Cell Death: Many Ways to Die.

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Brief History of Cell Death Research

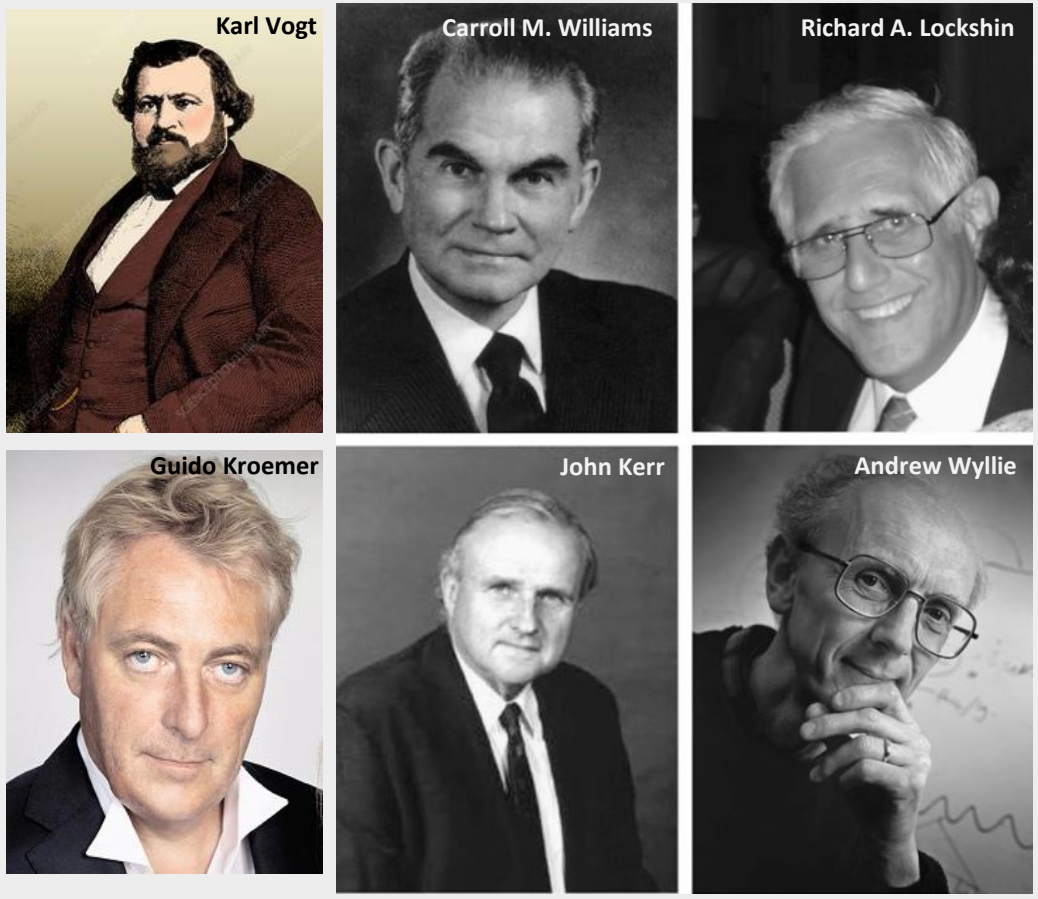
1842 - Karl Vogt noticed dying cells in toads (formation of vertebrae). The first scientific observation of regulated cell death (RCD).

1965 - Lockshin and Williams - specific cells die during the metamorphosis of the silkworm, this type of cell death is 'programmed' because these cells were destined to die according to a 'construction manual' for the insect.

1972 - Kerr *et al*. - specific type of cell death in human tissues in which the cells and nuclei became condensed and fragmented, and they called this cell death process 'apoptosis'. They proposed that apoptosis is crucial for regulating cell populations during tissue development and turnover

1973 – Schweichel and Merker originally described three forms of programmed cell death which they called types I (apoptosis), II (autophagy) and III (necrosis).

2005 – present, NCCD (Nomenclature Committee on Cell Death) publication (Guido Kroemer et.al.).



Lockshin, R. Programmed cell death 50 (and beyond). *Cell Death Differ* **23,** 10–17 (2016). https://doi.org/10.1038/cdd.2015.126

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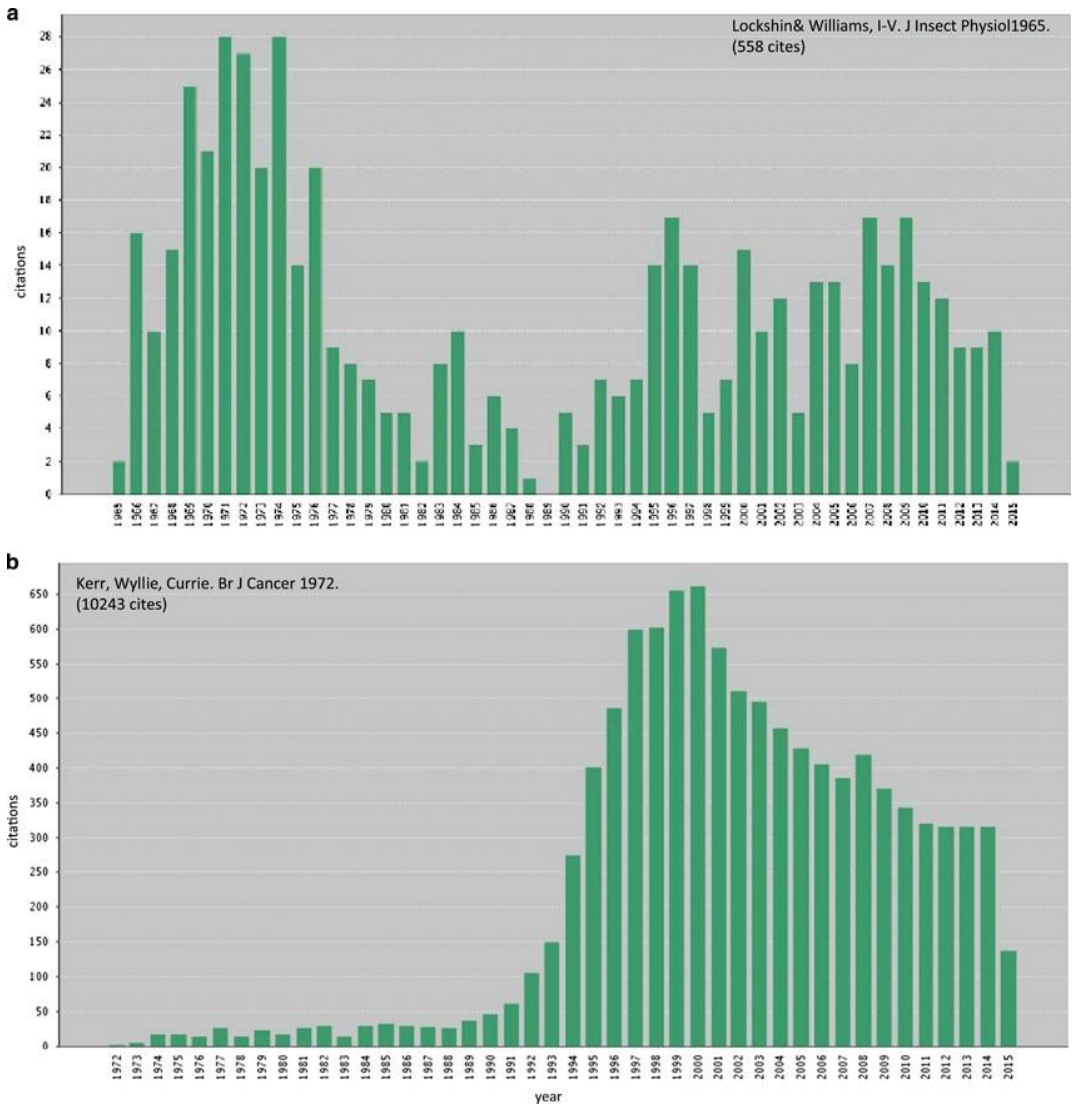
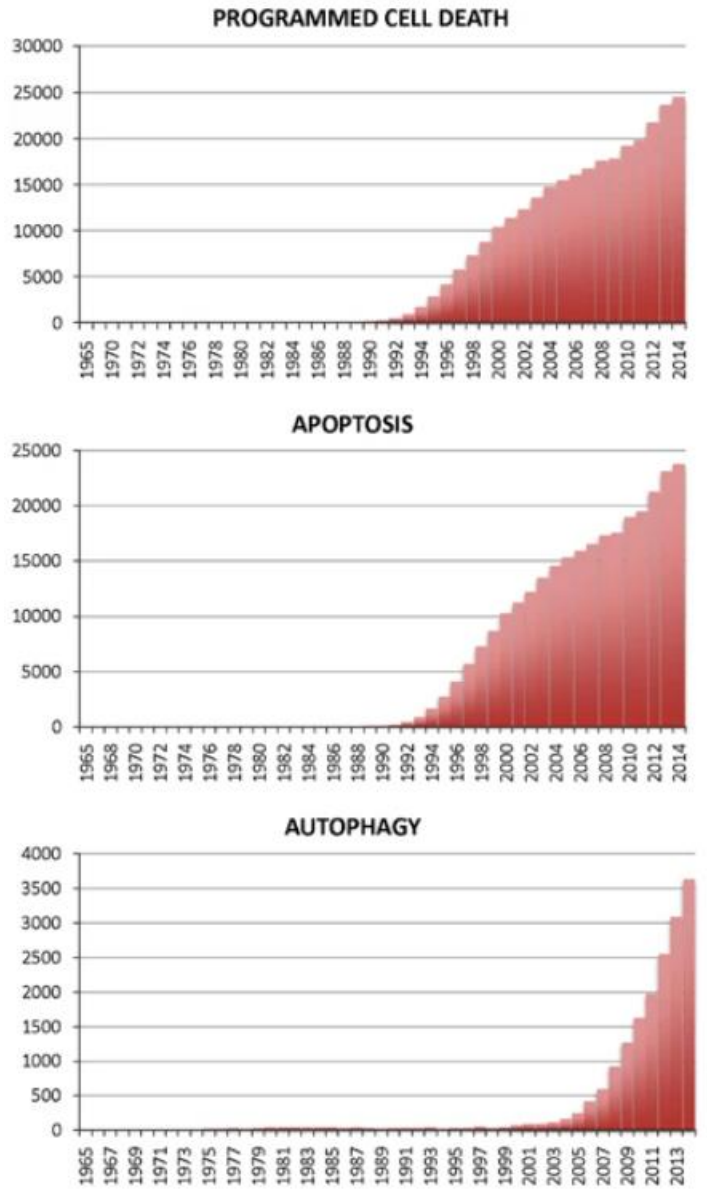
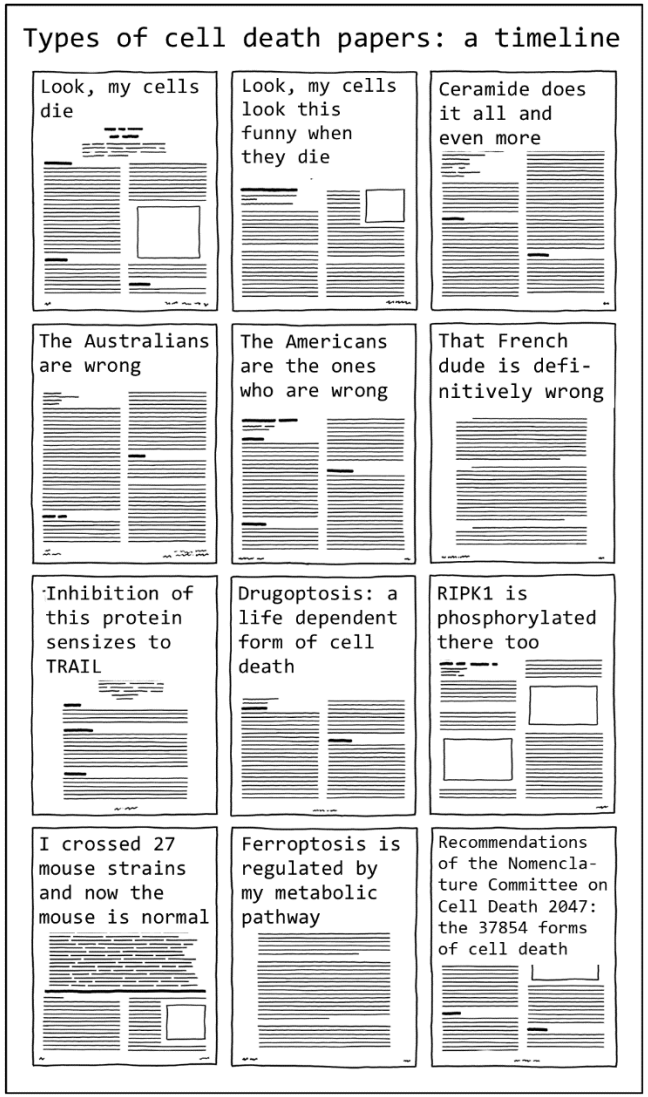
Brief History of Cell Death







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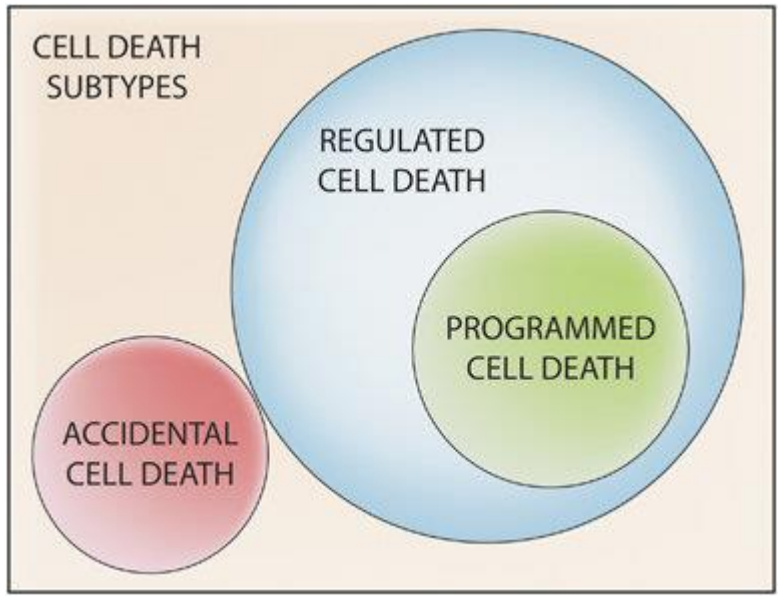
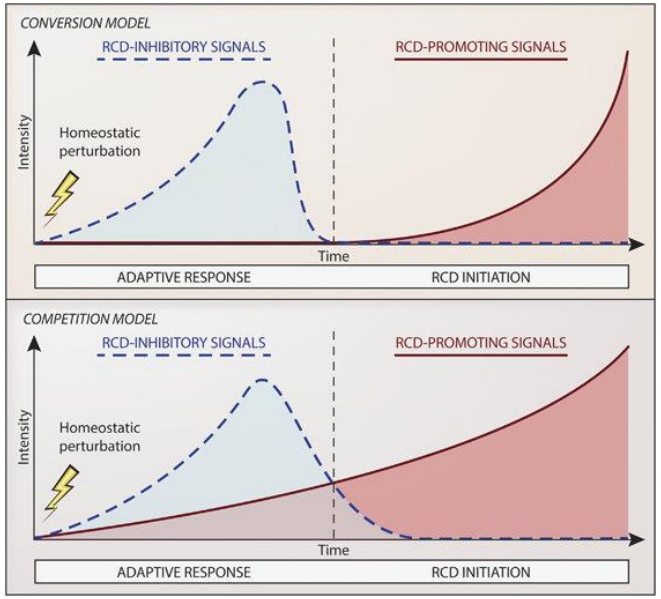
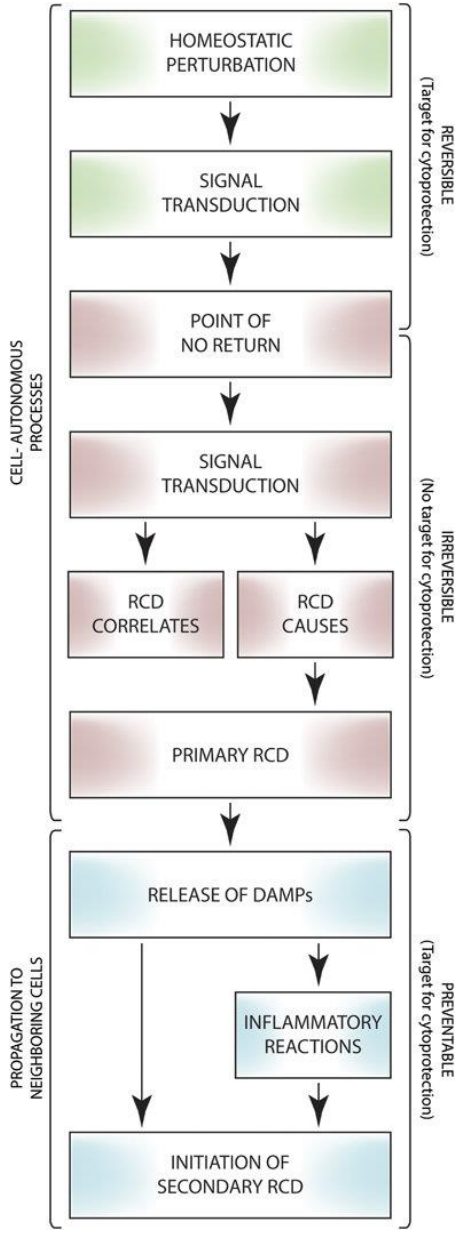
Accidental vs. Regulated Cell Death

- **Cell death plays a central role in all aspects of life**. It is involved in the development of multicellular organisms and tissue homeostasis where cell death depletes dispensable cells.
- Cells may die from **accidental cell death** (ACD) or **regulated cell death** (RCD).
- **ACD is a biologically uncontrolled process**, whereas **RCD involves tightly structured signaling cascades and molecularly defined effector mechanisms**.
- Cell death is critical for fighting off infections and is associated with multiple diseases that are caused by deregulated or dysfunctional cell death signaling.

