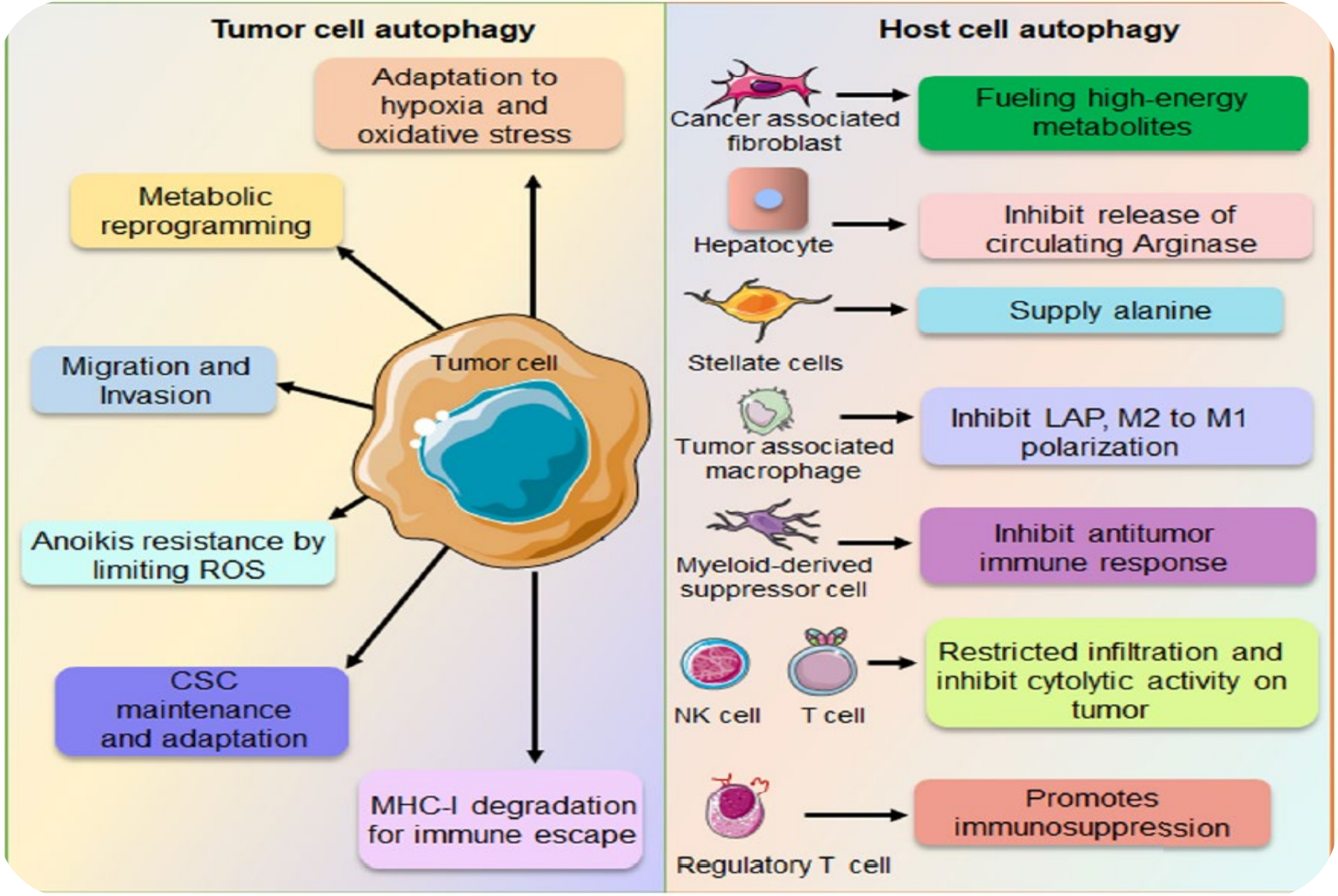
Autophagic regulation of hypoxia



