Signal Transduction in Immune Cells

-2-

07.05.2025

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RUB

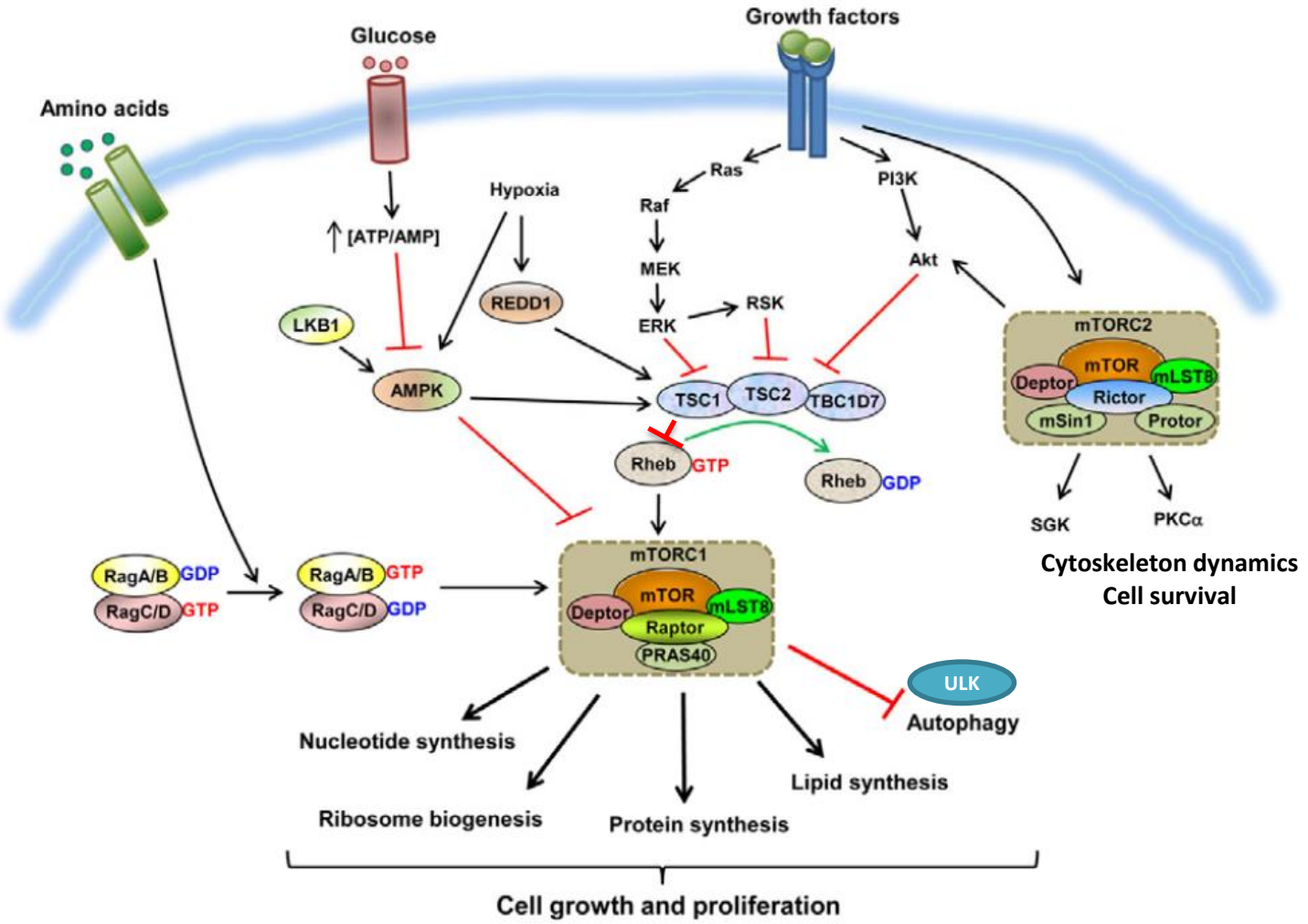
Molecular Immunology

Index

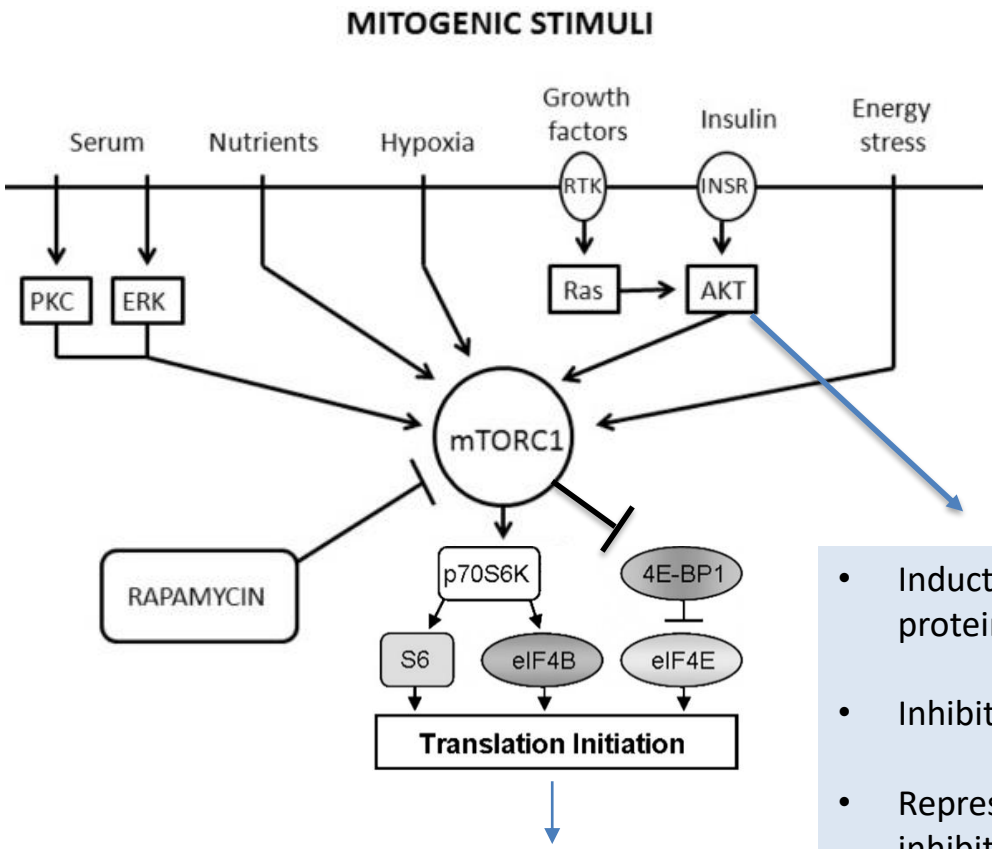
- mTOR pathway
- Autophagy
- TNF receptors pathways
- NF-κB pathway
- Programmed cell death:
  - Apoptosis
  - Necroptosis
  - Pyroptosis

mTOR pathway

- mTOR protein kinase is crucial in cellular and organismal physiology of all eukaryotes.
- mTOR is the central node in a network that controls cell growth.
- mTOR integrates information about the availability of energy and nutrients to coordinate the synthesis or breakdown of new cellular components.



DOI: 10.1007/s10059-013-0138-2

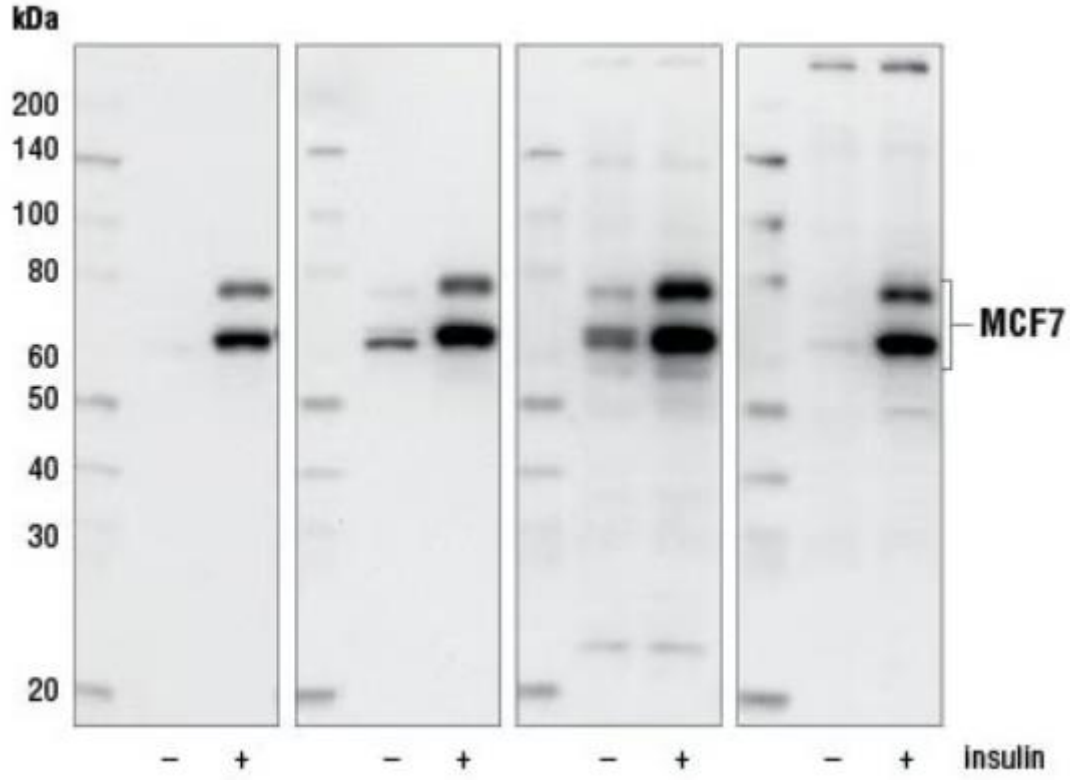


Cell growth/proliferation

- Induction of anti-apoptotic proteins (Bcl2 and XIAP)
- Inhibition of p53 (via MDM2)
- Repression of BIM via FOXO inhibition

mTOR activity measurement

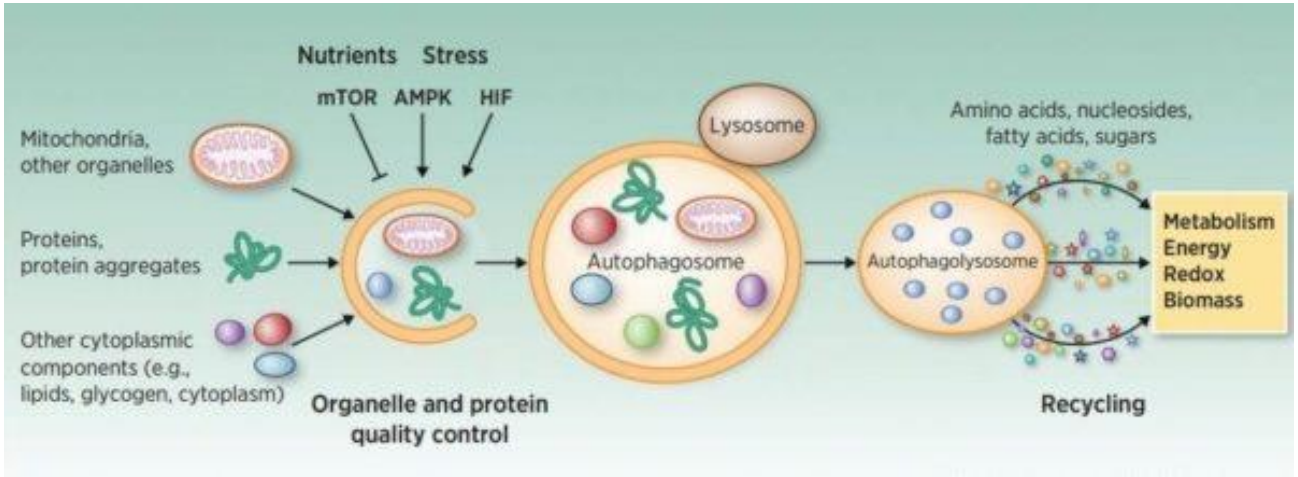
Phospho-p70 S6 Kinase (Thr389) Antibodies



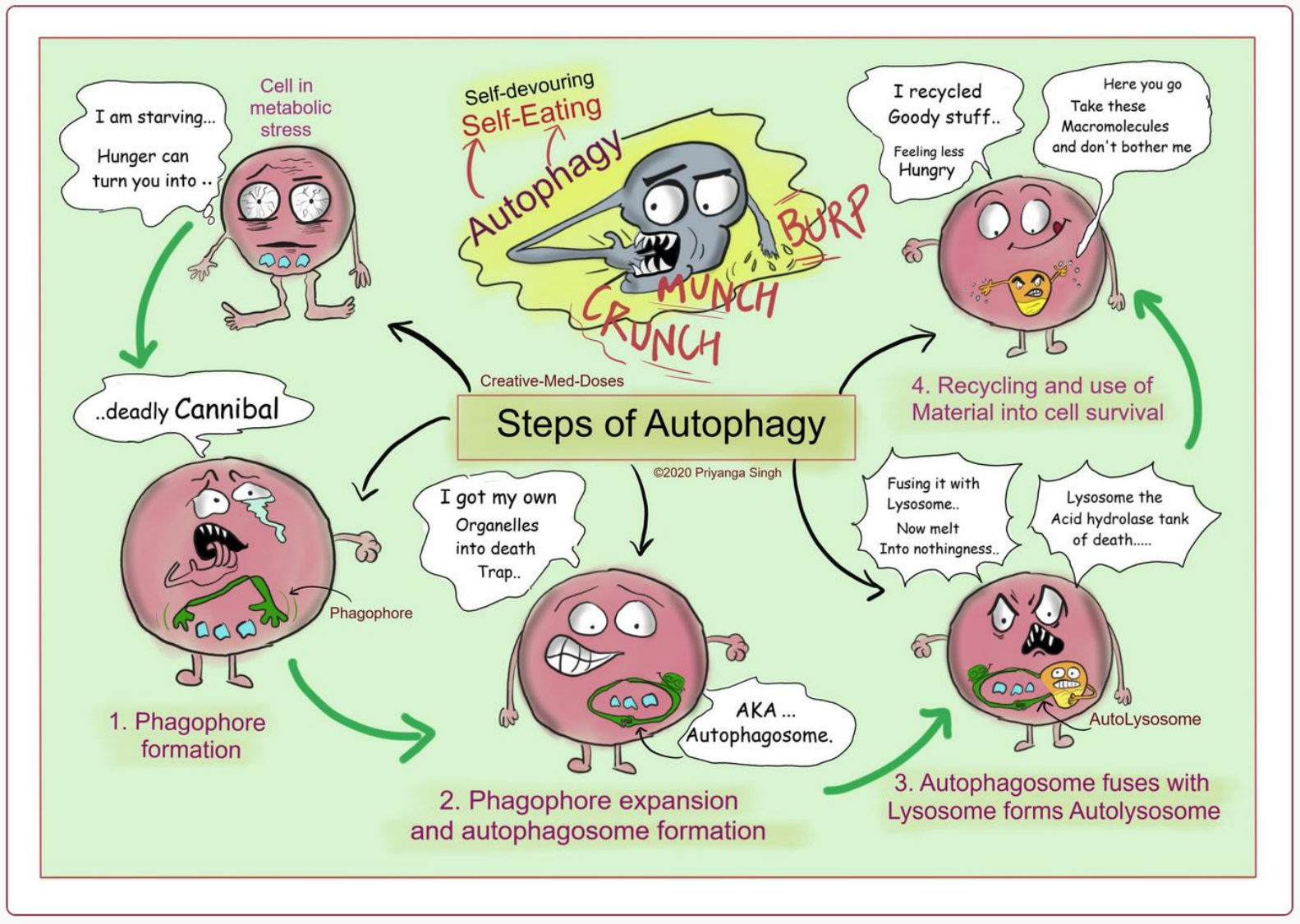
Autophagy

Autophagy

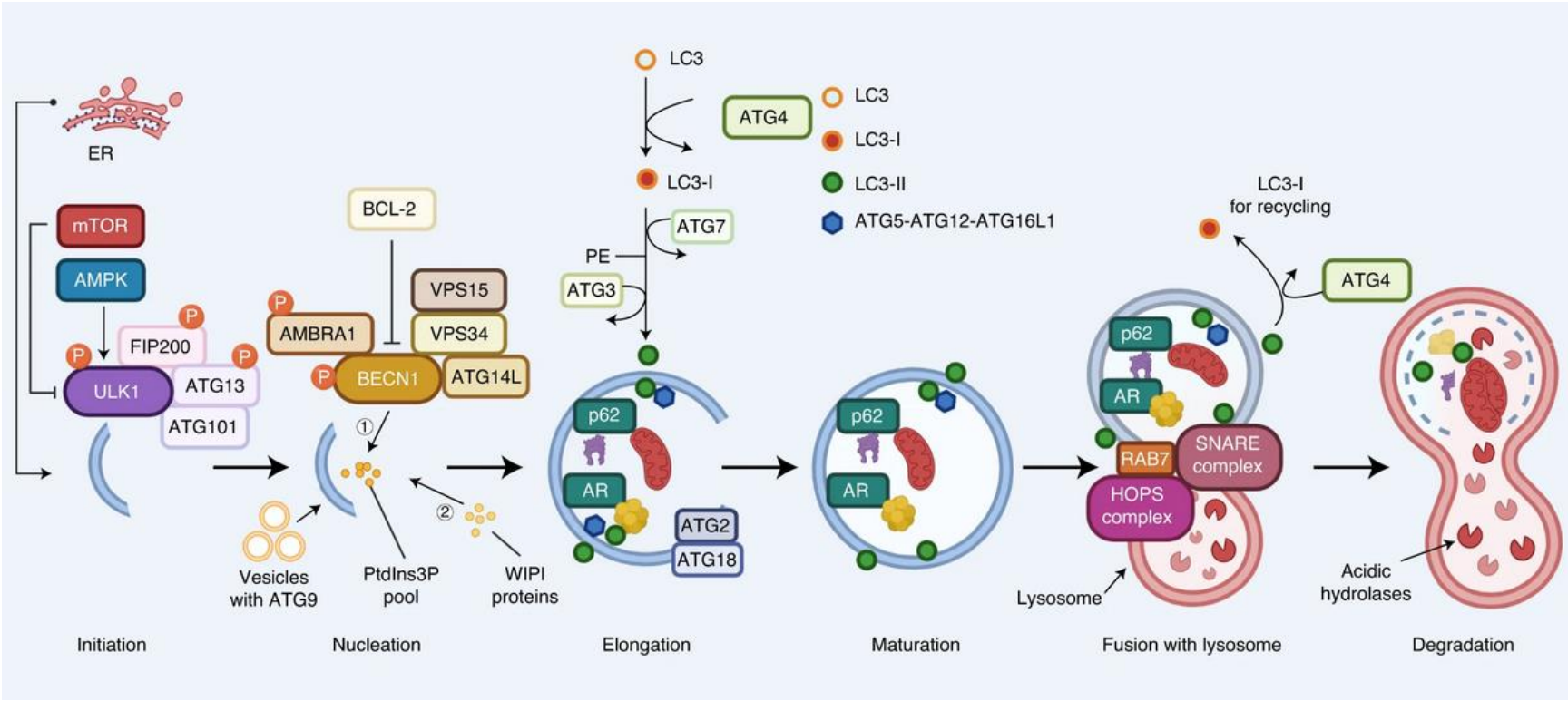
Autophagy is a fundamental cellular process that eliminates molecules and subcellular elements, including nucleic acids, proteins, lipids and organelles, via lysosome-mediated degradation to promote homeostasis, differentiation, development and survival.



