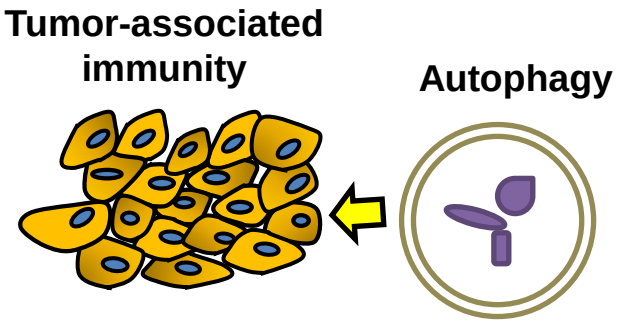
Autophagy regulates hepatocellular carcinoma-associated M2 macrophage polarization

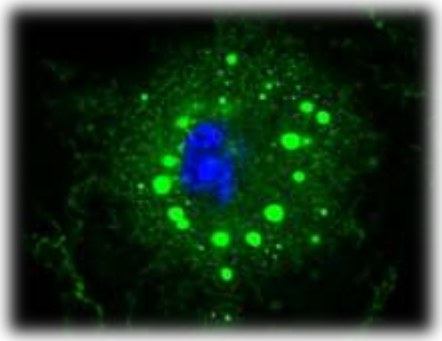
Chih-Peng Chang, Ph.D.

Assistant Professor

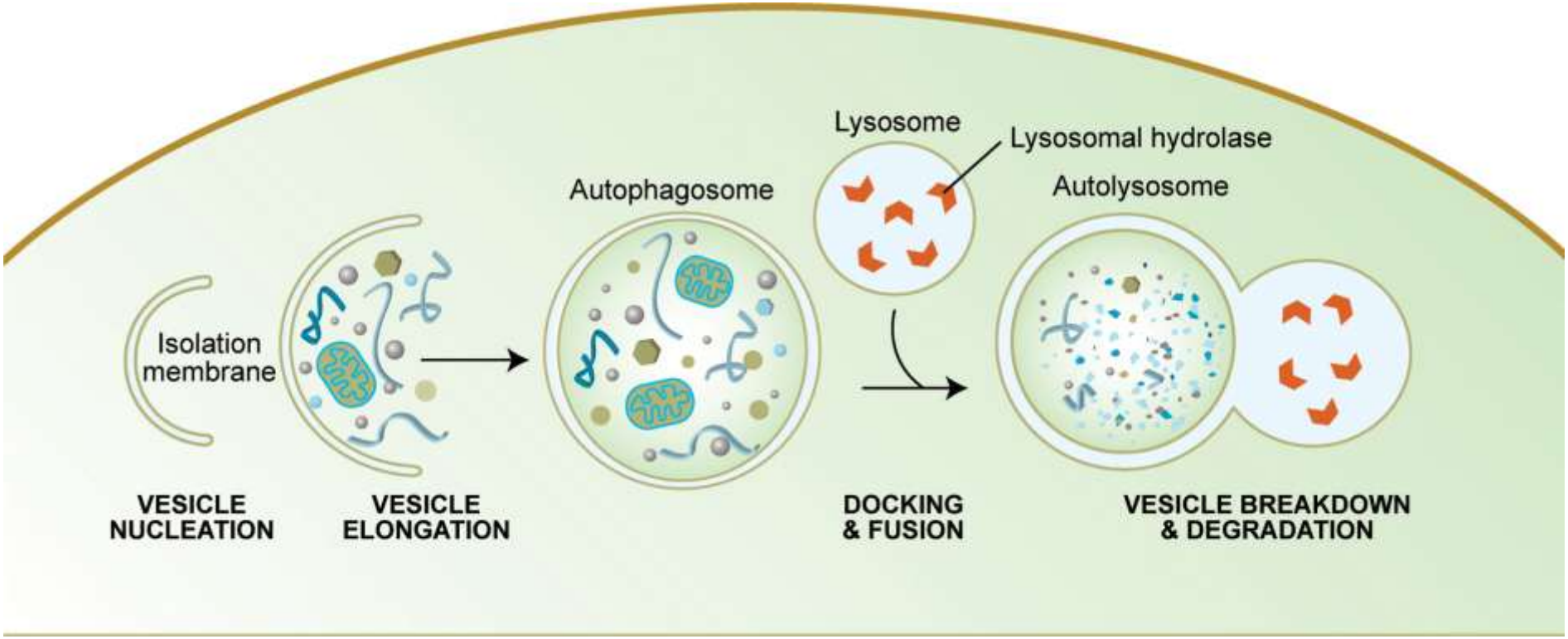
Department of Microbiology and Immunology, College of Medicine,

National Cheng Kung University



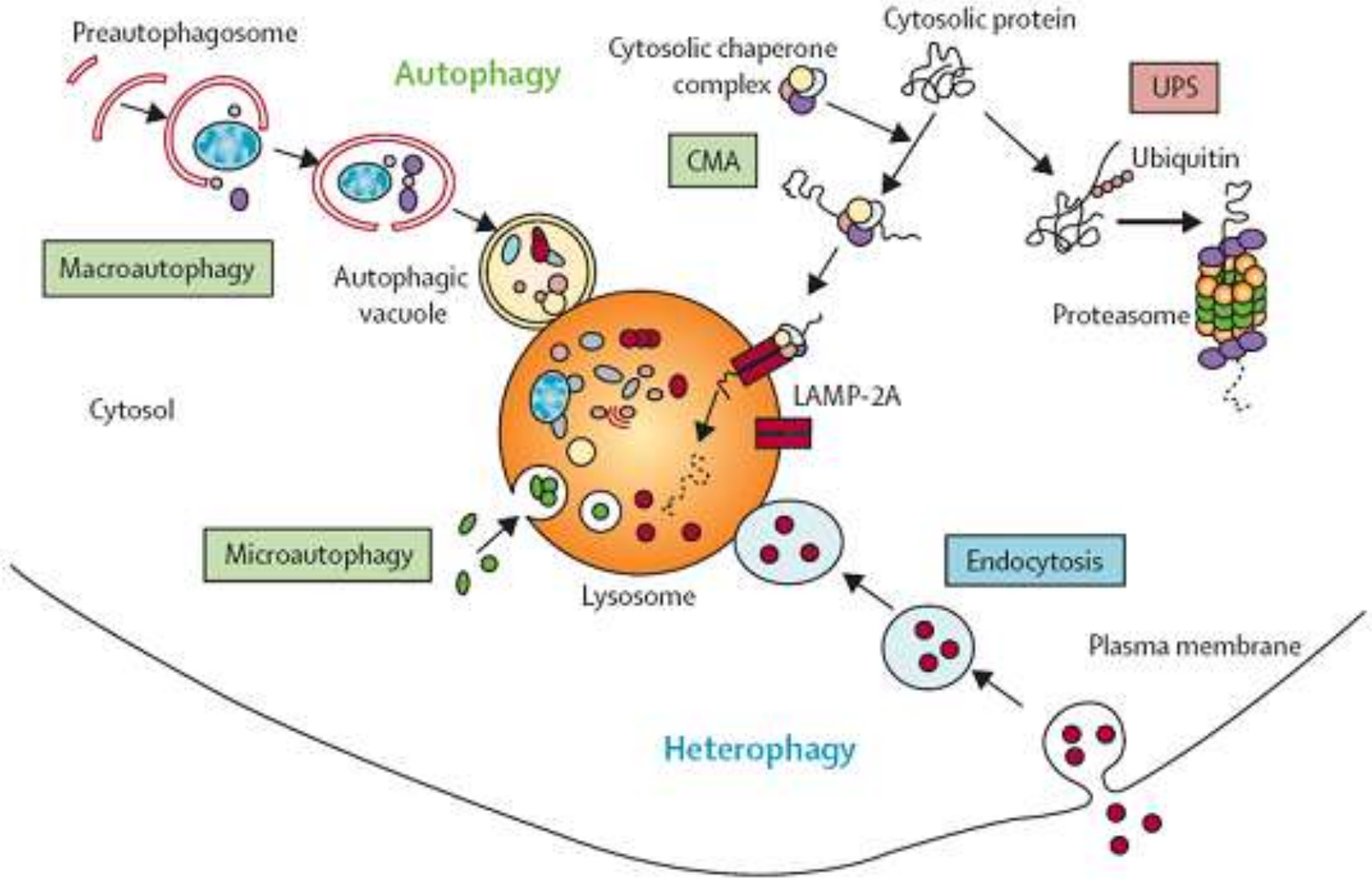


Autophagy



Meléndez, A. and Levine, B. (August 24, 2009), WormBook, ed.

Intracellular protein degradation systems



Martinez-Vicente M et al. *Lancet Neurol*. 2007.

Autophagy history

Timeline | **A history of autophagy**

1955 — C. de Duve and others discover the lysosome[1].

1963 — de Duve describes the morphological process and coins the name 'autophagy'.

1967 — de Duve and R. Deter show that glucagon induces autophagy[14].

1973 — R. Bolender and E. Weibel demonstrate the selective sequestration of an organelle[25].

1977 — J. Beaulaton and R. Lockshin suggest that autophagy functions as a cell-death mechanism[26].

G. Mortimore and C. Schworer find that amino acids inhibit autophagy[16].

1982 — P. Seglen and P. Gordon carry out the first biochemical analysis of autophagy and identify 3-methyladenine as an inhibitor[17,76].

1988 — Gordon and Seglen identify the amphisome as a convergence point between autophagy and endocytosis[9].

1992 — Y. Ohsumi and colleagues show the morphology of autophagy in yeast[11].

1993 — The Ohsumi laboratory reports the first screen to identify yeast autophagy mutants[38]. Several groups use different methods to isolate autophagy mutants (reviewed in REF. 39).

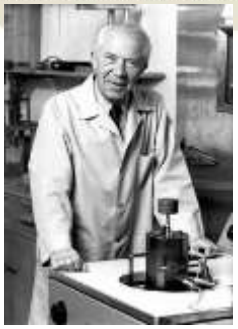
1995 — A. Meijer and colleagues document the stimulatory role of rapamycin[20].

1997 — The Meijer laboratory finds a stimulatory role for PI3K[21].

The Ohsumi group clones yeast *ATG1* (REF. 40). Thirty more *ATG* genes were identified in yeasts[39,41,77,78].

1998 — Mizushima *et al.* identify the first mammalian autophagy gene and show conservation of Atg12–Atg5 conjugation[47].

