ORGANELLES INVOLVED IN CELL DEATH

Organelles	*Apoptosis*	*Autophagy*	*Necrosis / Necroptosis*
- Mitochondria	+	+ **(mitophagy)**	+
- Lysosomes	+ / -	+	+ / -
- Endoplasmic-reticulum (ER)	+ / -	+	+ / -
- peroxisome	?	+ **(pexophagy)**	?

Bröker LE et al. Clin Cancer Res 2005, 11: 3155-3162.

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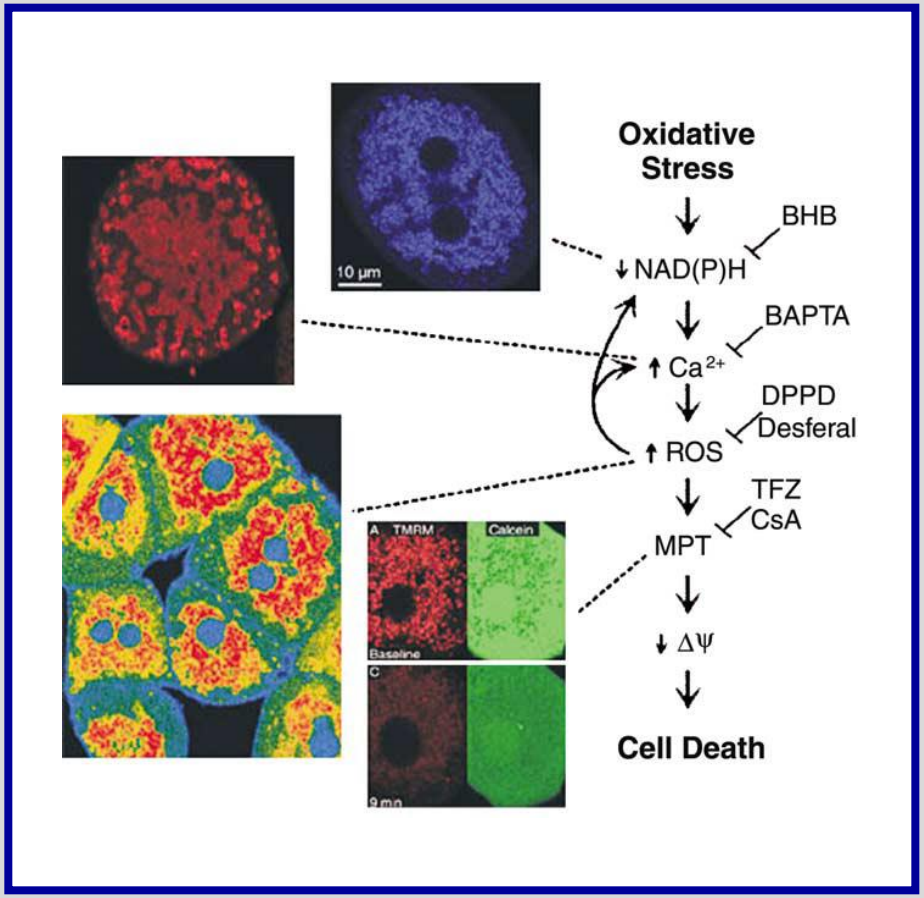
Mitochondrial permeability transition: a common pathway to necrosis and apoptosis

Jae-Sung Kim, Lihua He, and John J. Lemasters*

Department of Cell and Developmental Biology, University of North Carolina at Chapel Hill, CB#7090, 236 Taylor Hall, Chapel Hill, NC 27599-7090, USA

Received 10 February 2003



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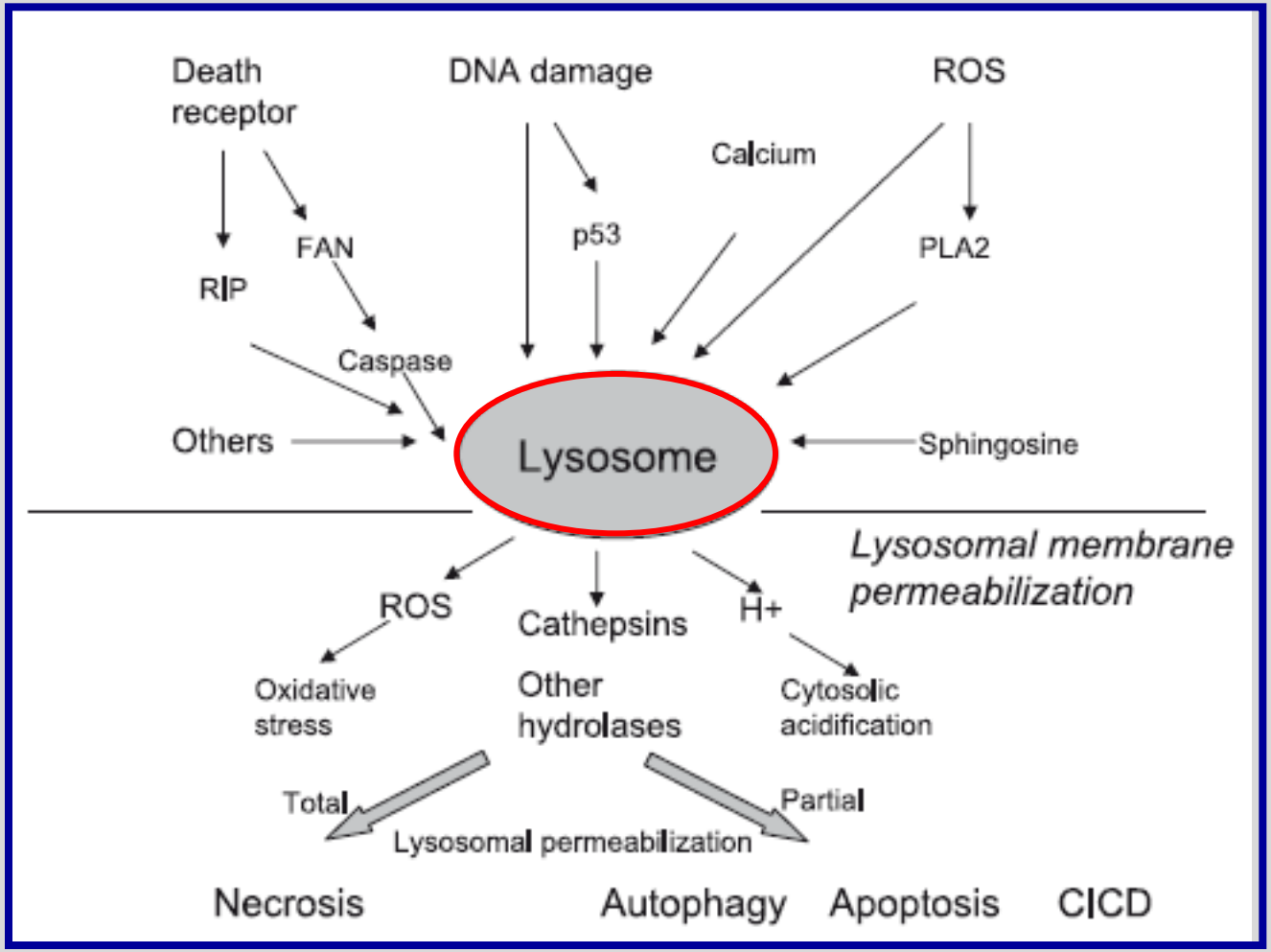
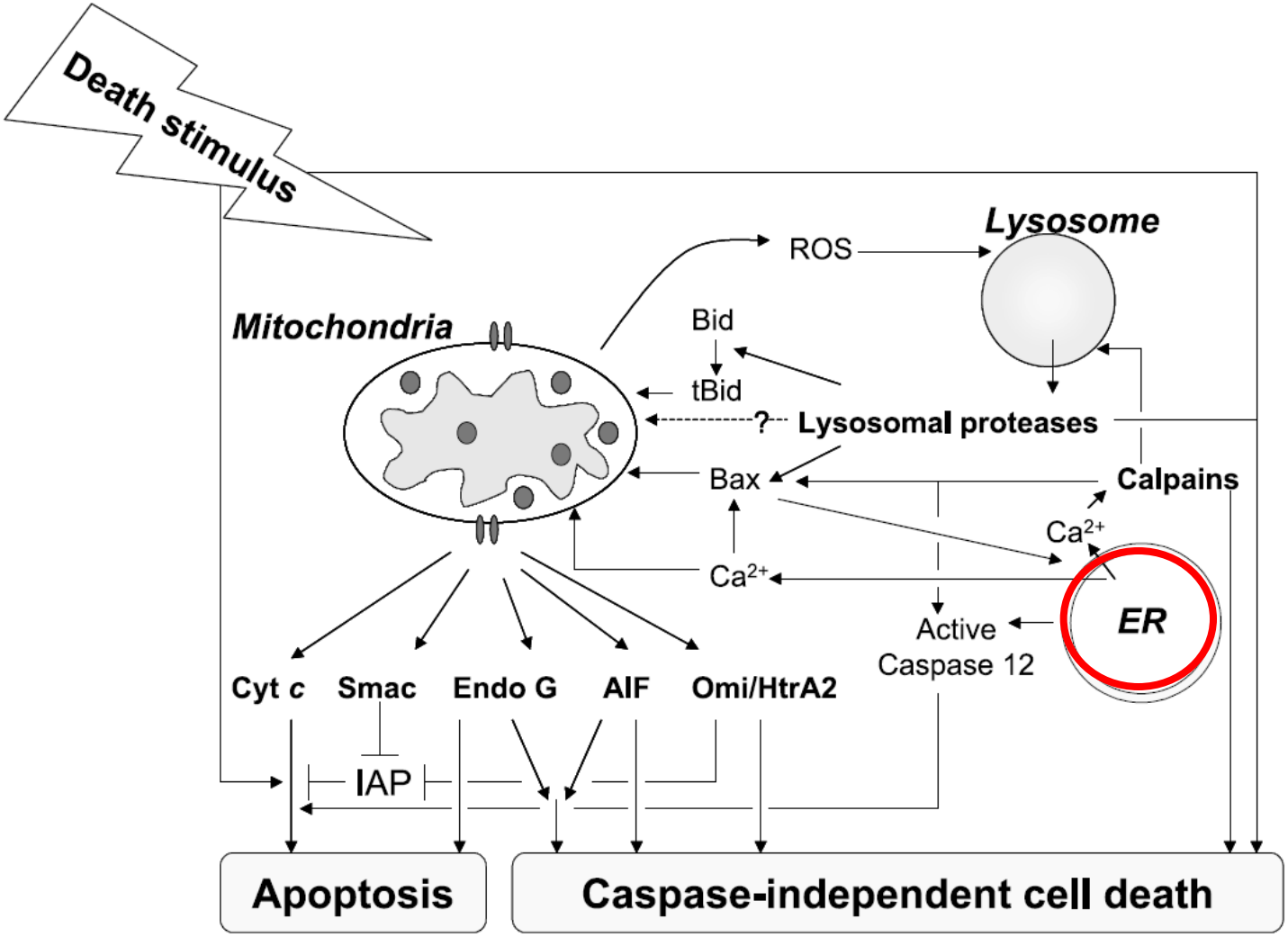
REGULATION OF LYSOSOMAL PERMEABILITY AND ROLE OF LYSOSOMAL PROTEINS IN CELL DEATH



