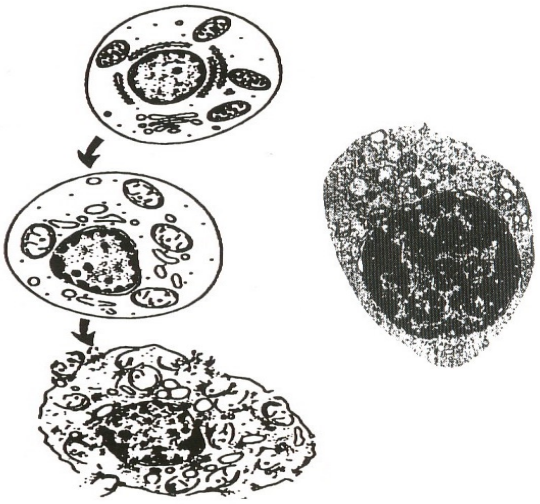
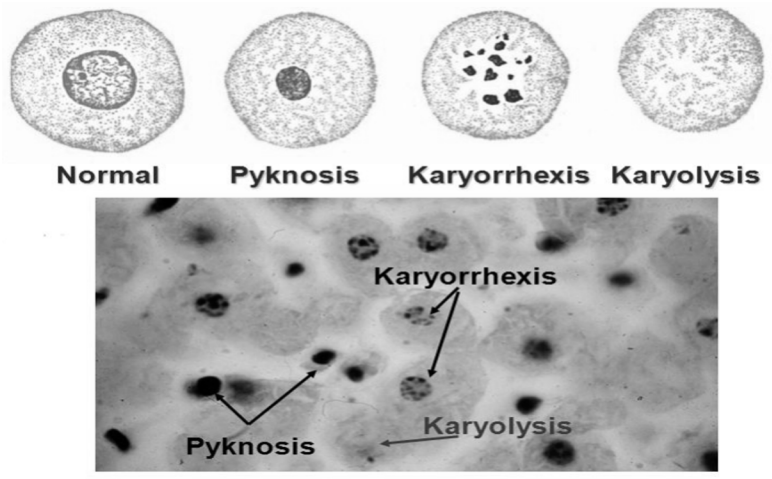
CELL DEATH: NECROSIS



Adapted fromCantelli Forte, Galli, Hrelia, Marinovich "Tossicologia molecolare e cellulare" Ed. UTET



Adapted from: http://slideplayer.com/slide/8876020/

Morphological evolution of necrosis

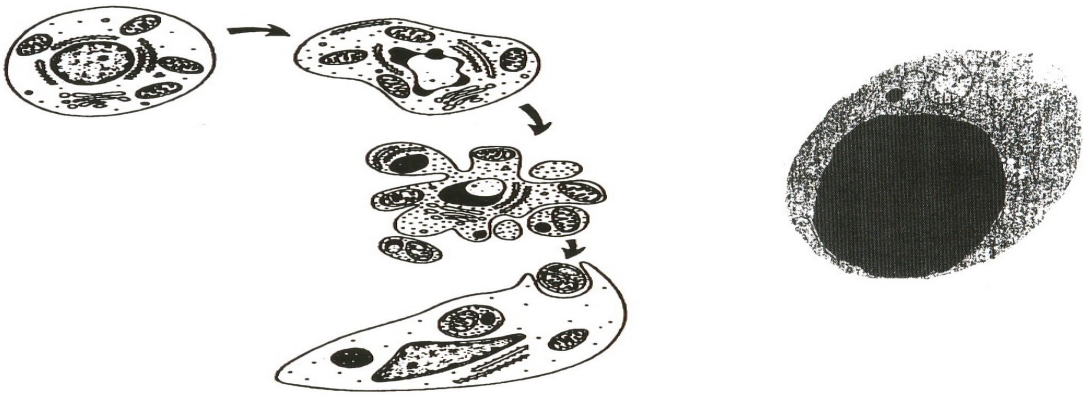
In a first phase:

- Cell swelling
- Mitochondria swelling
- Pycnosis

In a second phase:

- Karyorrhexis/karyolysis, degradation of organelles, cytoskeleton and plasma membrane
- Cells lyse and release all content in the extracellular space, initiating inflammatory processes (recruitment of macrophages, granulocytes, etc.) that can also damage neighbouring cells.

CELL DEATH: APOPTOSIS



Adatpted from Cantelli Forte, Galli, Hrelia, Marinovich "Tossicologia molecolare e cellulare" Ed. UTET

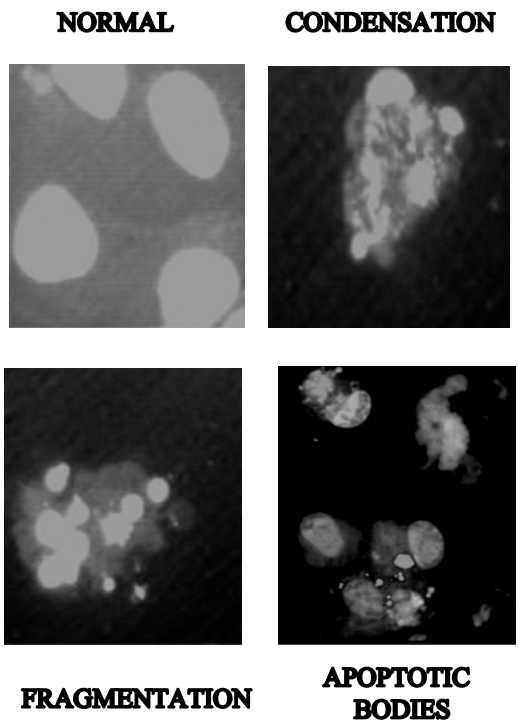
Morphologic evolution of apotosis

In a first phase

- Cell shrinks, chromatin is condensed along nuclear membrane. Cell organelles look normal.
- Nucleus fragments into pieces enveloped by nuclear membrane. Nuclear fragments and organelles are confined in plasma membrane blebs.

In a second phase

• Plasma membrane blebs seal and detach (budding), forming the "apoptotic bodies" that are phagocytosed and degraded by macrophages or parenchimal cells. Usually, there is no associated inflammation.



