

СНК Онкологии ПМГМУ им. И.М. Сеченова

**Аутофагия, как новая мишень в лекарственной терапии
метастатической меланомы**

Выполнил:

Студент 5 курса 21 группы
лечебного факультета
Жуликов Ярослав

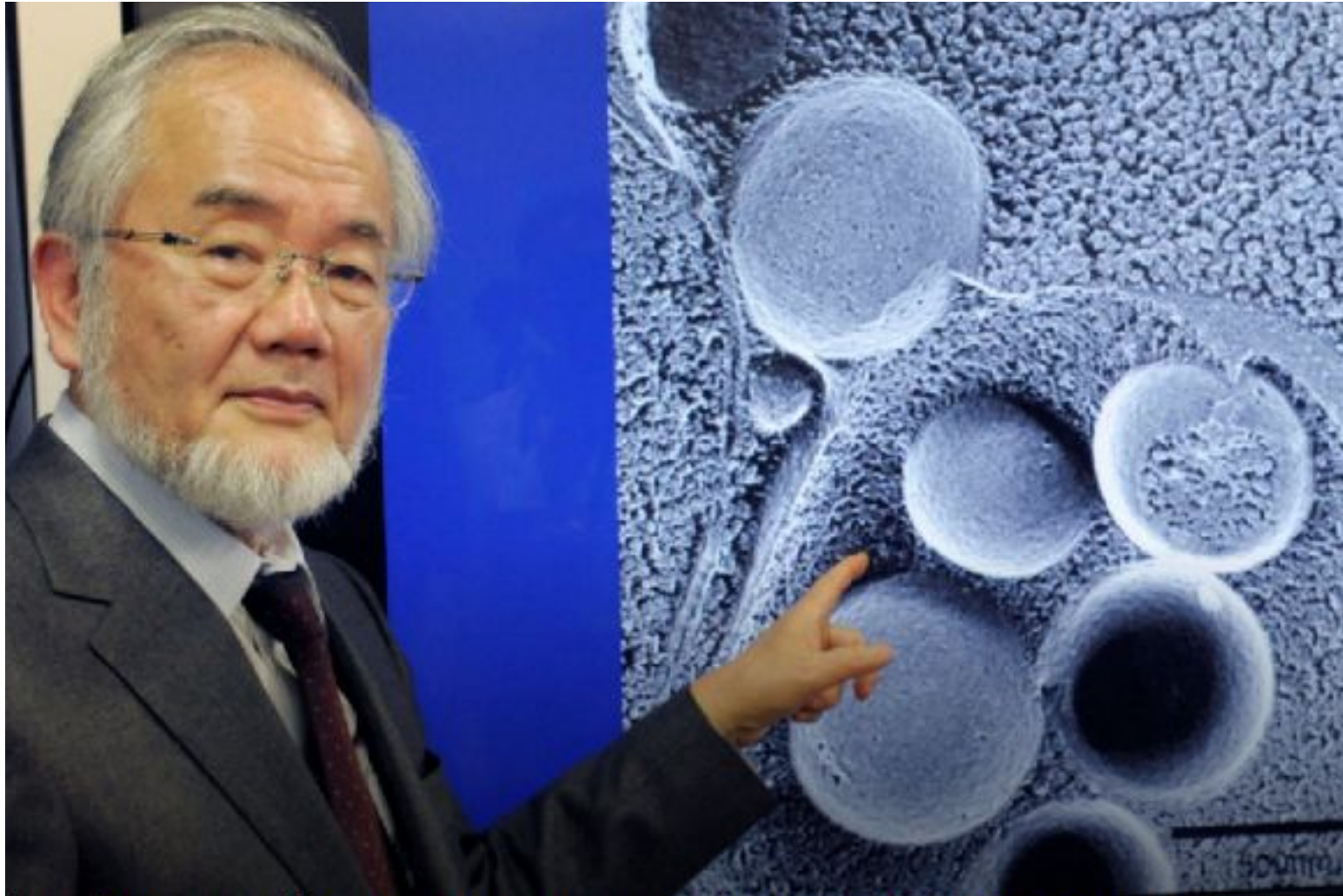
Научный руководитель:

к.м.н., ассистент кафедры онкологии
ПМГМУ им. И.М. Сеченова
Синельников Игорь Евгеньевич

История

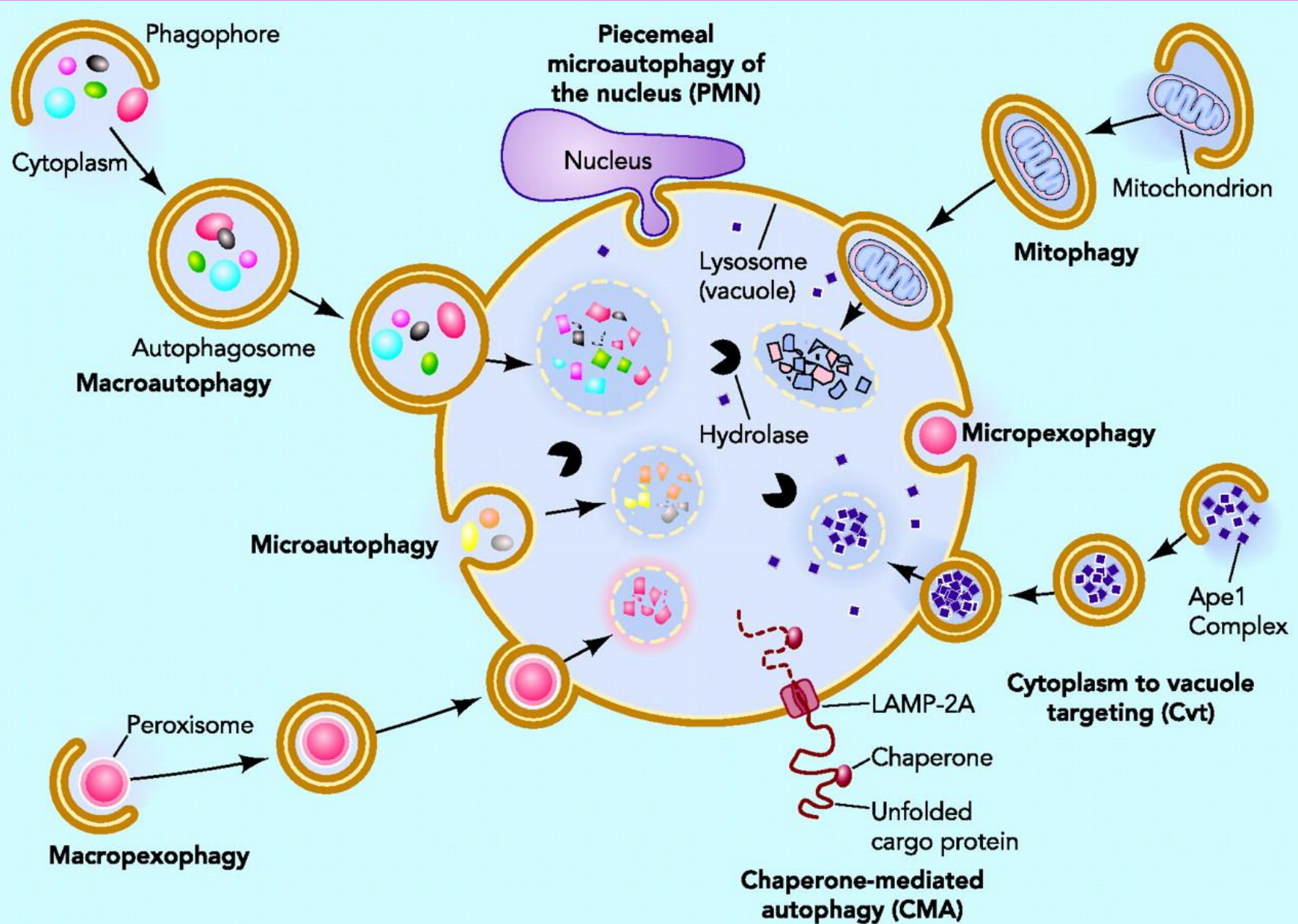


Christian René de Duve
1974- нобелевская премия за открытие
ЛИЗОСОМ

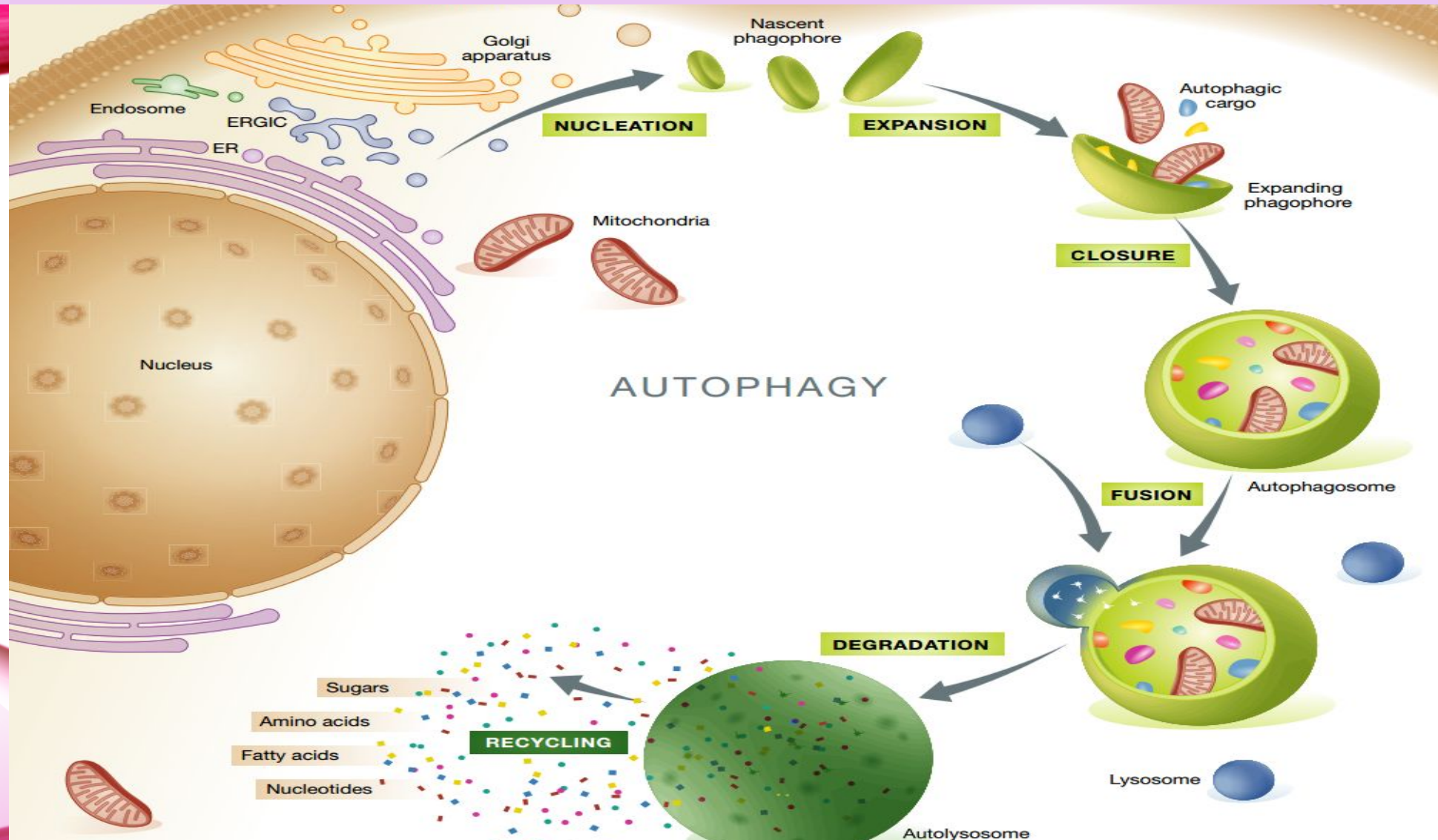


Yoshinori Ohsumi
2016- роль аутофагии в процессах старения,
похудения, канцерогенеза

Виды аутофагии



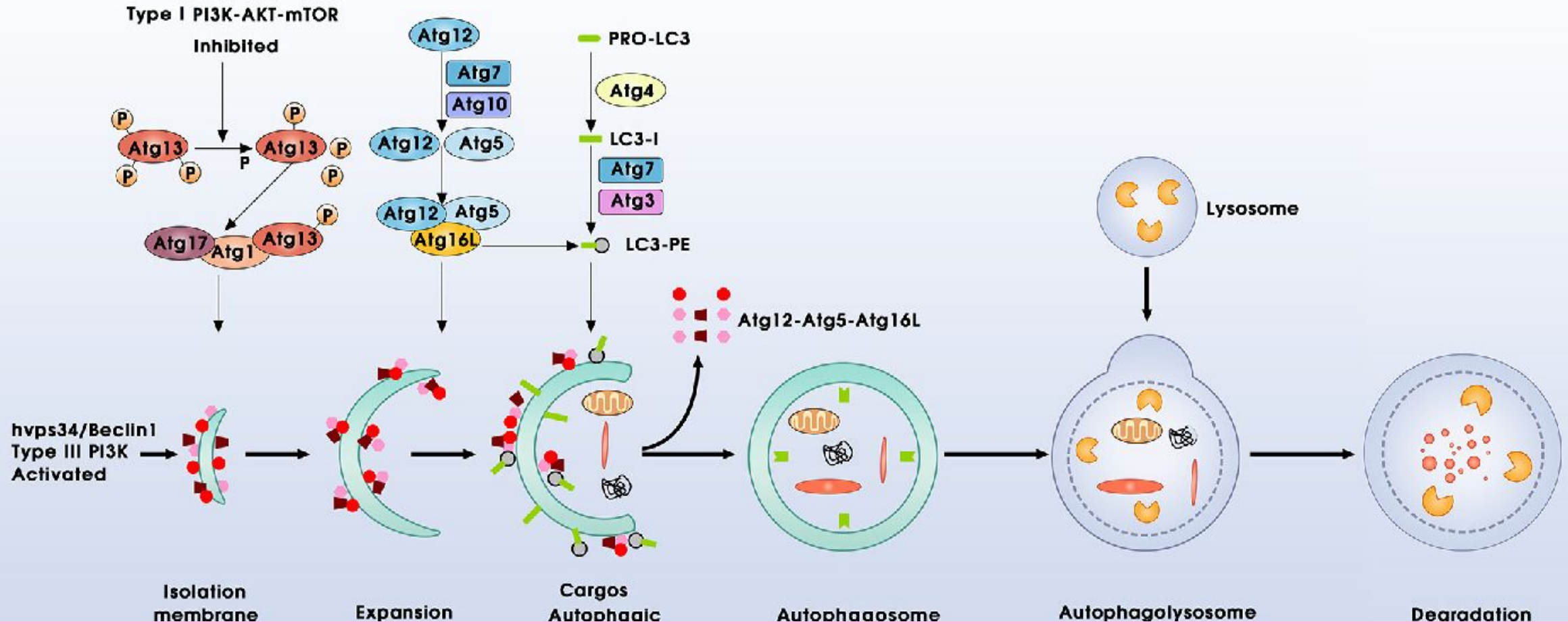
Макроаутофагия



*Lorenzo Galluzzi, Federico Pietrocola, José Manuel Bravo-San Pedro, Ravi K
Autophagy in malignant transformation and cancer progression. The EMBO Journal Vol 34 | No 7 | 2015