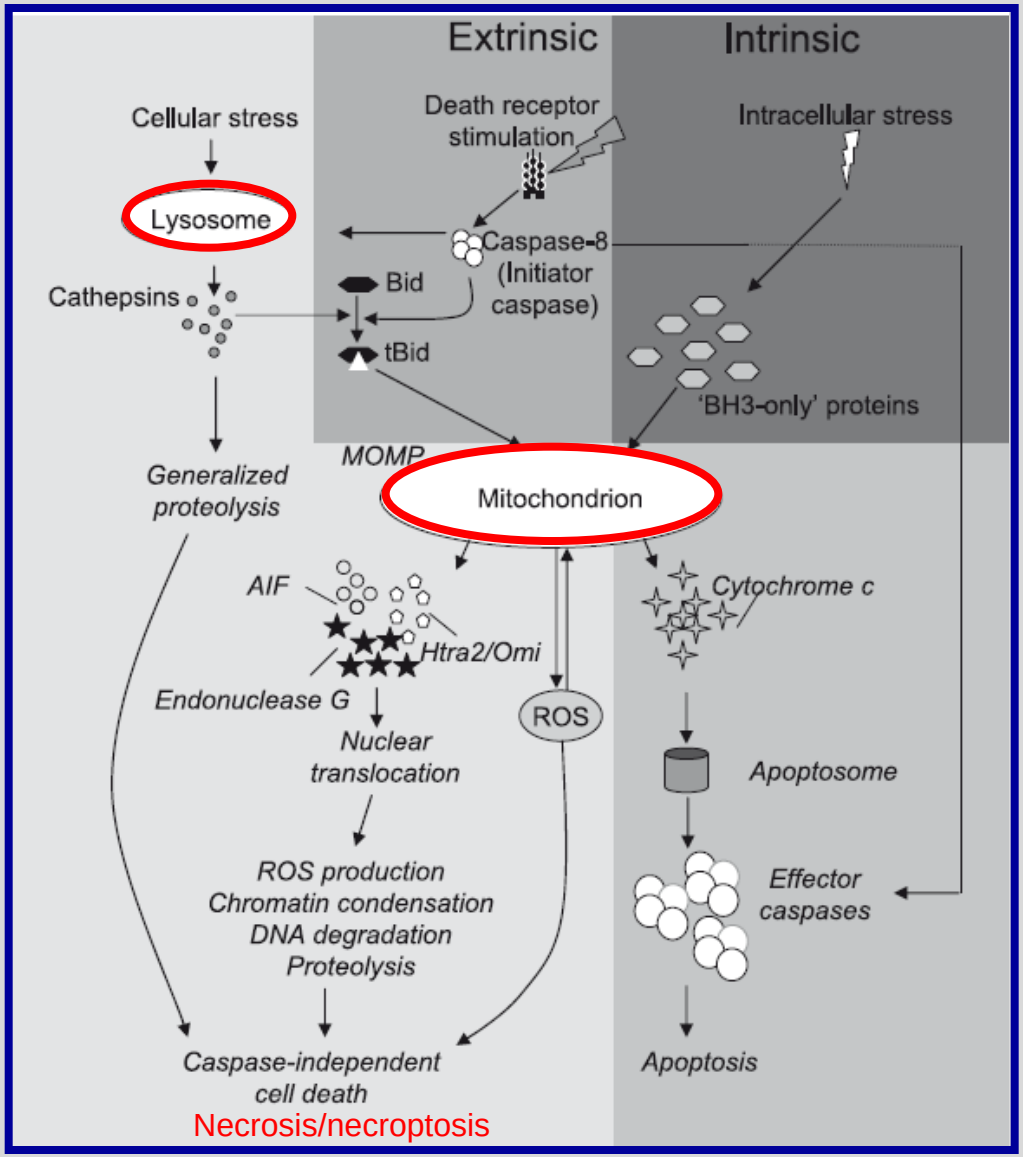
Tang PS et al. Am J Physiol Lung Cell Mol Physiol 2008, 294: 632-641.



Either necrosis or other modes of cell death

Bröker LE et al. Clin Cancer Res 2005, 11: 3155-3162.

CONNECTION BETWEEN LYSOSOME AND MITOCHONDRIA



Tang PS et al. Am J Physiol Lung Cell Mol Physiol 2008, 294: 632-641.

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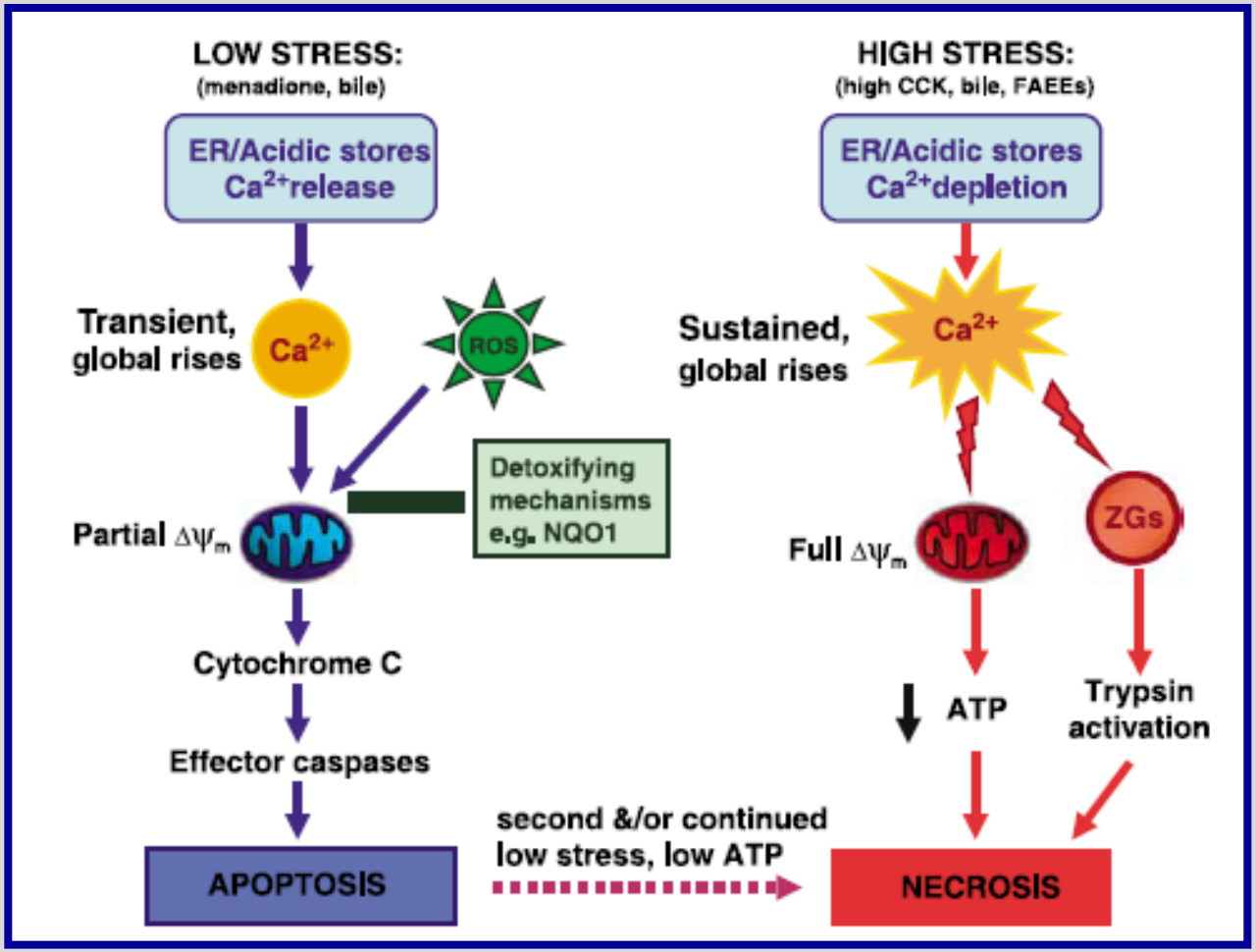
CONNECTION BETWEEN ENDOPLASMIC RETICULUM (ER) AND MITOCHONDRIA