Adapted from Padanilam B.J. (2003) Am. J. Physiol. 284, F608-627

REGULATION OF APOPTOSIS

A) Extrinsic pathway

Activation of different receptors (death receptors) triggers apoptosis

• CD95 receptors (Fas - APO1)

Activated by CD95 ligand (CD95L, FasL, Apo1L), a protein present on activated T cells.

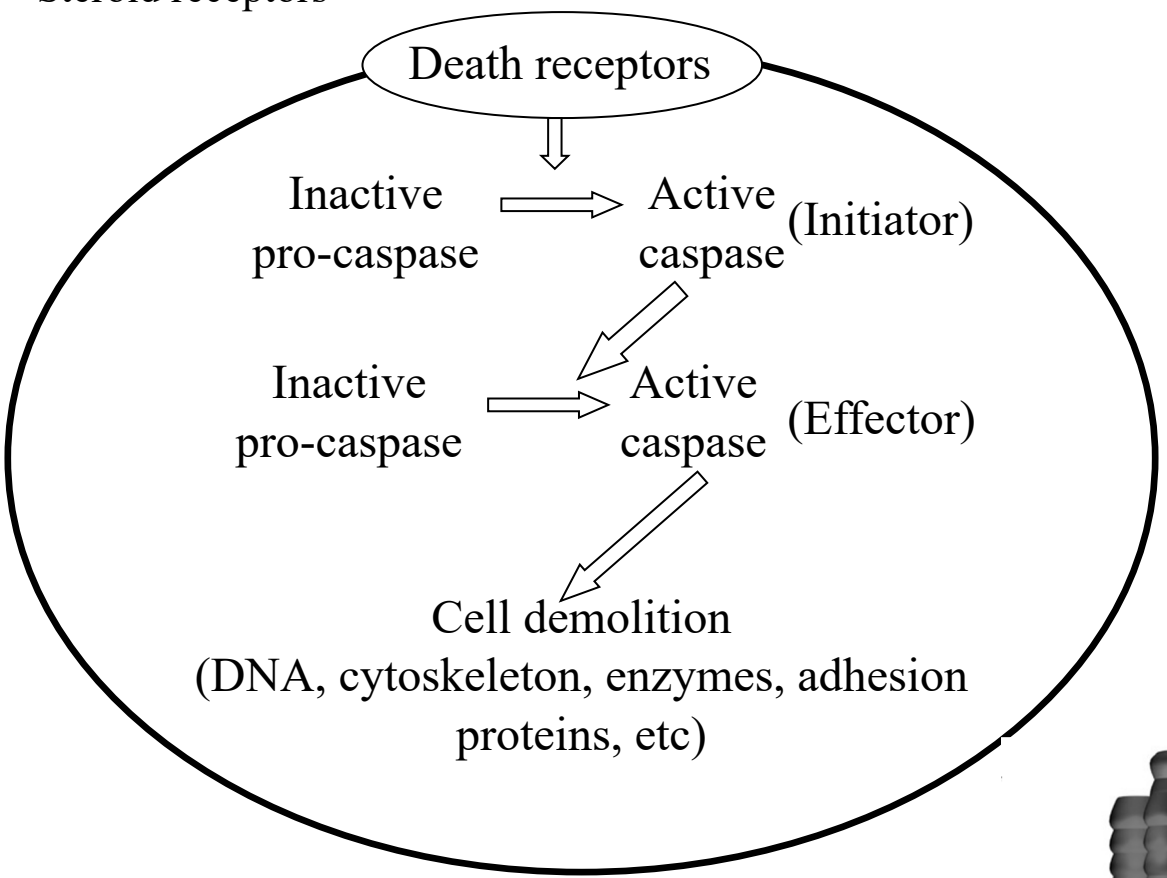
• TRAIL receptors (TRAILR)

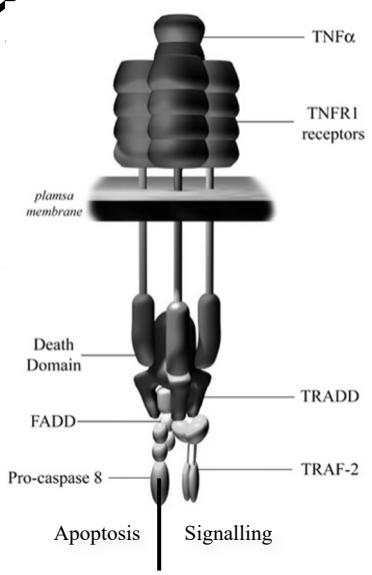
Activated by TRAIL (TNF-related apoptosis-inducing ligand)/Apo2L

• TNF receptors (TNFR-1)

Activated by Tumor Necrosis Factor alfa (TNF-α), a cytokine mainly produced by macrophages and T cells, but also by other cell types.