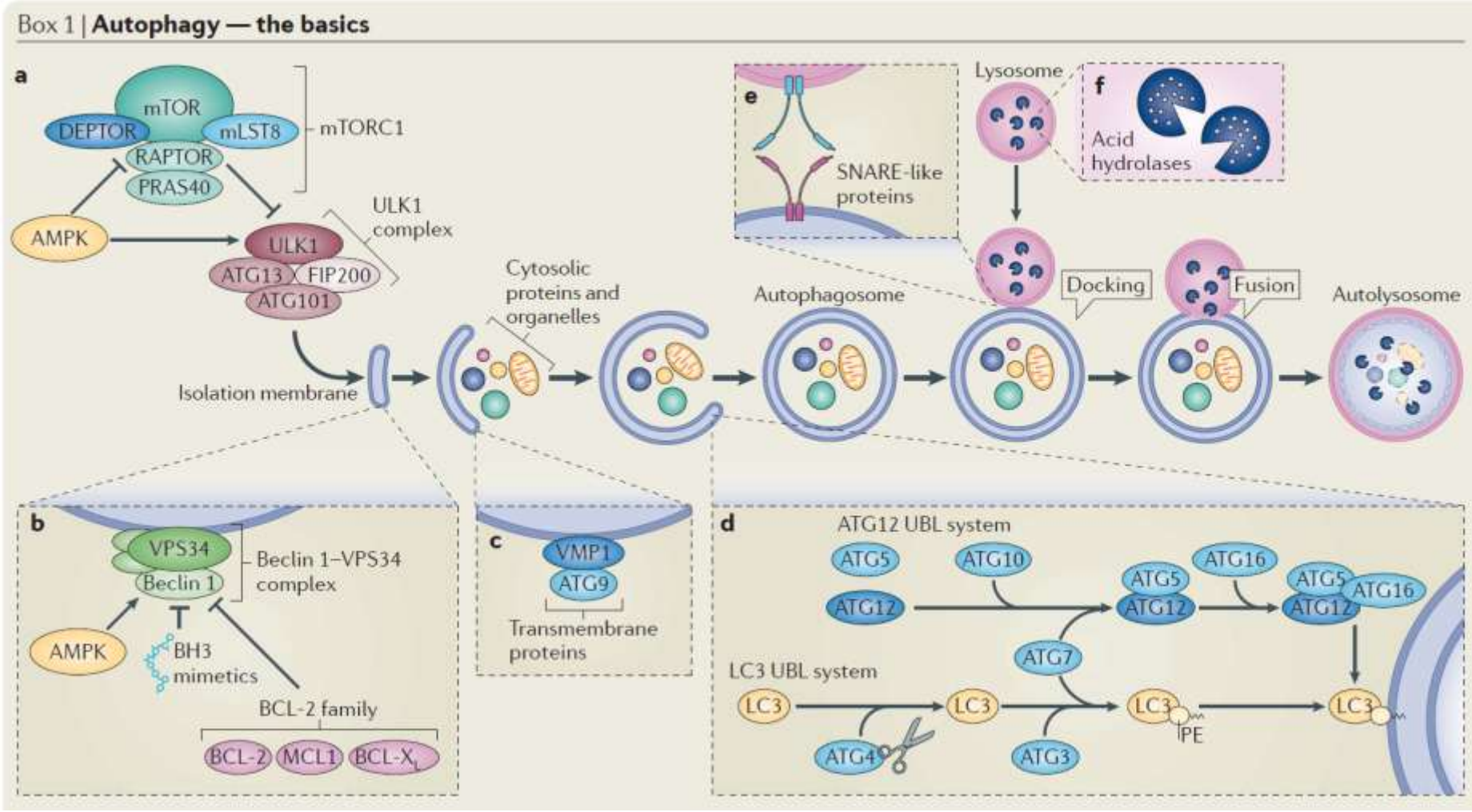
ATG1, autophagy-related gene-1; BCL2, anti-apoptotic protein B-cell lymphoma-2; *BECN1*, be … alian Atg8 homologue; PI3K, phosphatidylinositol 3-



Nobel Prize for Physiology or Medicine 1974

Klionsky DJ. *Nat Rev Mol Cell Biol*. 2007

Autophagosome formation



Mariño G et al. *Nat Rev Mol Cell Biol*. 2014

Autophagy in human disease

Neurodegeneration

Pro: Basal autophagy is a homeostatic process that prevents intracellular proteins from accumulating to toxic levels.

Con: Inefficient lysosomal clearance results in intracellular accumulation of autophagosomes, which may process the amyloid precursor protein into toxic forms.

Myopathies

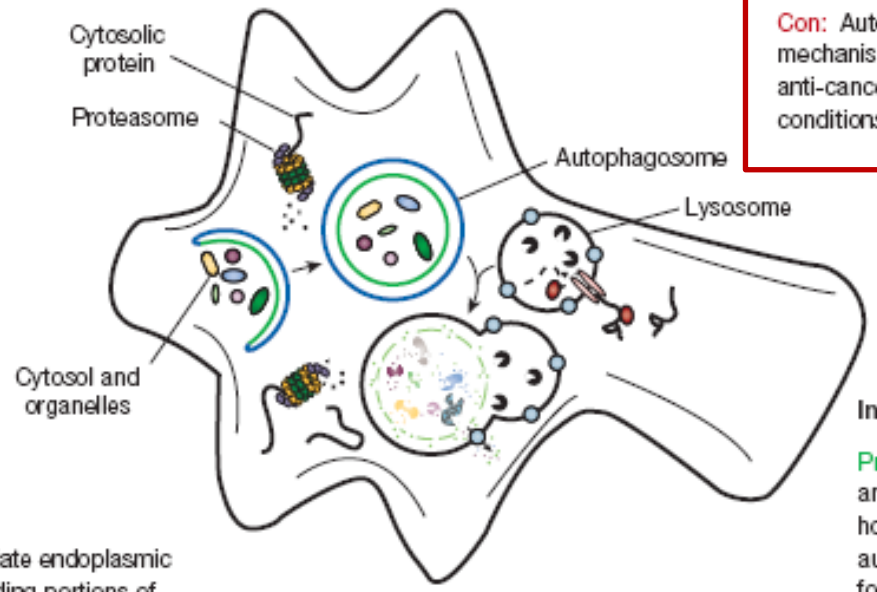
Pro: Autophagy prevents aggregate-prone protein accumulation that leads to physiological dysfunction.

Con: Autophagy may contribute to muscle wasting and defective autophagosome clearance may interfere with cellular function.

Cancer

Pro: Autophagy acts in tumour suppression by removing damaged organelles and possibly growth factors, and reduces chromosome instability.

Con: Autophagy acts as a cytoprotective mechanism that helps cancer cells resist anti-cancer treatments and survive in conditions of low nutrient supply.



Ageing

Pro: Autophagy removes damaged organelles and can limit production of reactive oxygen species.

Infection and immunity

Pro: Intracellular bacteria, viruses and protozoans are removed from host removed from host cells by autophagy, and antigens are processed for MHC class II presentation. Autophagy may prevent auto-immune and inflammatory diseases.

Con: Some microbes have evolved to subvert autophagy to establish a replicative niche.

Liver disease

Pro: Autophagy can alleviate endoplasmic reticulum stress by degrading portions of the organelle containing misfolded proteins.

Con: Excessive autophagy may cause liver damage.

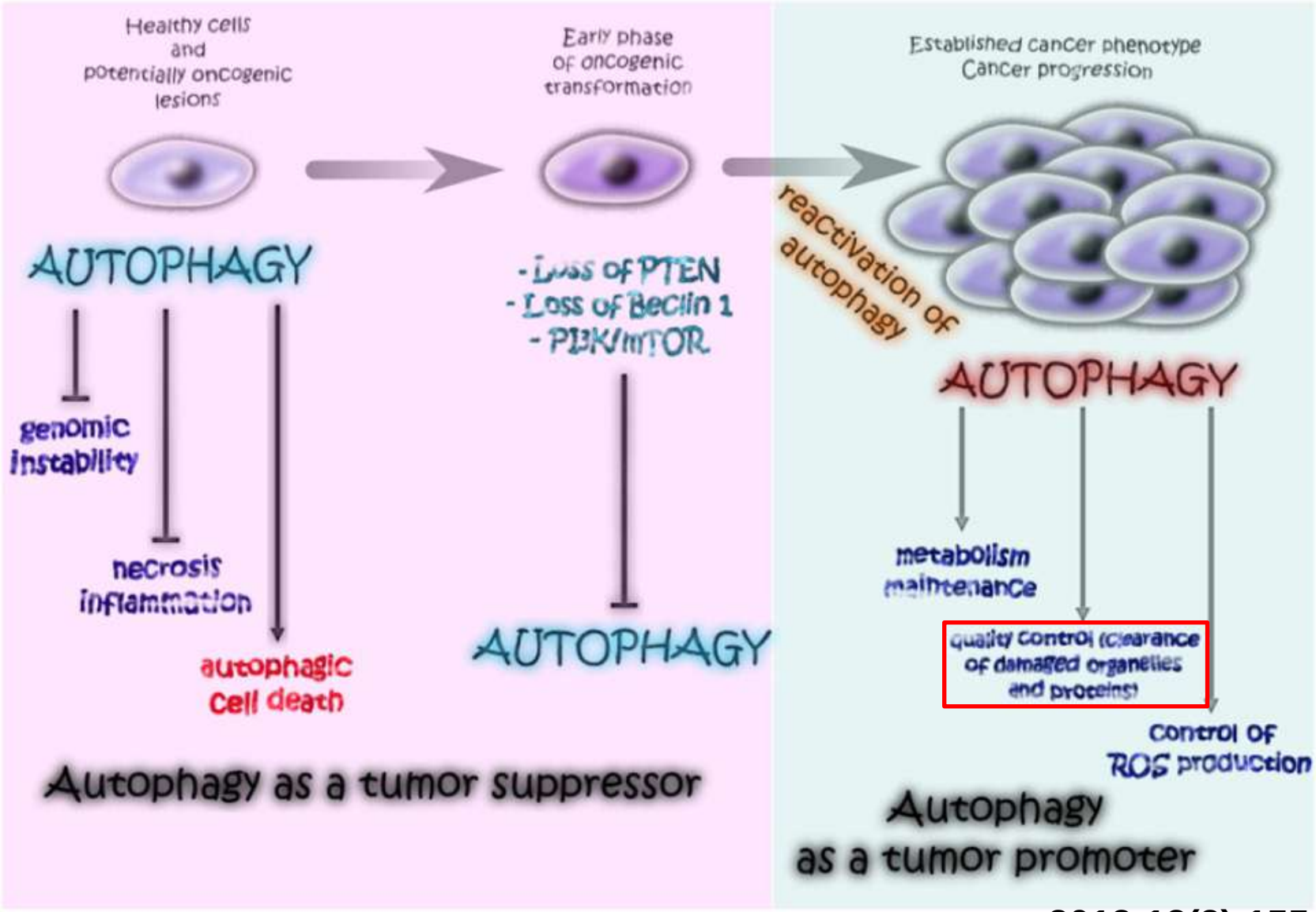
Heart disease

Pro: Autophagy may be protective during ischaemia and pressure overload.