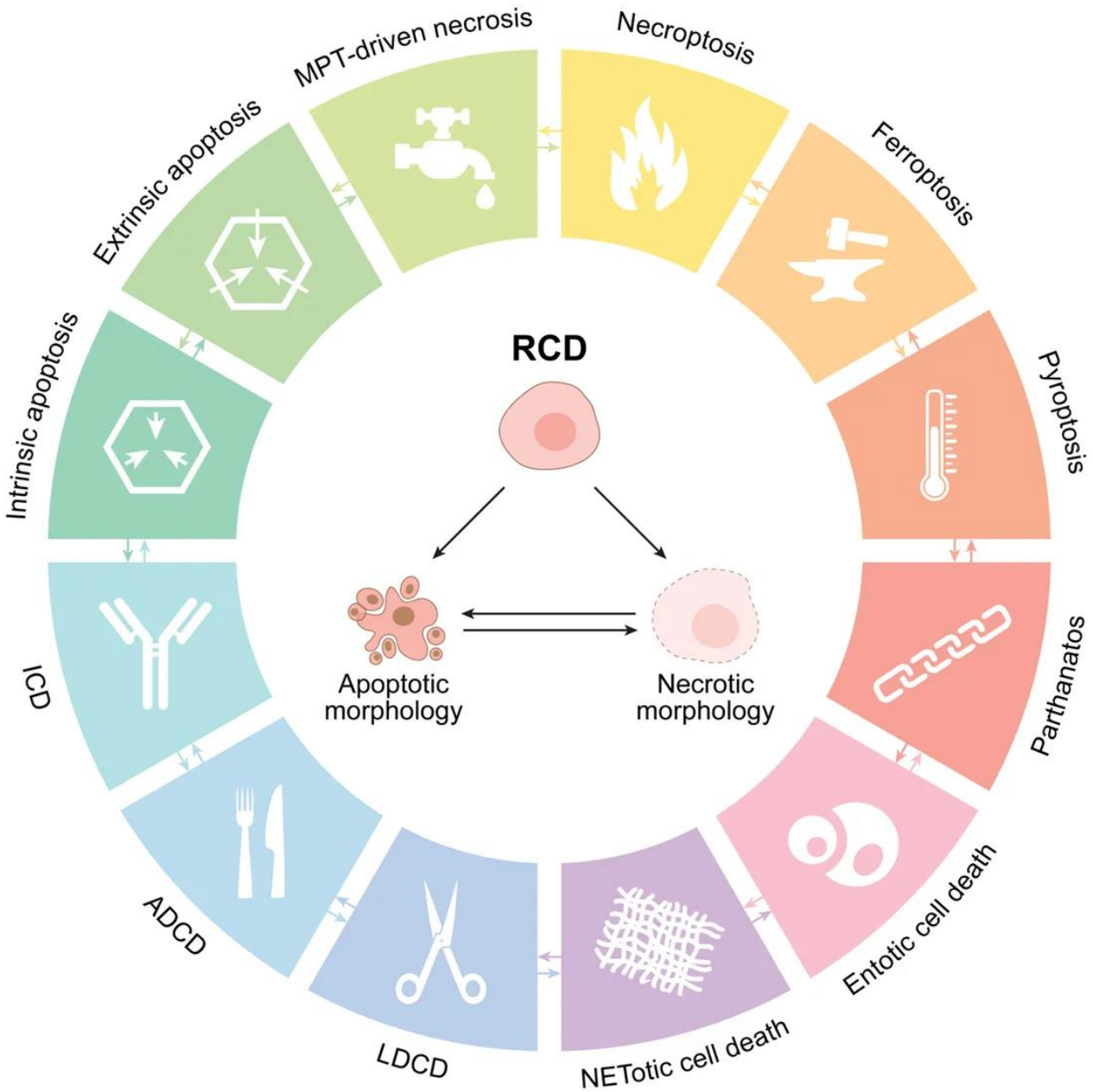


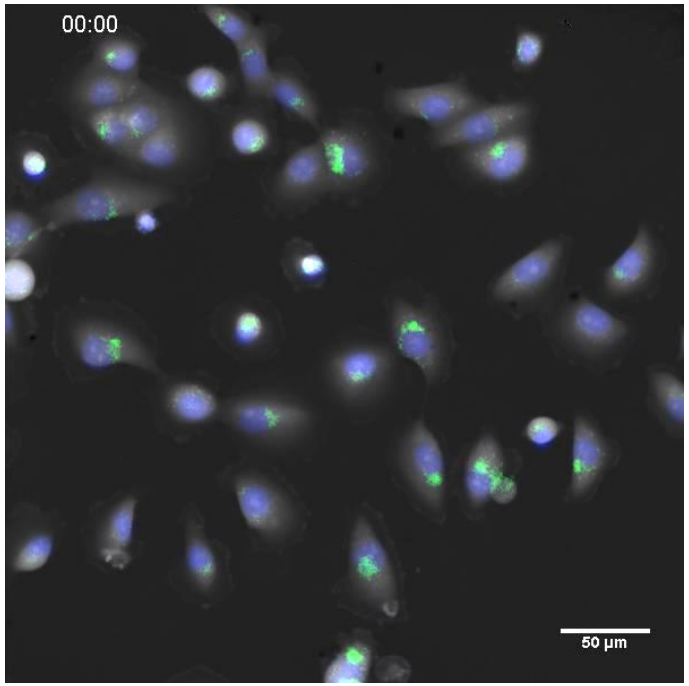




Galluzzi, L., Bravo-San Pedro, J., Vitale, I. *et al.* Essential *versus* accessory aspects of cell death: recommendations of the NCCD 2015. *Cell Death Differ* **22,** 58–73 (2015). https://doi.org/10.1038/cdd.2014.137

Regulated Cell Death





Galluzzi L, Vitale I, Aaronson SA, et al. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. Cell Death and Differentiation. 2018;25(3):486-541.

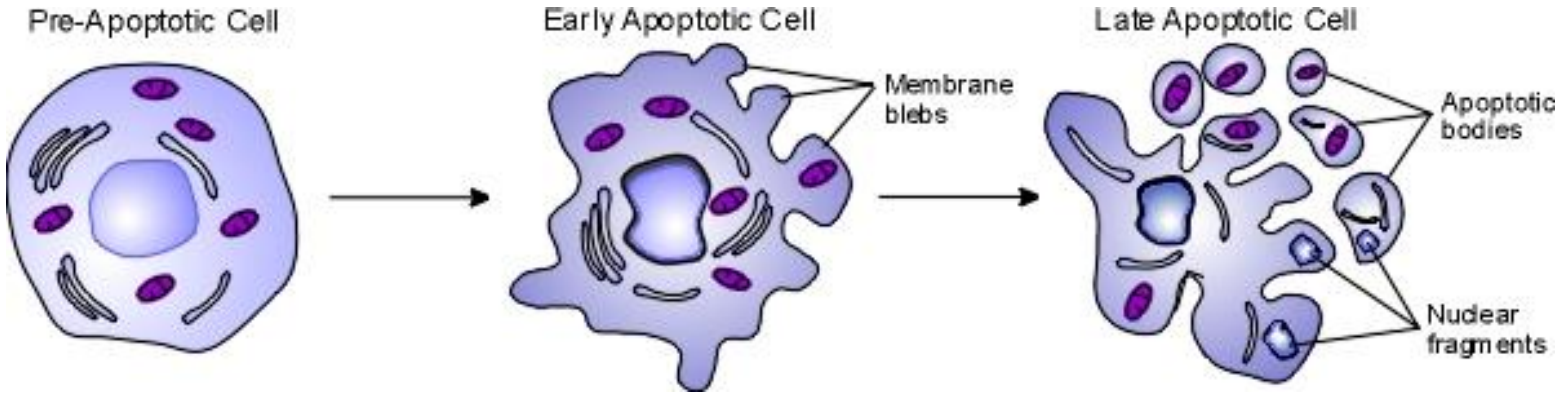
Apoptosis

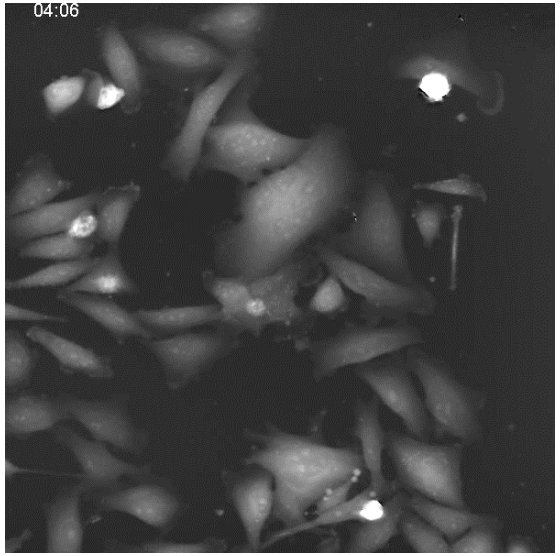
- Apoptosis is the first described form of programmed cell death, and it plays a critical role in tissue homeostasis.
- It contributes to cell turnover, the proper functioning of the immune system, and embryonic development.
- There are several **key characteristics of apoptosis**:

cellular, organelle, and DNA fragmentation and formation of apoptotic bodies

active, energy consuming process executed by a subset of cellular proteins

Even though, in general, this **process is immunological silent**, apoptosis has been shown to be involved in inflammatory pathologies as well.





Apoptosis

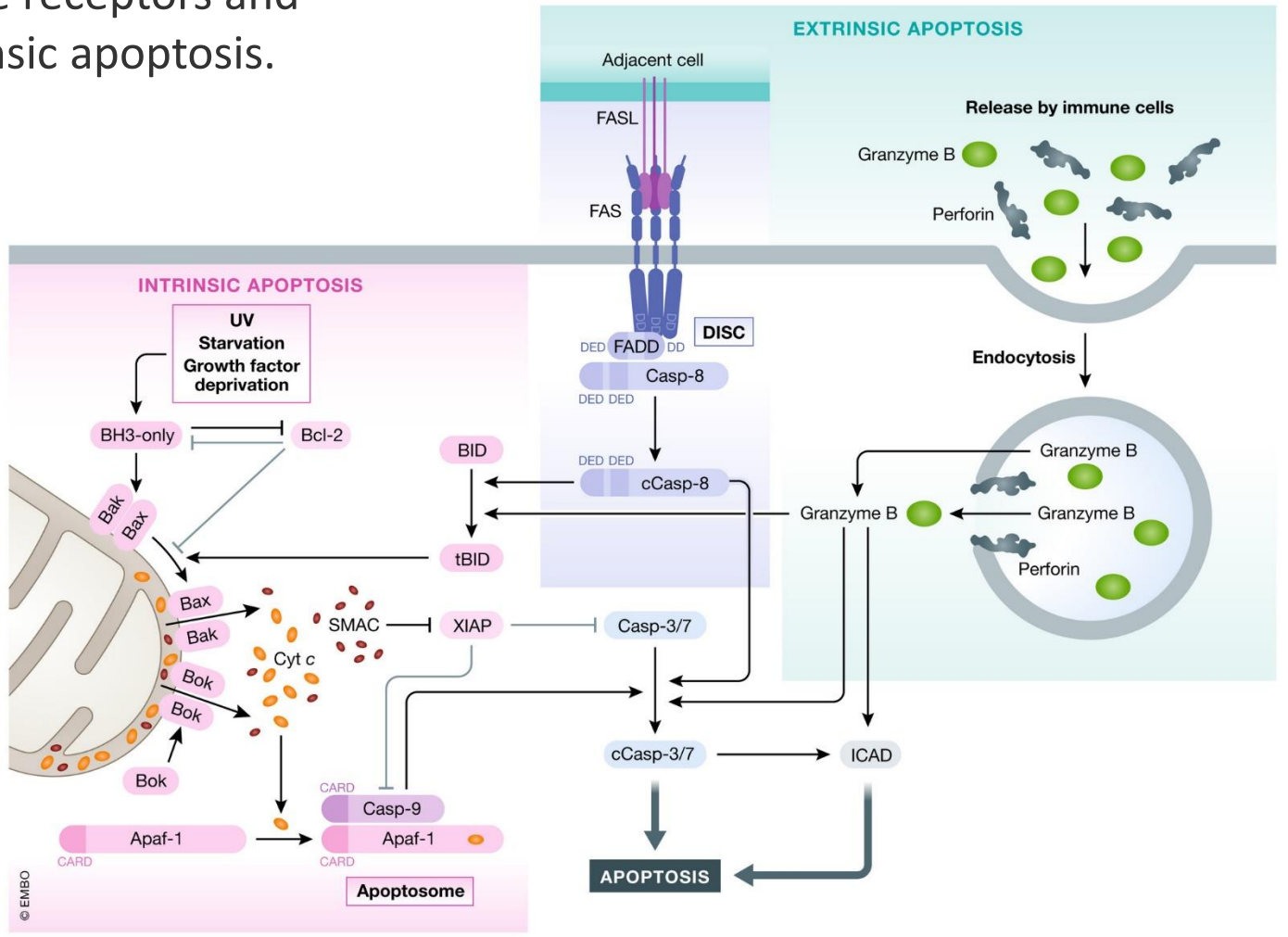
There are two (or 3) major pathways that mediate apoptosis: intrinsic and extrinsic pathways.

During **extrinsic apoptosis**, **TNF** (tumor necrosis factor) superfamily (TNFSF) can induce cell death by binding to their cell surface receptors and activating a deathly signaling cascade causing extrinsic apoptosis.

Intrinsic apoptosis is controlled by the equilibrium of the different **Bcl-2 (B-cell lymphoma 2) family members** which can be disrupted by various stimuli leading to cell death.

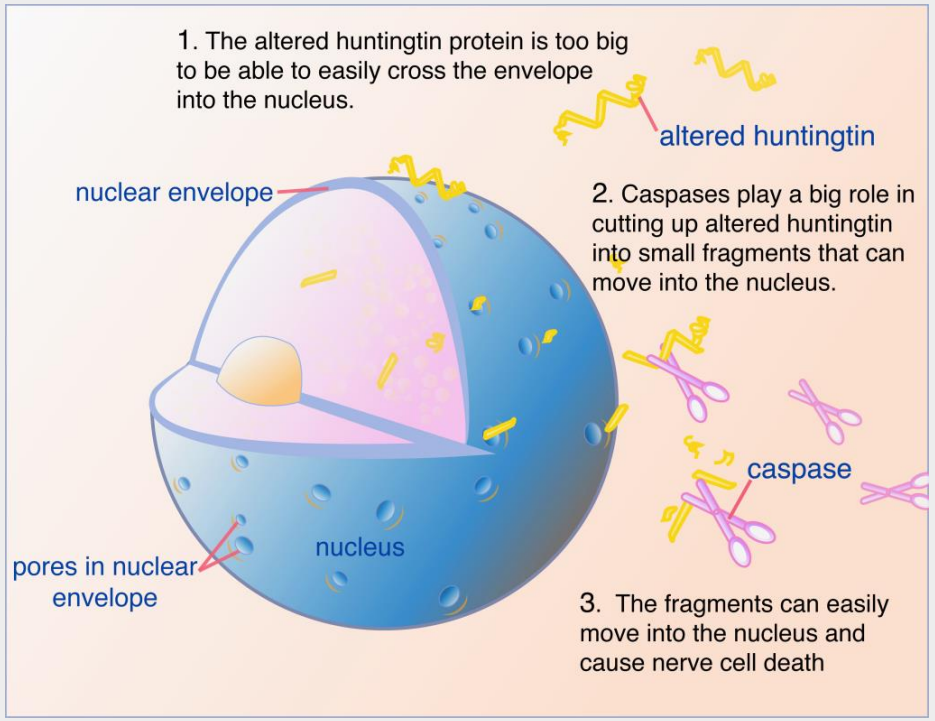
The third modality of apoptosis induction is **cell-based**. **Cytotoxic T cells** can engage cells that present non-self-antigens leading to cell death induction by **proteases called granzymes**.

All apoptotic pathways converge on the central proteases of this pathway: **caspases**, which are either playing a role in transmitting cell death stimulus **(initiator caspases)** or in the execution **(effector caspases).**



Caspases

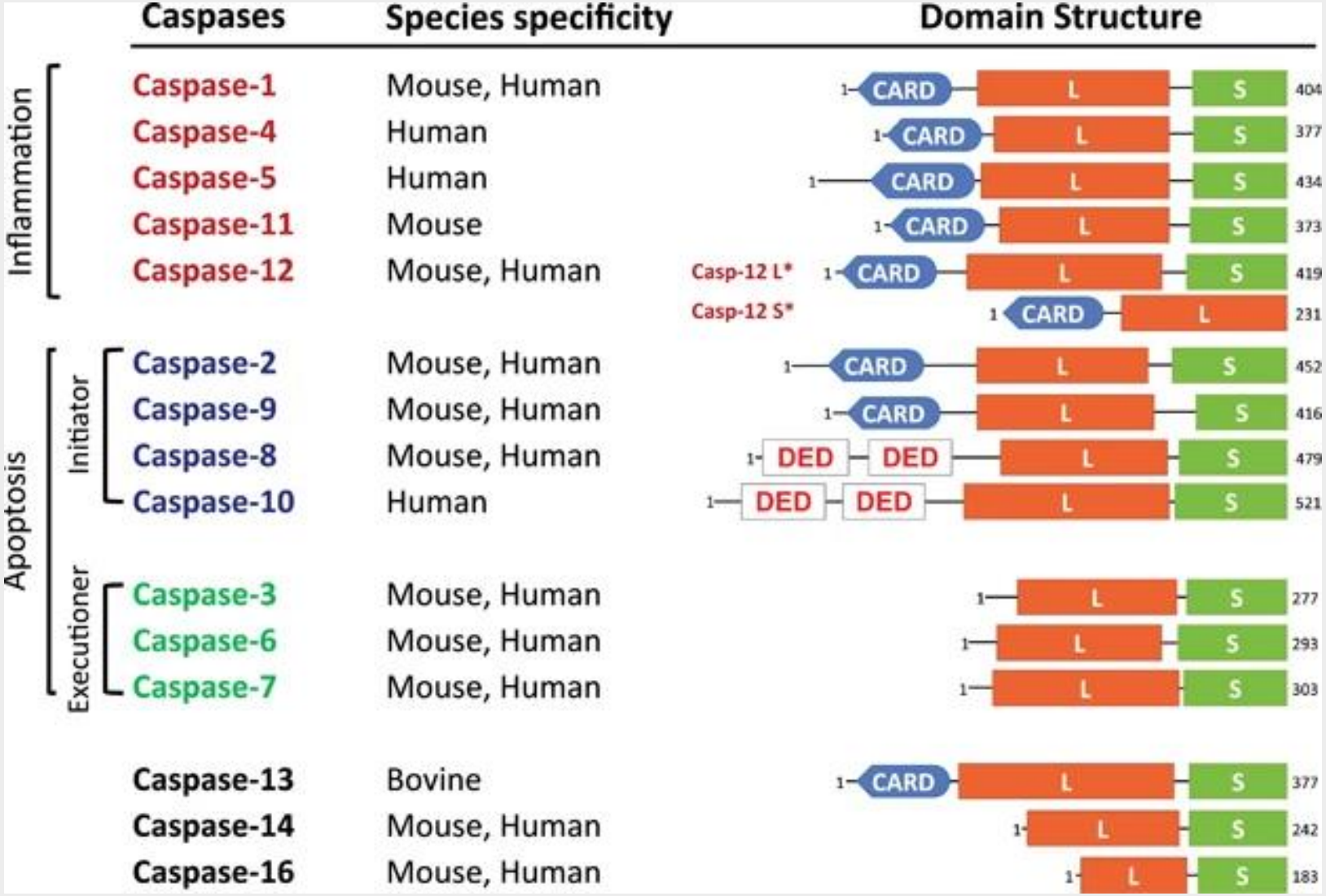
- Caspases (cysteine-aspartate proteases) are proteolytic enzymes generally known for their role in controlling cell death and inflammation.
- Their role in cell death was described more than 20 years ago with the discovery of ced-3 as a trigger for cell death during the development of Caenorhabditis elegans.
- Caspases are involved in cell death by apoptosis, necroptosis and pyroptosis. Caspase function is not just about cell death.
- Non-apoptotic roles of caspases include proliferation, tumor suppression, differentiation, nervous system development and axon navigation, aging and angiogenesis.



https://hopes.stanford.edu/caspase-6-inhibition/

Shalini S, Dorstyn L, Dawar S, Kumar S. Old, new and emerging functions of caspases. Cell Death & Differentiation. 2015;22(4):526-539.

Caspases



Domain structure and functional classification of placental mammalian caspases.

Caspase-1, -4, -5, -11 and -12 are inflammatory caspases.

Apoptotic caspase-2, -8, -9 and -10 are initiators

Caspase-3, -6 and -7 are key executioner caspases.