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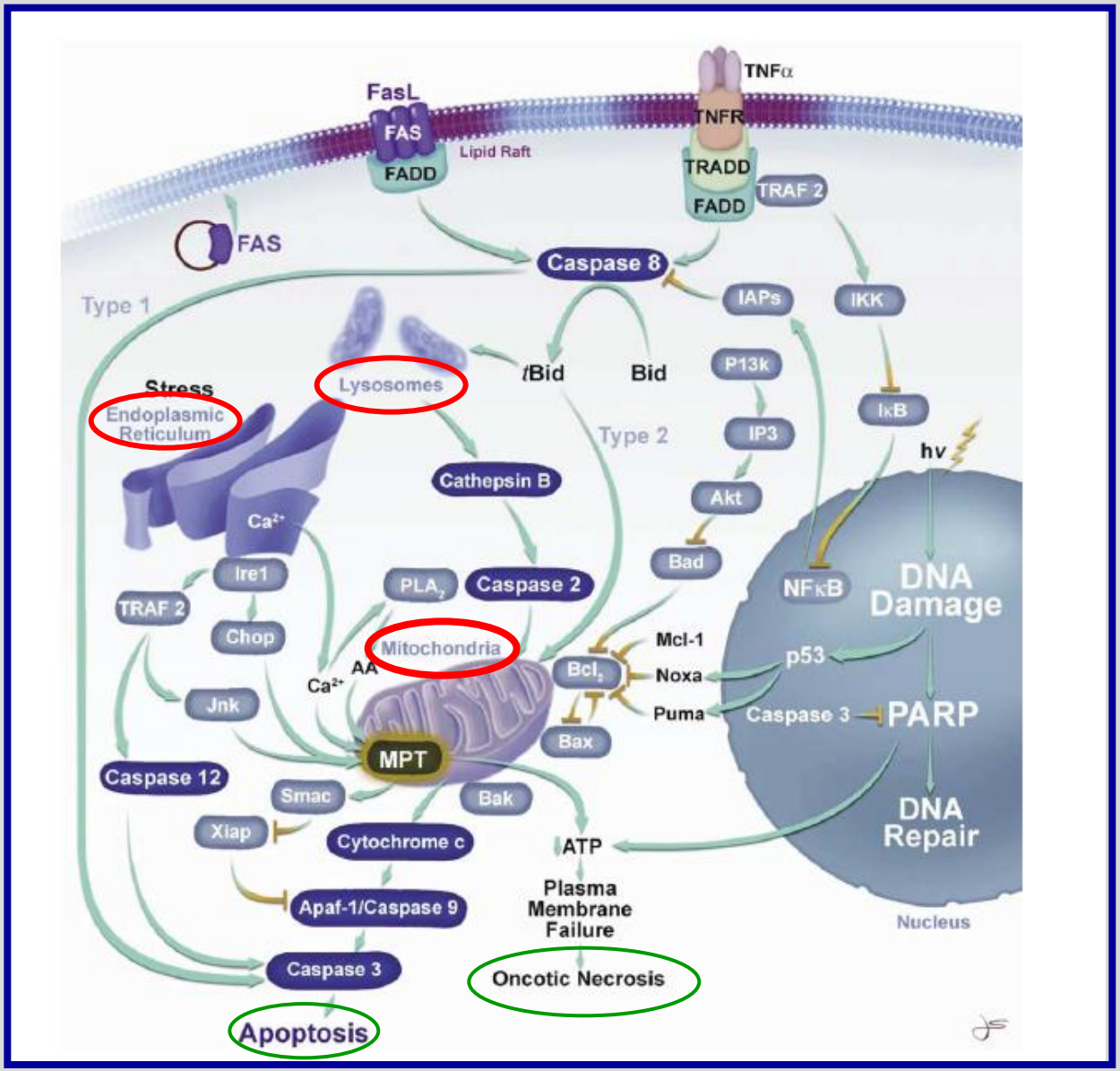
REDUNDANT PATHWAYS FROM DIFFERENT ORGANELLES TO APOPTOSIS AND NECROSIS



Lemasters JJ Gastroenterology 2005, 129: 351-360.

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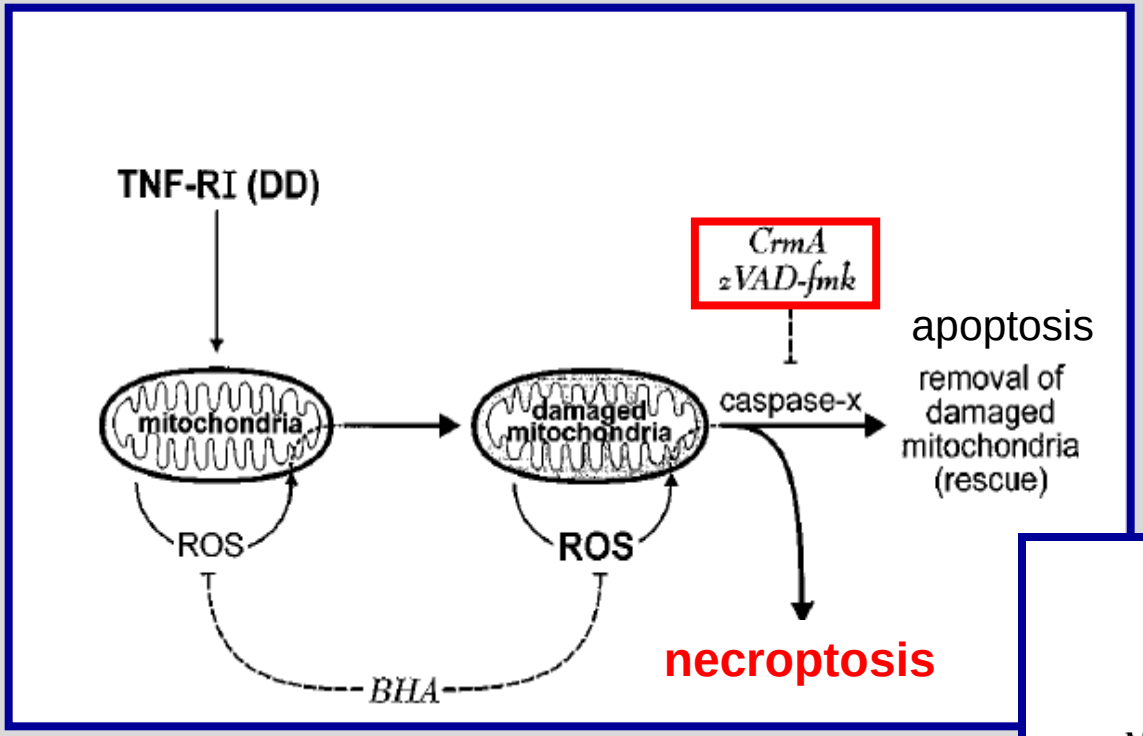
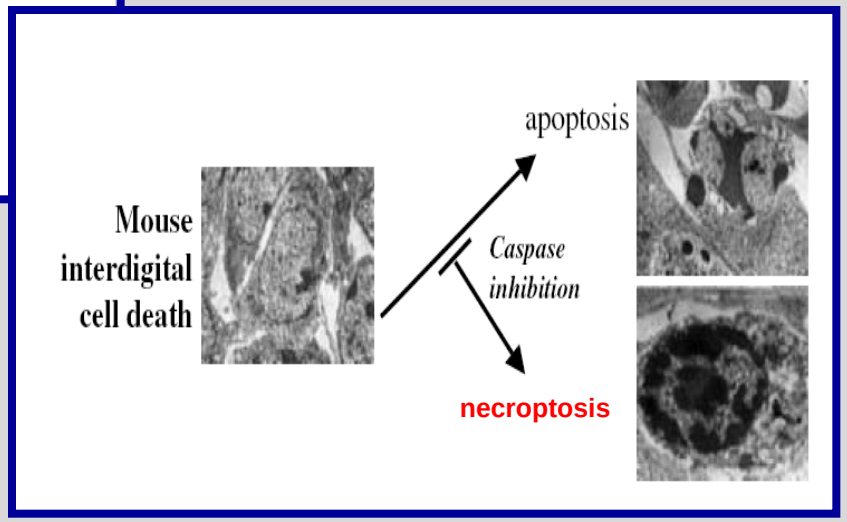
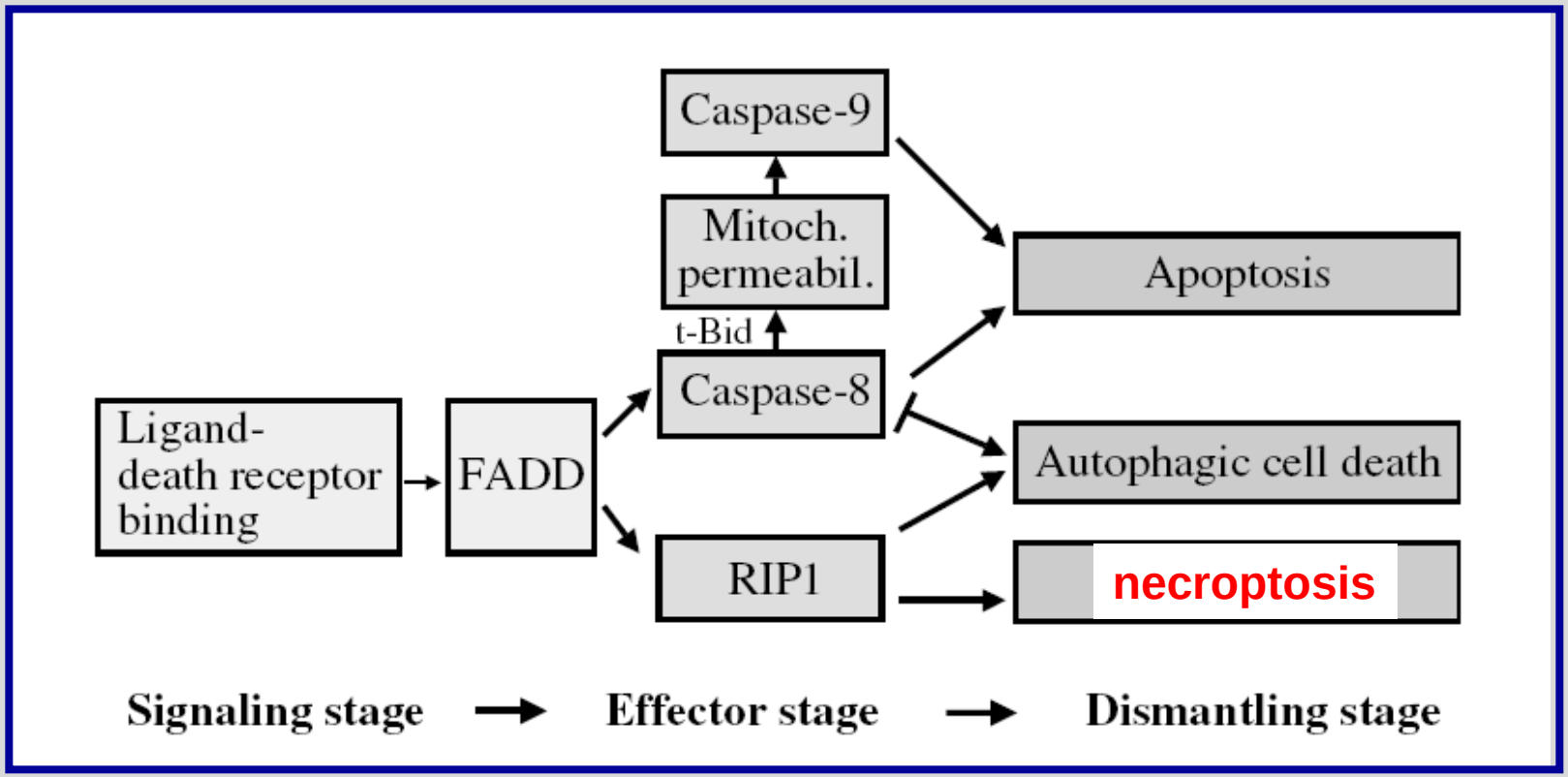