Con: Autophagy is harmful during reperfusion.

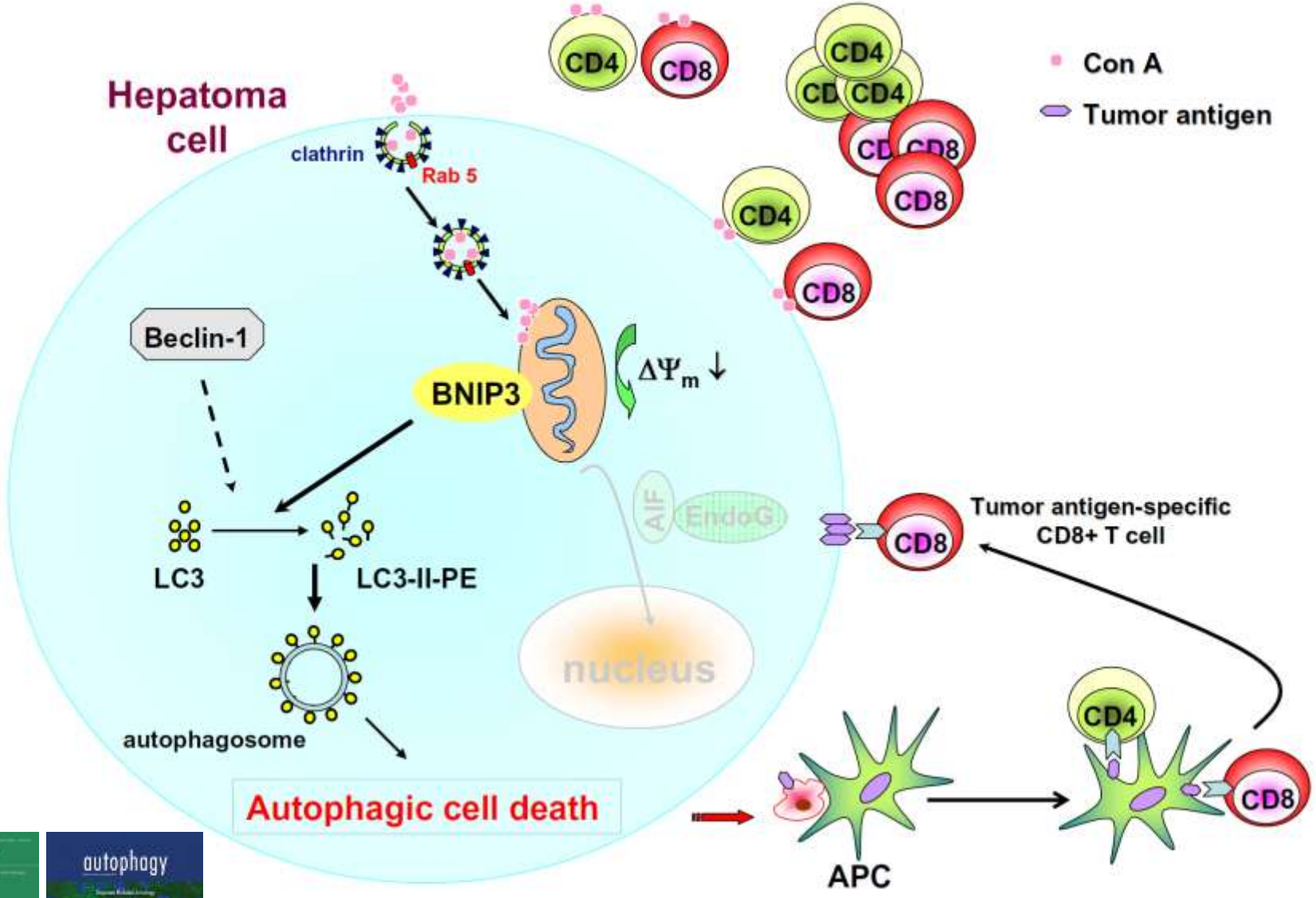
Nature. 2008 ;451:1069-75.

