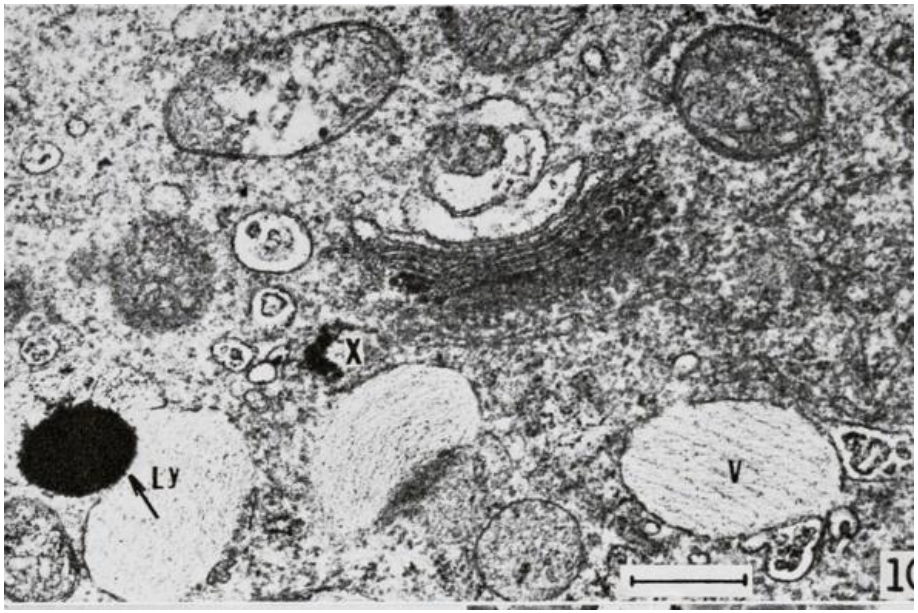
Autophagy and Cancer (Lung Cancer)



By: Dr. Firas Subhi Saleh

Cancer Research Department

Iraqi Centre for Cancer and Medical Genetics Research (ICCMGR)

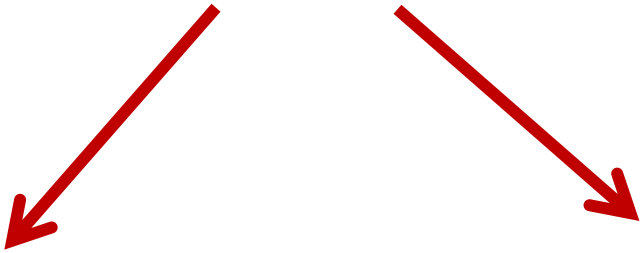
Mustansiriyah University

18. Oct. 2018

Cellular Homeostasis

- constant turnover of continuous synthesis of cellular components
- clearance of damaged or superfluous proteins and organelles.

Degradation pathways



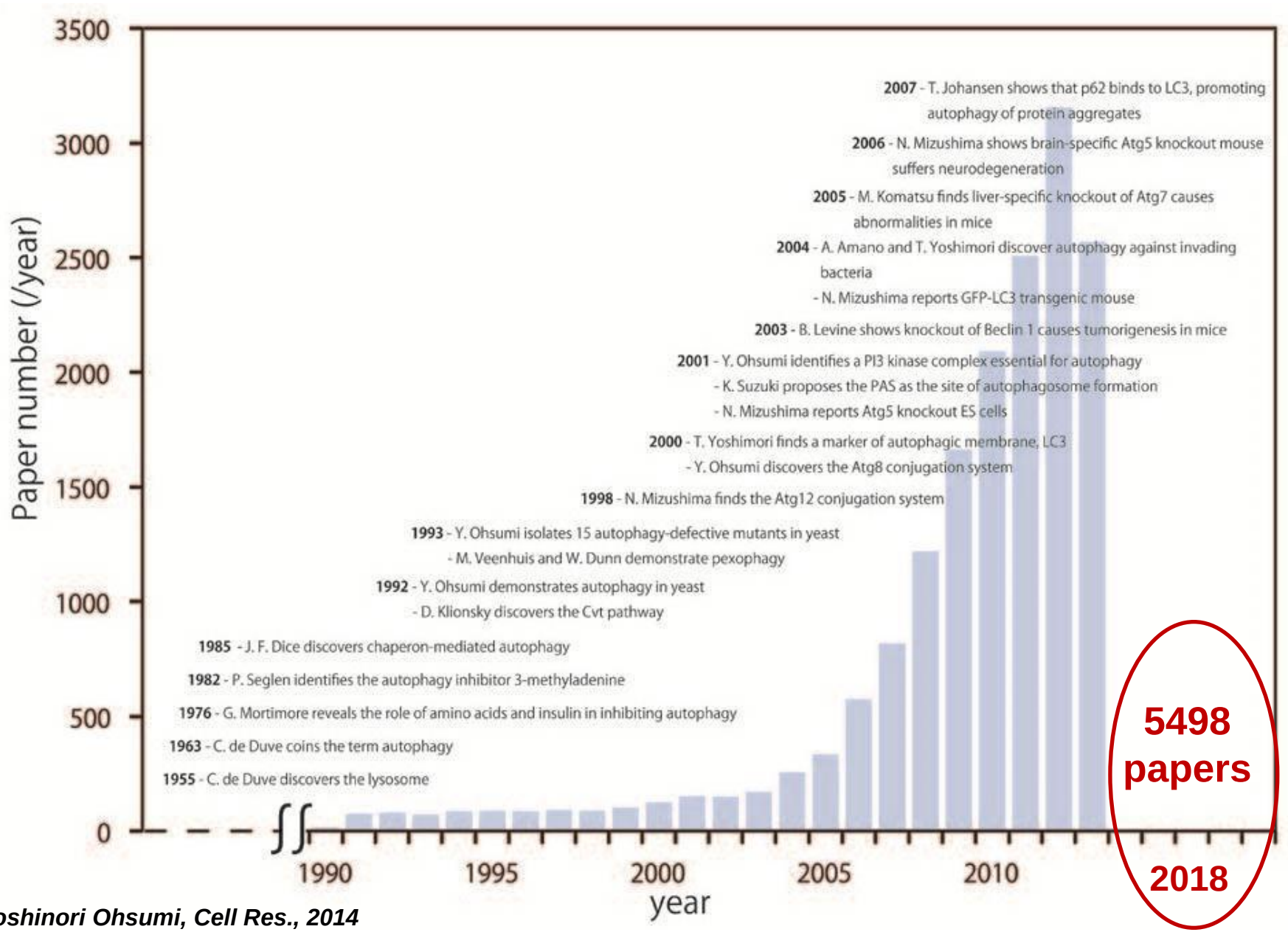
Ubiquitin-Proteasome System (UPS)