Different pathways can co-exist in the same cell and can be switched on by specific stimuli

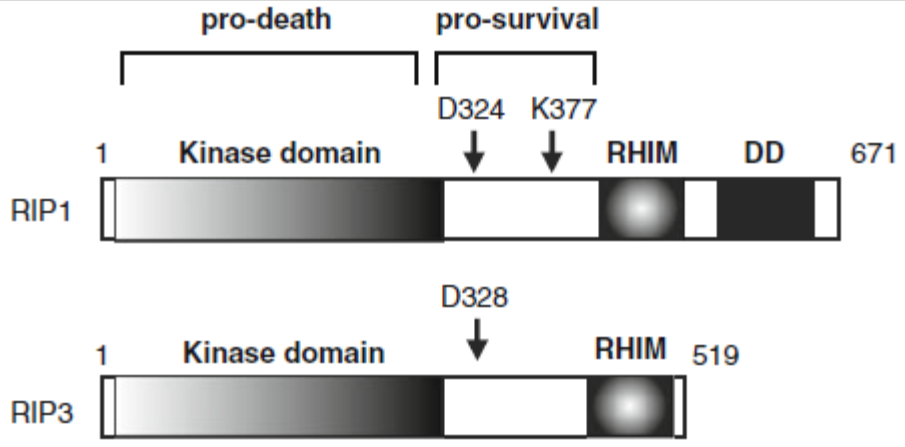
Fiers W et al. Oncogene 1999, 18: 7719-7730.
Golstein P & Kroemer G 2005, 12: 1490-1495.



Holler N et al. Nat Immunol 2000, 1: 489-495.

Gérard Lizard

Domain Structures of RIP1 and RIP3 kinases



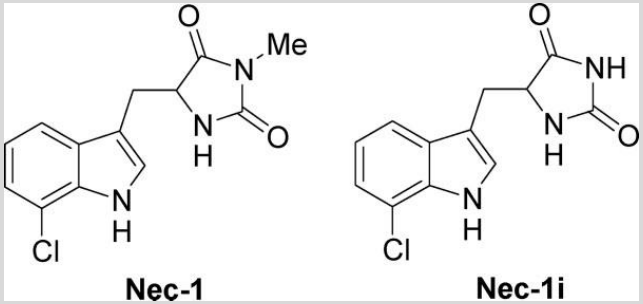
Domain structures of RIP1 and RIP3, the two crucial kinases for programmed necrosis. The kinase and RHIM domains of RIP1 and RIP3 are required for death cytokine (TNF, FasL, and TRAIL)-induced programmed necrosis. Evidence indicates that the kinase activity of RIP1 is also required for assembly of an alternative caspase-8 activating complex in response to apoptosis induced by TNF and IAP antagonist [33]. In contrast, cleavage by caspase-8 at D324 (for RIP1) [45] and D328 (for RIP3) [46] releases the kinase domains from the RIP kinases and likely prevents the phosphorylation and activation of downstream substrates. Polyubiquitination of RIP1 at K377 inhibits TNF-induced apoptosis, possibly by blocking the transition of the receptor-associated complex to the cytoplasmic death signaling complexes [41]. *DD* death domain

RIP: receptor interacting protein

- RIP1 and RIP3 interact via their RIP homotypic interaction motif (RHIM) domains.

- The two proteins share 33% similarity in the kinase domain.

- Despite this similarity in the kinase domain, Nec-1 (necrostatin-1) is specific to RIP1 and does not inhibit RIP3



