

# Cell death and immunometabolism

## What we can learn from dying cells

Gunter Schlegel,

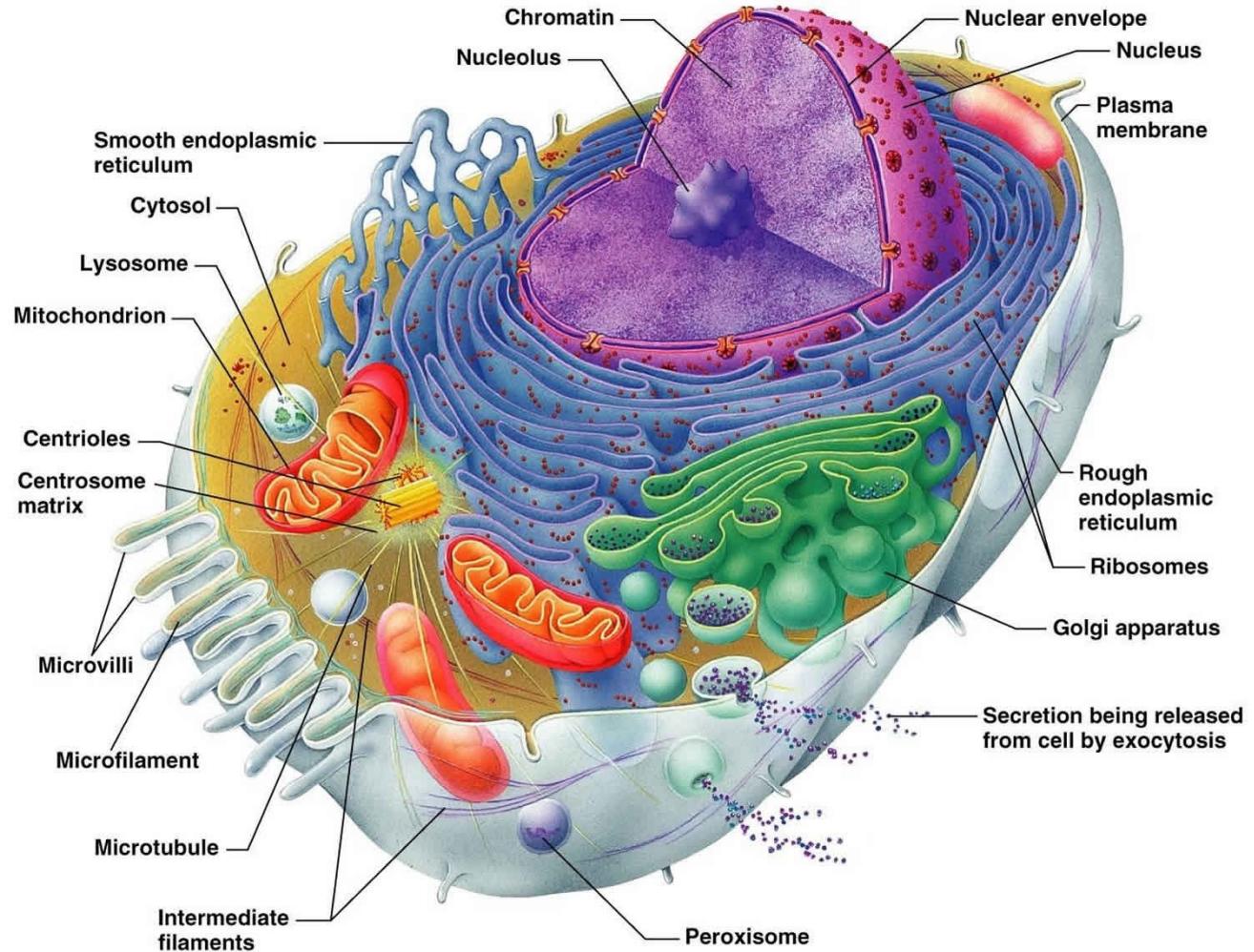
Practical physician, lymphologist and microimmunotherapist

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*“It is normal to give away a little of one’s life in order not to lose it all.” – Albert Camus*

- Cells die for each other having an idea of the greater or the greatest meaning of life.
- Two of the big challenges in holistic medicine are the following:
  - counteracting the survival of senescent cells and the associated inflammatory processes (inflammaging)
  - controlling the self-controlled dividing cancer cells
- Therefore, immunometabolic therapeutic interventions directed at fine-tuning cell death pathways hold one of the keys to restoring homeostasis.

# What is a cell life cycle? And what are the factors to end it?

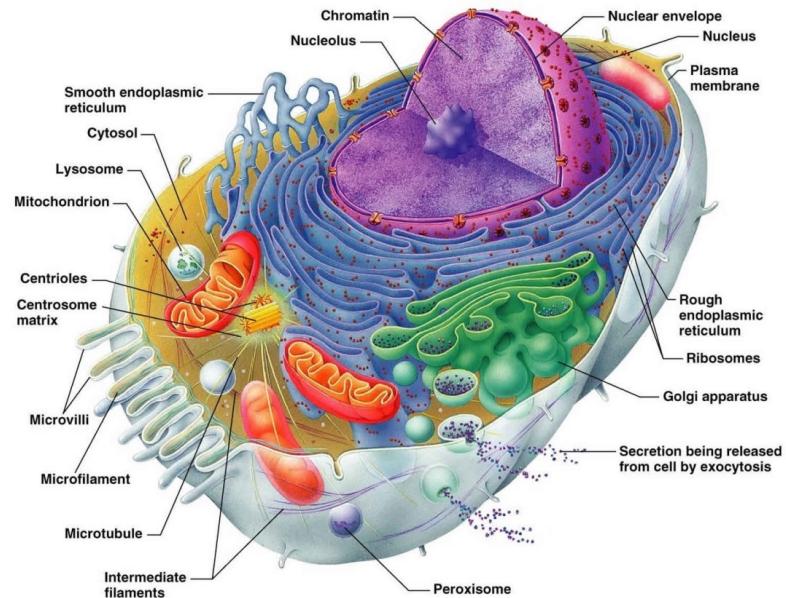


<https://healthjade.net/apoptosis/>

# Role of cell death pathways in different clinical conditions

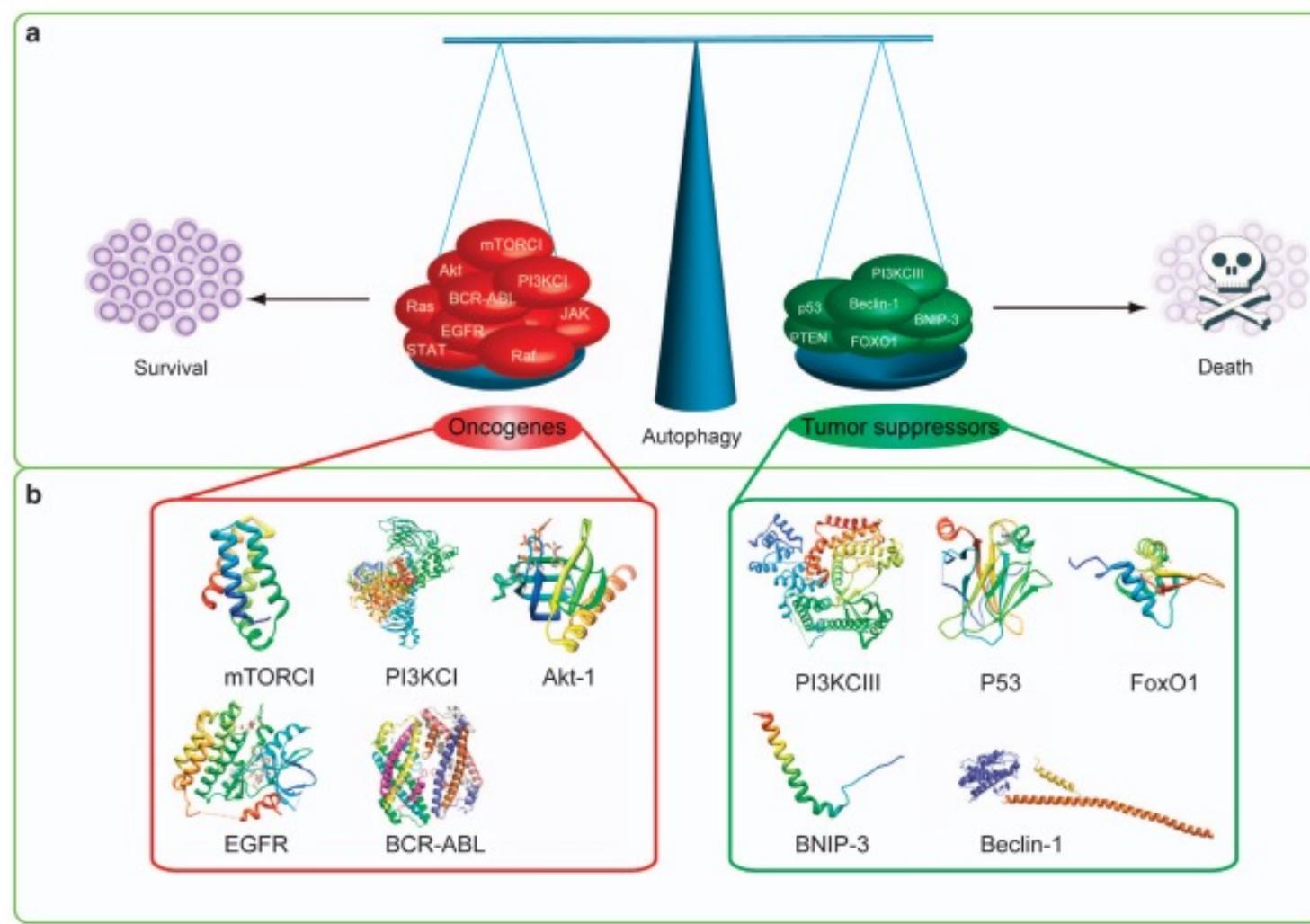
We should think about therapeutic interventions to fine-tune cell death in these cases:

- senescence and aging
- inflammaging
- neurodegeneration
- self-poisoning
- SNP Single Nucleotide Polymorphism
- mast cell activation
- leaky gut and leaky brain
- glymphatic pathway
- fatigue
- cancer
- autoimmunity
- infectious diseases
- and also many more



<https://healthjade.net/apoptosis/>

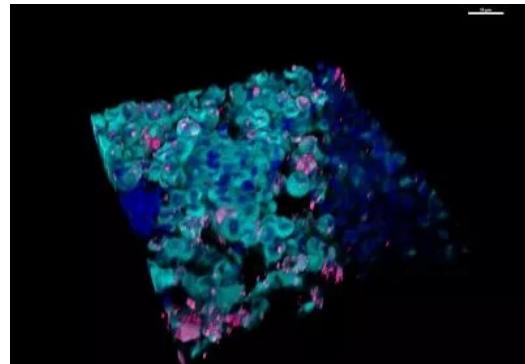
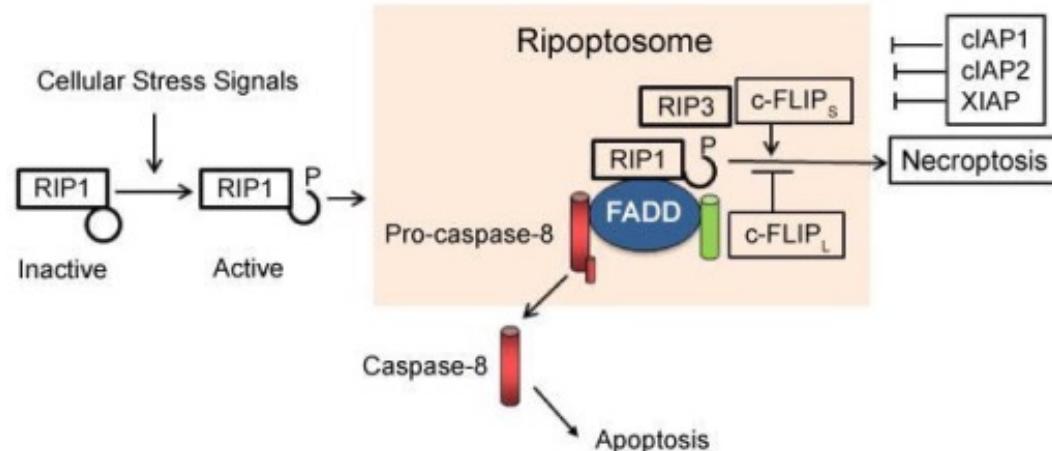
# Cell life is a balance between oncogenes and tumor suppressor genes and their associated proteins



# There are some organelles we need to look at very carefully to understand cell death in its different forms

1. the mitochondria
2. the **apoptosome**
3. the inflammasome
4. the lysosome
5. the (auto) phagosome
6. the peroxisomes
7. the endoplasmatic reticulum
8. NETs = Neutrophil Extracellular Traps
9. the golgi complex
10. the ripoptosome RIP = Receptor Interacting Protein
11. the frodosome: a liquid-liquid phase separation forming membraneless fluid like structures

Safa AR. Roles of c-FLIP in Apoptosis, Necroptosis, and Autophagy.  
J Carcinog Mutagen. 2013;Suppl 6:003.



Meet the 'frososome', a brand new organelle  
By Yasemin Saplakoglu published March 24, 2021

# Physiology of cell death

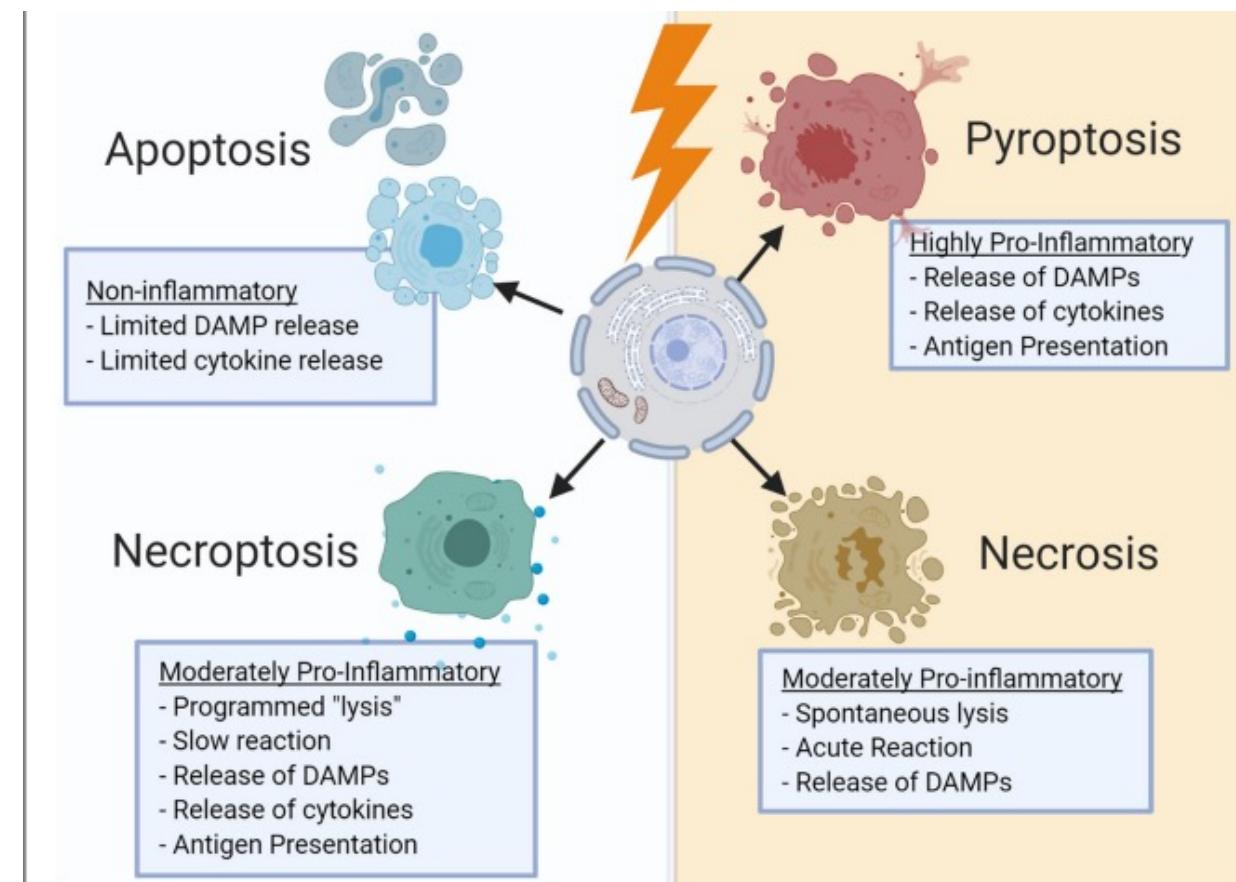
- **The propaedeutic of cell death of humans in data:**
  - We have about 100 trillion cells in our body. 100.000.000.000.000
  - There are about 50 million cells dying per second. 50.000.000
  - There are about 3 billion cells dying per minute. 3.000.000.000
  - There are about 180 billion cells dying per hour. 180.000.000.000
  - There are about 4,320 trillion cells dying every day. 4.320.000.000.000
  - Every 4 years nearly all cells of the whole body are renewed.
  - All these cells are almost immediately replaced but not all of them.
  - Most of the cells in the body are less than ten years old.
- Source: [www.spektrum.de](http://www.spektrum.de)