Dual role of autophagy in carcinogenesis

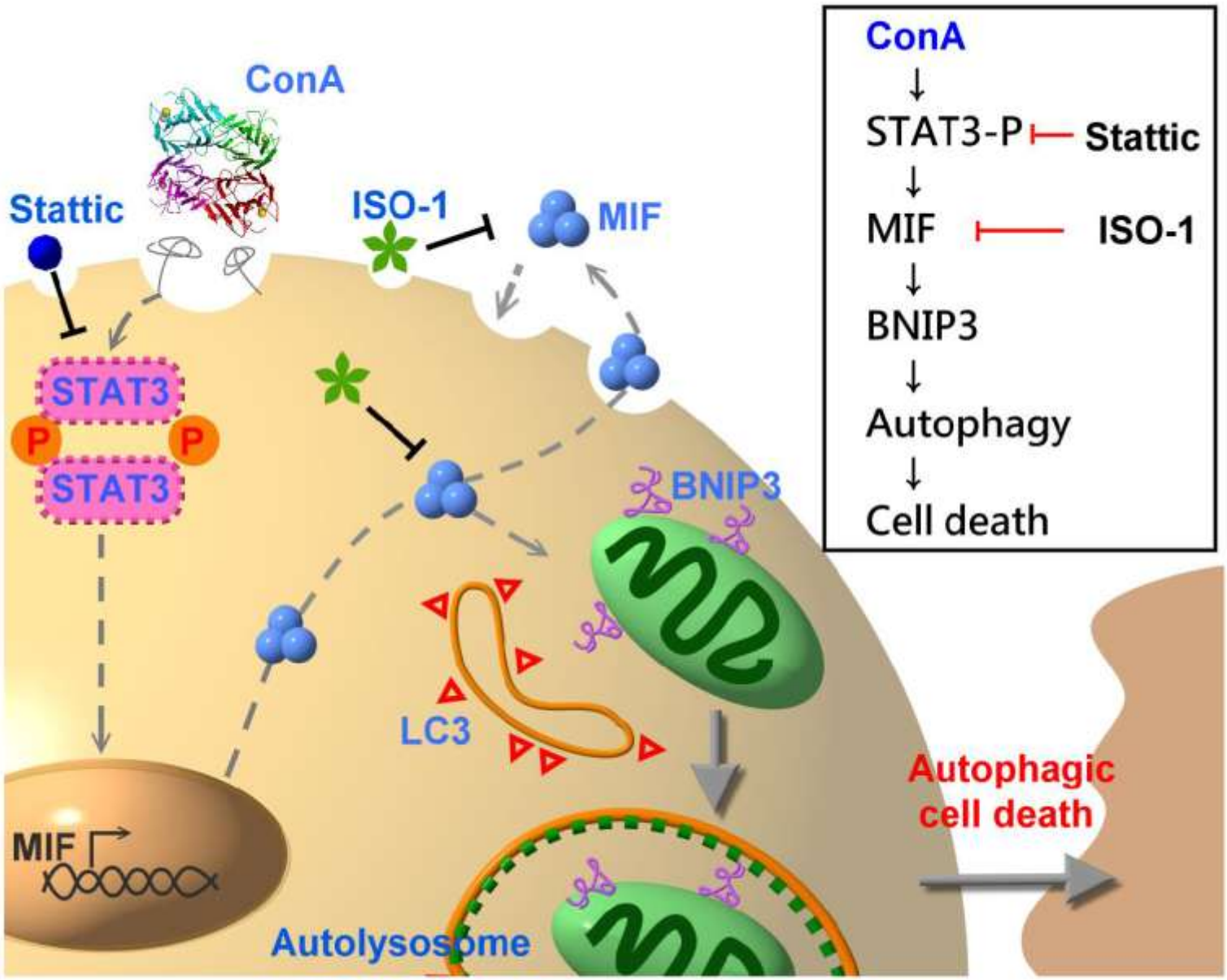


Mitochondrion. 2013;13(3):155-62

Concanavalin A induces autophagy against hepatoma

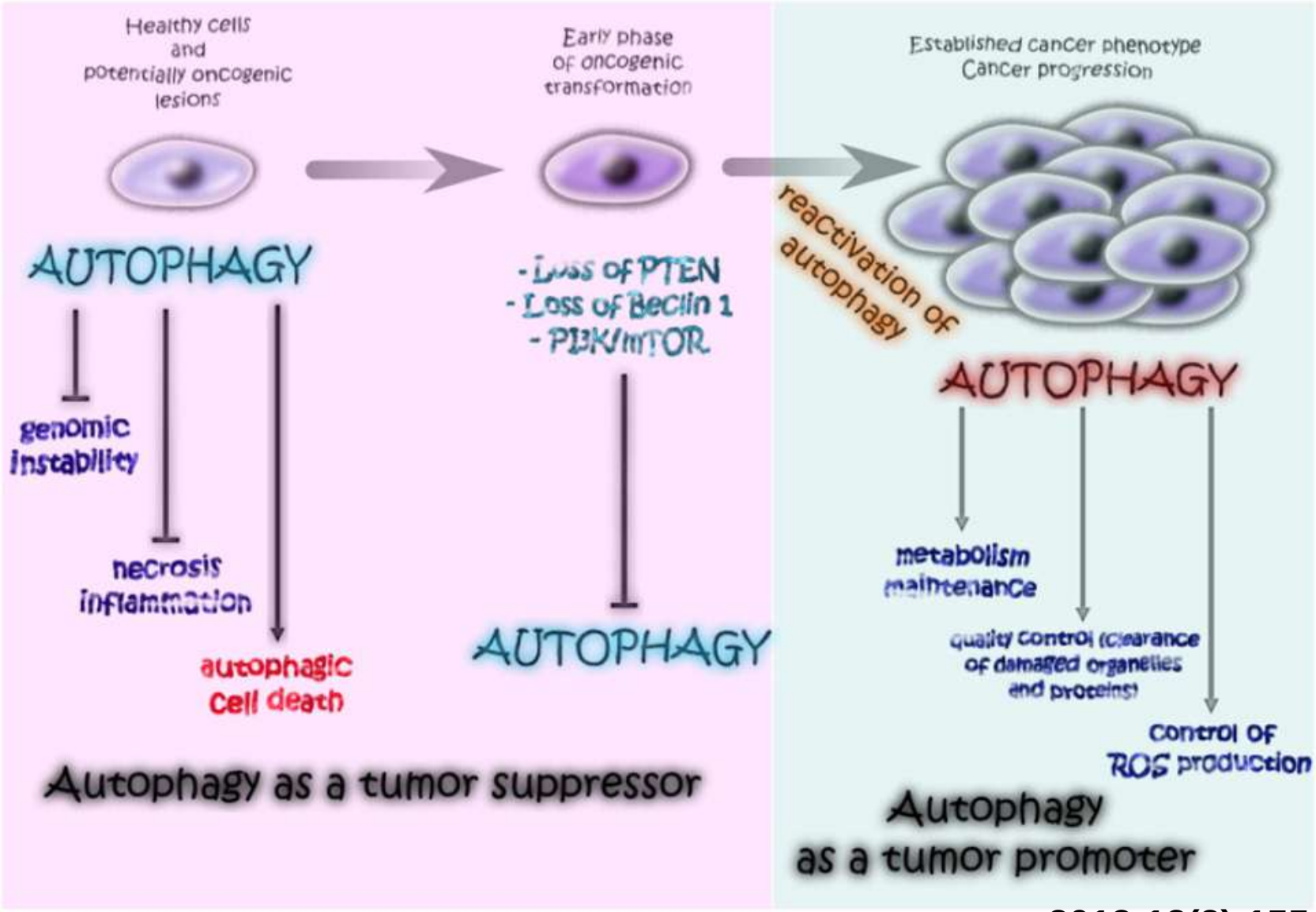


Chang CP, et al. *Hepatology*. 2007; 45:286-96
Lei HY and Chang CP. *J Biomed Sci*. 2009;19;16:10.