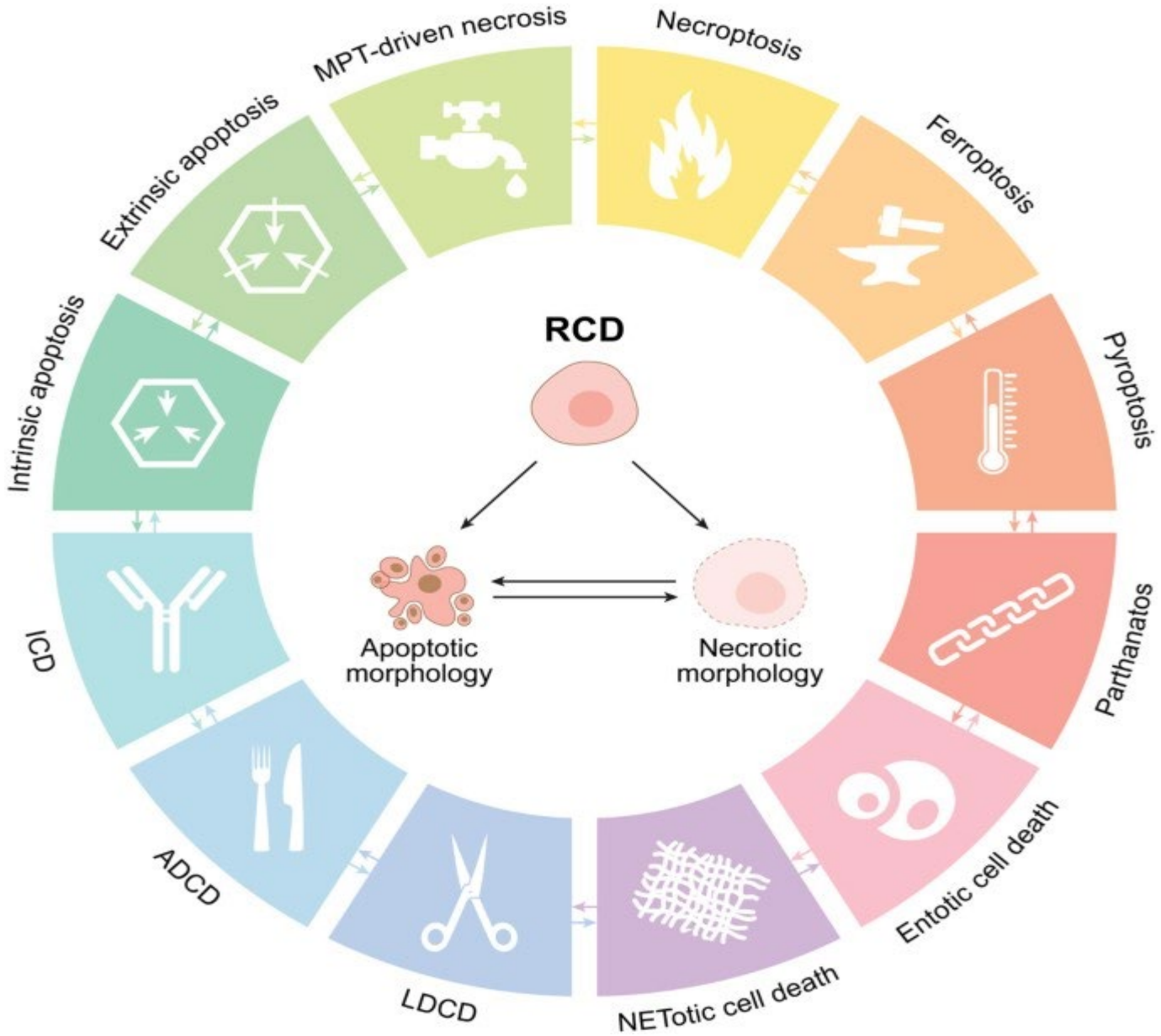
Tumor microenvironment and autophagy in cancer