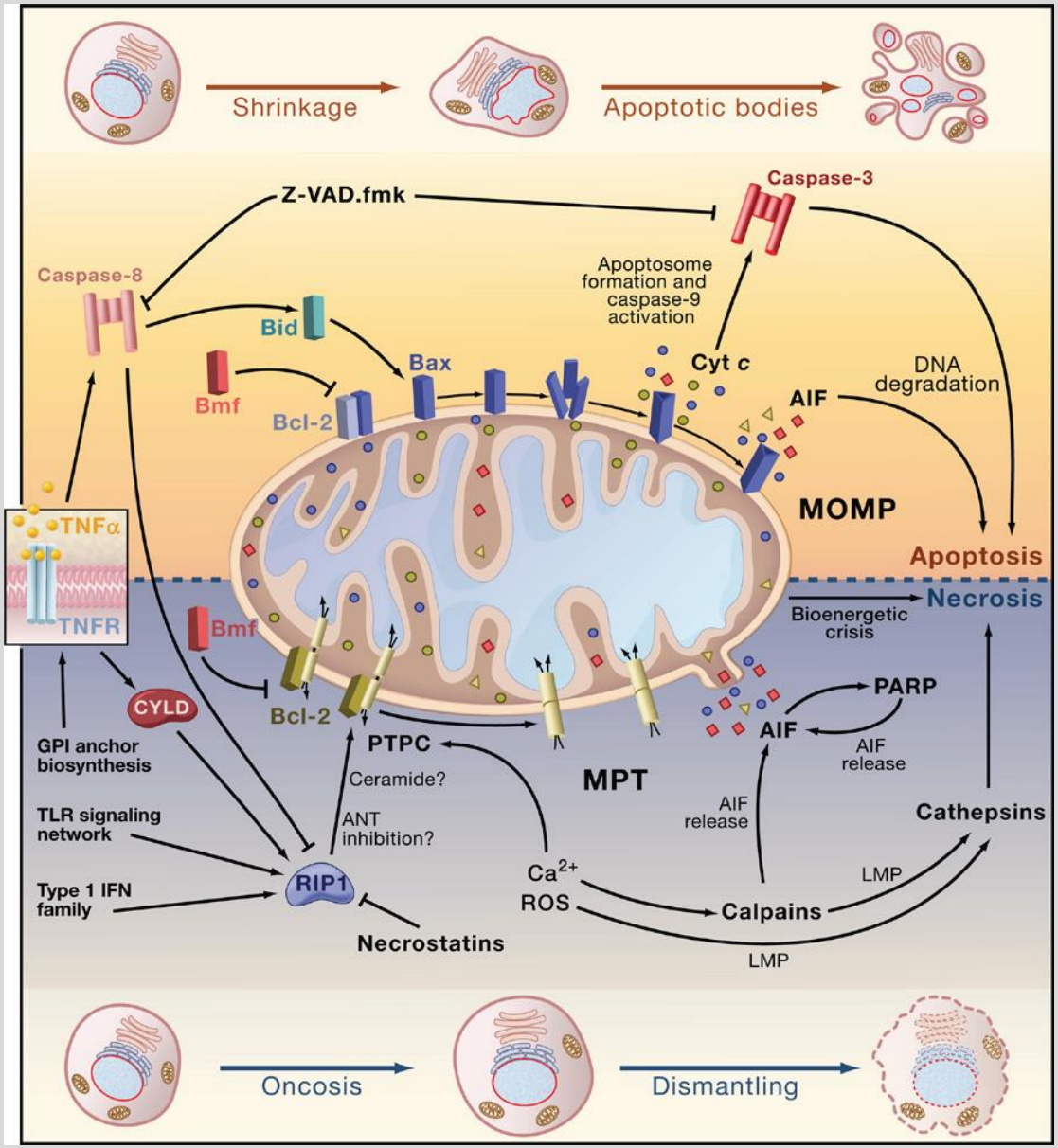
Nec-1i: inactive homologue of Nec-1

Going up in flames: necrotic cell injury and inflammatory diseases

Sreerupa Challa • Francis Ka-Ming Chan - ***Cell. Mol. Life Sci. (2010) 67:3241–3253***

Gérard Lizard,

SWITCHING FROM APOPTOSIS TO NECROPTOSIS



Galluzi & Kroemer G Cell 2008, 135: 1161-1163; Hitomi J et al. Cell 2008, 135: 1311-1323.

Gérard Lizard,

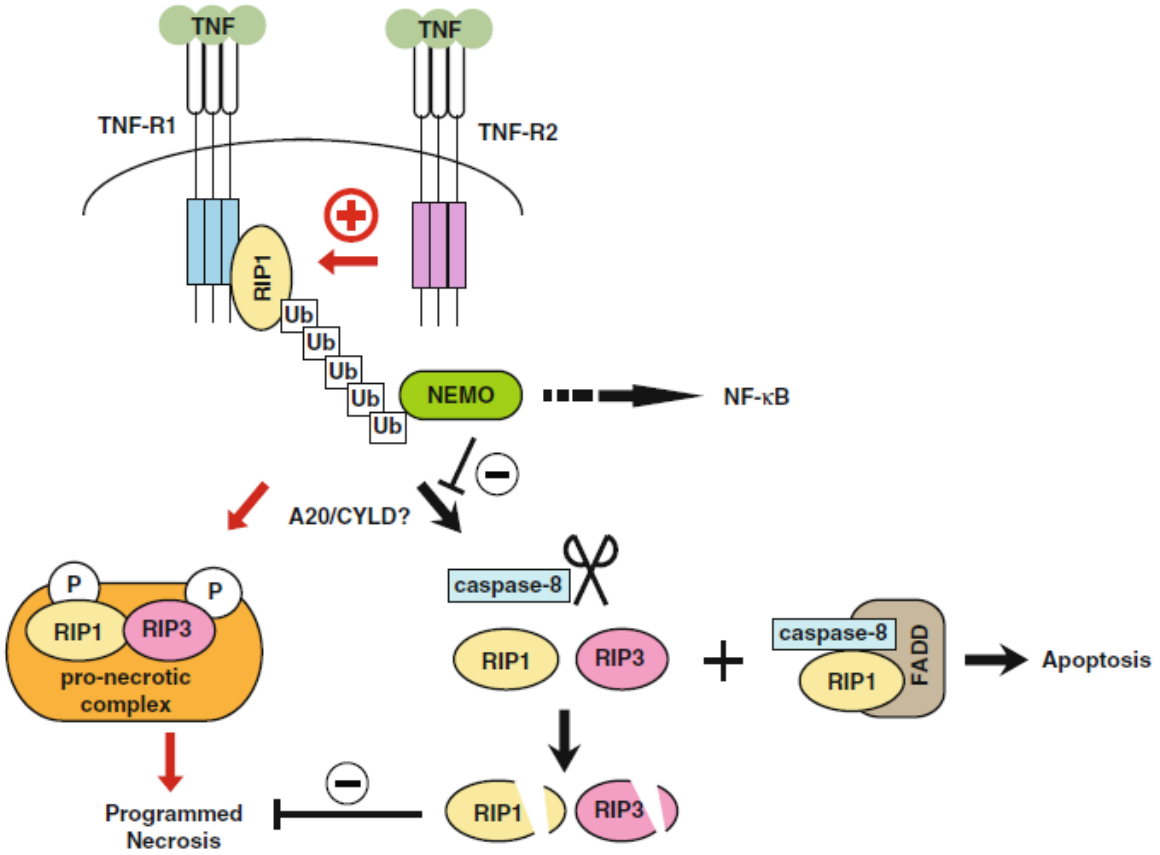
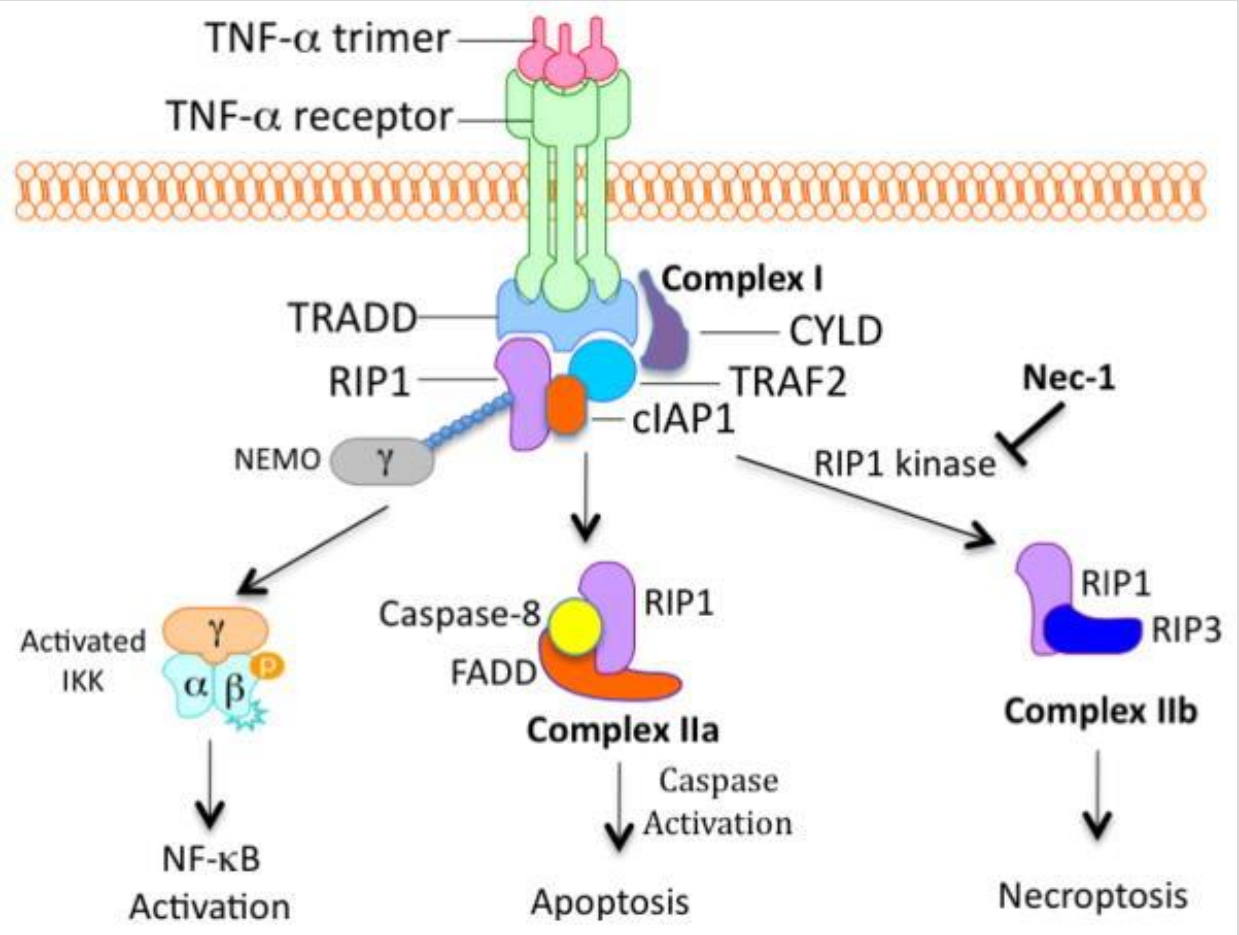