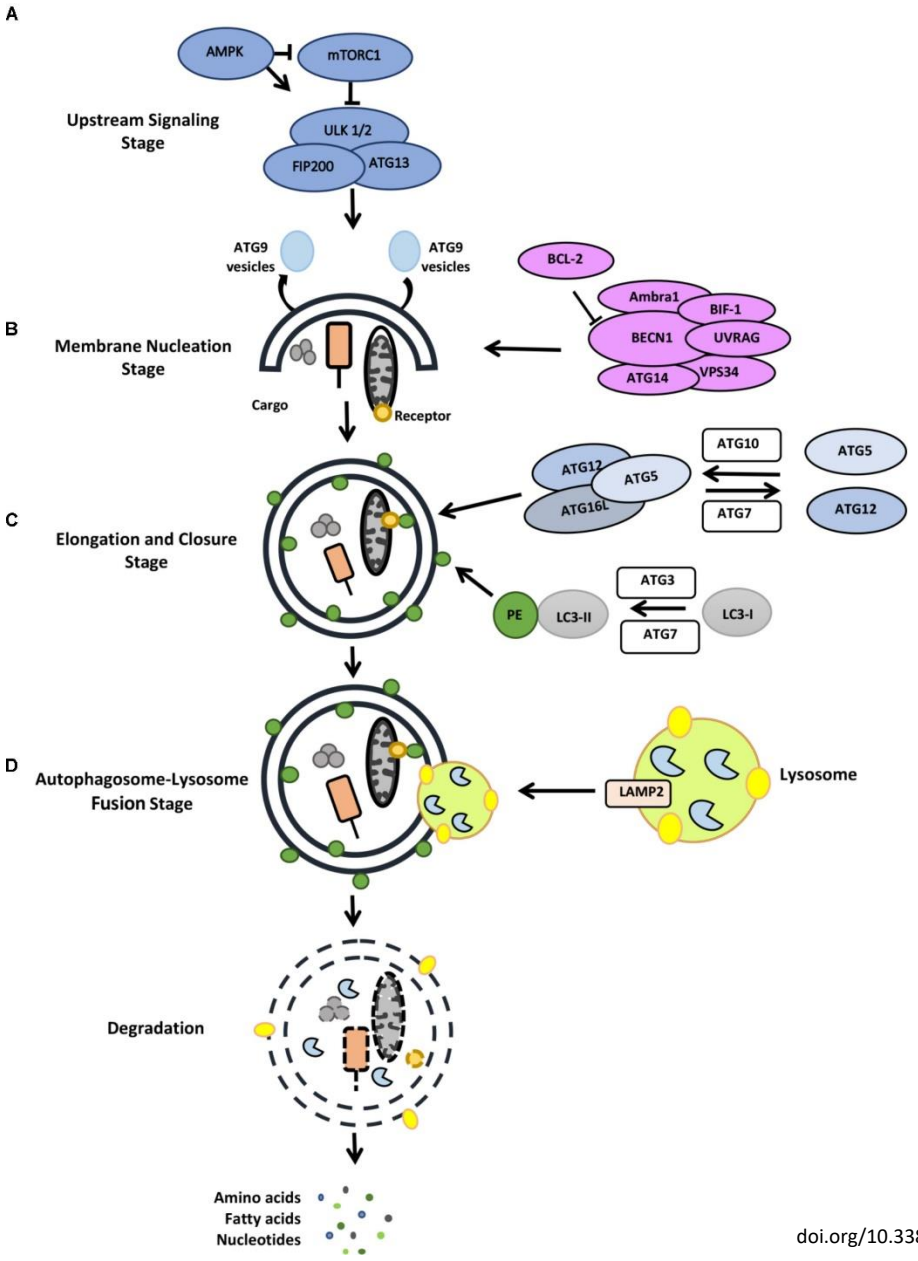
Autophagy



creativemeddoses.com

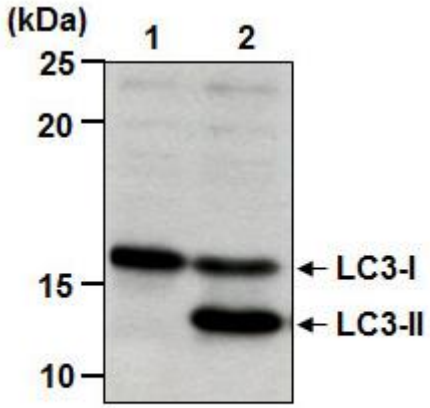


doi.org/10.1038/s43587-021-00098-4

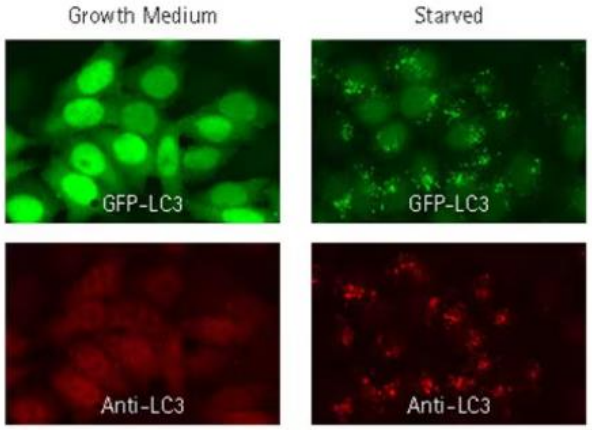


doi.org/10.3389/fcell.2018.00128

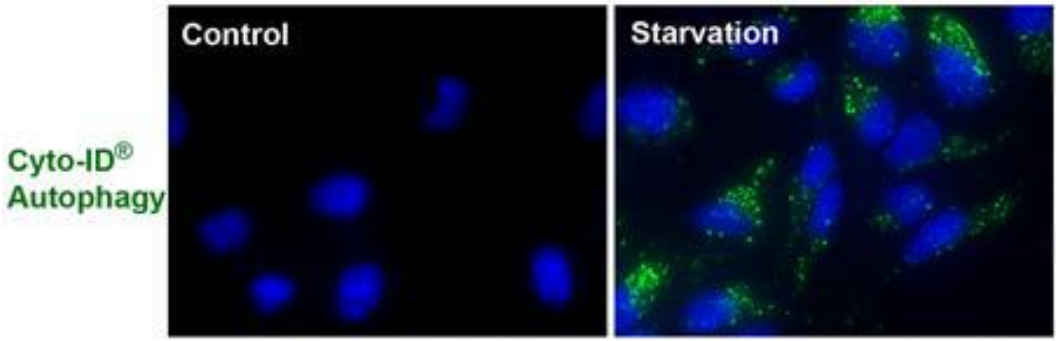
Autophagy measurement

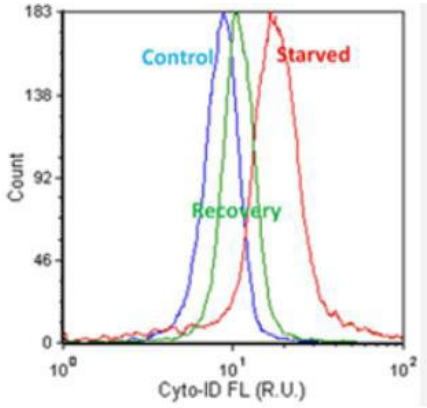


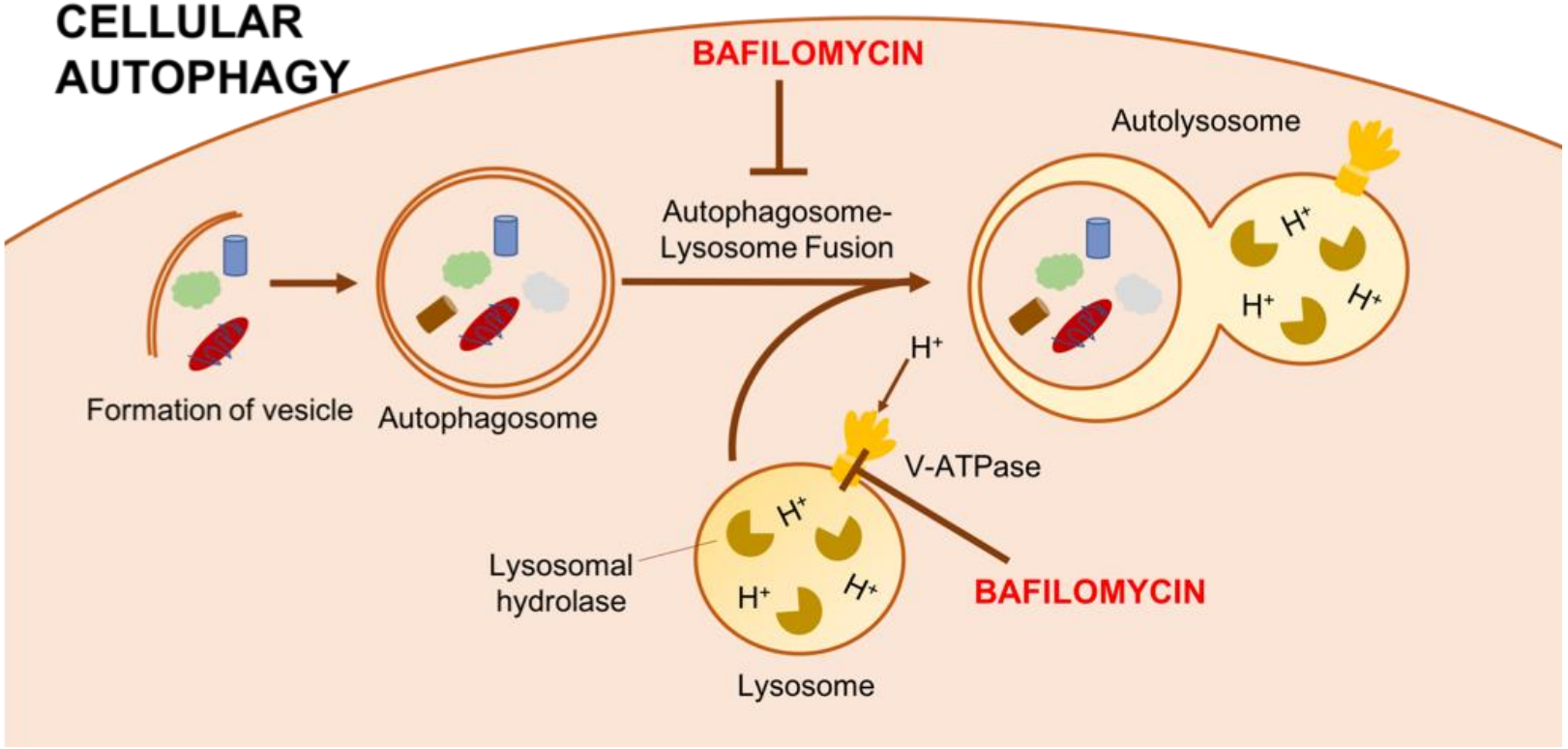
Lane 1: Atg5$^{-/-}$MEF
Lane 2: Wild-type MEF



LC3 fluorescent reporter



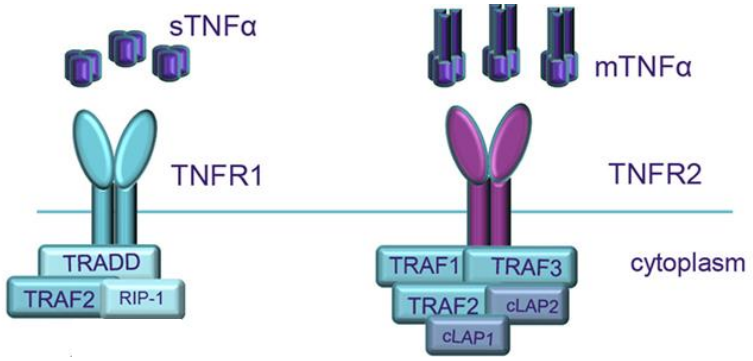



CELLULAR AUTOPHAGY
BAFILOMYCIN
Autolysosome
Autophagosome-Lysosome Fusion
H+
H+
H+
Formation of vesicle
Autophagosome
H+
V-ATPase
H+
Lysosomal hydrolase
H+
BAFILOMYCIN
Lysosome

TNF signaling pathway

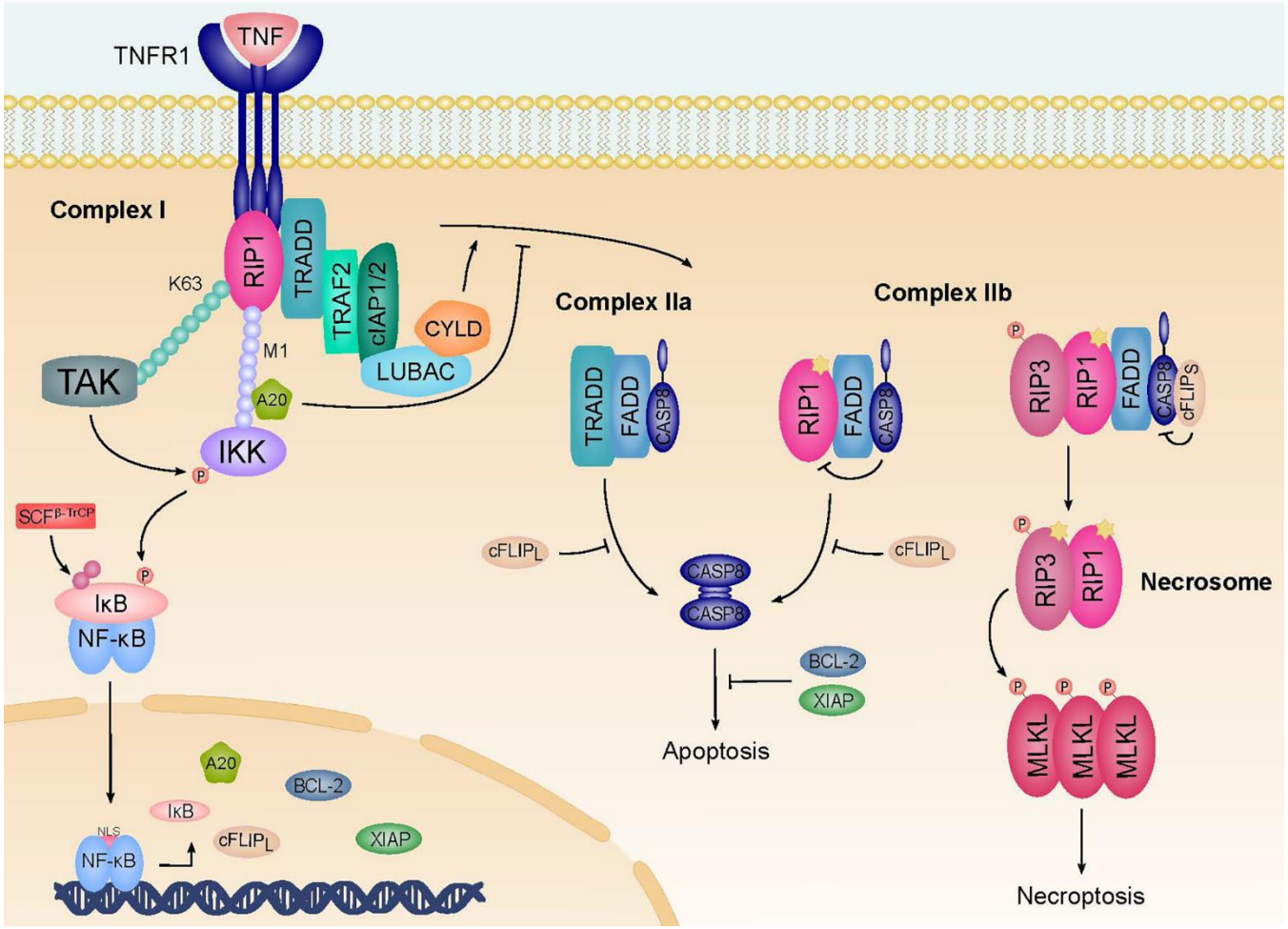
TNF (Tumor necrosis factor) signaling

- Induction of inflammation
- Cell death
- Cell proliferation and differentiation



