

Biomedical Science

Molecular Genetics



BMS 23110B | Fall 2026-2027

Inherited Neurological Disorders

Cell Death Mechanisms of Neurodegeneration

جميع الأوراق والمحتويات التابعة للمنصة محمية بموجب حقوق الملكية الفكرية.
يُمنع منعاً باتاً نسخ، أو نشر، أو مشاركة أي محتوى أو مستندات تخص المنصة بأي شكل
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Introduction

Neurodegenerative diseases are caused by interactions of **genetic factors** and **environmental influences**.



Common pathogenic features

shared by these disorders

excitotoxicity

synaptic dysfunction

protein misfolding and aggregation

oxidative stress (ROS)

mitochondrial dysfunction

calcium dysregulation

chronic neuroinflammation

FROM DEFENCE TO PROGRAMMED CELL DEATH

Disrupted cell functions together with aging-induced accumulation of DNA damage and oxidative stress



Gradually & progressively **impair intrinsic cellular defense mechanisms** — incl. the protein quality control system (e.g., ubiquitin and autophagy) and others



Leading to a **shift in life–death balance**



Ending in programmed cell death (PCD)

It is likely that **multiple cell death pathways** are involved in the cell loss in neurodegenerative diseases and in animal or cellular models of neurodegeneration.



Survival or death balance & the major path to death

"how to die" — depends on:

THE STRESSOR

source

duration

dose

THE CELL

type

prior stress exposures

metabolic conditions

SEVERAL TYPES OF CELL DEATH MAY BE INVOLVED IN NEURODEGENERATION



Apoptosis

BRIEFLY



Necroptosis

BRIEFLY



Autophagy

BRIEFLY



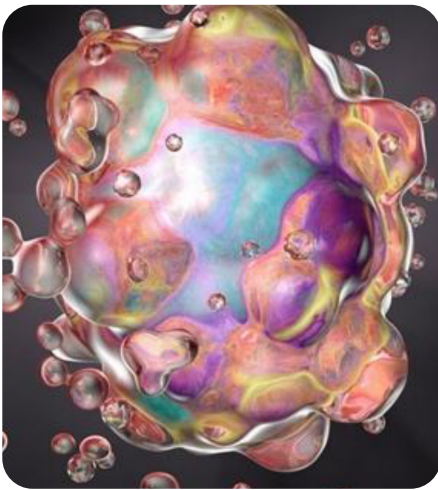
Parthanatos

FOCUS

We will briefly discuss apoptosis, necroptosis and autophagy, and **focus on Parthanatos** — exploring their roles and therapeutic potential in neurodegenerative diseases.



Apoptosis



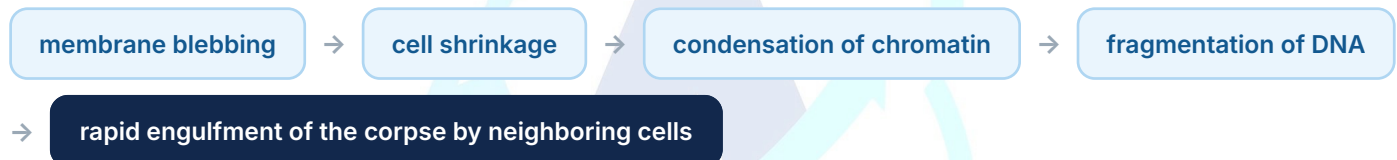
DEFINITION

The **most studied and well-known** form of **programmed cell death (PCD)**, found in both **development** and **diseases**.

IRREVERSIBLE

Caspase activation commits a cell to death, and the **engulfment genes** serve the purpose of dead cell removal.

THE ORCHESTRATED COLLAPSE OF A CELL



Markers of apoptosis are found in...

postmortem tissues of patients, and cell & animal models of neurodegenerative disorders

AD

Alzheimer's disease

HD

Huntington's disease

PD

Parkinson's disease

ALS

amyotrophic lateral sclerosis



Shared features

ROS, DNA damage, loss of mitochondria membrane potential, and aggregation of misfolded proteins are all common features associated with most neurodegenerative disorders and major forms of neuronal death.



Blocking caspases

Inhibiting cell death by a **pan caspases blocker** usually results in **delayed death** by **autophagy or necrosis**.



