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Review

From necroptosis to neuroinflammation: Unraveling mechanisms and therapeutic targets in age-related cognitive decline

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ABSTRACT

Aging is the major risk factor for several chronic conditions, including cognitive decline and dementia. It is accompanied by profound immune alterations characterized by a progressive decline in immune competence, a process known as immunosenescence. The resulting dysregulation of immune function leads to the overproduction of proinflammatory cytokines and fuels a persistent, low-grade inflammatory state termed inflammaging. This chronic inflammation contributes to dysfunction across the central and peripheral nervous systems, promoting neuronal damage and accelerating neurodegenerative processes such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and other age-related cognitive disorders. Within this framework, prolonged activation of inflammatory pathways can trigger regulated forms of cell death. Among these, necroptosis has recently emerged as a potential mediator linking inflammaging to neurodegeneration. Its core molecular effectors, including the receptor-interacting protein kinases RIPK1 and RIPK3 and the mixed-lineage kinase domain-like protein (MLKL), are increasingly expressed in aged neural tissues, promoting the release of damage-associated molecular patterns (DAMPs) that amplify glial activation, oxidative stress, and blood–brain barrier disruption. Growing evidence suggests that necroptotic signaling may be upregulated in the aging brain and in neurodegenerative disorders, where it could contribute to neuronal loss and cognitive impairment. This review discusses the potential role of necroptosis in the continuum between inflammation and neurodegeneration, highlighting emerging diagnostic and therapeutic perspectives. Epigenetic and circulating biomarkers, such as phosphorylated MLKL and specific microRNAs, may support early detection, while pharmacological and nutraceutical strategies targeting necroptosis show promising neuroprotective effects in preclinical studies.

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1. Introduction

The global aging population presents significant challenges in healthcare and scientific research [1,2]. Cognitive decline is a major concern in aging, with cognitive impairment and dementia being among the most prevalent syndromes affecting older people [3]. Therefore, understanding the molecular mechanisms that drive cognitive decline is crucial to develop effective preventive and therapeutic strategies for aging populations [4].

Cellular senescence is now recognized as a central process contributing to neurodegeneration and cognitive decline in aging [5–7]. Senescent cells adopt a senescence-associated secretory phenotype (SASP) characterized by irreversible cell-cycle arrest, that in turn induces the secretion of pro-inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-1β [8]. Altogether, these mechanisms sustain a chronic, low-grade inflammation known as inflammaging [9–11]. This persistent inflammatory milieu disrupts neuronal homeostasis, promotes glial activation, and accelerates synaptic dysfunction [12,13]. The intensity of inflammaging varies among individuals, depending on genetic, epigenetic, and environmental determinants [9,11].

This persistent inflammatory status has been shown to contribute to an active form of cell death, known as programmed cell death (PCD), which is implicated in tissue atrophy and neurodegenerative diseases [14,15]. Unlike non-PCD processes like necrosis, PCD is a regulated process involving controlled intracellular signalling cascades that play a crucial role in tissue homeostasis and development [14,15]. PCD pathways can be further divided into apoptosis, necroptosis, and pyroptosis [16].

Apoptosis is a caspase-dependent and generally non-lytic form of cell death initiated either through death receptor signalling (caspase-8-driven extrinsic pathway) or mitochondrial outer membrane permeabilization with apoptosome formation and caspase-9 activation (intrinsic pathway) [17]. Activation of executioner caspase-3 and caspase-7 leads to controlled dismantling of cellular structures, chromatin condensation, and apoptotic body formation, typically without sustained inflammation.

In contrast, necroptosis is a regulated lytic pro-inflammatory process that is triggered when caspase-8 activity is impaired [18]. It is defined by the assembly of the Receptor-interacting serine/threonine-protein kinase 1 (RIPK1)-RIPK3 necrosome and subsequent phosphorylation and oligomerization of mixed-lineage kinase domain-like (MLKL), which disrupts plasma membrane integrity and promotes the release of damage-associated molecular patterns.

Pyroptosis represents an inflammasome-driven, gasdermin-mediated lytic cell death pathway. Upon activation of inflammatory caspases (classically caspase-1, or caspase-4/5/11 in the non-canonical pathway), gasdermin D is proteolytically processed, producing an active N-terminal fragment that forms membrane pores and facilitates the release of IL-1β and IL-18 [19]. It is involved in many pathological conditions, including liver fibrosis [20] and spinal cord injury [21,22].

Notably, these pathways are functionally interconnected and not mutually exclusive. Coordinated supramolecular complexes, collectively referred to as PANoptosomes, integrate molecular components of apoptosis, necroptosis, and pyroptosis into a unified cell death platform. PANoptosis is defined as a coordinated form of programmed cell death in which multiple PCD pathways are simultaneously engaged in a manner that cannot be explained by any single component alone [23]. It is involved in many pathological conditions, including ischemic complications of diabetes mellitus [24] and pulmonary diseases [25].

In the present review, we focus primarily on necroptosis, while explicitly addressing areas of molecular convergence with apoptotic and pyroptotic signalling when relevant to neuroinflammatory amplification and neuronal vulnerability in the context of brain aging and neurodegeneration.

Although the exact role of necroptosis in age-related cognitive decline remains under investigation, recent findings suggest that necroptosis may contribute to neurodegeneration in aging brains [26–28]. Increasing evidence indeed supports the idea that necroptosis is markedly activated in the brains of Alzheimer's disease (AD) patients; recent studies have revealed that enhanced expression of key necroptosis proteins RIPK1, RIPK3, and (MLKL, not only occurs in hippocampal neurons of AD brains [29], but it is also specifically localized within granulovacuolar degeneration (GVD) bodies, i.e. cytoplasmic vacuolar lesions that represent a hallmark of AD [30]. This GVD-associated necroptosis represents an AD-specific delayed form of neuronal death that correlates with tau pathology and precedes overt neuronal loss. Moreover, independent neuronal necroptosis can drive neuroinflammation and cognitive decline even in the absence of complete cell death [31].