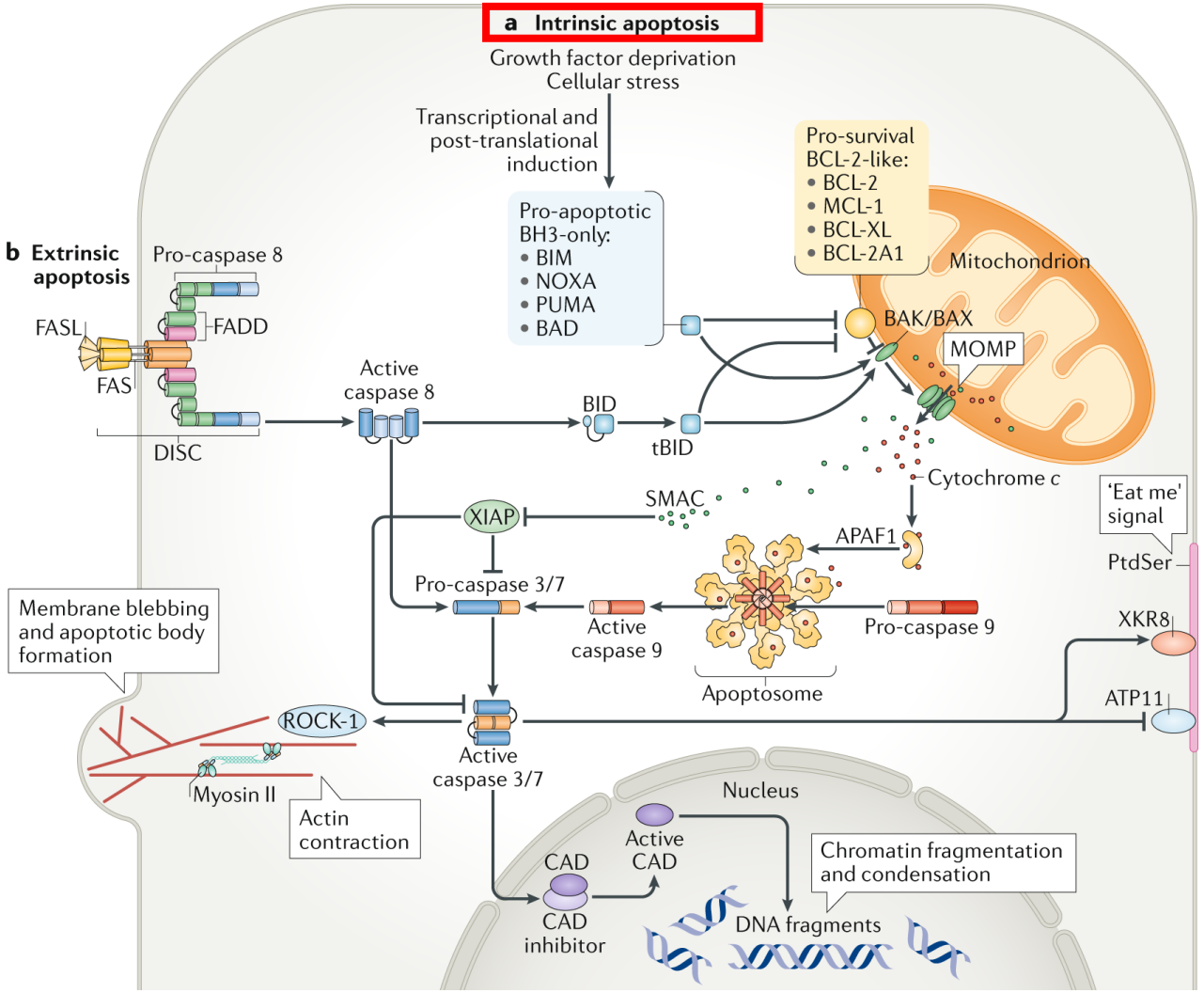
CARD, caspase recruitment domain;
DED, death effector domain;
L, large subunit;
S, small subunit;
S*, short form;
L*, long form

Shalini S, Dorstyn L, Dawar S, Kumar S. Old, new and emerging functions of caspases. Cell Death & Differentiation. 2015;22(4):526-539.

Intrinsic Apoptosis

- Involves increases in the expression or activity of pro-apoptotic BH3-only proteins that bind with high affinity to members of the pro-survival BCL-2 protein family, which in healthy cells keep the effectors of apoptosis, BAX, and BAK, in inactive states.
- When all pro-survival BCL-2 proteins within a cell are functionally neutralized by BH3-only proteins, BAK and BAX are unleashed in order to oligomerize and assemble into structures that cause a breach of the outer mitochondrial membrane, thereby inducing mitochondrial outer membrane permeabilization (MOMP).
- MOMP causes the release of mitochondrial proteins.
- Cytochrome *c* binds to APAF-1 promoting formation of the apoptosome.
- Pro-forms of the initiator caspase 9 are recruited into the apoptosome, resulting in caspase 9 activation promoting the downstream proteolytic activation of the effector caspases 3 and 7.

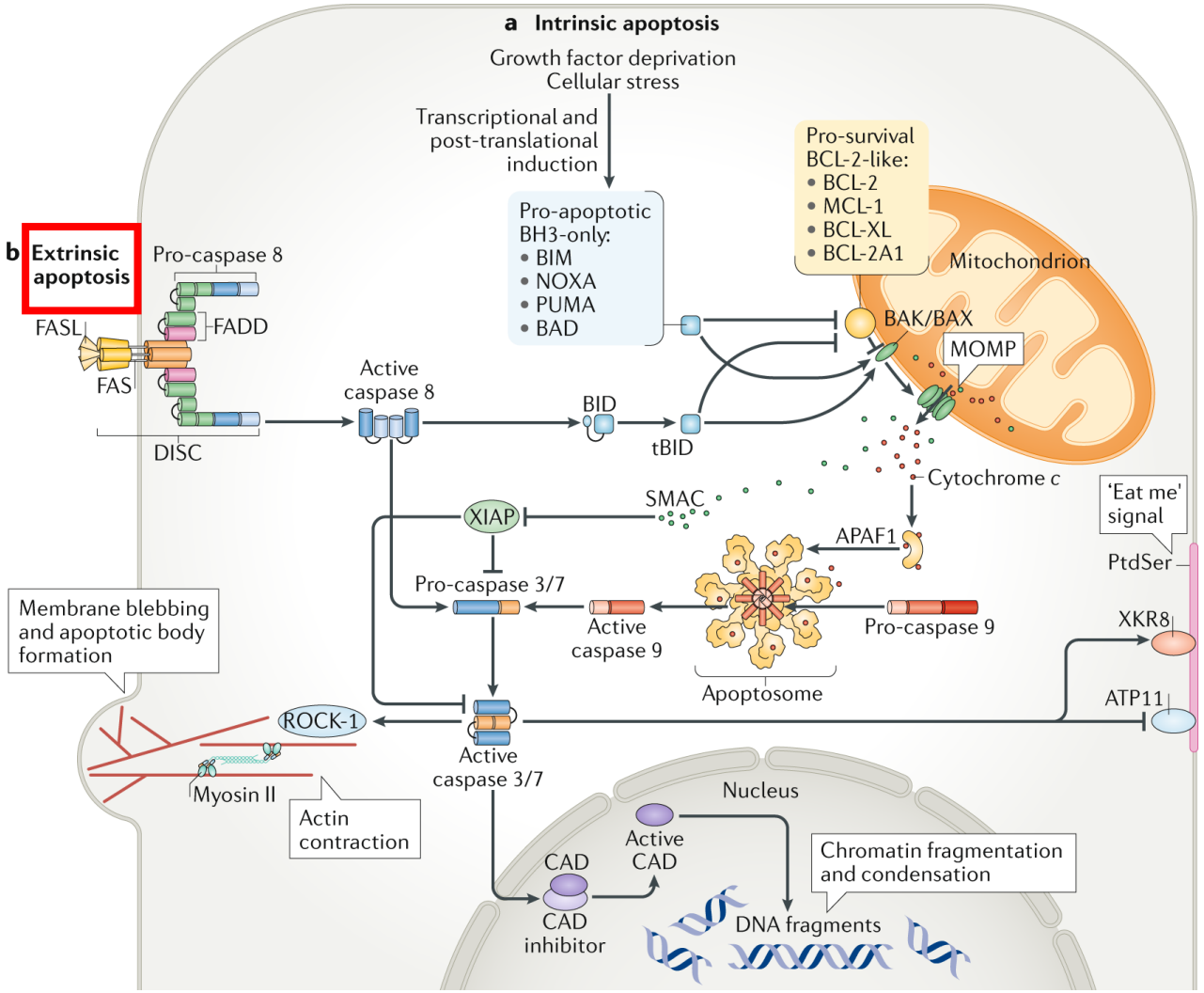
- Activation of caspase 3 and 7 cascade can be attenuated by XIAP, one of the inhibitor of apoptosis proteins (IAPs). MOMP also causes the release of SMAC (also known as DIABLO) and HTR2, which both can block XIAP and thereby prevent it from inhibiting caspases.



Bedoui, S., Herold, M.J. & Strasser, A. Emerging connectivity of programmed cell death pathways and its physiological implications. *Nat Rev Mol Cell Biol* **21,** 678–695 (2020). https://doi.org/10.1038/s41580-020-0270-8

Extrinsic Apoptosis

- Triggered by **TNF family ligand-receptor interactions**, most prominently by TNF family ligands: TNF, FasL, TRAIL, and TL1A.
- The receptor complexes either recruit FADD (Fas-associated protein with death domain) or TRADD (TNFRSF1A-associated via death domain) to the oligomerized complex.
- FasL binds to its transmembrane receptor Fas, which recruits FADD via death domain (DD) interactions.
- FADD contains a DD and also a death effector domain (DED), which allows the recruitment of caspase-8 forming the death inducing signaling complex—DISC.
- The proximity of multiple **caspase-8** molecules induces the **transactivation by proteolytic cleavage**.
- **Cleavage results** in the p18 and p10 fragments which **activate caspase-3 and caspase-7** (type I apoptosis).
- Insufficient activation of caspase-3 leads to type II apoptosis in which caspase-8 cleaves the BH3-only protein BID to generate its activated form: truncated BID (tBID).
- tBID stimulates intrinsic apoptotic pathway by directly binding to Bax/Bak inducing MOMP (type II apoptosis).
- The two pathways are cell line dependent, and their activation is differentially regulated by XIAP expression.



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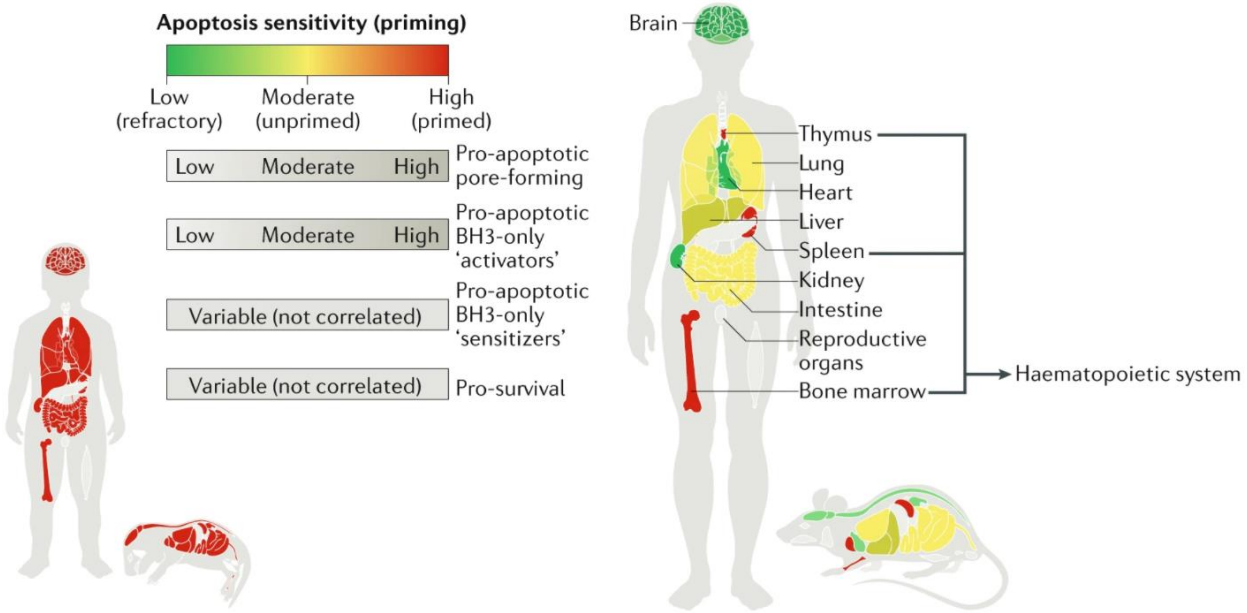
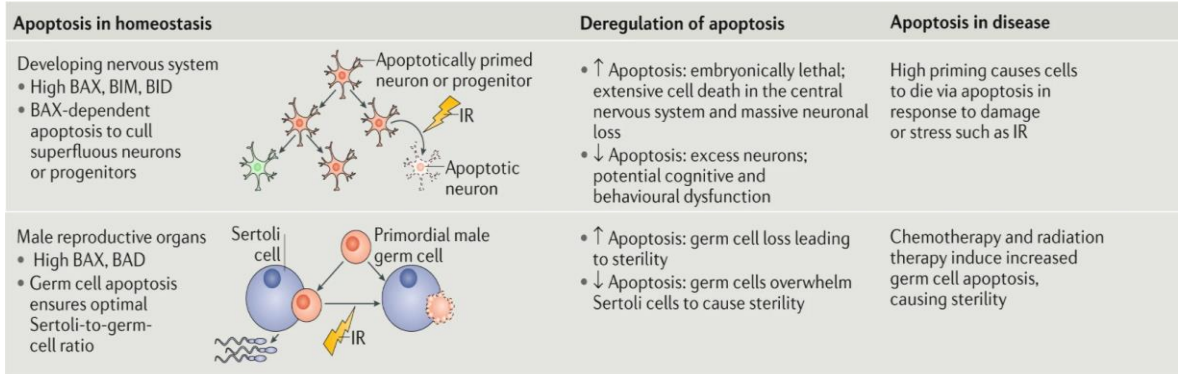
The EMBO Journal (2021) 40: e106700.

Apoptosis sensitivity during development

Apoptosis is differently and dynamically regulated across the mammalian lifespan.

Tissues that are highly proliferative (developing tissues, adult haematopoietic system) are typically primed for apoptosis (red).
High apoptotic priming in these tissues makes them highly sensitive to various insults .
Tissues that are largely postmitotic are apoptosis refractory (green), whereas tissues that are characterized as unprimed (yellow) contain highly heterogeneous cell types that differ in apoptosis sensitivity.
The level of priming within cells or tissues is dependent on the expression of BCL-2 family proteins BAX and/or BAK.

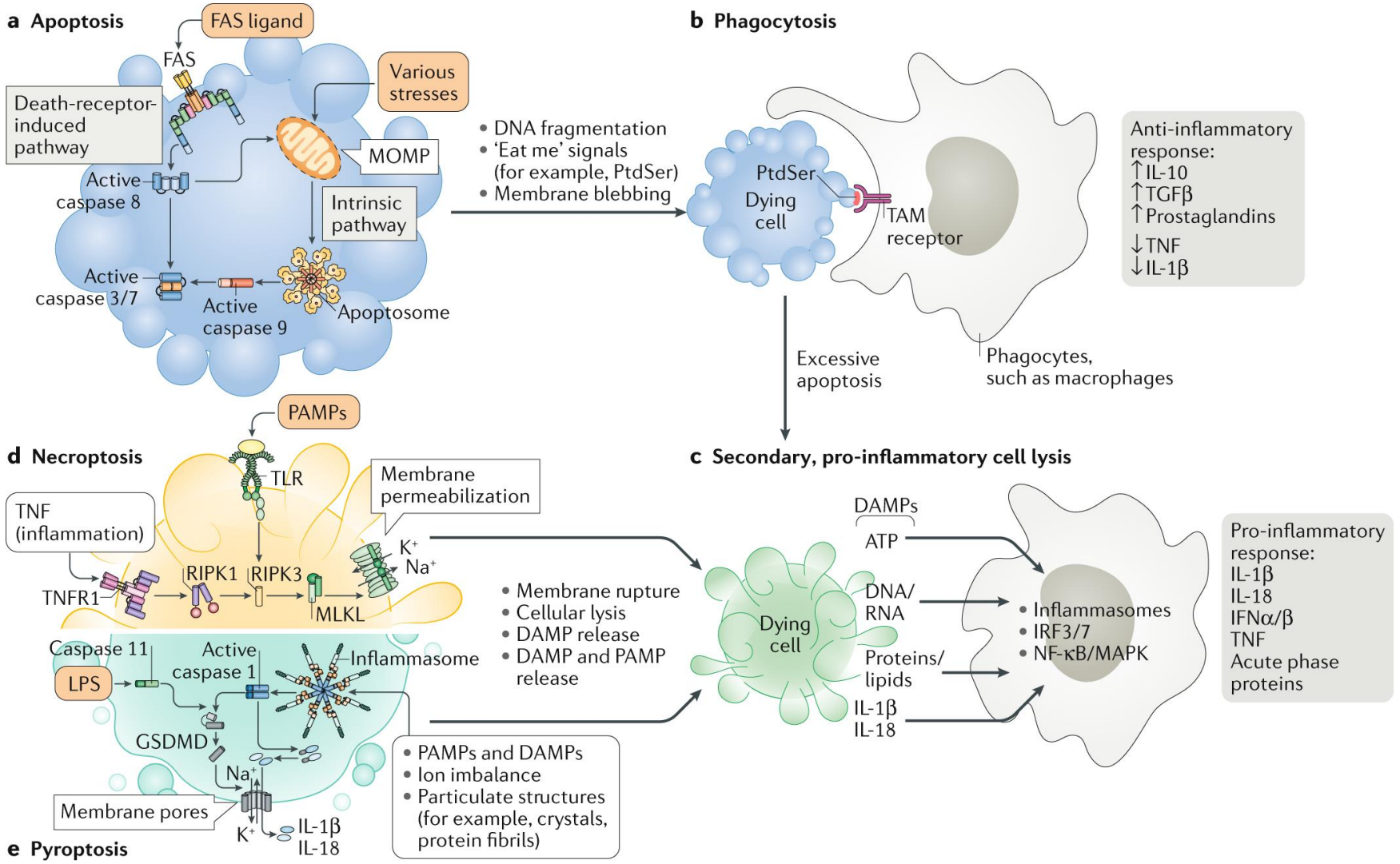




Singh R, Letai A, Sarosiek K. Regulation of apoptosis in health and disease: the balancing act of BCL-2 family proteins. Nature Reviews Molecular Cell Biology. 2019;20(3):175-193.

Regulated Necrosis vs Apoptosis - Lytic vs Non-lytic cell death

- **Non-lytic cell death, apoptosis (the integrity of plasma membrane is sustained).**
- **Plasma membrane rupture (PMR) is the final cataclysmic event in lytic cell death (regulated or accidental necrosis).**
- **PMR releases intracellular molecules known as damage-associated molecular patterns (DAMPs) that propagate the inflammatory response.**



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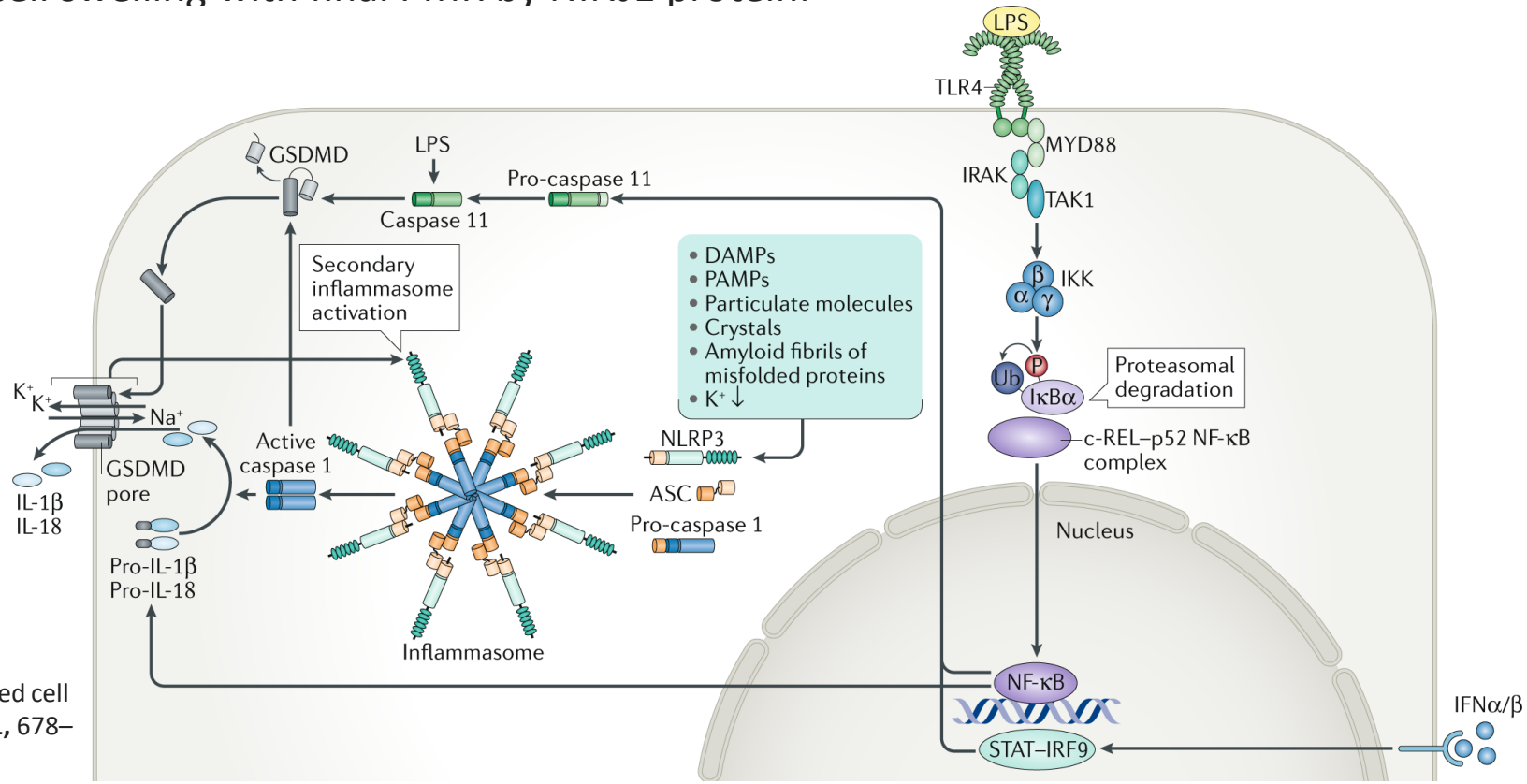
Pyroptosis

Pyroptosis is a potent inflammatory mode of lytic cell death triggered by diverse infectious and sterile insults. It is driven by the pore-forming fragment of gasdermin D (GSDMD) and releases two exemplar proteins: **pro-inflammatory cytokine IL-1β, and LDH**, a standard marker of PMR and lytic cell death.