Молекулярные механизмы аутофагии

■ Atg12 ● Atg5 ● Atg16 — PRO-LC3 — LC3-I ● LC3-PE — LC3-II ● Hydrolases

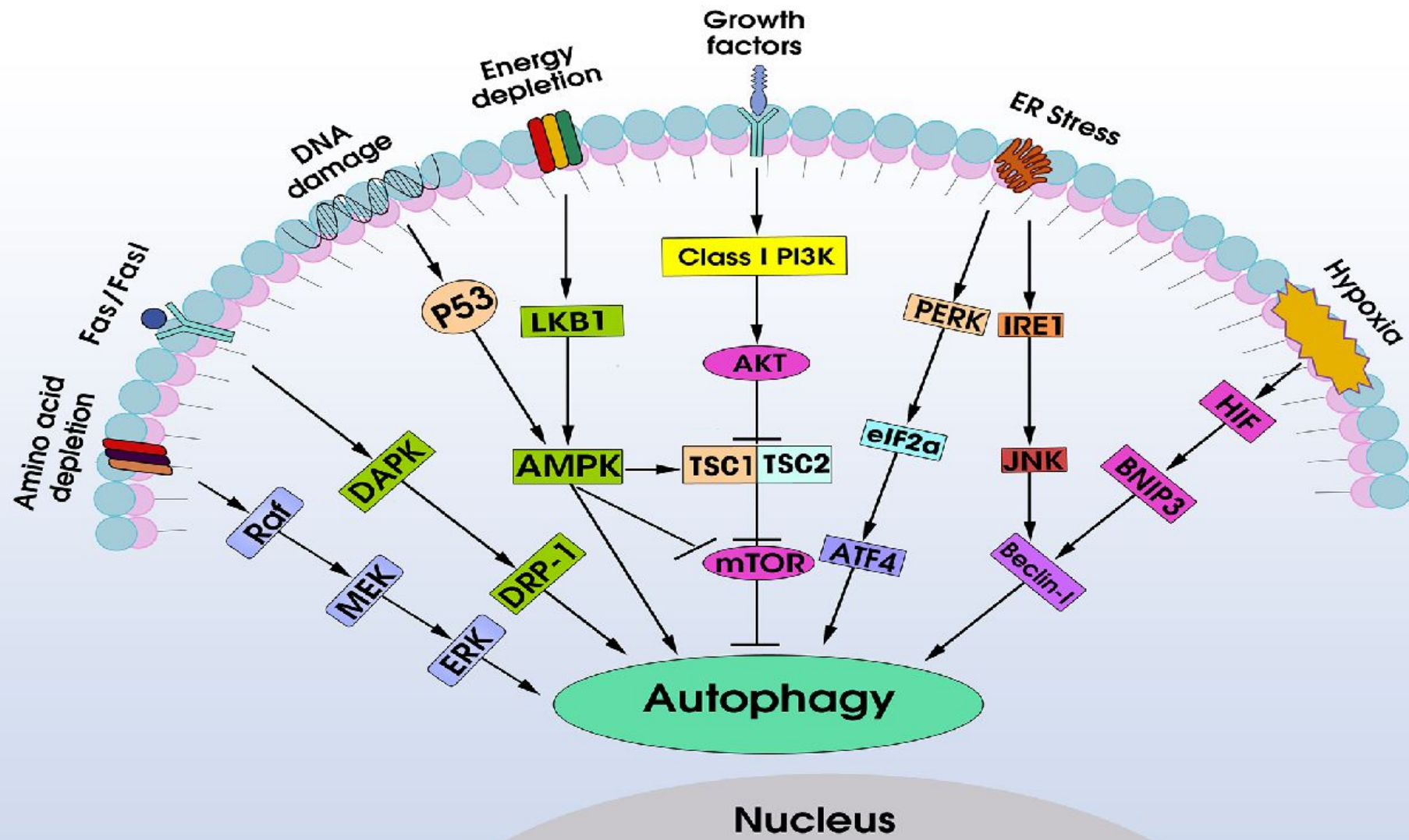


* Liangshun You, Shenhe Jin, Li Zhu, Wenbin Qian.

Autophagy, autophagy-associated adaptive immune responses and its role in hematologic malignancies.

Oncotarget, 2017, Vol. 8, (No. 7), pp: 12374-12388

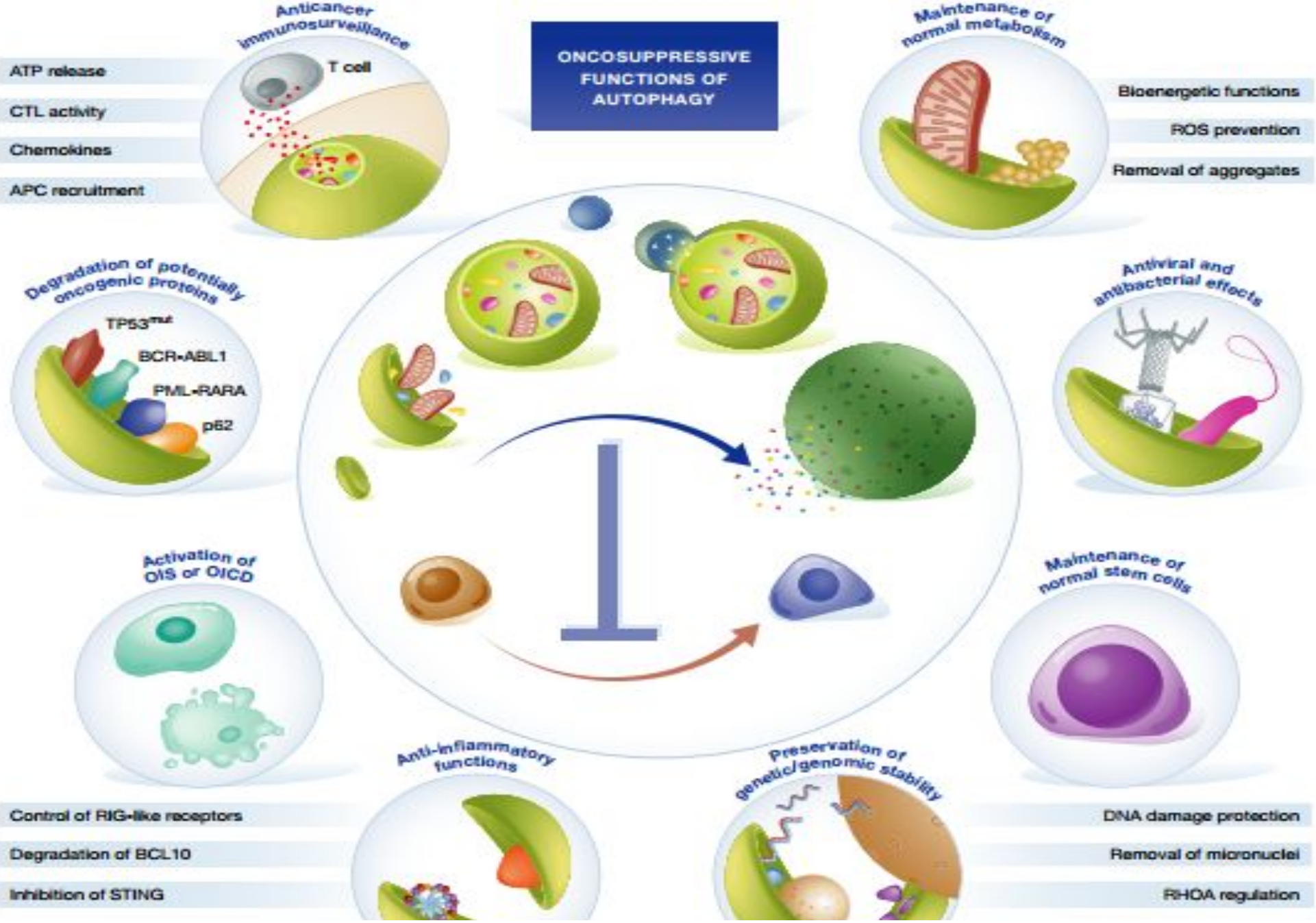
Регуляция аутофагии



* Liangshun You, Shenhe Jin, Li Zhu, Wenbin Qian. Autophagy, autophagy-associated adaptive immune responses and its role in hematologic malignancies. *Oncotarget*, 2017, Vol. 8, (No. 7), pp: 12374-12388

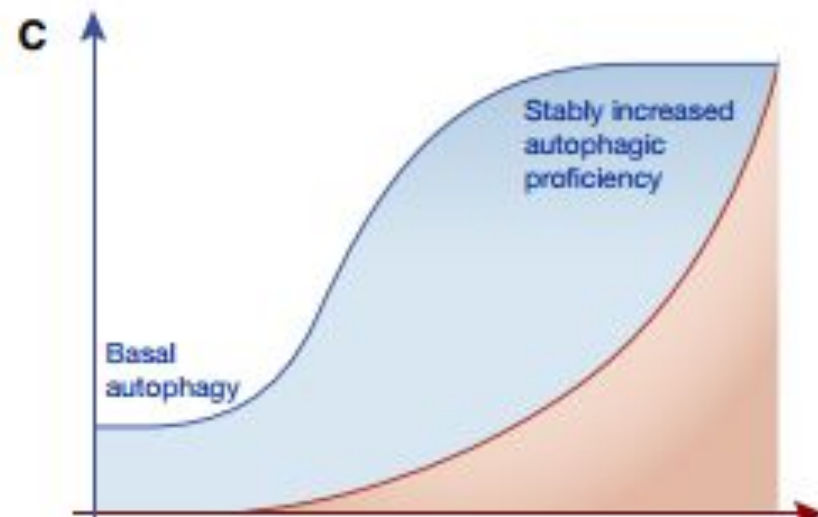
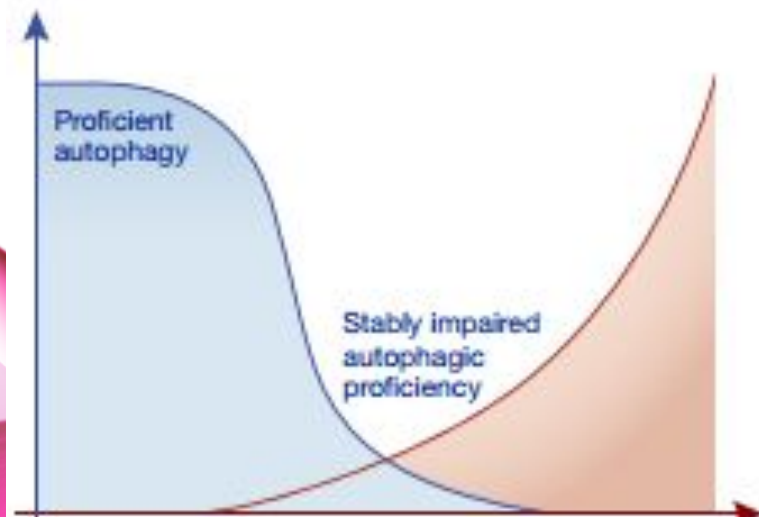
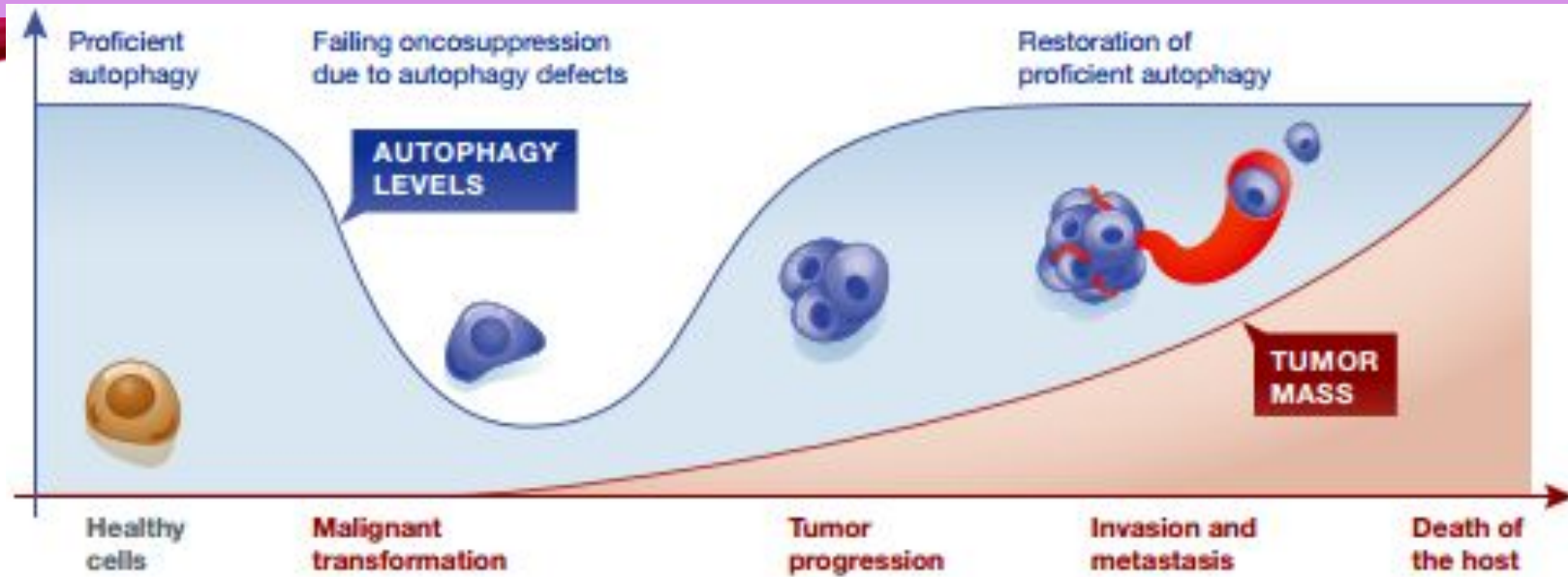
Онкопресорная роль аутофагии