Necroptosis is regulated by genetic, molecular, environmental, and lifestyle factors [32] and is initiated through death receptor (DR) activation by various exogenous and endogenous stimuli, including nucleic acid sensors, pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), and toxins [15]. By inducing neuronal death and amplifying neuroinflammation, necroptosis may represent both a mechanistic hallmark and a therapeutic target in age-related cognitive decline and dementia [33].

Within this framework, the present review critically examines the molecular and cellular mechanisms linking necroptosis to neuroinflammation and neurodegeneration, highlighting emerging opportunities for early detection and therapeutic modulation in frail and pre-frail older adults [33]. In other words, based on available evidence, this narrative review aims to address the following research questions: (1) may necroptosis represent a key connection between neuroinflammation and neurodegeneration? (2) may necroptosis represent a target to be exploited to contrast neurodegenerative disorders progression?

2. Necroptosis, neuroinflammation, and age-related cognitive decline

Aging is frequently associated with a progressive decline in cognitive function, which can range from subtle cognitive impairment to severe dementia. Several biological processes contribute to this decline, among which progressive neuroinflammation and cell death play key roles [34]. These interconnected mechanisms drive neuronal damage and exacerbate age-related cognitive impairment. Chronic inflammation of the central nervous system (CNS), called neuroinflammation, is considered a hallmark of aging and has been proposed as a mediator of age-related cognitive decline [35]. Microglia, the innate immune cells of the CNS, orchestrate this response by releasing proinflammatory cytokines upon activation. Under chronic stress, sustained microglial activation induced mainly by DAMPs transitions from protective to neurotoxic, promote synaptic pruning, excitotoxicity, and neuronal death [36]; since necroptosis in neurons and glia may directly fuel the inflammatory cascade by releasing DAMPs that activate microglial receptors such as toll-like receptor 4 (TLR4) and Nucleotide-binding domain, Leucine-rich repeat family pyrin domain containing 3 (NLRP3), an age-associated increase in necroptosis could contribute to increased neuroinflammation and neurodegeneration [26,37–41]. Both animal models of aging and post-mortem analyses of AD and Parkinson's disease (PD) brains showed upregulation of necroptosis, particularly in the hippocampus and cortex, regions essential for learning and memory [27,42]. Increased activation of necroptosis in turn not only drives neuronal death but may also reprogram microglia and astrocytes toward a proinflammatory phenotype, compounding synaptic dysfunction.

In the next paragraphs, we summarize the available evidence about the putative link between necroptosis and neuroinflammation in the framework of age-related neurodegeneration.

2.1. Necroptosis, an alternative form of PCD

Based on the involvement of inflammatory response, PCD can be grouped into two broad categories: apoptotic cell death and non-apoptotic cell death [16]. Apoptotic cell death is the canonical form of PCD and represents a "silent" process of non-inflammatory cell self-destruction, that tends to limit tissue damage induced by an aggressive immune response [43]. In contrast, necroptosis and pyroptosis, two forms of non-apoptotic cell death, are associated with cell swelling, loss of plasma membrane permeability, membrane rupture, and the release of specific DAMPs and proinflammatory signals into the cellular microenvironment, similarly to necrotic events [16,37–41]. However, whereas pyroptotic cell death is generally a primary response to acute injuries, or to infectious microorganisms, necroptosis mimics the features of both apoptosis and necrosis, playing an important role in chronic inflammation.

Apoptotic and necroptotic cells initiate their own demise through a cellular "program" activated by the stimulation of DRs. However, whereas both apoptosis and pyroptosis are dependent on caspase (CASP) activation, necroptosis is a caspase-independent process that occurs when apoptotic signalling is inhibited [44]. CASPs are cysteine proteases considered the executioners of the sequential events leading to cell death. Among the members of this family, CASP-8 has been shown to be the initiator of the extrinsic apoptosis pathway. In addition, CASP-8 can inhibit the necroptosis pathway mediated by RIPK3 and the pore-forming protein MLKL. Consequently, the inhibition of CASP-8 by specific molecules shifts extrinsic apoptosis to necroptosis, through the activation of RIPK3 and MLKL. Once activated, MLKL translocates to the membrane, causing pore formation and the release of intracellular components [45,46]. Therefore, necroptosis can be defined as an alternative mode of PCD that occurs in RIPK3-expressing cells when normal CASP-8-dependent events are inhibited [47–49].

Necroptosis can be initiated by a range of threat- and danger-related stimuli [28,50] through two main groups of signalling pathways: the canonical or RIPK-1-dependent pathway, triggered by tumor necrosis factor (TNF)-receptor superfamily members and leading to RIPK1-dependent RIPK3 activation, and the non-canonical RIPK-1-independent pathway, which can be initiated by TLRs agonists. These in turn activate RIPK3 via the adaptor protein TIR-domain-containing adapter-inducing interferon-β (TRIF),; alternatively, especially in the context of an infection (typically a viral infection, for instance influenza virus A infection), necroptosis can be activated by the sensor Z-DNA binding protein (ZBP1) [51].

Accordingly, necroptotic stimuli can be divided into two main groups: endogenous stimuli, acting mainly through the canonical pathway (RIPK-1-dependent), include TNF-α, the FS7-associated cell surface antigen (Fas), the TNF-related apoptosis-inducing ligand (TRAIL), and interferon (IFN)I, among others; and exogenous stimuli, which mainly trigger necroptosis via the RIPK-1-independent pathway and include pathogen-associated molecular patterns (PAMPs), lipopolysaccharides (LPS), double-stranded RNA (dsRNA), and viruses [52].