Two sequential steps for pyroptosis:

- initial formation of a small plasma membrane pore that causes the release of IL-1β and non-selective ionic fluxes
- subsequent PMR attributable to oncotic cell swelling with final PMR by NINJ1 protein.

Caspase 1 and caspase 11 (caspase 4 and caspase 5 are the human homologues of mouse caspase 11) have important roles in pyroptosis, that is widely considered to be involved in defending the organism against pathogens



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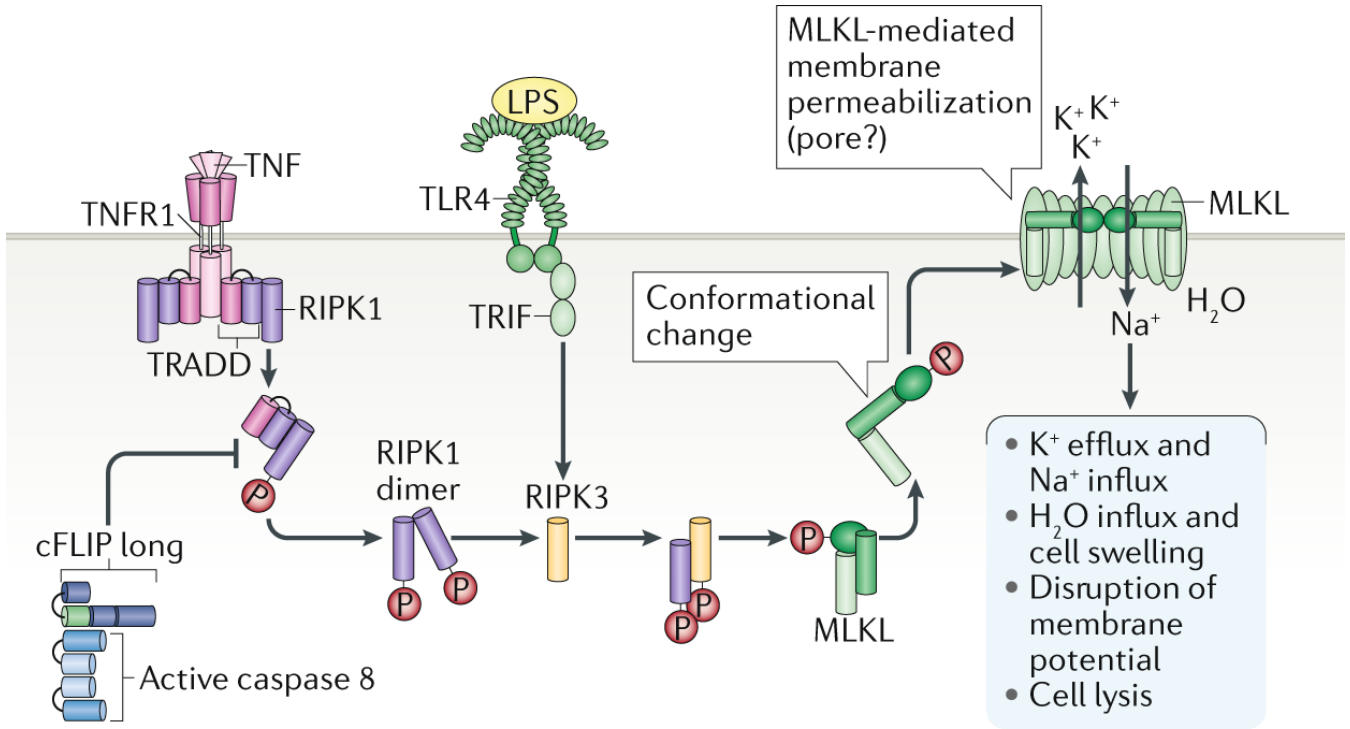
Necroptosis

Necroptosis is a pathway for genetically **programmed lytic cell death** that is thought to have a role in the killing of pathogen-infected cells and/or damaged cells during certain degenerative or inflammatory disorders.

Necroptosis can be induced by multiple innate immune signaling pathways.
These pathways all lead to the phosphorylation and activation of the necroptotic kinase RIPK3, which in the case of death-receptor-induced necroptosis also requires RIPK1 activity. RIPK3 activates MLKL through phosphorylation and allows trafficking of MLKL to the plasma membrane, where it induces membrane permeabilization.



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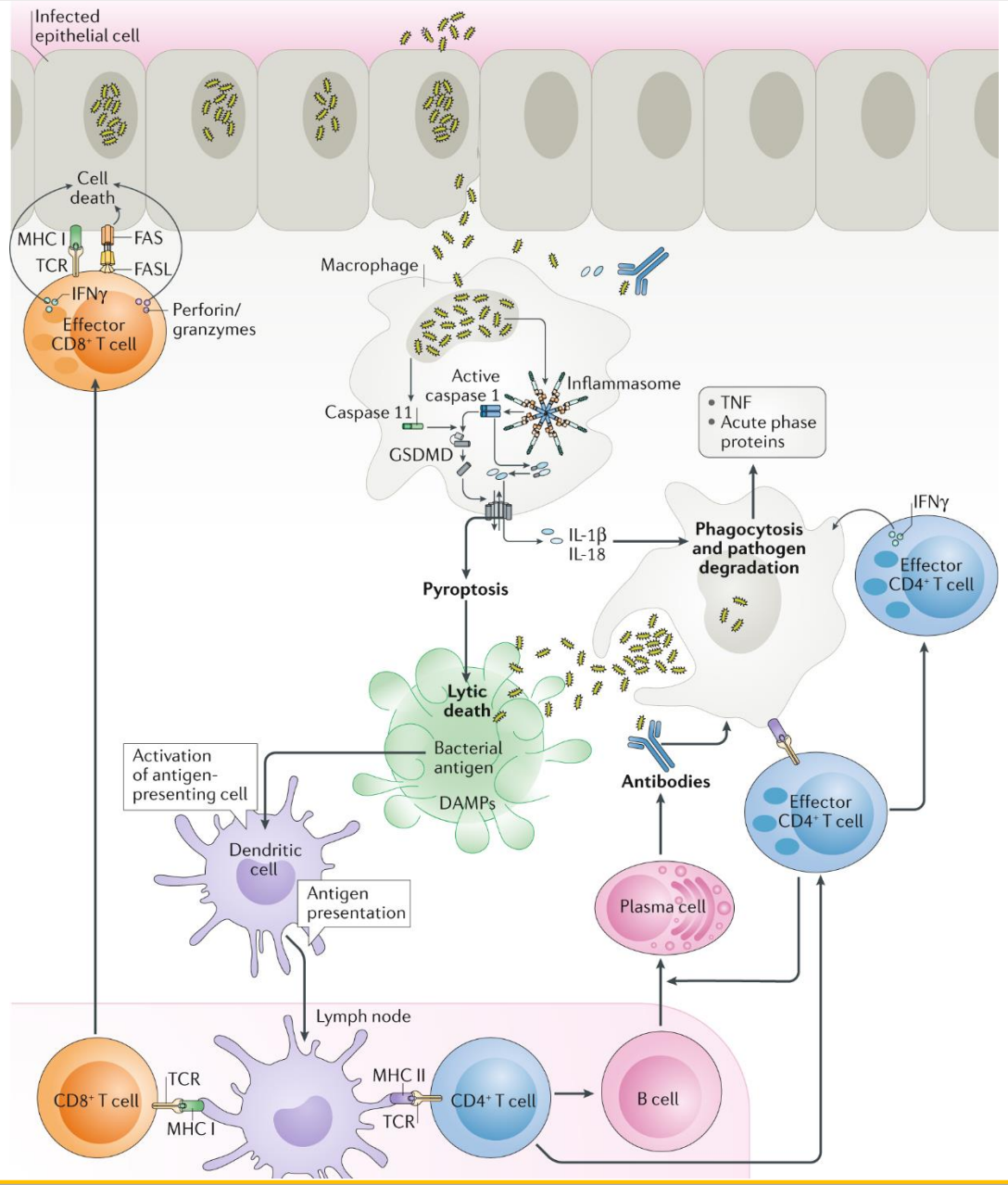
The role of cell death in host responses to infection.

Intracellular pathogens released from dying cells can be engulfed by nearby macrophages and neutrophils whose subsequent activation results in the secretion of cytokines and chemokines that support the immune response (for example, via recruitment of cells involved in adaptive immunity).

DAMPs, PAMPs and antigens released from dying cells are also sensed and engulfed by dendritic cells, and this allows these potent antigen-presenting cells to prime naive T lymphocytes, which enables them to find and destroy additional infected cells, as well as aiding in the differentiation of B cells into plasma cells that produce pathogen-specific antibodies



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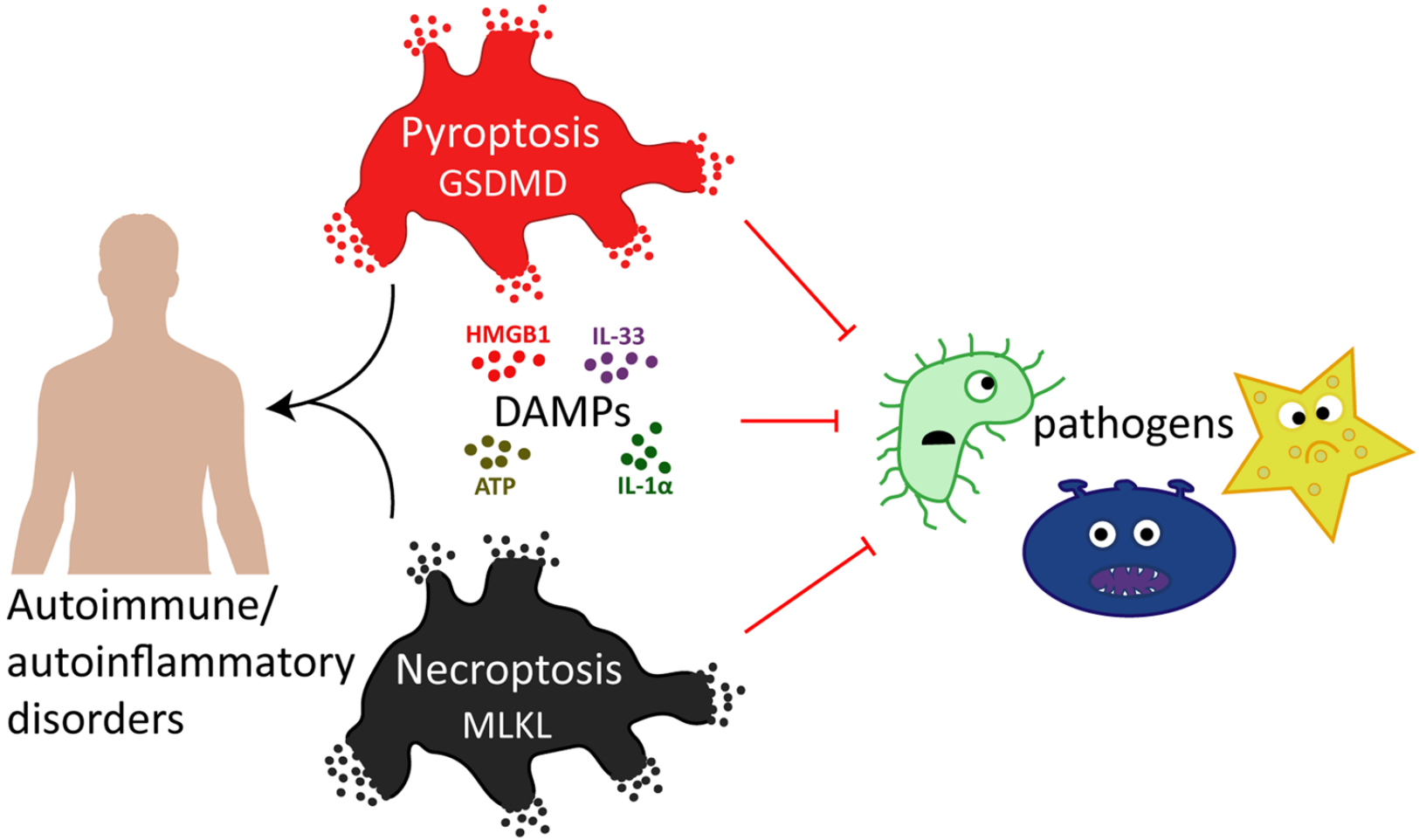
The role of cell death in host responses to infection.

Pathogen	Disease	Characteristics	Host cell death	Experimental condition	Pathogen strategy Recognition by host	Cell death outcome	Ref
Chlamydiae spp.	Chlamydia STD	OI, G-, cocci, non-motile	↓ Apoptosis	Infection of HeLa and U937 cells. Chlamydiae protected cells from apoptosis by different apoptotic stimuli	Inhibition at the level of cytochrome *c* release	Pathogen survival	13
R. rickettsii	Rocky Mountain spotted fever	OI, G-, α-proteobacteria, cocci and bacilli, non-motile	↓ Apoptosis	Infection of endothelial cells. Cells survived unless NF-kB was inhibited	↑ NF-κB	Pathogen survival	12
B. pertussis	Pertussis or whooping cough	FI, G-, β-proteobacteria, coccobacilli, motile	Apoptosis?	Infection of J774A.1 and alveolar macrophages. DNA fragmentation and nuclear condensation observed	?	Pathogen survival	14
B. pseudomallei	Melioidosis	FI, G-, β-proteobacteria, bacilli, motile	Pyroptosis	Infection of THP-1 cells. Oncosis phenotype observed Caspase1$^{-/-}$ PEMs are resistant to cytotoxicity at low MOIs	?	?	51
L. pneumophila	Legionnaires' disease	FI, G-, g-proteobacteria, bacilli, motile	Pyroptosis	Ipaf$^{-/-}$ and caspase-1$^{-/-}$ mice are susceptible to infection[a]	Flagellin recognition by the IPAF inflammasome. Role of Naip5 in restriction of bacterial growth.	Pathogen clearance[a]	48,49,84 108
			Autophagy			Pathogen survival	
P. aeruginosa	Infection of the respiratory tract (Cystic Fibrosis patients)	FI, G-, γ-proteobacteria, bacilli, motile	Apoptosis	Mice deficient in CD95 signaling were more susceptible to P. aeruginosa-induced sepsis. In WT mice, infection led to lung epithelial cell apoptosis	?	Pathogen clearance	26
			Pyroptosis	In response to strains not expressing ExoU Ipaf$^{-/-}$ mice are susceptible to infection[a]	Recognition by the Ipaf inflammasome, not completely dependent on flagellin	Pathogen clearance[a]	46,81,86
			Caspase-1-independent death	In response to strains expressing ExoU	ExoU induces cell death and caspase-1-dependent inflammation	Pathogen survival	46
S. typhimurium	Samonellosis gastroenteritis	FI, G-, γ-proteobacteria, bacilli, motile	Pyroptosis	Pyroptosis, rather than apoptosis, is the main death mode since caspase-1$^{-/-}$ macrophages are resistant to cell death. Caspase-1$^{-/-}$ mice are susceptible to infection[a]	Flagellin recognition by the IPAF inflammasome	Pathogen clearance[a]	39–44, 76–79
			Apoptosis	Infection of HeLa cells. Apoptosis detected by Annexin V staining	AvrA ↓ NF-κB	?	21
Y. pestis Y. pseudotuberculosis	Bubonic plague	FI, G-, γ-proteobacteria, bacilli, motility is temperature-dependent	Apoptosis	Infection of macrophages inhibit NF-kB and MAPK signaling in a YopJ-dependent manner	YopJ NF-kB and MAPK signaling	Pathogen survival	22,23
			Pyroptosis	TLR stimulation switches the death mode from apoptosis to pyroptosis	YopJ-independent	Pathogen clearance	50
H. pylori	Gastric ulcers, gastric cancer	E, G-, ε-proteobacteria, helical, motile	Gastric EC apoptosis	Infection of Fas-deficient mice resulted in a more severe disease. In WT mice, infection led to gastric epithelial cell apoptosis	?	Milder disease	27
S. pneumoniae	Pneumonia, otitis media, meningitits	E, G+, capsulated, cocci, non-motile	Apoptosis	Macrophages expressing Mcl-1 as a transgene exhibit a delay in apoptosis and bacterial killing	Induction of a BH3-only Mcl-1 splice variant	Pathogen clearance	25
L. monocytogenes	Listeriosis gastroenteritis	FI, G+, bacilli, motile at lower temperatures	Pyroptosis	Bacterial killing was delayed in caspase-1-deficient mice. Caspase-1$^{-/-}$ mice are susceptible to infection[a]	Listeria is detected by the Nalp3 inflammasome	Pathogen clearance[a]	45,76
			Autophagy			Pathogen clearance	104
B. anthracis	Anthrax	FI, G+, capsulated, bacilli, form endospores	Apoptosis	Treatment of LPS-activated BMDM or J774A.1 with LF induces apoptosis	LF processes MKK6 and p38 signaling	?	24
			Pyroptosis		LT recognition by the Nalp1b inflammasome	?	80
Rhinovirus	Common cold	Picornaviridae family single-stranded positive-sense RNA genome	Autophagy			Pathogen survival	

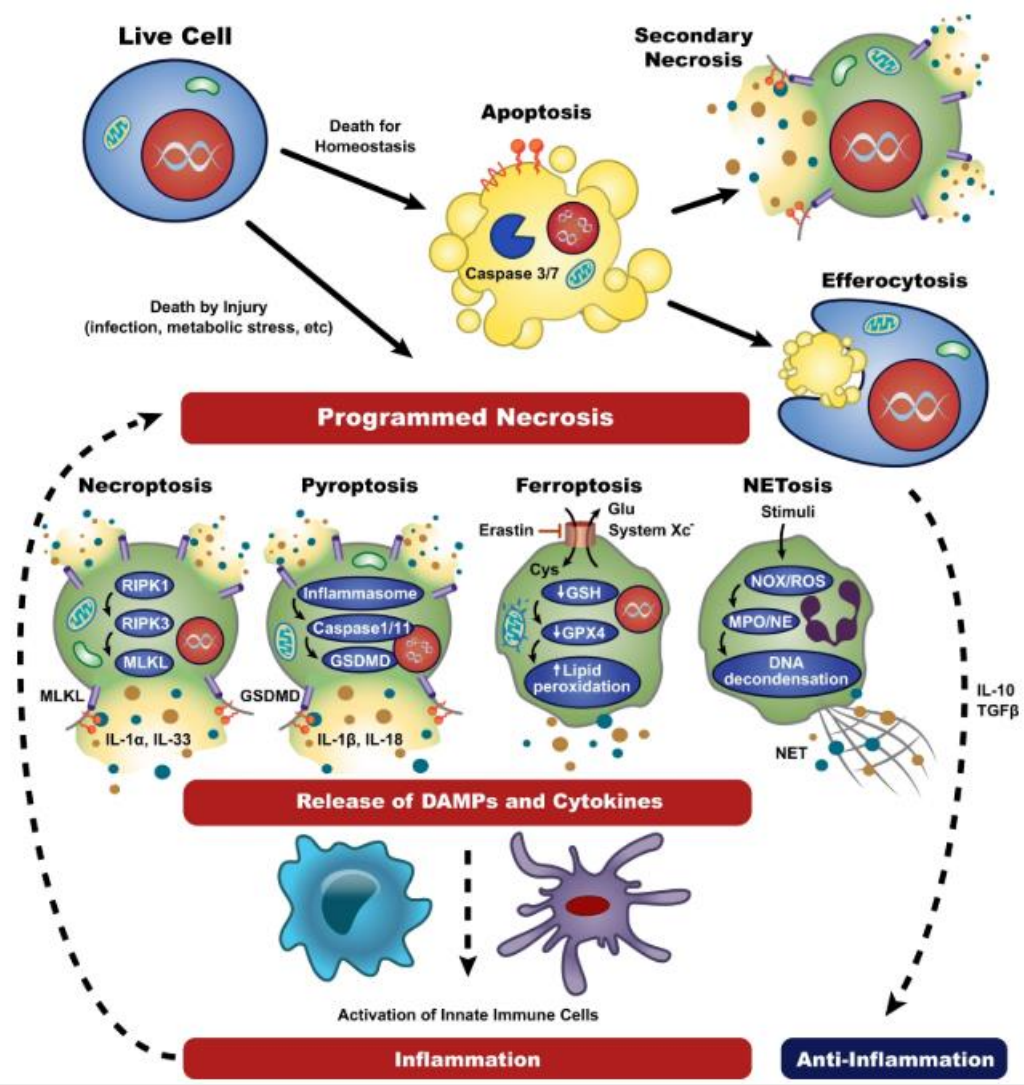
OI, obligate intracellular; G-/+, gram negative/positive; FI, facultative intracellular; PEM, peritoneal exudates macrophage; EC, epithelial cell; BMDM, bone marrow-derived macrophage; BCG, Bacillus Calmette-Guerin; MTB, mycobacterium tuberculosis; TLR, toll-like receptor; RNA, ribonucleic acid; LPS, lipopolysaccharide. [a]However it is difficult to conclude that cell death in this case is required for pathogen clearance since caspase-1 is also needed for cytokine production. In certain infections, administration of recombinant IL-18 reversed the phenotype, enhanced pathogen clearance and rendered caspase-1-deficient mice more resistant to the infection. The question is then whether pyroptosis is required for cytokine release?