high selectivity
short-lived proteins

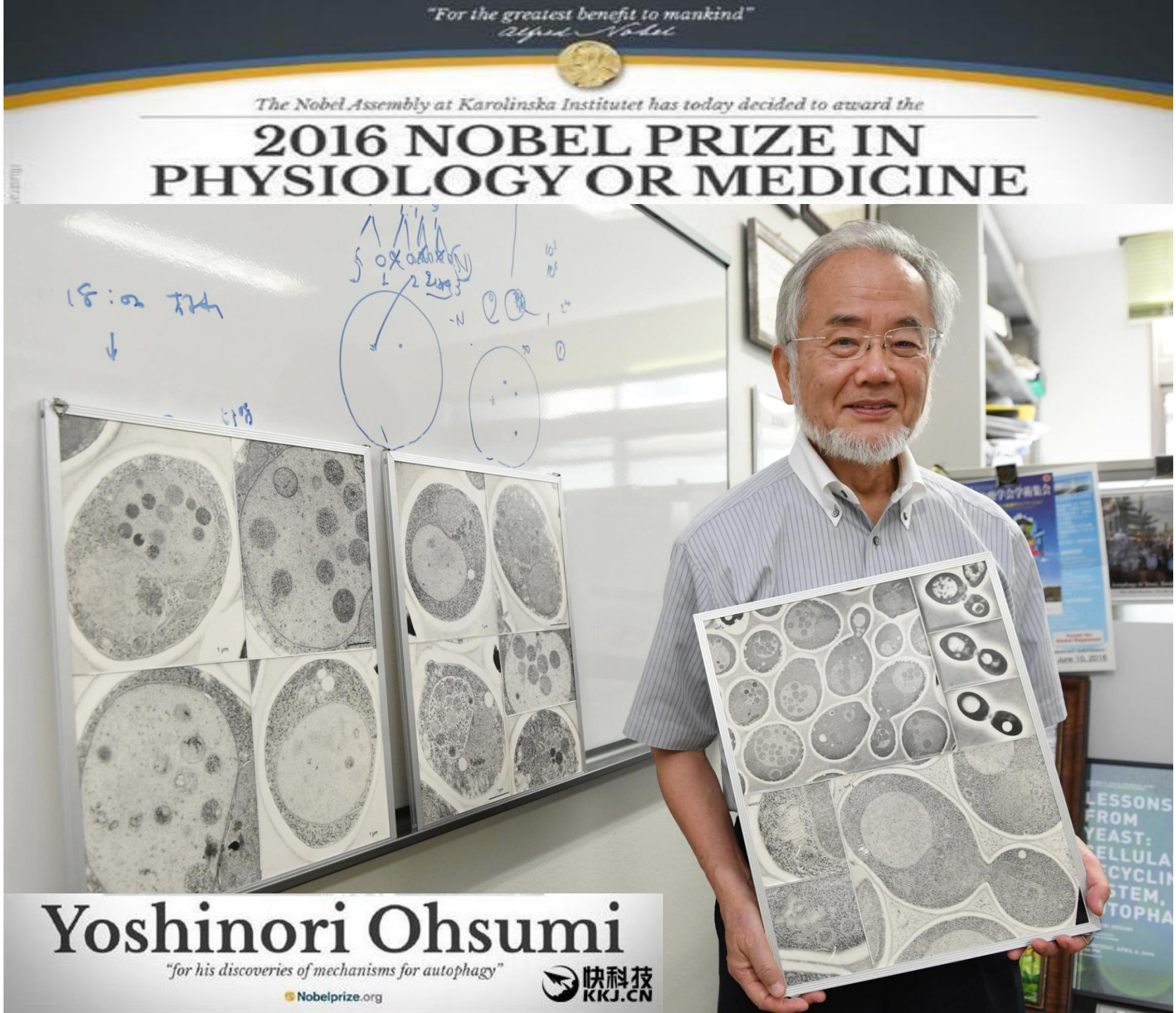
Lysosomal pathway

Autophagy

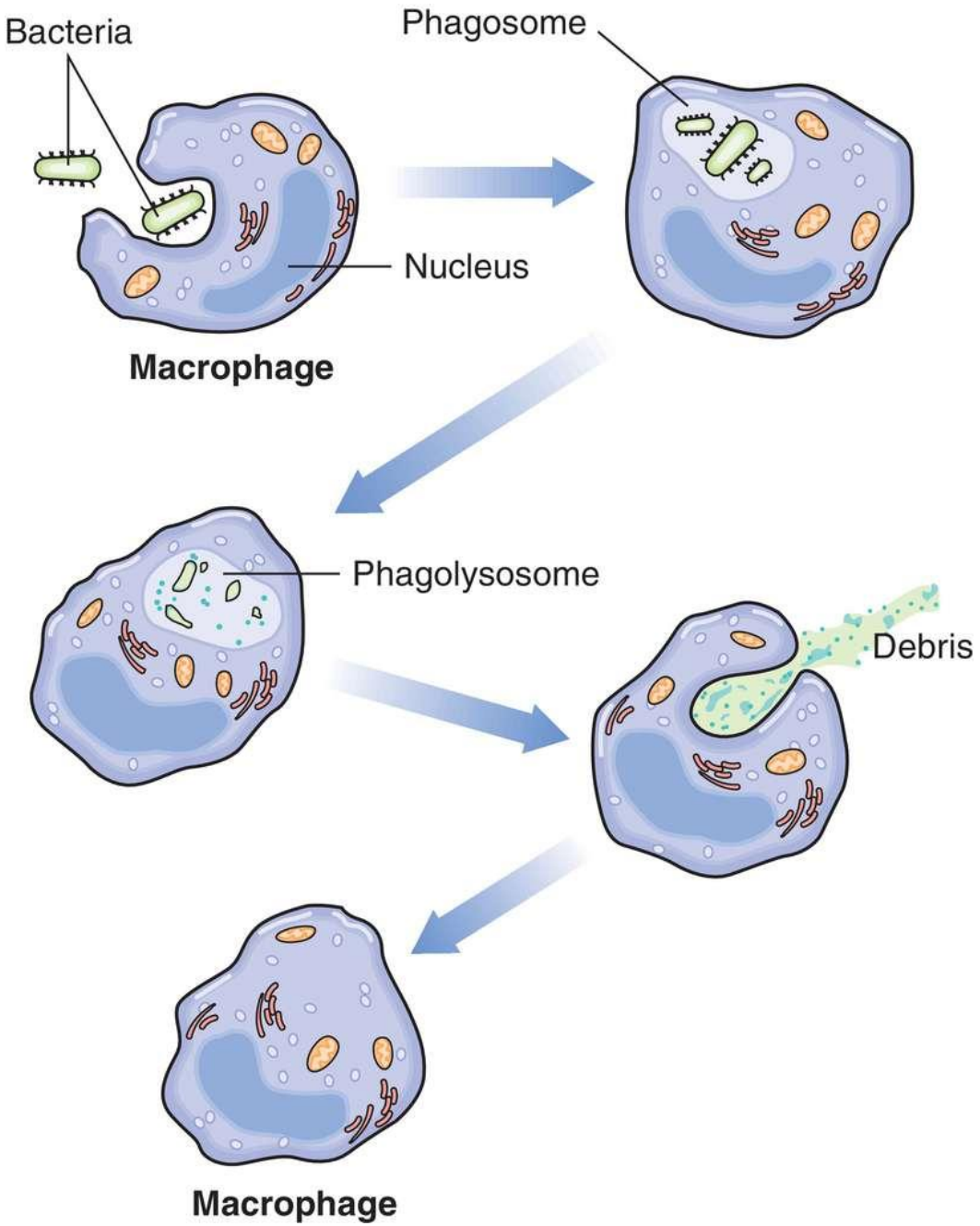
Chronology



Yoshinori Ohsumi, Cell Res., 2014


"For the greatest benefit to mankind"
The Nobel Assembly at Karolinska Institutet has today decided to award the
2016 NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE
Yoshinori Ohsumi
"for his discoveries of mechanisms for autophagy"
Nobelprize.org
快科技 KKJ.CN

Phagocytosis



Autophagy is totally different

What is Autophagy?

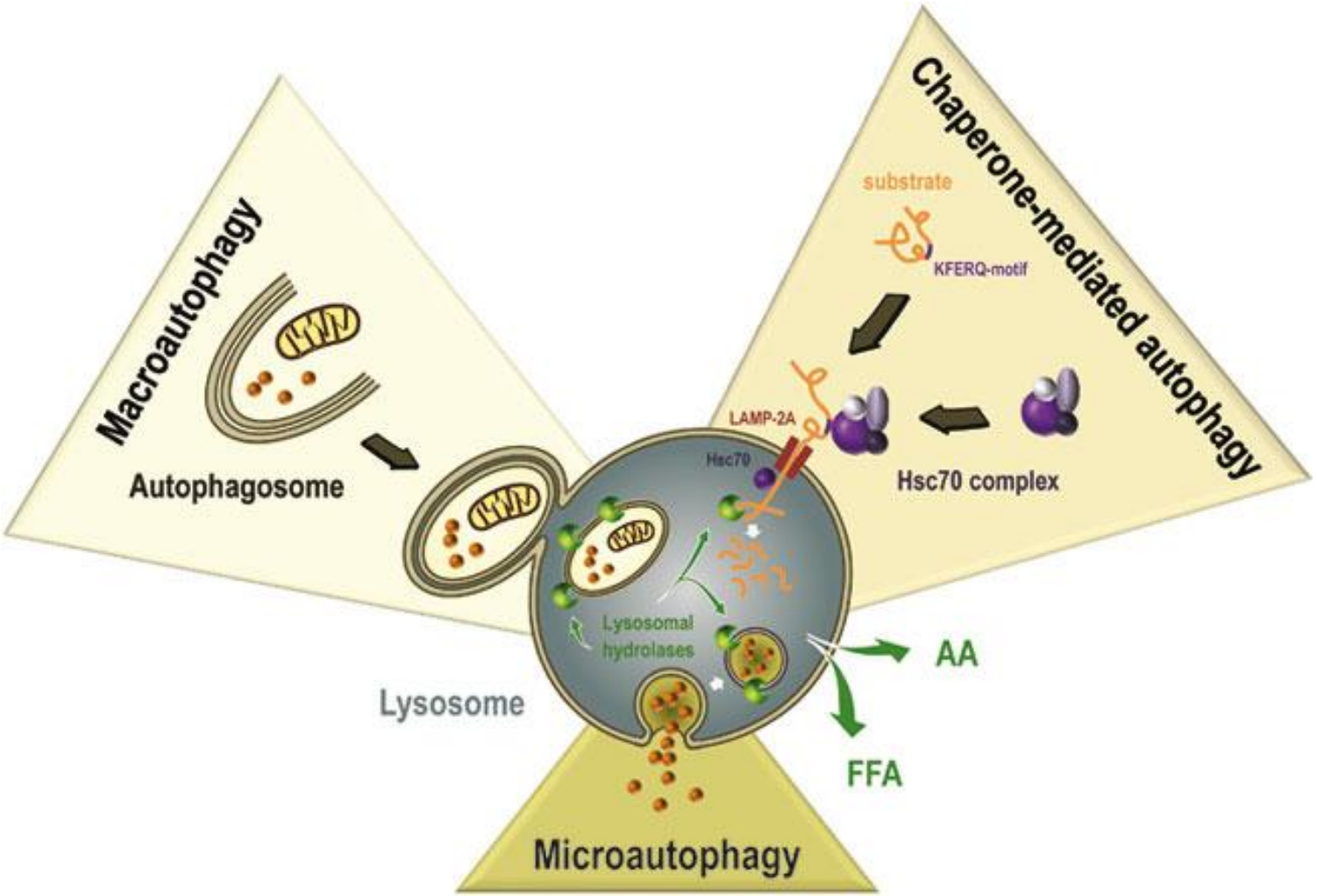
“Self-eating”

From the Greek words, *auto* "self" and *phagein* "to eat"

Catabolic process through which the cell recycles its own constituents.

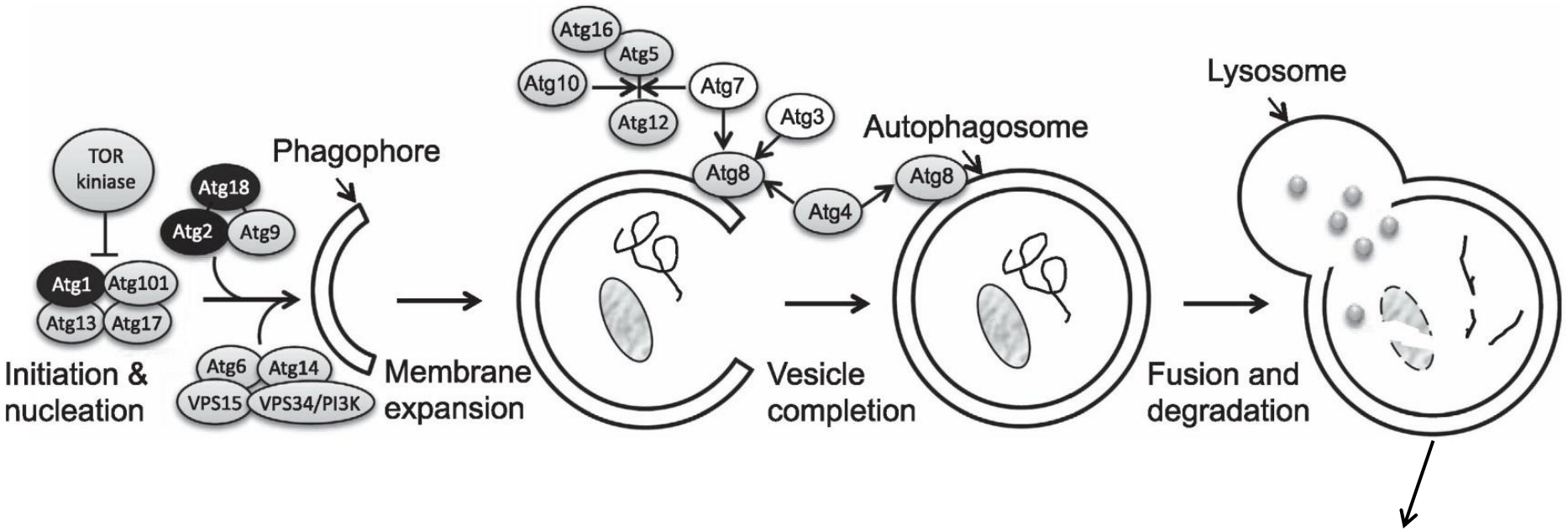
Pathway that lead to the elimination of cytoplasmic components by delivering them into lysosomes.

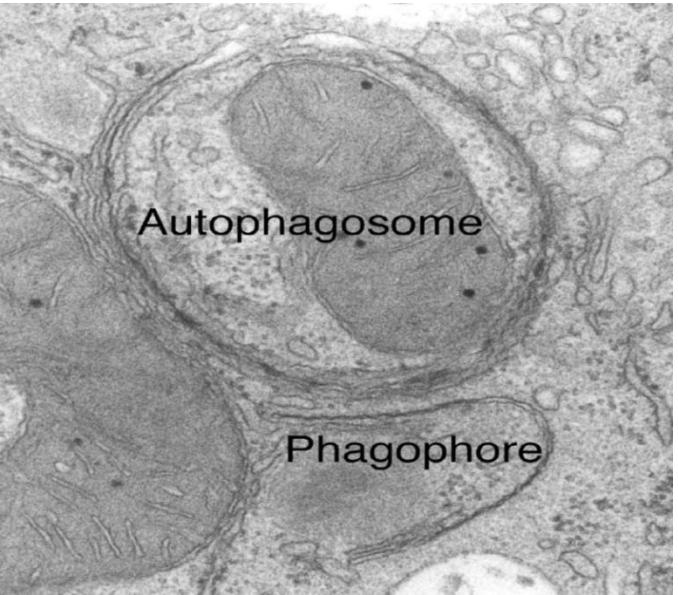
Types of Autophagy



Wirawan et al., Cell Res., 2012

Mechanism of Autophagy





Denton et al., Immunol Cell Biol., 2015

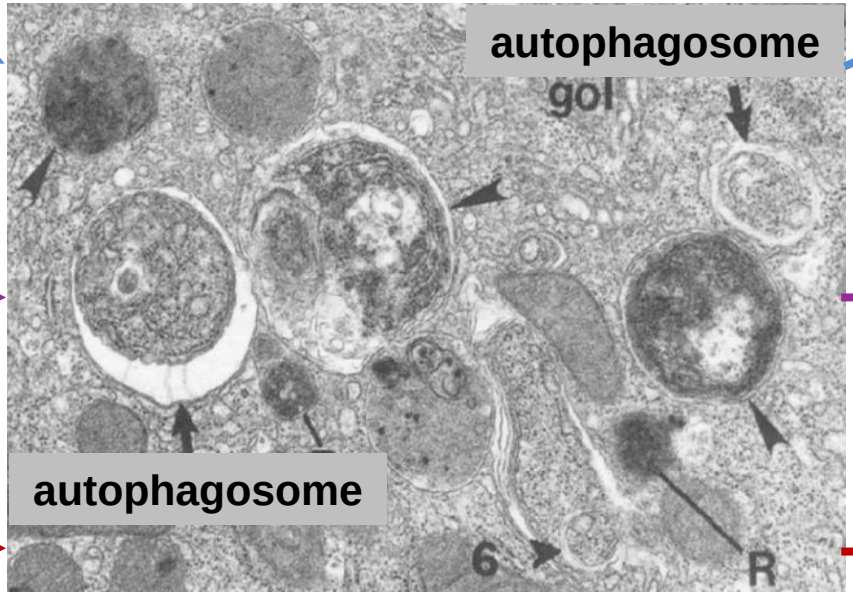
Multiple Functions of Autophagy

- Occurs in all eukaryotic cells
- Bulk degradative process that ends in lysosomes
- Degradation of intracellular components