2.1.1. Endogenous stimuli of necroptosis

Among the several members of the TNF family of ligands and receptors, TNF-α is the best-known trigger of necroptosis. Although enhanced TNF shedding is a general phenomenon of lytic cell death rather than a specific apoptosis- or necroptosis-related feature, TNF-α is indeed considered a necroptosis-associated alarmin. This interpretation is also supported by the positive effects of TNF receptor 1 (TNFR1) or TNF removal in improving inflammation associated with necroptosis [53]. It has recently been proposed that TNF-α produced in the meninges may diffuse into the underlying grey matter, causing TNFR1-dependent necroptotic neuronal cell death either directly or through glial cell activation [54]. A relevant interplay between TNF and IFN pathways in the induction of necroptosis has also been reported [55–57]. Furthermore, FAS and TRAIL, two other members of the TNF superfamily, have also been found to activate the necroptosis pathway, through IFN-I and TNF signalling [45].

Furthermore, several investigations have shown that mammalian target of rapamycin (mTOR) is a potent inducer of necroptosis, through its interaction with the TNF pathway and by inhibiting the autophagy process [58,59]. In physiological conditions, mTOR contributes to maintaining homeostasis by removing senescent, defective, or malignant cells, both by directly regulating the removal and interaction of RIPKs, and by exploiting reactive oxygen species (ROS). Specifically, ROS production and calcium dyshomeostasis in mitochondria promote necroptosis via a mechanism that is universal for all cell types [60]. Interestingly, in neurodegenerative processes, mitochondrial damage, oxidative stress, and abnormalities in calcium signalling in neurons and astrocytes have been identified [61,62]. The increased intracellular calcium concentration observed in the cytosol and mitochondria of senescent cells, such as hippocampal neurons, alongside altered calcium homeostasis and/or iron overload associated with the overproduction of ROS, supports the hypothesis that intracellular calcium dyshomeostasis is a mechanism underlying cognitive deficits seen in both normal aging and neurodegenerative diseases [63], putatively representing a biochemical link between necroptosis and neurodegeneration. Endogenous mitochondrial DNA (mtDNA) released into the cytosol during mitochondrial stress or damage in CNS cells can act as a DAMP. In neurons and glial cells, cytosolic mtDNA may activate nucleic-acid sensing pathways, including sensors such as ZBP1, with consequent innate immune activation and sterile neuroinflammation that may favor necroptotic signaling [64]. The most common endogenous stimuli of necroptosis and their prevalence in brain cells of older individuals are summarized in Table 1.

2.1.2. Exogenous stimuli of necroptosis

PAMPs are potent exogenous initiators of necroptosis, due to many bacterial compounds that stimulate RIPK3-mediated pathways. *Salmonella typhimurium* promotes the production of IFN-I, which drives necroptosis of macrophages and allows bacterial immune evasion [68,69]. Furthermore, there is evidence that bacterial heptameric β-pore-forming toxins, including *Staphylococcus aureus* α-toxin, *Escherichia coli* hemolysin, *Helicobacter pylori* vacuolating cytotoxin A, *Clostridium perfringens* ε-toxin, and enterotoxin, also induce necroptosis [70]. *Mycobacterium tuberculosis*, the cause of chronic lung infections and other systemic infections, including those affecting the CNS, is another example of an intracellular microorganism capable of stimulating the necroptotic pathway [71,72], and, in subjects aged 65 or older, the susceptibility and mortality from tuberculosis infection increase significantly [73]. The lipopolysaccharide (LPS), also known as endotoxin, is a component of the outermost membrane of the cell envelope of Gram-negative bacteria [74] and has also been associated with both necroptosis of brain microvascular endothelial cells and cognitive dysfunction [75]. LPS is able to activate Toll-like receptor 4 (TLR4) [76], a member of the TLR

Table 1
Endogenous stimuli levels and susceptibility in older people.

Endogenous stimuli	CNS target cells	Increased levels in aging
TNF-α, IL-1β, RIPK3	Microglia, neurons [45]	Yes [26]
Fas, TRAIL	Glial cells [55–57]	No data
ROS and Ca^{2+}	Neurons and astrocytes [60–62]	Yes [63,65]
Endogenous mtDNA	Microglia [64] and neurons [66]	Yes [67]

Notes: Ca = calcium; CNS = central nervous system; Fas = FS7-associated cell surface antigen; IL = interleukin; RLR = Retinoic acid-inducible gene I (RIG-I)-like receptors; ROS = reactive oxygen species; TLR = toll-like receptor; TNF = tumor necrosis factor; RIPK = Receptor-interacting serine/threonine-protein kinase 3; TRAIL = TNF-related apoptosis-inducing ligand; ZBP1 = Z-DNA binding protein 1.

superfamily. Both TLR3 (typically activated by viruses) and TLR4 (typically activated by LPS expressed by Gram negative bacteria) are potent necroptosis activators via a mechanism that leads to necrosome formation [50]. The altered expression of the transmembrane receptor TLR4 plays a pivotal role in aging-associated diseases, as shown by the TLR4-dependent persistent inflammation and necroptosis, which correlate with the onset and exacerbation of common age-related conditions [77]. Furthermore, recent studies have reported a link between the activation of endosomal TLR3 and senescence [78]. The endosomal transmembrane receptor TLR3 indeed triggers a complex intracellular cascade that leads to necroptosis of CNS cells. In contrast, TLR3 suppression in neonatal mice affected by cognitive dysfunction (experimentally induced by sevoflurane) has been reported to have a protective effect against necroptotic events [79,80].