# The 12 different, well-defined types of cell death known so far

1. Apoptosis – intrinsic or extrinsic pathways
2. Oncoisis – ischemic cell death
3. MPT – mitochondrial permeability transition - driven necrosis
4. Necroptosis – a kind of programmed lysis of the cell
5. Ferroptosis – iron dependant form of cell death
6. Pyroptosis – a kind of feverish cell death
7. Parthanatos – cell death by overactivated PARP-1 in failed DDR
8. Entotic Cell Death – a kind of cannibalistic cell death
9. Netotic Cell Death - a suicidal death of neutrophils and eosinophils by extracellular traps
10. LCD = Lysosome Dependent Cell Death
11. ADCD = Autophagy Dependent Cell Death
12. ICD = Immunogenic Cell Death

# What is accidental cell death and what is regulated cell death?

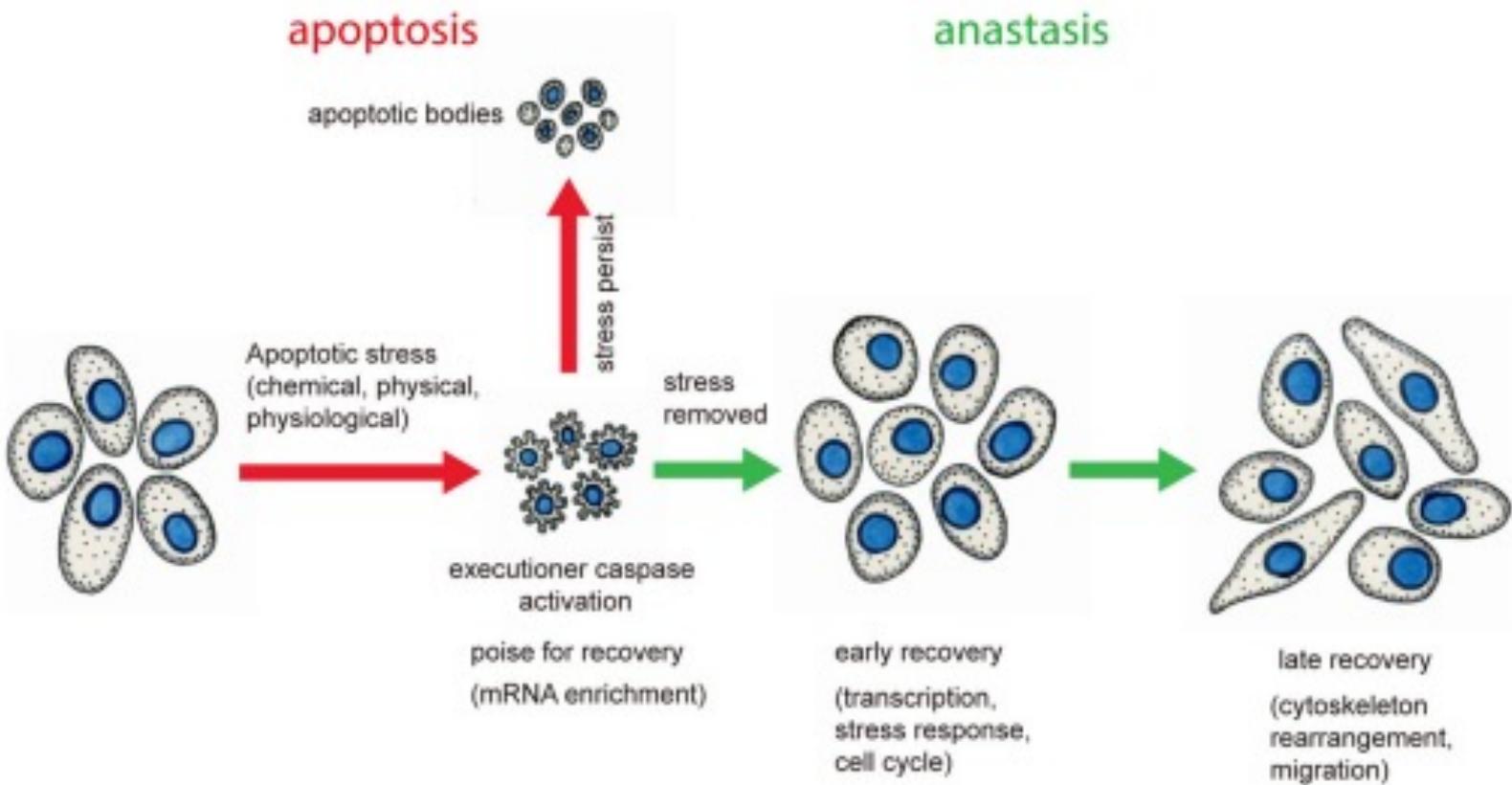
- What is programmed cell death or regulated cell death in comparison to necrosis ?
- **It is important to distinguish between cell death with and without INFLAMMATION!**



Brock RM, Beitel-White N, Davalos RV, Allen IC. Starting a Fire Without Flame: The Induction of Cell Death and Inflammation in Electroporation-Based Tumor Ablation Strategies. *Front Oncol.* 2020;10:1235.

# What is the difference between apoptosis and anastasis?

Sun G, Montell DJ. Q&A: Cellular near death experiences-what is anastasis? BMC Biol. 2017 Oct 24;15(1):92.



- It is important to distinguish between reversible and irreversible cell death !

# What is the border between regulated cell death and cell senescence?

- There is a smooth transition between cell death and cell cycle arrest and cell senescence.
- Biogerontology has some interesting answers – one is senolytics as therapeutics which are able to restore senescent cells back to normal function.
- Resveratrol, curcumin and spermidin play an important role in this context.