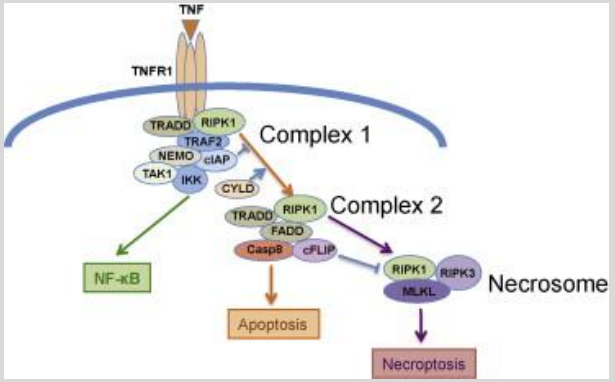
Fig. 3 Regulation of programmed necrosis by ubiquitination, phosphorylation, and caspase cleavage. TNF-induced programmed necrosis is regulated at multiple steps involving positive (indicated by *red arrows*) and negative (indicated by *black arrows*) mechanisms. TNF-R2 signaling enhances TNF-R1 mediated programmed necrosis through a poorly defined mechanism [32, 43]. Upon binding to TNF-R1, RIP1 becomes modified by polyubiquitination at K377. Polyubiquitinated RIP1 binds to NEMO, the regulatory subunit of NF-κB, to promote NF-κB activation. NF-κB activation counters the death signals by inducing pro-survival genes. The plasma membrane-associated receptor signaling complex containing polyubiquitinated RIP1 migrates to the cytoplasm where the receptor falls off the complex and RIP1 becomes deubiquitinated. The deubiquitinating enzymes A20 or CYLD may facilitate this reaction. In the presence of caspase-8 inhibition, RIP1 and RIP3 interact with each other via the RHIM to form the pro-necrotic signaling complex. This interaction is further stabilized by phosphorylation of both kinases. However, active caspase-8 cleaves RIP1 and possibly RIP3 to blunt the pro-necrotic complex. The active caspase-8 complex can go onto cleave additional substrates, culminating in cell death by apoptosis

Going up in flames: necrotic cell injury and inflammatory diseases

Sreerupa Challa • Francis Ka-Ming Chan - ***Cell. Mol. Life Sci. (2010) 67:3241–3253***

Gérard Lizard,





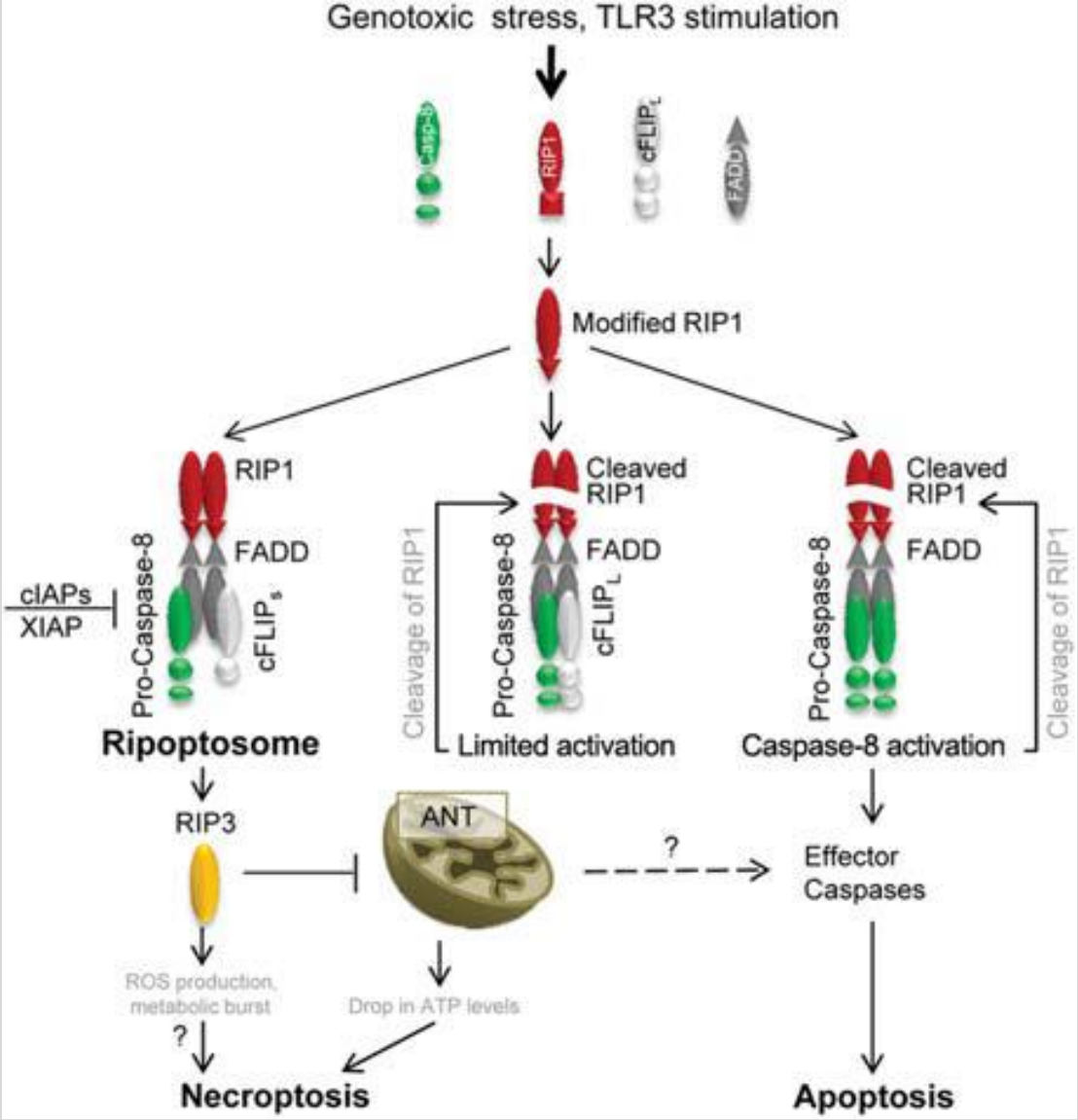
The signaling complexes are induced by TNFa to mediate NF-kB activation, apoptosis, and necroptosis. Stimulation of TNFR1 by TNFa leads to the formation of an intracellular complex at the cytoplasmic membrane (complex I) that includes TRADD, TRAF2, RIP1, and cIAP1.

Ubiquitination of RIP1 at K377 by cIAP1 leads to the recruitment of NEMO, a regulatory subunit of IKK complex that in turn activates NF-kB pathway. RIP1 is also involved in the formation of complex IIa including FADD and caspase-8 to activate a caspase cascade to mediate apoptosis. Under apoptosis-deficient conditions or when cells are infected by certain viruses, RIP1 interacts with RIP3 to form complex Iib which is involved in mediating necroptosis. The formation complex IIb requires the kinase activity of RIP1 that is inhibited by Nec-1.

Necroptosis as an alternative form of programmed cell death. Christofferson DE & Yuan J*.*
Curr Opin Cell Biol 2010, 22: 263-268.
Functions of caspase 8: the identified and the mysterious. Salvesen GS, Walsh CM.
Semin Immunol. 2014;26:246-52.

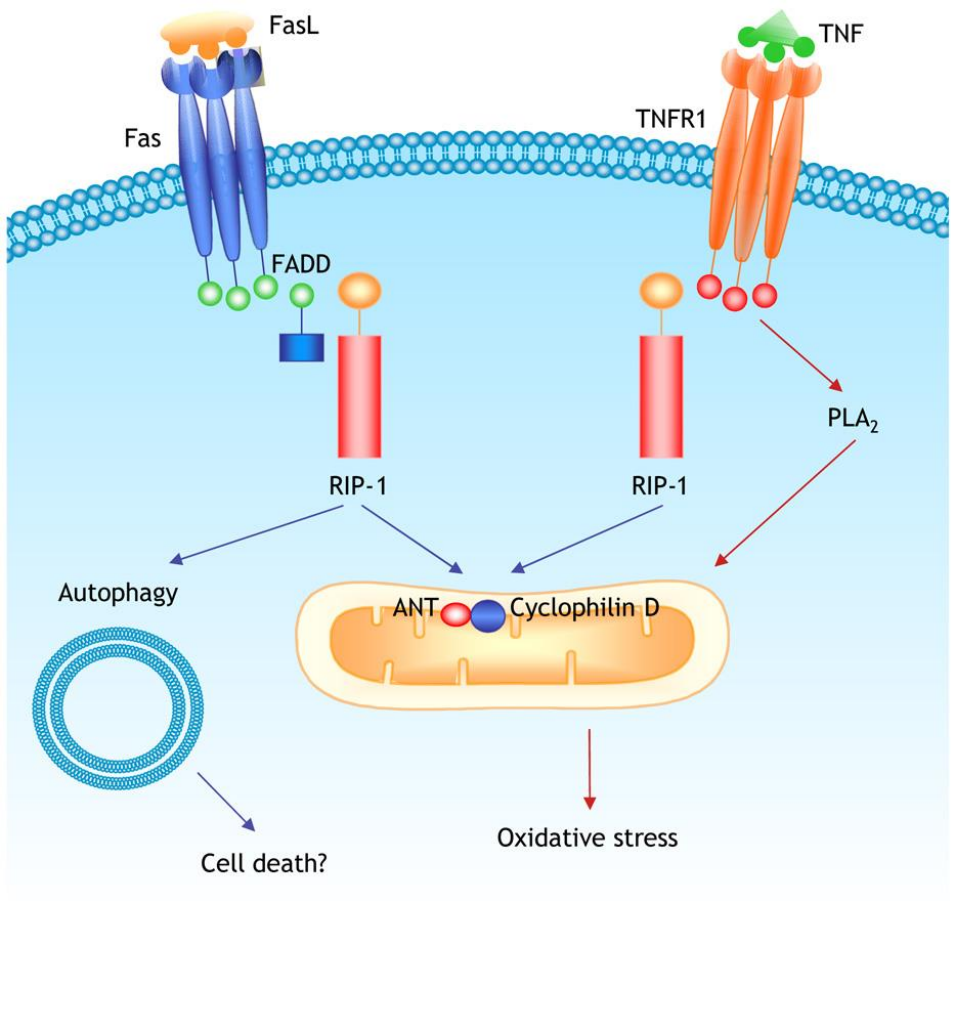
Gérard Lizard,

Ripoptosome : a IAP-regulated cell death-signalling platform



Imre G, Larisch S, Rajalingam K. Ripoptosome: a novel IAP-regulated cell death-signalling platform. J Mol Cell Biol. 2011;3(6):324-6.