Beyond the interaction with TLR3, viral infections can trigger necroptosis by means of the ZBP1-RIPK3-MLKL pathway. ZBP1, a double-stranded DNA (dsDNA) sensor, which is traditionally known for activating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling in response to pathogen invasion [81], has recently been identified as another important sensor of necroptosis during both viral and non-viral infections. ZBP1 can sense an unusual form of RNA known as Z-RNA, which tends to form under certain stress conditions, and trigger necroptosis. Endogenous Z-RNA is generated under oxidative stress conditions through the ZBP1-RIPK3-MLKL pathway [82]. Studies are currently underway to characterize the regulatory role of ZBP1 in α-synuclein-induced necroptosis and pyroptosis of glial cells [83]. ZBP1 can also induce, in response to infecting pathogens, a type of inflammatory cell death known as PANoptosis, which includes pyroptosis, necroptosis and apoptosis simultaneously [84–86]. Recent research suggests also that the Zbp1 gene plays a role in several aspects of aging, such as cellular senescence, chronic inflammation, DNA-damage response, and mitochondrial dysfunction [87,88].

Overall, ZBP1 may represent a key link between infections (typically viral), necroptosis, and brain aging.

Also, retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), representing the key sensors for virus detection, have been associated with the induction of necroptotic pathways [68,80,89]. RLRs, are able to mediate the transcriptional induction of IFN-I and the stimulation of interferon genes (STING), thus leading to the secretion of IFN-I and proinflammatory cytokines in response to cytosolic nucleic acids [68,89]. RLR-induced necroptosis is promoted by lysosomal destabilization and cathepsin D release into the cytoplasm and has also been observed in dendritic cells [90].

Beyond infections, among other frequent exogenous inducers of necroptosis, there are some stimuli able to promote extracellular stress, including hyperoxia exposure, ischemia-reperfusion injury, osmotic stress, heat stress, and drug stimulation [18]. Emerging evidence has suggested that ionizing radiation at different doses also produces different types of cell death. Indeed, whereas low-dose X-rays (<5 Gy/fraction) activate mitotic catastrophe and apoptosis, high-dose X-rays (8–30 Gy/fraction) induce necrosis and necroptosis [91]. Radiation has been shown to induce senescence in different cell types, including neurons, microglia, astrocytes, and cerebral endothelial cells, contributing to brain aging and the development of various neurological and neuropsychological disorders [92]. In addition, increasing evidence shows a close relationship between human radiation sensitivity and age-related health effects [93]. Hyperoxia exposure has been reported to cause significant lung damage by inducing oxidative stress, which in turn may activate necroptosis. Moreover, through an increased production of ROS, hyperoxia promotes epigenetic alterations of gene expression, leading to cell senescence and death. In addition, hyperoxia inhibits mitochondrial respiration and promotes cardiolipin oxidation and cytochrome c release, further contributing to the induction of cell death pathways [94,95]. The necroptotic pathway can also be triggered by cerebral ischemia and cerebral ischemia/reperfusion injury [96,97], and by heat stress [98]. Exposure to high temperature has been shown to induce cognitive impairment in both experimental animals and humans naturally exposed to extreme hyperthermia [99]. In addition to environmental high temperature, mainly caused by increasing global warming, older adults, because of their increased vulnerability to heat-related injuries following exposure to heat stress, show an increased risk of “heatstroke”, a heat stress-induced life-threatening condition associated with circulatory failure and multiple organ dysfunction, and characterized by a raised core body temperature and CNS dysfunction, a condition known as hyperthermia syndrome [100].

Table 2
Exogenous stimuli levels and susceptibility in older people.

Exogenous stimuli	Target cells	Increased susceptibility in aging
Salmonella typhimurium	Macrophages [68]	Yes [69,101]
Mycobacterium tuberculosis	Neurons and microglia [71,72]	Yes [73]
LPS	CNS microvascular endothelial cells [75]	Yes [75]
Ionizing radiation	Neurons, microglia, astrocytes, and cerebral endothelial cells [91,92]	Yes [93]
Hyperoxia exposure and osmotic stress	CNS cells [94,95]	No data
Ischemia–reperfusion injury	Neurons [96,97]	No data
Heat stress	Neurons [98]	Yes [99,100]

Notes: CNS = central nervous system; LPS = lipopolysaccharide.

The most common exogenous stimuli of necroptosis and their prevalence in older individuals are summarized in Table 2.

2.2. Molecular mechanisms of necroptosis

2.2.1. The pivotal role of RIKP1 and RIPK3

Necroptosis is a tightly regulated form of programmed necrosis governed by the serine/threonine kinases RIPK1 and RIPK3, and the effector protein MLKL. The two pathways of activation of necroptosis are described in Fig. 1. The canonical pathway is typically triggered by TNF-α binding to TNF receptor 1 (TNFR1), which promotes the assembly of Complex I, composed of TNFR1-associated death domain protein (TRADD), TNF receptor-associated factors 2 and 5 (TRAF2/TRAF5), RIPK1, cellular inhibitors of apoptosis proteins (cIAP1 and cIAP2), and the linear ubiquitin chain assembly complex (LUBAC) [45,102]. Complex I represents a critical checkpoint between cell survival and cell death. When RIPK1 is extensively polyubiquitinated, NF-κB and mitogen-activated protein kinase (MAPK) pathways are activated, thereby promoting cell survival and inflammation resolution. While Complex I acts as the upstream decision node, the shift to Complex II represents the commitment step toward necroptosis. This process involves the deubiquitination of RIPK1, its recruitment of the Fas-associated death domain (FADD) protein, and the formation of a cytosolic death-inducing complex containing RIPK1, RIPK3, FADD, and caspase-8 (CASP-8) [103].