Extra caution when classifying a death as apoptosis

- ▶ Certain cell death-related phenomenon may **accompany** a cell death process while the **final execution** is carried out by a **different cell death mechanism**.



Apoptosis — Characteristics



Cellular Regulation

A **controlled process** regulated by a complex interplay of genes and signaling pathways.

- Essential for maintaining **tissue homeostasis**
- Eliminates **damaged, infected, or surplus** cells



Morphological Changes

- Cell shrinkage
- Chromatin condensation
- Formation of membrane-bound **apoptotic bodies**

Apoptotic bodies contain cell components and are efficiently phagocytosed by neighboring cells or immune cells, **preventing inflammation.**



Cell Signaling

apoptosis can be initiated through two main pathways

INTRINSIC · MITOCHONDRIAL

- Activated by **intracellular stress signals**, such as DNA damage or protein misfolding
- Involves the **release of cytochrome c** from mitochondria

vs

EXTRINSIC · DEATH RECEPTOR

- Activated by the **binding of death ligands** to cell surface **death receptors**



Caspases

central to apoptosis

Caspases are **proteases** that cleave specific cellular proteins, leading to the **controlled dismantling** of the cell.

INITIATOR CASPASES

Activated **early** in the process



TRIGGER

the activation of effector caspases



EFFECTOR CASPASES

Carry out the **final steps** of cell degradation



Apoptosis — Characteristics (cont.)



Role in Development

Critical during **embryonic development** to shape and sculpt tissues and organs.

- Removes excess cells
- Defines tissue boundaries

EXAMPLE

The formation of **fingers and toes** involves apoptosis between the digits.



Immune System

Plays a role in regulating the immune system:

- Eliminates immune cells that are **no longer needed** or have become **potentially harmful**
- Contributes to the **resolution of immune responses**



Pathological Conditions

dysregulation of apoptosis can lead to various diseases



Too much apoptosis

Associated with **degenerative diseases.**



Too little apoptosis

- ◆ Cancer
- ◆ Autoimmune diseases
- ◆ Certain viral infections



Cancer and Therapeutics

Cancer cells often **evade apoptosis**, allowing them to **proliferate uncontrollably.**

- Many cancer treatments, such as **chemotherapy** and **radiation therapy**, work by inducing apoptosis in cancer cells
- Developing drugs that **selectively induce apoptosis** in cancer cells is an active area of research



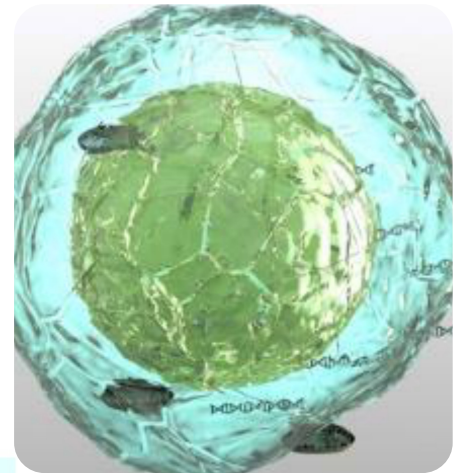
Necroptosis

DEFINITION

A distinct, **caspase-independent** form of **regulated cell death**.

- Shares some similarities with **necrosis** — a more chaotic and uncontrolled type of cell death
- Still distinct from **apoptosis** — another well-regulated form of cell death

Necroptosis has gained attention in recent years as an important cellular process involved in various **physiological and pathological conditions**.



First defined in 2005

A regulated form of **non-apoptotic** cell death with **necrotic cell morphology**



Triggered by **TNF α receptor 1 (TNFR1)**



Can be inhibited by the RIPK1 inhibitor **necrostatin 1 (Nec-1)**

EVIDENCE & TRIGGERS



ROS

Besides death receptor activators, such as **TNF**, **ROS** have also been shown to promote necroptosis.



Ischemic brain injury

Contributes to **delayed mouse ischemic brain injury**, which can be inhibited by necrostatin 1.



Multiple sclerosis

Activation of **RIPK1 and RIPK3** detected in MS patient cortical samples.

The RIPK1 inhibitor **Nec-1** **reduced oligodendrocyte death** in two MS animal models.



Necroptosis — Characteristics



Regulated Cell Death

A **programmed and regulated** form of cell death — unlike necrosis, which is typically uncontrolled and associated with cell damage and inflammation.