• Steroid receptors

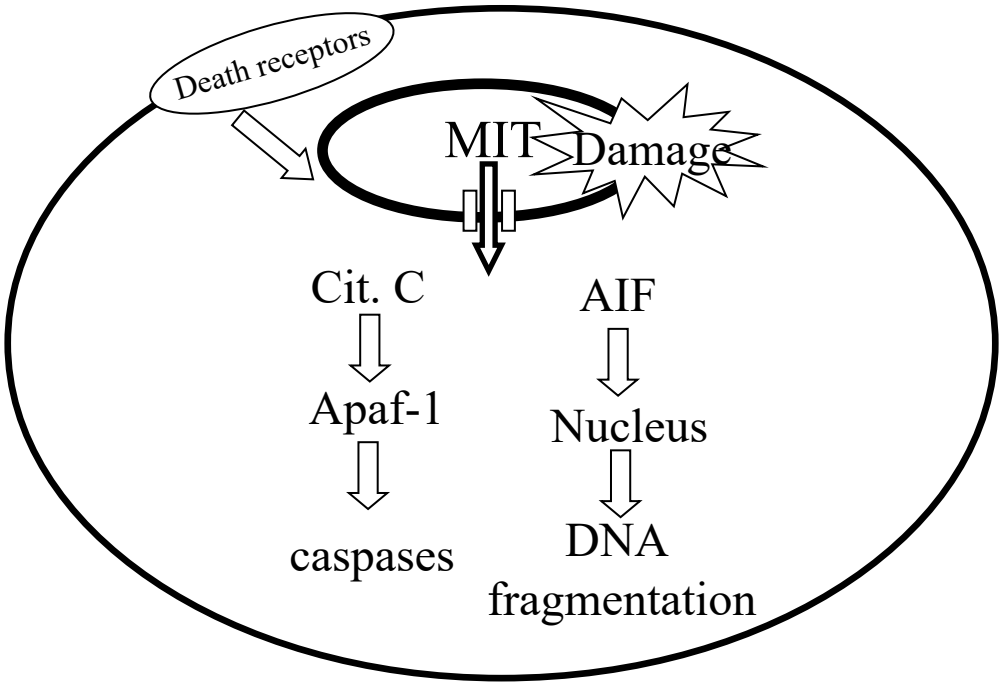




Adapted from: http://www.reading.ac.uk/nitricoxide/ intro/apoptosis/receptor.htm

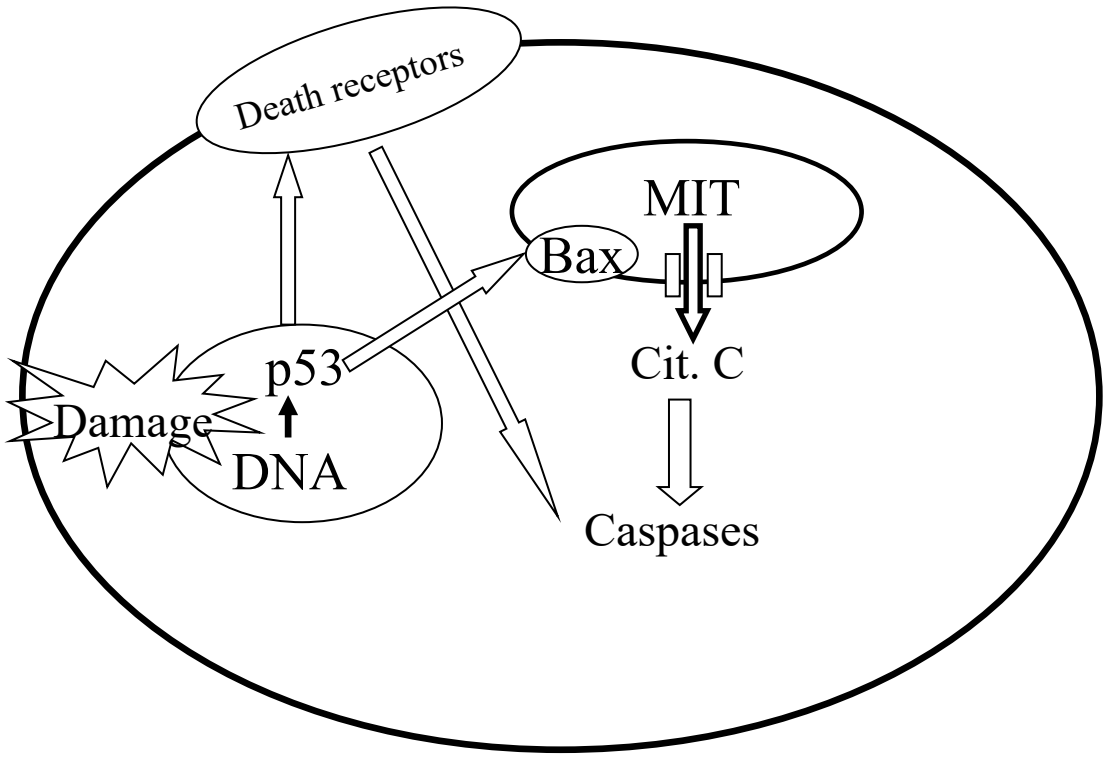
B) Intrinsic (mitochondrial) pathway

In this case, apoptosis is triggered by mitochondrial damage but it can also be triggered by receptor-activated caspases.



C) DNA damage

DNA damage increases p53 expression that, in turn, is able to trigger enhancement of death receptors and induction of the mitochondrial pathway.