Basal autophagy
Quality control

Nutrient/
Growth factor
deprivation

Uncontrolled
autophagy

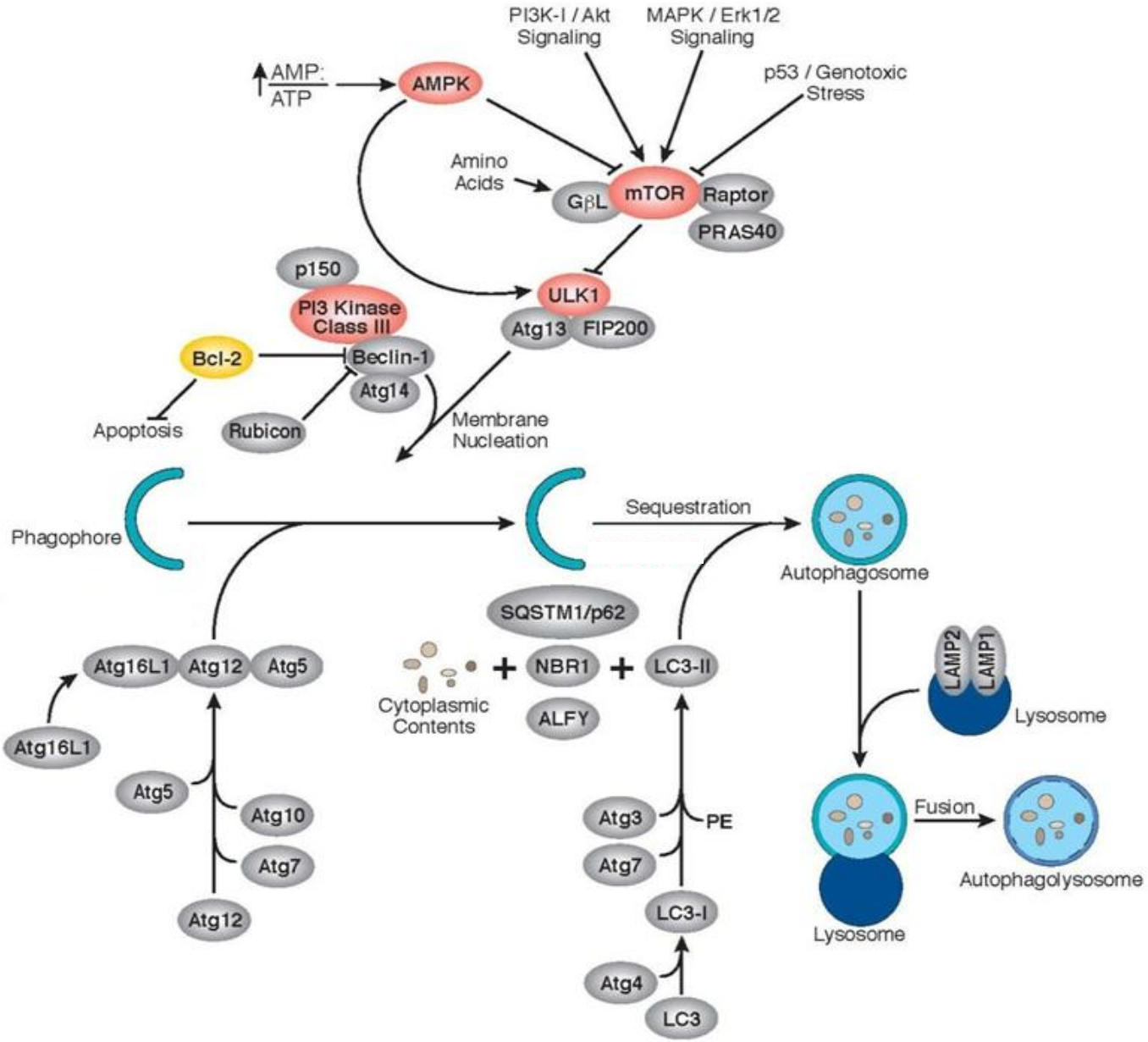


Removal of
obsolete organelles
and protein aggregates

Metabolic substrates
(energy, nutrient)

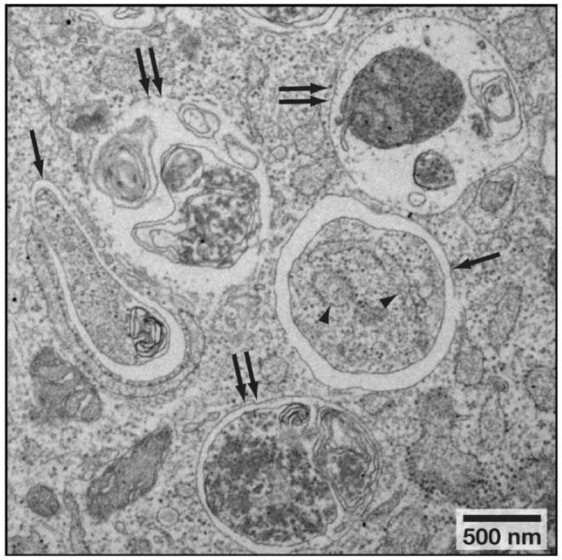
Autophagic
cell death

Autophagy Signalling Pathway

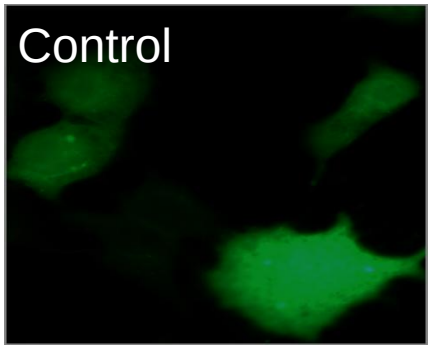


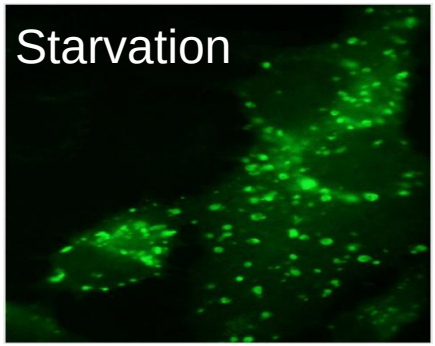
How can We Monitor Autophagy?