Initiation

- Initiated in response to specific signals, often when **apoptosis is blocked or inhibited**
- In some cases, triggered by **extracellular factors** or **intracellular damage**



Mechanisms

receptor-interacting protein kinases (RIPKs)

RIPK1

+

RIPK3

→

necrosome complex

→

execution of necroptosis

When activated, RIPK1 and RIPK3 form a complex known as the necrosome.



Morphological Features

- Swelling of organelles
- Plasma membrane rupture
- Release of intracellular contents

This release can induce **inflammation** and an immune response in surrounding tissues.



Inflammatory Response

Associated with the release of **damage-associated molecular patterns (DAMPs)**, which trigger inflammation and immune responses.

This **distinguishes necroptosis from apoptosis**, which is typically immunologically silent.



Roles in Disease

neurodegenerative

ischemic injury

inflammatory disorders

viral infections

Blocking or modulating necroptosis has shown promise as a potential therapeutic approach.



Therapeutic Potential

Understanding and manipulating necroptosis pathways may yield novel therapeutic strategies — valuable where **excessive cell death and inflammation** are problematic.

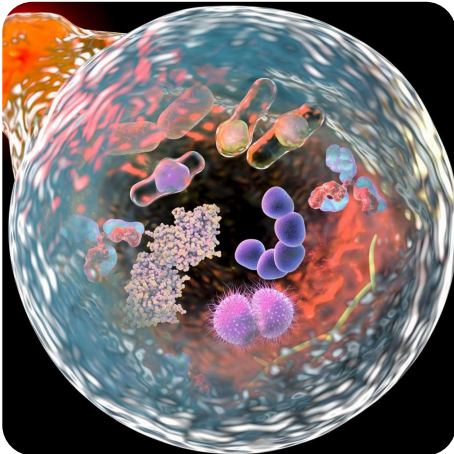


Necroptosis in Cancer

In some contexts, it can play a role in **suppressing tumor growth**. Inducing necroptosis in cancer cells has been explored as a potential anticancer strategy.



Autophagy

**auto**

self

+

phagy

eating

Greek — a cell “eating” its own components

DEFINITION

A cellular process that involves the **degradation and recycling** of cellular components and organelles.

A CRITICAL ROLE IN



Maintaining cellular homeostasis



Removing damaged or unwanted cellular materials



Responding to various stress conditions



Autophagy deficits in neurodegeneration

pathological mutations of proteins in AD, PD, HD and ALS

substrate recognition

lysosome
acidification

trafficking

membrane
permeabilization

Autophagy plays an important role in **cleaning up damaged mitochondria** and **aggregated proteins** — thus its **dysfunction contributes** to neurodegenerative pathology.

Defects in autophagy primarily play a role in neurodegeneration, but autophagy itself can also be **involved in several forms of cell death**.



Autophagy — Characteristics



Types of Autophagy

Macroautophagy

most well-known & extensively studied

Microautophagy

Chaperone-mediated autophagy



Process

in macroautophagy

A **double-membraned** autophagosome forms around cellular cargo (damaged organelles, protein aggregates)



The autophagosome **fuses with lysosomes**, which contain enzymes capable of breaking down the cargo



Degradation and recycling of the enclosed material



Regulation

A **highly regulated** process. Signaling pathways, including the **mTOR** (mammalian target of rapamycin) pathway, initiate or inhibit autophagy in response to **nutrient availability and stress conditions**.



Physiological Roles

- ◆ Removes damaged or dysfunctional organelles
- ◆ Clears misfolded or aggregated proteins
- ◆ Recycles cellular components
- ◆ Involved in cell differentiation and development



Stress Response

Often **upregulated** in response to nutrient deprivation, oxidative stress, and infection — allowing cells to **survive adverse conditions** by recycling components to provide essential nutrients.



Role in Disease

Dysregulation is associated with **neurodegenerative disorders** (Alzheimer's, Parkinson's), cancer and metabolic disorders. Autophagy may **promote or inhibit** disease progression, depending on the context.



A dual role — Cancer & Therapeutic Implications

CANCER

- ▶ **Promotes tumor survival** — provides nutrients and mitigates stress
- ▶ **Suppresses tumor initiation** — removes damaged cells and maintains genomic stability

Complex and context-dependent.