The role of cell death in host responses to infection.



Although necrosis and pyroptosis are important barriers against microbial pathogens, disruption of their regulation causes numerous autoimmune and inflammatory conditions leading to various diseases.

Regulated Cell Death



Necroptosis, pyroptosis, ferroptosis, and NETosis are types of programmed necrosis where lytic cell death is mediated by an activatable genetic program.

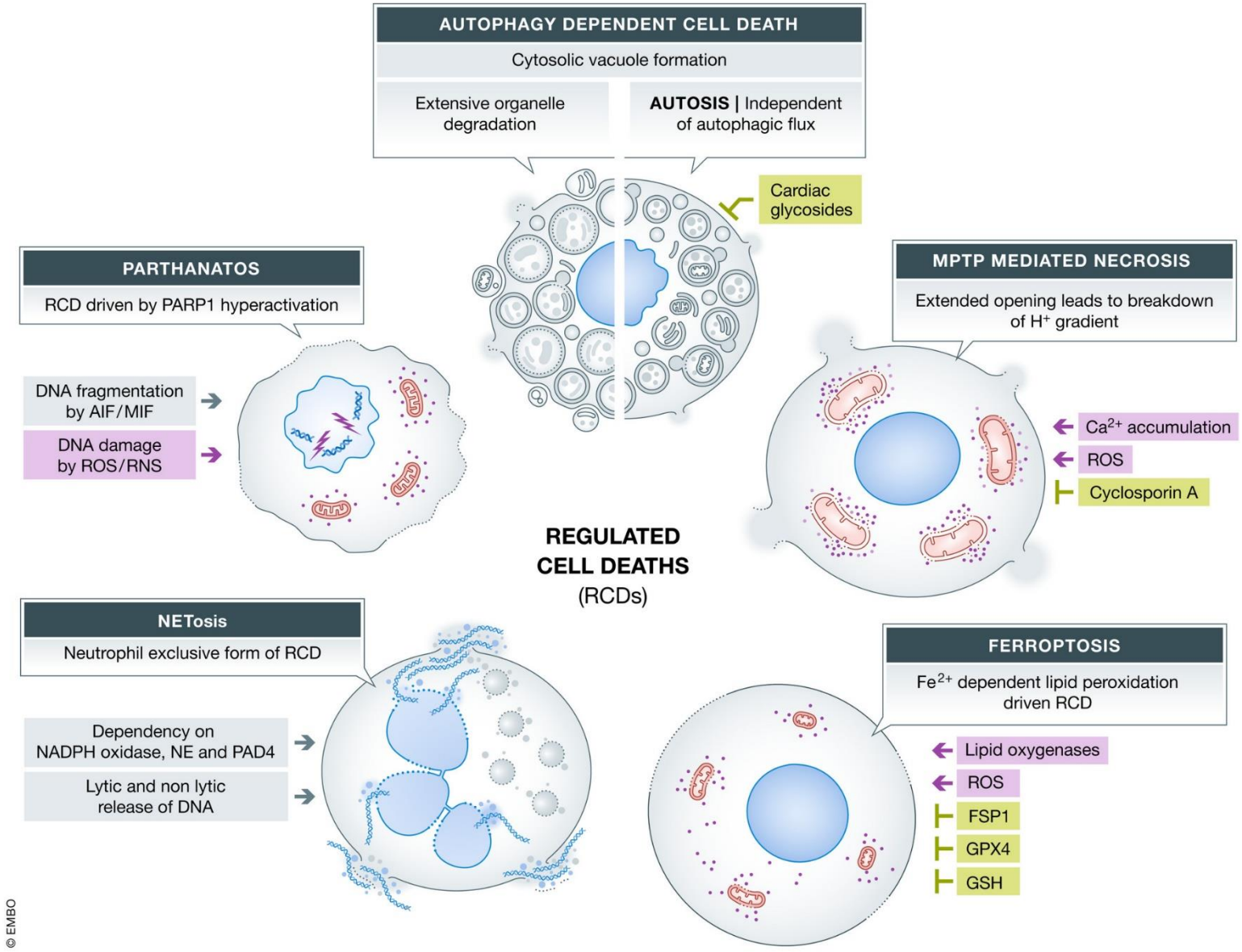
Accidental and programmed necrosis share morphological features: Swelling of the cell and permeabilization of the cell membrane associated with the release of potentially dangerous contents of the dying cell (DAMPs) - induction of inflammation.

Inflammation associated with necrosis is caused by inflammatory cytokines and DAMPs (cell molecules released into the environment with loss of membrane integrity) from cells subject to necrotic cell death.

Defects in programmed necrosis and efferocytosis are associated with the development of inflammation and autoimmune diseases.

Ahmed A, Tait SWG. Targeting immunogenic cell death in cancer. Molecular Oncology. 2020;14(12):2994-3006.

Other forms of regulated cell death

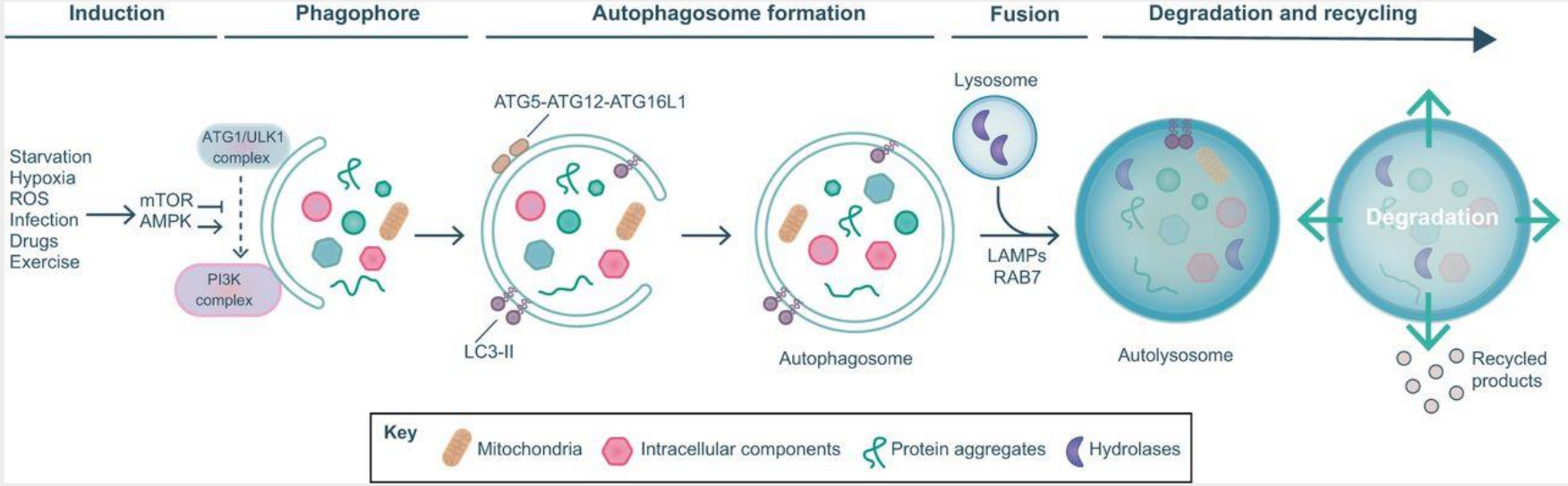


Autophagy

The process of recycling cellular material, adaptation and maintenance of homeostasis of the internal environment of the cell.

Under physiological conditions, it contributes to genome stability by regulating damaged proteins and organelles.
An important process in the differentiation of cells of the immune system and other tissues.
An important role in the adaptation of the newborn to oral food.
Disruption of this process is associated with many human pathologies: Neurodegenerative diseases (Alzheimer, Parkinson,…) - insufficient degradation of proteins by autophagy (eg. beta amyloid in the plaques of NS cells) is the cause of these diseases.

Cancer diseases:
An important mechanism of resistance (including MDR) and tumor cell metastasis (testing of inhibitors and inducers of autophagy in clinical trials).



https://www.youtube.com/watch?v=Hqs1WzTwBEU&ab_channel=WallStreetJournal

Autophagy-dependent cell death (ADCD)

Autophagy-dependent cell death (ADCD) relies exclusively on the autophagic pathway components, which is an important distinction given that autophagy can also coincide with other forms of cell death.

ADCD can proceed by two different pathways:

- Cell death induced by extensive degradation of organelles which is dependent on the autophagic flux.
- Autosis, does not depend on the fusion of autophagosomes and lysosomes.

In both cases, vacuole formation in the cytoplasm can be detected. Treatment of cancer cells with resveratrol triggers the autophagic flux-dependent ADCD, without activating apoptosis or necroptosis.

The massive degradation by lysosome fusion leads to a breakdown of the cytoplasmic organization with loss of organelles such as endoplasmic reticulum or mitochondria.

Autosis can be induced by starvation or hypoxia, which leads to cell swelling and eventually rupture of the plasma membrane. Autotic cells were also identified in samples of patients with severe anorexia nervosa.

ADCD has been shown in association with physiological process as well as various pathologies including reperfusion injuries and various forms of cancer.

Other forms of regulated cell death

Mitochondrial permeability transition pore (MPTP)-mediated necrosis

MPTP can mediate necrosis based on changes in the intracellular microenvironment. Two factors that can induce opening of the pores are oxidative stress and cytosolic/ mitochondrial Ca^{2+} accumulation. The pores allow the flux of molecules leading to breakdown of the H^+ gradient and subsequently halting the ATP synthesis.

Parthanatos

Parthanatos is a form of regulated cell death dependent on poly(ADP) ribose polymerase 1 (PARP1). PARP1 is part of the DNA repair machinery which binds DNA. Severe DNA damage by prolonged generation of reactive oxygen species or reactive nitrogen species (RNS) induces recruitment and activation of PARP1 to the leading to the formation of PAR polymers and depletion of NAD^+ and ATP, which might be fatal for the cell.

NETosis

Neutrophils are part of the innate immune system, and their main task is to neutralize pathogens by phagocytosis or degranulation. Another form of host defense is the formation of NET (neutrophil extracellular traps). NETosis describes the process of neutrophil DNA release into the extracellular space. The release of neutrophil DNA containing different proteins with anti-pathogenic activity can be associated with cell death but can be independent of it as well.

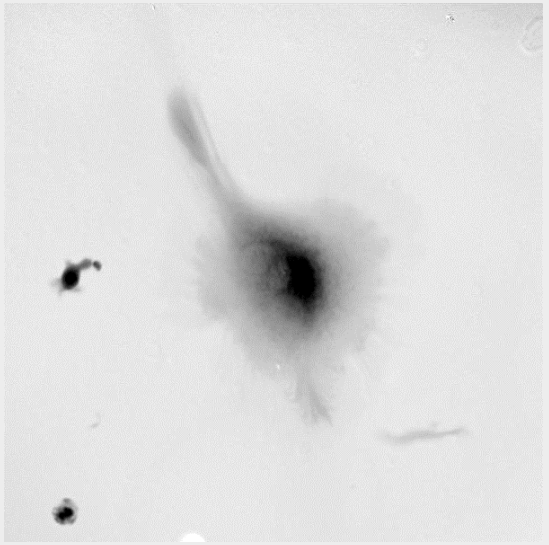
Ferroptosis

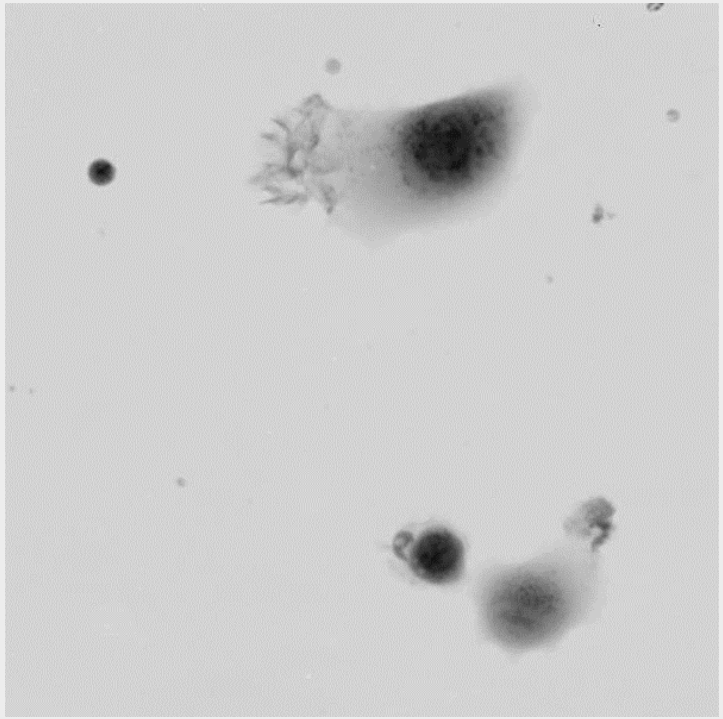
Ferroptosis is a form of regulated cell death that depends on iron (Fe^{2+})-mediated lipid peroxidation induced by ROS.

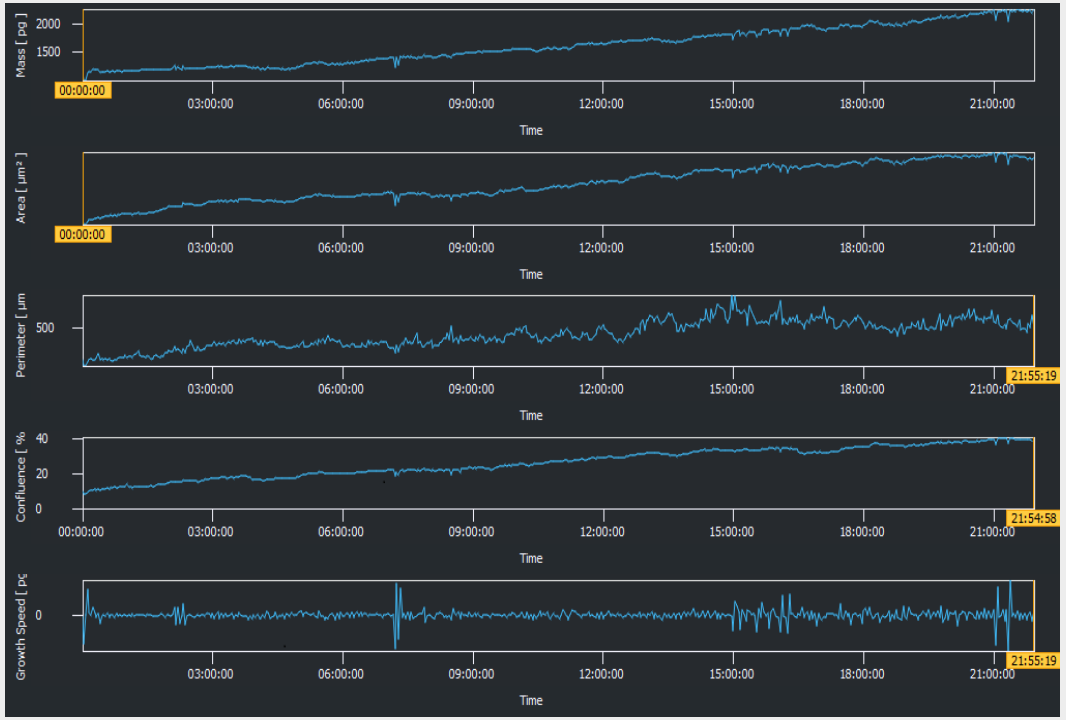
Entosis and Cannibalism

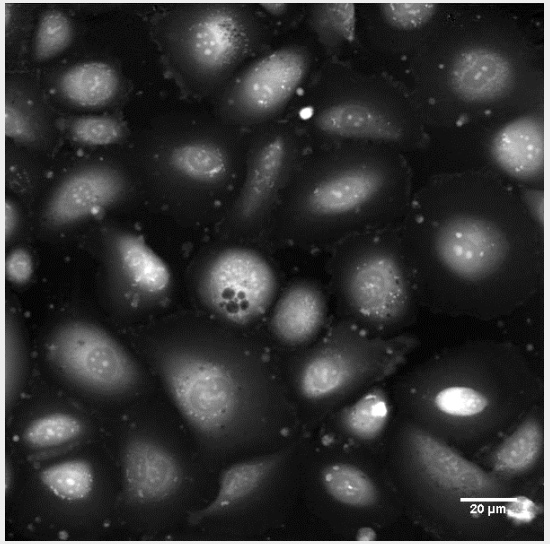
Digestion of engulfed homotypic or heterotypic cell.