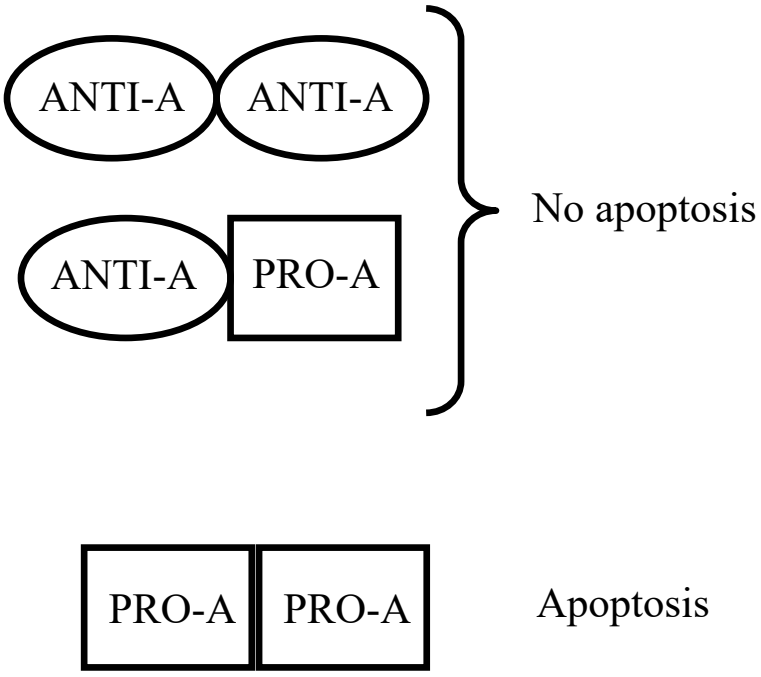


APOPTOSIS REGULATION

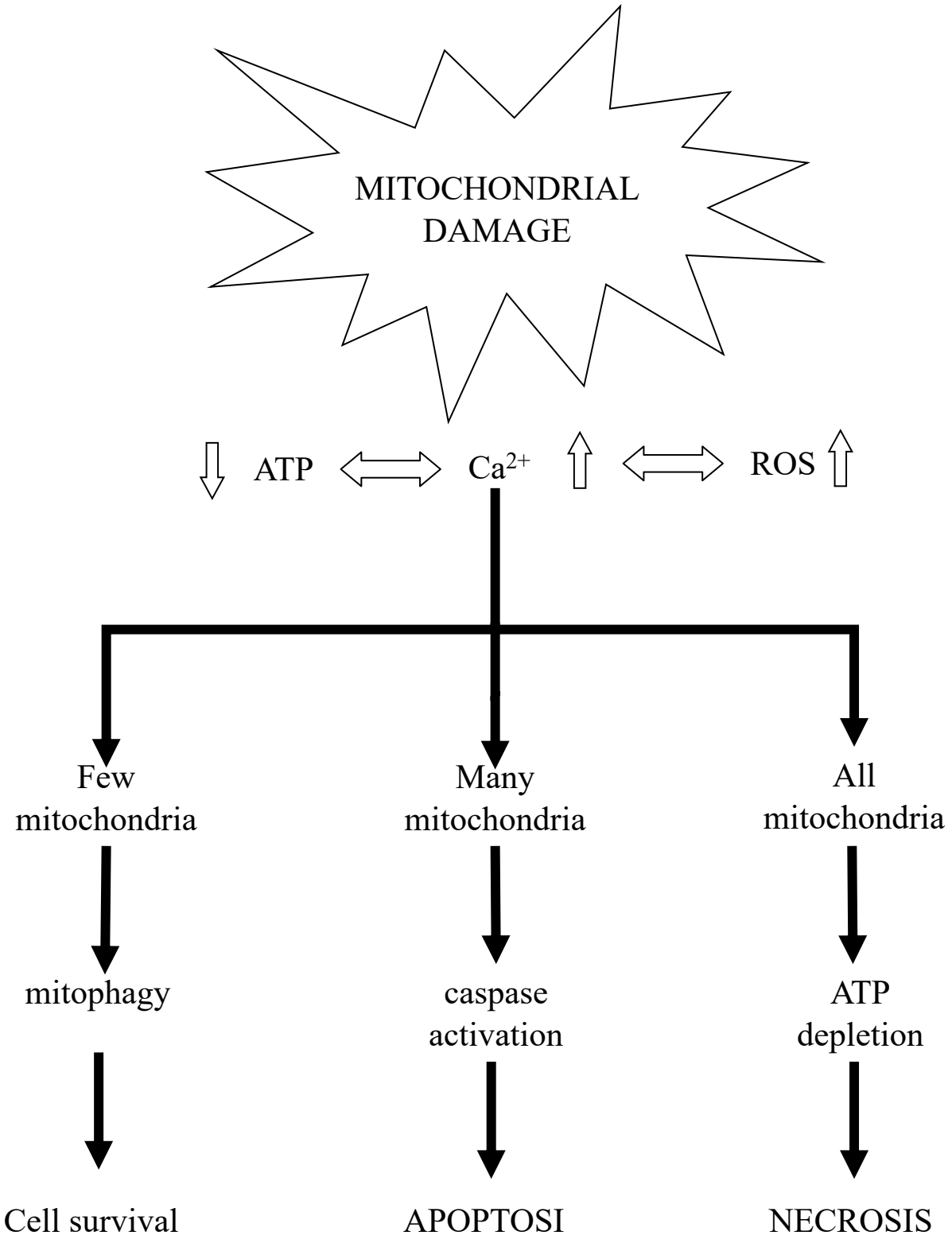
Apoptosis is also regulated by the family of Bcl-2 proteins

Bcl-2 Bcl-XL	antiapoptotic activity (ANTI-A)	Bax Bad Bcl-XS	proapoptotic activity (PRO-A)

These proteins can form homo- and heterodimers



NECROSIS OR APOPTOSIS



AUTOPHAGY

Autophagy is a key process for maintaining cell homeostasis by digestion of dysfunctional organelles/proteins.

It also represents a survival strategy to obtain energy under limiting nutrient conditions/starvation.

However, both autophagy hyperactivation and failure can lead to cell death.

Progress in Neurobiology 112 (2014) 24–49

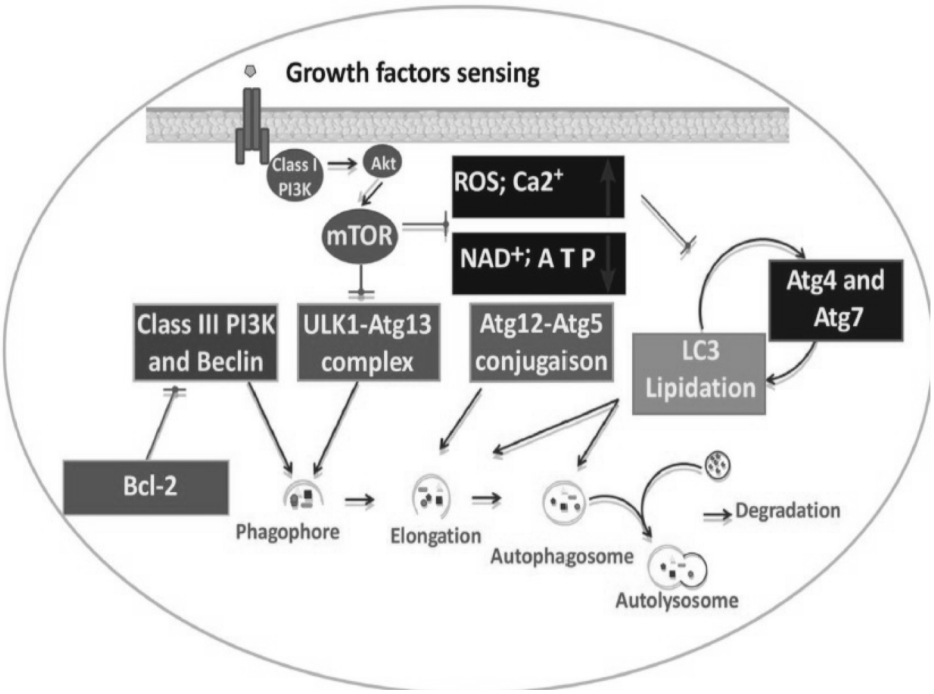
Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Autophagy and apoptosis dysfunction in neurodegenerative disorders

Saeid Ghavami[a,b,c,1], Shahla Shojaei[d,1], Behzad Yeganeh[b,l,1], Sudharsana R. Ande[e], Jaganmohan R. Jangamreddy[f], Maryam Mehrpour[g], Jonas Christoffersson[f], Wiem Chaabane[f,h], Adel Rezaei Moghadam[i], Hessam H. Kashani[a,b], Mohammad Hashemi[j,k], Ali A. Owji[d,2,**], Marek J. Łos[f,2,*]