EM



IF LC3





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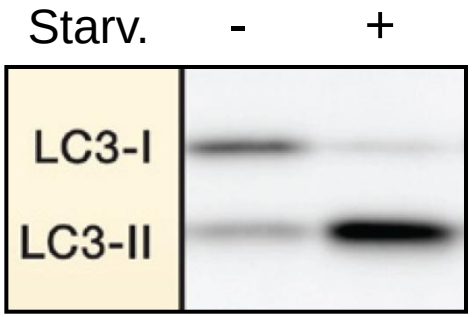
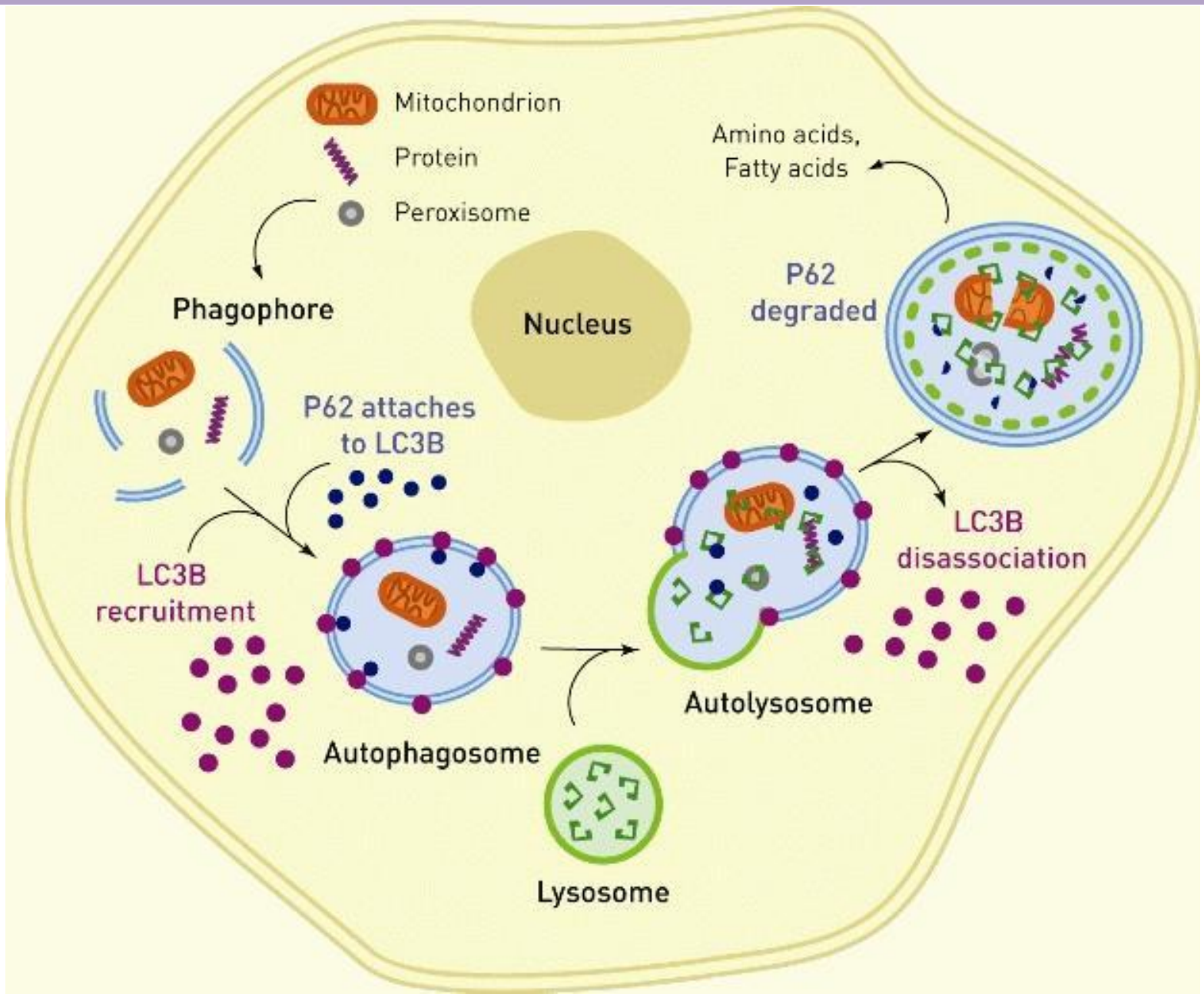
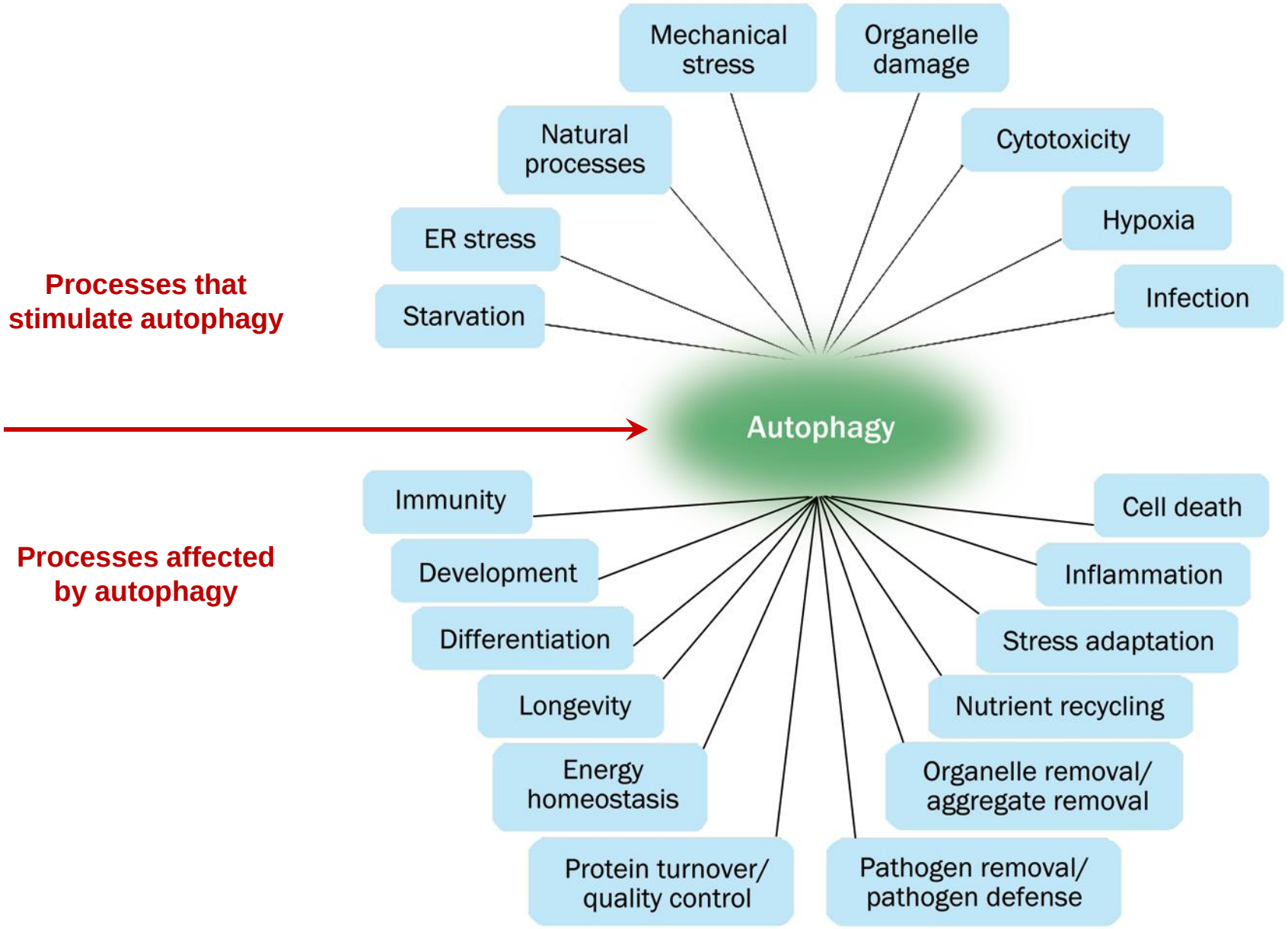


How can We Monitor Autophagy?



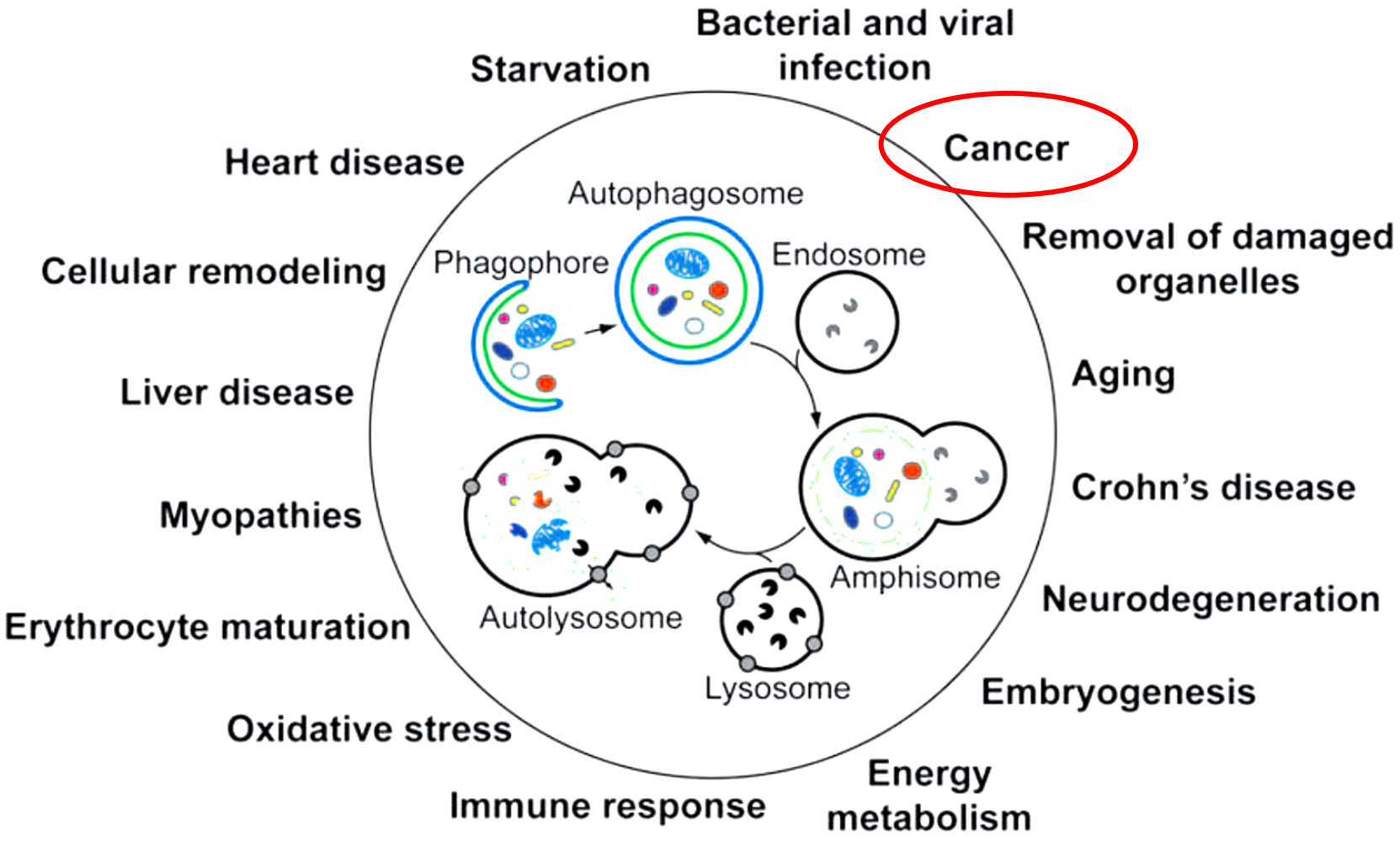
Induction of Autophagy

Processes that stimulate autophagy



Processes affected by autophagy

Autophagy and Diseases



Klionsky DJ, Dev Cell. 2010

Autophagy and Cancer

The connections between autophagy and cancer occur at two aspects:

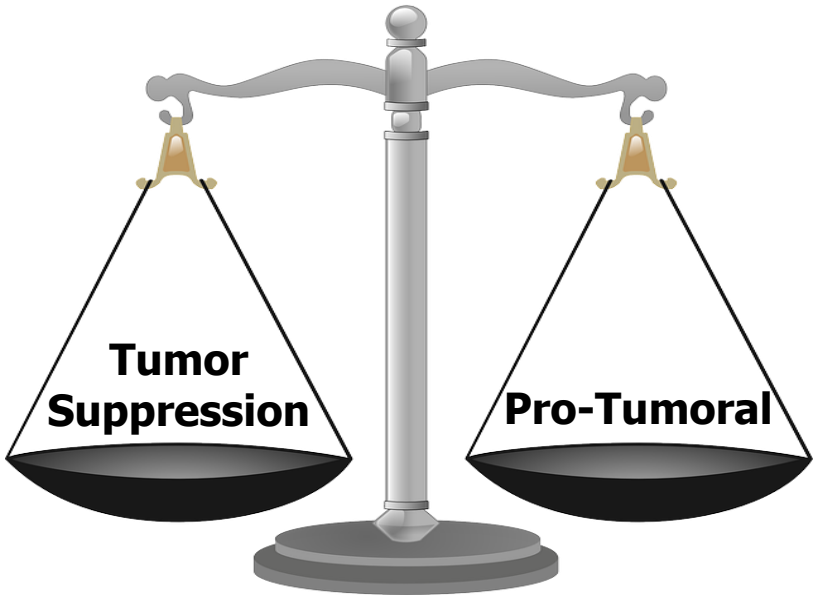
First at the level of tumor initiation and progression,

Second during cancer treatment.