THERAPEUTIC MODULATION

- ▶ In some cases, **enhancing** autophagy may be beneficial
- ▶ In others, **inhibiting** autophagy may be desirable

Depends on the specific disease and circumstances.

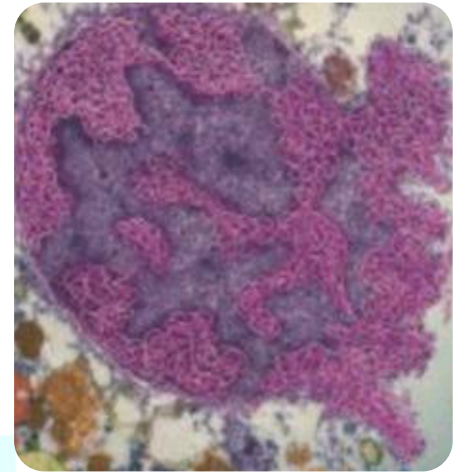


Parthanatos

DEFINITION

A type of **programmed cell death** that is **distinct from** apoptosis, necroptosis, and autophagy.

Characterized by activation of a specific pathway involving the enzyme **poly(ADP-ribose) polymerase (PARP)** and the subsequent release of **apoptosis-inducing factor (AIF)** from mitochondria.



IMPLICATED IN

neurodegenerative diseases

ischemic injury

CHARACTERISTICS



PARP Activation

initiated by hyperactivation of PARP

PARP is a **nuclear enzyme** involved in DNA repair and genomic stability. In response to DNA damage, PARP catalyzes the synthesis of **poly(ADP-ribose) (PAR) chains** as a signaling molecule.



Excessive PAR Formation

Excessive PAR forms due to **persistent DNA damage or cellular stress**. This hyperactivation of PARP consumes cellular energy resources, such as **NAD⁺** (nicotinamide adenine dinucleotide), leading to **energy depletion**.



Release of AIF

Excessive PAR triggers the translocation of **AIF** from the **mitochondria to the nucleus**. AIF then causes **chromatin condensation and DNA fragmentation**, leading to cell death.



Parthanatos — Characteristics (cont.)



Distinct from Apoptosis

in terms of molecular mechanisms and morphological features

APOPTOSIS

- Cell shrinkage
- Formation of apoptotic bodies

vs

PARTHANATOS

- Chromatin condensation
- Nuclear changes



Role in Disease

Parkinson's

Alzheimer's

stroke

myocardial infarction

Excessive activation of PARP and the subsequent cell death **contribute to tissue damage and degeneration.**



Therapeutic Implications

Research has led to potential strategies aimed at **blocking or modulating** the pathway.

Inhibitors of PARP have been investigated as potential treatments.



Components of Parthanatos

Several key components are involved in the process of Parthanatos:

PARP-1

Poly(ADP-ribose) polymerase 1 — the major isoform of a family of nuclear enzymes with multiple regulatory function

PARG

Poly(ADP-ribose) glycohydrolase — the major enzyme responsible for the catabolism of poly(ADP-ribose). Found in many tissues; may be subject to proteolysis generating smaller, active products

PAR

Poly(ADP-ribose)