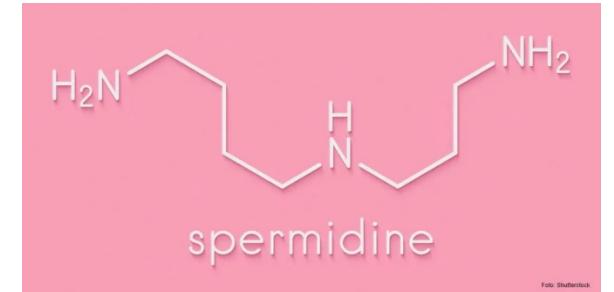
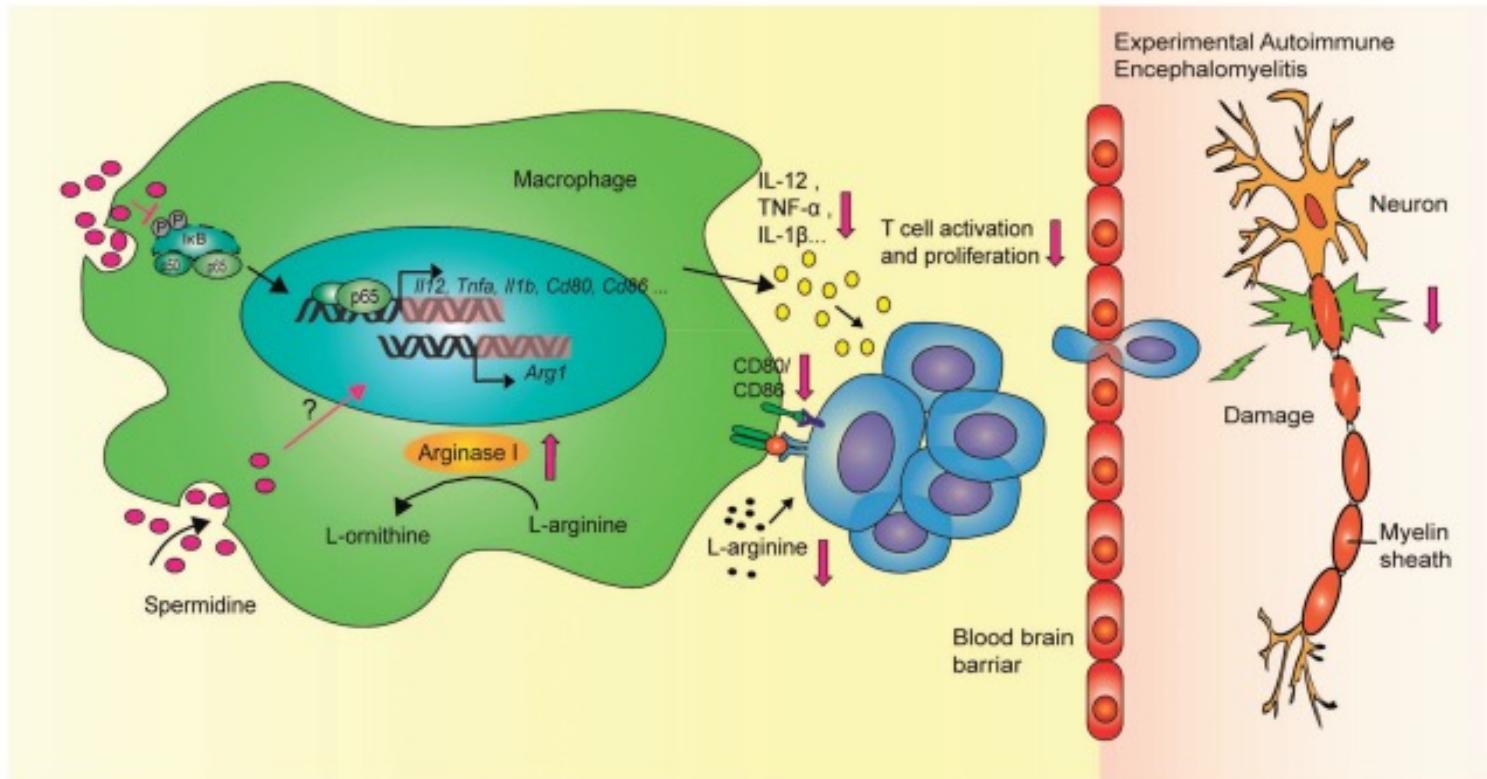
# Therapeutics of cell death and cell senescence – Spermidine ameliorates EAE

Spermidine modulates macrophages to ameliorate EAE

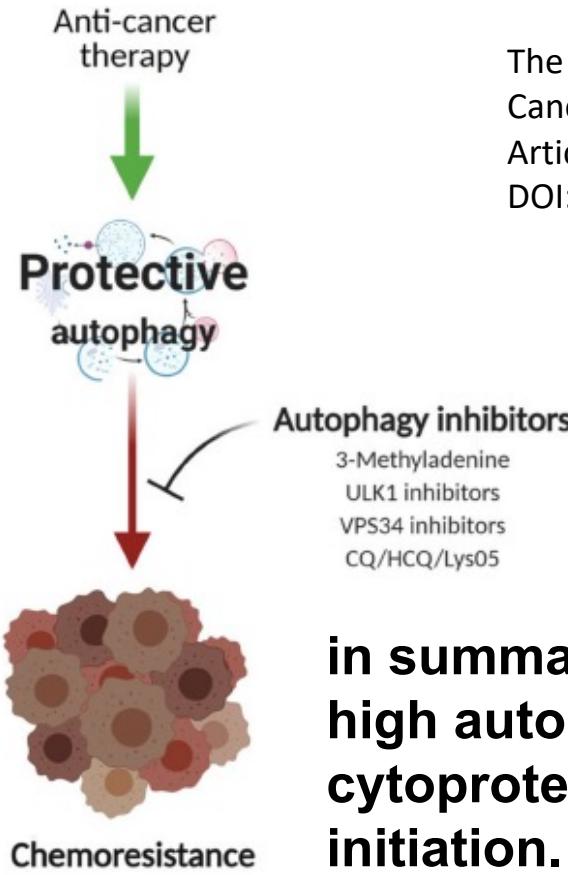
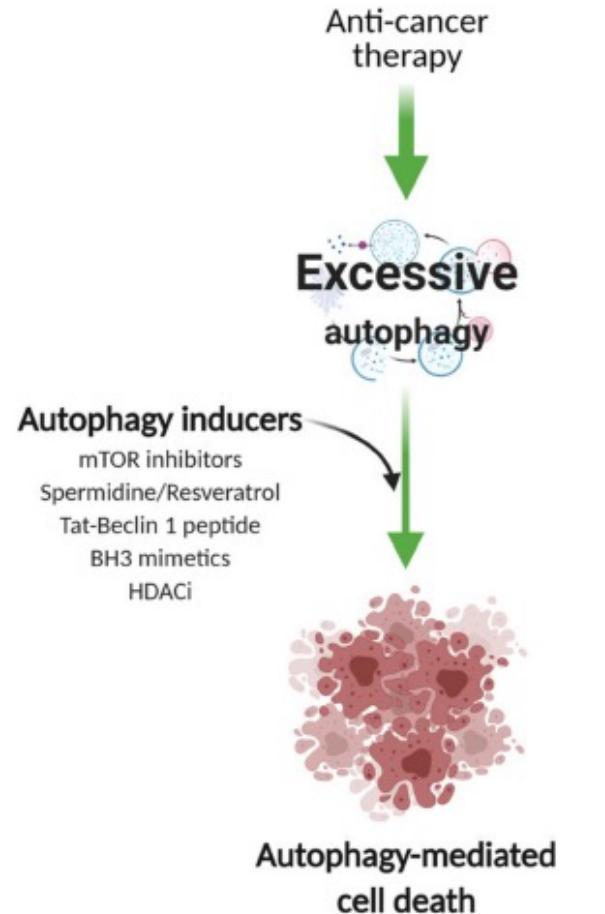
Q Yang et al

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Dementia seems to be an interesting indication for spermidine