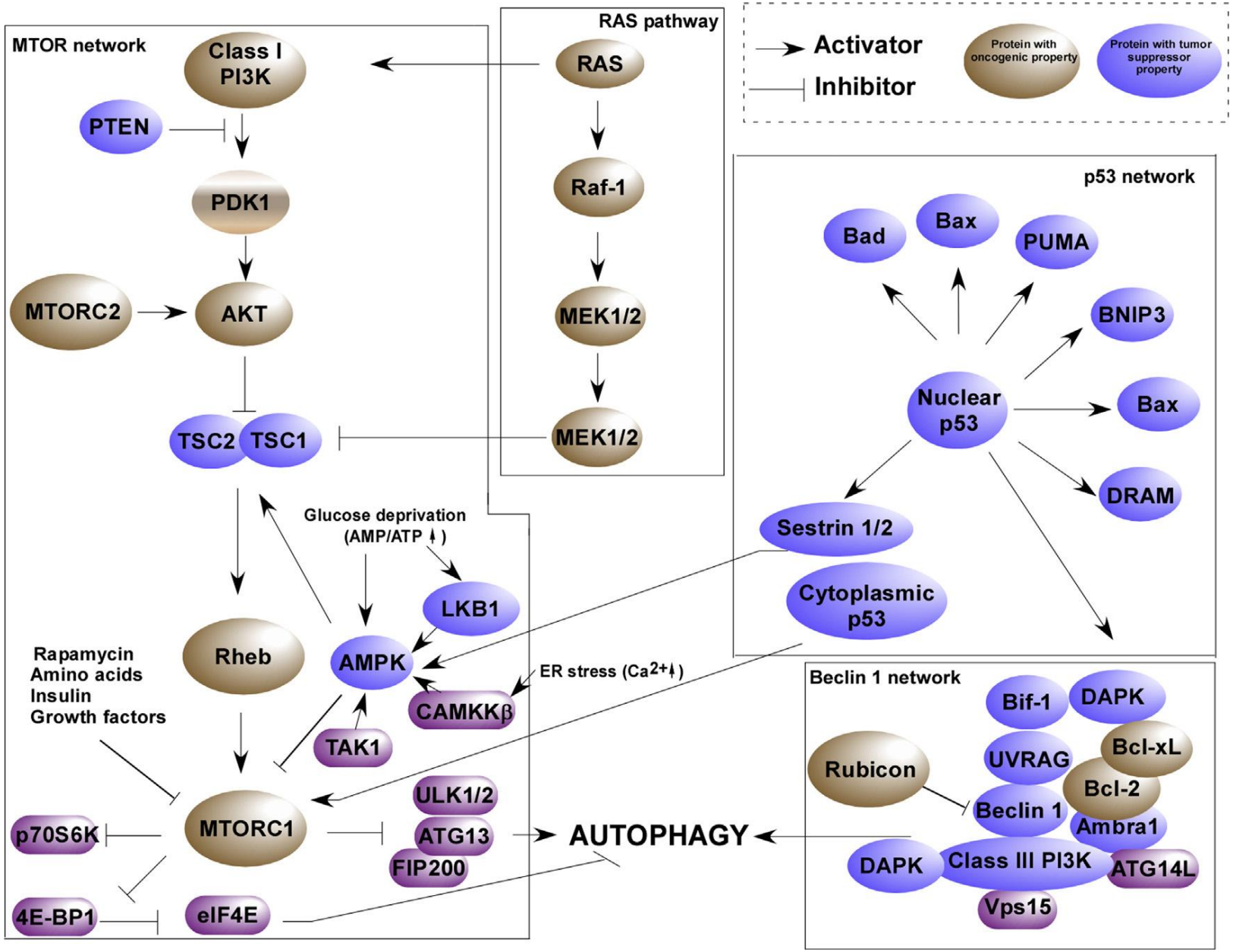
Autophagy in Tumor Initiation and Progression

The role of autophagy in cancer is complex and likely tissue and genetic context-dependent.

Dual role of Autophagy



Principal signalling pathways involved in the autophagy-related cancer interconnections



Lorin et al., Seminars in Cancer Biology, 2013

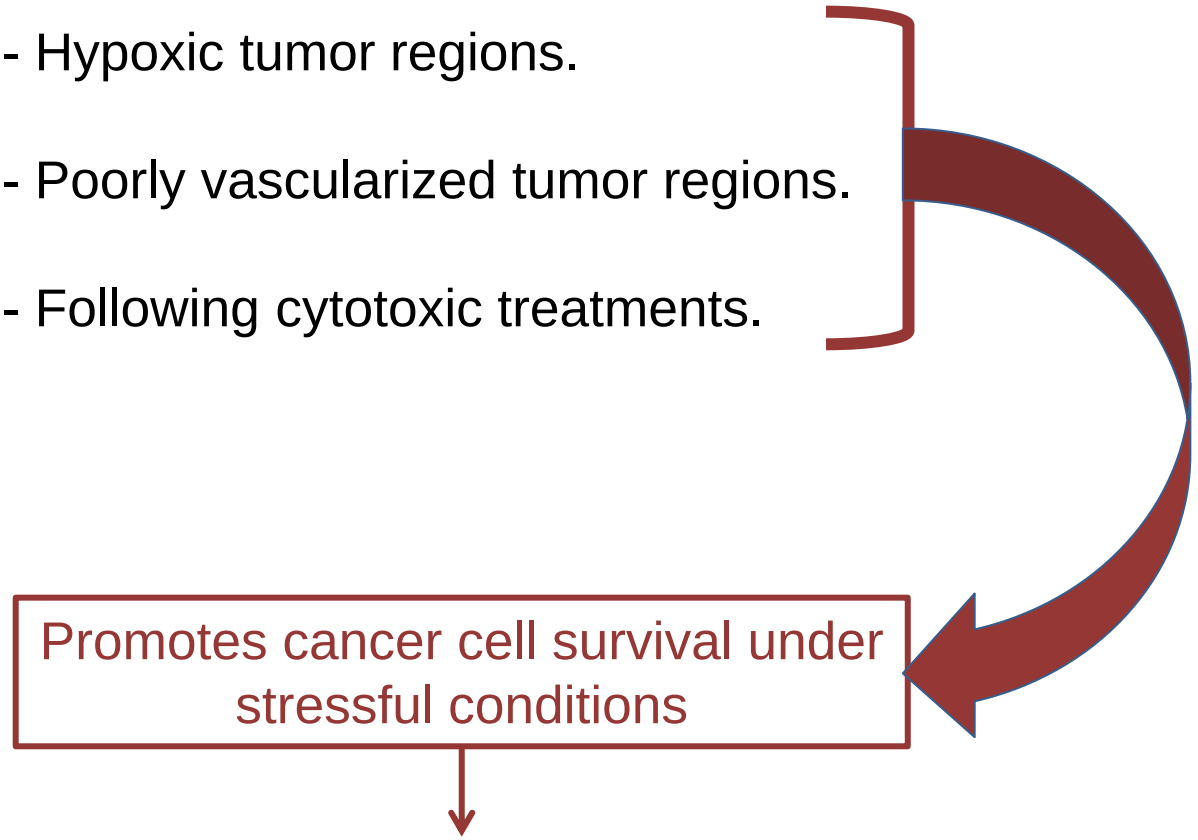
Autophagy in Cancer Treatment

Autophagy induction have been found to spatially localize to:

1- Hypoxic tumor regions.

2- Poorly vascularized tumor regions.

3- Following cytotoxic treatments.



Autophagy in Cancer Treatment

Therapeutic Agent	Model	Autophagy Inhibition	Response
Temozolomide	Human malignant glioma cell lines	3-Methyladenine Bafilomycin A	Decreased cytotoxicity Increased cytotoxicity
Cyclophosphamide	Murine Myc-induced lymphoma cancer	Chloroquine	Increased antitumor response
5-Fluorouracil	Human colon cancer cell lines	3-Methyladenine	Increased apoptosis
5-Fluorouracil	Human colon cancer cell lines and xenograft		Increased cytotoxicity
5-Fluorouracil	Human colon cancer cell line (HT29)	Chloroquine	Increased cytotoxicity
5-Fluorouracil	Human hepatic carcinoma cell lines	3-Methyladenine	Increased apoptosis
5-Fluorouracil	Murine colon cancer cell line and tumor xenograft	Chloroquine	Increased apoptosis
5-Fluorouracil	Human NSCLC cell line (A549)	3-Methyladenine	Increased apoptosis
Cisplatin	Esophageal SSC cell line (EC9706)	3-Methyladenine	Increased apoptosis
Cisplatin	Human cholangiocarcinoma cell lines	3-Methyladenine Wortmannin	Increased cytotoxicity
Cisplatin	Human cervical cancer cell line (HeLa)	3-Methyladenine Chloroquine	Increased apoptosis
Cisplatin	Human hepatic carcinoma cell lines	3-Methyladenine	Increased apoptosis
Cisplatin	Laryngeal cancer cells (Hep-2)	3-Methyladenine	Increased apoptosis
Cisplatin	Human NSLC cell line (A549)	3-Methyladenine	Increased apoptosis
Oxaliplatin	Human colon cancer cell lines and xenograft	Chloroquine	Increased cytotoxicity and tumor control
Paclitaxel	Human NSLC cell line (A549)	3-Methyladenine	Increased apoptosis
Etoposide	Human hepatocellular carcinoma cell line (HepG2)	3-Methyladenine	Increased cytotoxicity
Doxorubicin	Human multiple myeloma cell lines, patient-derived multiple myeloma cells, human plasmacytoma xenograft	Hydroxychloroquine 3-Methyladenine	Increased apoptosis
Epirubicin	Human breast cancer cell line (MCF7)	Bafilomycin A	Increased apoptosis
Melphalan	Human multiple myeloma cell lines, patient-derived multiple myeloma cells, human plasmacytoma xenograft	Hydroxychloroquine 3-Methyladenine	Increased apoptosis
Topotecan	Human NSLC cell line (A549)	Chloroquine	Increased cytotoxicity
Camptothecin	Human breast cancer cell lines	Wortmannin 3-Methlyadenine Bafilomycin A	Increased apoptosis in selective cell lines

Autophagy in Cancer Treatment

Therapeutic Agent	Model	Autophagy Inhibition	Response
Imatinib	Human glioma cell lines	3-Methyladenine Bafilomycin A	Decreased cytotoxicity Increased cytotoxicity
Imatinib	Human Philadelphia chromosome positive CML cells	Chloroquine	Increased cytotoxicity
HDACi/vorinostat	Human colon cancer cells and xenografts	Chloroquine	Increased cytotoxicity Decreased growth
HDACi/panobinostat	Human triple negative breast cancer cells and xenografts	Chloroquine	Increased cytotoxicity Decreased tumor growth
HDACi/SAHA	Human CML cell lines and primary CML cells	Chloroquine	Increased cytotoxicity
HDACi/valproic acid	Human t(8;21) acute myeloid leukemia cells	Chloroquine	Increased cytotoxicity
HSP90i/DMAG	Human multiple myeloma cell lines	3-Methyladenine	Increased cytotoxicity
Erlotinib	Human glioblastoma cell lines	Chloroquine	Increased cytotoxicity
Sorafenib	Human hepatocellular carcinoma cell lines and xenografts	Chloroquine 3-Methyladenine	Increased cytotoxicity and decreased tumor growth
Sorafenib	Human hepatocellular carcinoma cell lines and xenografts	Chloroquine	Increased cytotoxicity and decreased tumor growth
Sunitinib	Rat PC12 cells	Ammonium chloride	Increased cytotoxicity
AKTi/AZD5363	Human prostate cancer cell lines and xenograft	3-Methyladenine Chloroquine Bafilomycin A	Increased cytotoxicity and decreased tumor growth
METi/PHA665752 and EMD1214063	Human gastric adenocarcinoma cell line	3-Methyladenine	Increased cytotoxicity
Vandetanib	Human glioblastoma cell lines and xenograft	3-Methyladenine Chloroquine	Increased cytotoxicity and decreased tumor growth
Bevacizumab	Human hepatocellular carcinoma xenografts	Chloroquine	Decreased tumor growth
Bortezomib	Human multiple myeloma cell line (U266)	3-Methyladenine Bafilomycin A	Decreased cytotoxicity Increased cytotoxicity
Bortezomib	Human hepatocellular carcinoma cell lines and xenografts	Chloroquine	Increased apoptosis