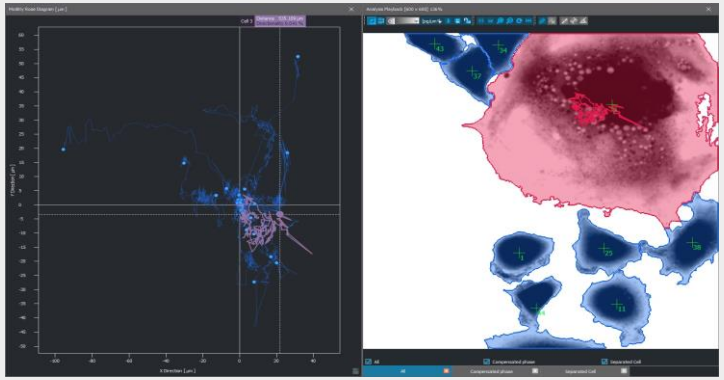
Holographic Microscopy and Quantitative Phase Imaging (QPI)





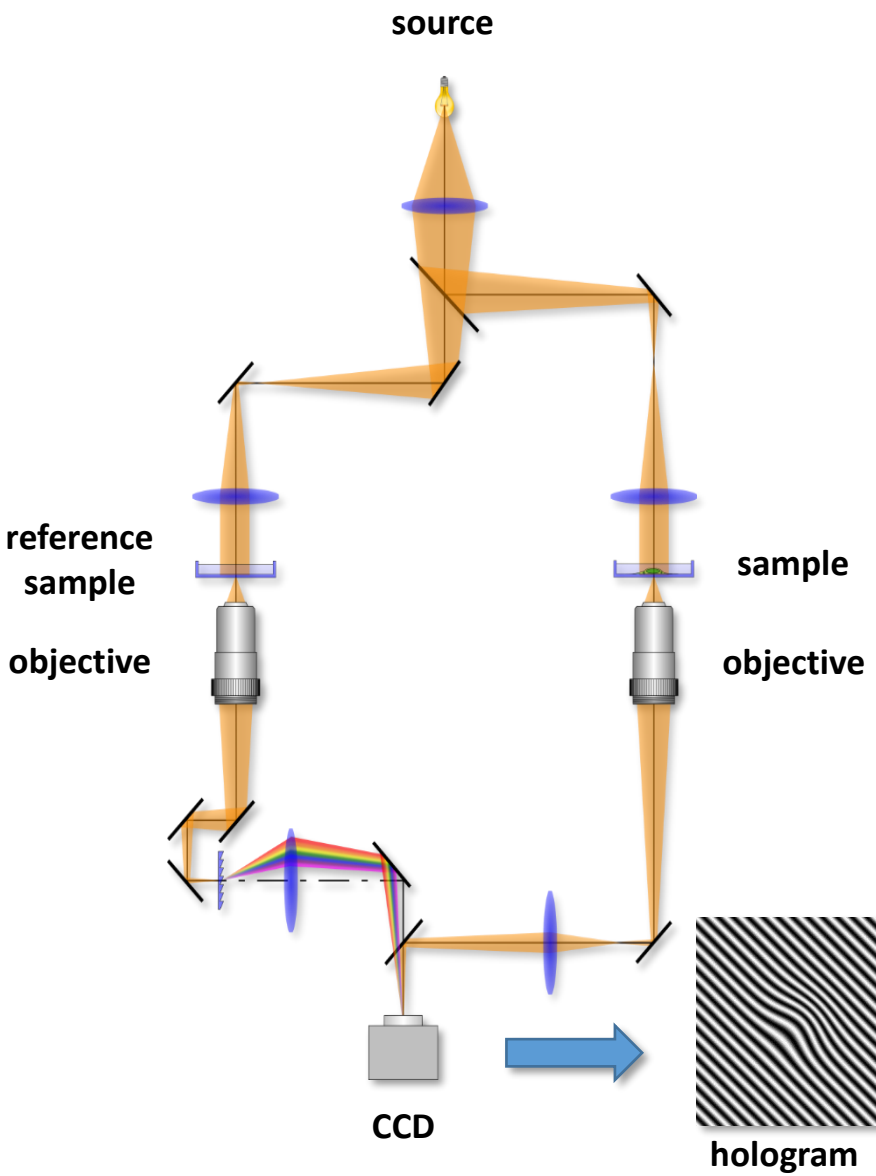




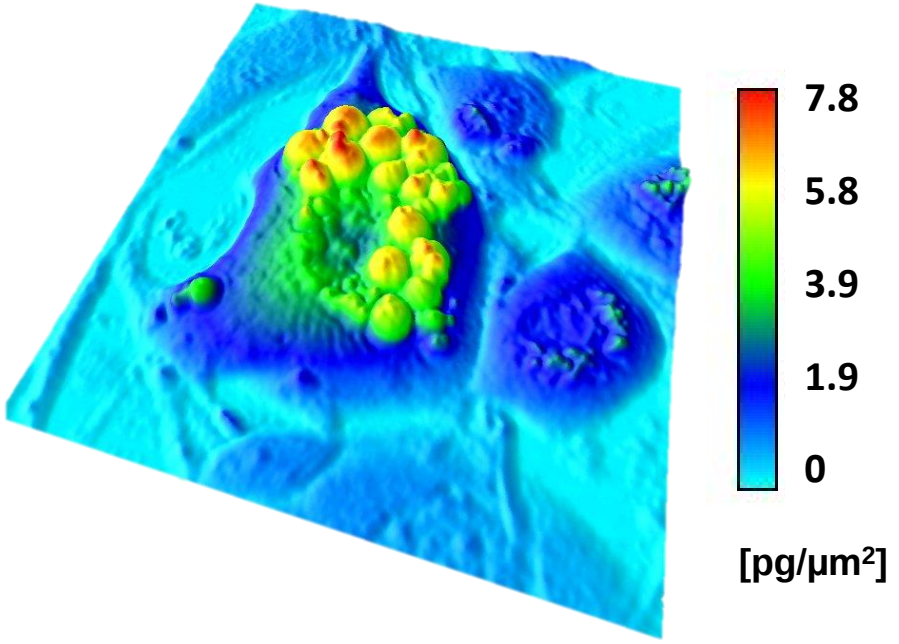


- **Long-term monitoring of the cell population**
- **Analysis of morphological and dynamic parameters in time**

Holographic Microscopy and Quantitative Phase Imaging (QPI)



- Beams from both arms are focused onto the CCD camera
- The beams interfere and form a hologram
- The hologram is recorded and further processed on PC to produce quantitative phase image



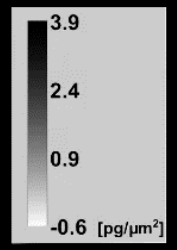
QPI

Time-lapse imaging of untreated PC-3 cells

PC-3 metastatic prostate cancer cell line

Time-lapse **quantitative phase imaging** using Tescan Q-PHASE microscope with objectives 10x/0.30

Used grayscale:

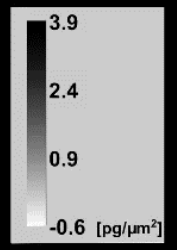


Time-lapse imaging of entosis and oncosis

PC-3 metastatic prostate cancer cell line
2 uM plumbagin treatment

Time-lapse **quantitative phase imaging** using Tescan Q-PHASE microscope with objectives 10x/0.30

Used grayscale:

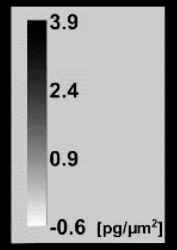


Time-lapse imaging of cannibalism with cell fusion (digestion of engulfed cell)

PC-3 metastatic prostate cancer cell line
2 uM plumbagin treatment

Time-lapse **quantitative phase imaging** using Tescan Q-PHASE microscope with objectives 10x/0.30

Used grayscale:

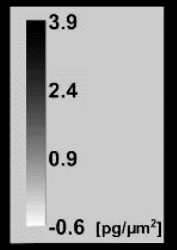


Time-lapse imaging of reverse oncosis

PC-3 metastatic prostate cancer cell line
2 uM plumbagin treatment

Time-lapse **quantitative phase imaging** using Tescan Q-PHASE microscope with objectives 10x/0.30

Used grayscale:



Cell death detection using QPI

As a dead cell can be considered:

Cell whose membrane has lost its barrier function.

Cell which has disintegrated into separate bodies, often referred to as apoptotic bodies.

Cell which was engulfed by professional phagocytes or surrounding cells.

All these processes are associated with changes in cell mass!

Cell Death and Differentiation (2015) 22, 58–73

www.nature.com/cdd

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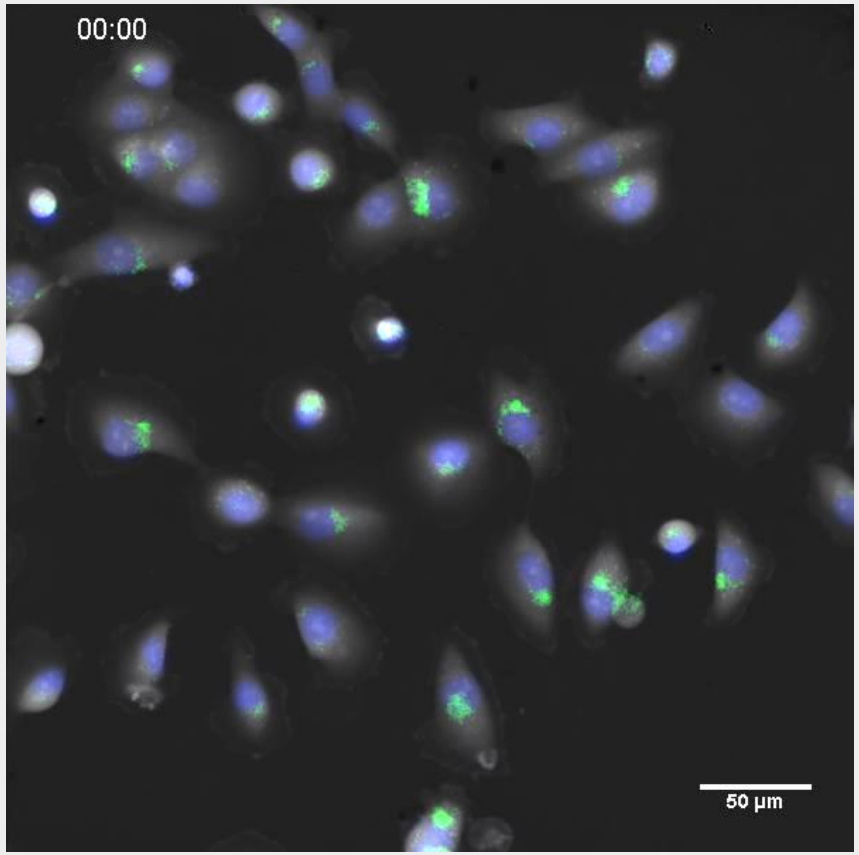
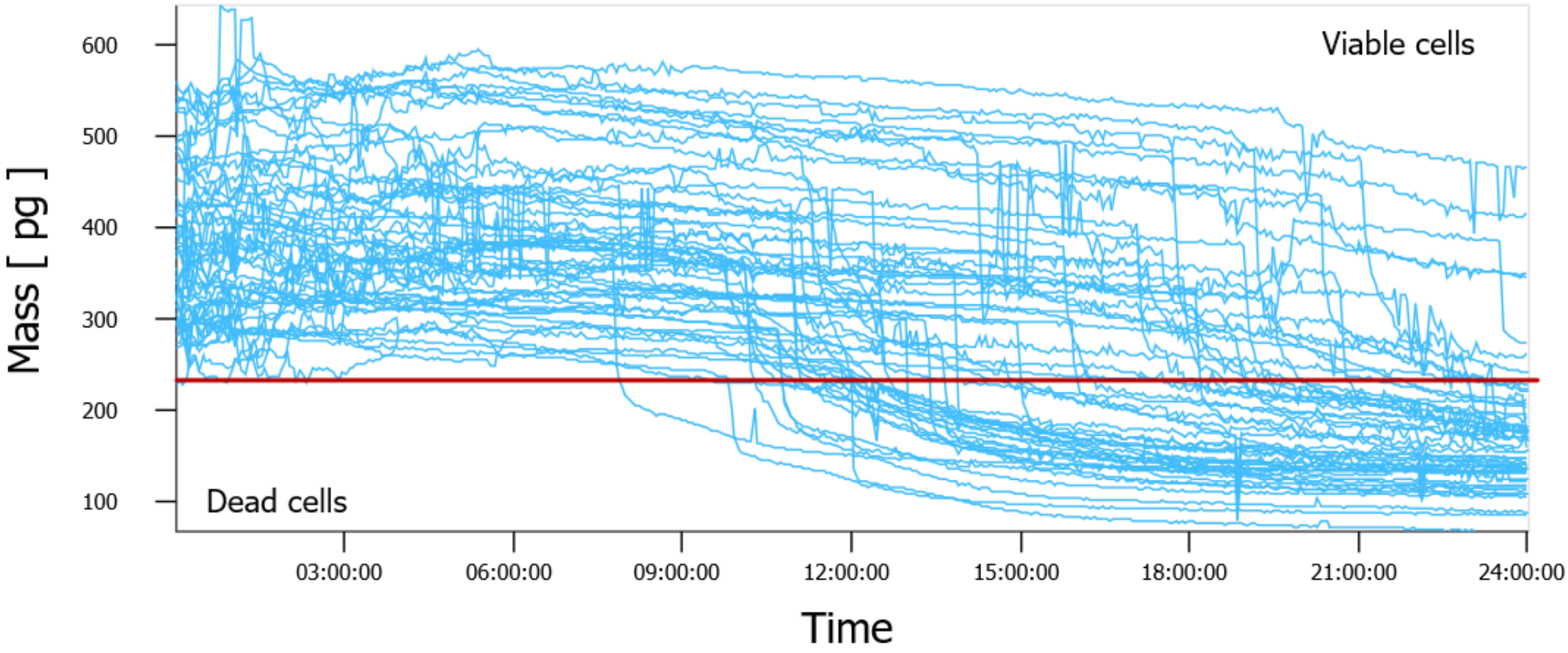
Review

Essential *versus* accessory aspects of cell death: recommendations of the NCCD 2015

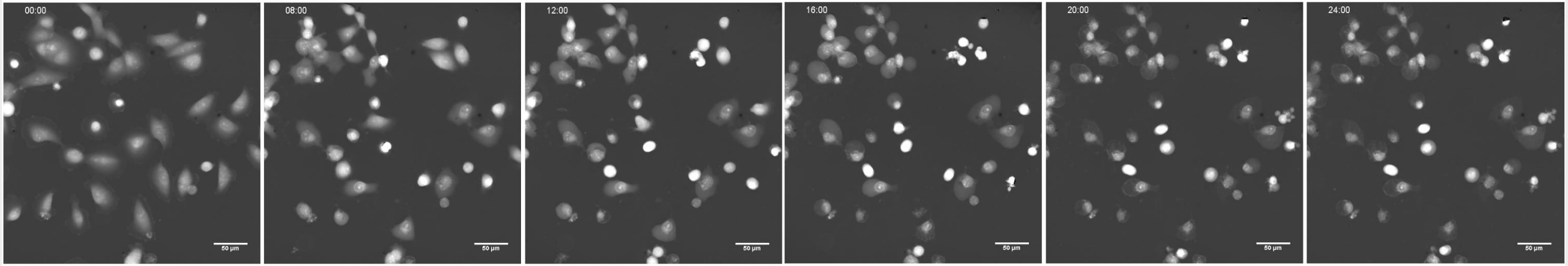
L Galluzzi[*,1,2,3,126], JM Bravo-San Pedro[1,2,4], I Vitale[5], SA Aaronson[6], JM Abrams[7], D Adam[8], ES Alnemri[9], L Altucci[10], D Andrews[11], M Annicchiarico-Petruzzelli[12], EH Baehrecke[13], NG Bazan[14], MJ Bertrand[15,16], K Bianchi[17,18], MV Blagosklonny[19], K Blomgren[20],