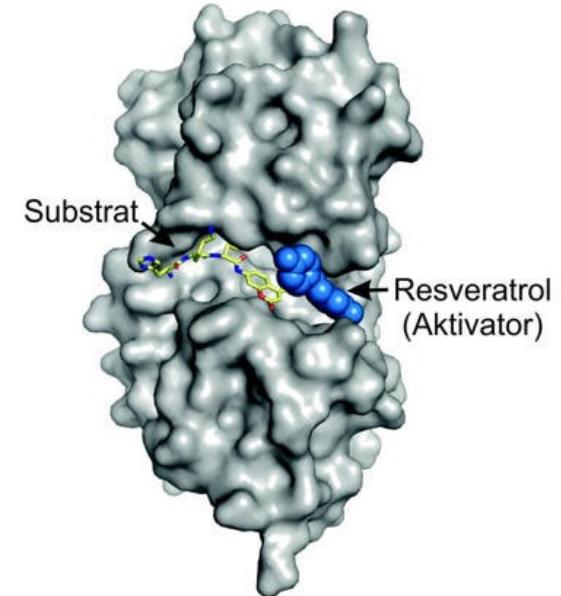
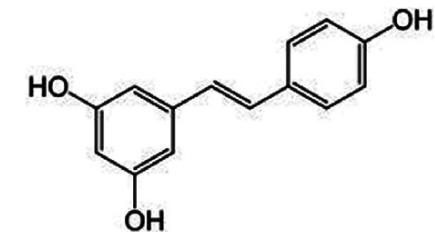
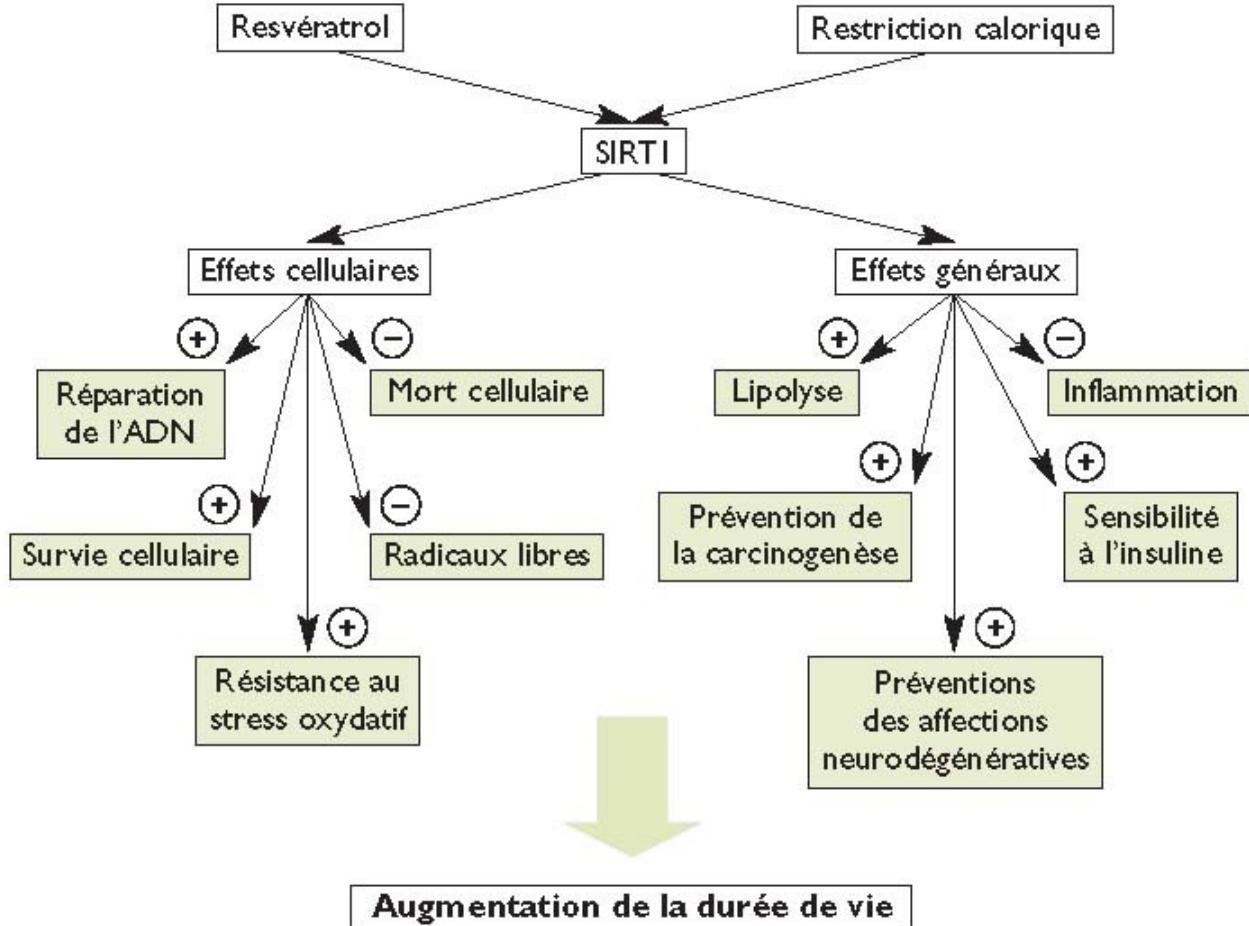
# Spermidine and autophagy in cancer therapy



The Multifaceted Functions of Autophagy in Breast Cancer Development and Treatment  
Article in Cells · June 2021  
DOI: 10.3390/cells10061447

**in summary :**  
**high autophagic activity is predominantly cytoprotective and hence prevents cancer initiation. It can be supported by autophagy Inducers like spermidine and resveratrol**

# Therapeutics of cell death and cell senescence – Resveratrol

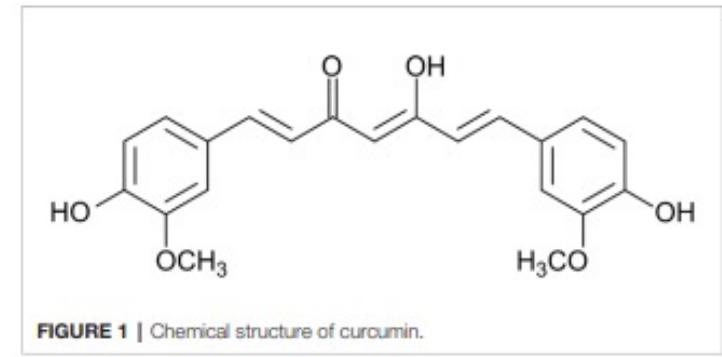
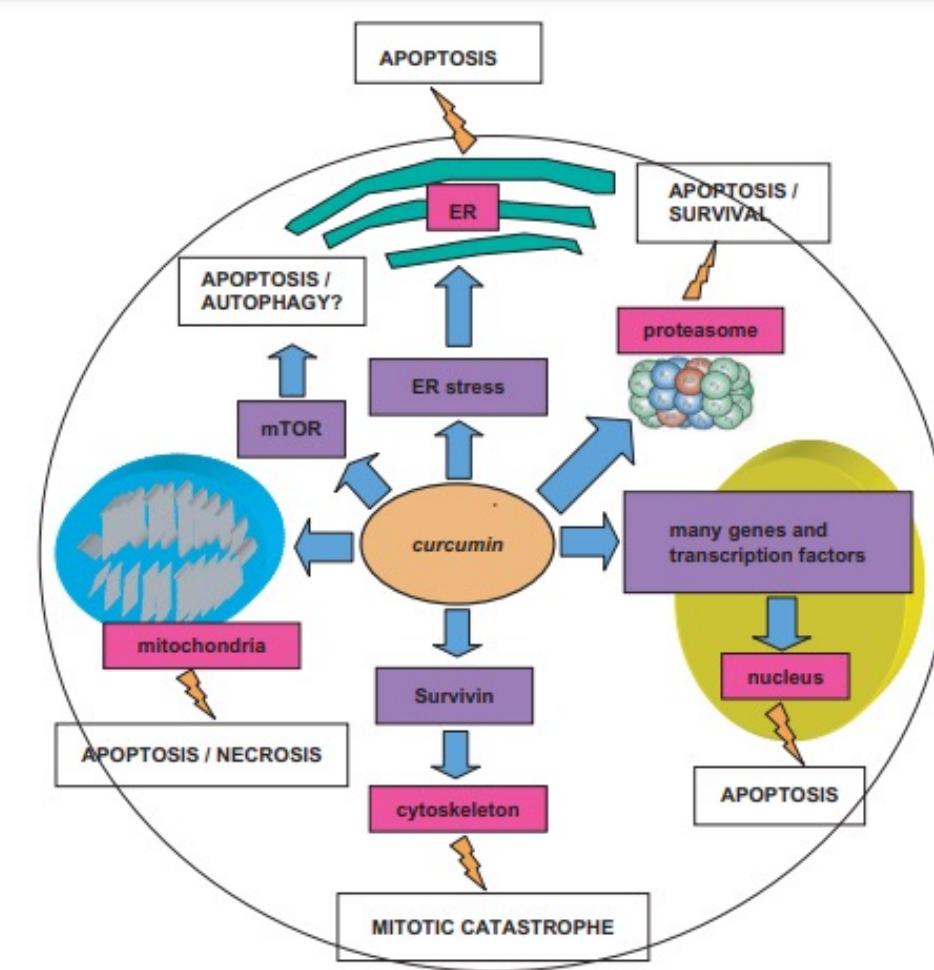


[https://www.organische-chemie.ch/chemie/2012/nov/sirtuin\\_e.shtml](https://www.organische-chemie.ch/chemie/2012/nov/sirtuin_e.shtml)