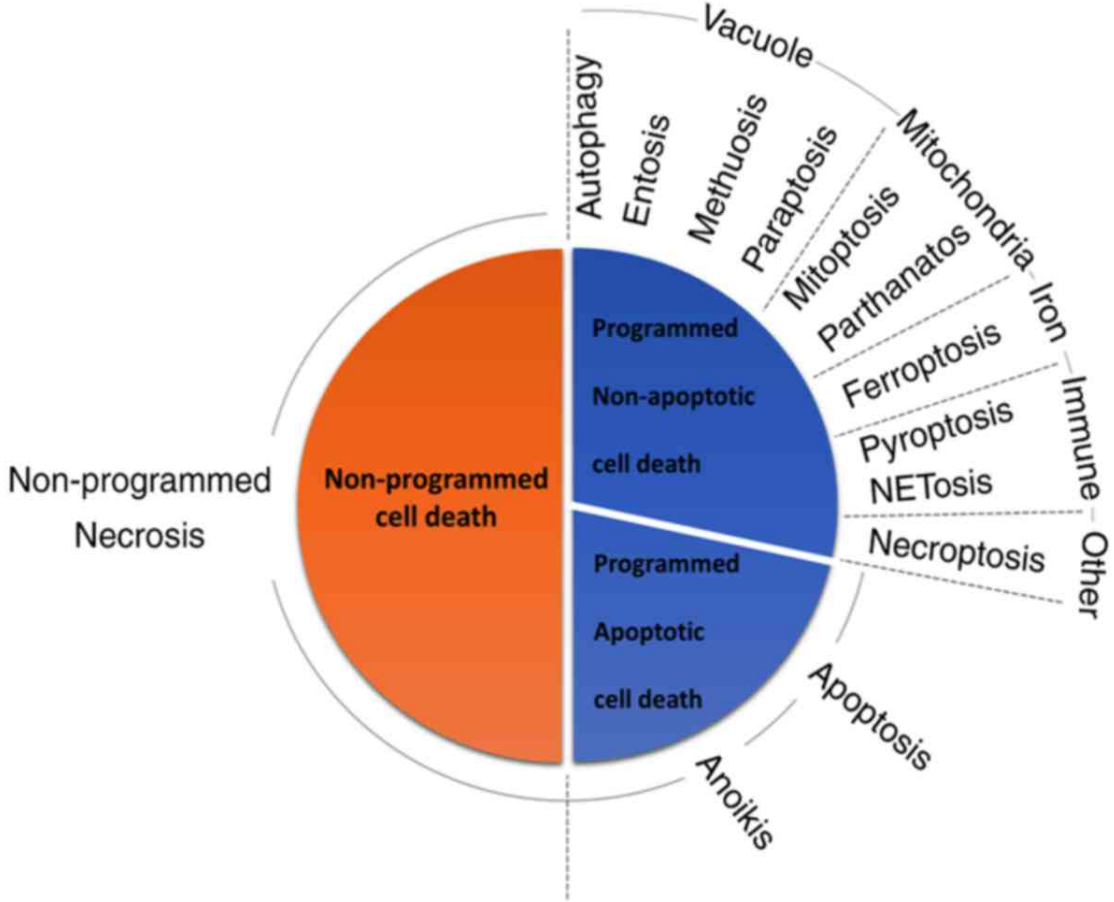


The role of tumor cell and host cell autophagy to determine the fate of a tumor cell in the tumor microenvironment