AIF

Apoptosis-inducing factor

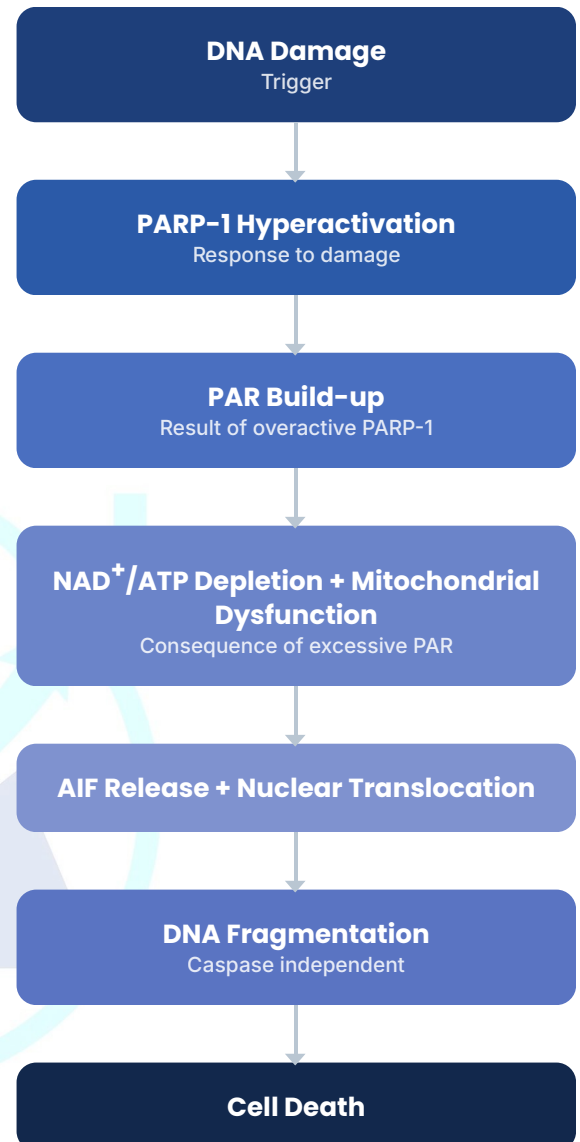
Iduna

A poly(ADP-ribose) (PAR)-dependent E3 ubiquitin ligase that regulates DNA damage



Sequence of Events in Parthanatos

- 1 **DNA damage** occurs (e.g., oxidative stress, ischemia, neurotoxic insults)
- 2 **PARP-1** gets activated to repair the damage
- 3 PARP-1 uses **NAD⁺** to create long chains of **PAR** (poly-ADP-ribose)
- 4 If the damage is too much:
 - PARP-1 becomes overactivated
 - Leads to excessive PAR production
 - Depletes cellular NAD⁺ and ATP → **energy crisis**
- 5 PAR (the polymer) itself acts as a **death signal**
 - It translocates to mitochondria
 - Signals the release of AIF (Apoptosis-Inducing Factor)
- 6 **AIF moves to the nucleus** and causes large-scale DNA fragmentation
- 7 **Cell dies by Parthanatos**



REGULATORY BRAKES ON THE PATHWAY



PARG

Acts as a **regulatory brake** by **degrading PAR** as it's being produced.



IDUNA

A **PAR-binding protein** that inhibits parthanatos by **blocking AIF translocation** and promoting DNA repair.



Parthanatos & Neurodegenerative Diseases

- Some research suggests the Parthanatos pathway may be involved in the **pathogenesis of neurodegenerative diseases**, particularly in the context of DNA damage and cell death.
- Excessive activation of PARP-1 and the subsequent initiation of Parthanatos can lead to **neuroinflammation and cell death in neurons**, contributing to the progression of certain neurodegenerative diseases.
- The exact role of Parthanatos in these diseases, and potential therapeutic interventions targeting this pathway, is an **active area of research** — with significant developments in this field.



PARP-1 — Characteristics

A **nuclear enzyme** that **detects DNA damage**.

17

mammalian PARP family proteins — PARP-1 is the **most abundant** and **best characterized**

>90%

of cellular PAR polymers are produced by PARP-1

500-fold

rise in activity within a few seconds when sensing mild DNA damage

Under physiological conditions, PARP-1 activity remains at a **low level**.



Mild or moderate stress

PARP-1 activation results in:

- DNA repair and transcription regulation to restore genome stability
- Degradation of oxidized or damaged proteins
- Maintenance of homeostasis

vs



Severe or sustained stress

Hyperactivation of PARP-1 causes cell death programs, such as **parthanatos**.



PARP-1 and Neurodegeneration

PARP-1 has emerged as a **major death regulator** in both acute neuronal injury and neurodegenerative disorders. **Oxidative stress** — one of the most important common features of neurodegenerative disorders and aging diseases — is able to activate PARP-1.

PARP inhibitors and genetic deletion of PARP-1 are **strongly neuroprotective** in NO-mediated toxicity, NMDA excitotoxicity, and experimental models of ischemic injury, traumatic brain injury, AD, HD, and PD.

INVOLVEMENT OF PARP-1 FOUND IN HUMAN PATIENT BRAINS, AND CELLULAR & RODENT MODELS OF

stroke

trauma

spinal cord injury

AD

PD

HD

MS

ALS

PARP-1 has been the subject of research due to its involvement in several mechanisms that contribute to neurodegenerative diseases:



DNA Repair

PARP-1 is primarily known for its role in DNA repair. It **senses DNA damage**, such as single-strand breaks, and facilitates the repair process. In neurodegenerative diseases, especially those associated with aging, **accumulated DNA damage and impaired DNA repair** can lead to neuronal dysfunction and cell death.