**ONCOSUPPRESSIVE
FUNCTIONS OF
AUTOPHAGY**

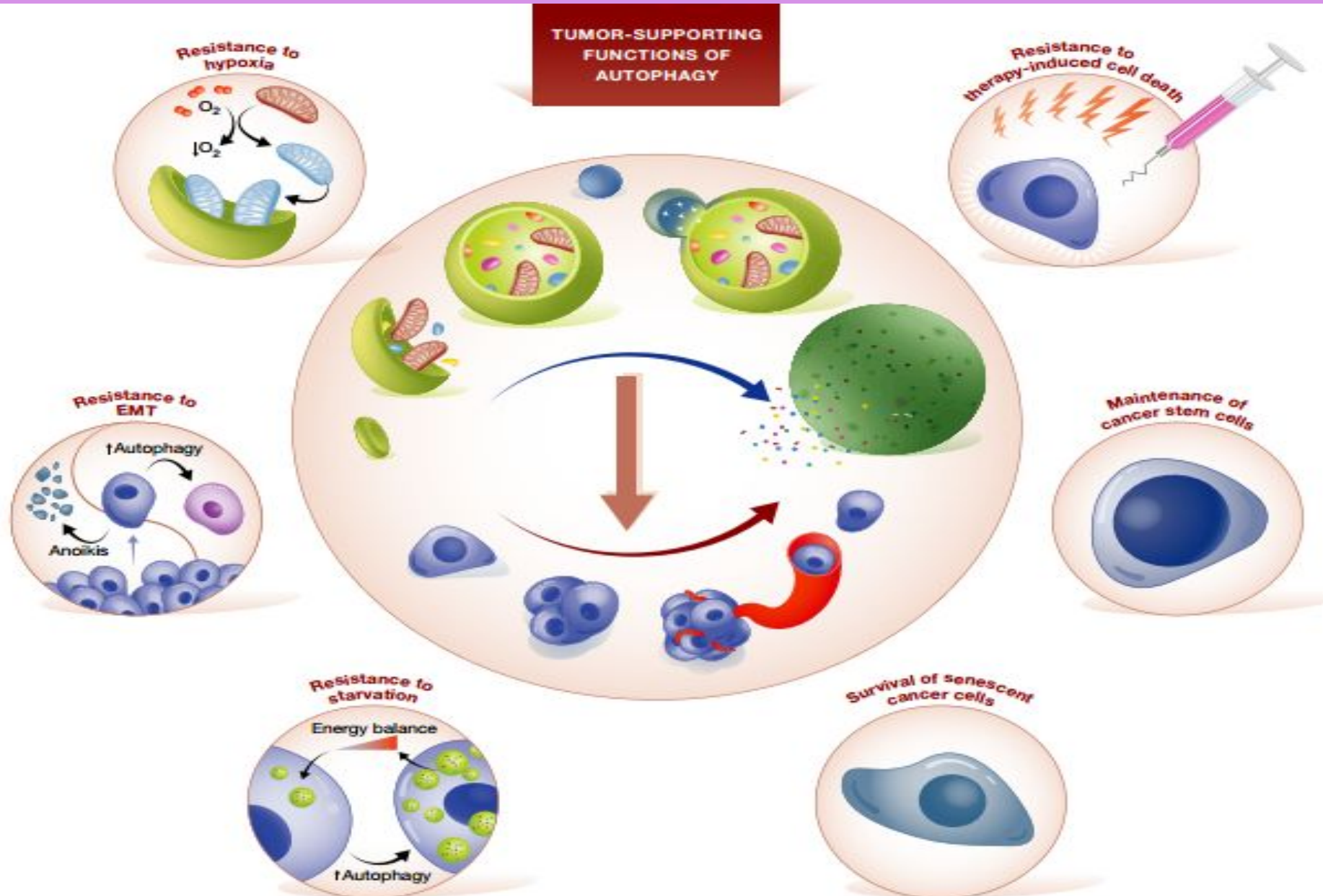


*Lorenzo Galluzzi, Federico Pietrocola, José Manuel Bravo-San Pedro, Ravi K
Autophagy in malignant transformation and cancer progression. The EMBO Journal Vol 34 | No 7 | 2015

Аутофагия и опухолевая прогрессия



Аутофагия и опухолевая прогрессия



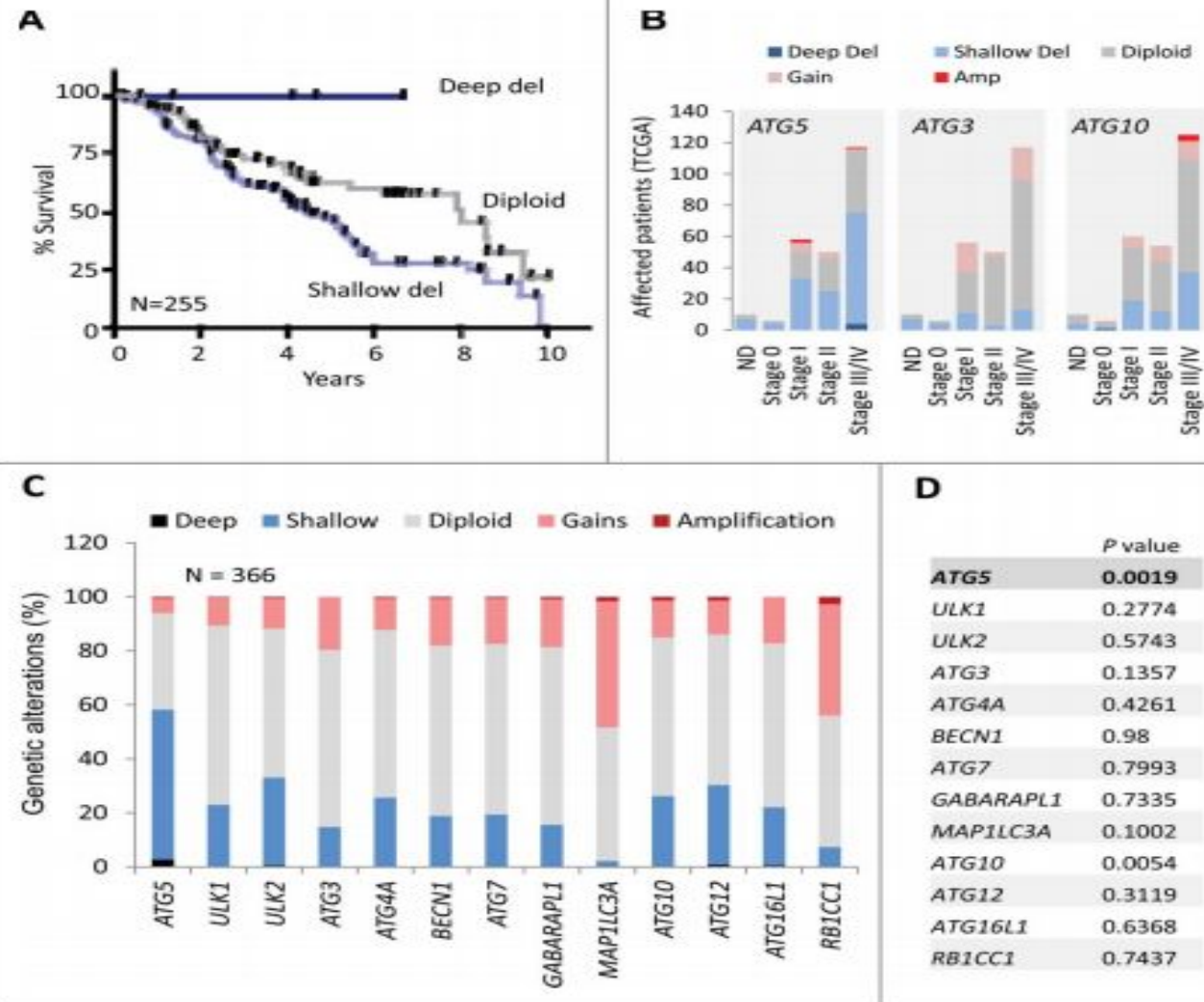


*I'm
starving!*

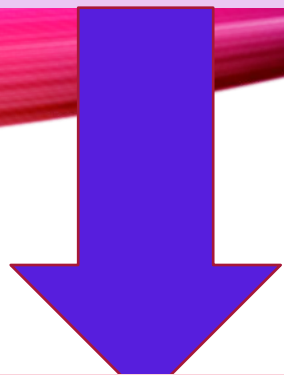
*Why don't you
eat your old
proteins and
organelles?*



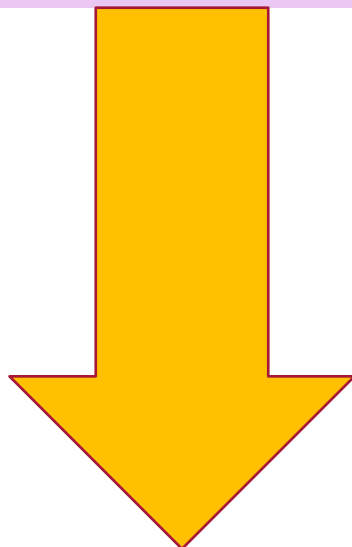
Дисрегуляция аутофагии при меланоме кожи



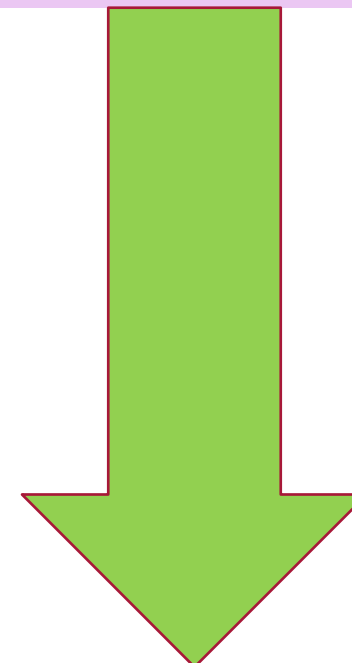
Направления лекарственной терапии меланомы



Химиотерапия

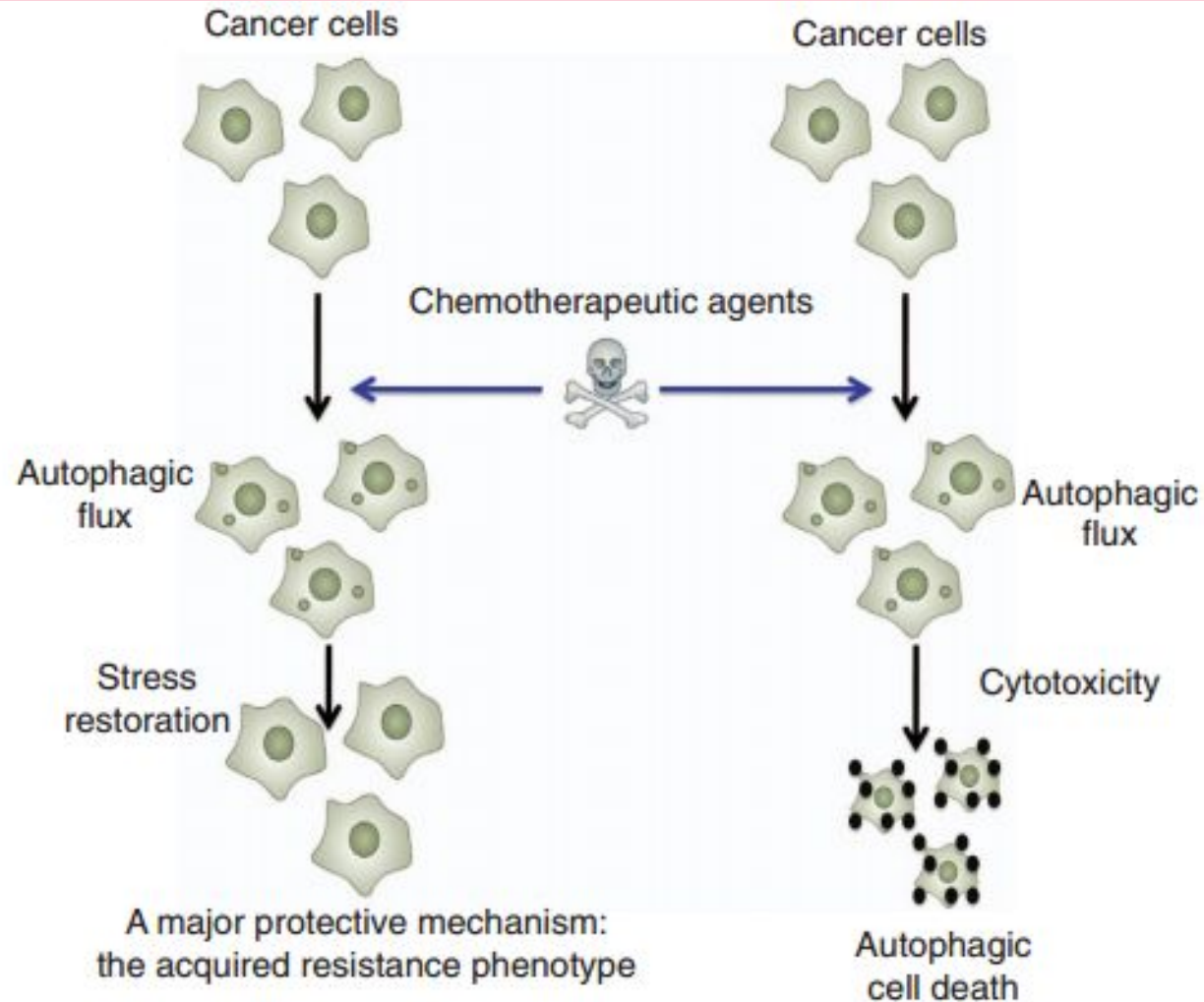


**Ингибирование
BRAF и MEK**



**Модуляторы
иммунных
синапсов**

Аутофагия и чувствительность к химиотерапии



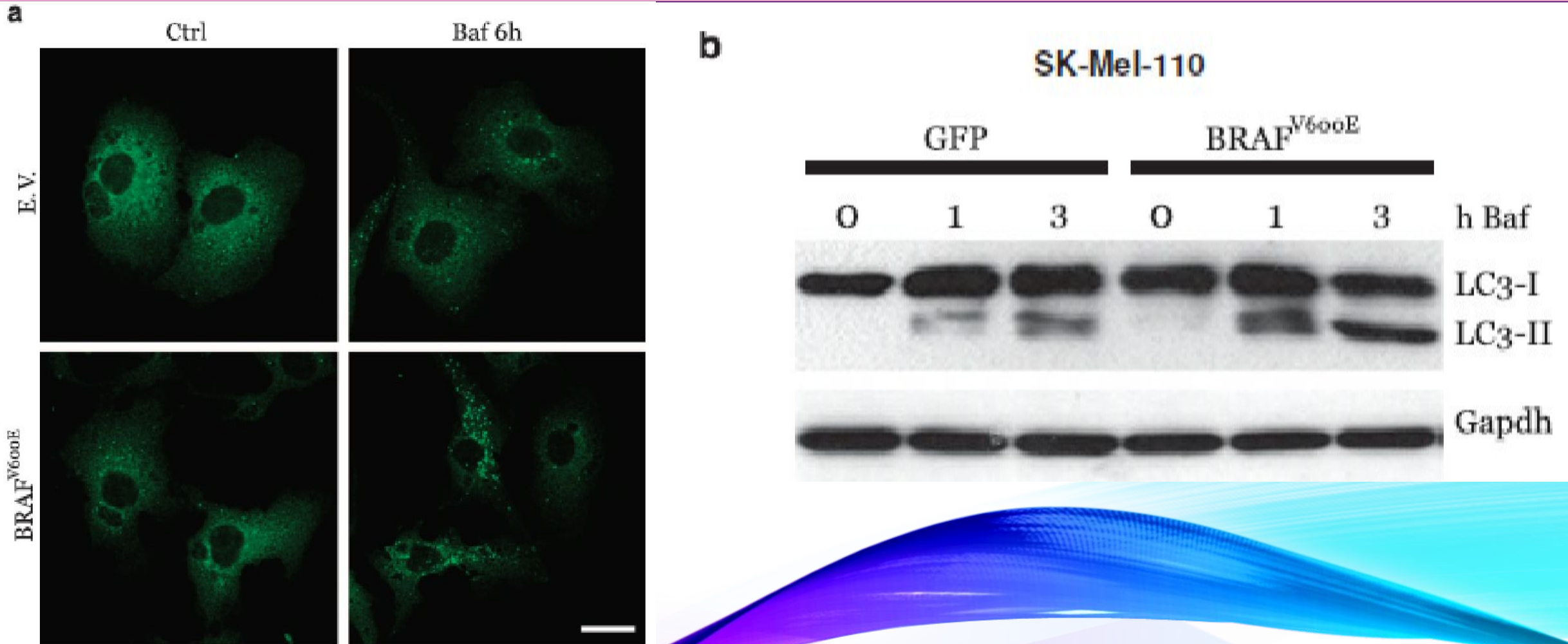
Индукция аутофагии различными противораковыми препаратами