REGULATED NECROSIS

1. NECROPTOSIS
2. PARTHANATOS
3. FERROPTOSIS
4. PYROPTOSIS

NECROPTOSIS

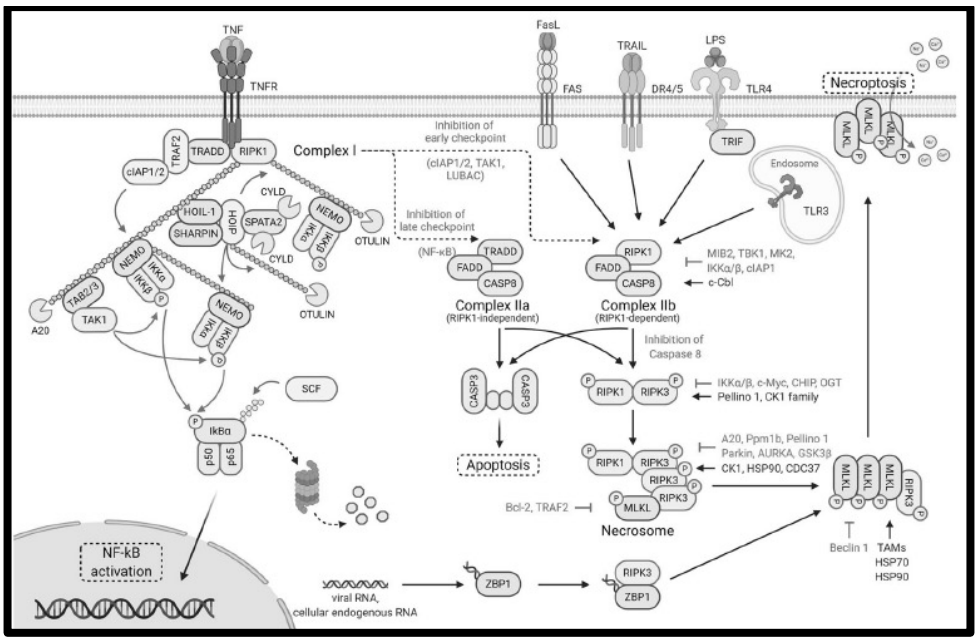
Seo et al. *Experimental & Molecular Medicine* (2021) 53:1007–1017
https://doi.org/10.1038/s12276-021-00634-7

Experimental & Molecular Medicine

REVIEW ARTICLE Open Access

Necroptosis molecular mechanisms: Recent findings regarding novel necroptosis regulators

Jinho Seo[1], Young Woo Nam[2], Seongmi Kim[2], Doo-Byoung Oh[1,3] and Jaewhan Song[2]



Necroptosis is a form of regulated necrosis that can be activated by TNFα, FasL, TRAIL stimulation, when the apoptotic pathway is inhibited.

It has been hypothesised that necroptosis represents an ancestral necrotic death mechanism that has been replaced by apoptosis/autophagy during evolution but that can act as a backup if other death pathways are blocked.

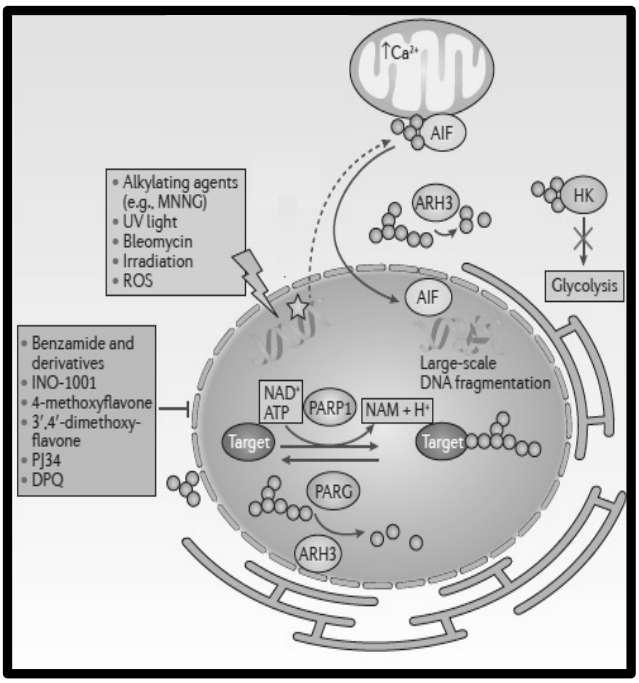
Necroptosis inhibitors could be useful as neuroprotective drugs in cerebral ischemia and neurodegenerative disorders.

Necroptosis inducers could be useful anticancer drugs.