Within Complex II, the balance between apoptosis and necroptosis depends on the regulatory role of the cellular FLICE-like inhibitory protein (cFLIP). The long isoform ($cFLIP_L$) promotes CASP-8 activation and subsequent apoptosis, whereas the short isoform ($cFLIP_S$) inhibits CASP-8 activity, thereby preventing apoptosis and favoring necroptosis [103,104]. When caspase-8 is inhibited, RIPK1 and RIPK3 interact via their RIP homotypic interaction motif (RHIM) domains, leading to mutual phosphorylation and necrosome formation. Activated RIPK3 then phosphorylates MLKL at Thr357 and Ser358, inducing MLKL oligomerization and translocation to the plasma membrane, where it forms cation-permeable pores that disrupt ionic homeostasis, cause cell swelling, and culminate in plasma membrane rupture [28]. As a result,

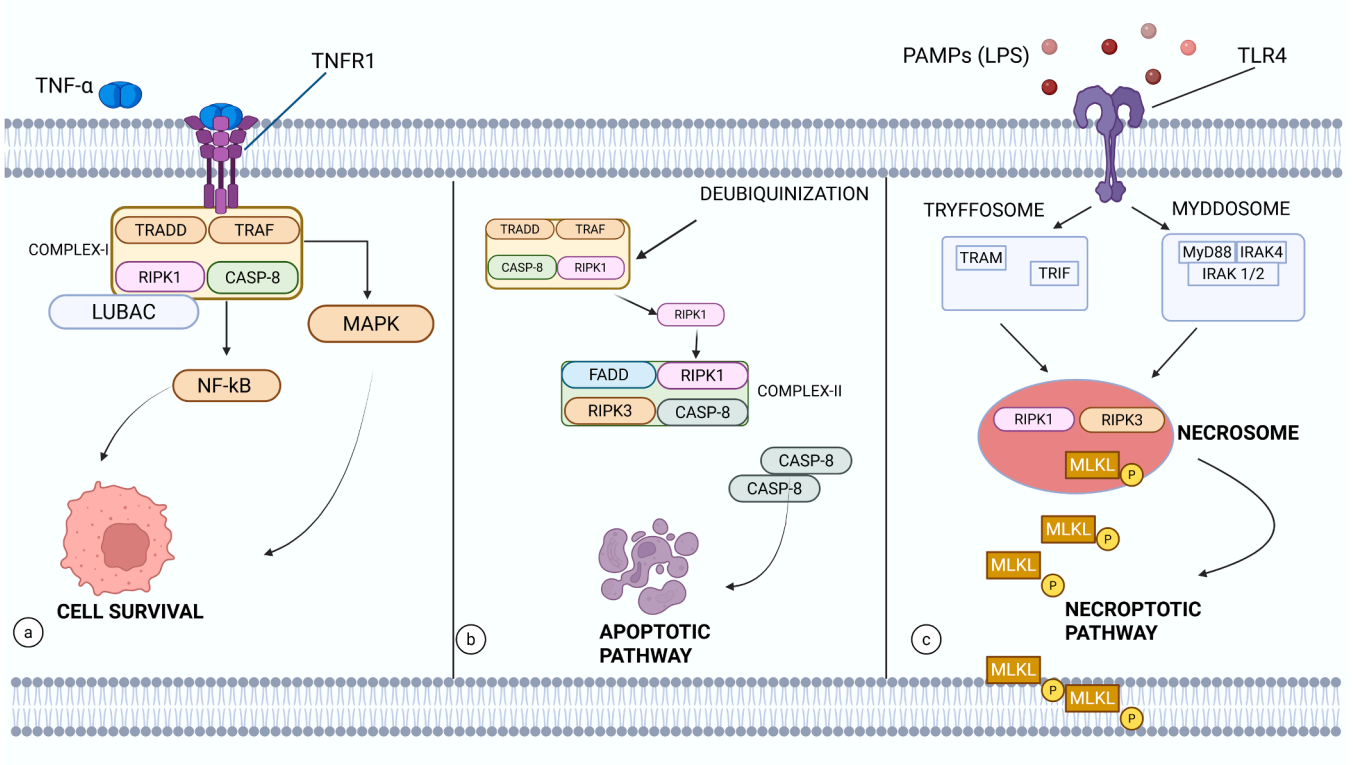

Fig. 1. Molecular mechanisms of necroptotic pathways This figure summarizes the major signaling pathways leading to cell survival, apoptosis, or necroptosis following activation of tumor necrosis factor receptor 1 (TNFR1) or Toll-like receptor 4 (TLR4). (a) **TNFα-mediated survival signaling**. Binding of tumor necrosis factor- α (TNF- α) to TNFR1 induces the assembly of Complex I at the plasma membrane. This complex consists of TNFR1-associated death domain protein (TRADD), TNF-receptor-associated factors 2 and 5 (TRAF2/TRAF5), RIPK1, and cellular inhibitors of apoptosis proteins 1 and 2 (cIAP1 and cIAP2). Recruitment of the linear ubiquitin chain assembly complex (LUBAC) promotes RIPK1 ubiquitination, which stabilizes Complex I and activates downstream NF-κB and mitogen-activated protein kinase (MAPK) signaling, ultimately promoting cell survival. (b) **Apoptotic signaling.** In contrast, deubiquitination of RIPK1 promotes its dissociation from membrane-associated Complex I, allowing the formation of cytosolic Complex II, composed of RIPK1, RIPK3, Fas-associated death domain (FADD), and caspase-8 (CASP-8), which drives the apoptotic pathway, resulting in programmed cell death. (c) **Necroptotic signaling.** In TLR-mediated necroptosis, activation of Toll-like receptor 4 (TLR4) by pathogen-associated molecular patterns such as lipopolysaccharide (LPS) induces the formation of two different signaling complexes: the "Myddosome", created by the oligomerization of the MyD88 death domain and composed of six MyD88 molecules, four IRAK4 molecules and four IRAK1/2 molecules arranged in a single-stranded helix, and the TRIF-dependent signaling complex ("Triffosome"), composed of the adaptor protein TRAM and TRIF. Activation of TRIF promotes the recruitment of RIPK1 and RIPK3, which in turn activate, via phosphorylation, MLKL, leading to necrosome formation. Activation of the endosomal TLR3 by poly I:C also determines the recruitment of TRIF, followed by RIPK1 and RIPK3. In both cases, RIPK3 phosphorylates (P) MLKL, promoting its activation, translocation to the membrane, oligomerization and, ultimately, necroptosis.