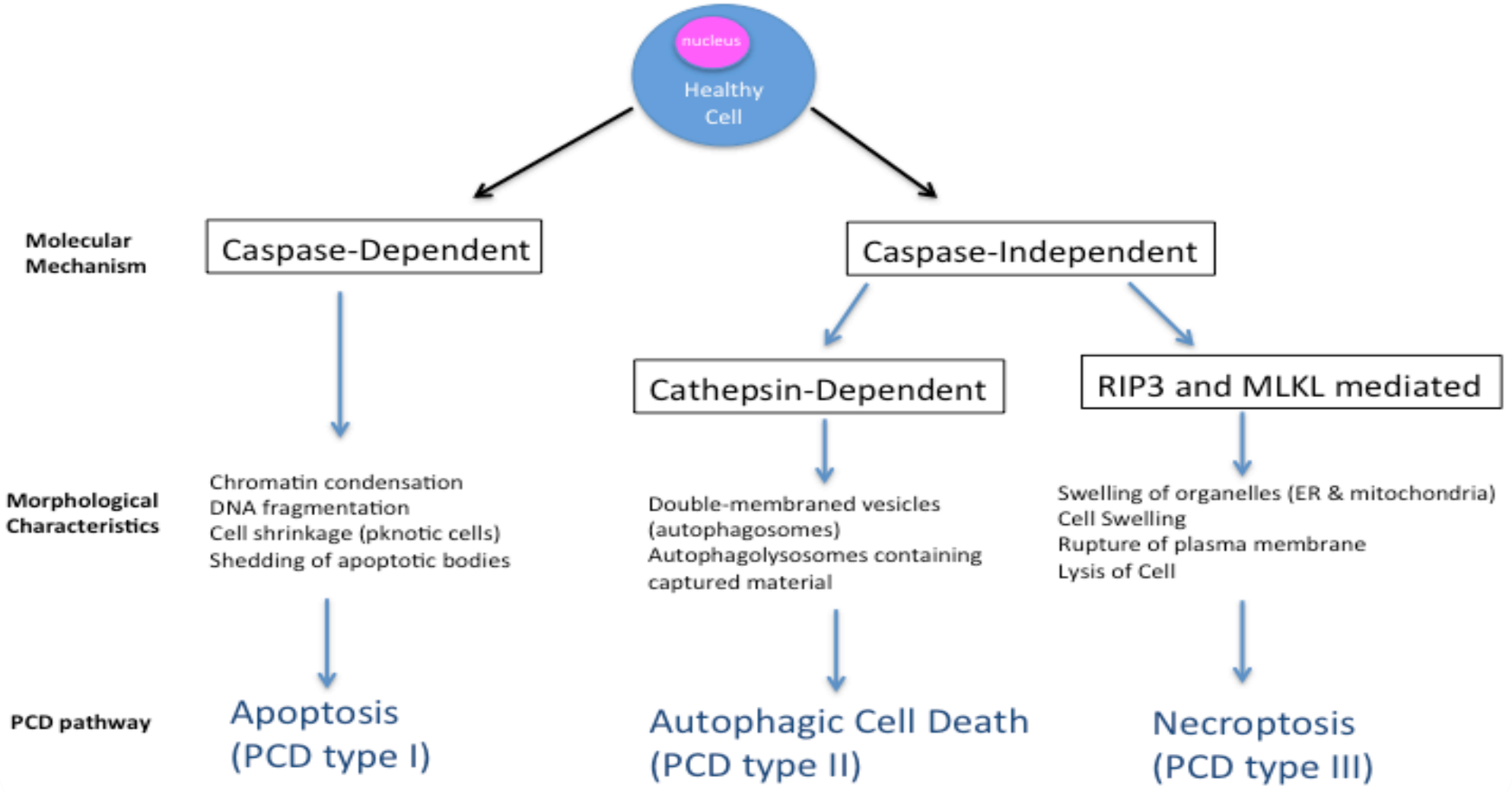


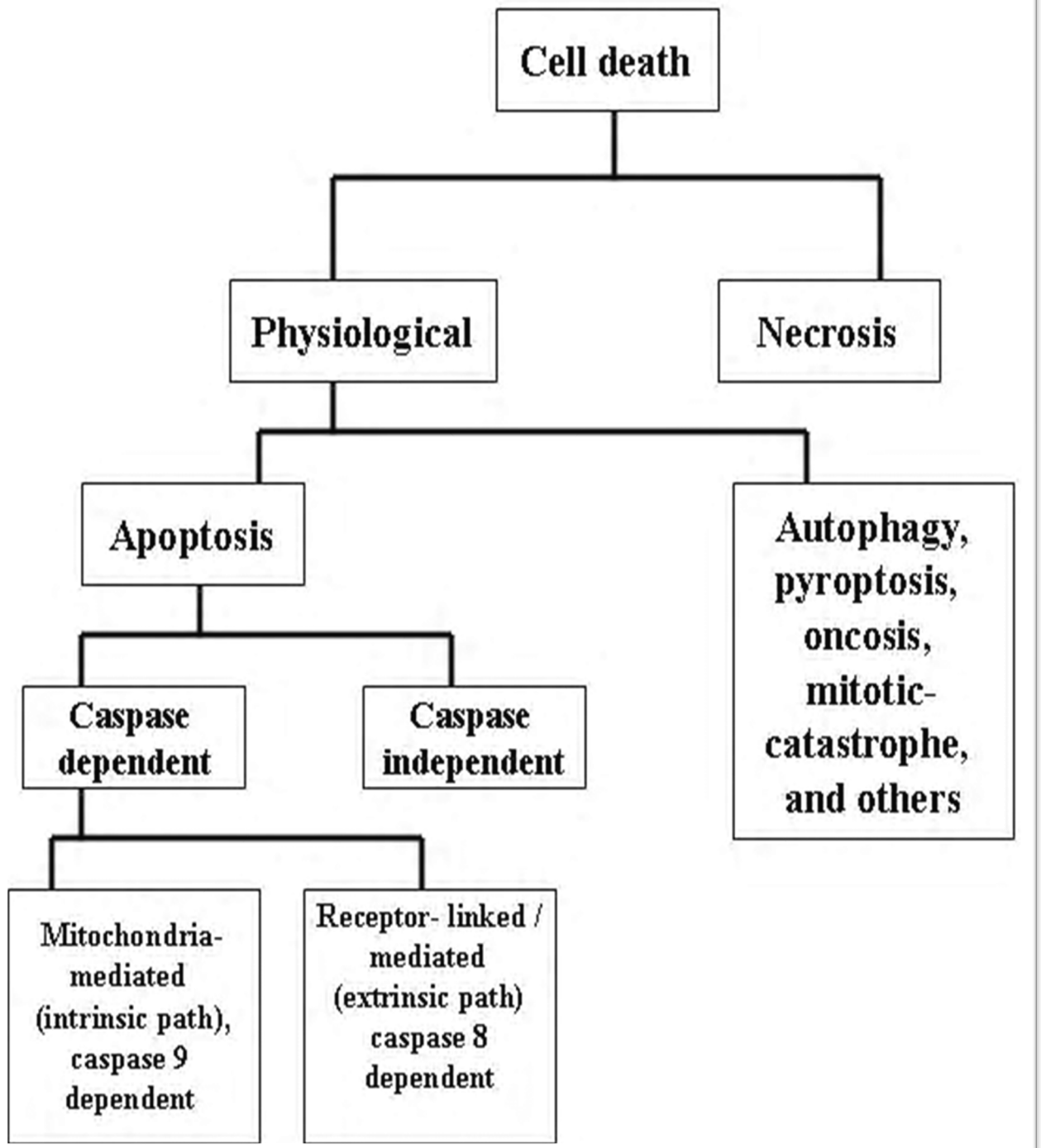
Cell Death


RCD
Apoptotic morphology
Necrotic morphology
MPT-driven necrosis
Necroptosis
Ferroptosis
Pyroptosis
Parthanatos
Entotic cell death
NETotic cell death
LDCD
ADCD
ICD
Intrinsic apoptosis
Extrinsic apoptosis


Non-programmed
Necrosis
Non-programmed cell death
Programmed
Non-apoptotic
cell death
Programmed
Apoptotic
cell death
Vacuole
Autophagy
Entosis
Methuosis
Paraptosis
Mitoptosis
Parthanatos
Ferroptosis
Pyroptosis
NETosis
Necroptosis
Mitochondria
Iron
Immune
Other
Apoptosis
Anoikis

Comparison of PCD Pathways





AUTOPHAGY VERSUS APOPTOSIS

AUTOPHAGY	APOPTOSIS
Autophagy is a self-degradative process of its own components, balancing the sources of energy during development	Apoptosis is a pre-defined cell suicide, where the cell actively destroys itself, maintaining a smooth functioning in the body
Balances the energy sources in the cell depending on the cellular requirements	Balances the number of cells in a multicellular organism
Caused by cellular stress like starvation	Caused by intracellular programs
Lysosomes are fused with autophagosomes, forming autolysosomes	The contents in lysosomes are not involved in the process
Mitochondria do not become leaky	Mitochondria become leaky
Freely floating in the mitochondrial matrix	Enclosed by the nucleus
Allows the cell to survive stress	Does not allow the cell to survive
Excessive autophagy leads to cell death	Excessive apoptosis leads to atrophy
3-Methyladenine is an inhibitor	Z-VAD-FMK is a well-defined apoptosis modulator