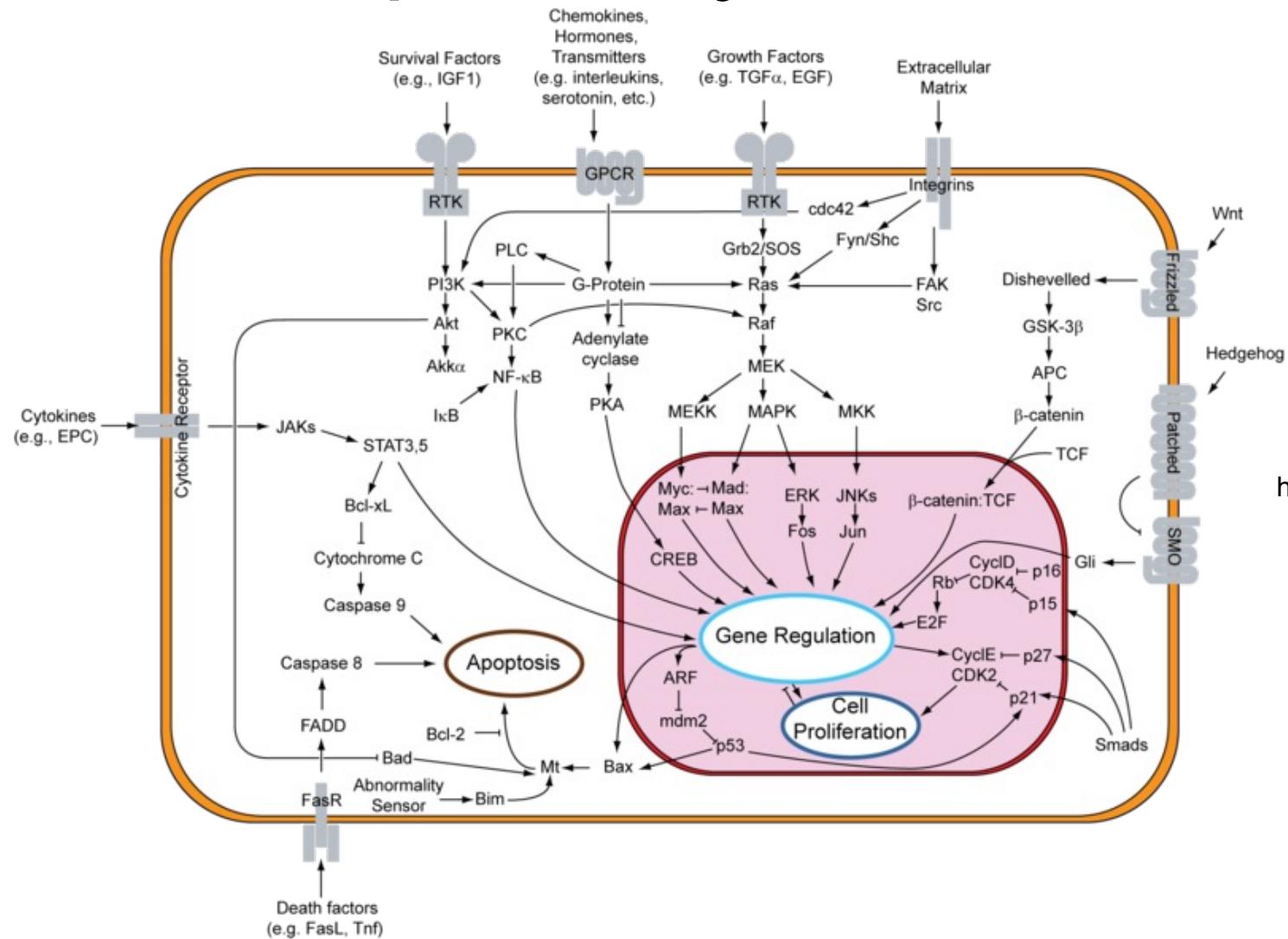
Balaphas A. et al. Manger moins pour vivre plus : la restriction calorique livre ses premiers secrets. Rev Med Suisse 2008 ; 4 : 999-1000.

# Therapeutics of cell death and cell senescence – Curcumin

Salvioli S, Sikora E, Cooper EL, Franceschi C. Curcumin in cell death processes: a challenge for CAM of age-related pathologies. *Evid Based Complement Alternat Med.* 2007;4(2):181-190.



# Apoptosis: the pathways



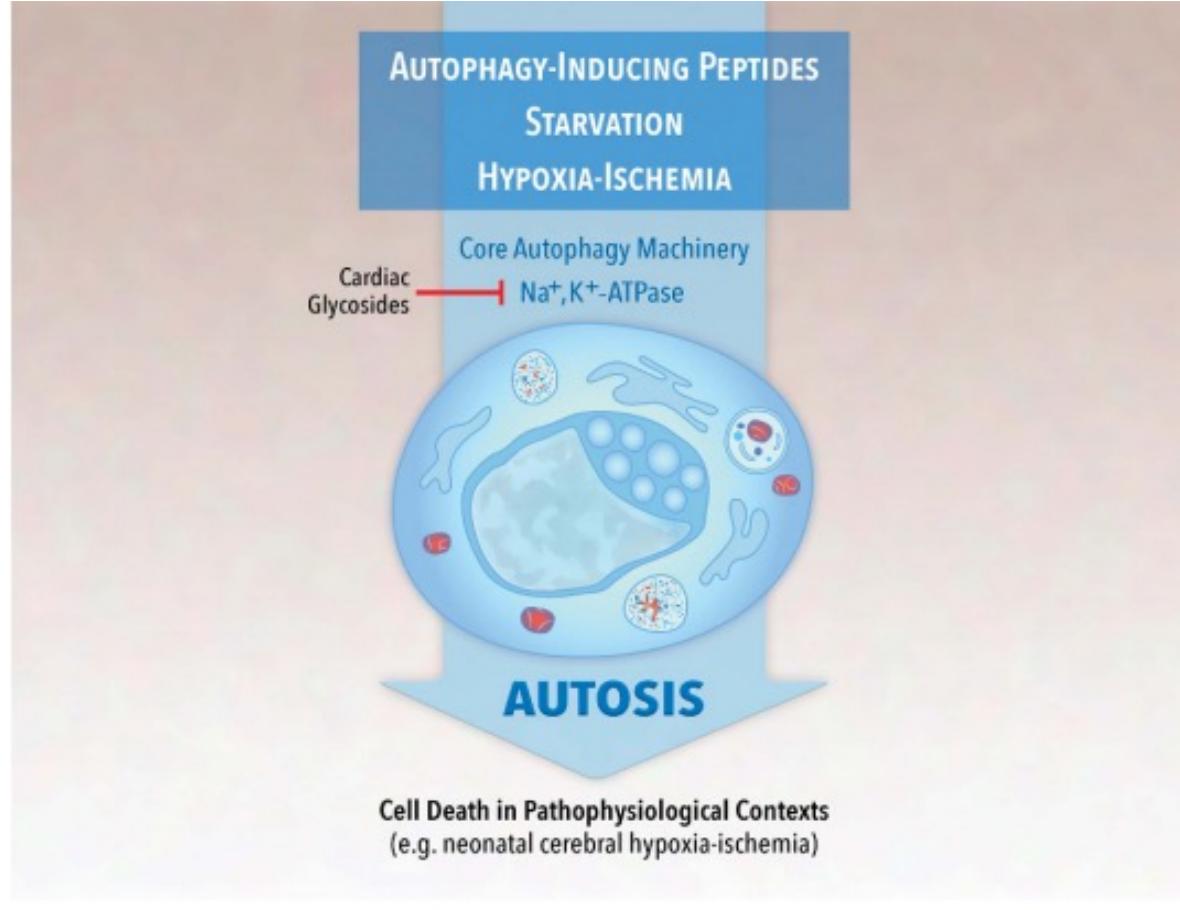
Roadnottaken, CC BY-SA 3.0,  
<https://commons.wikimedia.org/w/index.php?curid=2163484>

There are some more types of cell death not clearly defined so far and still under research

1. PANOPTOSIS: a form of combined apoptosis, necroptosis and pyroptosis
2. MITOTIC CATASTROPHE – cell death caused by unreparable damages in mitosis leading maybe also to senescence
3. ANOIKIS – cell death caused by the loss of contact to neighbour cells
4. AUTOSIS – an autophagy-dependent kind of cell death by excessive accumulation of autophagosomes
5. and many more

# Autosis is a process mainly observed in cardiac or cerebral hypoxia

- The use of cardiac glycosides such as Strophantus, Bufo marina and Helleborus niger can be useful.



Liu Y, Levine B. Autosis and autophagic cell death: the dark side of autophagy. *Cell Death Differ.* 2015 Mar;22(3):367-76.