Class	Target	Type of cancer	Autophagy role	Method used to evaluate autophagy
<i>Autophagy inducers</i>				
Aurora kinase A	mTOR	Breast	Prosurvival	siRNA (LC3, Atg5) CQ
Suberoylanilide hydroxamic acid (SAHA)	HDAC inhibitor	CML	Prosurvival	Bafilomycin A 3-MA Bafilomycin A
Epirubicin (EPI)	Anthracyclines	Breast Breast	Prodeath Prosurvival	3-MA siRNA (Beclin 1, Atg7) Bafilomycin A
5-Fluorouracil	Thymidylate synthase inhibitor	Colorectal	Prosurvival	siRNA (Atg7) 3-MA
Atorvastatin	AMPK	Digestive malignancies	Prodeath Prosurvival	3-MA siRNA (Atg5) Bafilomycin A
Irinotecan	MAPK14/p38 α	Colorectal	Prosurvival	siRNA (Atg5, Atg7) Bafilomycin A 3-MA
Cisplatin Oxaliplatin	Genotoxic stress Genotoxic stress	Esophageal Hepatocellular carcinoma	Prosurvival Prosurvival	3-MA siRNA (Atg5) CQ 3-MA
Bevacizumab	Angiogenesis inhibitor	Hepatocellular carcinoma	Prosurvival	CQ 3-MA
Sorafenib	ER stress	Hepatocellular carcinoma	Prosurvival	CQ
High-mobility group box 1 protein (HMGB1)	Genotoxic stress DAMP molecule	CML	Prodeath Prosurvival	siRNA (Beclin 1)
Gefitinib or Erlotinib	EGFR tyrosine kinase inhibitor	Lung	Prosurvival	siRNA (Atg5, Atg7) CQ 3-MA
Topotecan RAGE	Genotoxic stress Genotoxic or metabolic stress	Lung Pancreatic	Prosurvival Prosurvival	CQ
NVP-BEZ235	PI3K/AKT/mTOR inhibitor	Renal Urothelial	Prosurvival Prodeath	CQ
Ursolic acid	Genotoxic stress	Prostate Cervical	Prosurvival Prodeath	siRNA (Atg5, Beclin 1) 3-MA siRNA (Atg5) Wortmannin
Imatinib	Tyrosine kinase inhibitor	Glioma	Prosurvival Prodeath	Bafilomycin A RTA 203 siRNA (Atg5, Beclin 1) 3-MA
FK-16 Temozolomide Mono-Pt	Fragment of LL-37 Genotoxic stress Genotoxic stress	Colon Glioblastoma Ovarian	Prodeath Prodeath Prodeath	siRNA (Bax, Bcl-2) mTOR inhibitor RAD001 siRNA (Atg7, Beclin 1) 3-MA CQ
Cannabinoids	ER stress AMPK	Glioma Pancreatic Hepatocellular carcinoma	Prodeath Prodeath Prodeath	Bafilomycin A siRNA (Atg1) 3-MA CQ siRNA (Atg5) 3-MA

Текущие исследования комбинированного лечения метастатической меланомы ингибиторами аутофагии и химиотерапией

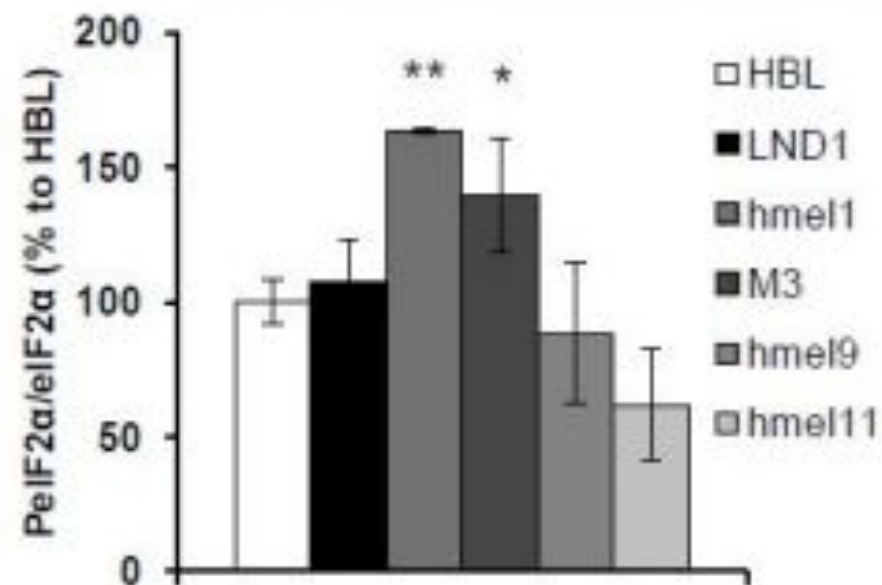
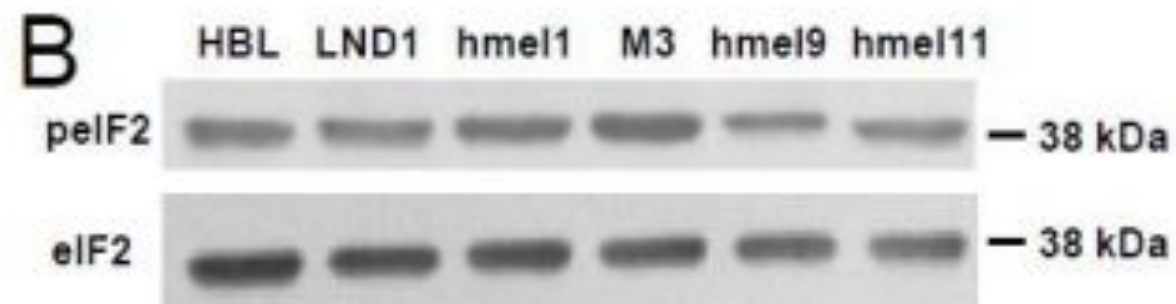
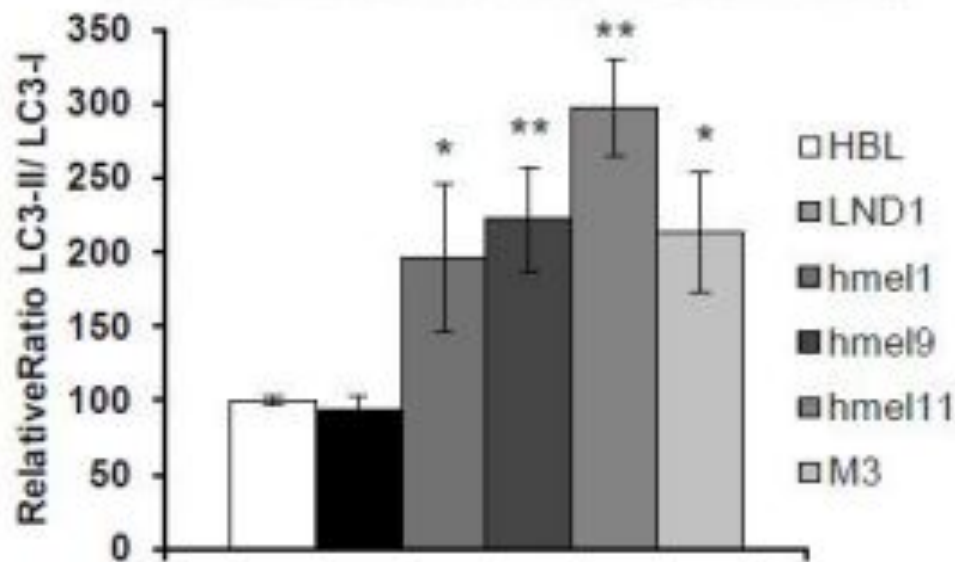
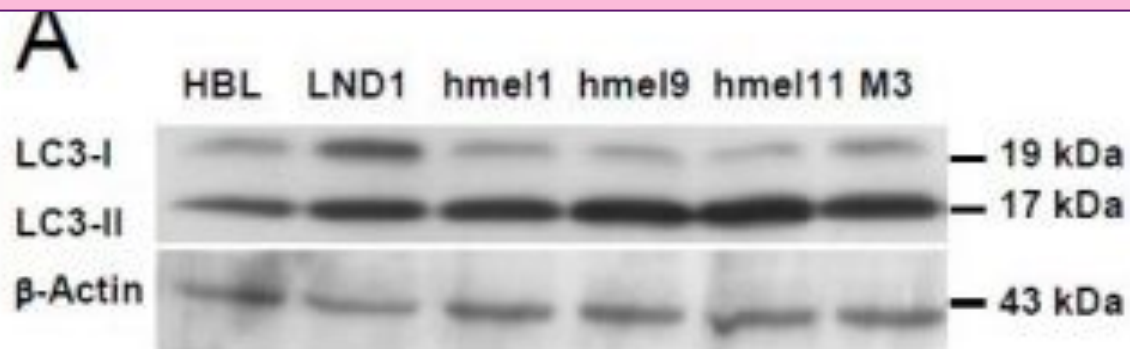
Cancer type	Therapeutic combinations	Outcome
Melanoma	Phase I temozolomide/HCQ	Accumulation of autophagy vacuoles

Аутофагия и активирующие мутации в BRAF



* M Corazzari, F Rapino, F Ciccocanti, P Giglio. Oncogenic BRAF induces chronic ER stress condition resulting in increased basal autophagy and apoptotic resistance of cutaneous melanoma. *Cell Death and Differentiation* (2014), 1–13

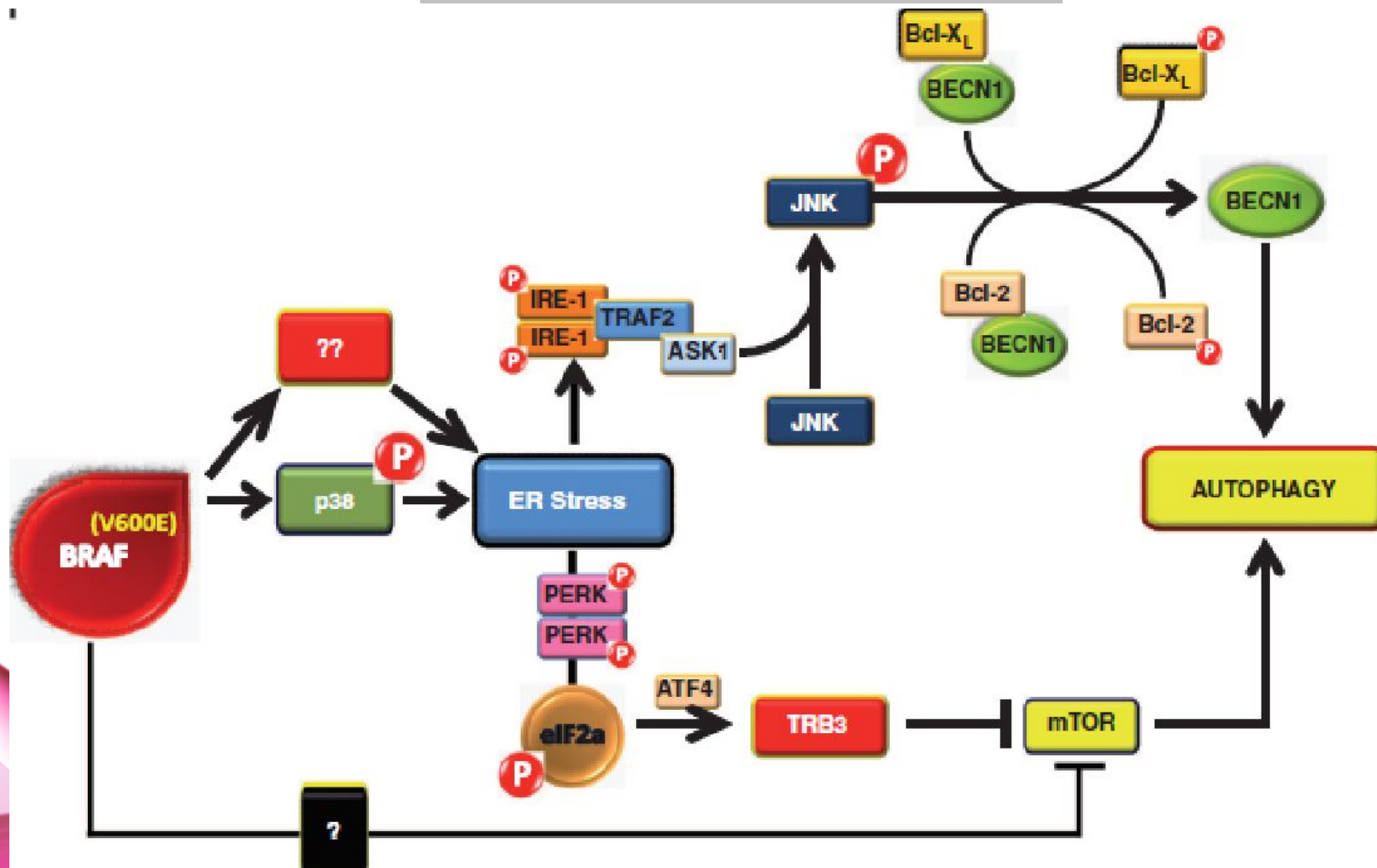
Аутофагия и активирующие мутации в BRAF



*Anna Ferrettaa, Immacolata Maida, Stefania Guidab, Amalia Azzaritic. New insight into the role of metabolic reprogramming in melanoma cells harboring BRAF mutations.