Regulation of Autophagy

I. The PI3K/Akt/TSC/mTOR pathway

II. The AMPK/TSC/mTOR pathway

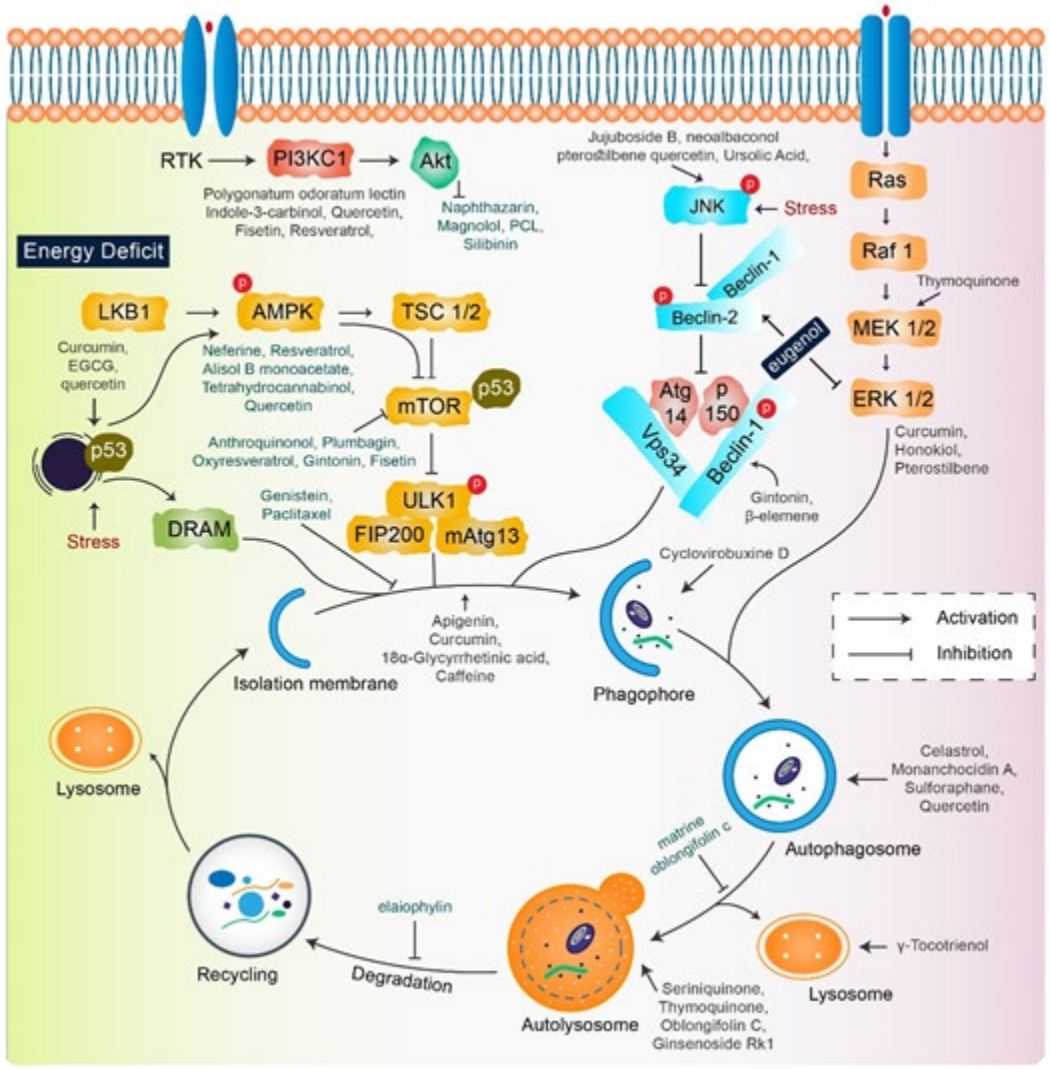
III. The Rag/mTOR pathway

IV. The Ca2+/ calpain pathway

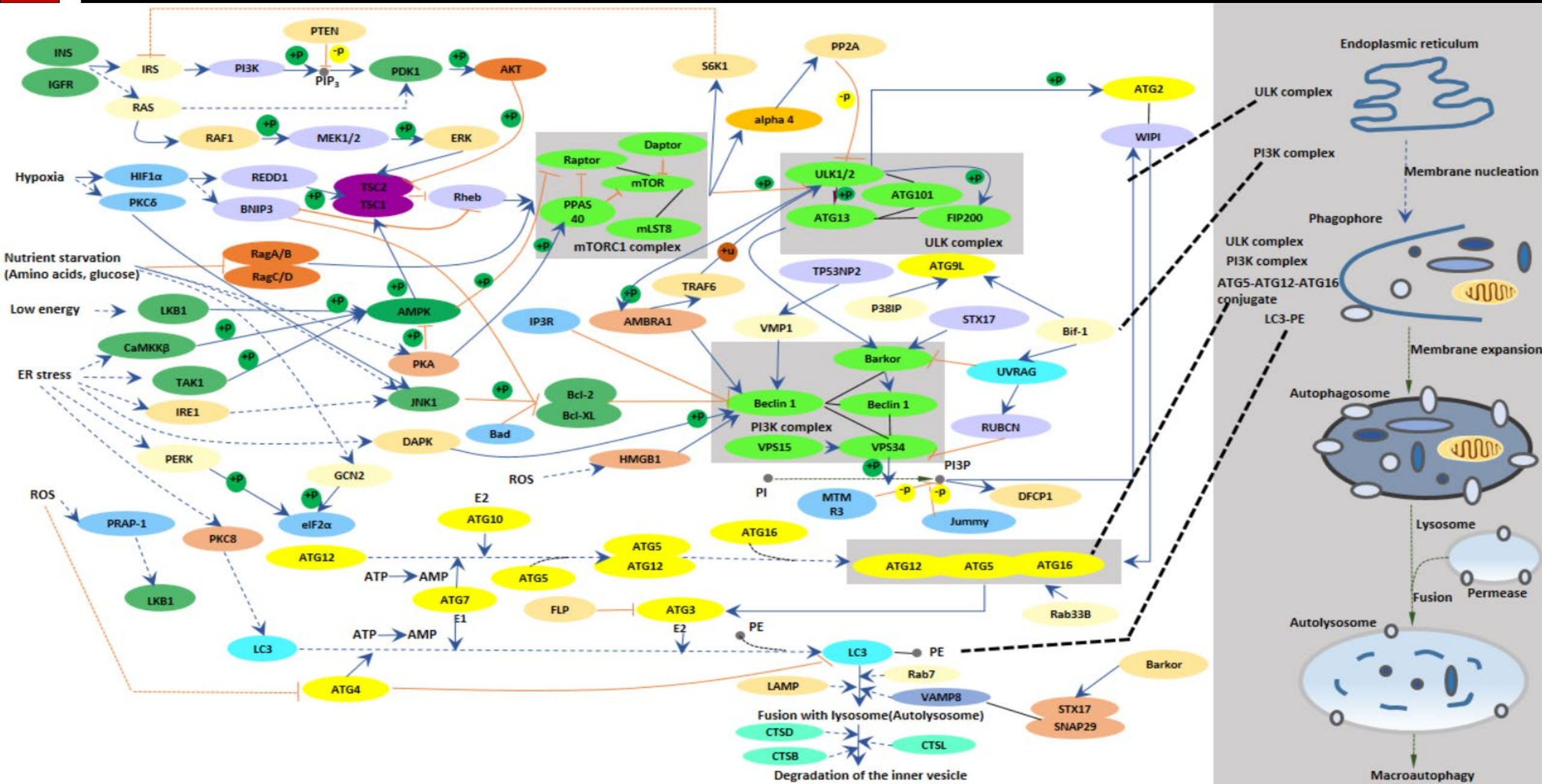
V. The inositol-dependent pathway

VI. The cAMP/EPAC/PLC pathway

VII. The JNK1/Beclin-1/PI3K pathway



Regulation of Autophagy



Autophagy-targeted oncotherapy

The most recent progress of autophagy-targeted oncotherapy can be traced by understanding the clinical trials. One such study named CHOICES (CHlorOquine and Imatinib Combination to Eliminate Stem cells) trial (NCT01227135) involved a phase II trial which is compared with co-treatment of imatinib mesylate (IM) and hydroxychloroquine, establishing a proof of concept of autophagy inhibitors use in leukemia treatment.

The ongoing cancer clinical trials using autophagy targeted therapy.

Clinical trial identifier	Treatment	Tumor type
NCT03037437	Sorafenib +Hydroxychloroquine (HCQ)	Hepatocellular carcinoma
NCT04214418	Cobimetinib+ HCQ + Atezolizumab	Gastrointestinal Cancer
NCT04386057	ERK inhibitor LY3214996 +HCQ	Pancreatic cancer
NCT03377179	Sphingosine kinase-2 (SK-2) inhibitor ABC294640+HCQ	Cholangiocarcinoma
NCT03979651	MEK inhibitor Trametinib +HCQ	Metastatic NRAS Melanoma
NCT04201457	Dabrafenib + Trametinib+HCQ	Glioma
NCT03598595	Gemcitabine + Docetaxel+HCQ	Osteosarcoma
NCT04163107	Carfilzomib +HCQ	Multiple Myeloma
NCT04524702	Paricalcitol +HCQ + Gemcitabine + Nab-Paclitaxel	Pancreatic cancer
NCT04132505	Binimetinib +HCQ	Pancreatic cancer


Discussion


Thank
You