Oxidative Stress

PARP-1 is activated in response to oxidative stress, a common feature of many neurodegenerative disorders, including AD, PD, and ALS. **Overactivation** can decrease cellular NAD⁺ and ATP levels, leading to **energy depletion** and further oxidative damage.



Inflammation

PARP-1 can modulate inflammation by regulating the activity of transcription factors such as **NF-κB**. Inflammatory processes are implicated in several neurodegenerative diseases, and PARP-1's involvement in promoting inflammation can **worsen neuronal damage**.



Excitotoxicity

In conditions like **ischemic stroke** or **traumatic brain injury**, excessive activation of PARP-1 can lead to neuronal death through Parthanatos, involving mitochondrial dysfunction, release of mitochondrial DNA, and cell death.



Mitochondrial Dysfunction

PARP-1 activation can lead to mitochondrial dysfunction — a central feature in the pathogenesis of many neurodegenerative diseases — contributing to **energy deficits** and the generation of **ROS**, further damaging neurons.



PARP Inhibitors for Neurodegenerative Diseases



Concerns

Long-term use for **chronic** neurodegenerative diseases, due to potential side effects including **genome instability**.



However...

PARP-1 knockout mice are viable and resistant to numerous toxic stimuli — suggesting PARP family members may also play a role in DNA repair and maintaining genome stability.



Nevertheless

New potent, selective PARP-1 inhibitors that **cross the blood-brain barrier** could be beneficial in preventing or delaying disease progression.

AG-014699

AG14361



In Summary



Parthanatos plays important roles in

EXCITOTOXICITY

ACUTE NEUROLOGICAL DISEASES

ischemic stroke · traumatic injury

NEURODEGENERATIVE DISORDERS

PD · AD · HD · ALS · MS

Although cell death itself is the **endpoint event** at the late stage of neurodegeneration...

...pharmacological inhibitors and genetic deletions of cell death mediators show **beneficial effects** in cellular and animal models of neurodegenerative diseases.

Preventing or reducing cell loss are still **promising therapeutic interventions** that could probably slow down the disease progress.

LOOKING AHEAD — ESSENTIAL NEXT STEPS



Further investigation

Of parthanatos-signaling mechanisms and roles of Parthanatos mediators in different neurologic and neurodegenerative disorders.



Interactions

Understanding the interactions between Parthanatos and other major forms of cell death in neurodegenerative diseases.



Major Forms of Cell Death in Neurodegenerative Diseases

Forms of death		Apoptosis	Necroptosis	Autophagic cell death	Parthanatos
Triggers related to neuro-degeneration	Excitotoxicity	●	—	—	●
	Oxidative stress	●	●	—	●
	DNA damage	—	—	—	●
	Cytosolic calcium overload	●	—	—	●
	Aggregation of misfolded proteins	—	—	●	●
	Trophic factor withdrawal	●	—	—	—
	Nutrient starvation	—	●	●	—
Cell morphology		Chromatin condensation, small DNA fragmentation, apoptotic bodies, cell membrane blebbing	Cellular swelling, cell membrane rupture and release of intracellular content; usually accompanied by autophagy	Autophagic vacuoles	Loss of membrane integrity, chromatin condensation, large DNA fragmentation
Key mediators		Caspases, Bak, Bax, Cytochrome C	RIPK1, RIPK3	mTOR, PI3K, Beclin 1, ATG	PARP-1, AIF
Inhibitors		Caspases inhibitors, Bcl-2	Necrostatin 1	3-MA	PARP inhibitors, PARG, Iduna
Loss of membrane integrity		No	Yes	Yes	Yes
Energy-required		Yes	No	Yes	No
Inflammation		No	Yes	No	No
Example of neurologic & neurodegenerative diseases		AD, PD, HD, ALS, ataxias, ischemia	Ischemia, ALS, HD, MS	AD, HD, PD, ALS	Ischemia, PD, AD, HD, ALS
Landmark cellular events		Caspases activation	RIPK3 activation	Autophagosome formation, lysosome degradation	AIF translocation to nucleus

● trigger related to that form of death