Gérard Lizard



Death receptor activated necroptosis

When caspase activity is blocked, death receptor activation can drive necroptosis through upregulation of PLA_2 activity that, in turn, increases oxidative stress.

RIP-1 kinase is also activated triggering necroptosis by directly acting upon mitochondrial function or, perhaps, by effecting autophagy.

Caspase independent cell death: leaving the set without the final cut. Tait SWG and Green DR.
Oncogene 2008; 27: 6452-6461.

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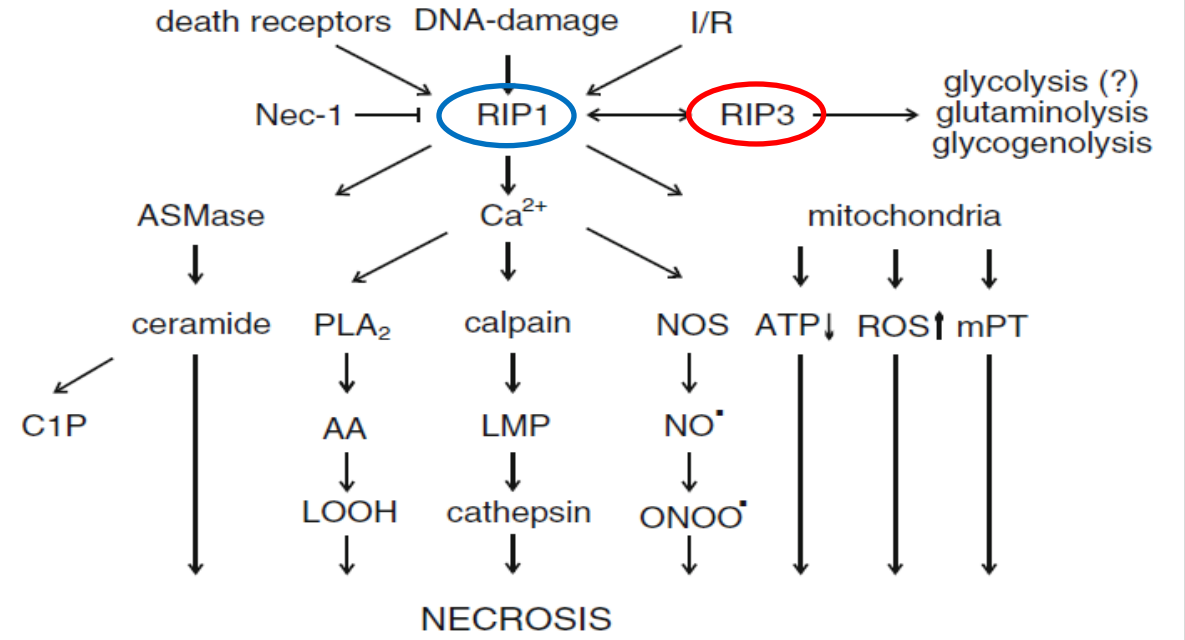
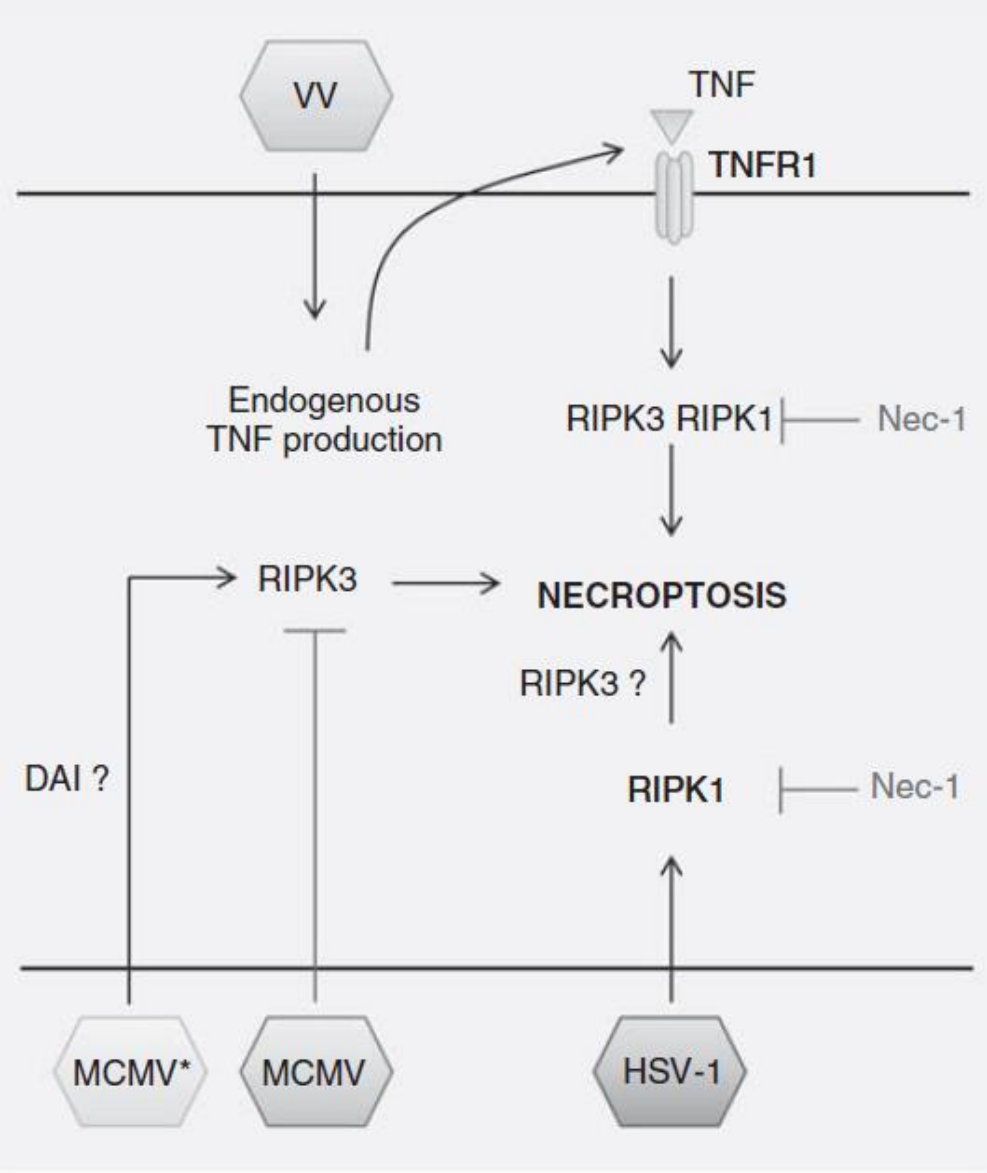


Necrotic cell death is the result of interplay between several signaling cascades. Kinase activity of RIP1 is needed to induce necrosis in several in vitro and in vivo models. The main players in the propagation of necrosis are RIP3, calcium and mitochondria. RIP3 interacts with RIP1 and binds to several enzymes of the carbohydrate and glutamine metabolism. Calcium controls activation of PLA_2, calpains and NOS, which induce a series of events leading to necrotic cell death. Mitochondria contribute to necrosis by excessive ROS formation, mPT, and ATP depletion due to mitochondrial dysfunction. Several of these mediators are implicated in a self-amplifying loop. See text for details

Tumor necrosis factor-mediated cell death: to break or to burst, that's the question

Franky Van Herreweghe • Nele Festjens •Wim Declercq • Peter Vandenabeele ***Cell. Mol. Life Sci. (2010) 67:1567–1579***



Virus-induced necroptosis: VV infection enhances TNF-induced necroptosis, probably by endogenous TNF production. In contrast, infection with MCMV rescues cells from TNF-induced necroptosis through M45-mediated inhibition of RIPK1-RIPK3 interaction. Infection with a RHIM-mutated M45 or M45-deficient MCMV strain (MCMV*) induces RIPK1-independent, RIPK3- dependent necroptosis. HSV-1 infection induces necroptosis, which can be blocked by Nec-1 treatment