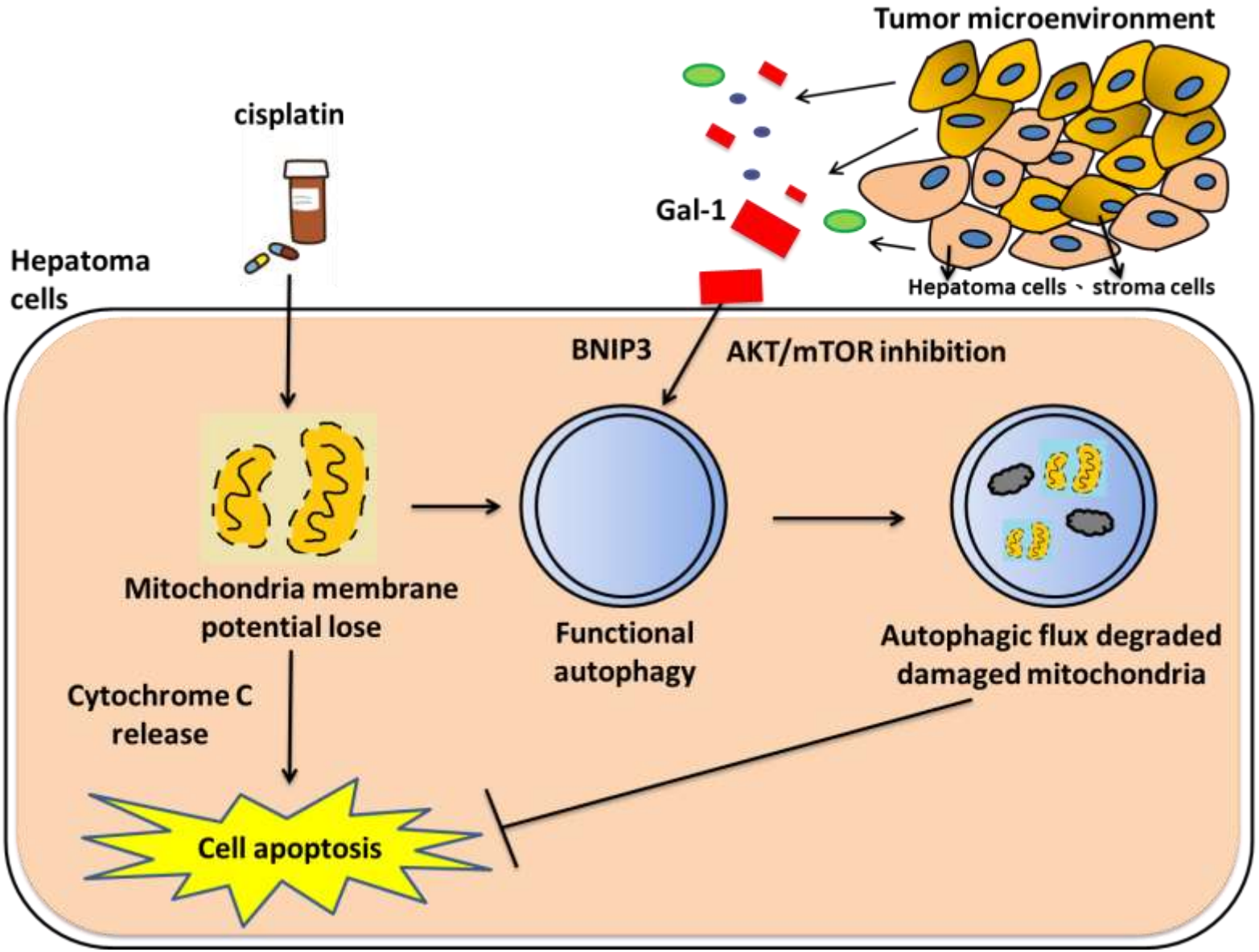
Lai YC, et al. *Cell Death Dis.* 2016

Dual role of autophagy in carcinogenesis



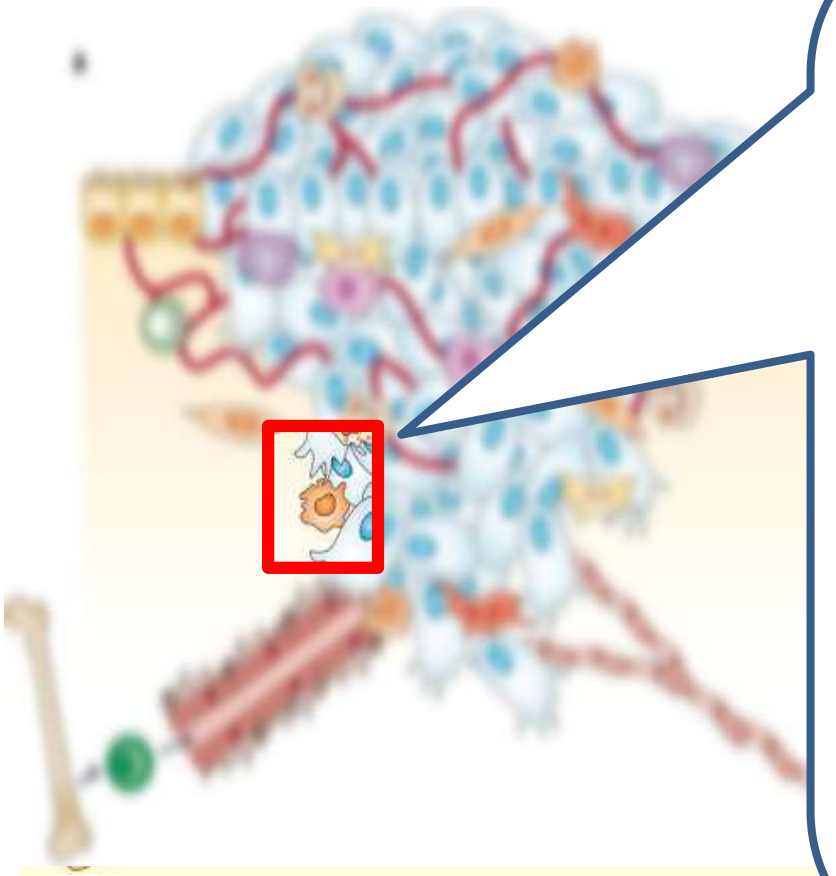
Mitochondrion. 2013;13(3):155-62

Galectin-1 induces autophagy facilitates cisplatin resistance

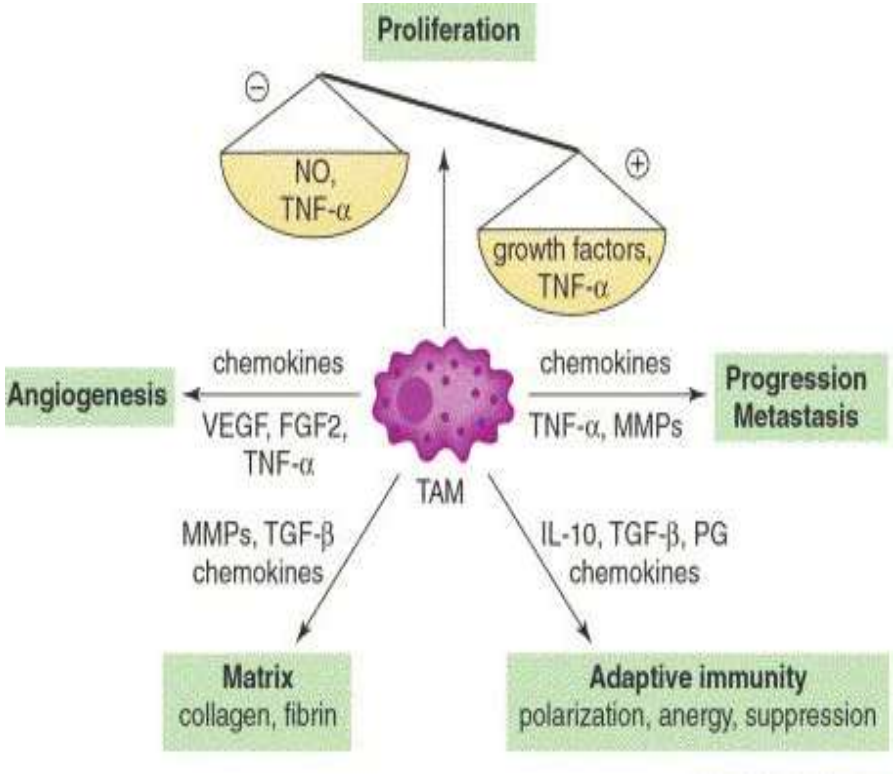