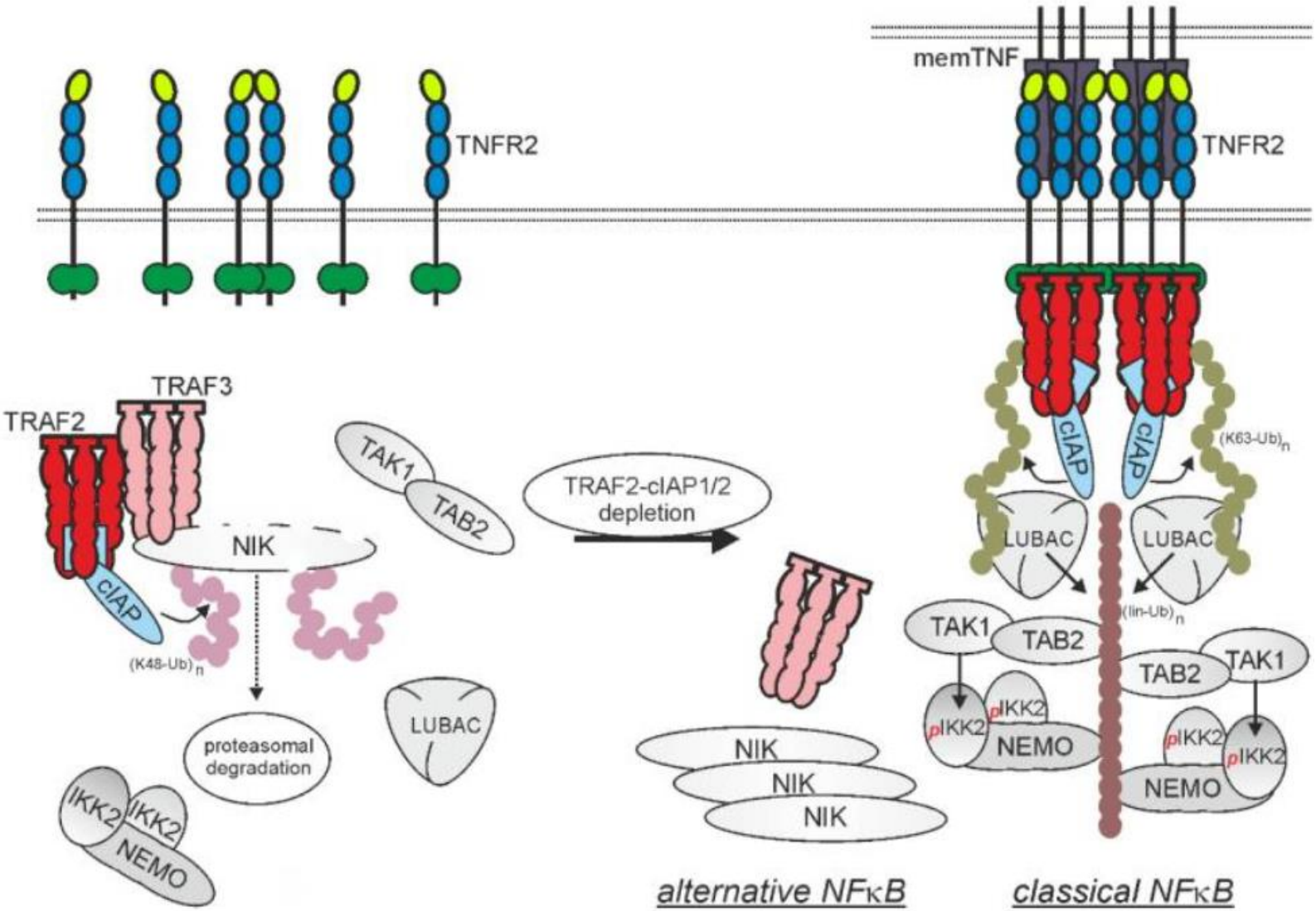
- ❖ sTNF → TNFR1
- ❖ mTNF → TNFR1 and TNFR2