BBA - Molecular Cell Research (2016), doi: 10.1016/j.bbamcr.2016.08.007

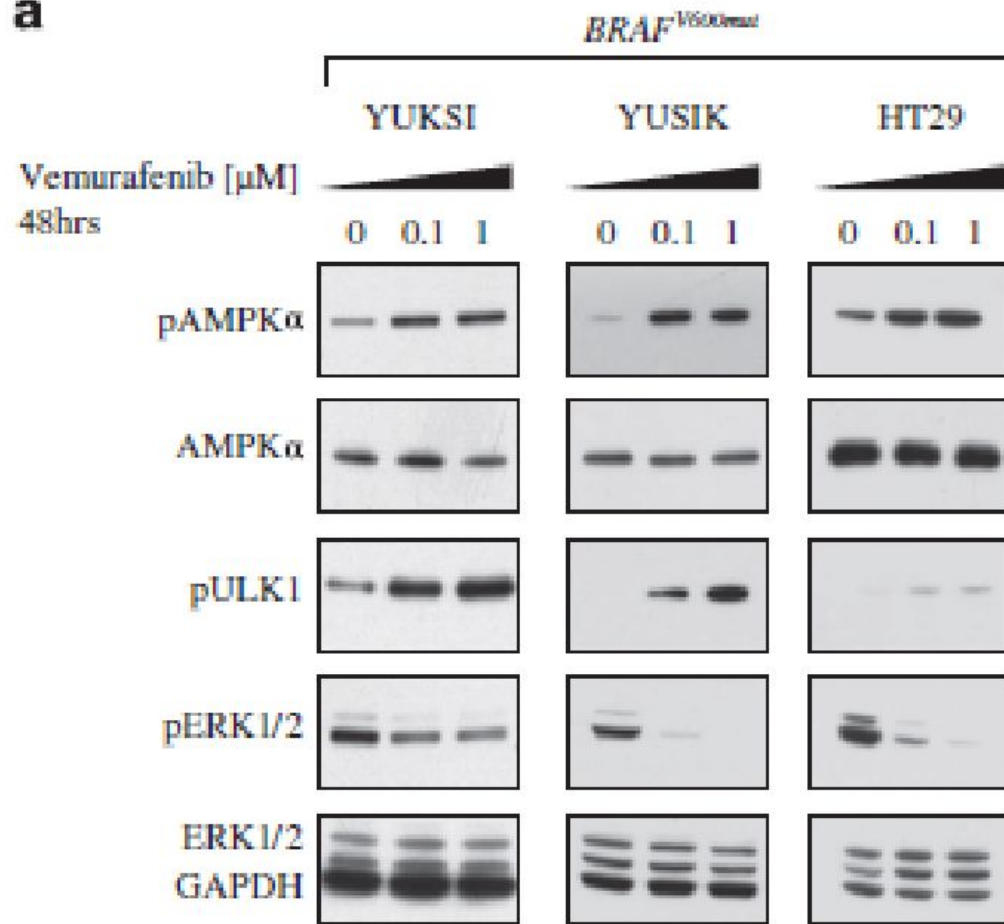
Регуляция аутофагии в BRAF+ меланомах



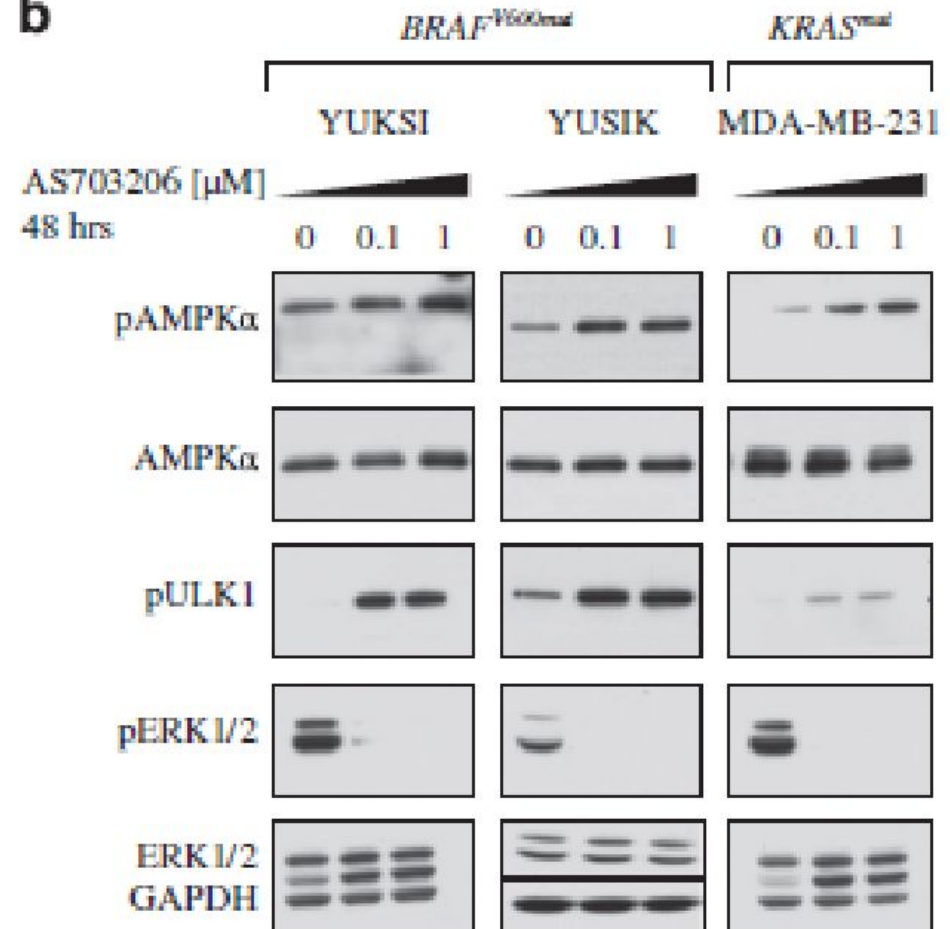
* M Corazzari, F Rapino, F Ciccocanti, P Giglio. Oncogenic BRAF induces chronic ER stress condition resulting in increased basal autophagy and apoptotic resistance of cutaneous melanoma. Cell Death and Differentiation (2014), 1–13

Изменение базального уровня аутофагии при терапии BRAFi и MEKi

a



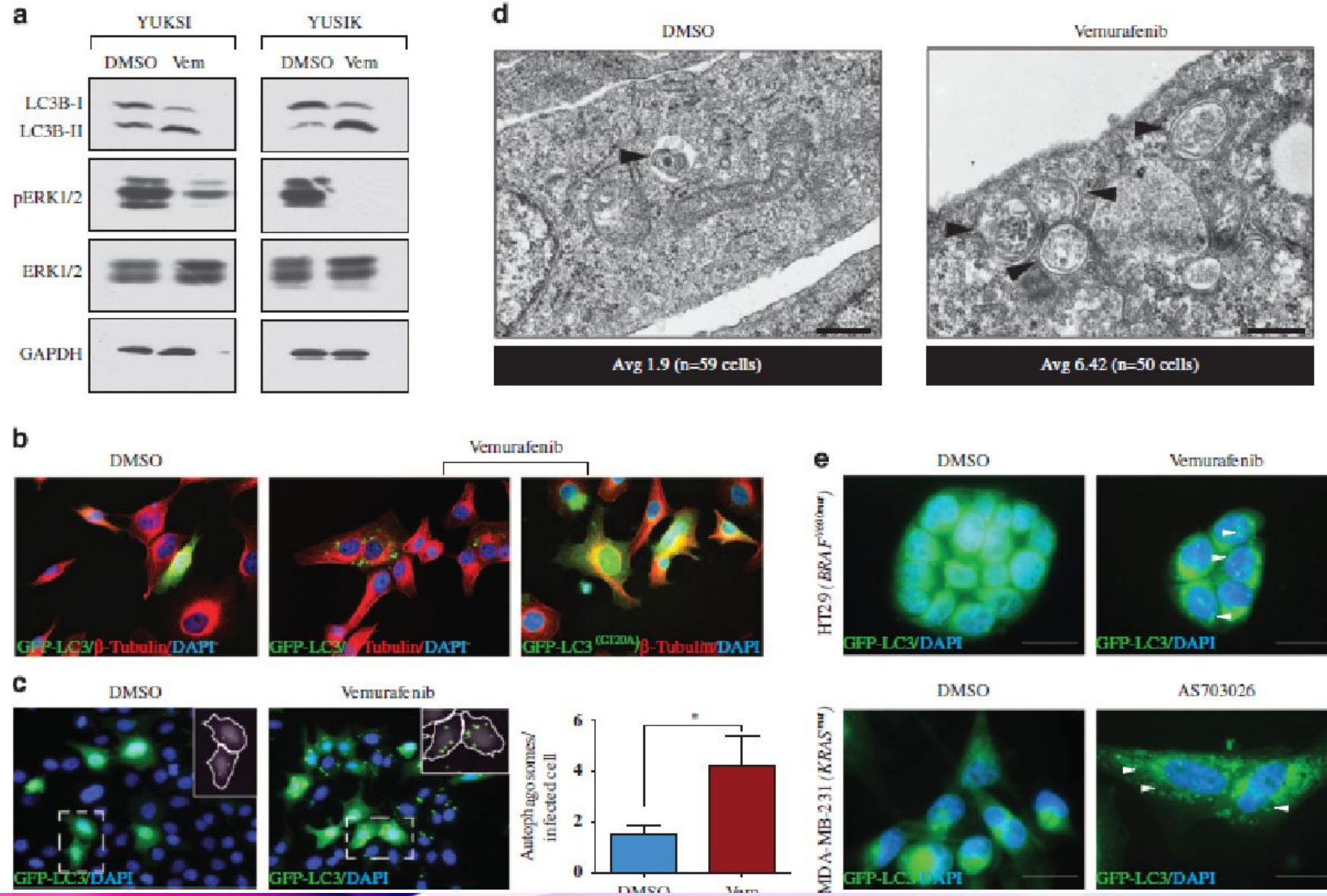
b



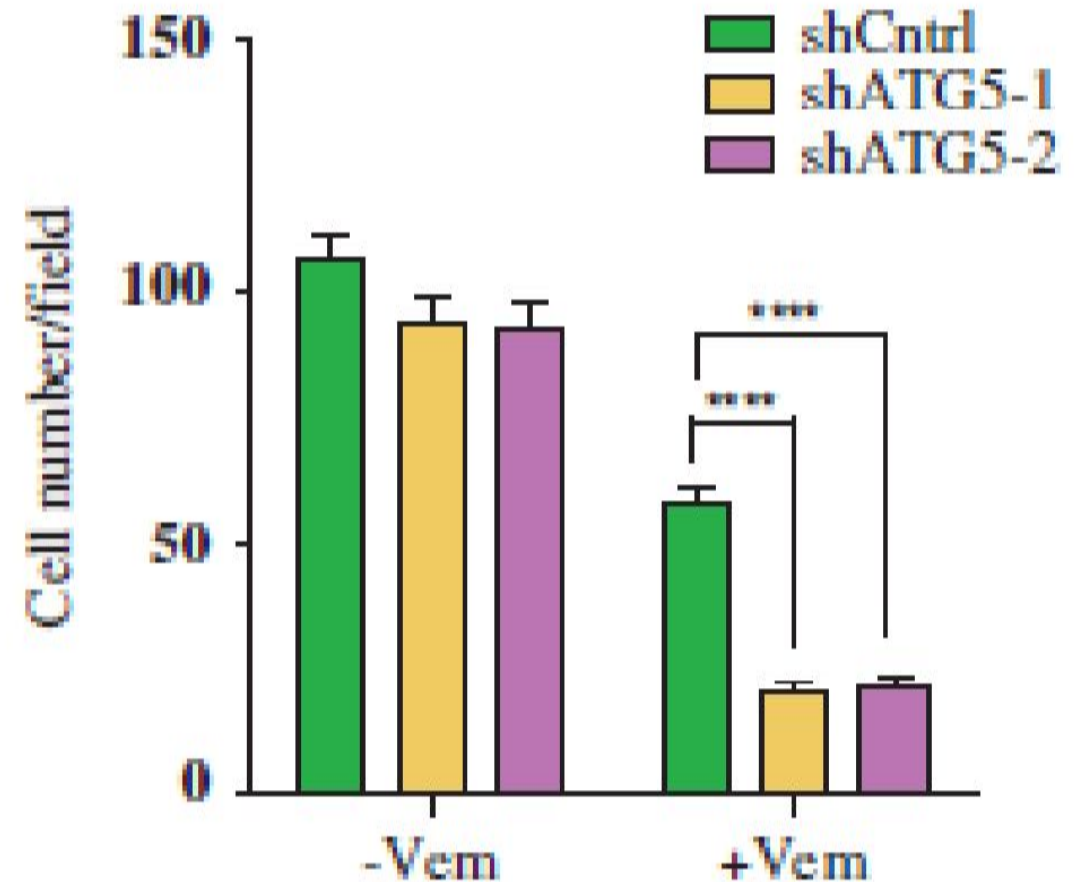
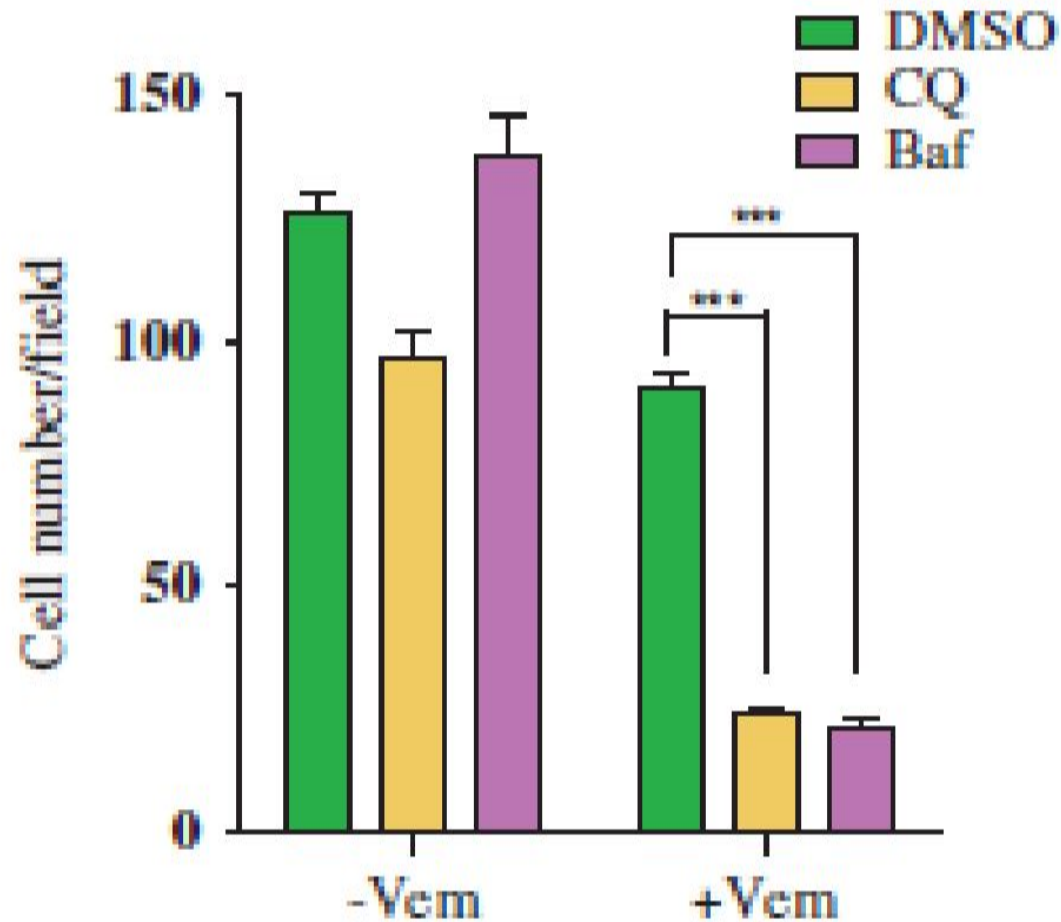
*S Sanduja, Y Feng, RA Mathis, ES Sokol, F Reinhardt, R Halaban.