Su YC, et al. *Plos One.* 2016 in press

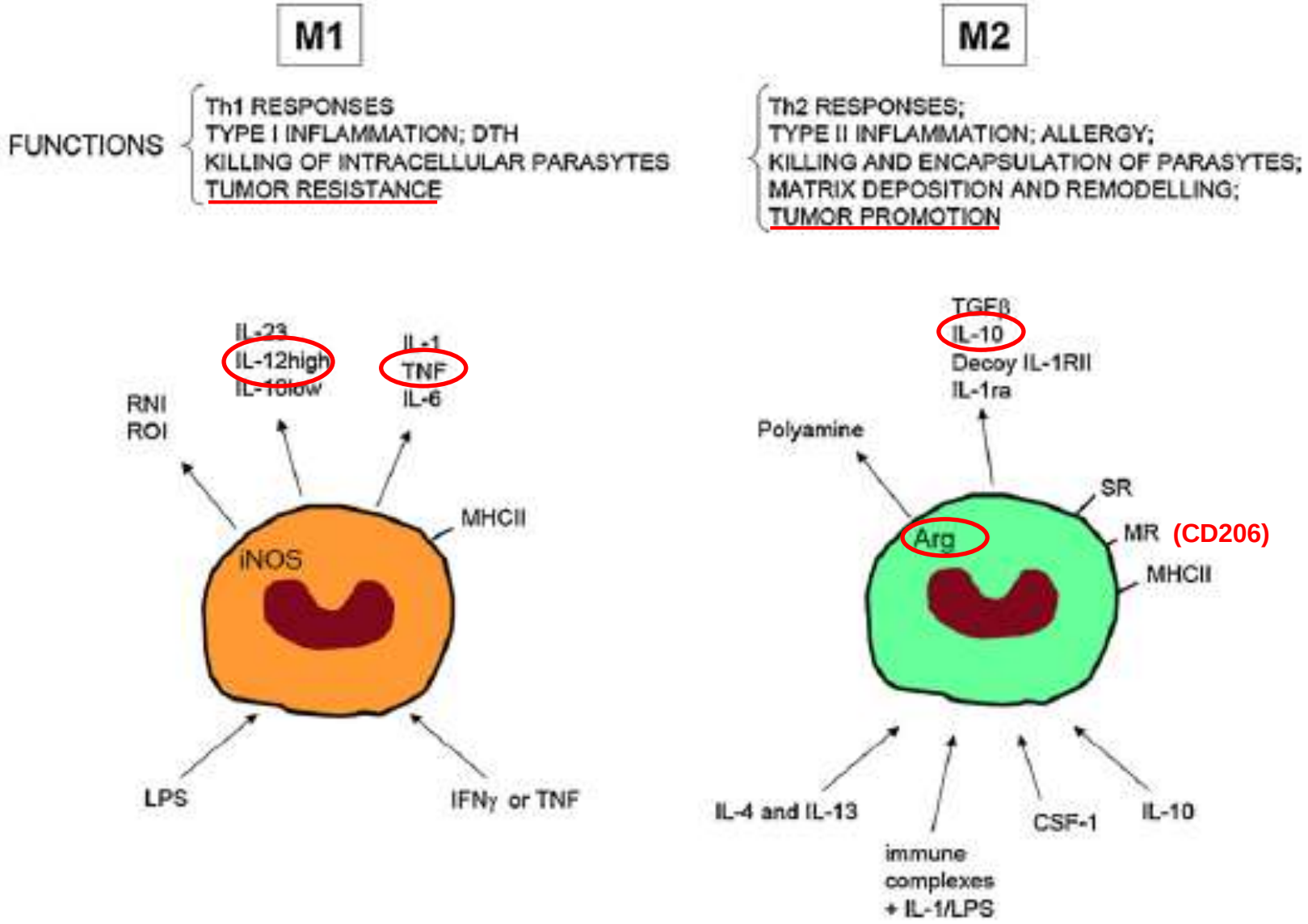
Tumor microenvironment



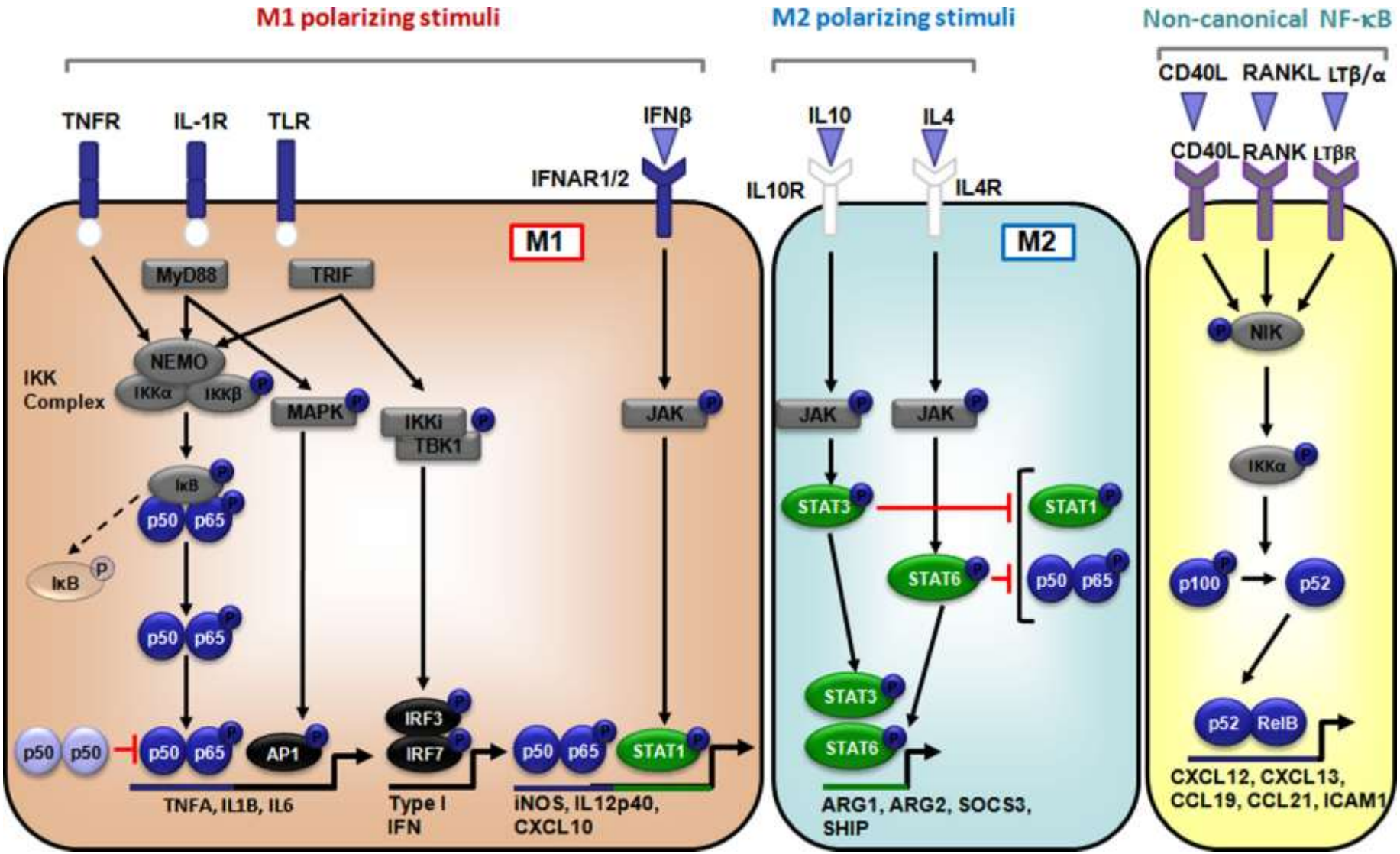
Nature Reviews Cancer . 2009; 9 239-252



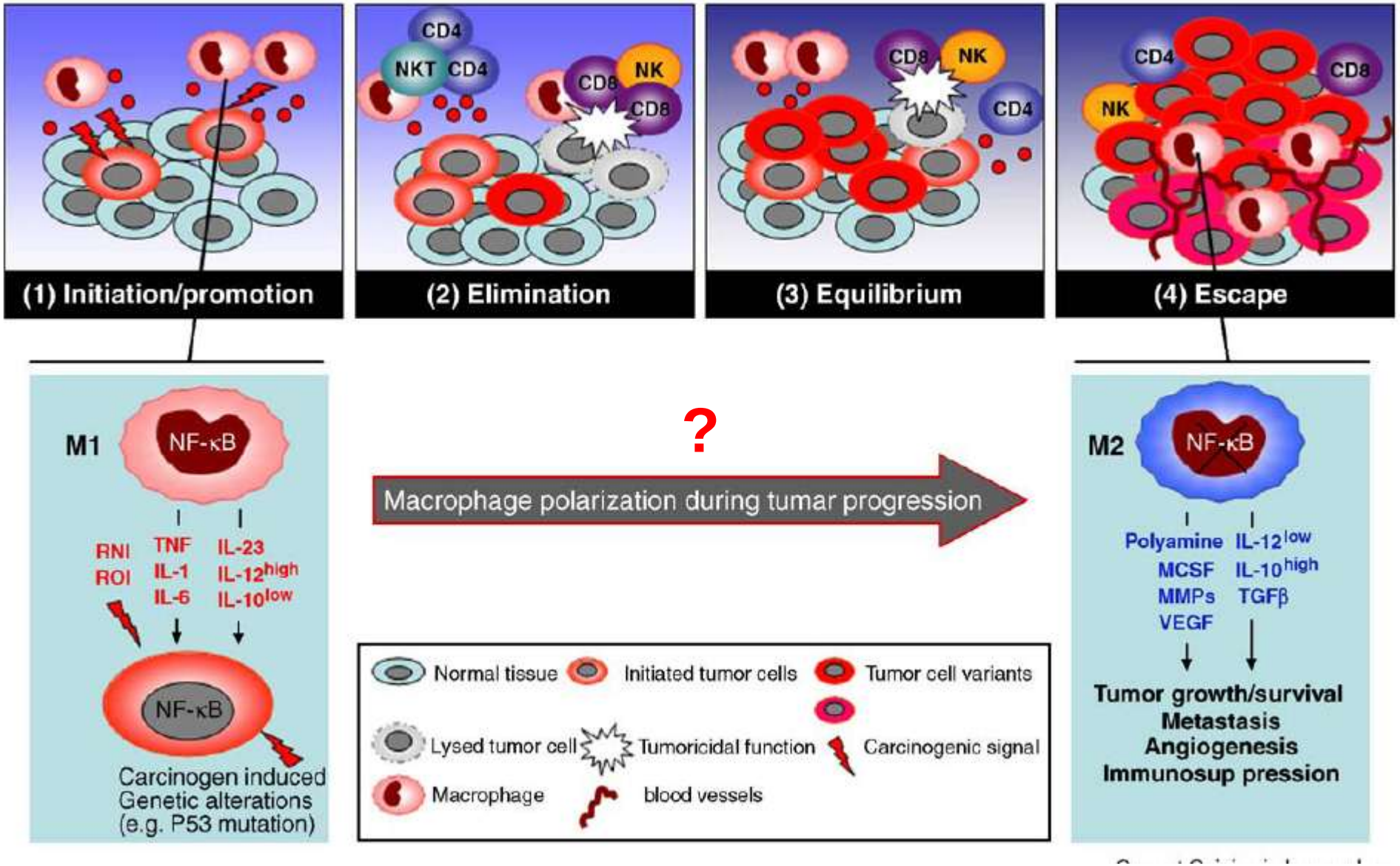
***Am J Transl Res*. 2012; 4(4): 376–389.**