TNFR1 signaling



doi.org/10.1371/journal.pcbi.1010383

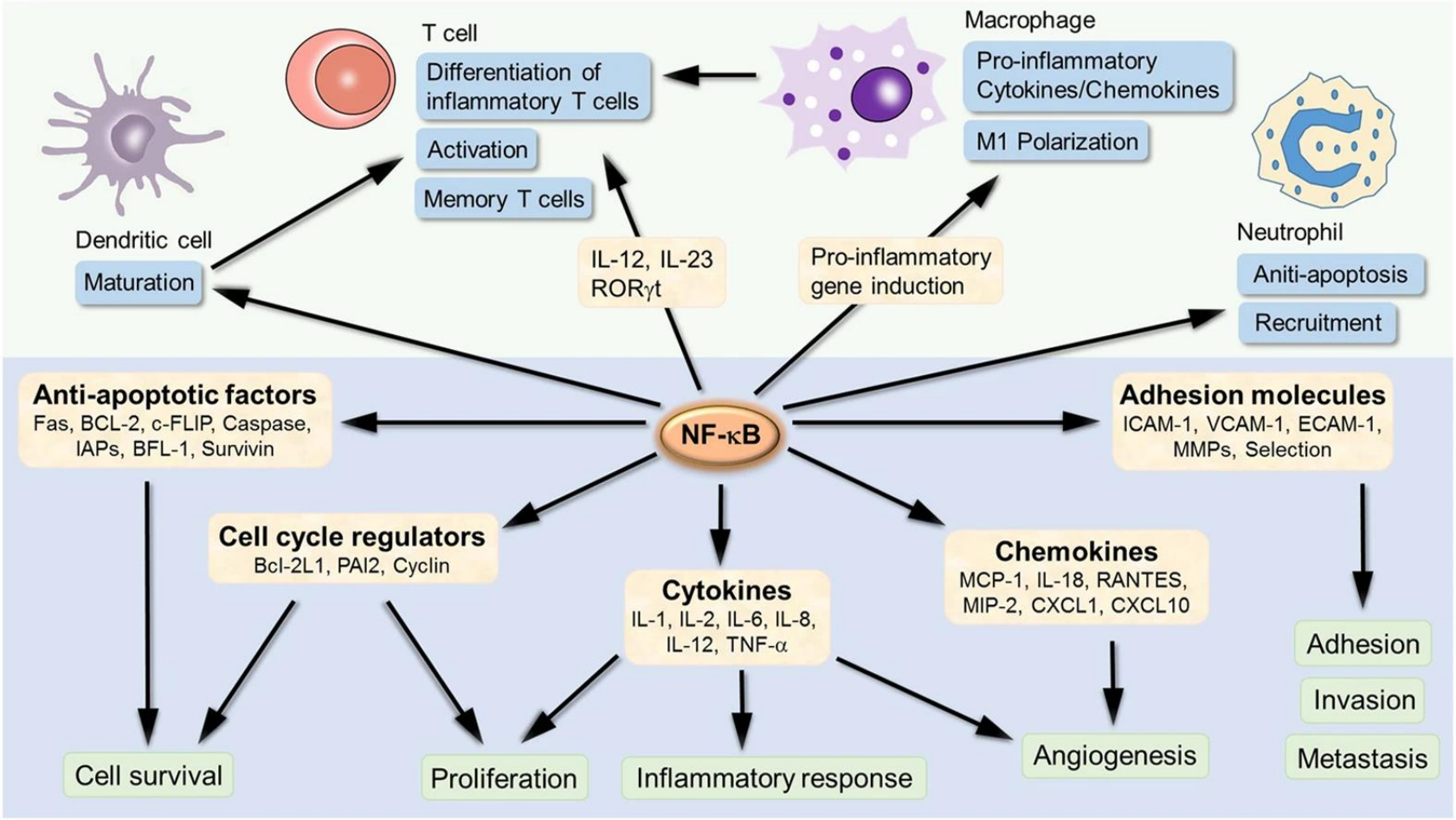
TNFR2 signaling



doi: 10.3390/cancers14112603

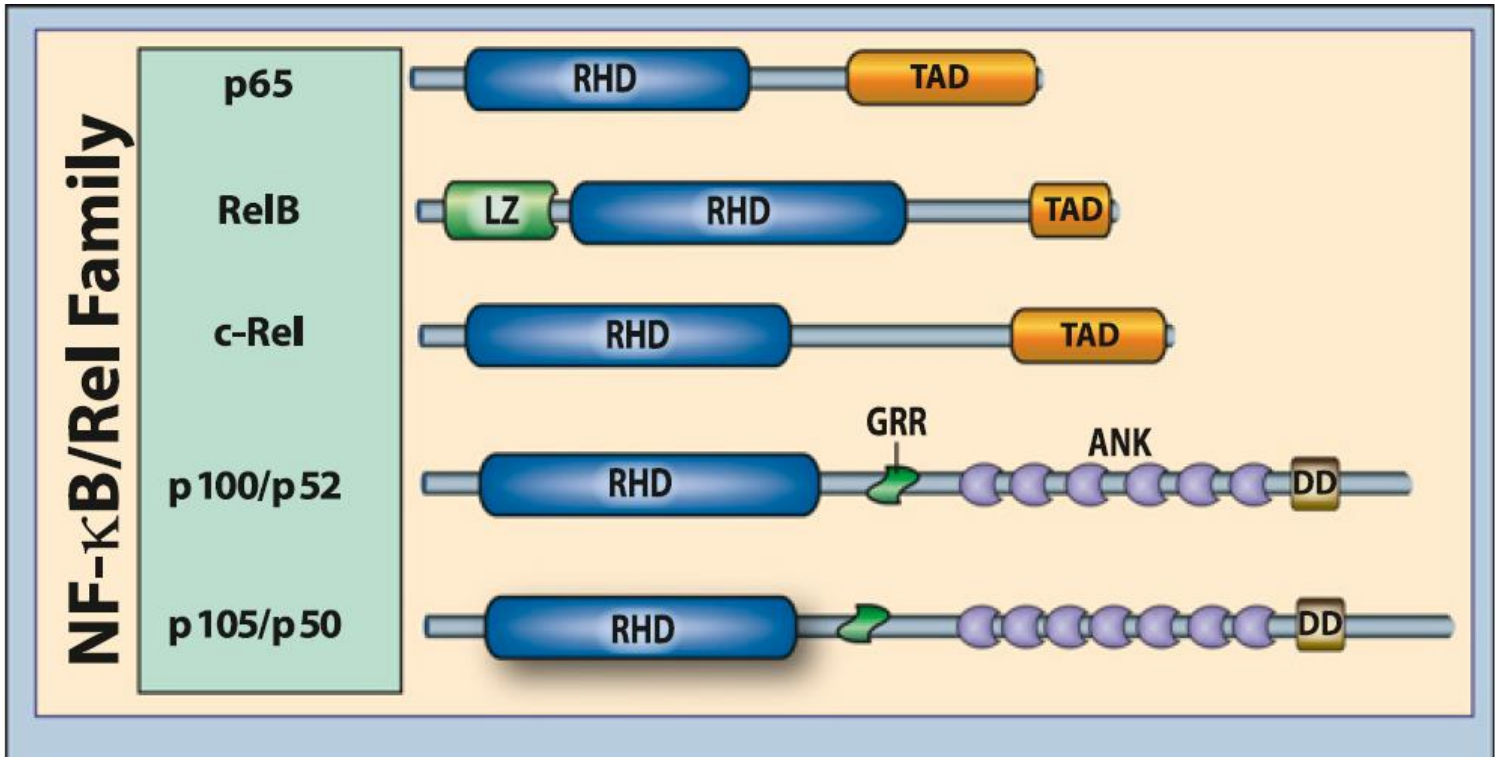
NF-κB pathway

NF-κB and immunity



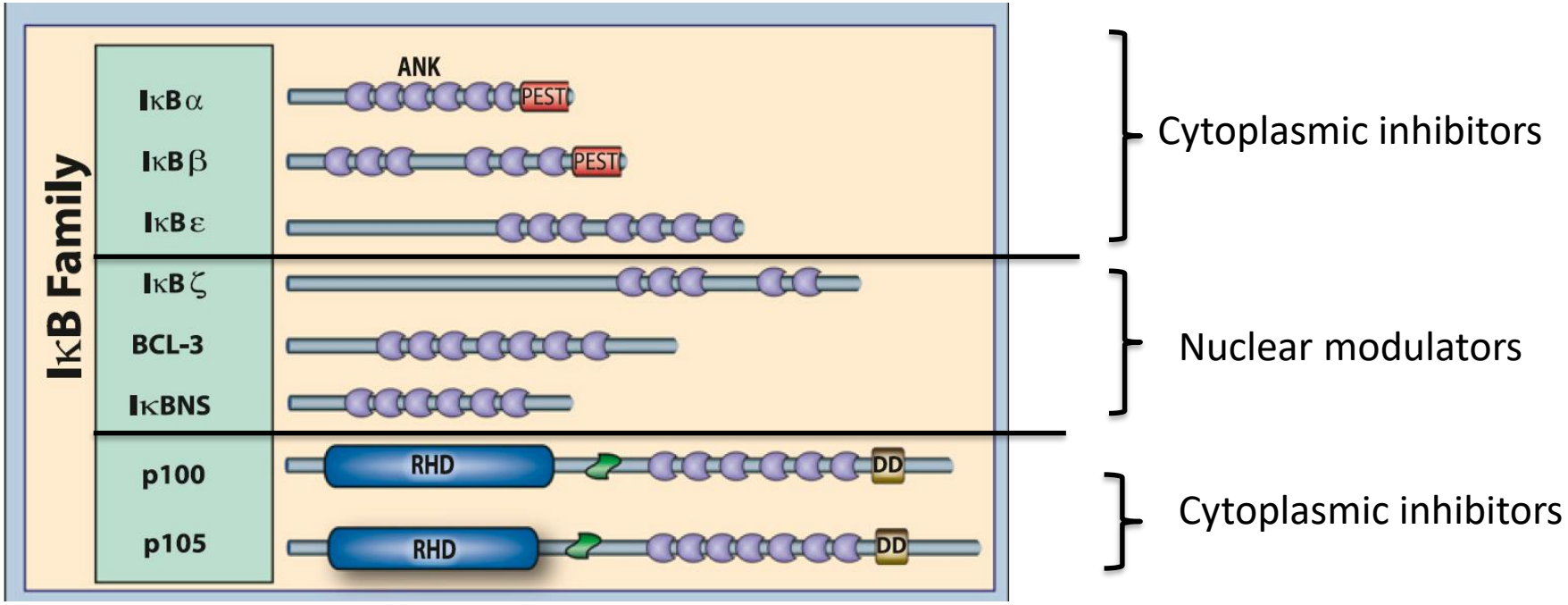
Liu. 2017

NF-κB family members



Hayden & Gosh. 2012

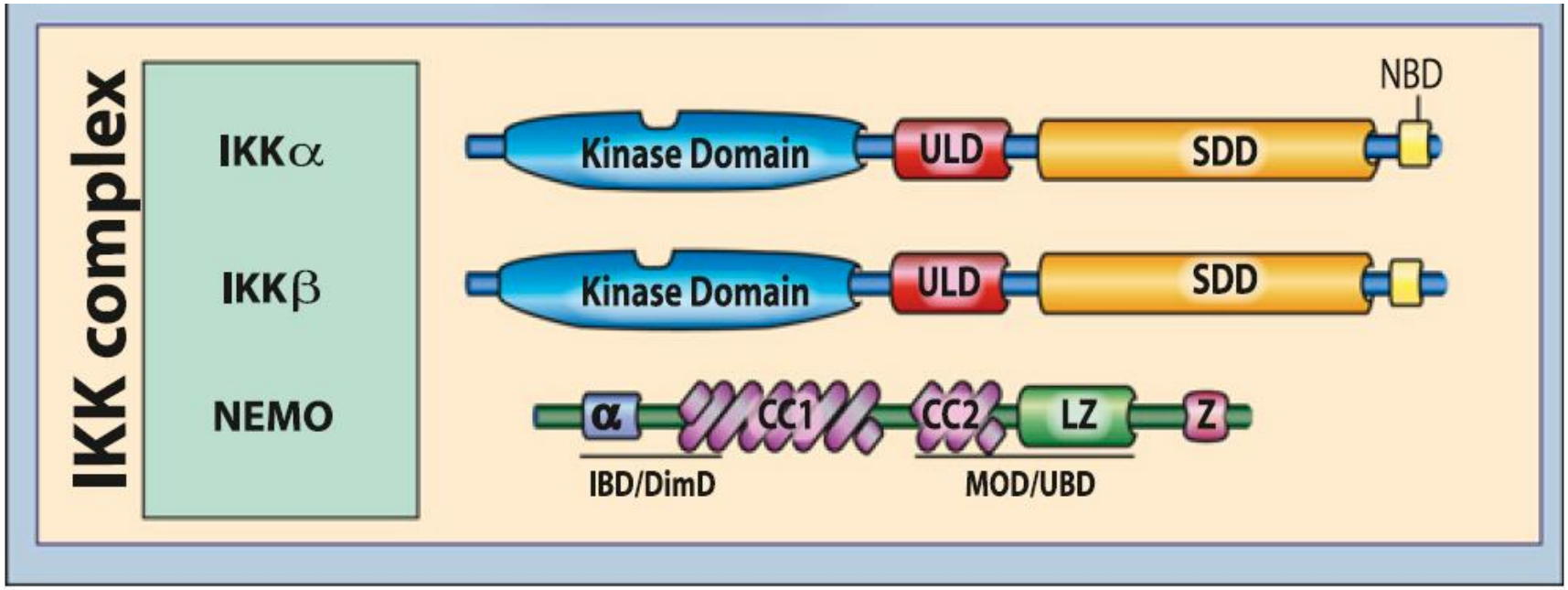
NF-κB family members



Hayden & Gosh. 2012

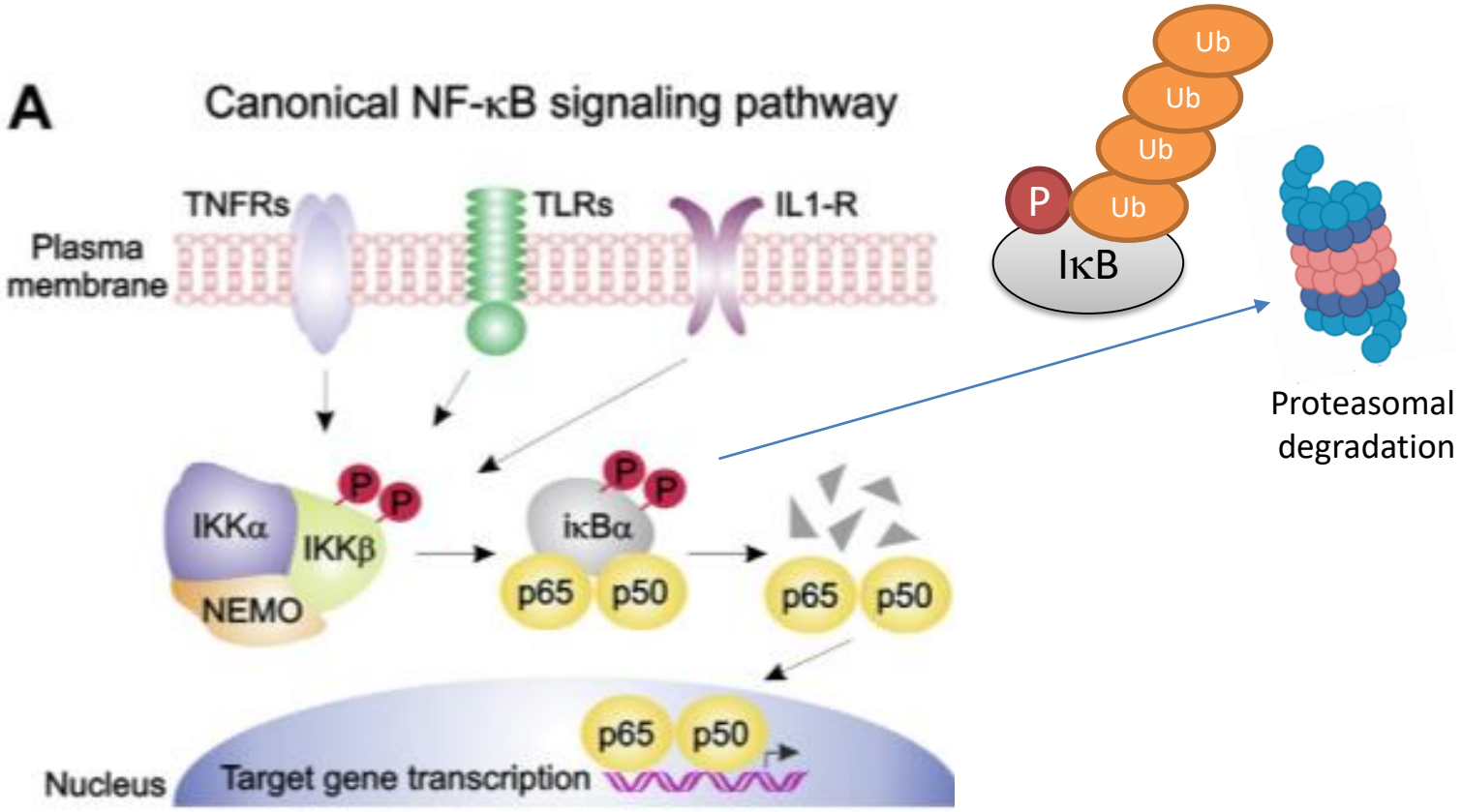
NF-κB family members

Activatory kinase complex



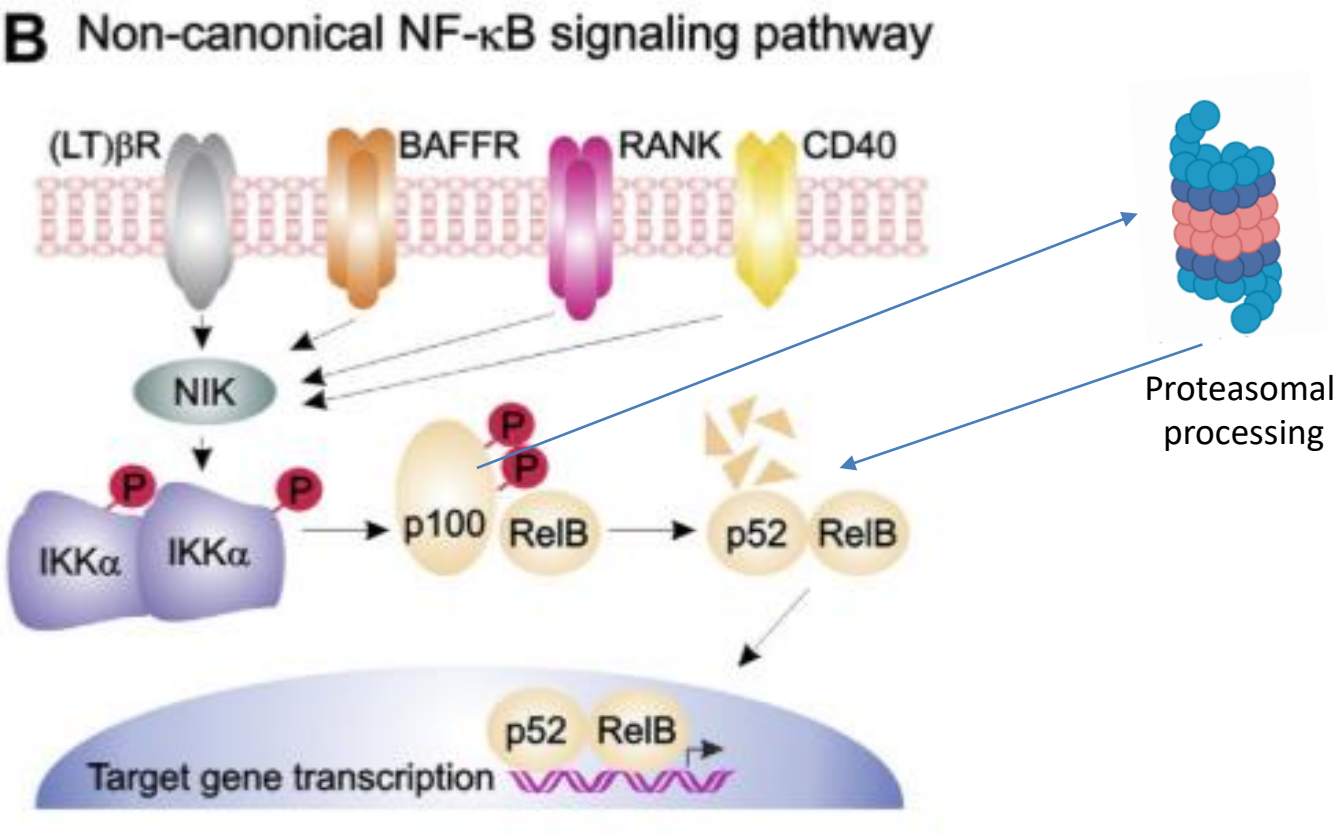
Hayden & Gosh. 2012

NF-κB canonical pathway



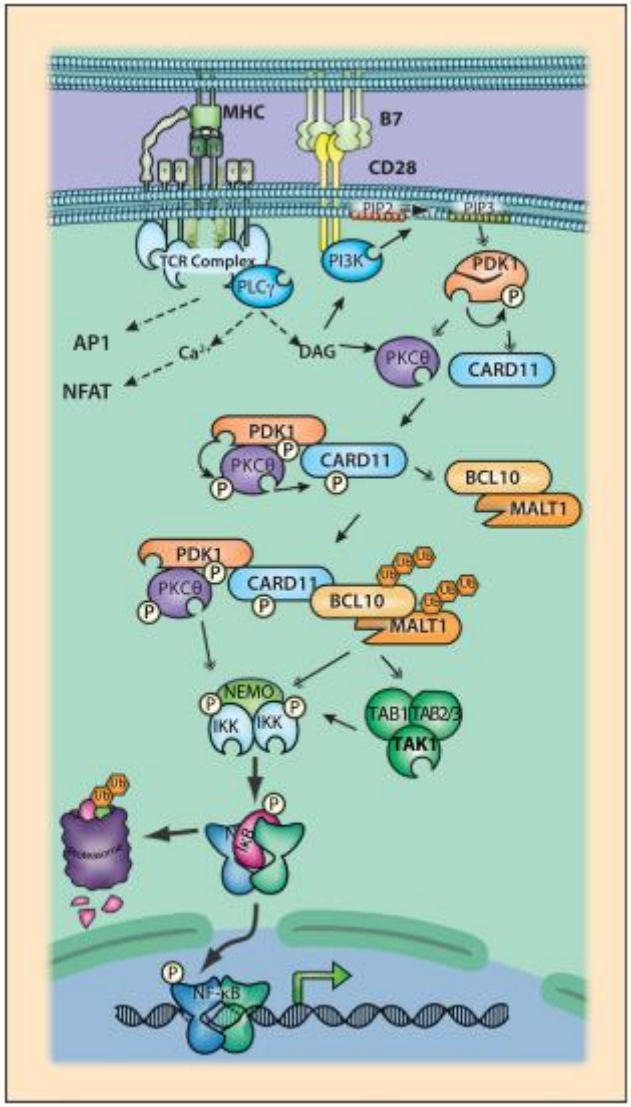
Espín-Palazón & Traver, 2016

NF-κB non-canonical pathway



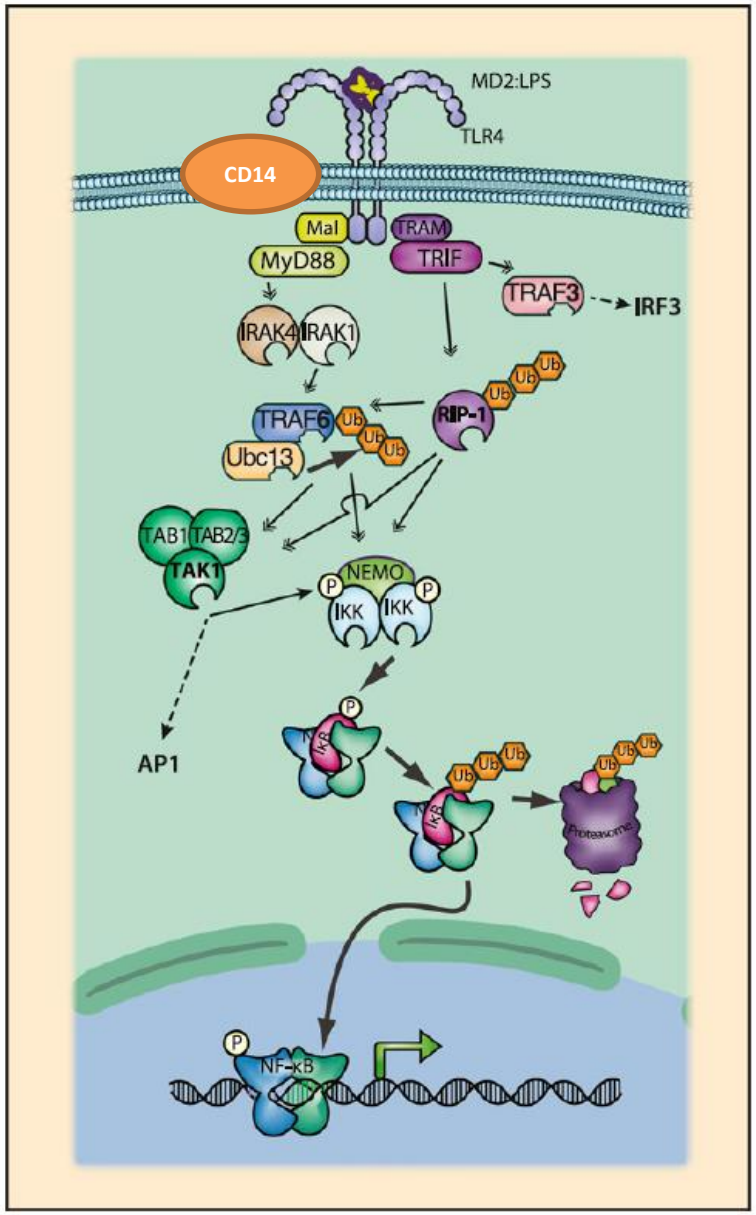
Espín-Palazón & Traver, 2016

TCR and NF-κB pathway

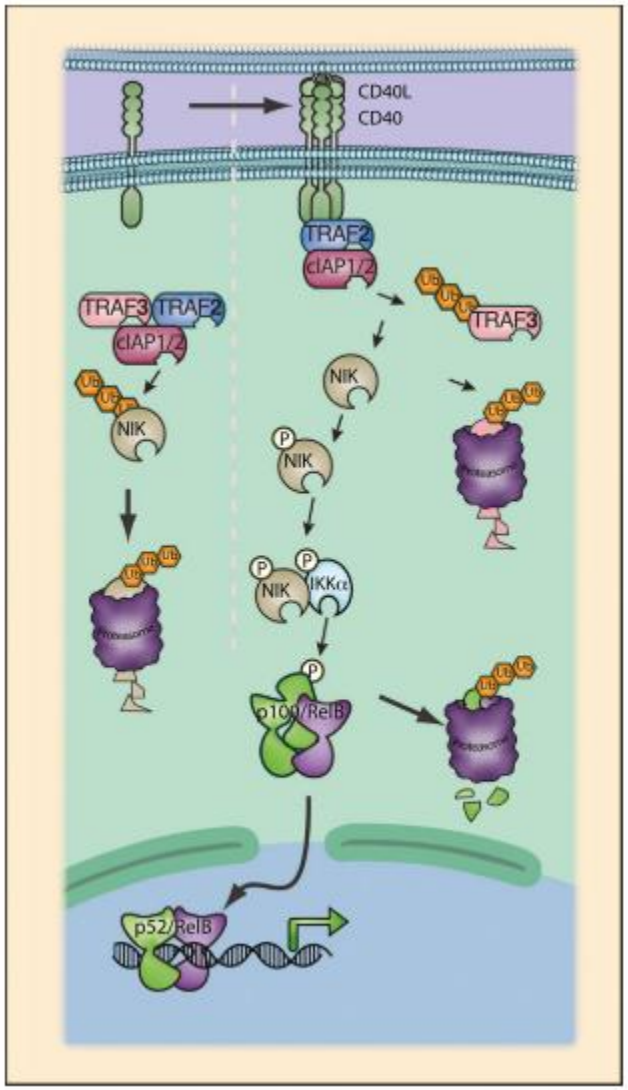


Hayden & Gosh. 2012

TLR4 and NF-κB pathway

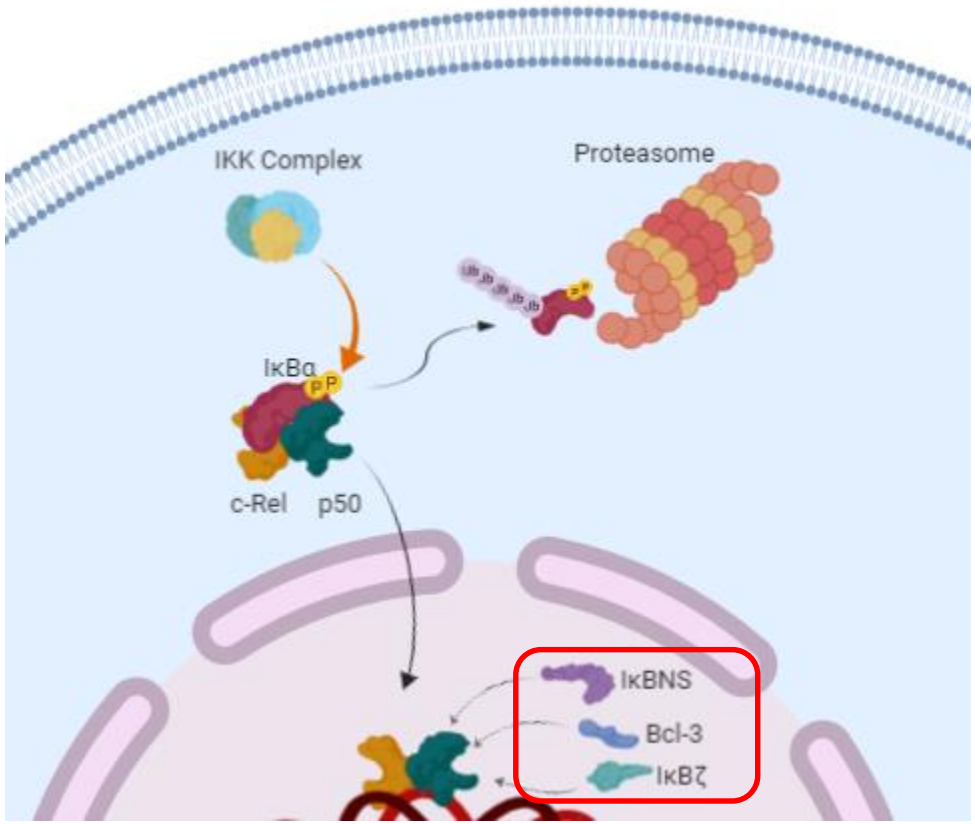


CD40 and NF-κB pathway



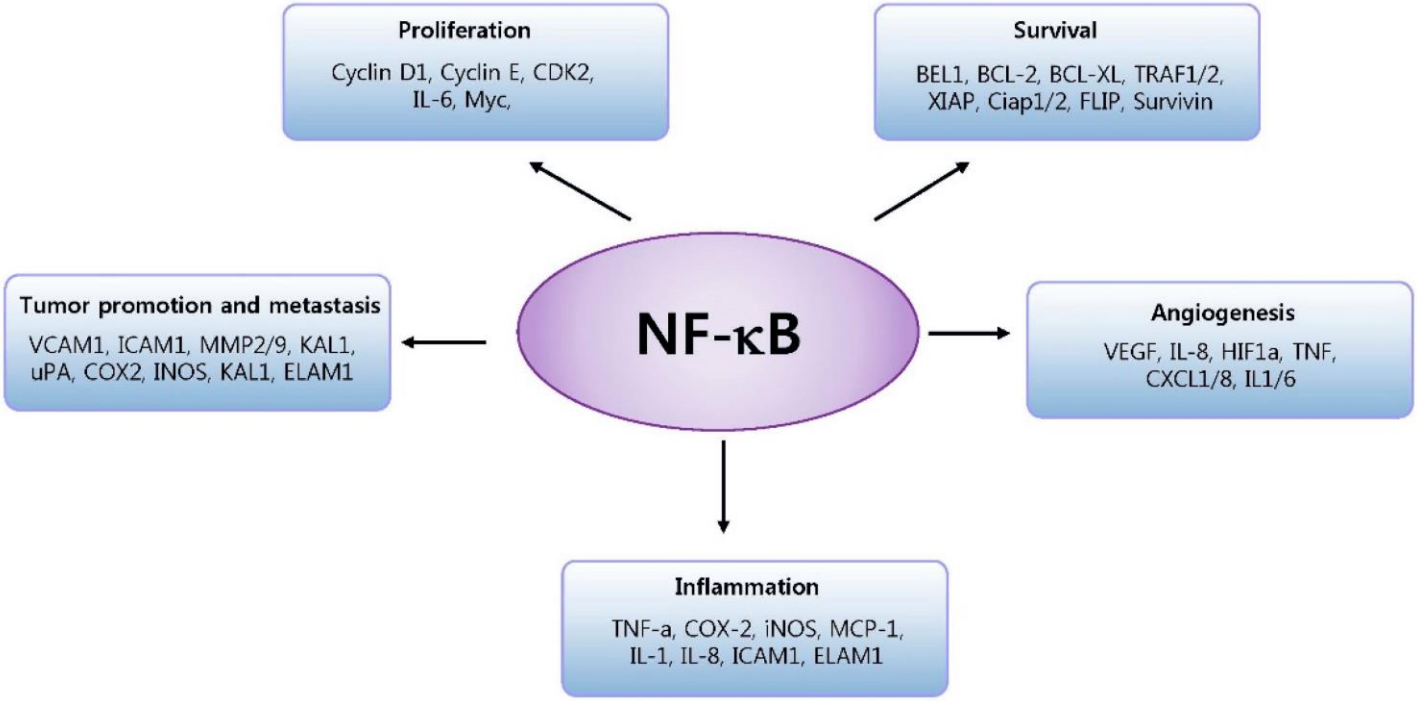
Hayden & Gosh. 2012

Atypical IκBs