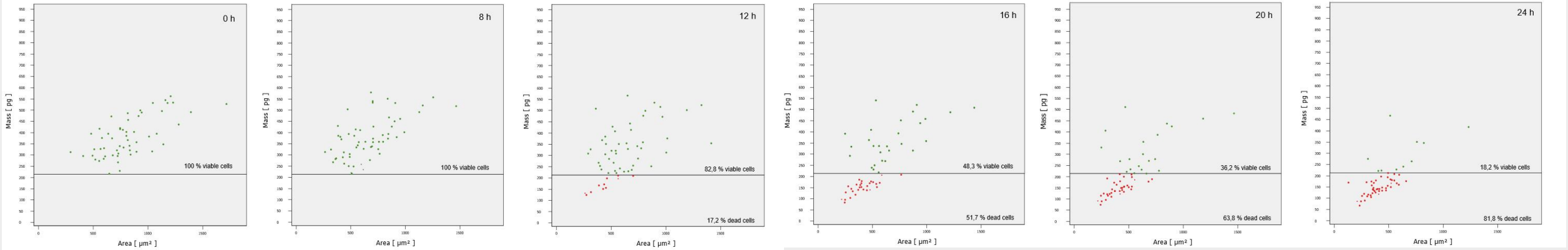


Detekce buněčné smrti pomocí QPI



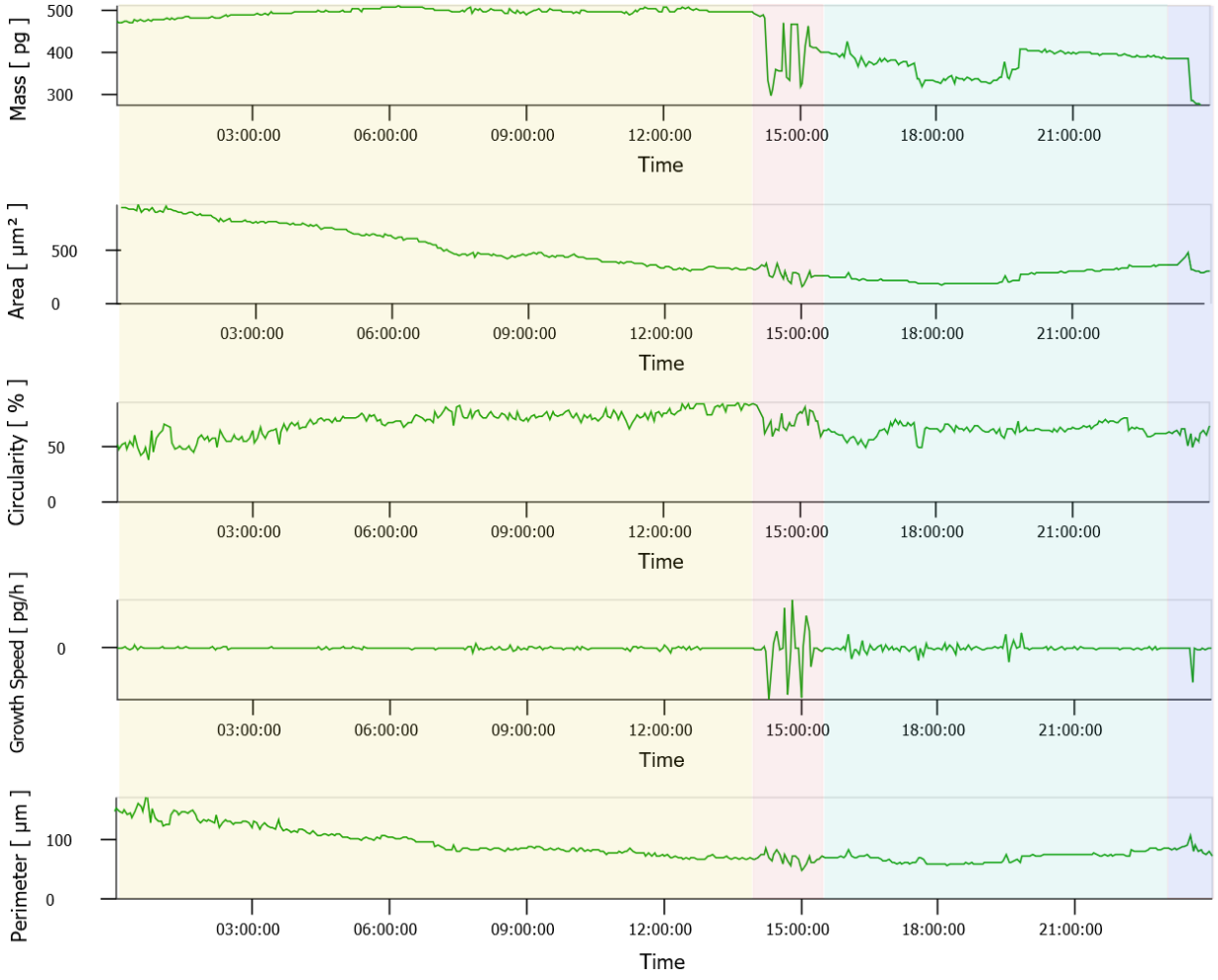
Detekce buněčné smrti pomocí QPI



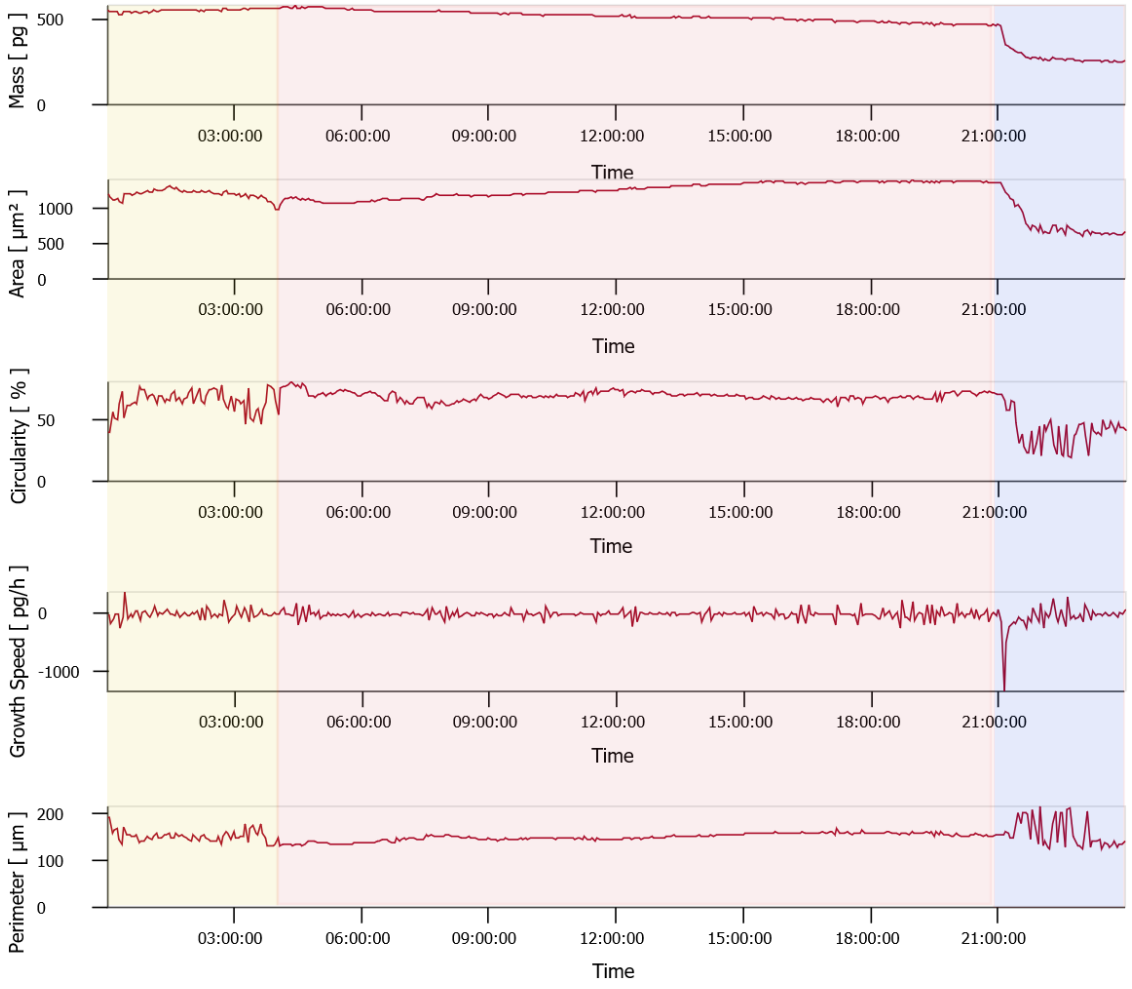


Rozlišení mezi apoptózou a nekrózou

Caspase-dependent (apoptosis)



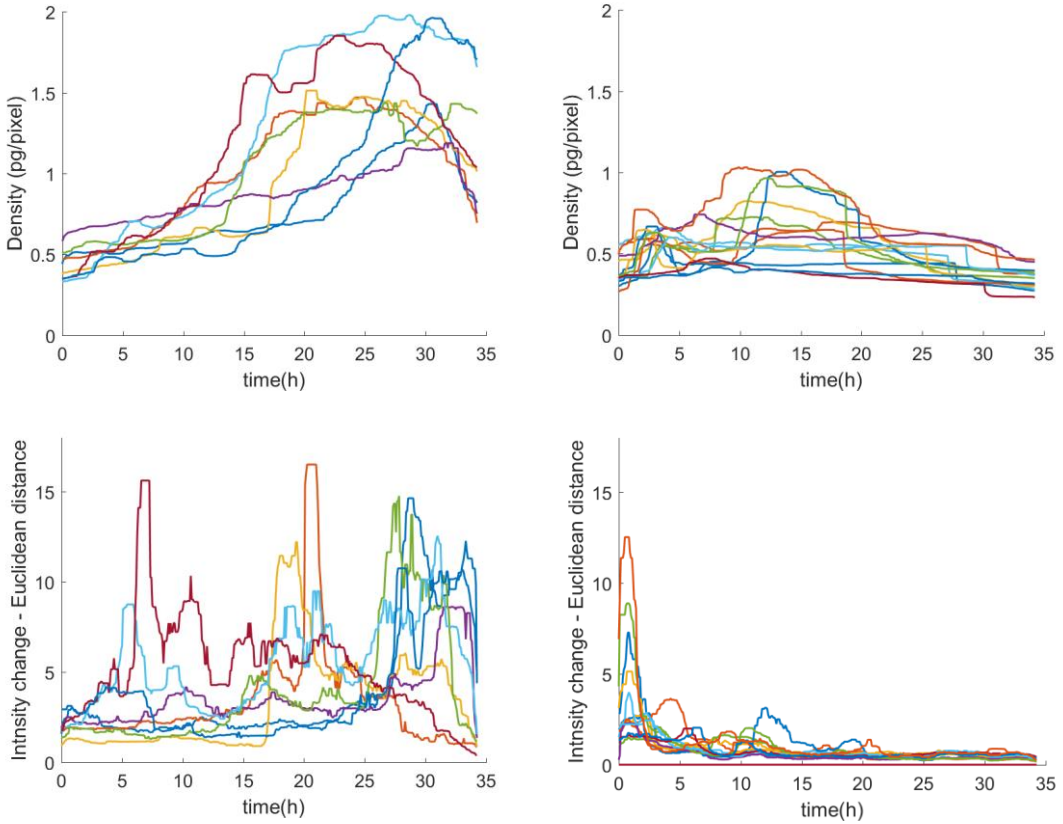
Caspase-independent (necrosis/necroptosis)

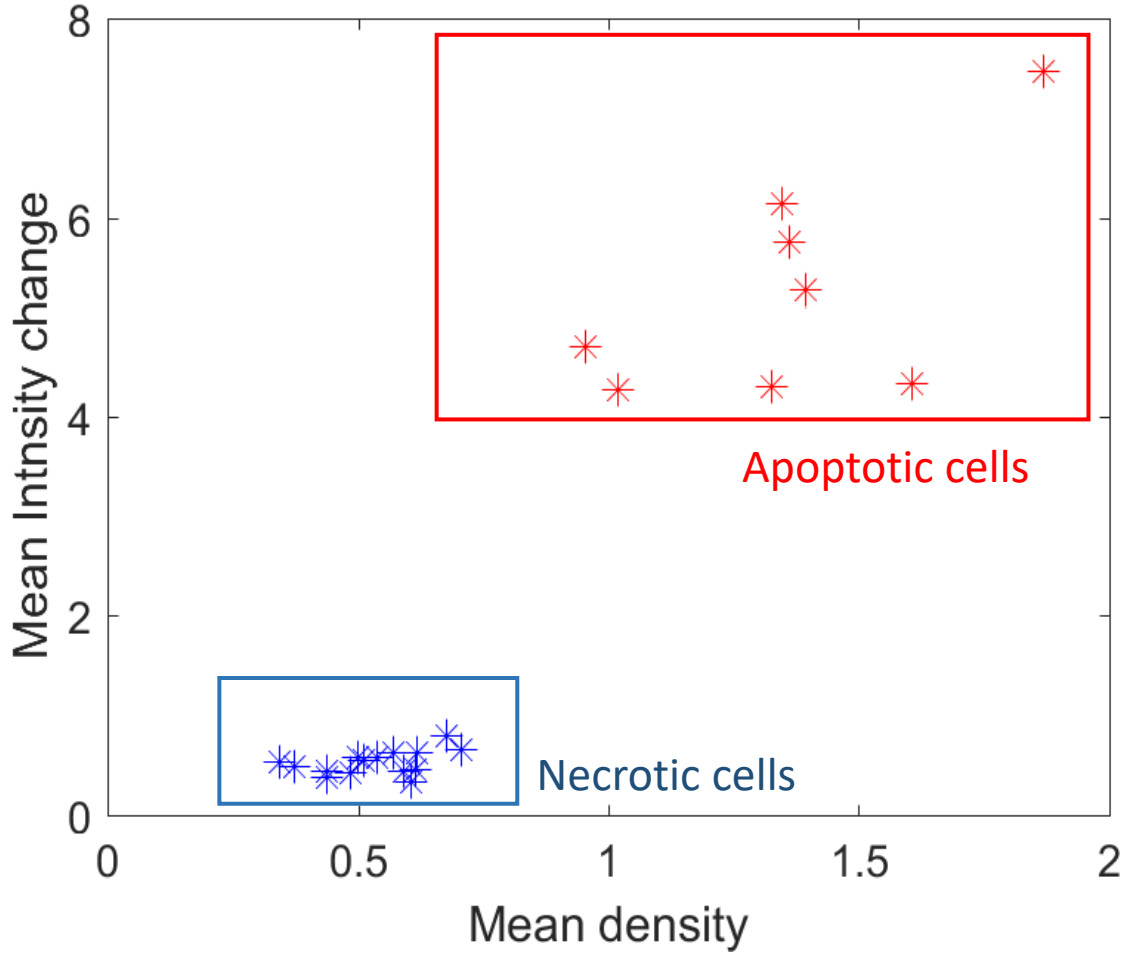


Rozlišení mezi apoptózou a nekrózou

Apoptotic cells

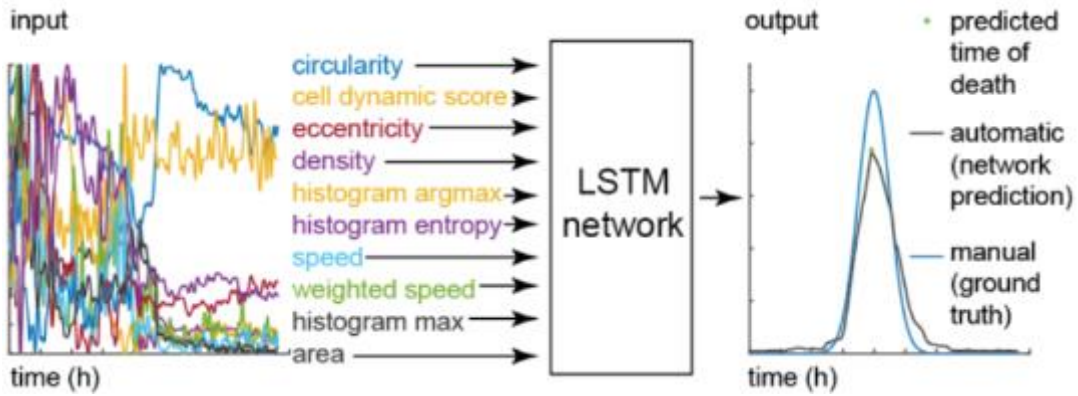
Necrotic cells

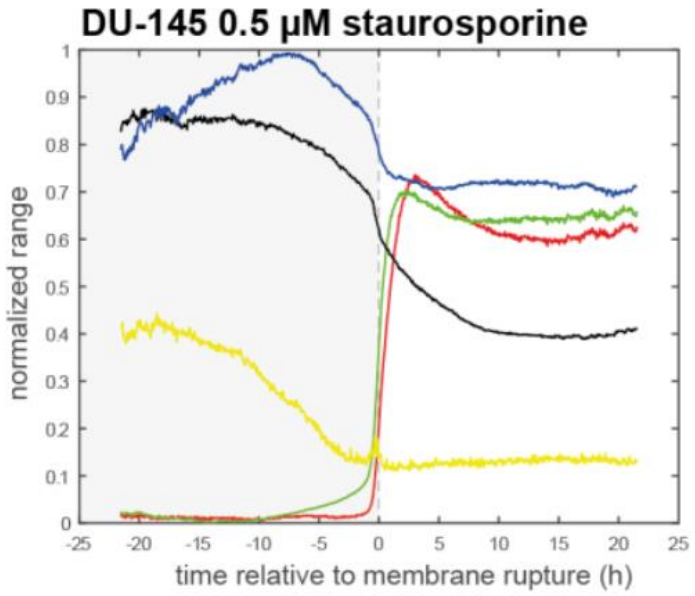


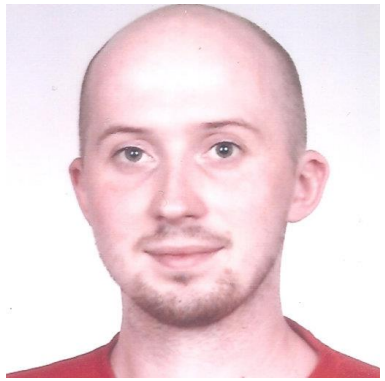


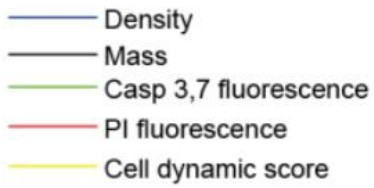
Based on morphological and dynamic parameters, we are able to automatically distinguish two distinct populations of cells. Without the use of dyes, only on the basis of a light microscopic method.

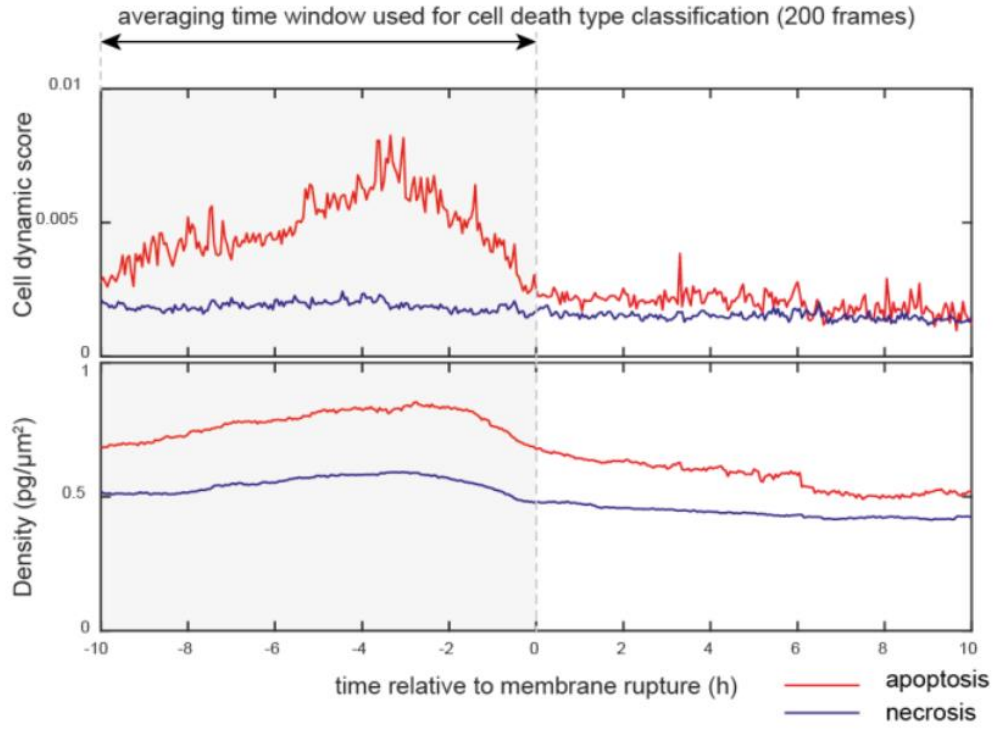
Rozlišení mezi apoptózou a nekrózou











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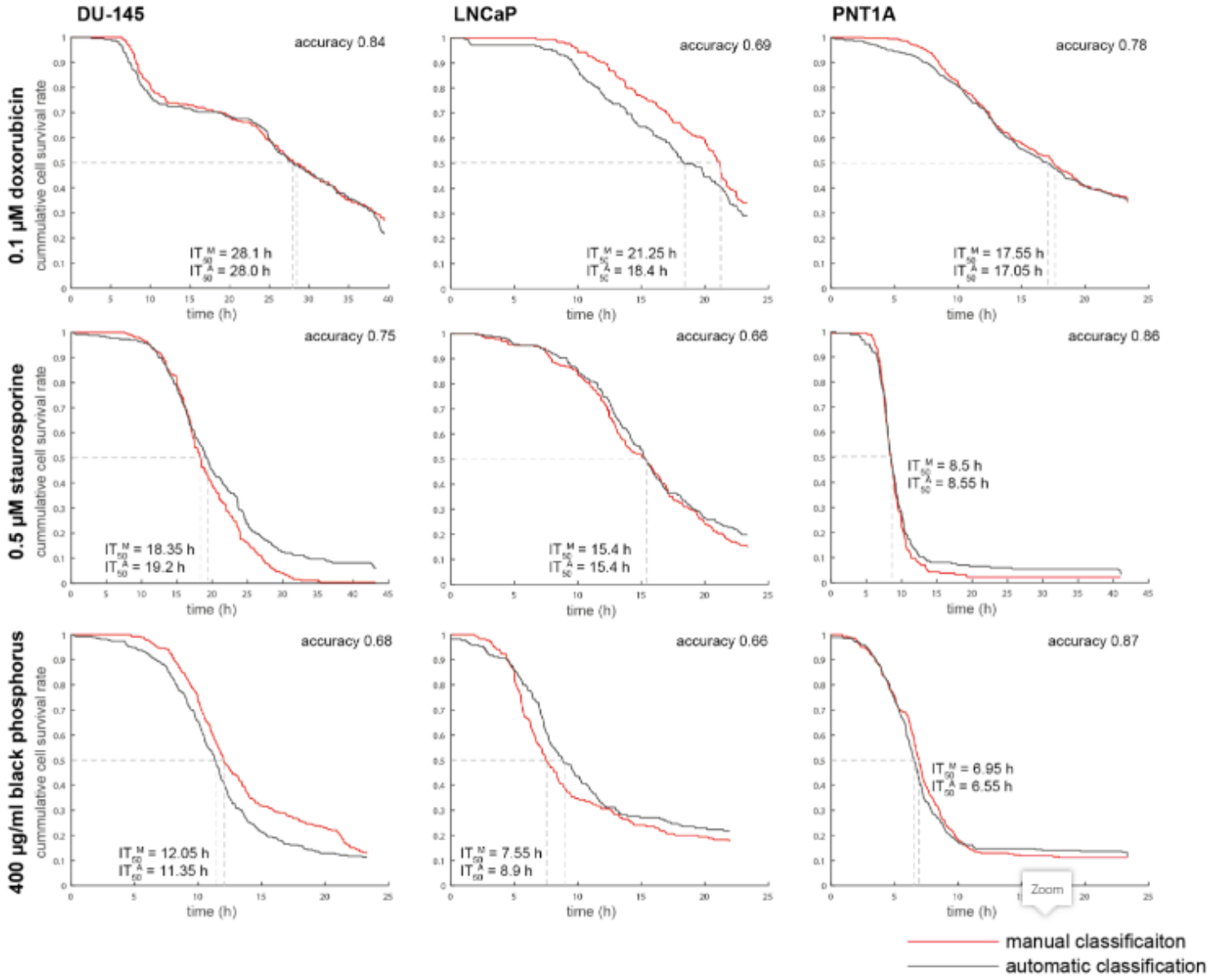