AMPK promotes tolerance to Ras pathway inhibition by activating autophagy. *Oncogene* (2016), 1–9

Изменение базального уровня аутофагии при терапии BRAFi и MEKi



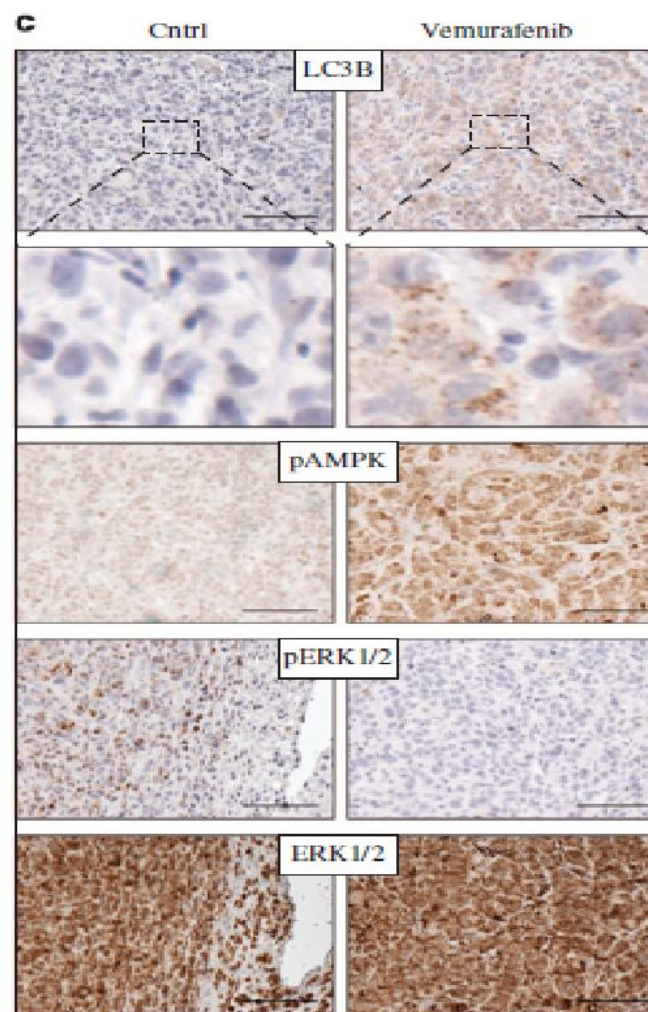
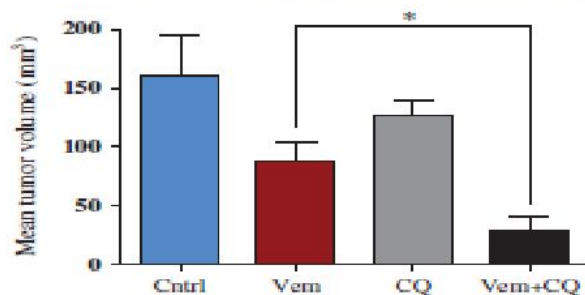
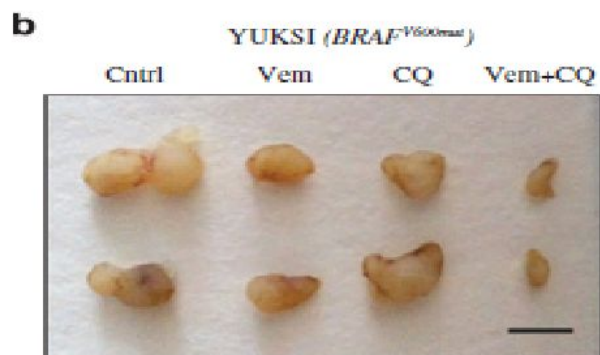
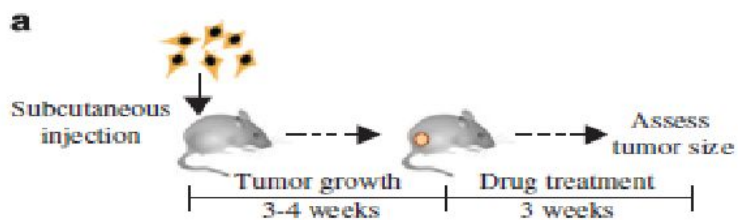
Ингибирование аутофагии сенсibiliзирует клетки к действию вемурафениба



*S Sanduja, Y Feng, RA Mathis, ES Sokol, F Reinhardt, R Halaban.

AMPK promotes tolerance to Ras pathway inhibition by activating autophagy. *Oncogene* (2016), 1–9

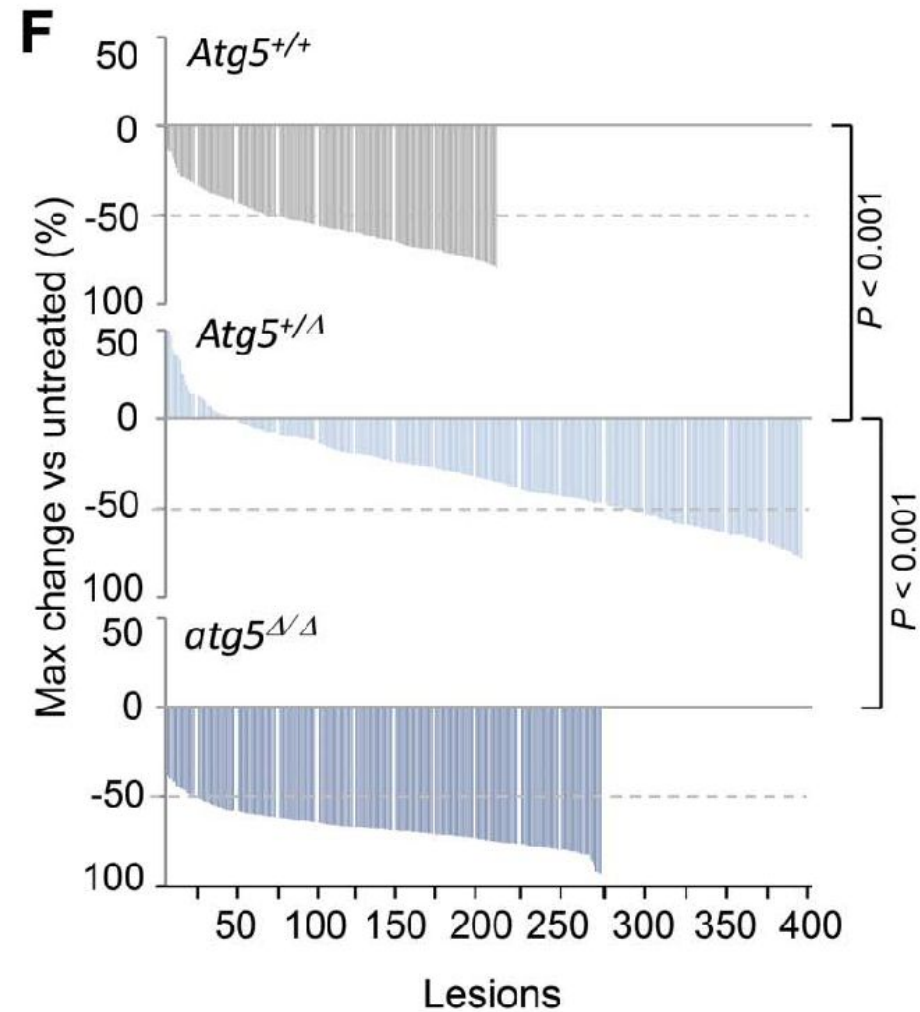
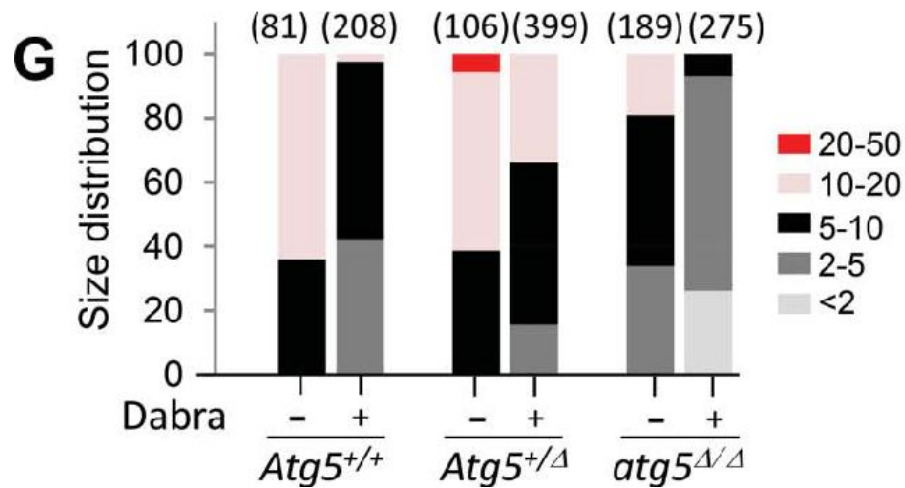
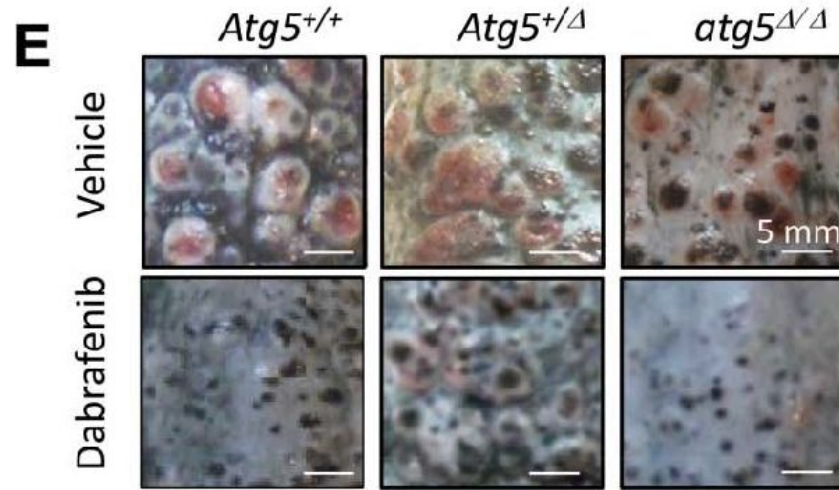
Синергизм BRAFi и ингибиторов аутофагии на мышинных моделях



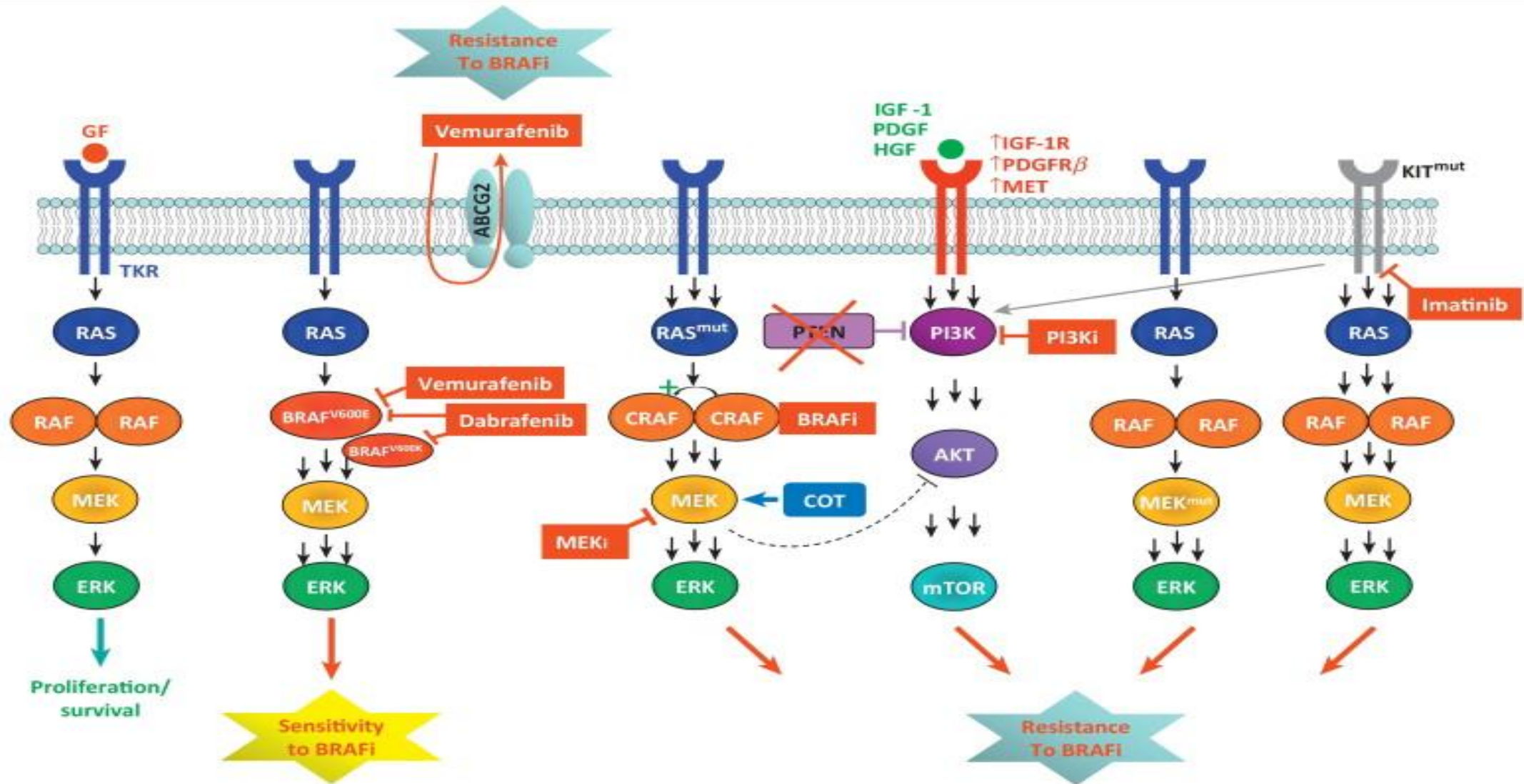
*S Sanduja, Y Feng, RA Mathis, ES Sokol, F Reinhardt, R Halaban.