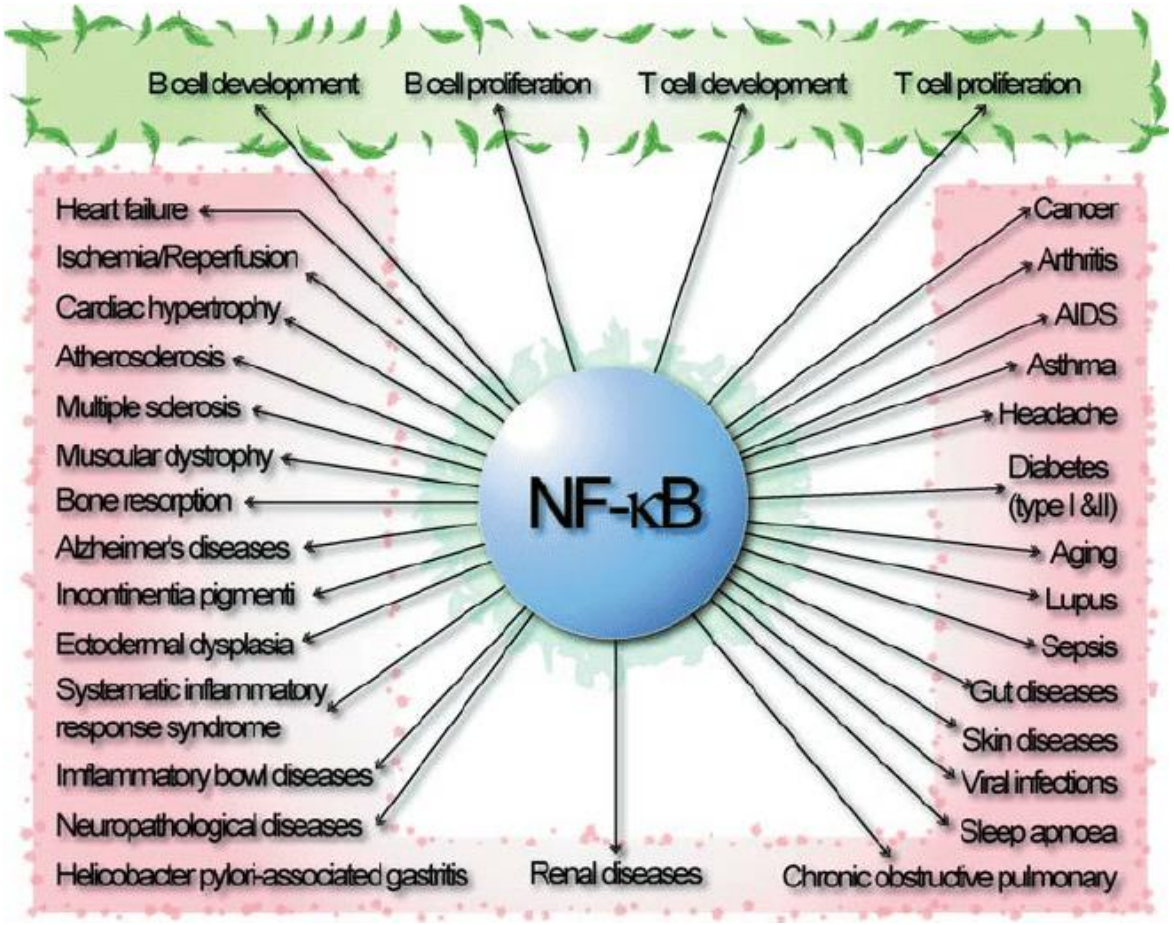


- IκBNS, Bcl-3 and IkBζ
- Nuclear localization
- Regulate positively or negatively NF-κB transcriptional activity

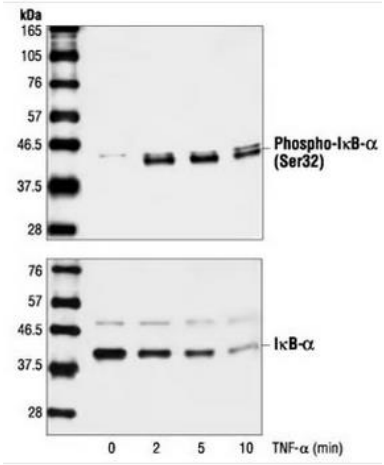
NF-κB pathway



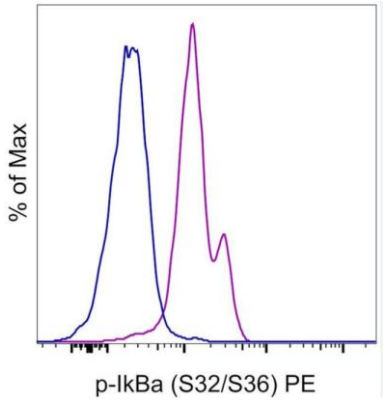
NF-κB pathway dysregulation

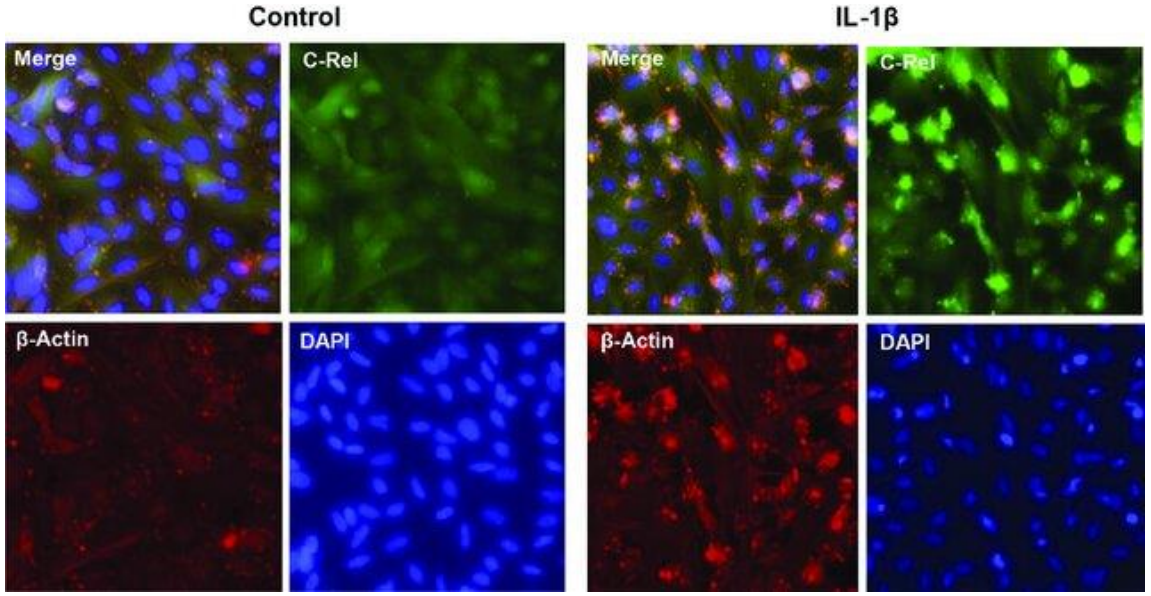


NF-κB activity measurement



Western blot analysis of extracts from HeLa cells treated with TNF-alpha for the indicated times, using Phospho-IkappaB-alpha (Ser32) Antibody (upper) or IkappaB-alpha Antibody #9242 (lower).



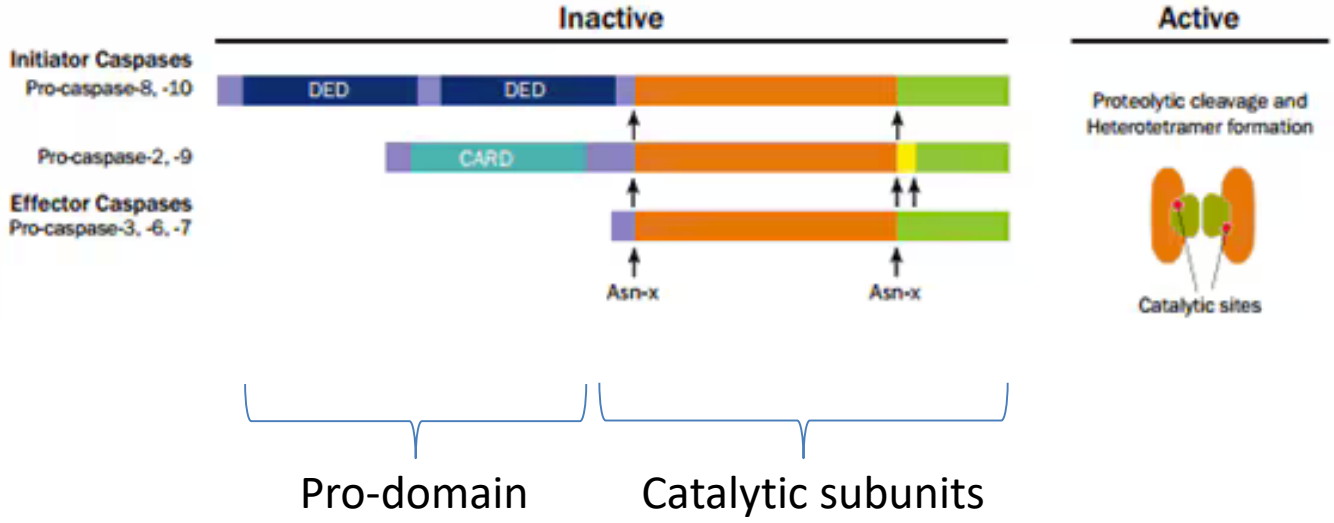


Apoptosis

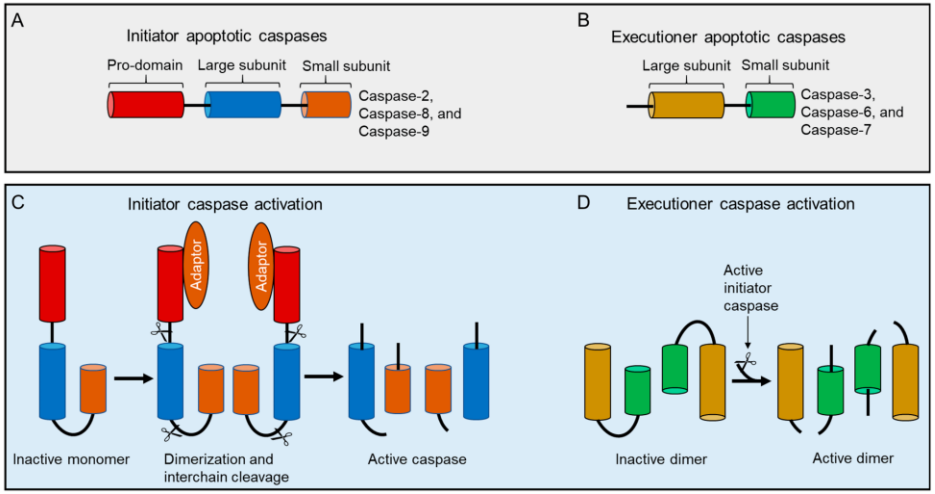
Caspases

Cysteine-**asp**artic prote**ases**

Zymogen



Pro-domain Catalytic subunits



Caspases

Initiators → Caspase-8 and -10 (Extrinsic pathway)
Caspase-9 (Intrinsic pathway)

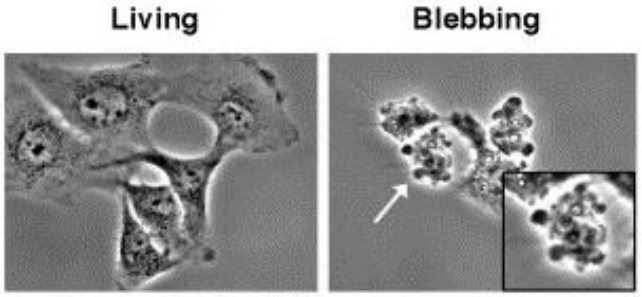
Effectors → Caspase-3, -6 and -7

TARGETS ↓

Cytokeratins, PARP, the plasma membrane cytoskeletal protein alpha fodrin, the nuclear protein NuMA and others