necroptosis is activated when CASP-8–mediated apoptotic pathways are inhibited. Fig. 1B schematically depicts this CASP-8 checkpoint.

Beyond TNFR1 signaling, necroptosis can also be indirectly induced through the activation of TLRs, particularly TLR3 and TLR4 (Fig. 1C), in response to PAMPs and DAMPs. TLR4 and TLR3 are respectively activated by LPS and polyinosine-polycytidylic acid (poly I:C), a synthetic dsRNA [105,106]. In both pathways, RIPK3 phosphorylates MLKL, driving its activation, oligomerization, and translocation to the plasma membrane, ultimately culminating in necroptosis. The formation of a TRIF-dependent necrosome, composed of TRIF, RIPK3, and MLKL, represents a key event in this necroptotic signaling route, bypassing RIPK1 in certain cell types [105,107]. The resulting MLKL activation and membrane permeabilization play a critical role in necroptotic execution.

In addition to TLR pathways, ZBP1 has also emerged as a crucial cytosolic regulator of necroptosis due to its capacity to interact with RIPK3 and RIPK1 [81,108,109]. ZBP1 can also initiate necroptosis, by recognizing Z-nucleic acids (unusual left-handed conformations of RNA or DNA) formed during viral infection, oxidative stress, or endogenous retroelement activity. Upon recognition, ZBP1 directly interacts with RIPK3 via its RHIM domain, inducing RIPK3 phosphorylation and MLKL activation independently of RIPK1. Both exogenous and endogenous double-stranded RNA can activate ZBP1 [110–112].

Together, these interconnected signaling routes (TNFR1, TLR3/4, and ZBP1) converge on RIPK3-mediated MLKL activation, constituting a networked necroptotic signaling architecture leading to cell membrane disruption and inflammatory cell death. The integration of death-receptor, innate immune, and nucleic-acid sensing pathways explains why necroptosis is a recurring feature in chronic neuroinflammation and neurodegeneration, where both inflammatory cytokines and endogenous nucleic acids accumulate.

2.2.2. Necrosome formation and the role of MLKL on membrane permeabilization

The cytosolic Complex IIc, also known as the "necrosome", is a supramolecular organelle essential for necroptosis, whose formation is significantly enhanced by CASP-8 inhibition [113]. Necrosome assembly is initiated by the interaction of RIPK1 and RIPK3 via their RIP homotypic interaction motif (RHIM) domains [16]. This interaction promotes the auto- and trans-phosphorylation of both kinases, leading to the recruitment of MLKL, a key effector protein in necroptosis signaling. Subsequently, RIPK3-mediated phosphorylation at Thr357/Ser358 of MLKL triggers its activation [16]. More specifically, once activated, RIPK3 undergoes autophosphorylation before phosphorylating MLKL through interactions between MLKL and its

pseudo-kinase domain. This interaction induces a conformational change in the pseudokinase domain of MLKL, driving its oligomerization and translocation from the cytosol to the inner leaflet of the plasma membrane. Once there, MLKL integrates into the membrane, where it forms cation-selective pores that disrupt ionic gradients and promote Na^+ and Ca^{2+} influx; these ionic perturbations lead to osmotic swelling, mitochondrial depolarization, and plasma membrane rupture, ultimately leading to cellular lysis [45,114–117]. Beyond direct membrane disruption, MLKL activation triggers a cascade of inflammatory amplification: MLKL-mediated membrane permeabilization allows the passive release of intracellular DAMPs such as high mobility group box 1 (HMGB1), histones, heat shock proteins, IL-1 family cytokines, and adenosine triphosphate (ATP) [41,118]. These DAMPs bind to TLR4, TLR9, and RAGE on glial cells, stimulating NF-κB and inflammasome activation. The resulting release of proinflammatory cytokines creates a feed-forward loop in which necroptosis perpetuates sterile neuroinflammation, linking molecular death execution to tissue-level pathology in the aging brain [28,119].

2.3. Impact of necroptosis in CNS cells

In the CNS, during aging, a general and paradoxical activation of inflammatory mediators has been shown to induce an uncontrolled and prolonged neuroinflammatory state, known as neuroinflammaging [9]. This condition is characterized by the chronic activation of microglia and astrocytes, which secrete pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α [15]. Sustained neuroinflammation contributes to synaptic dysfunction, neuronal loss, and cognitive deficits [120]. Necroptosis amplifies this neuroinflammatory cycle by releasing DAMPs, further increasing the production of inflammatory mediators [15]. This feedforward loop leads to a prolonged, uncontrolled and self-sustained inflammatory response, accelerating neuronal aging and neurodegeneration.