AMPK promotes tolerance to Ras pathway inhibition by activating autophagy. *Oncogene* (2016), 1-9

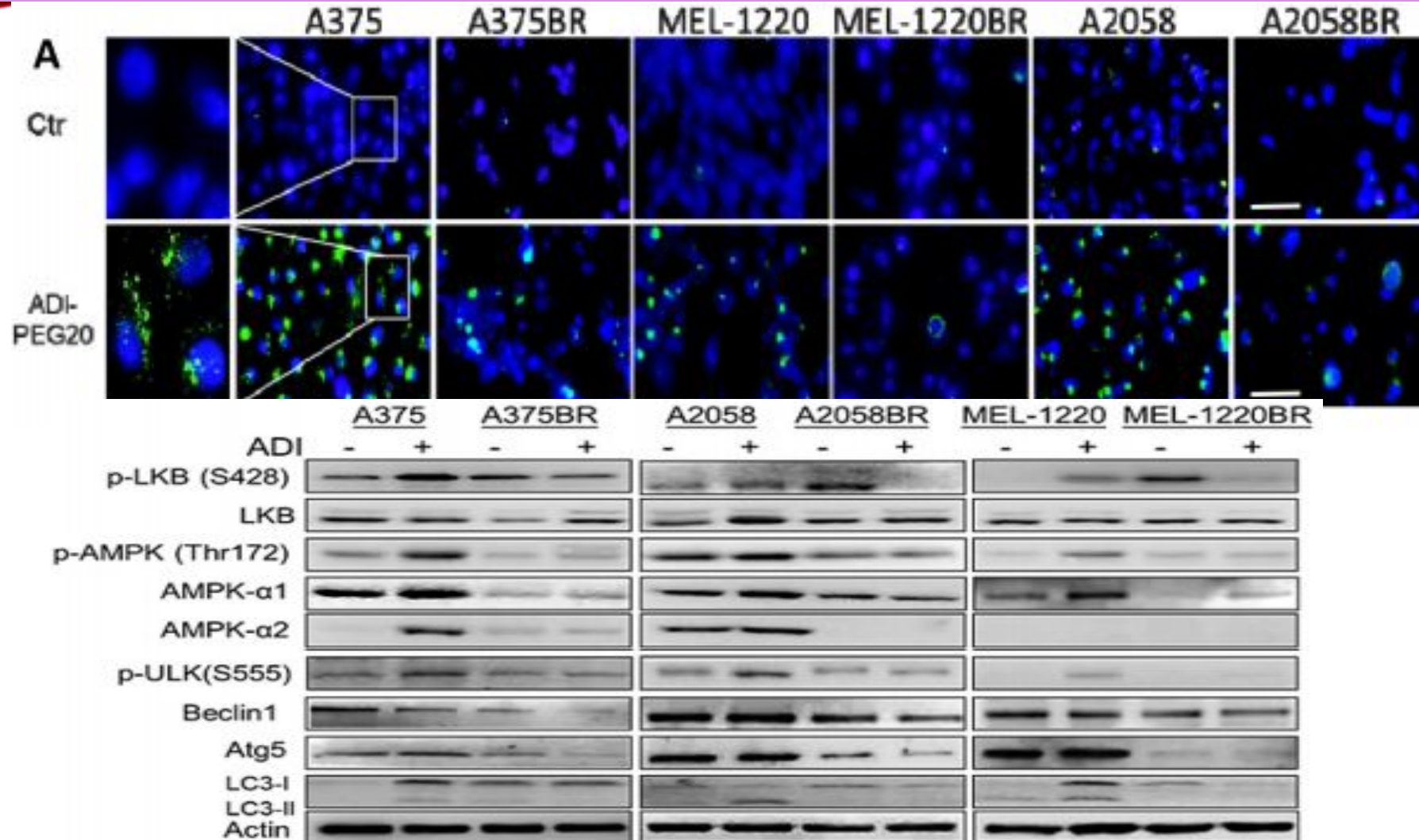
Влияние копияности *Atg5* на чувствительность к дабрафенибу



Основные механизмы резистентности к вемурафенибу



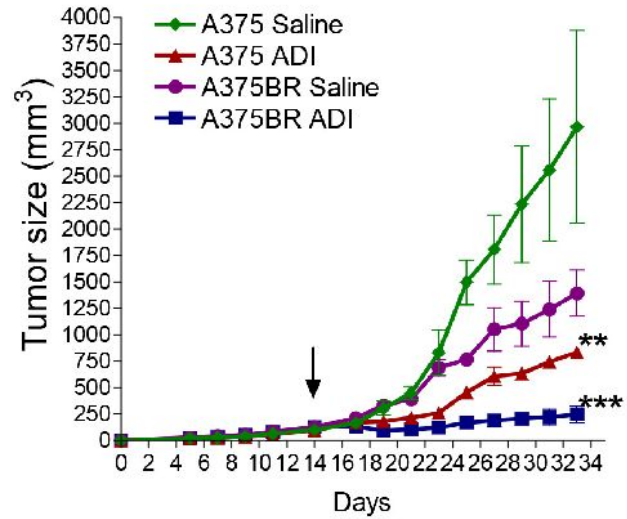
Меланомы резистентные к BRAFi имеют низкий базальный уровень аутофагии



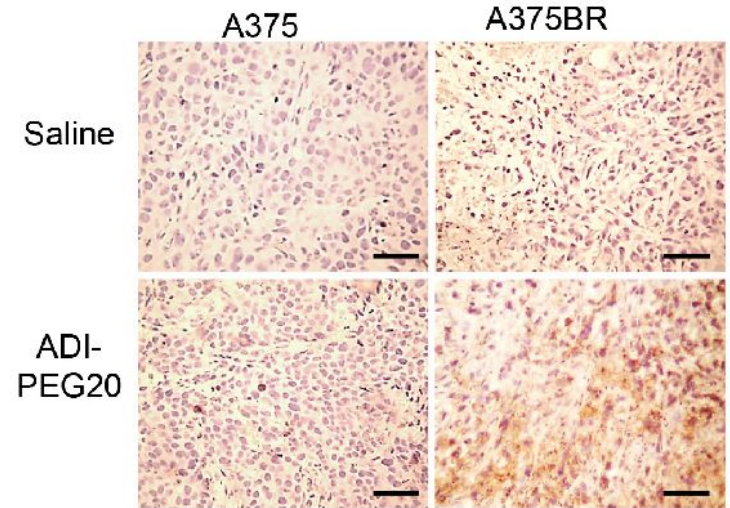
*Ying-Ying Li, Chunjing Wu, Shu-Mei Chen, Sumedh S. Shah. BRAF inhibitor resistance enhances vulnerability to arginine deprivation in melanoma. *Oncotarget* 2016, Vol. 7, No. 14

Меланомы резистентные к BRAFi чувствительны к ингибиторам ASS1

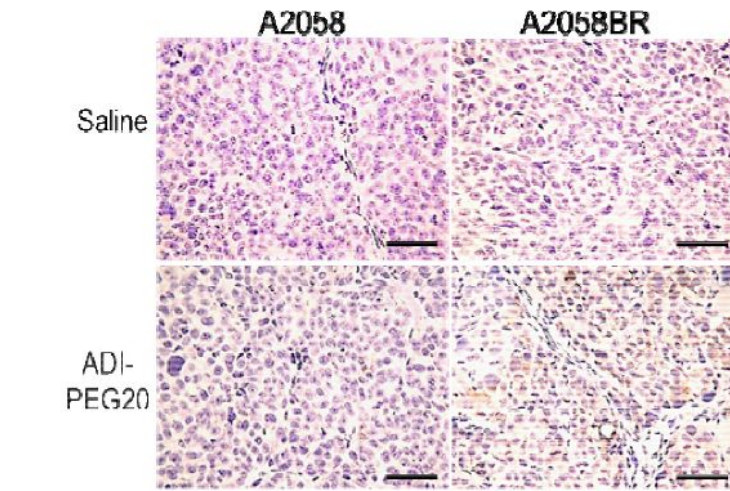
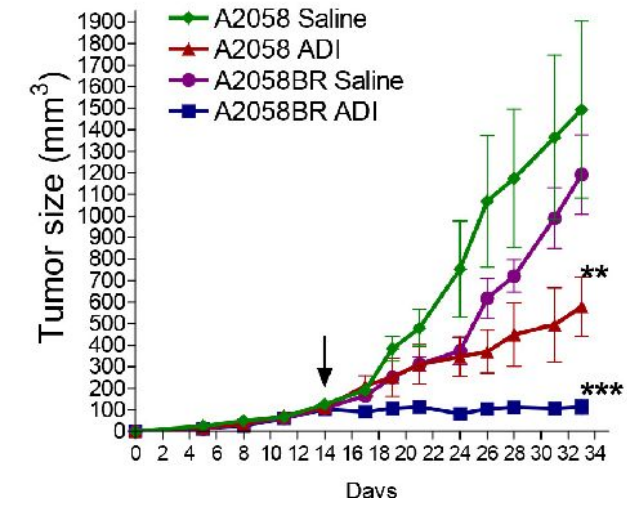
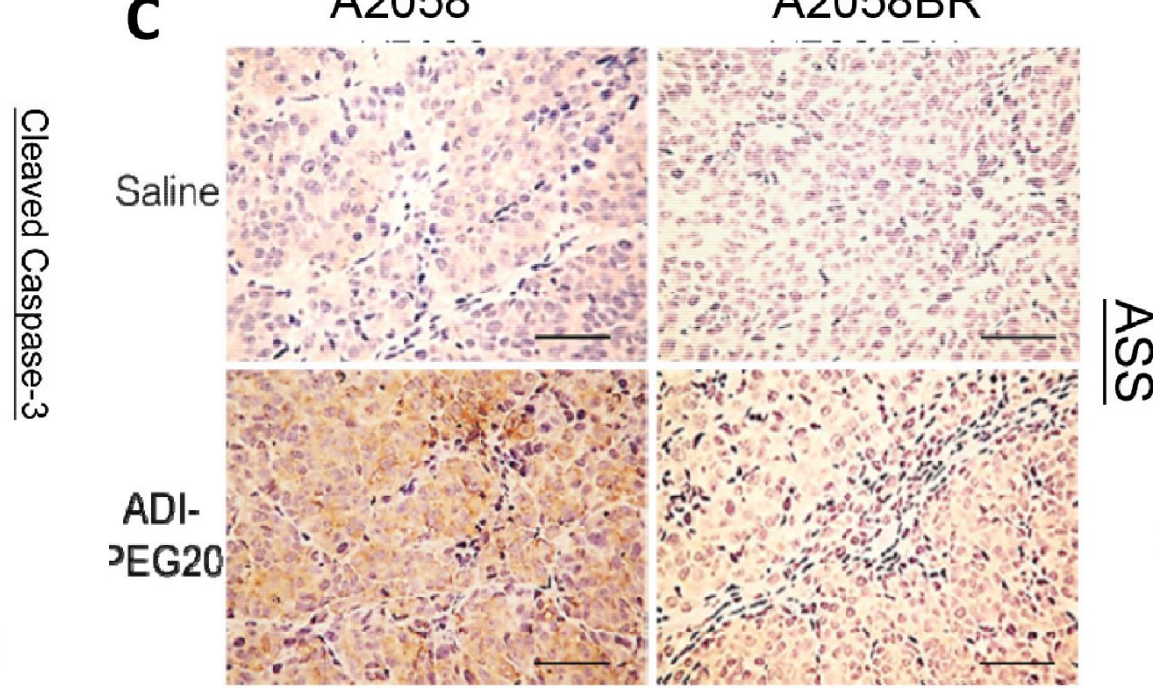
A



B

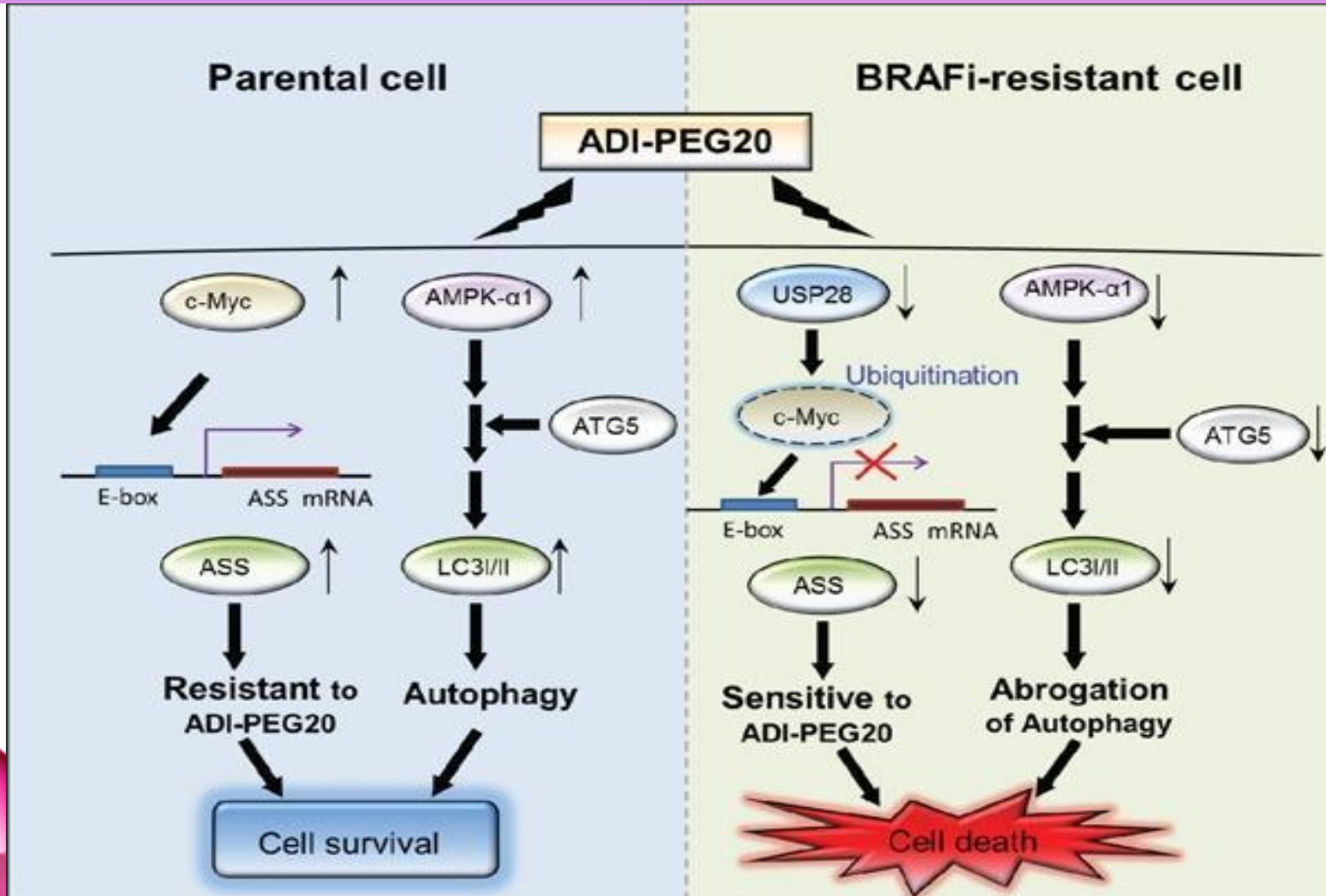


C



*Ying-Ying Li, Chunjing Wu, Shu-Mei Chen, Sumedh S. Shah. BRAF inhibitor resistance enhances vulnerability to arginine deprivation in melanoma. *Oncotarget* 2016, Vol. 7, No. 14

Меланомы резистентные к BRAFi чувствительны к ингибиторам ASS1



*Ying-Ying Li, Chunjing Wu, Shu-Mei Chen, Sumedh S. Shah. BRAF inhibitor resistance enhances vulnerability to arginine deprivation in melanoma. *Oncotarget* 2016, Vol. 7, No. 14

Исследования комбинированной терапии BRAFi и MEKi у пациентов с BRAF+ метастатической меланомой

The BAMB Trial: BRAF, Autophagy and MEK Inhibition in Metastatic Melanoma: A Phase I/2 Trial of Dabrafenib, Trametinib and Hydroxychloroquine in Patients With Advanced BRAF Mutant Melanoma

This study is currently recruiting participants. (see Contacts and Locations)

Verified June 2016 by Abramson Cancer Center of the University of Pennsylvania

Sponsor:
Abramson Cancer Center of the University of Pennsylvania

Information provided by (Responsible Party):
Abramson Cancer Center of the University of Pennsylvania

ClinicalTrials.gov Identifier:
NCT02257424

First received: October 2, 2014
Last updated: June 20, 2016
Last verified: June 2016
[History of Changes](#)

A Phase I Trial of Vemurafenib and Hydroxychloroquine in Patients With Advanced BRAF Mutant Melanoma

This study is ongoing, but not recruiting participants.