↓

Chromatin and cytoplasmic condensation
DNA degradation and nuclear fragmentation
Formation of apoptotic bodies



Apoptosis triggers

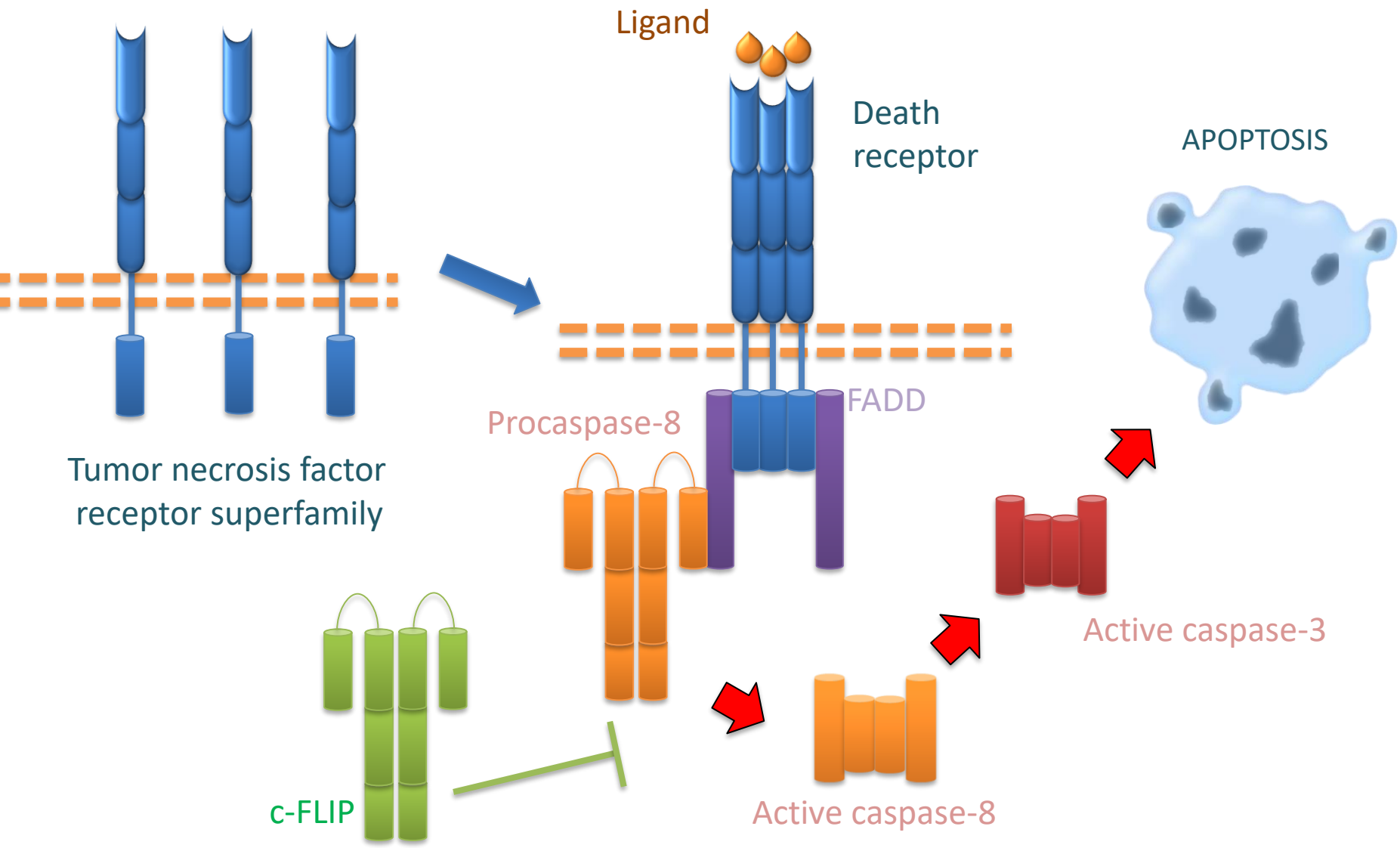
- Death ligands: Fas/CD95, TRAIL, TNF (Extrinsic pathway)

- Radiation, hypoxia, toxins, pro-survival factor (cytokines) deprivation (Intrinsic pathway)

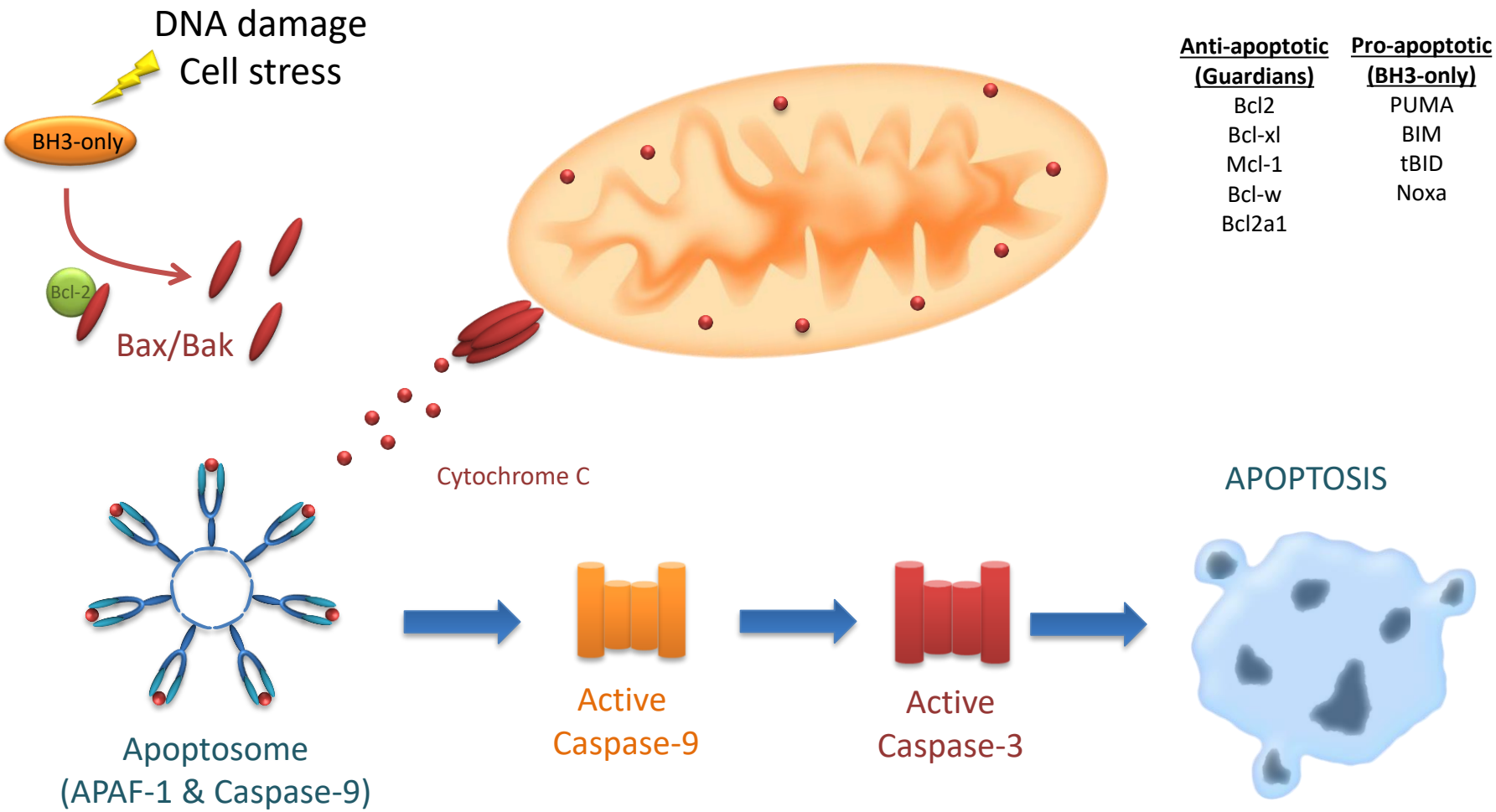
    - P53 (DNA damage sensor): Fas induction, Upregulation of Noxa, PUMA, BID and APAF-1

- Cytotoxic cells (Granzyme pathway)

Extrinsic or death-receptor-mediated pathway

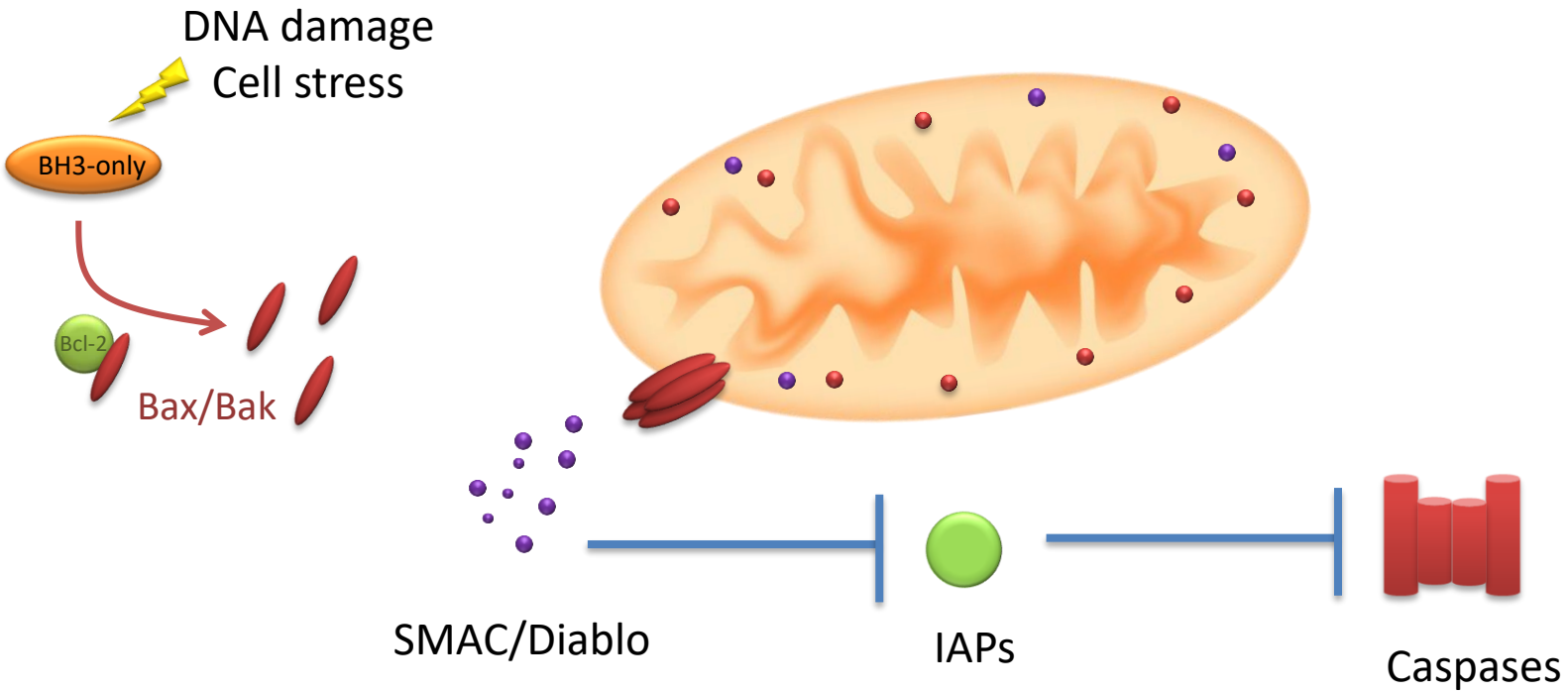


Intrinsic or mitochondrial pathway

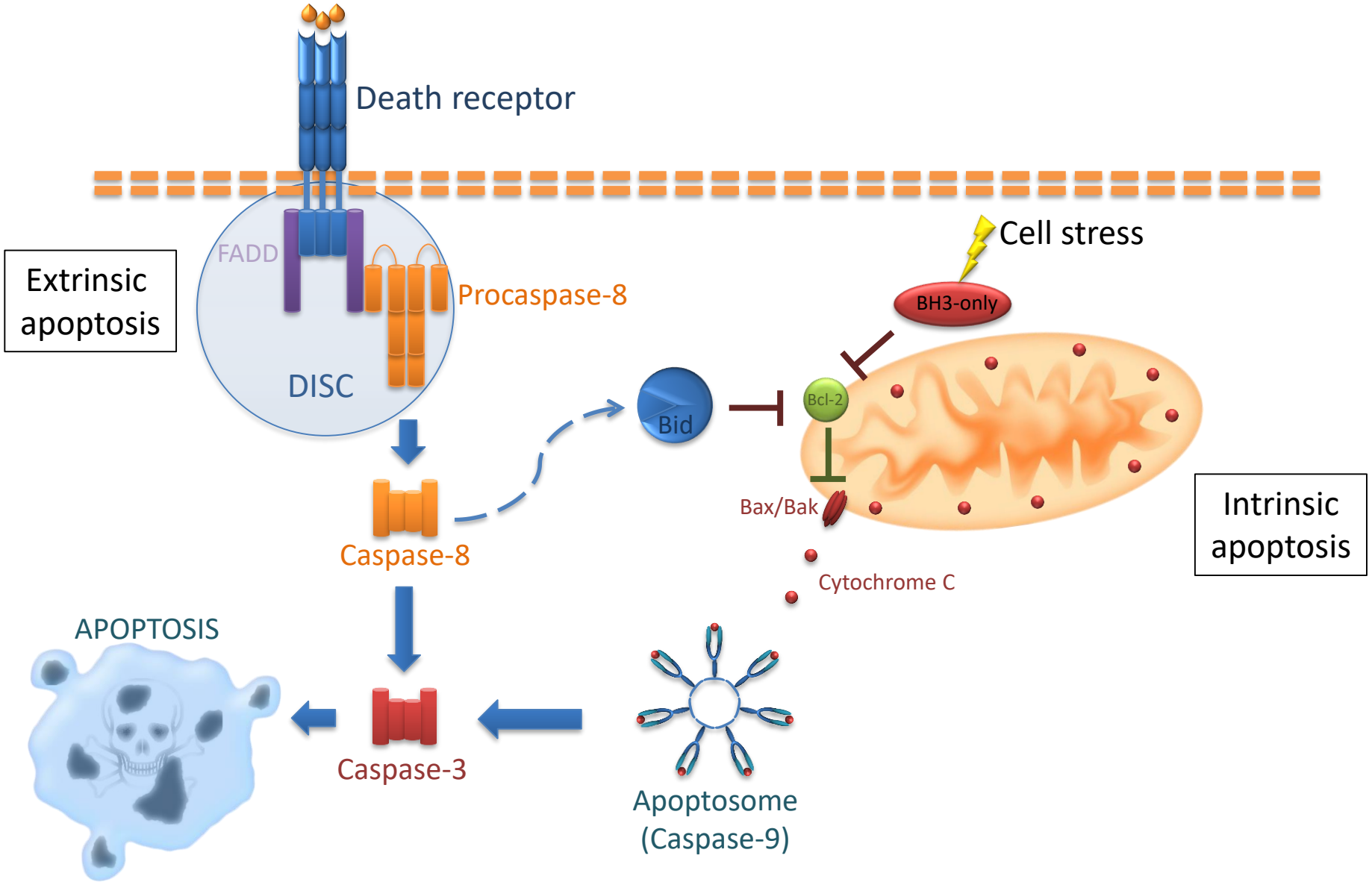


Anti-apoptotic (Guardians)	Pro-apoptotic (BH3-only)
Bcl2	PUMA
Bcl-xl	BIM
Mcl-1	tBID
Bcl-w	Noxa
Bcl2a1	