OPEN

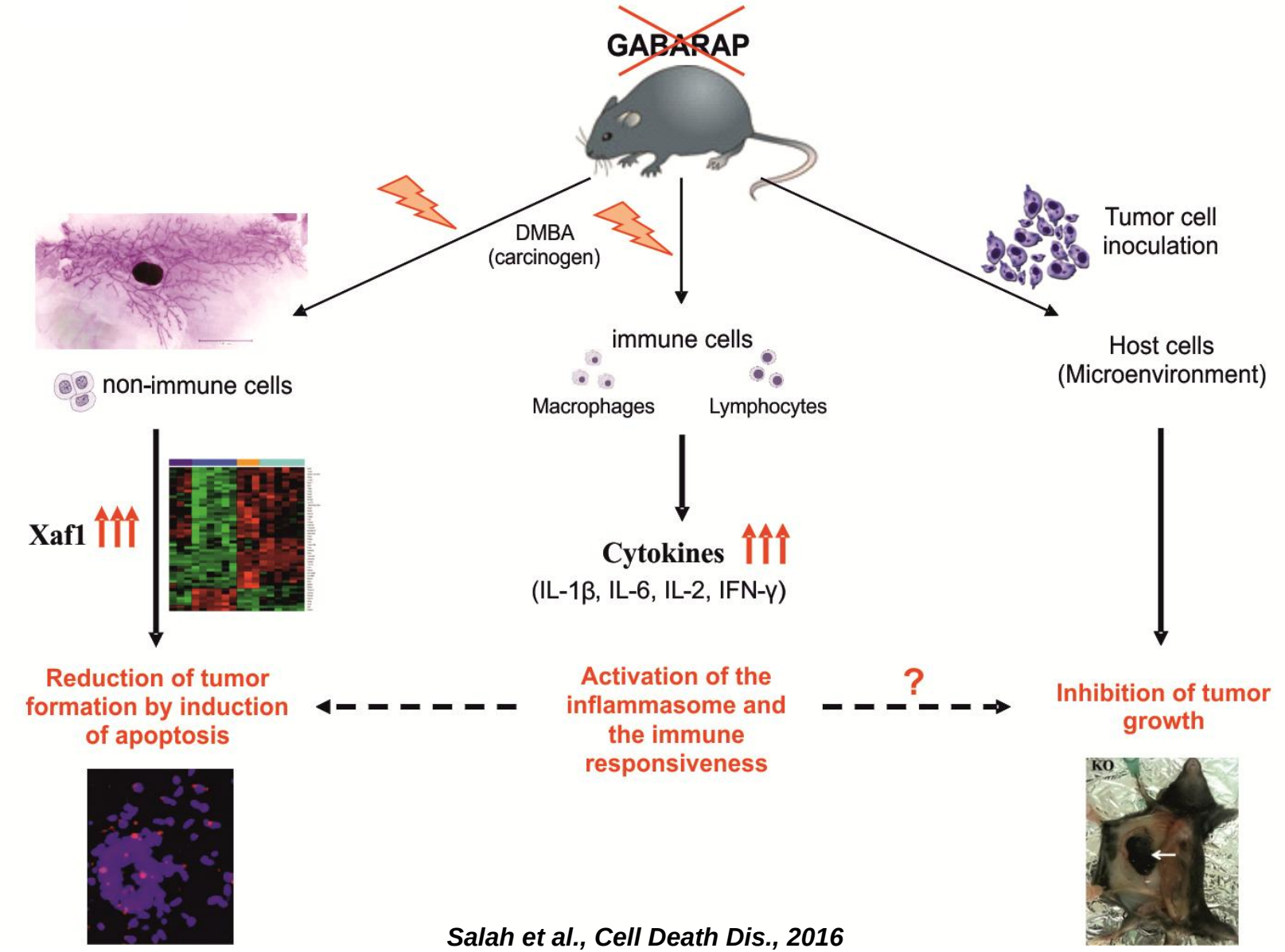
Citation: Cell Death and Disease (2016) 7, e2205; doi:10.1038/cddis.2016.93

www.nature.com/cddis

Tumor suppression in mice lacking GABARAP, an Atg8/LC3 family member implicated in autophagy, is associated with alterations in cytokine secretion and cell death

FS Salah[1,2], M Ebbinghaus[3], VY Muley[4,5], Z Zhou[6], KRD Al-Saadi[2], M Pacyna-Gengelbach[7], GA O'Sullivan[8], H Betz[8,9], R König[4,5], Z-Q Wang[6,10], R Bräuer[1] and I Petersen*[,1]

GABARAP belongs to an evolutionary highly conserved gene family that has a fundamental role in autophagy. There is ample evidence for a crosstalk between autophagy and apoptosis as well as the immune response. However, the molecular details for these interactions are not fully characterized. Here, we report that the ablation of murine GABARAP, a member of the Atg8/LC3 family that is central to autophagosome formation, suppresses the incidence of tumor formation mediated by the carcinogen DMBA and results in an enhancement of the immune response through increased secretion of IL-1β, IL-6, IL-2 and IFN-γ from stimulated macrophages and lymphocytes. In contrast, TGF-β1 was significantly reduced in the serum of these knockout mice. Further, DMBA treatment of these GABARAP knockout mice reduced the cellularity of the spleen and the growth of mammary glands through the induction of apoptosis. Gene expression profiling of mammary glands revealed significantly elevated levels of Xaf1, an apoptotic inducer and tumor-suppressor gene, in knockout mice. Furthermore, DMBA treatment triggered the upregulation of pro-apoptotic (Bid, Apaf1, Bax), cell death (Tnfrsf10b, Ripk1) and cell cycle inhibitor (Cdkn1a, Cdkn2c) genes in the mammary glands. Finally, tumor growth of B16 melanoma cells after subcutaneous inoculation was inhibited in GABARAP-deficient mice. Together, these data provide strong evidence for the involvement of GABARAP in tumorigenesis *in vivo* by delaying cell death and its associated immune-related response.
Cell Death and Disease (2016) 7, e2205; doi:10.1038/cddis.2016.93; published online 28 April 2016



Salah et al., Cell Death Dis., 2016

Published in final edited form as:
Cancer Discov. 2013 November ; 3(11): . doi:10.1158/2159-8290.CD-13-0397.

Autophagy Sustains Mitochondrial Glutamine Metabolism and Growth of BRAF^{V600E}–Driven Lung Tumors

Anne M. Strohecker[1,2], **Jessie Yanxiang Guo**[1,2], **Gizem Karsli-Uzunbas**[1,2], **Sandy M. Price**[1,2], **Guanghua Jim Chen**[1,2], **Robin Mathew**[1,2], **Martin McMahon**[3], and **Eileen White**[1,2,4]

[1]Cancer Institute of New Jersey, 195 Little Albany Street, New Brunswick NJ 08903

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[3]Helen Diller Family Comprehensive Cancer Center & Department of Cellular & Molecular Pharmacology, 1450 Third Street, MC 0128 PO Box 589001, University of California, San Francisco, CA 94158

Methods

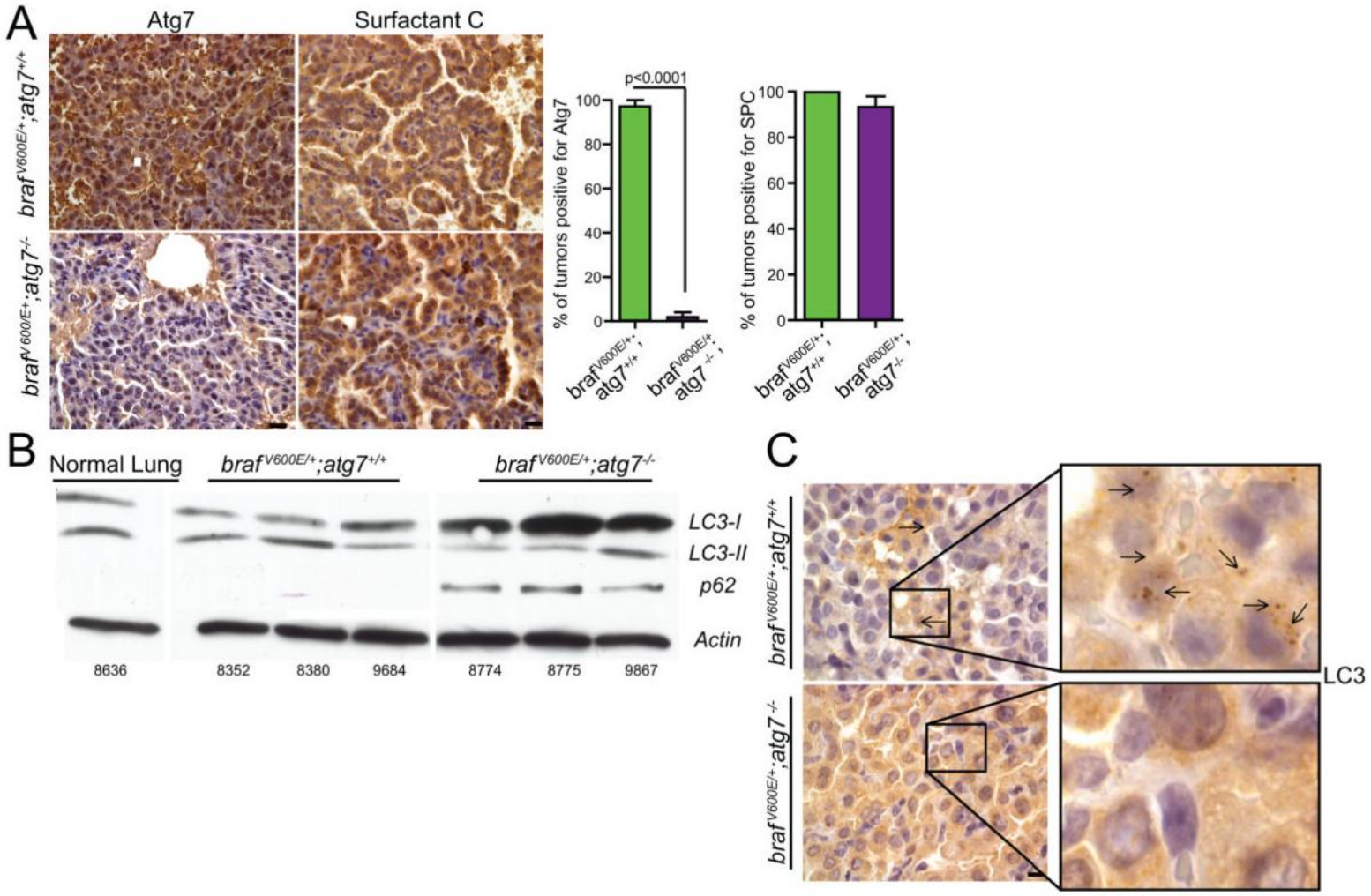
❖ This work was with genetically engineered mouse models of lung cancer in which the tumor-suppressive and tumor-promoting function of autophagy can be visualized in the same system.