Sponsor:
Abramson Cancer Center of the University of Pennsylvania

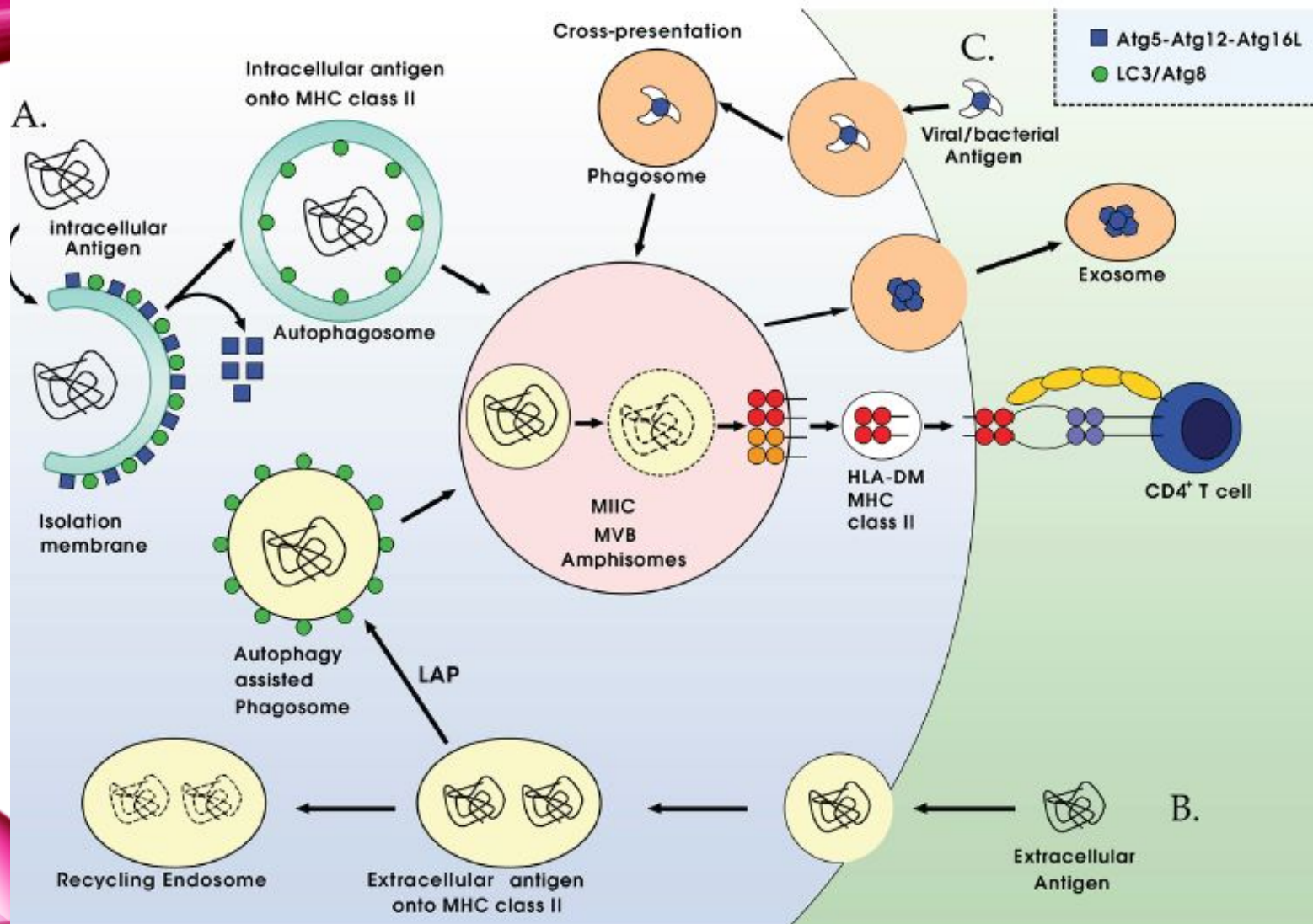
Information provided by (Responsible Party):
Abramson Cancer Center of the University of Pennsylvania

ClinicalTrials.gov Identifier:
NCT01897116

First received: June 26, 2013
Last updated: July 18, 2016
Last verified: July 2016
[History of Changes](#)

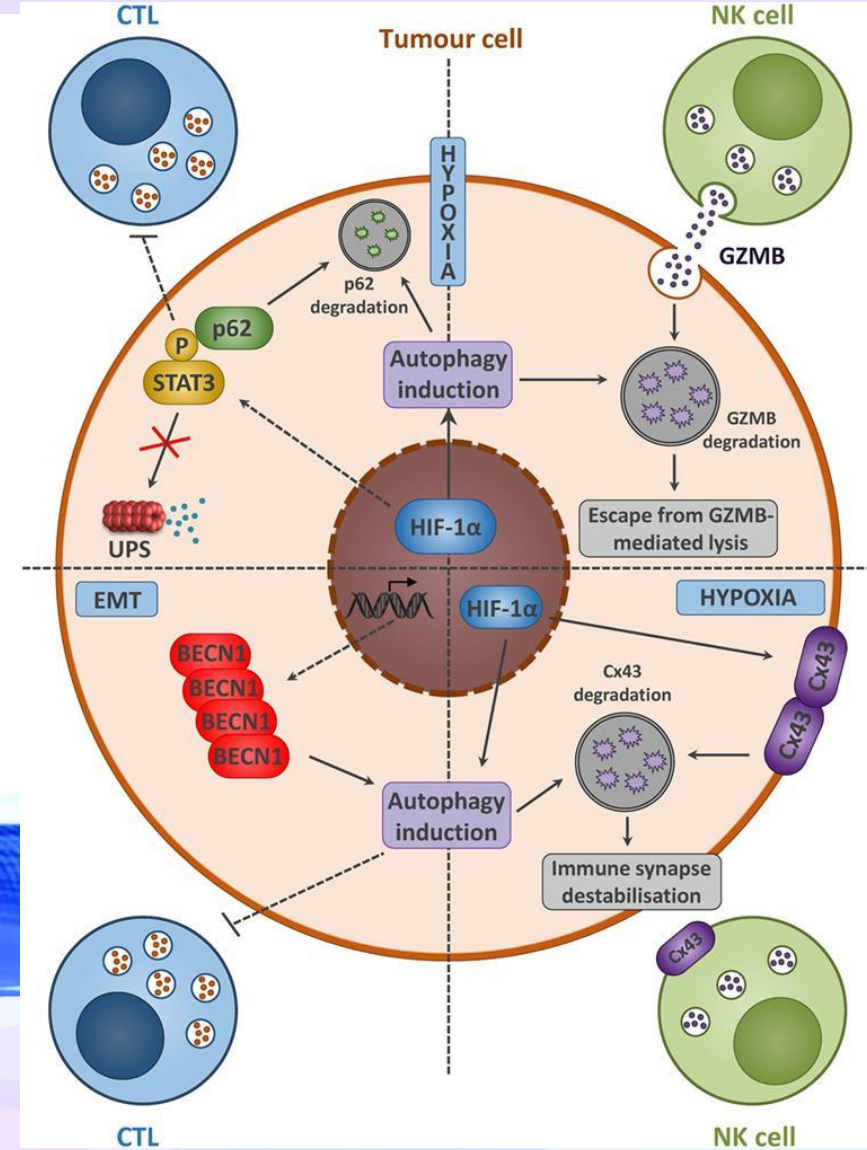
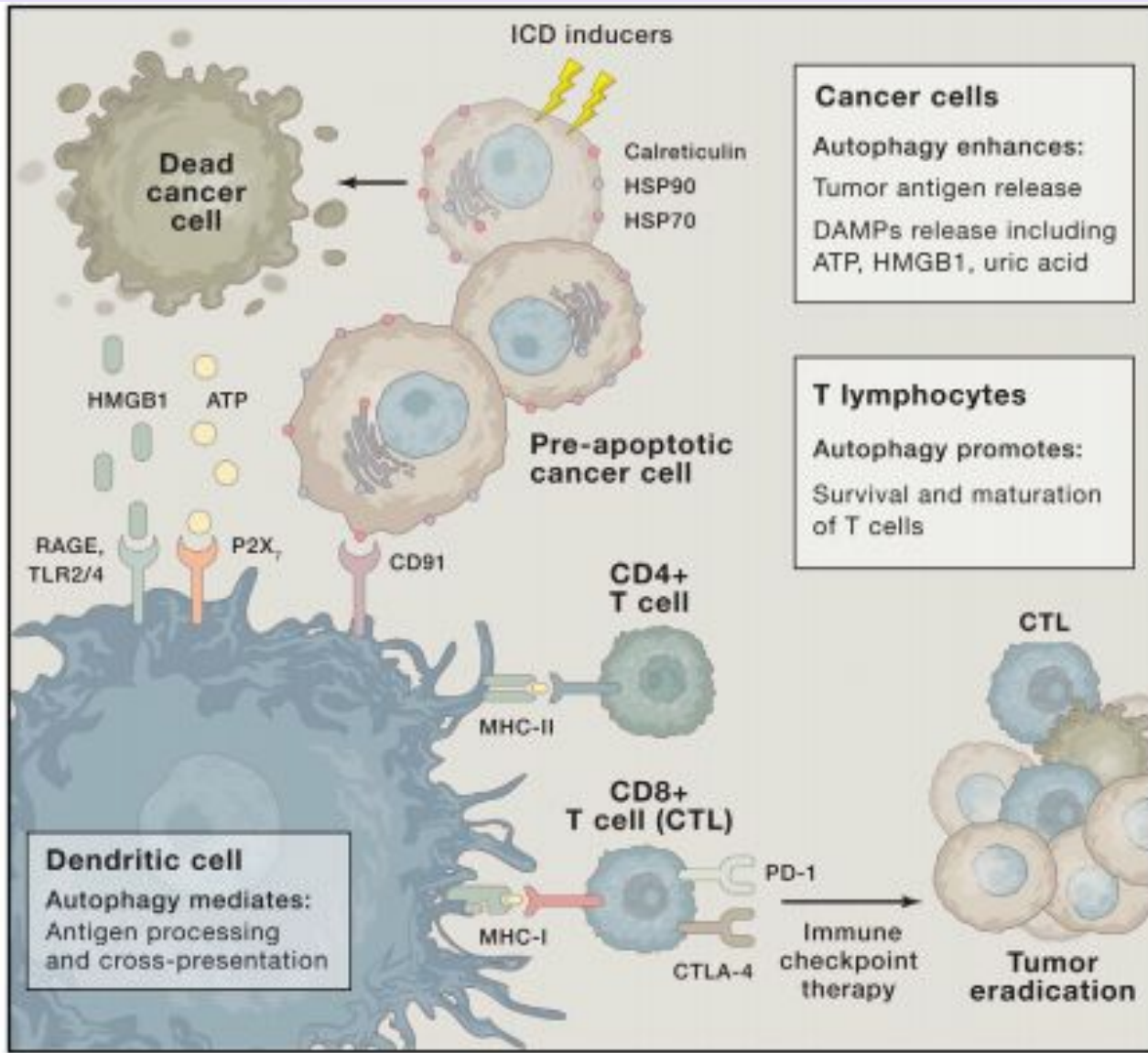


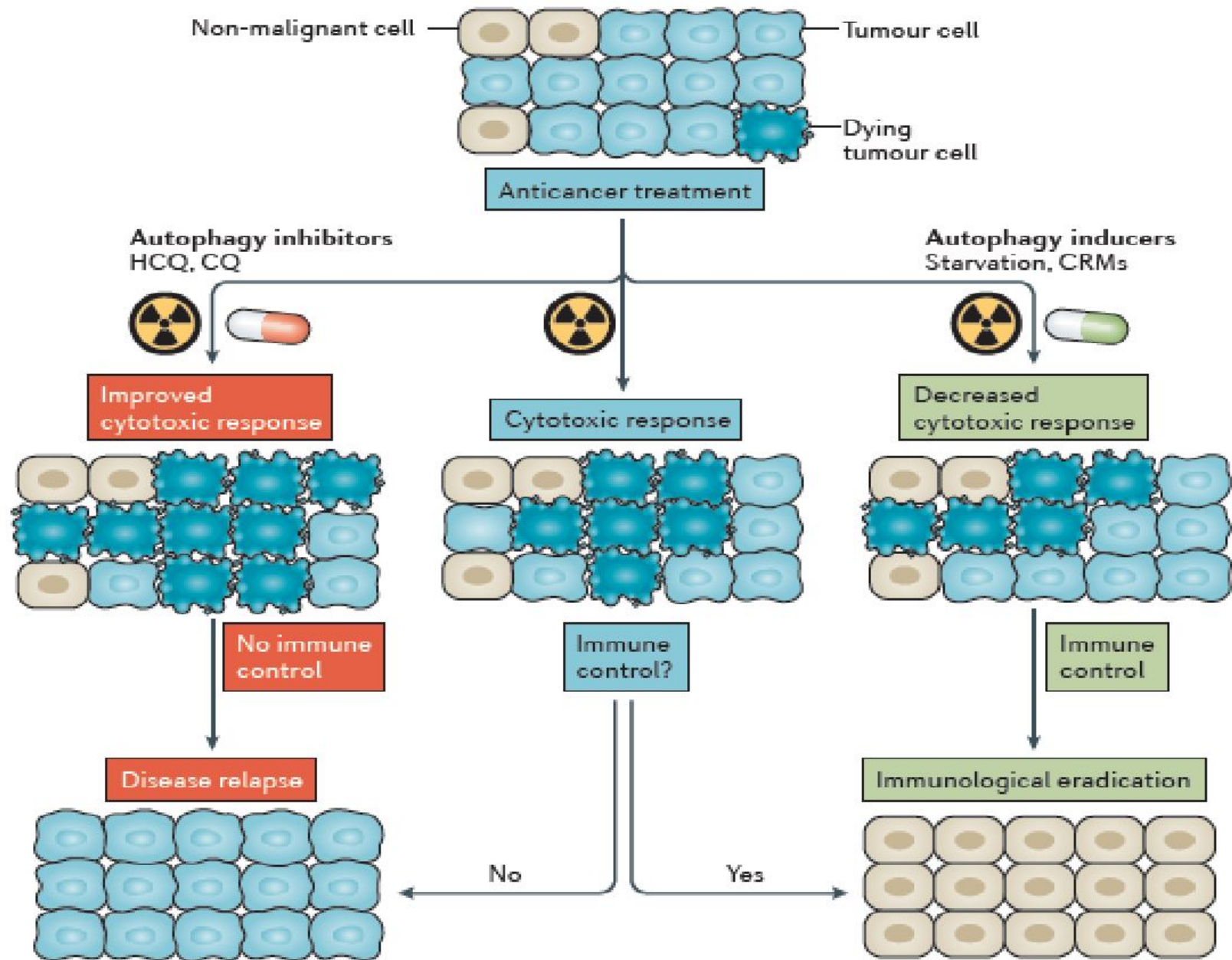
Роль аутофагии в антигенпрезентации



* Liangshun You, Shenhe Jin, Li Zhu, Wenbin Qian.
Autophagy, autophagy-associated adaptive immune responses and its role in hematologic malignancies.
Oncotarget, 2017, Vol. 8, (No. 7), pp: 12374-12388

Влияние аутофагии на развитие клеточного иммунного ответа







Спасибо за внимание!