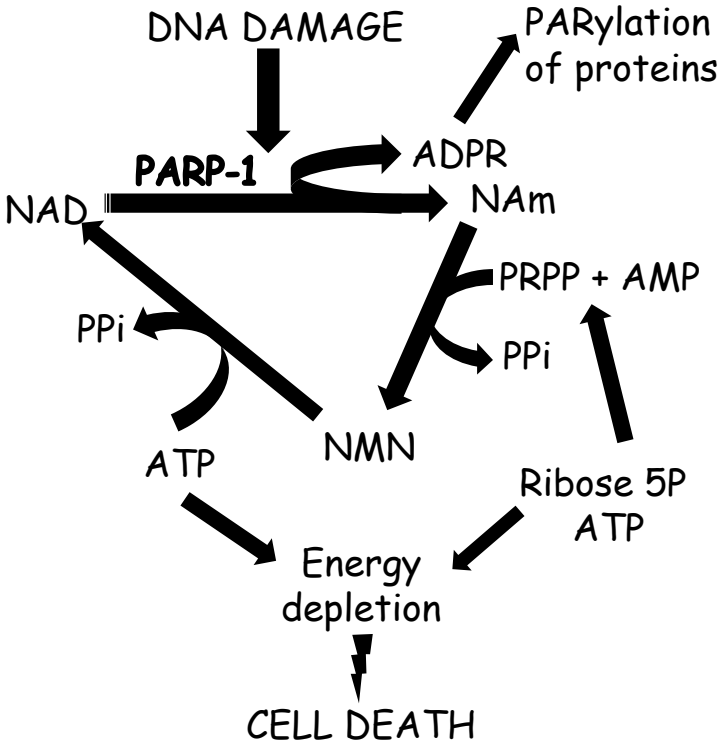
NECROPTOSIS EXECUTION

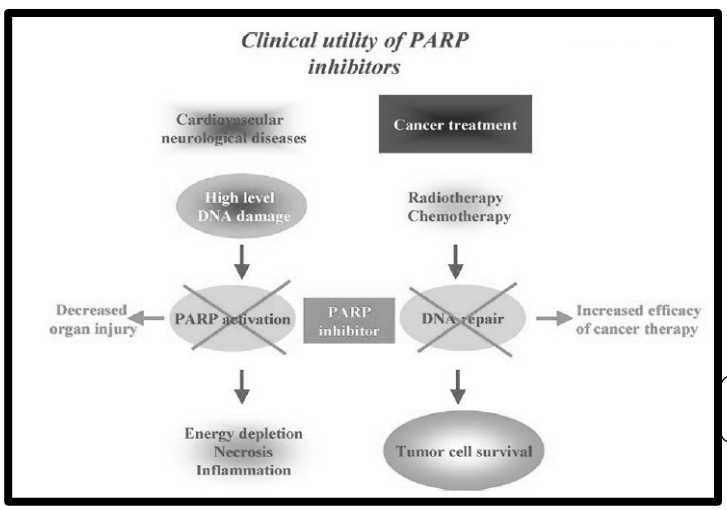
- Increased membrane permeability and rupture due to P-MLKL (mixed lineage kinase domain-like) oligomerization and pore fomation
- Oxidative stress (NOX, mitochondria)
- Alterations of mitochondria function
- NO production
- Activation of PLA2 and LOXs

PARTHANATOS
Poly-ADPribose-mediated cell death

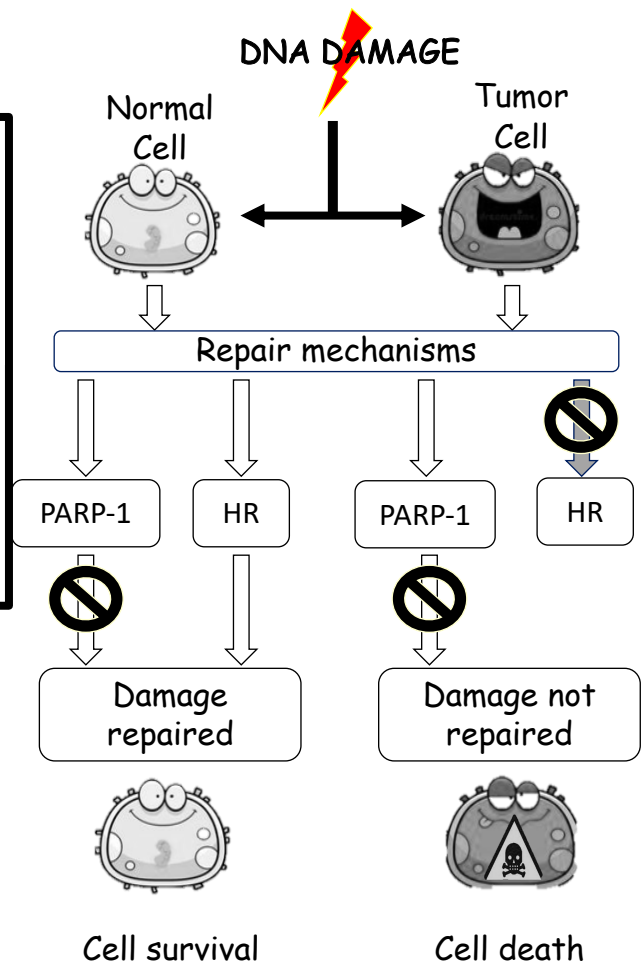


Adapted from: Conrad et al. (2016) Nature Reviews 15: 348-366





Adapted from: Graziani & Szabò Pharm. Res. 52, 109-118, 2005



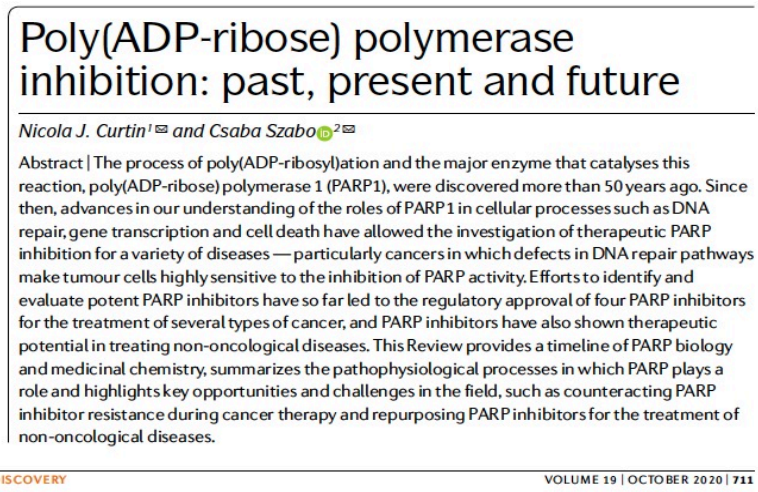
PARTHANATOS
Poly-ADPribose-mediated cell death

Parthanatos is a regulated form of necrosis that is dependent on overactivation of PARP-1 (poly-ADPribose polymerase) by various stimuli (e.g. DNA damage).

Death is induced by PARylation of:
- AIF that translocates to the nucleus
- Exokinase with inhibition of glycolysis.

In addition, excessive PARP activation can also induce ATP depletion.

Parthanatos is characterized by large scale DNA fragmentation, chromatin condensation, dissipation of mitochondrial potential, loss of membrane integrity.



Poly(ADP-ribose) polymerase inhibition: past, present and future

Nicola J. Curtin[1] ✉ and Csaba Szabo[2] ✉

Abstract | The process of poly(ADP-ribosyl)ation and the major enzyme that catalyses this reaction, poly(ADP-ribose) polymerase 1 (PARP1), were discovered more than 50 years ago. Since then, advances in our understanding of the roles of PARP1 in cellular processes such as DNA repair, gene transcription and cell death have allowed the investigation of therapeutic PARP inhibition for a variety of diseases — particularly cancers in which defects in DNA repair pathways make tumour cells highly sensitive to the inhibition of PARP activity. Efforts to identify and evaluate potent PARP inhibitors have so far led to the regulatory approval of four PARP inhibitors for the treatment of several types of cancer, and PARP inhibitors have also shown therapeutic potential in treating non-oncological diseases. This Review provides a timeline of PARP biology and medicinal chemistry, summarizes the pathophysiological processes in which PARP plays a role and highlights key opportunities and challenges in the field, such as counteracting PARP inhibitor resistance during cancer therapy and repurposing PARP inhibitors for the treatment of non-oncological diseases.