2.3.1. Necroptosis of glial cells

In the CNS, during aging, a general and paradoxical activation of inflammatory mediators has been shown to induce an uncontrolled and prolonged neuroinflammatory state, known as neuroinflammaging [9]. This condition is characterized by the chronic activation of microglia and astrocytes, which secrete pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α [15]. Sustained neuroinflammation contributes to synaptic dysfunction, neuronal loss, and cognitive deficits [120]. Necroptosis amplifies this neuroinflammatory cycle by releasing DAMPs, further increasing the production of inflammatory mediators [15]. This feedforward loop leads to a prolonged, uncontrolled and self-sustained inflammatory response, accelerating neuronal aging and neurodegeneration.

Necroptosis significantly impacts almost all CNS cells, particularly astrocytes, microglia, and neurons. Astrocytes, the most abundant glial cells in the human brain, play extensive roles in maintaining CNS homeostasis, including regulating synaptic activity and responding to ischemic injury. Notably, astrocytes have been shown to have neuroprotective effects in neurodegenerative diseases such as Alzheimer's disease [121–123]. However, when astrocytes undergo necroptosis, this can result in neuronal death due to the loss of their crucial supportive functions [124]. Such necroptotic events in astrocytes have been linked to the onset and progression of various neurodegenerative diseases, highlighting the dual role of astrocytes as both protective and potentially harmful agents in CNS pathology [121]. Microglia act as the resident immune cells of the brain, performing macrophage-like functions as the first line of defense against injury and disease. Recent studies indicate that microglial cells adopt various functional states in response to stimuli, including cellular senescence and different forms of programmed cell death, ranging from neuroprotective (M2-like) to neurotoxic (M1-like) phenotypes. Notably, necroptosis has emerged as a key mechanism in microglial responses, alongside apoptosis and ferroptosis, highlighting its relevance in neuroinflammatory and neurodegenerative processes [125]. Specifically, microglia can undergo necroptosis triggered by various factors, including TLR4 activation, which leads to neuroinflammation and subsequent neural damage [36]. The inflammatory response associated with microglial necroptosis exacerbates neuronal degeneration and has been recognized as a significant contributor to age-related neuroinflammation [26]. Both astrocytes and microglia release DAMPs during necroptosis [126], which in turn activate nearby CNS cells, leading to heightened transcription of RIPK3 and increased cytokine production, further fueling inflammation through cytokine release [110,127].

2.3.2. Necroptosis of neurons

In neurons, activated necroptotic signaling pathways have been identified in various animal models, suggesting a critical role for necroptosis in neurodegenerative conditions such as Alzheimer's disease and multiple sclerosis [54,128]. For instance, increased expression of MLKL, a critical effector of necroptosis, has been correlated with toxicity in neurons associated with amyloid pathologies [129]. Moreover, evidence suggests that necroptosis may underlie dopaminergic neuron death in Parkinson's disease via the formation of necrosomes, leading to mitochondrial dysfunction and increased ROS generation [130,131]. Notably, amyloid-beta aggregates have been shown to engage TLR4 signaling, resulting in delayed and sustained Myddosome formation, which may contribute to chronic neuroinflammation and sensitize neurons to necroptotic cell death [132].

Consequently, neuronal death may occur directly through necroptotic mechanisms or indirectly via necroptotic signaling in neighboring astrocytes and microglia in response to various endogenous and exogenous stimuli [133,134].

The intricate interplay between astrocytes, microglia, and neurons in the context of necroptosis underscores the complexity of CNS pathologies. Targeting necroptosis has emerged as a potential therapeutic strategy to mitigate neuroinflammation and neuronal death associated with various neurodegenerative diseases [135]. Thus, understanding the precise roles and interactions of glial cells and neurons during necroptotic processes is crucial for developing effective interventions aimed at preserving neuronal health in the face of CNS injuries and diseases.

2.4. Necroptosis and cognitive decline

Several factors may contribute to necroptosis-driven cognitive decline. Neuronal loss due to necroptotic cell death reduces the number of functional neurons, particularly in brain regions involved in memory and learning, such as the hippocampus [26]. In this context, necroptosis leads to the release of DAMPs, which may in turn stimulate surrounding immune and glial cells to produce inflammatory cytokines that impair synaptic plasticity and neurotransmission, which are critical for cognitive function. Chronic neuroinflammation compromises the blood-brain barrier (BBB) through local mechanisms within the neurovascular unit, while circulating inflammatory mediators associated with inflammaging may further exacerbate barrier disruption from the periphery, facilitating the infiltration of peripheral immune cells into neural tissue [136].

Additionally, oxidative stress is a major driver of brain aging and necroptosis. Age-related mitochondrial dysfunction leads to excessive production of ROS, which in turn damages mitochondrial DNA, impairs electron transport chain efficiency, and reduces ATP synthesis. This mitochondrial failure not only compromises neuronal energy homeostasis but also promotes the activation of necroptotic signaling pathways involving RIPK1 and RIPK3. ROS-mediated necroptosis, particularly in neurons and glial cells, contributes to chronic neuroinflammation and cellular loss during aging [59,137–139].

Another critical player is mTOR, a highly conserved serine/threonine kinase that regulates gene expression, metabolism, immune responses, and cell death. Evidence suggests that mTOR signaling, on one hand,

promotes necroptosis by modulating ROS production and activating RIPKs [59,138,140], and, on the other hand, it is involved in the pathophysiology of AD [141,142] and other age-related neurodegenerative diseases, including Parkinson disease [143]. Furthermore, increased levels of mTOR in AD mouse brains have been reported to be associated with increased amyloid-beta deposition, which is the main hallmark of AD [144]. Therefore, at the brain level, mTOR pathways may act by promoting both necroptosis and neurodegeneration.

Nowadays, the relationship between necroptosis and age-related cognitive decline is directly supported by an increasing amount of evidence, especially from pre-clinical investigations. In this regard, a recent study by Arrazola and colleagues reported a reduction of age-induced axonal degeneration and neuroinflammation in MLKL-knockout mice compared to wild-type mice. Furthermore, this study found that MLKL loss was associated with an improvement in memory and synaptic transmission, thus suggesting that modulation of MLKL might be an interesting target to counteract age-related cognitive decline [27].