❖ ***Braf*** activation

❖ Conditional ***Atg7*** deletion (in lung tissue)

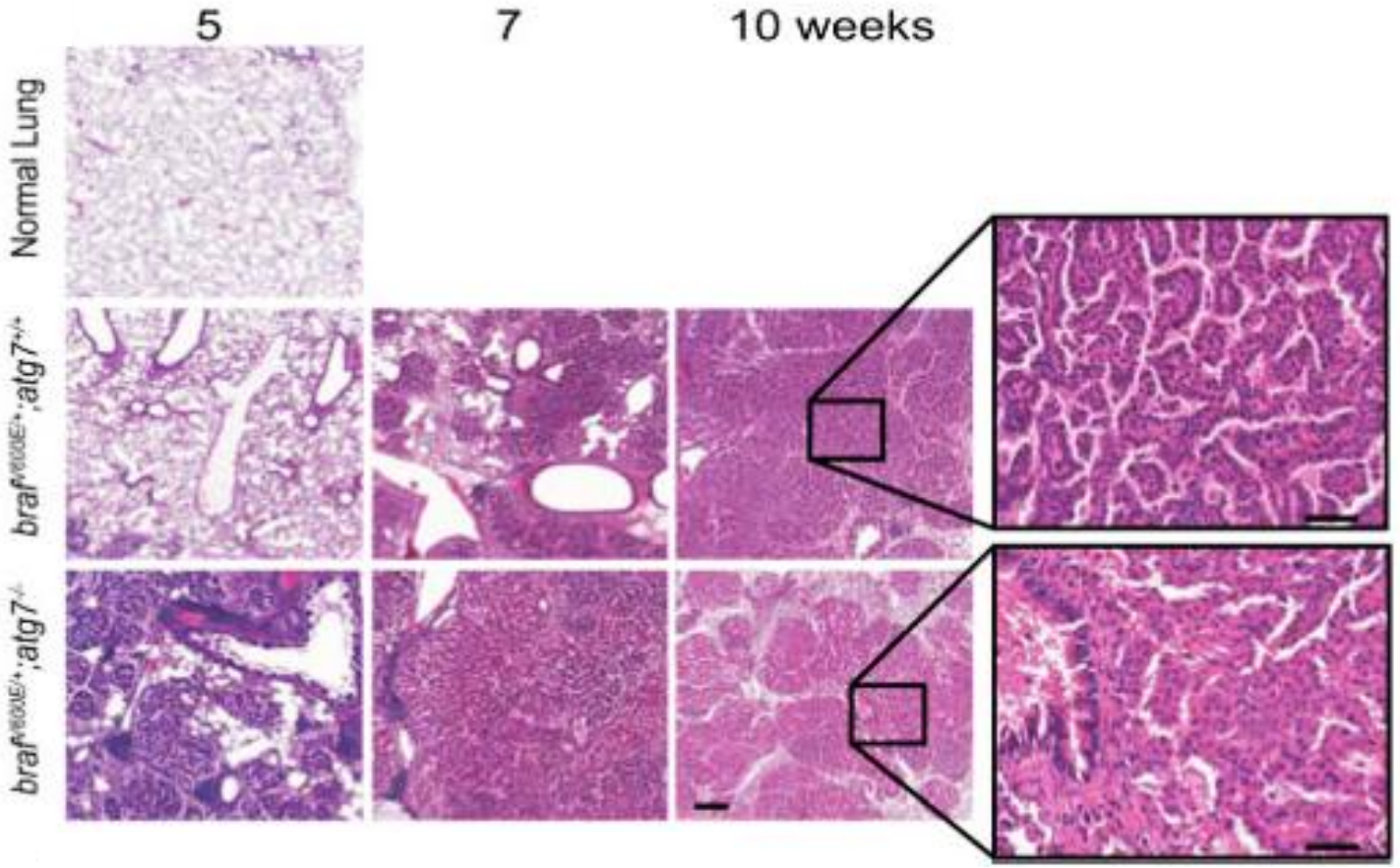
❖ Intra-nasal administration of adenoviral Cre recombinase

Atg7 deletion blocks autophagy in a mouse model of *braf*^{V600E}–driven lung tumorigenesis



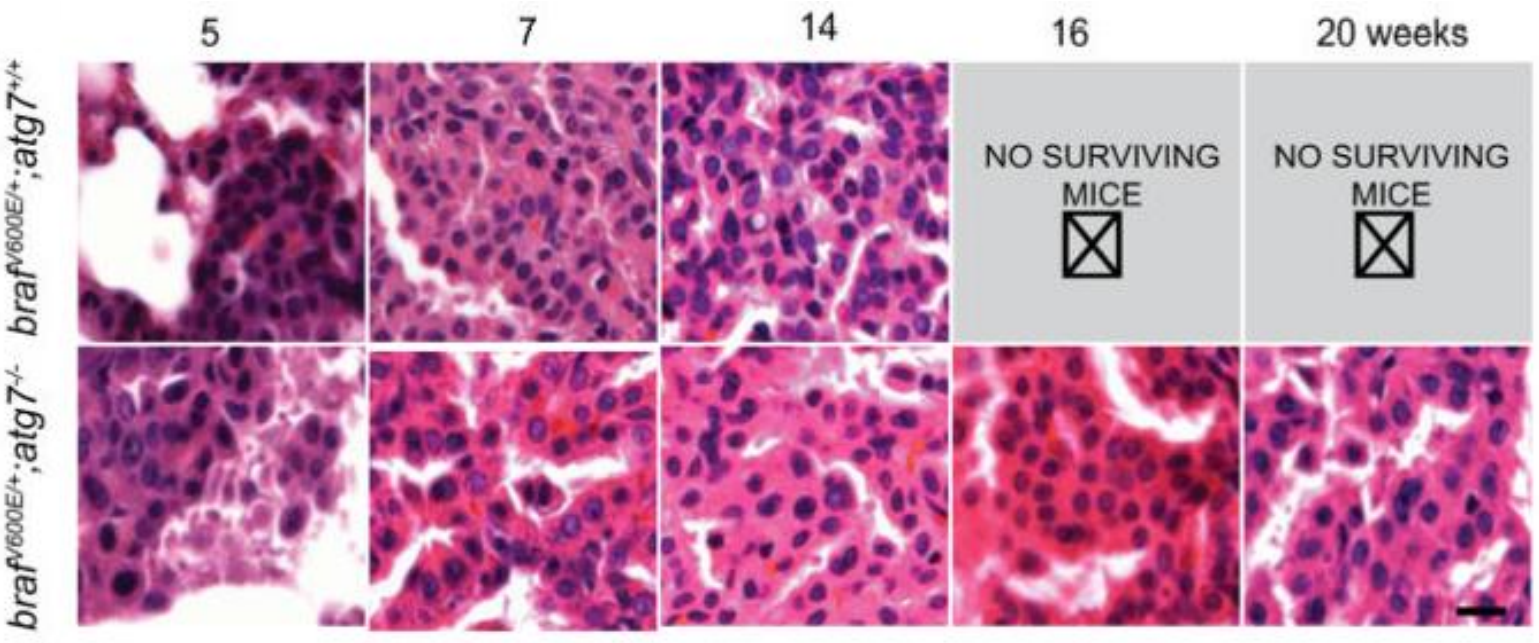
Strohecker et al., Cancer Discov., 2013

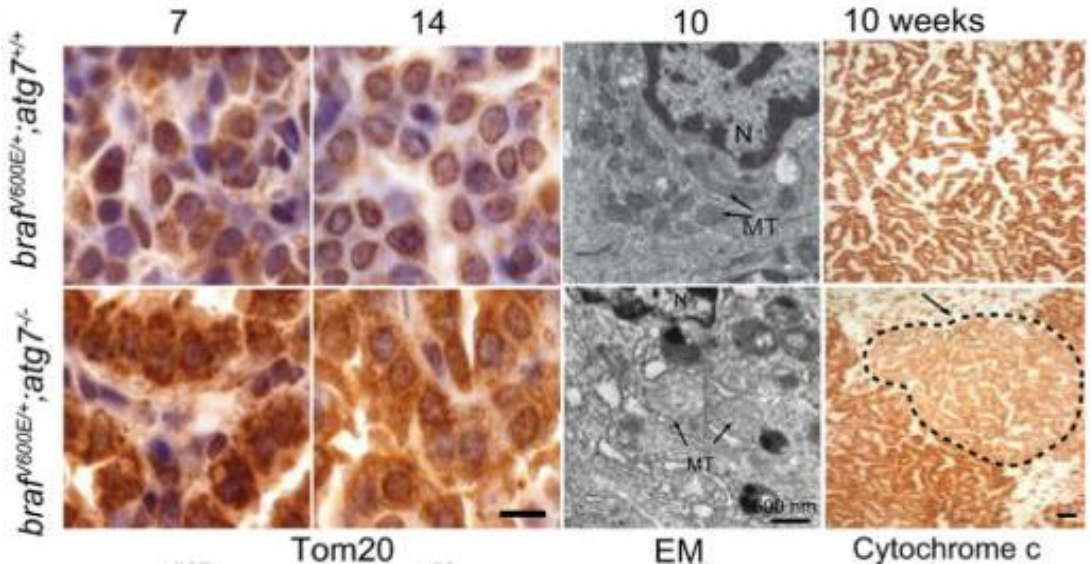
Atg7 deficiency has distinct consequences for tumor establishment and maintenance in *Braf^{V600E}*–driven lung tumors



Strohecker et al., Cancer Discov., 2013

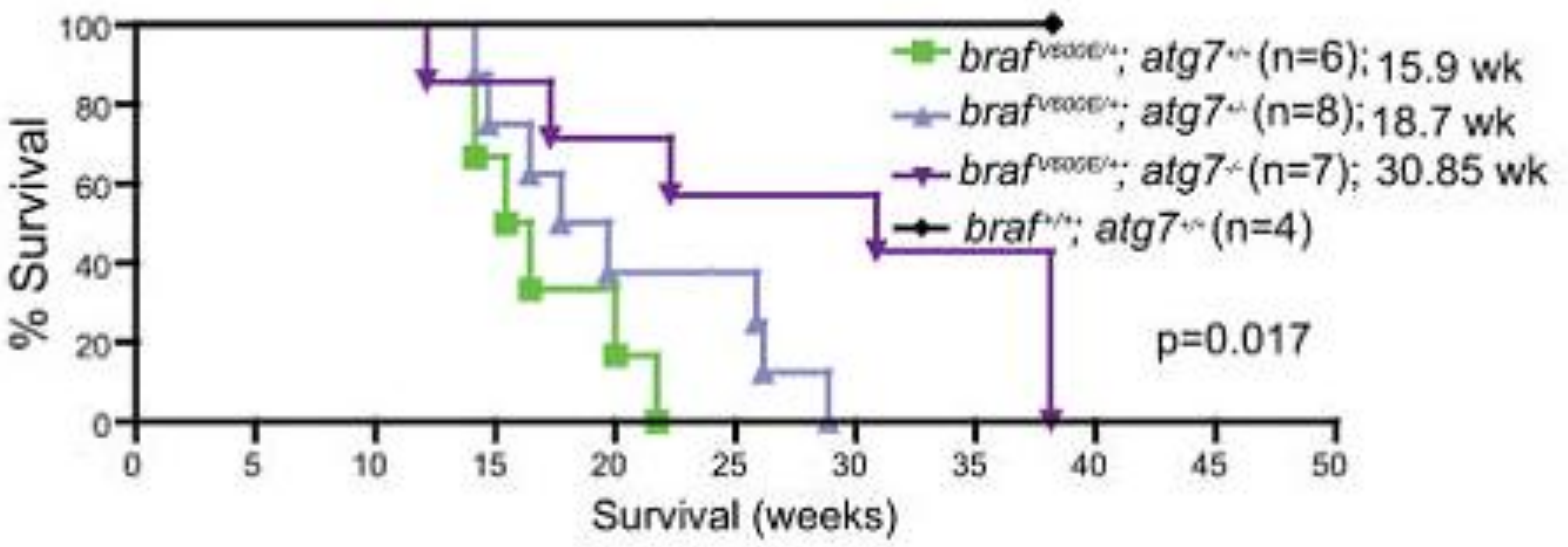
Increasing large cytoplasm in the *Braf* $^{V600E/+}$; *Atg7*$^{-/-}$ tumors indicative of oncocytoma





Autophagy ablation results in a functional defect in the mitochondria of these tumors

Kaplan Meier analysis of overall survival of *Braf* $^{V600E/+}$; *Atg7*$^{+/+}$ and *Braf* $^{V600E/+}$; *Atg7*$^{-/-}$ mice post Cre