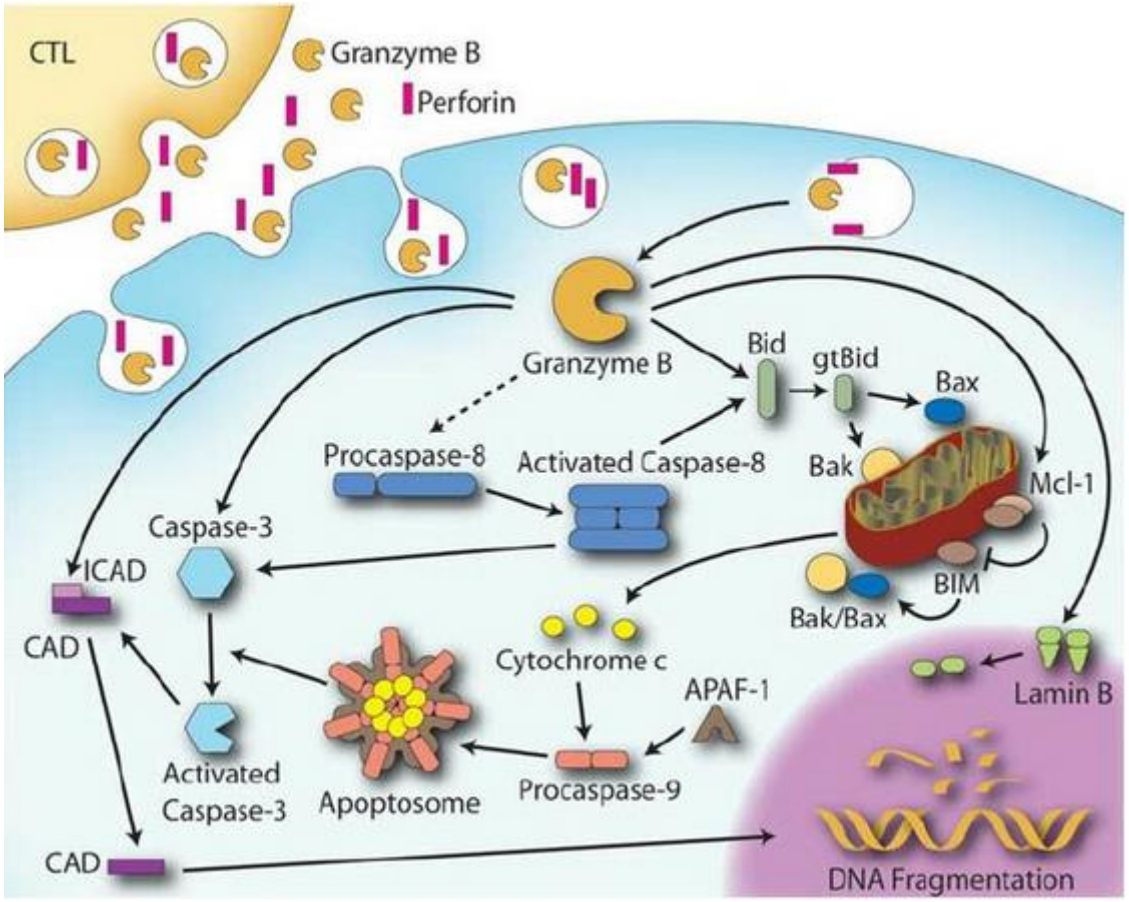
Intrinsic or mitochondrial pathway



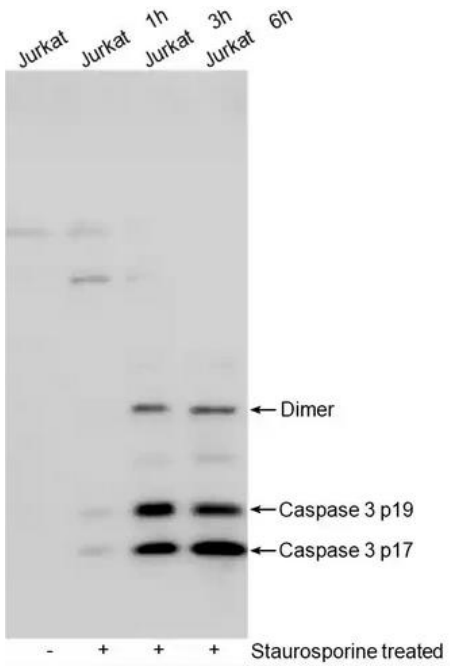
Cross-talk

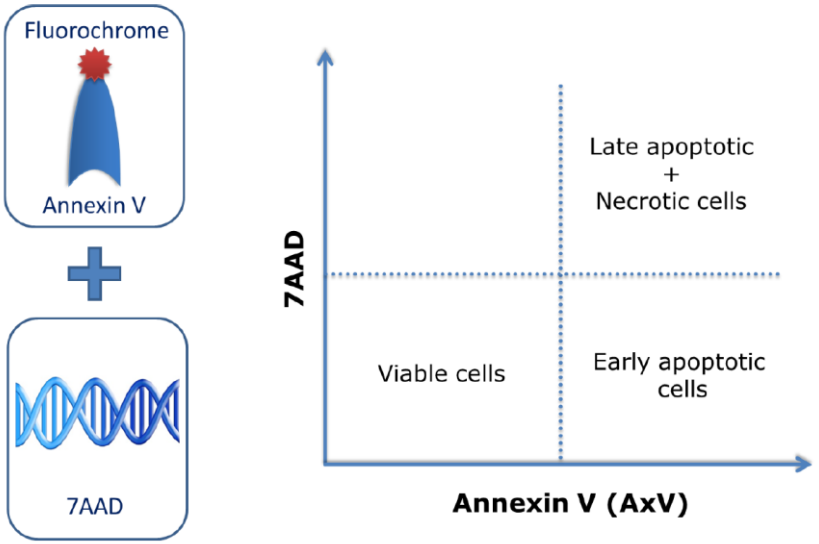

Death receptor
Extrinsic apoptosis
FADD
Procaspase-8
DISC
Caspase-8
Cell stress
BH3-only
Bid
Bcl-2
Bax/Bak
Cytochrome C
Intrinsic apoptosis
APOPTOSIS
Caspase-3
Apoptosome (Caspase-9)

Granzyme pathway

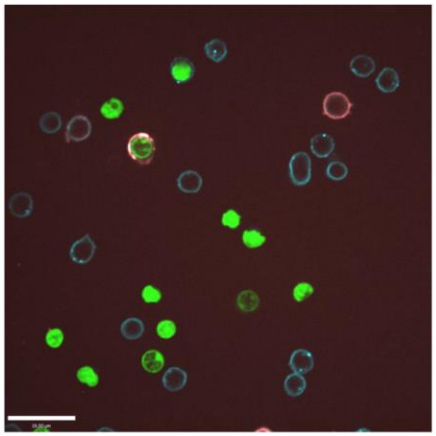


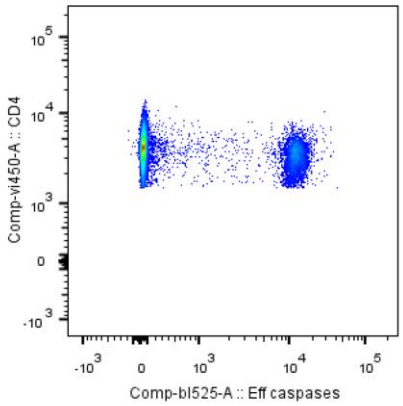
Apoptosis measurement





Fluorescent caspase substrate

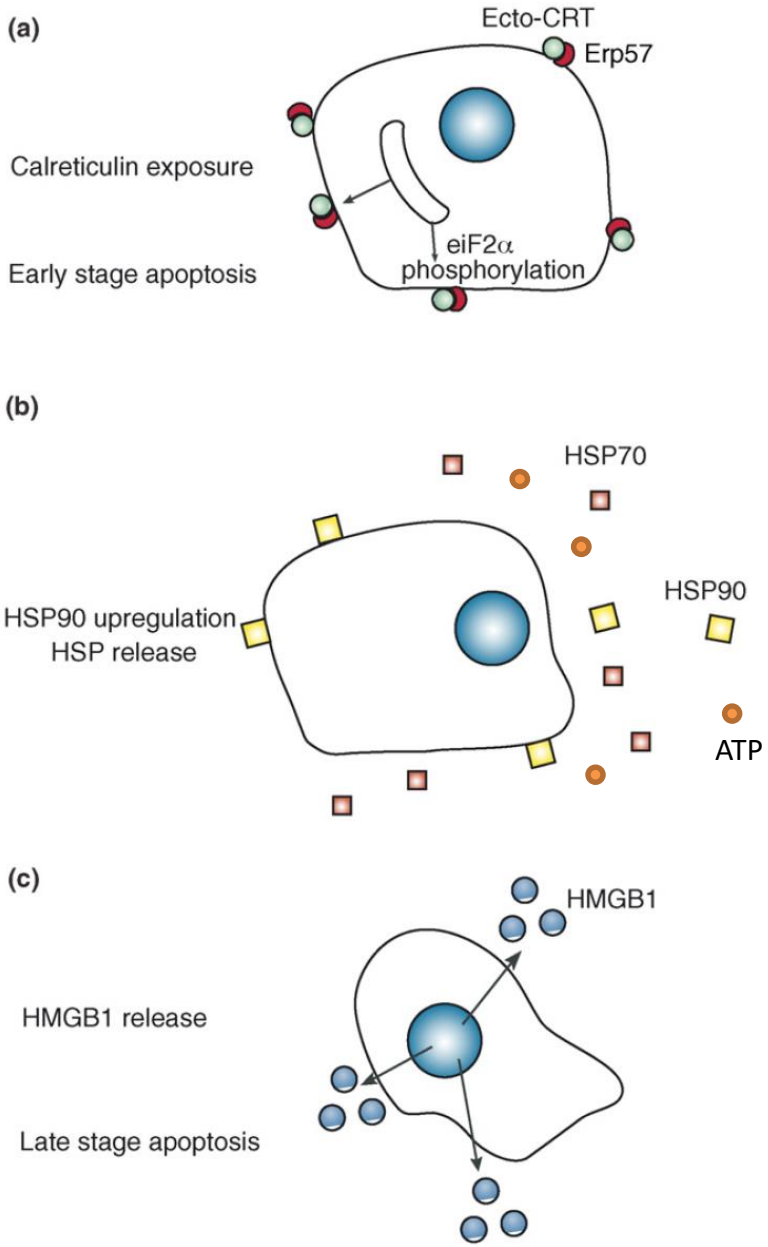




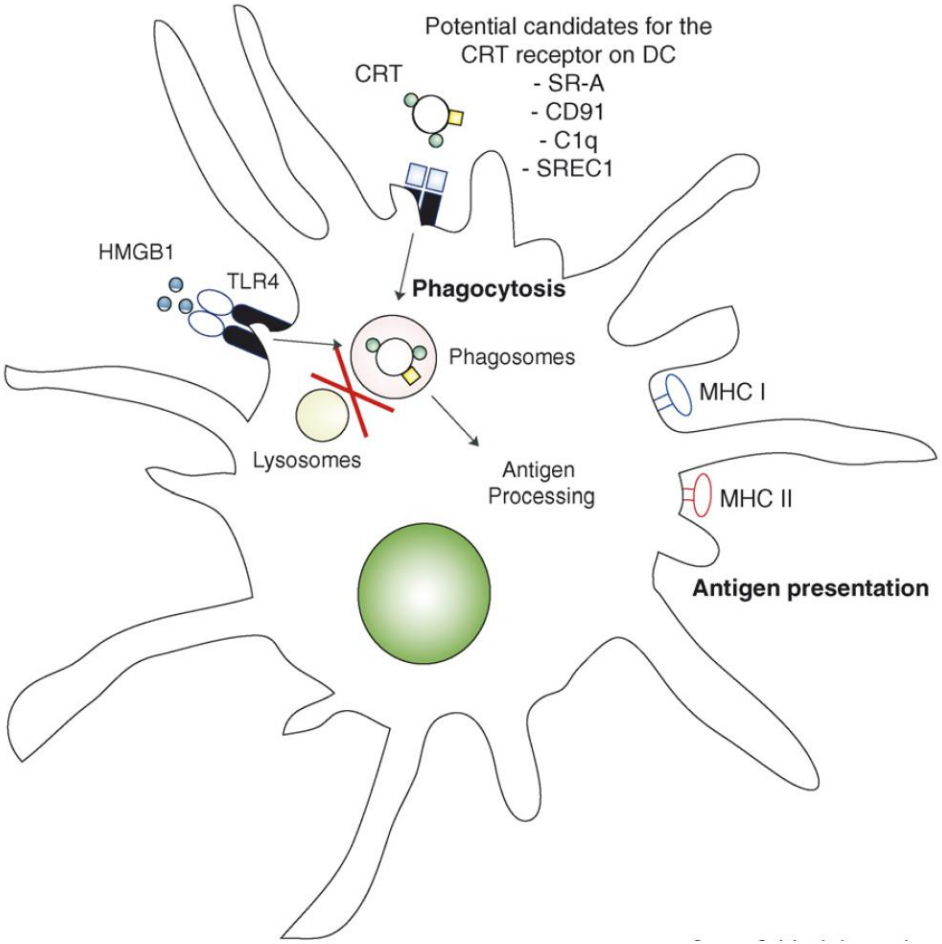
Immunogenic cell death (ICD)

ICD Triggers:

- Anthracyclines (cytostatics)
- Cisplatin
- Oxaliplatin
- γ-irradiation



DOI 10.1016/j.coi.2008.05.007



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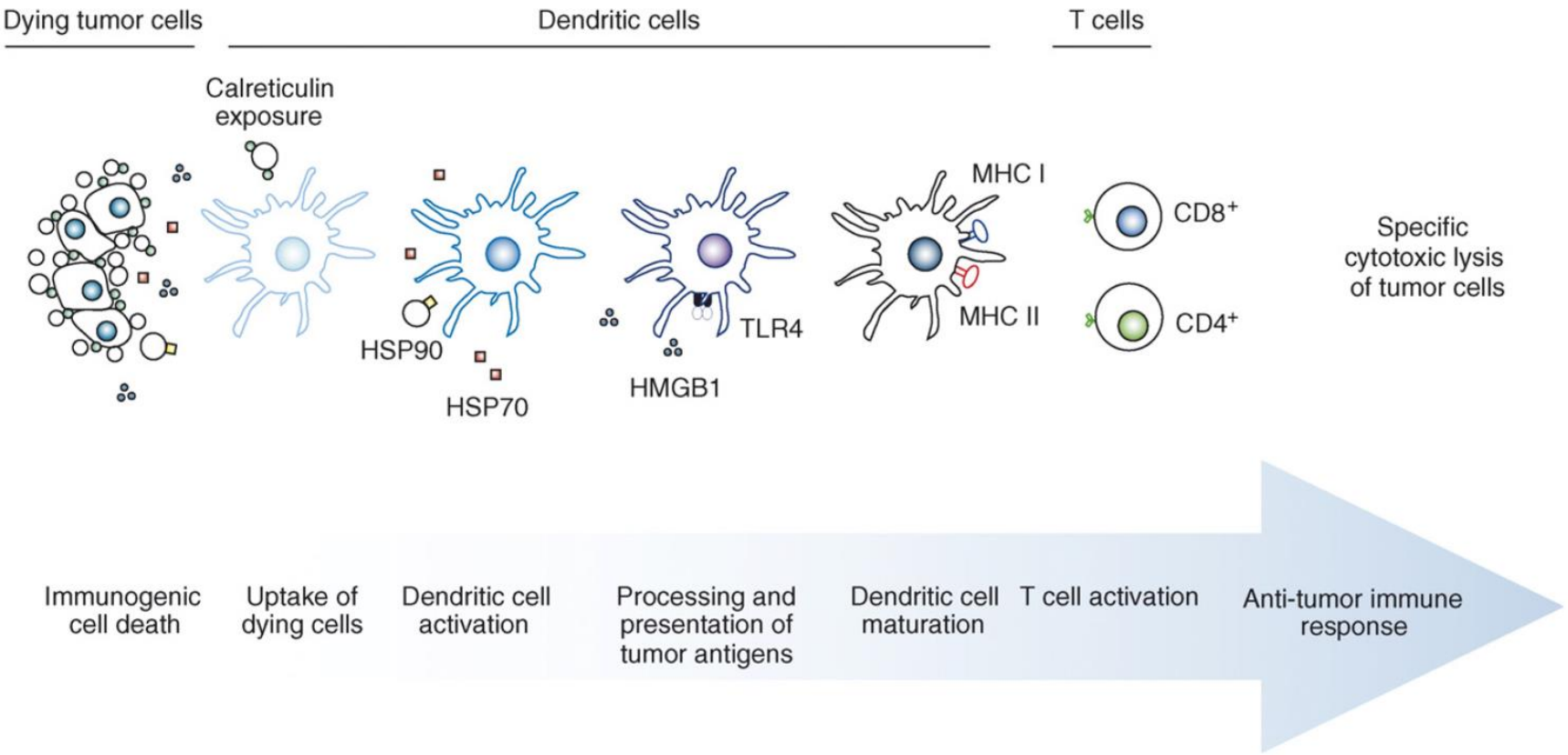
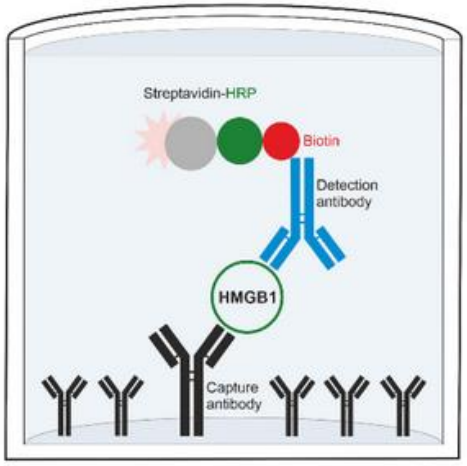
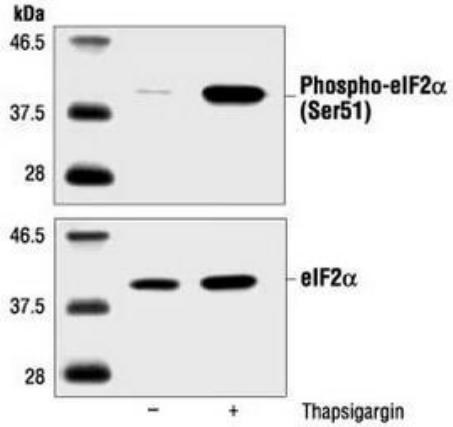