***Cancer Letters*. 2008**

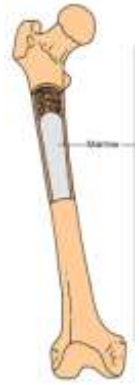


J. Leukoc. Biol. 2010, 88:877.



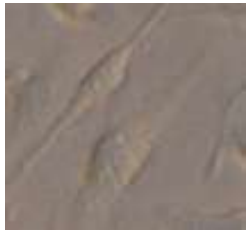
***Curr Opin Immunol*. 2010, 22:231.**

Hepatoma-secreted factors induce bone-marrow derived macrophage polarization



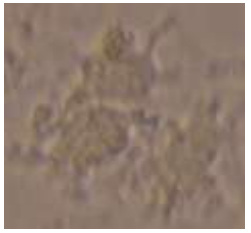
M-CSF
(5 days)

macrophage

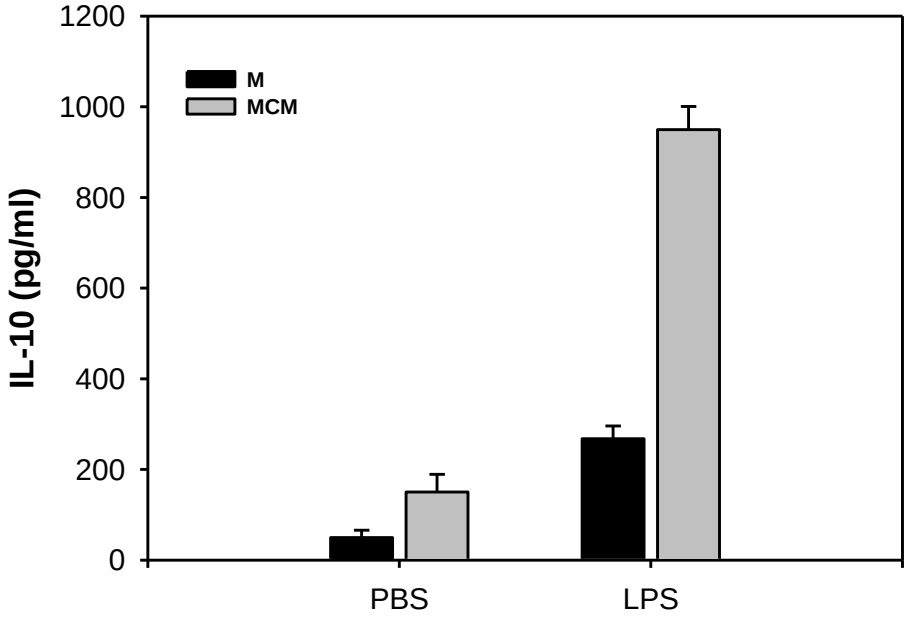


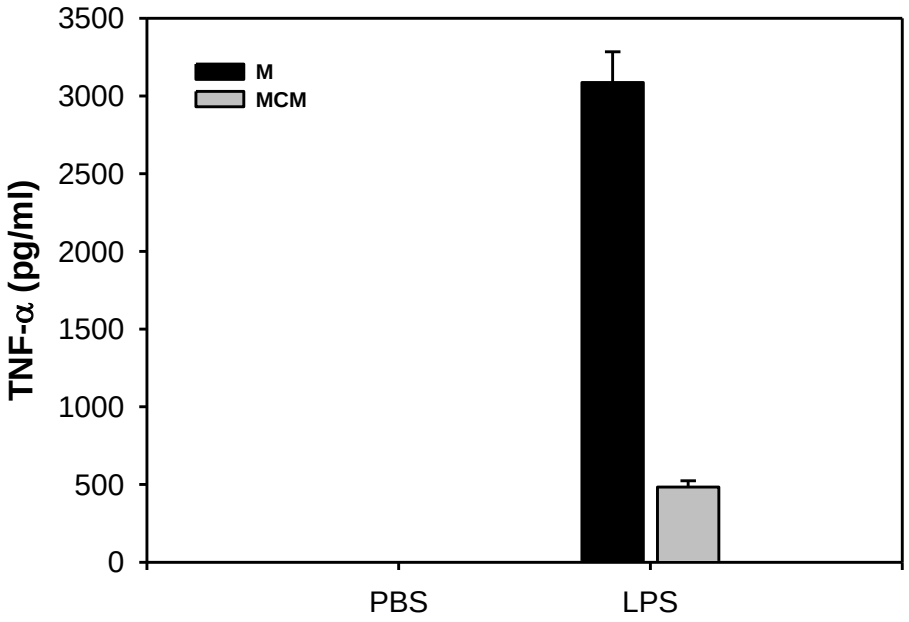
MCM

M2-like macrophage



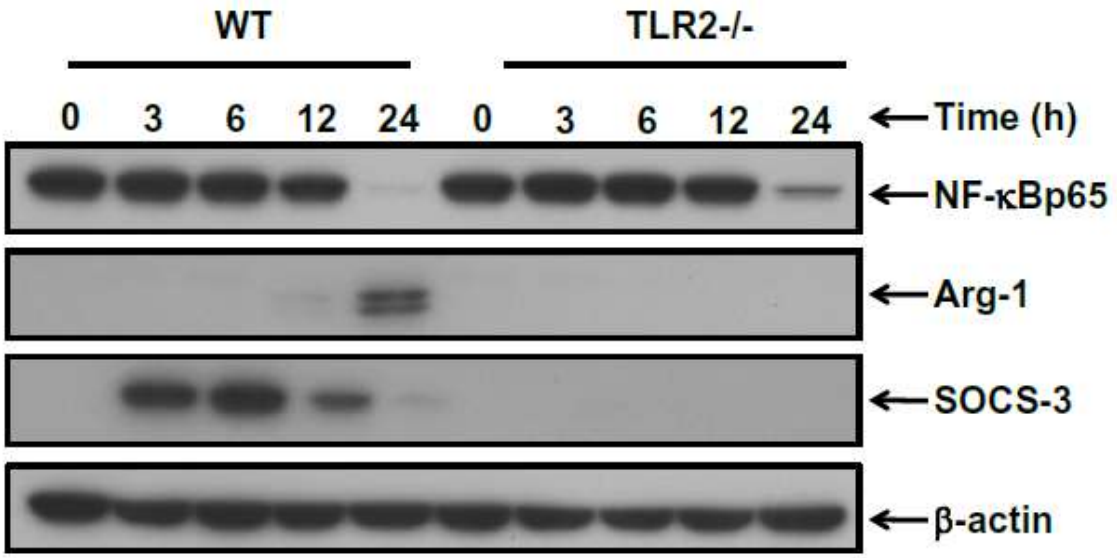
MCM: ML-1_{4a} condition medium

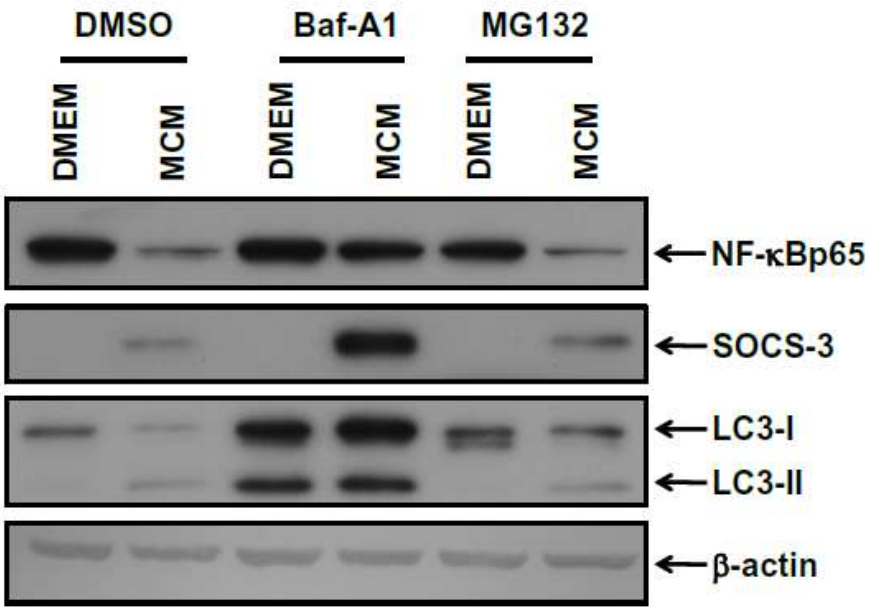




Chang CP, et al. *Cell Death Differ*. 2013

MCM causes lysosomal degradation of NF-κB p65



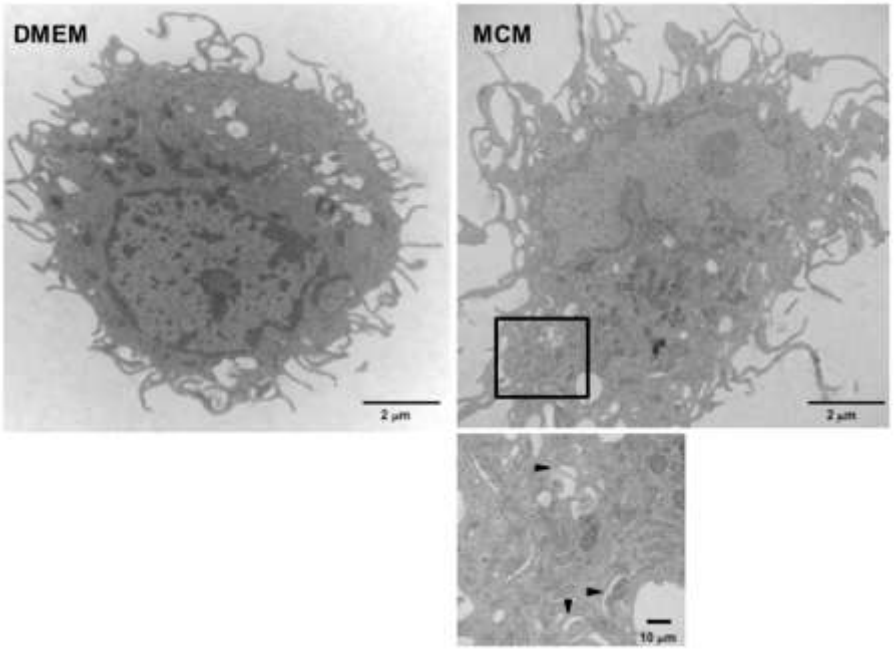


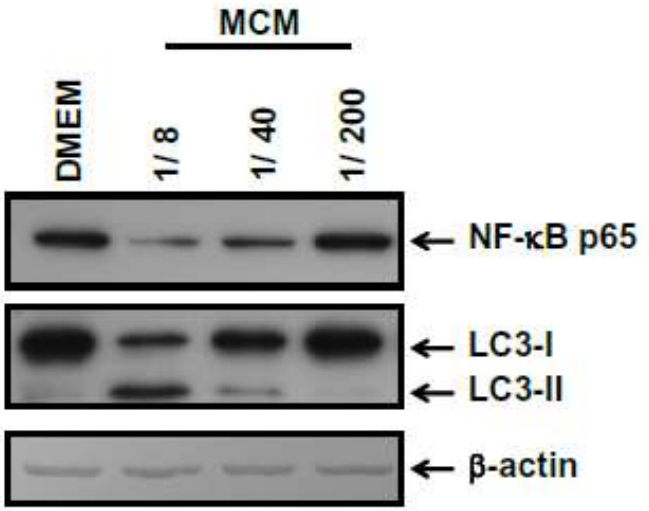
Bafilomycin A1: lysosomal inhibitor

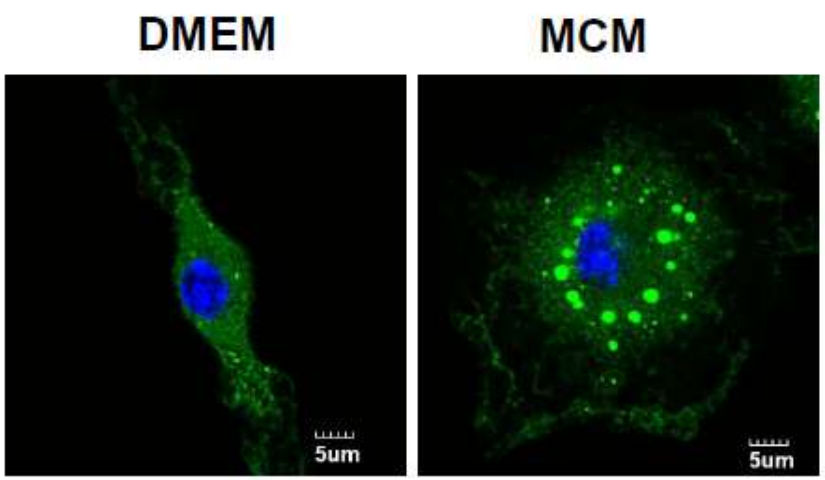
MG132: proteasome inhibitor

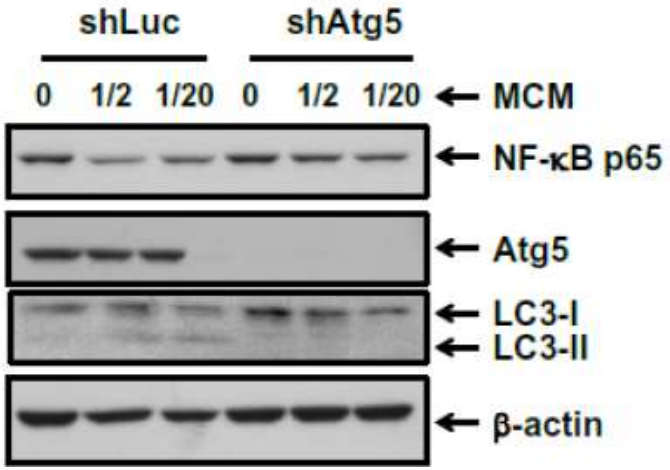
Chang CP, et al. *Cell Death Differ*. 2013