NATURE REVIEWS | DRUG DISCOVERY VOLUME 19 | OCTOBER 2020 | 711

International Journal of Molecular Sciences

MDPI

Review

ADP-Ribosylation as Post-Translational Modification of Proteins: Use of Inhibitors in Cancer Control

Palmiro Poltronieri [1,*], Masanao Miwa [2] and Mitsuko Masutani [3,*]

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[2] Nagahama Institute of Bio-Science and Technology, Nagahama 526-0829, Japan; m_miwa@nagahama-i-bio.ac.jp
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Abstract: Among the post-translational modifications of proteins, ADP-ribosylation has been studied for over fifty years, and a large set of functions, including DNA repair, transcription, and cell signaling, have been assigned to this post-translational modification (PTM). This review presents an update on the function of a large set of enzyme writers, the readers that are recruited by the modified targets, and the erasers that reverse the modification to the original amino acid residue, removing the covalent bonds formed. In particular, the review provides details on the involvement of the enzymes performing monoADP-ribosylation/polyADP-ribosylation (MAR/PAR) cycling in cancers. Of note, there is potential for the application of the inhibitors developed for cancer also in the therapy of non-oncological diseases such as the protection against oxidative stress, the suppression of inflammatory responses, and the treatment of neurodegenerative diseases. This field of studies is not concluded, since novel enzymes are being discovered at a rapid pace.

Keywords: ADP-ribosyl transferase (ART); poly ADP-ribose polymerase (PARP); ADP-ribose (ADPR); sirtuin (SIRT); poly ADP-ribose glycohydrolase (PARG); ADP-ribose hydrolase (ARH); macro-domain (MACRO)

check for updates

Citation: Poltronieri, P.; Miwa, M.; Masutani, M. ADP-Ribosylation as Post-Translational Modification of Proteins: Use of Inhibitors in Cancer Control. *Int. J. Mol. Sci.* **2021**, *22*, 10826. https://doi.org/10.3390/ijms221910829

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Poly (ADP-ribose) polymerase-1 as a promising drug target for neurodegenerative diseases

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ARTICLE INFO

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Parthanatos
Neurodegenerative diseases
PARP-1 inhibitors
Caspases
PI3K signalling
NF-κB signalling
ASK-JNK signalling

ABSTRACT

Aims: Poly (ADP-ribose) polymerase- (PARP)-1 is predominantly triggered by DNA damage. Overexpression of PARP-1 is known for its association with the pathogenesis of several CNS disorders, such as Stroke, Parkinson's disease (PD), Alzheimer's disease (AD), Huntington (HD) and Amyotrophic lateral sclerosis (ALS). NAD+ depletion resulted PARP related cell death only happened when the trial used extreme high oxidization treatment. Inhibition of PARP1/2 may induce replication related cell death due to un-repaired DNA damage. This review has discussed PARP-1 modulated downstream pathways in neurodegeneration and various FDA approved PARP-1 inhibitors.

Materials and methods: A systematic literature review of PubMed, Medline, Bentham, Scopus and EMBASE (Elsevier) databases was carried out to understand the nature of the extensive work done on mechanistic role of Poly (ADP-ribose) polymerase and its inhibition in Neurodegenerative diseases.

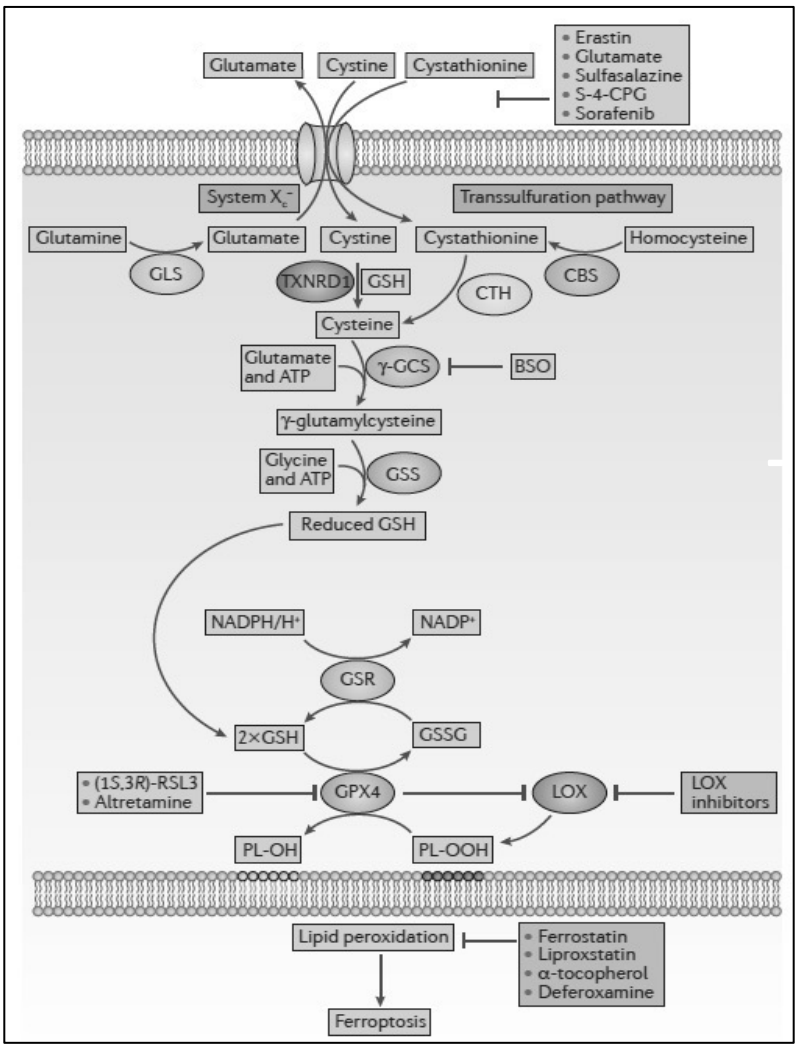
Key findings: Several researchers have put forward number of potential treatments, of which PARP-1 enzyme has been regarded as a potent target intended for the handling of neurodegenerative ailments. Targeting PARP using its chemical inhibitors in various neurodegenerative may have therapeutic outcomes by reducing neuronal death mediated by PARPi. Numerous PARP-1 inhibitors have been studied in neurodegenerative diseases but they haven't been clinically evaluated.