# The matrix as the basis of the cell's environment

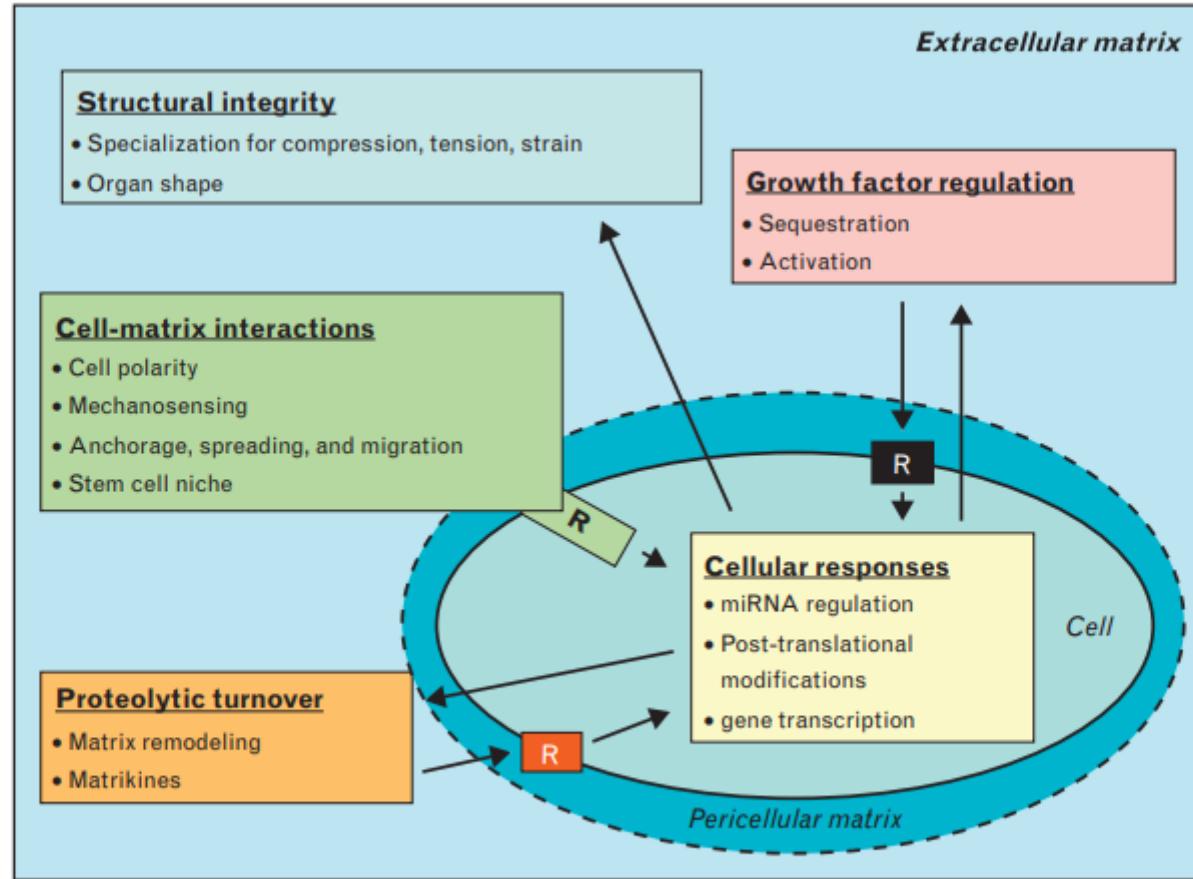
- regulates the cell's desires and protects it
- saves the cell's survival
- is one of the major influences on the cell's health
- connects all cells in the organism to each other
- is one of the most important communication systems of the body
- can store and antidote a lot of cell-poisoning molecules until a fixed amount (e.g. heavy metals, environmental poisons and others)
- is a powerful partner to a lot of therapies using the immune system and its numerous players
- is supported and drained well by manual lymphdrainage
- is restored by autophagic prozesses

# The different tasks of the extracellular matrix

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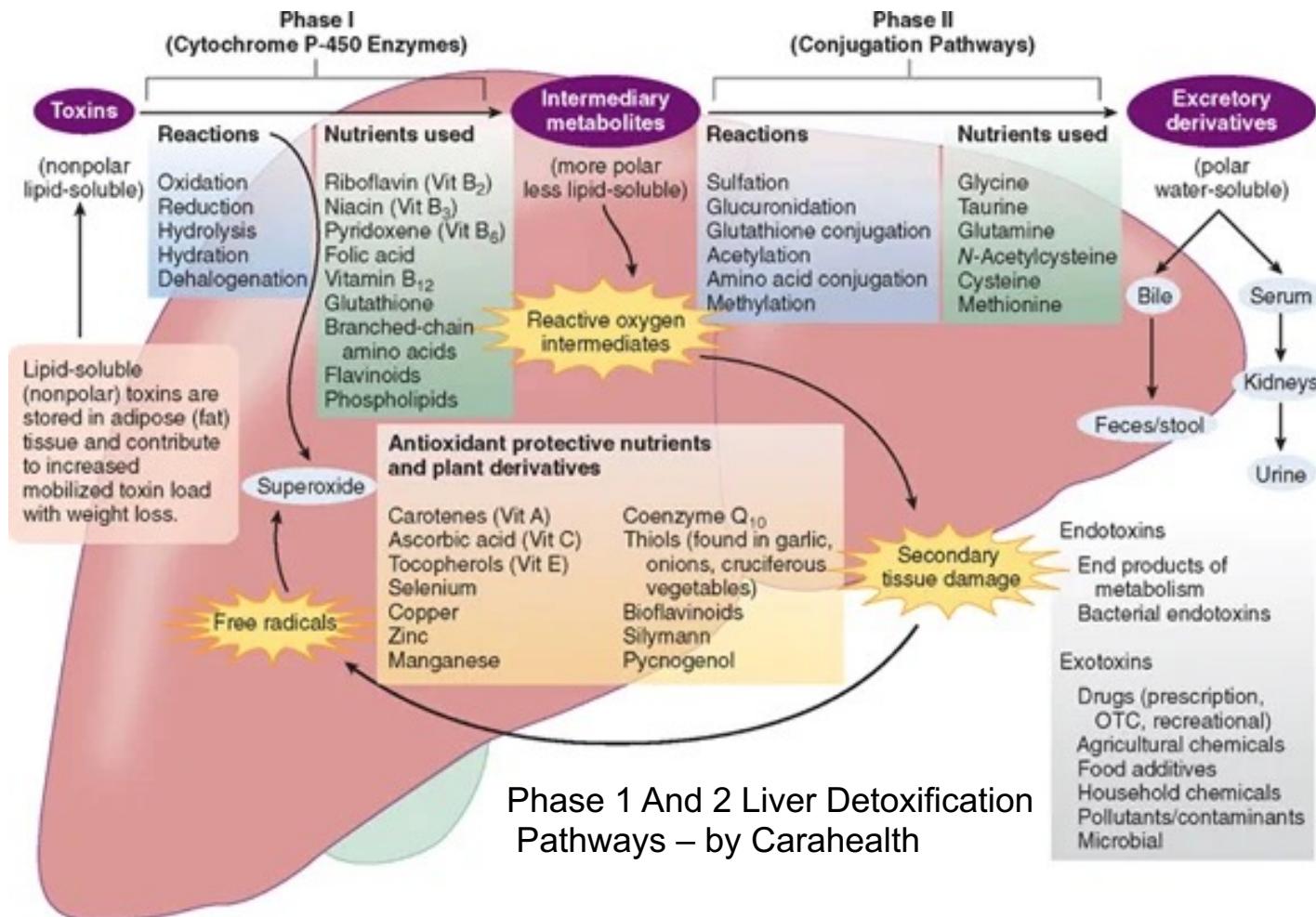
[www.co-rheumatology.com](http://www.co-rheumatology.com)

Hubmacher D, Apte SS. The biology of the extracellular matrix: novel insights. *Curr Opin Rheumatol.* 2013 Jan;25(1):65-70.