MCM induces autophagy to degrade NF-κB in BMDMs



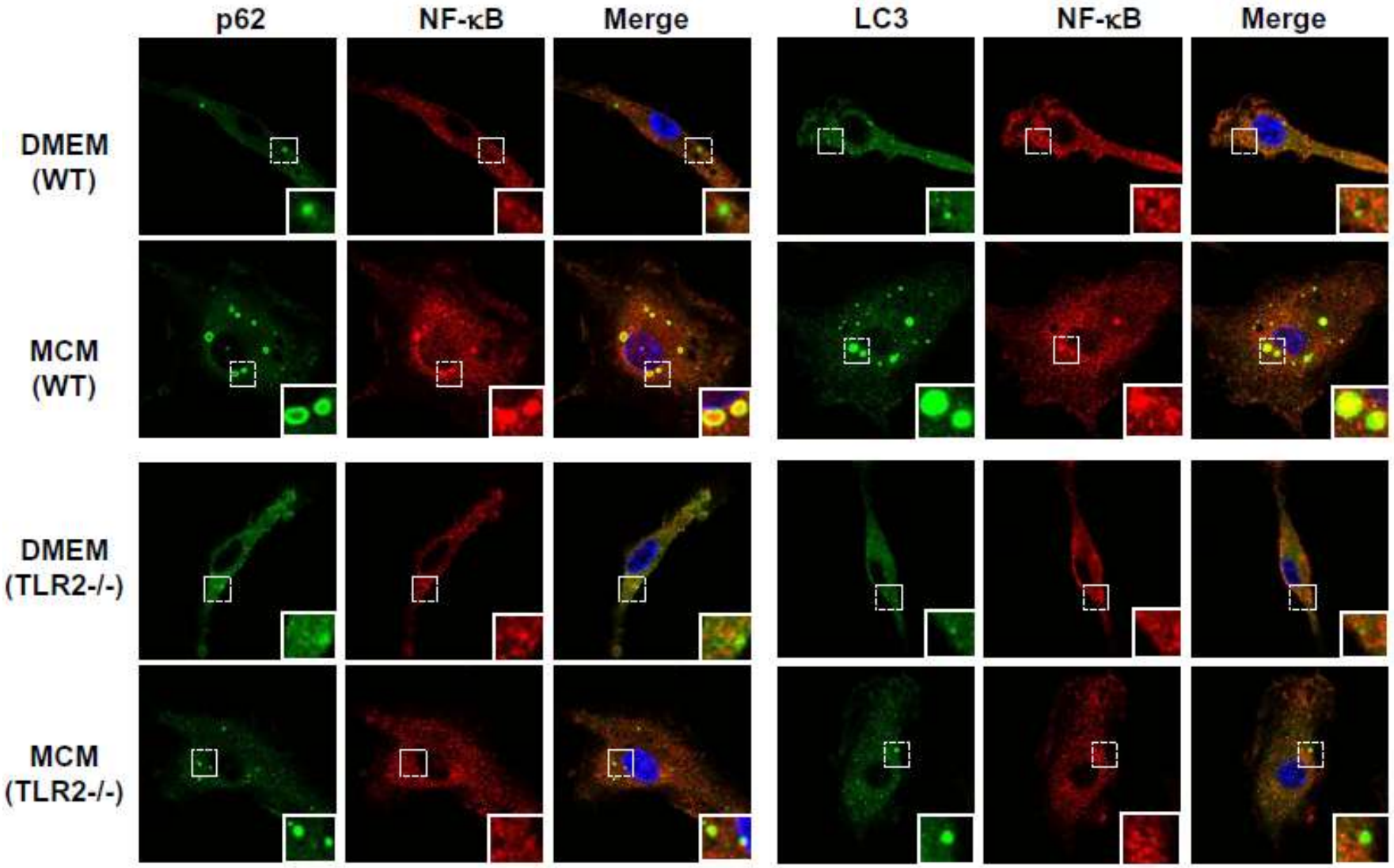




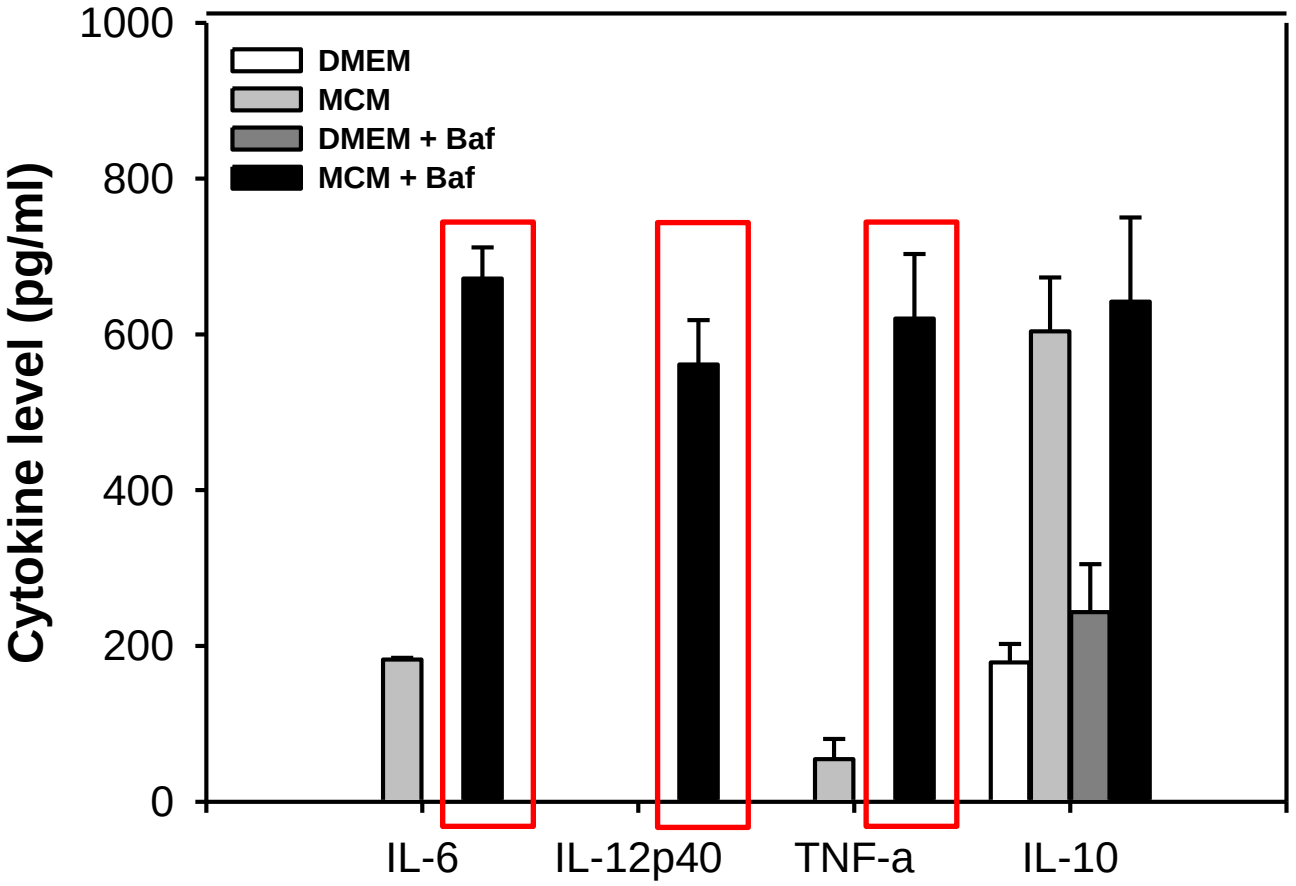


Chang CP, et al. *Cell Death Differ*. 2013

TLR2-signal from MCM is critical for p62 and LC3 to target NF-κB p65 in BMDMs

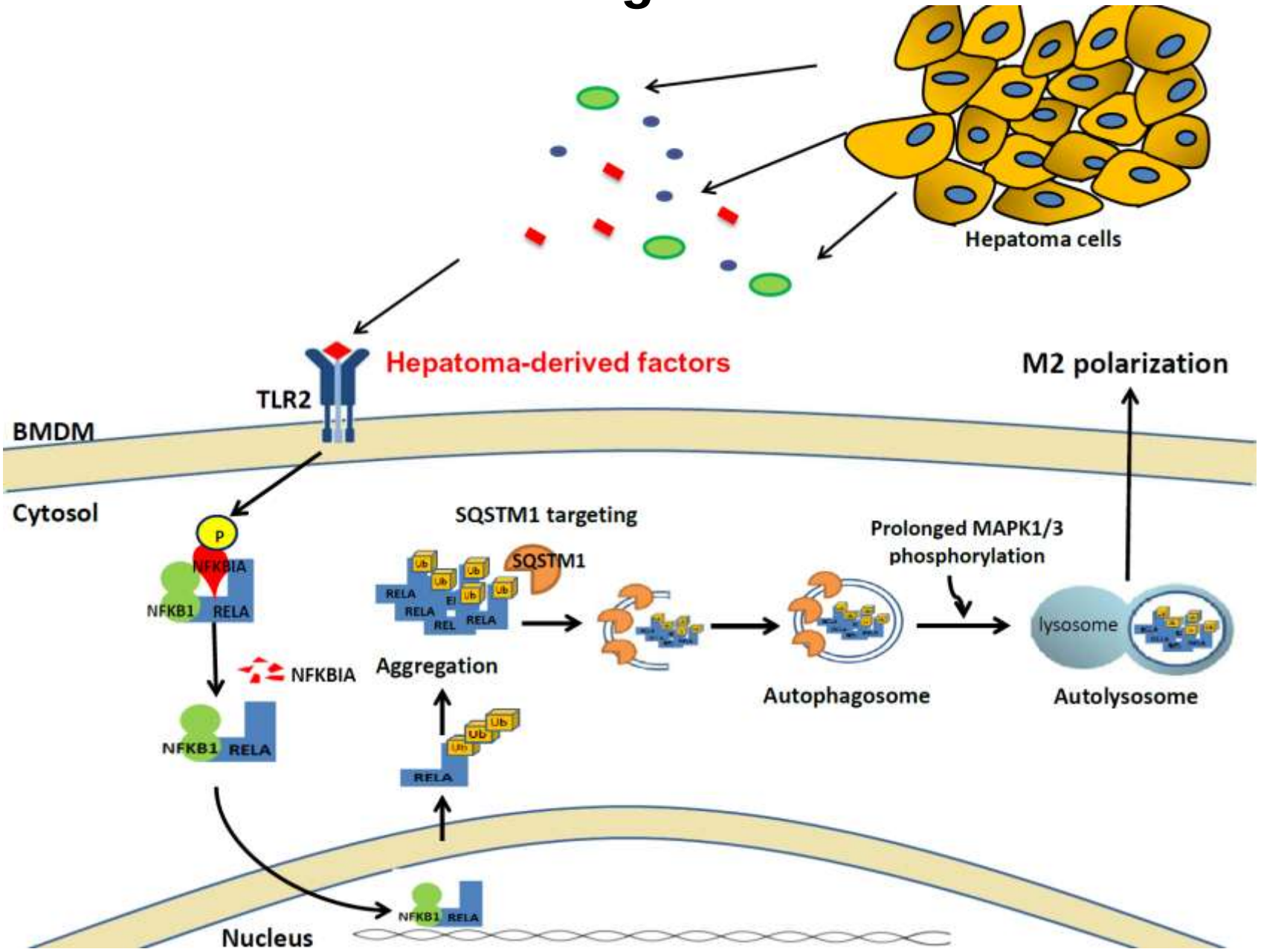


Inhibition of autophagy drives TAM to M1-like macrophages



Chang CP, et al. *Cell Death Differ*. 2013

Working model

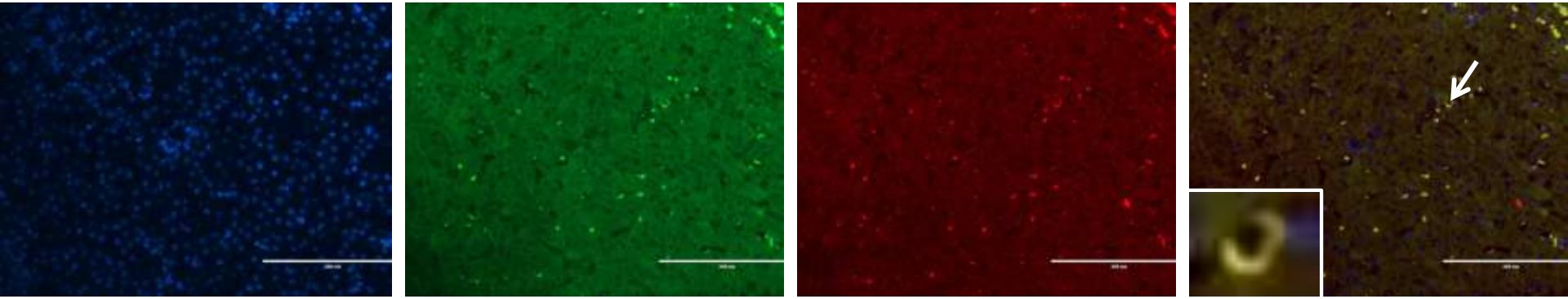


Chang CP, et al. *Cell Death Differ*. 2013 ; Chang CP, et al. *Autophagy*. 2013

High autophagy activity in hepatoma-associated macrophages

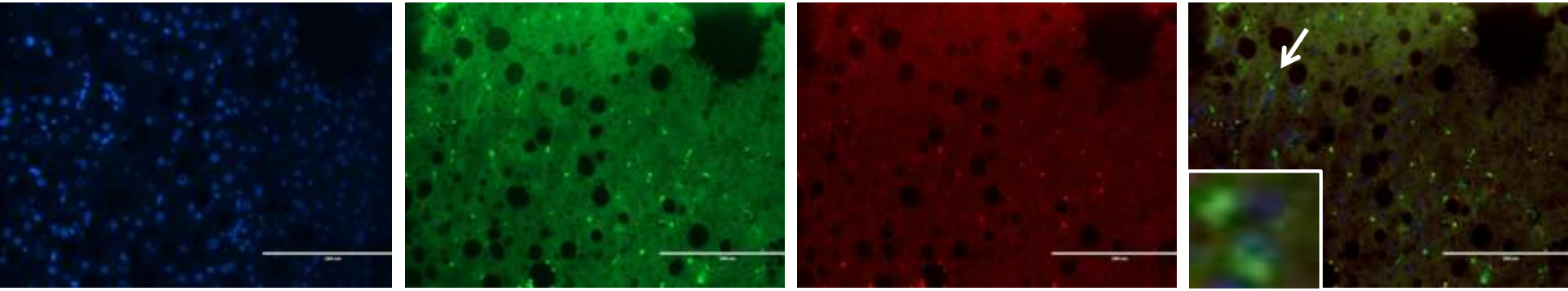
Tumor part

DAPI | CD68 | LC3 | Overlay



Non-Tumor part

DAPI | CD68 | LC3 | Overlay



Sample provided by Dr. Chien-Chin Chen