Significance: In this review, the pathological role of PARP-1 in various neurodegenerative diseases has been discussed along with the therapeutic role of PARP-1 inhibitors in various neurodegenerative diseases.

FERROPTOSIS

It represents another regulated form of necrosis that is dependent on cellular iron stores.

Characterized by:
- decreased ferritin
- increased iron uptake
- increased ROS formation
- reduced antioxidant defense (X_c)
- lipid peroxidation



Conrad et al. (2016) Nature Reviews 15: 348-366

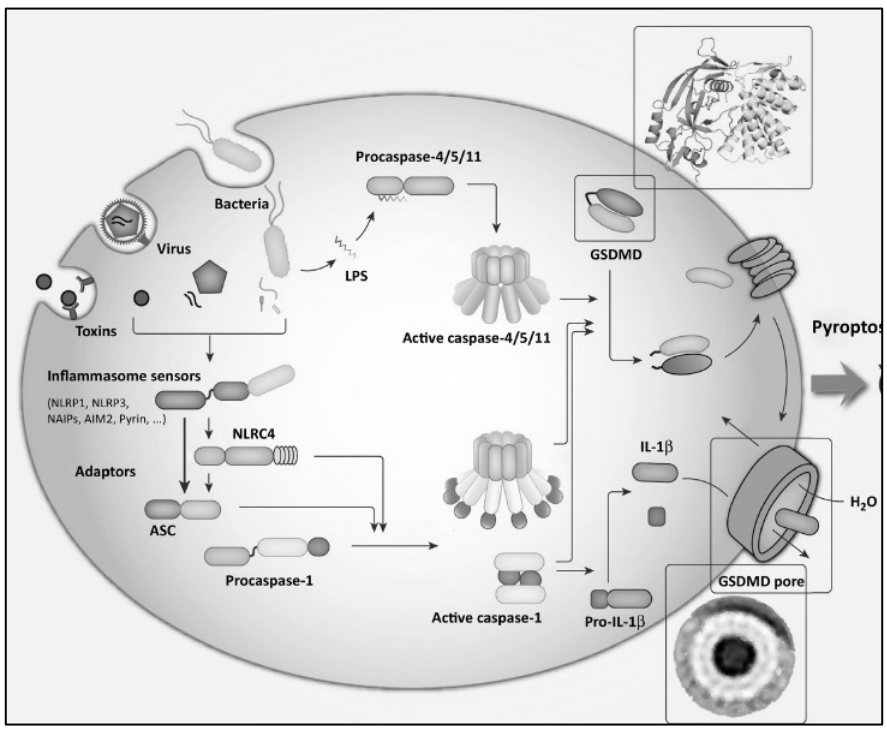
PYROPTOSIS

It represents another regulated form of necrosis that is dependent on formation of the cellular inflammasome following detection of cytosol contamination or perturbation (e.g. bacteria).

Inflammasome is a multiproteic platform formed by the oligomerization of several sensor proteins (e.g. NRL, AIM2, Pyrin).

It activates caspase 1 that, in turn, activates Gasdermin D.

Gasdermin D interacts with the plasma membrane, oligomerizes and forms the Gasdermin pore that causes cell swelling, membrane rupture and eventual lysis.



Adapted from: Shi et al. (2016) Trends Biochem. Sci. 42: 245-254

ALTERATIONS OF CELL FUNCTIONS

In this case, toxicants cause cell dysfunction by interfering with different processes.

- Alterations of cell imputs
  a) Decreased transmitter synthesis
  b) Vesicle depletion
  c) Interruption of transmitter release
  d) Inhibition of transmitter metabolism
  e) Reuptake inhibition

- Interactions with membrane/cytosolic receptors

- Alterations of signal trasduction
  a) Activation/blockade of ion channels
  b) Activation/blockade of second messenge cascades
  c) Activation/blockade of pumps

REPAIR MECHANISMS

MOLECULAR MECHANISMS

• Protein repair

Thioredoxin and Glutaredoxin ubiquitous proteins with two redox-active cysteines in the their catalytic centre. They can reduce oxidized proteins (Prot-SS, Prot1-S-S-Prot2, Prot-SOH) restoring their thiol groups.

Cytocrome b5 reductase restores hemoglobin from methemoglobin ($Fe^{3+} \Rightarrow Fe^{2+}$). If damage is extensive, proteins are degraded by lysosomal proteases or by proteasomes following ubiquitination.

• Lipid repair

Peroxidized lipids can be repaired by a ascorbic acid/a-tocopherol and glutathione peroxidase/oxidase acting in concert.

Fatty acid hydroperoxides present in membranes can be hydrolyzed by PLA2 and replaced by normal fatty acids.

• DNA repair

TISSUE MECHANISMS

These mechanisms are relevant only for tissues that are composed of renewing cells (e.g. bone marrow, lung and GI epithelium, the epidermis) or of conditionally dividing cells (hepatic or renal parenchymal cells)

In general: removal of damaged cells $\Rightarrow$ proliferation and migration of adjacent cells (growth factors, TGF-a, IL-6); and production of extracellular matrix (anchor/adesion proteins, proteoglycan glycoconjugates, glycos-aminoglycans, etc.) $\Rightarrow$ stop signals (e.g. TGF-b).

TISSUE NECROSIS: if repair mechanisms are overwhelmed by damage or if they are inefficient, toxicity progresses to tissue necrosis.

FIBROSIS: pathologic condition characterized by excessive deposition of an extracellular matrix with abnormal composition. It is another manifestation of dysrepair.

TISSUE MECHANISMS

Fibrosis is detrimental because:

- it compresses the parencymal cells and blood vessels decreasing blood supply;
- it represents a barrier to diffusion of nutrients to cells
- it causes an increase of rigidity that affects elasticity/flexibility of tissues (e.g. heart and lungs)