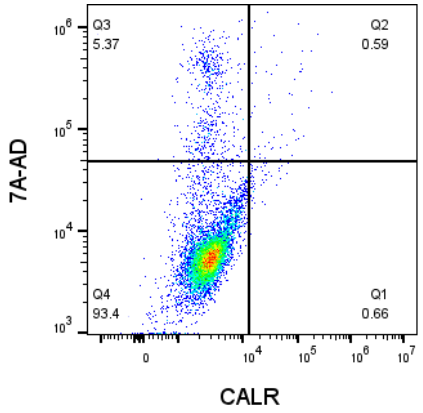
DOI 10.1016/j.coi.2008.05.007

ICD detection

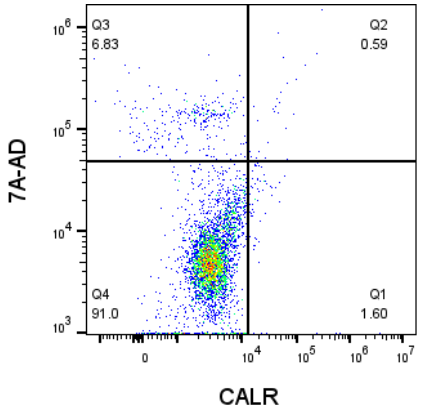




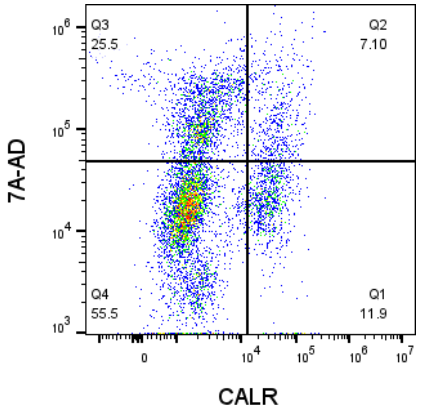
Untreated



Oxaliplatin (20µM)

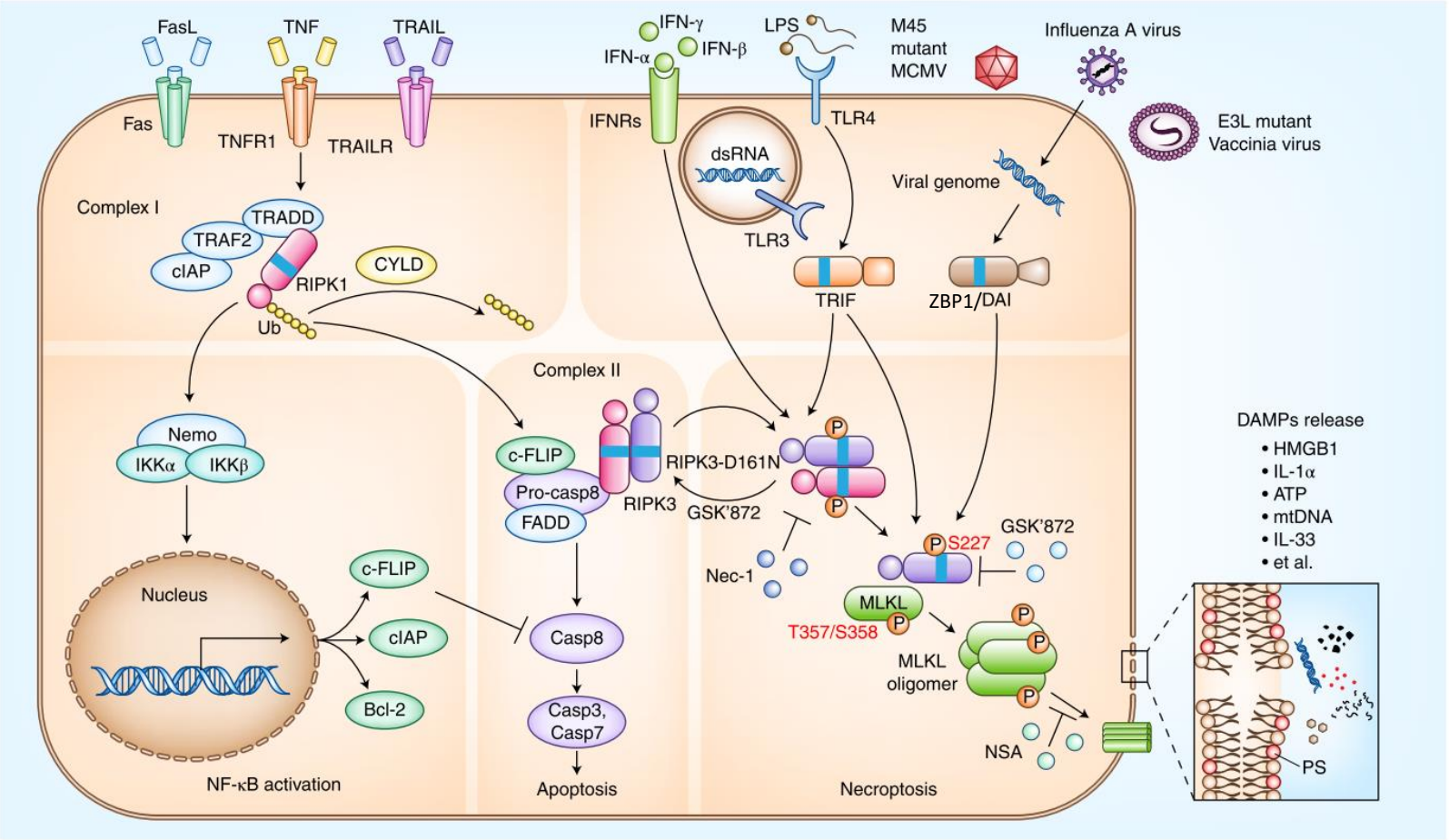


Oxaliplatin (300µM)



Necroptosis

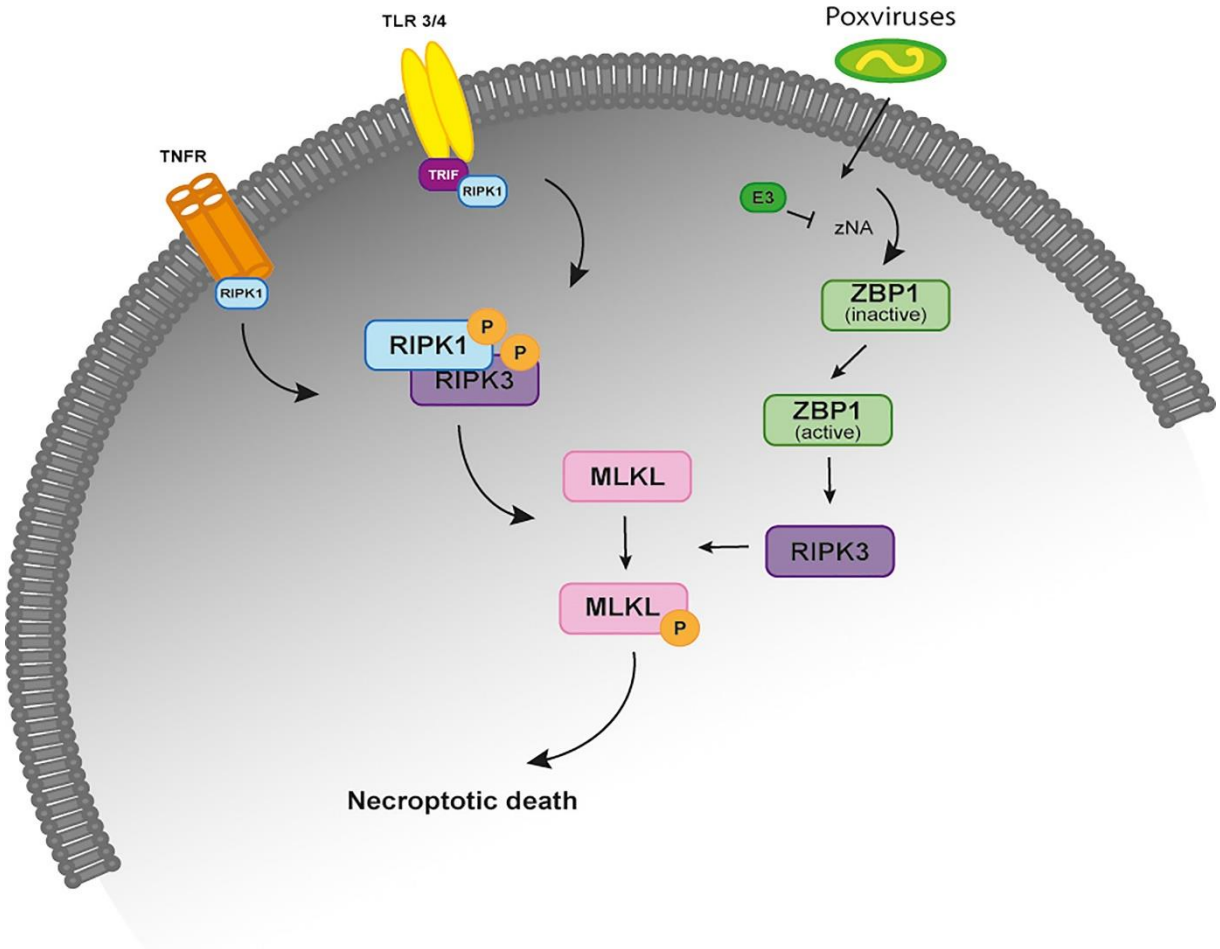
Necroptosis



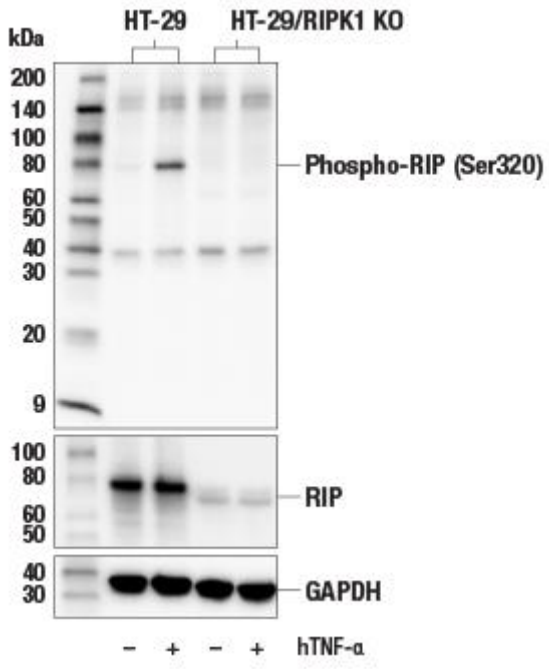
He & Wang 2018

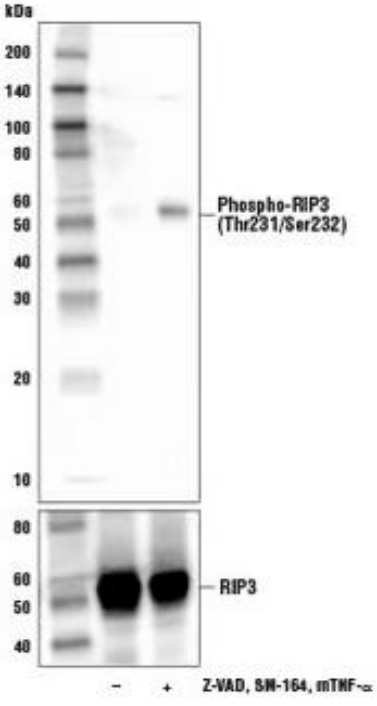
TNF: tumor necrosis factor
TRADD: TNFR1-associated death domain protein
TRAF2: TNF receptor-associated factor 2
cIAP: cellular inhibitors of apoptosis
RIPK1/3: receptor-interacting protein kinase 1/3
NEMO: NFkB essential modulator
FADD: Fas-associated protein with death domain
MLKL: mixed lineage kinase like

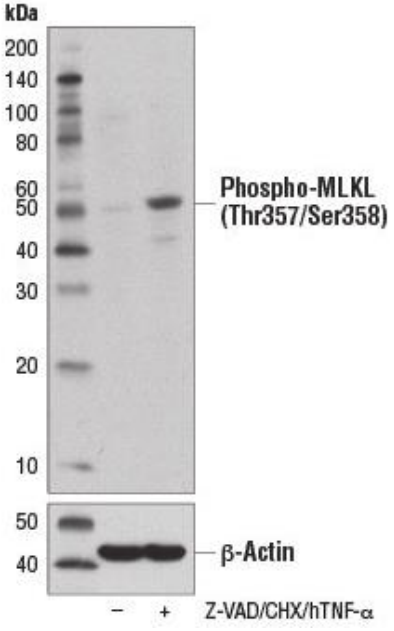
Necroptosis



Necroptosis measurement



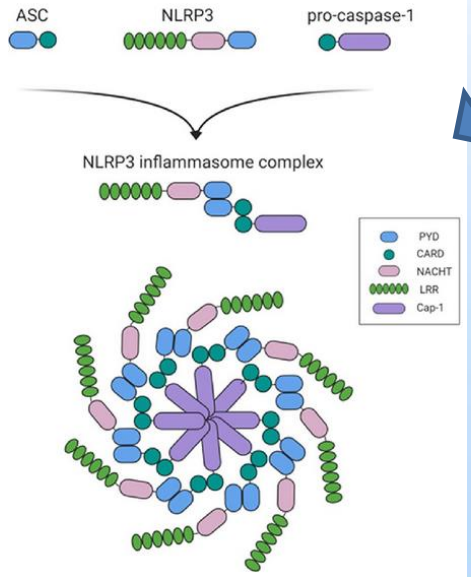




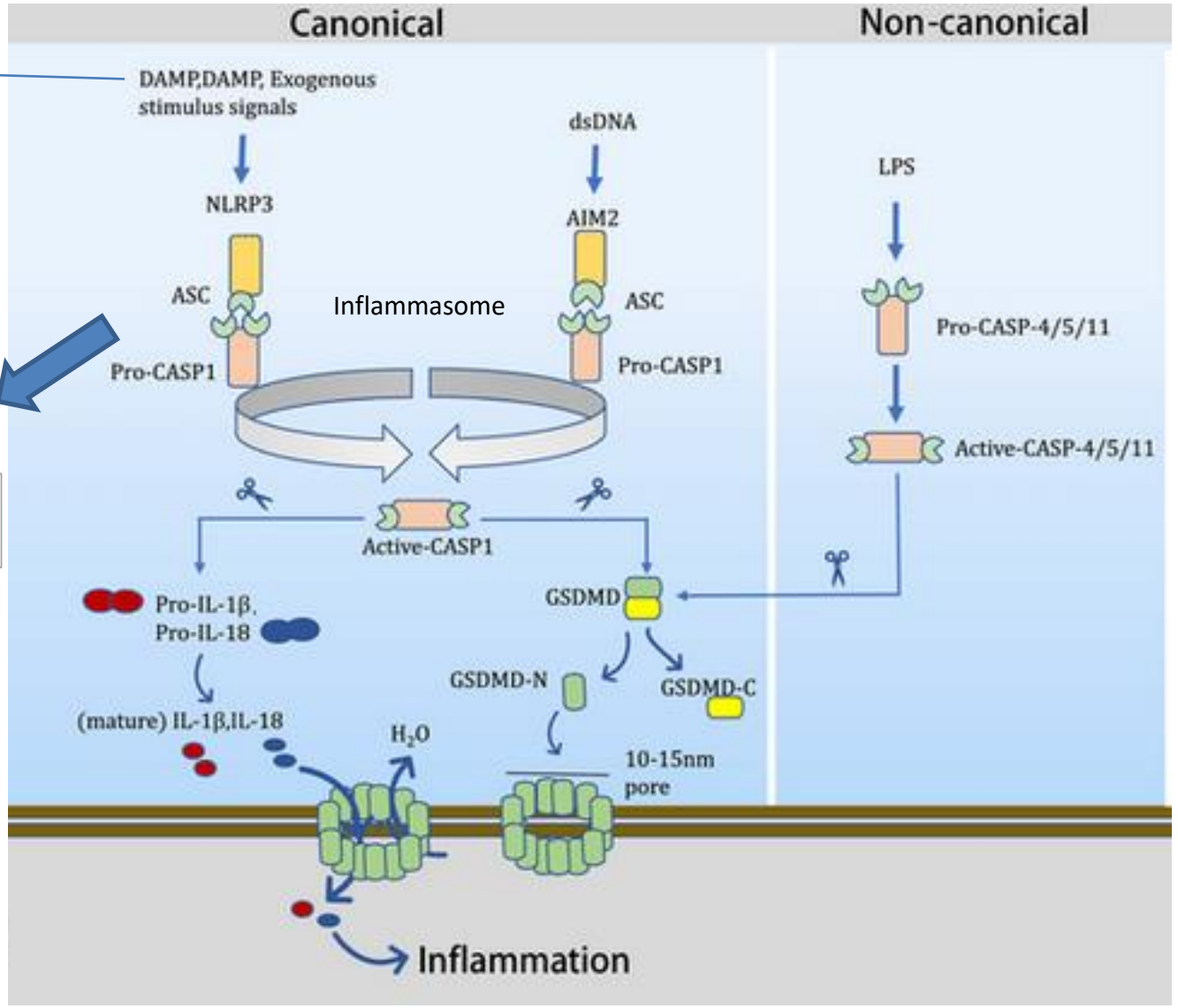
Pyroptosis

Pyroptosis

IL-1β upregulation



Inflammasome



Thank you for your attention!

Questions?

Please write to carlos.plazasirvent@rub.de