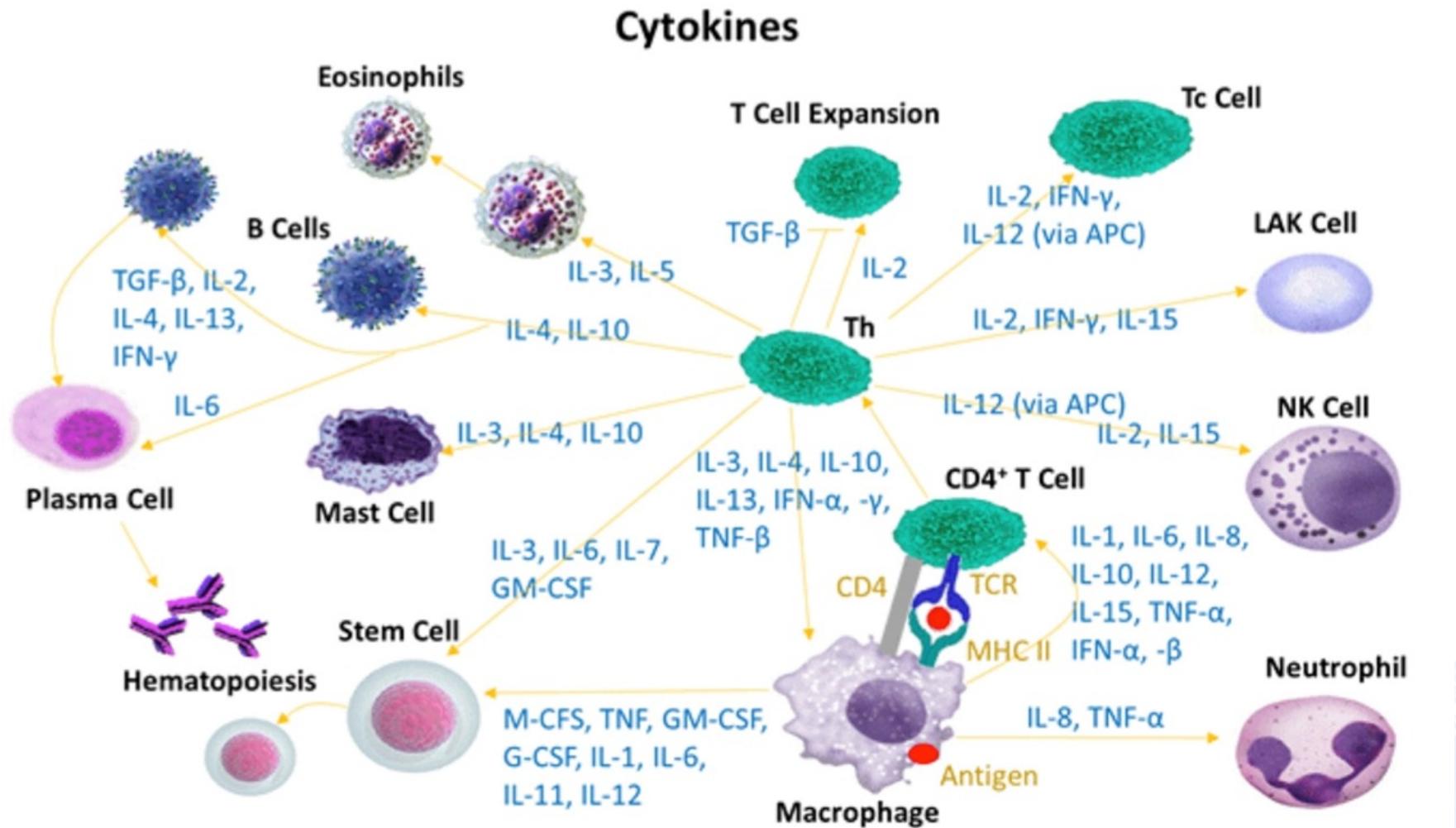


**FIGURE 1.** Functions of extracellular matrix (ECM) and crosstalk at the cell–matrix interface. The cartoon shows the various functions of ECM and exemplifies those that result in feedback to the cell.

# Detoxification is the key to restore the regulating function of the extracellular matrix



# The cytokine network



Open sources [www.biolab.com](http://www.biolab.com), cytokine data

# The micro-immunotherapy formula MIREG

This formula, which is based on a specific combination of cytokines and other immunomodulatory substances in low doses (LD) and ultra-low (ULD), has multiple objectives:

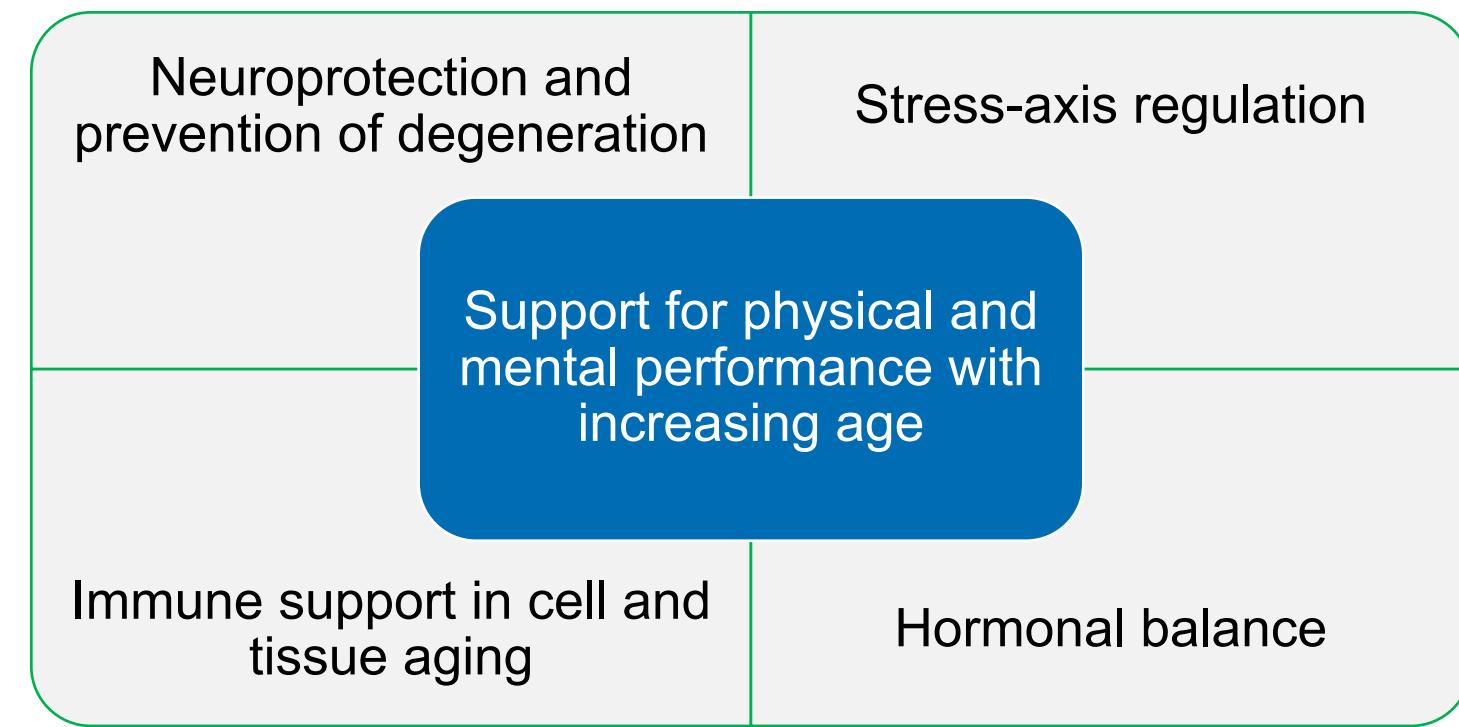
to dampen  
inflammation and  
reduce oxidative  
stress

to regulate the  
immune response

to optimise  
mitochondrial  
function and balance  
the cell energy  
metabolism

# The micro-immunotherapy formula SEN

This formula, which is based on a specific combination of cytokines and other immunomodulatory substances in low doses (LD) and ultra-low (ULD), has multiple objectives:



# Combination of micro-immunotherapy with senolytics

- 1 or 2 capsules per day of the **formula SEN** (not in the evening)
- After 20 days, add to the treatment 1 or 2 capsules of the formula MIREG
- Combine it with spermidine, quercetine and curcumine (dosage depends on the constitution and needs of your individual patient)

# Take home message

- Cell death regulation is a very important way to influence the health of our patients.
- Therefore, it is necessary to understand the pathways behind the different types of cell death in order to integrate, into clinical practice, more and more natural remedies directed at regulating immunometabolism and improving clinical outcomes.
- Keep on learning to use immunometabolism as a tool to restore health!