Gérard Lizard,

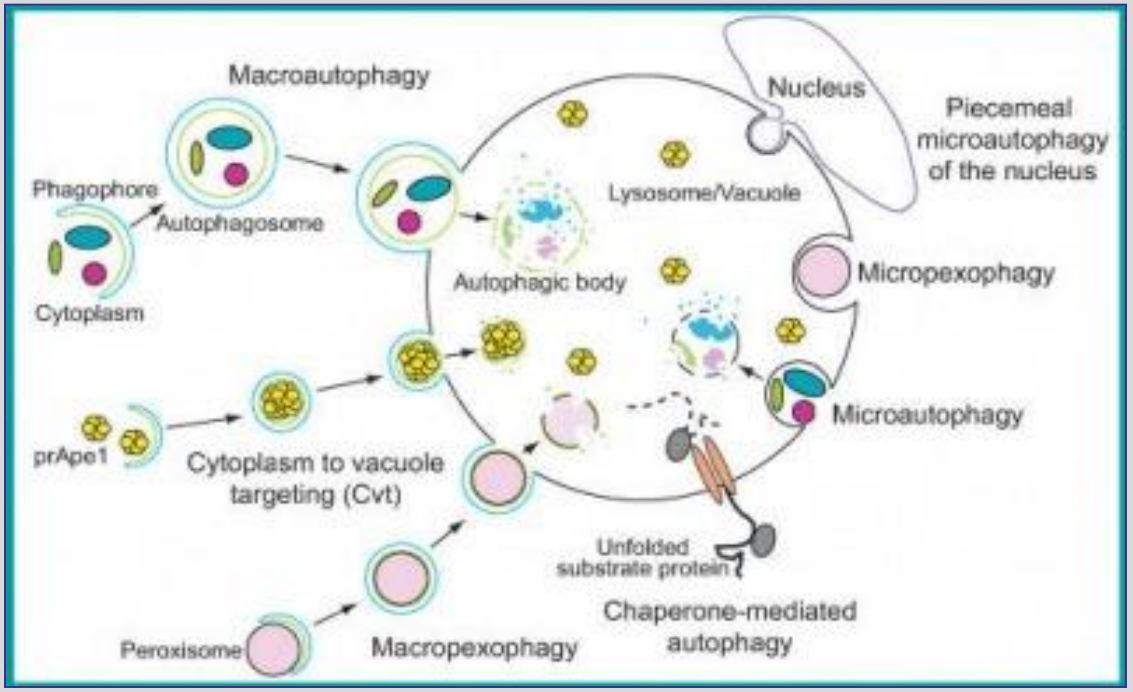
Vanlangenakker N, Vanden Berghe T, Vandenabeele P. Many stimuli pull the necrotic trigger, an overview. Cell Death Differ. 2012;19(1):75-86.

Three types of autophagy:

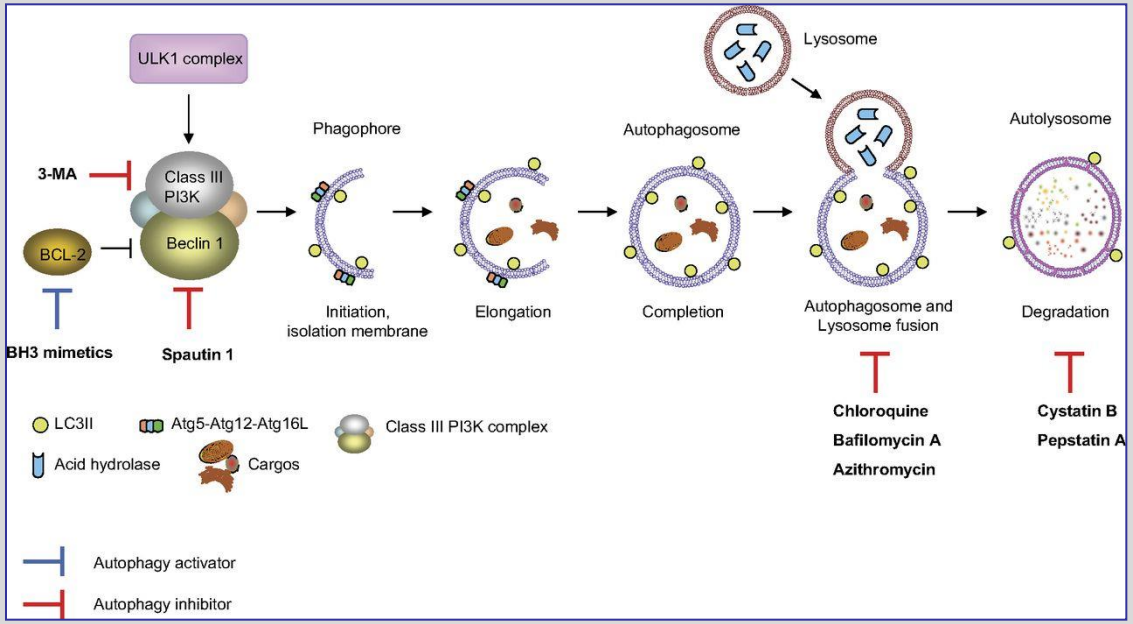
-Macroautophagy

-Microautophagy

-Chaperone-mediated autophagy



Sequences of autophagy



Klionsky *et al*., Autophagy 2012 8:4, 445-544

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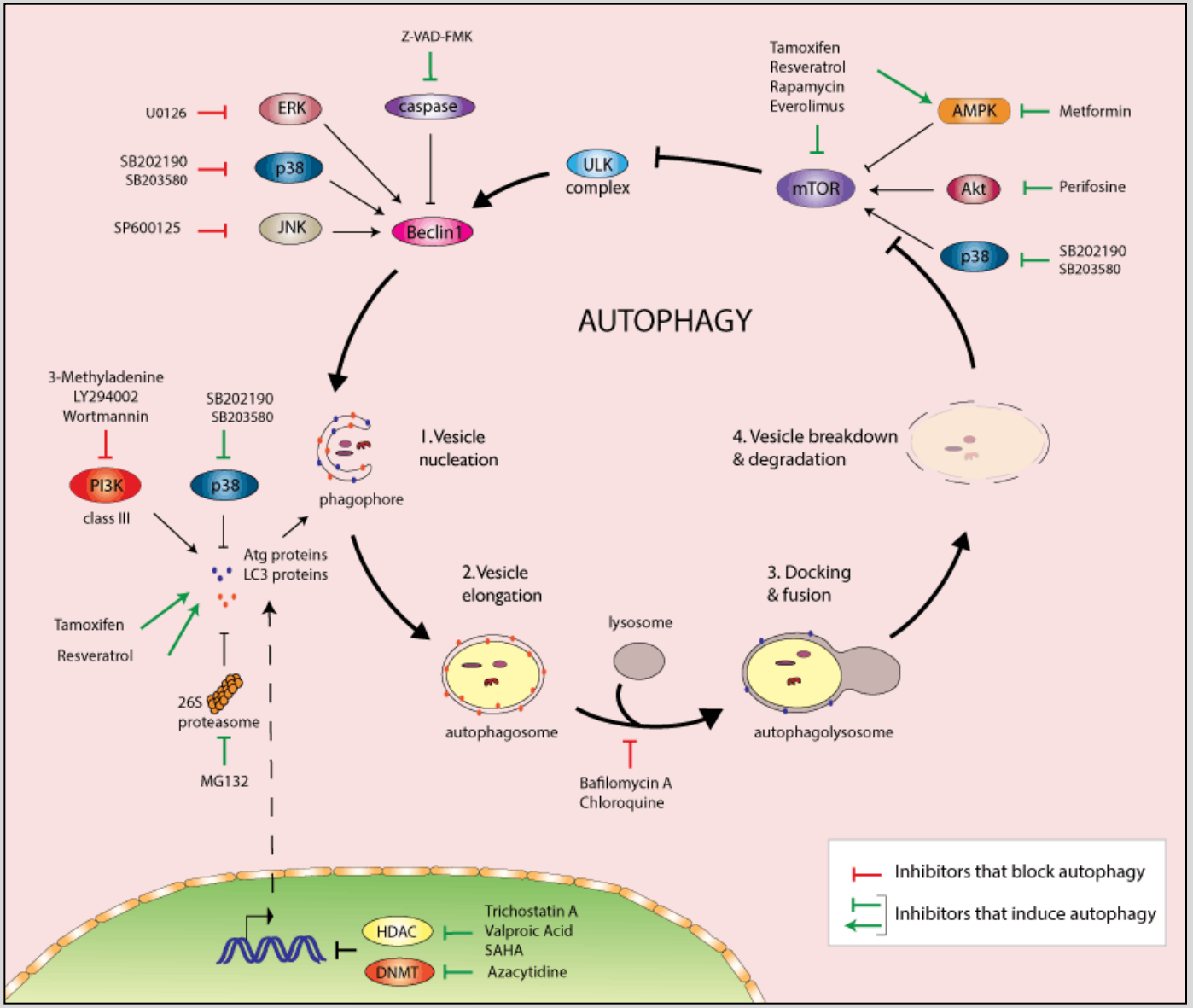
Molecular Mechanisms of Autophagy



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Autophagy (early and late phases)

LC3 interconversion (LC3I to LC3II) and autophagosome formation