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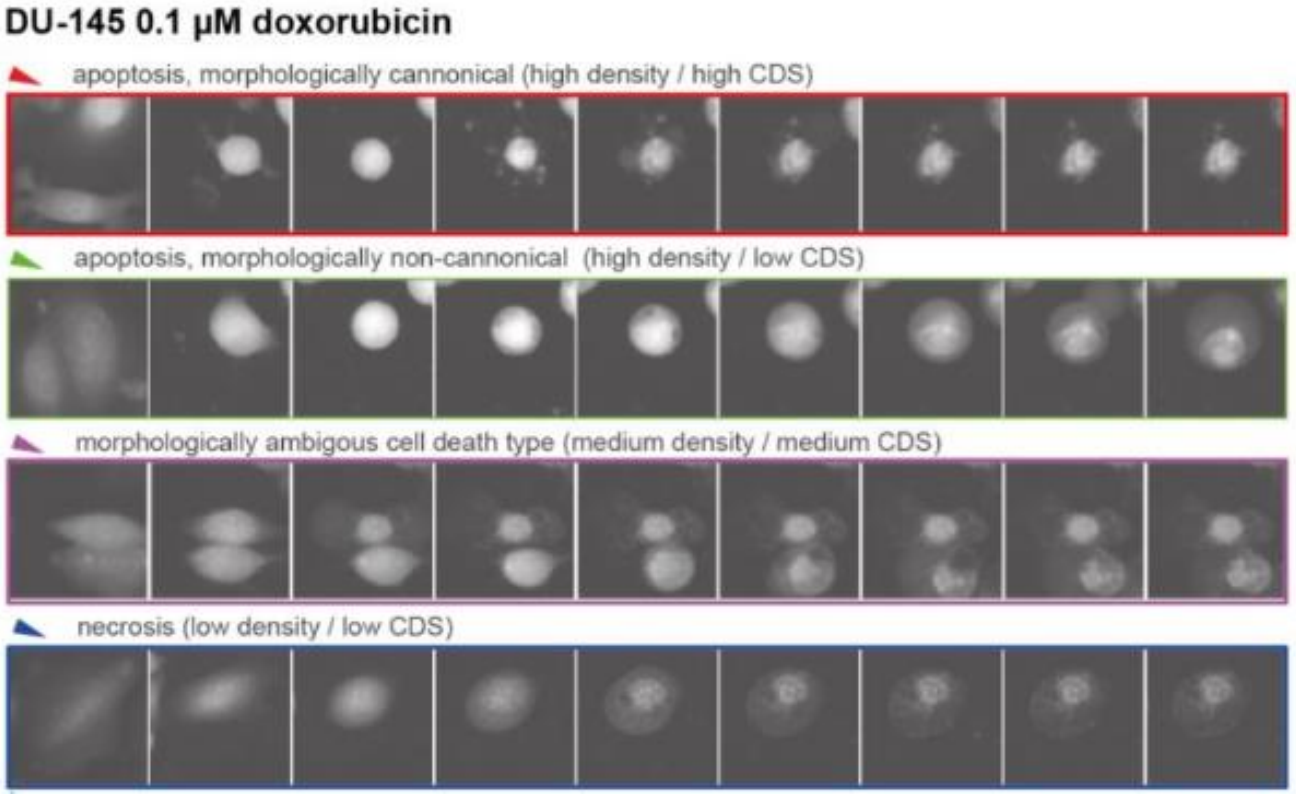

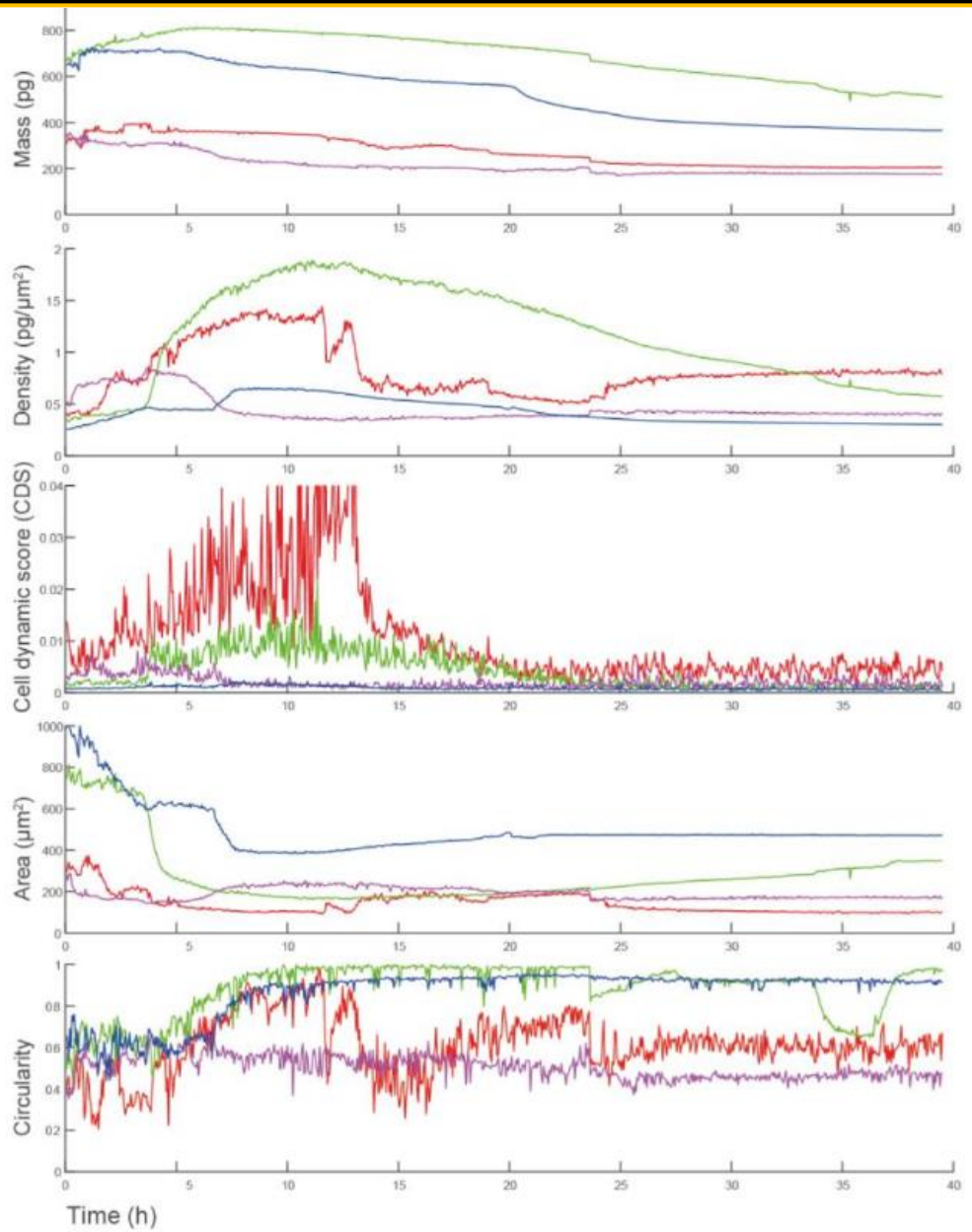

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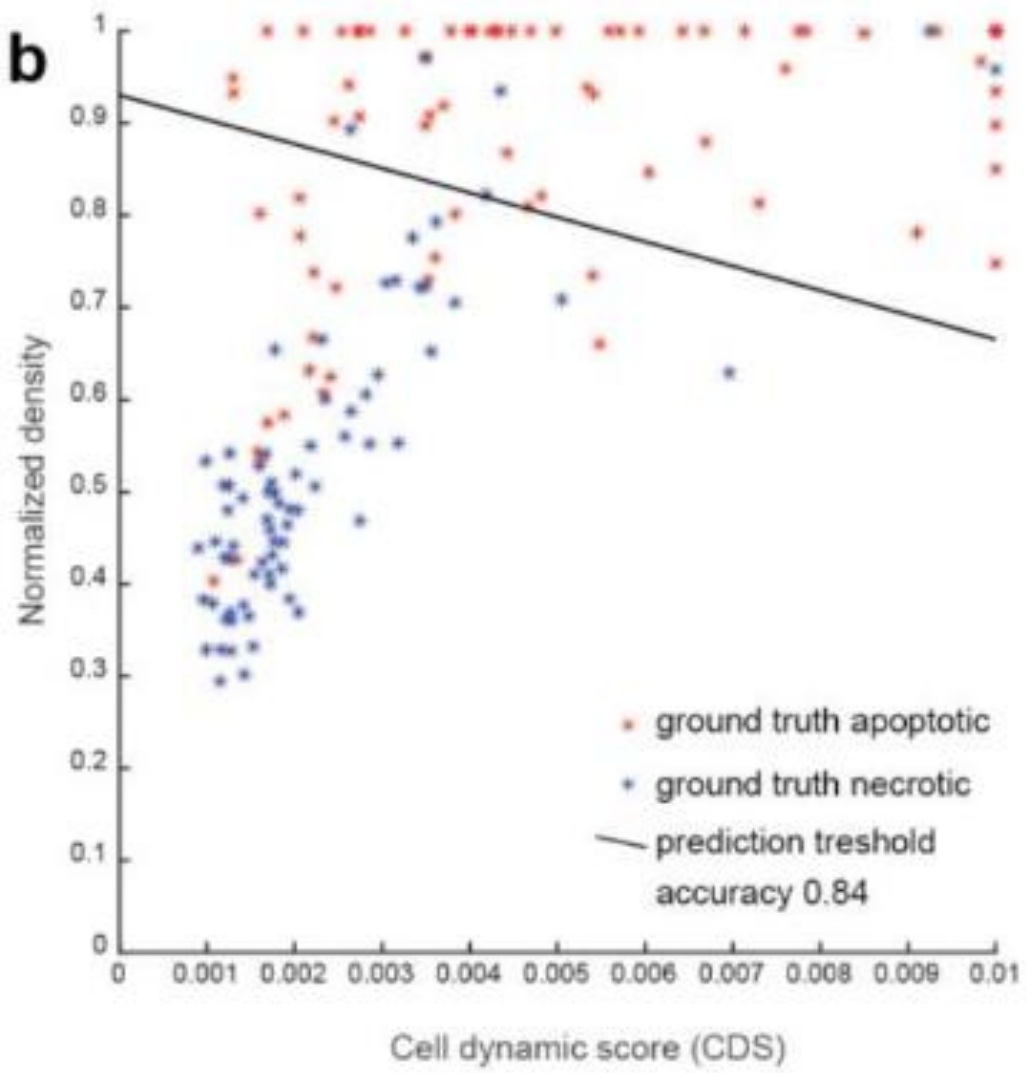
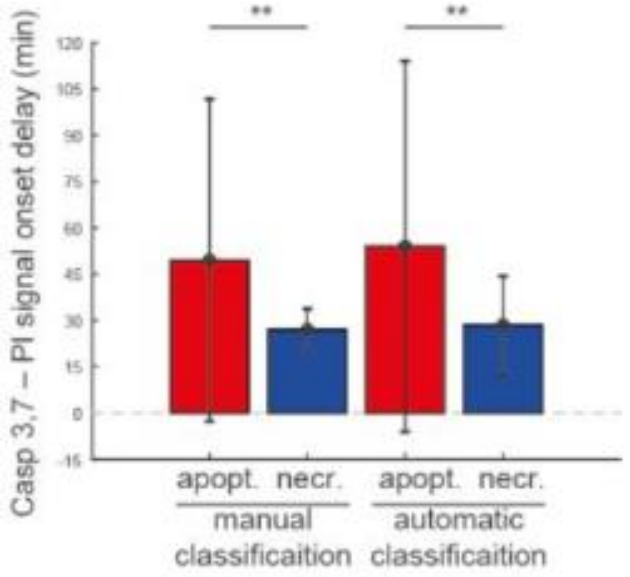
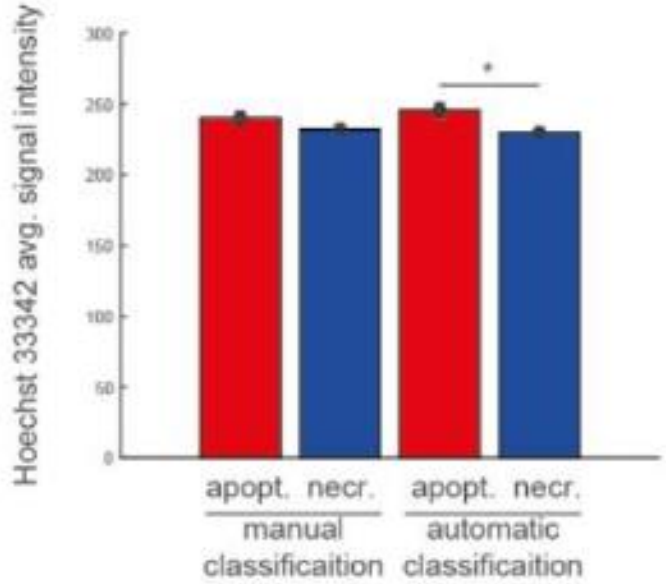
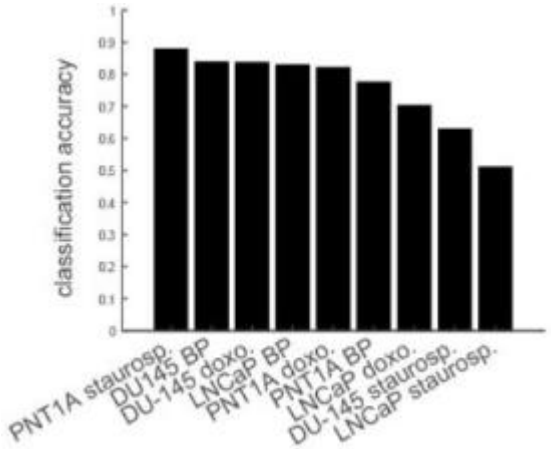
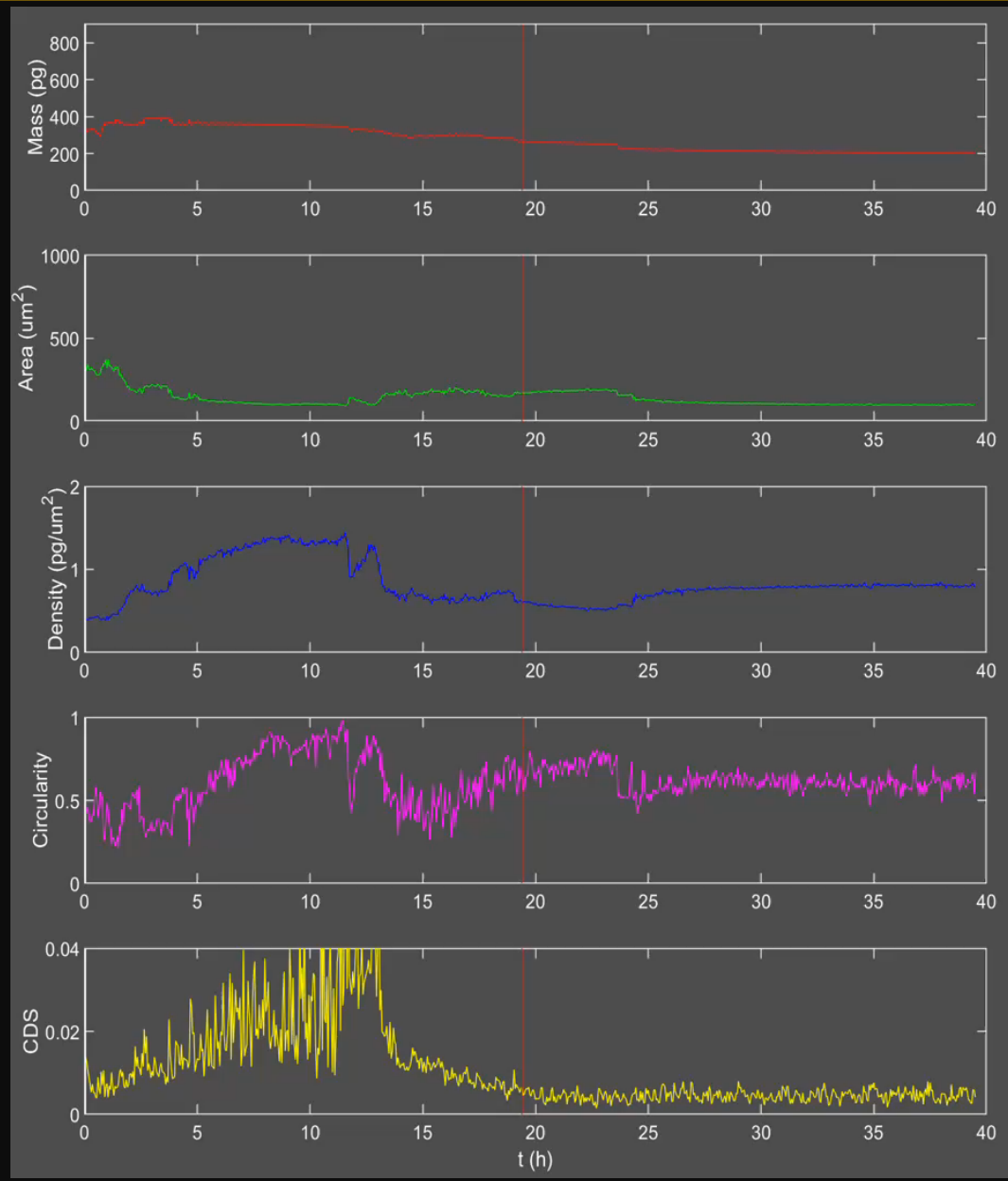


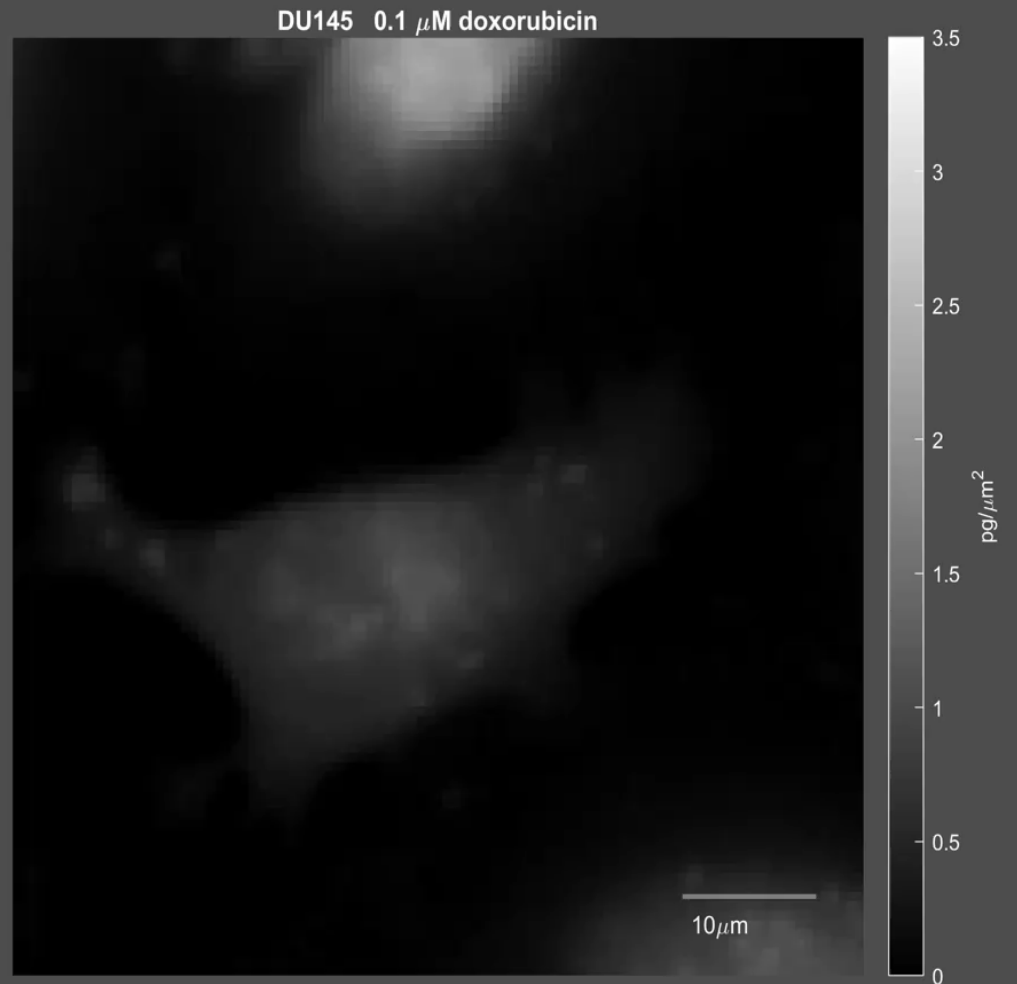






Rozlišení mezi apoptózou a nekrózou





Quantitative Phase Imaging, 10x magnification, 3 min/frame

apoptosis, morphologically cannonical (high density/high CDS)

Dr. Martina Raudenská

Doc. Michal Masařík


Thanks for your attention.