Strohecker et al., Cancer Discov., 2013

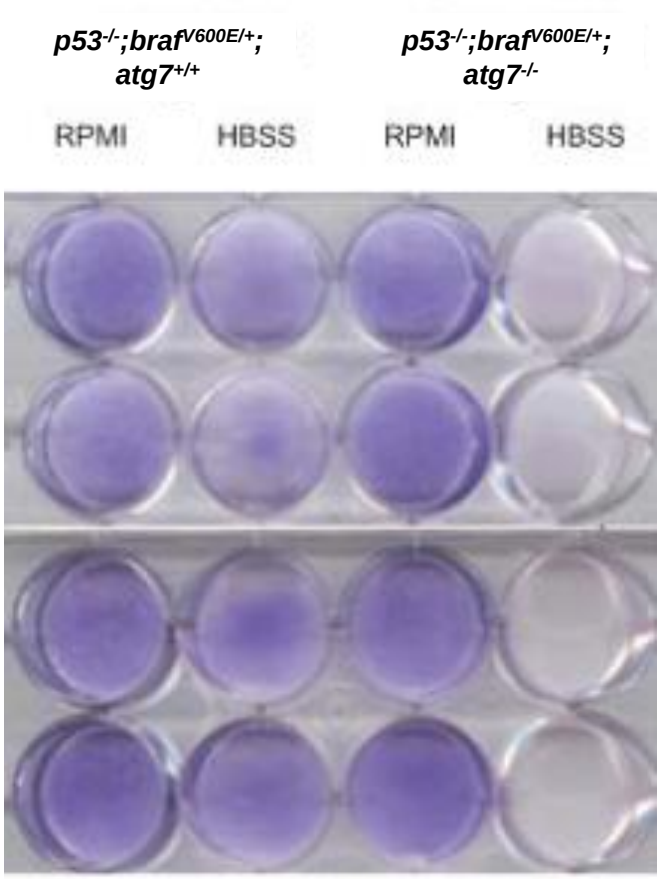
p53 Loss in *Braf*^{V600E}-driven Lung Tumors

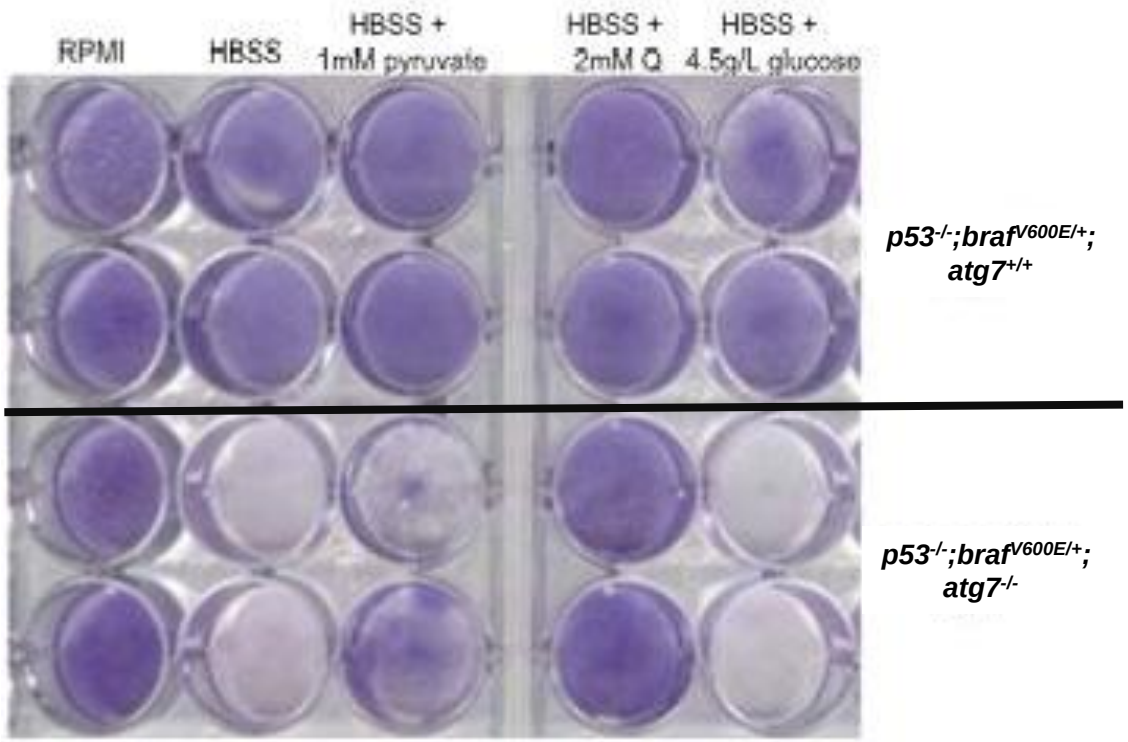
❖ Loss of p53 does not ablate the increased early tumorigenesis or life span extension of mice carrying *Braf* $^{V600E/+}$; *Atg7*$^{-/-}$ tumors.

❖ Loss of p53 in *Braf* $^{V600E/+}$; *Atg7*$^{+/+}$ tumors:

Adenoma ⟶ Adenocarcinoma

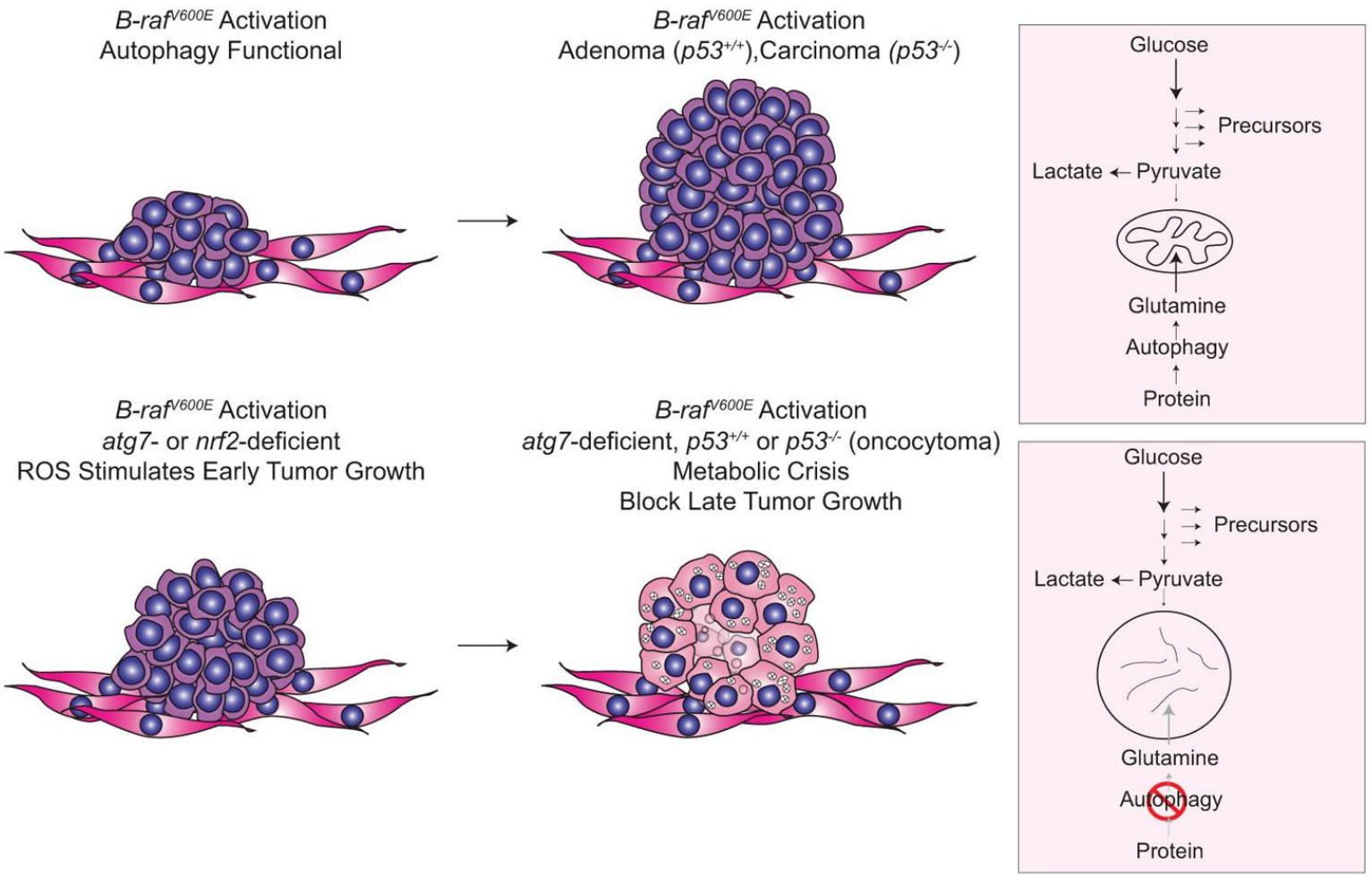
Loss of *Atg7* impairs mitochondrial metabolism and survival during starvation





Strohecker et al., Cancer Discov., 2013

Role of *Atg7* in the growth of *Braf*^{V600E}-driven lung tumors



❖ **Significance:** ***Braf*^{V600E}**-driven tumors require **autophagy** and likely autophagy-provided substrates to maintain mitochondrial metabolism and to promote tumor growth, suggesting that autophagy ablation may improve cancer therapy.

Strohecker et al., Cancer Discov., 2013

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1	☐	Not yet recruiting	**Autophagy** Bladder **Cancer**	• Bladder **Cancer**			• Assiut Assiut, Egypt
2	☐	Unknown †	**Autophagy** Inhibition Using Hydrochloroquine in Breast **Cancer** Patients	• Breast **Cancer**	• Drug: Hydrochloroquine	Phase 2	• University Medical Centre Nijmegen Nijmegen, Gelderland, Netherlands
3	☐	Completed	Modulation of **Autophagy** in Patients With Advanced/Recurrent Non-small Cell Lung **Cancer** - Phase II	• Non-small Cell Lung **Cancer** • Advanced Non-small Cell Lung **Cancer** • Recurrent Non-small Cell Lung **Cancer**	• Drug: Paclitaxel • Drug: Carboplatin • Drug: Hydroxychloroquine • Drug: Bevacizumab	Phase 2	• Robert Wood Johnson University Hospital at Hamilton Hamilton, New Jersey, United States • Rutgers **Cancer** Institute of New Jersey New Brunswick, New Jersey, United States
4	☐	Recruiting	Sorafenib Induced **Autophagy** Using Hydroxychloroquine in Hepatocellular **Cancer**	• Hepatocellular **Cancer**	• Drug: Sorafenib (SOR) • Drug: Hydroxychloroquine (HCQ)	Phase 2	• University of Texas Health **Cancer** Center San Antonio, Texas, United States
5	☐	Terminated	Hydroxychloroquine in Blocking **Autophagy** in Patients With Prostate **Cancer** Undergoing Surgery or Active Surveillance	• Prostate Carcinoma	• Drug: Hydroxychloroquine • Other: Laboratory Biomarker Analysis	Early Phase 1	• Rutgers **Cancer** Institute of New Jersey New Brunswick, New Jersey, United States
6	☐	Completed	Chloroquine as an Anti-**Autophagy** Drug in Stage IV Small Cell Lung **Cancer** (SCLC) Patients	• Small Cell Lung **Cancer**	• Drug: Chloroquine, A-CQ 100	Phase 1	• NKI/AvL Amsterdam, Netherlands • VU Medical Center Amsterdam, Netherlands


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