The complex crosstalk between necroptotic and inflammatory pathways could be supported, at least in part, by metabolic dysfunction. In this regard, both hyperthyroidism and diabetes have been reported to be associated with inflammation and necroptosis. Specifically, in a recent study, an animal model of diabetes, i.e. a leptin receptor-deficient mouse, showed reduced spatial learning and memory abilities, accelerated temporal lobe atrophy, signs of neurodegeneration of hippocampal cells, and increased levels of both necroptosis (RIP1, RIP3, MLKL) and inflammation (IL-6 and TNF-α) markers, compared to wild-type mice [145]. In another study, the experimental induction of Graves' disease (by means of an adenovirus containing thyrotropin receptor amino acid residues 1–289) in an AD animal model (APP/PS1 mice) induced accelerated neuronal loss and beta-amyloid deposition, together with neuroinflammation, microglia polarization and increased necroptosis induction [146].

In summary, necroptosis is associated with chronic neuroinflammation in aging brains, and preclinical models suggest it might contribute causally to neuronal loss and cognitive decline. In the next paragraphs, we will discuss promising strategies for mitigating the deleterious effects of necroptosis in the framework of age-related neurodegenerative disorders.

The main pathways potentially linking necroptosis to cognitive decline are described in Fig. 2.

3. Diagnostic strategies to intercept necroptosis and neuroinflammation

Age-related cognitive dysfunction has been significantly associated with dysregulation of immune responses [140,147]. Studies have shown increased depletion of B and $CD8^+$ T cells along with higher neutrophil levels and neutrophil-related markers of inflammation in patients with cognitive decline, compared to healthy individuals [148,149]. This observation supports the hypothesis that cognitive impairment is linked

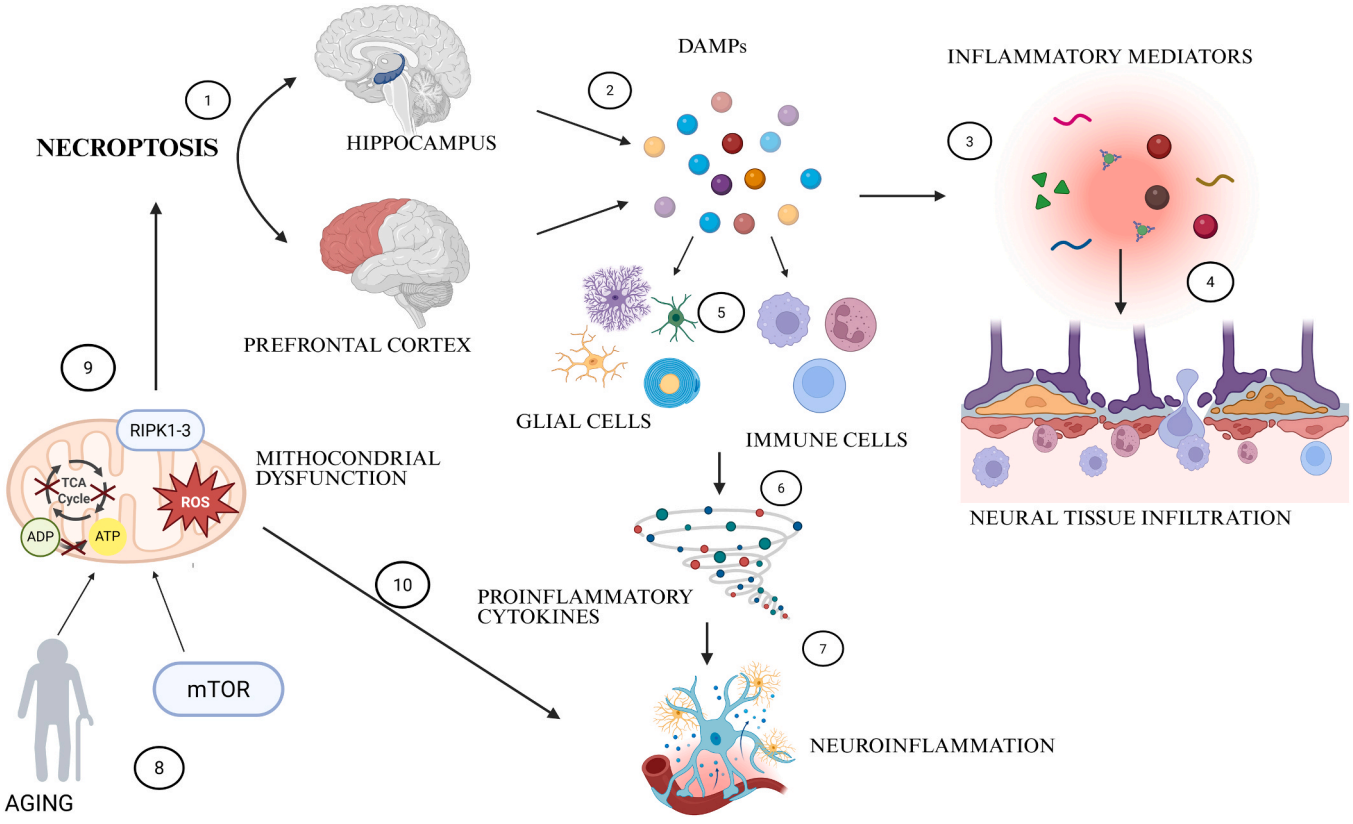

Fig. 2. Necroptosis and cognitive decline Necroptosis, a regulated form of inflammatory cell death, contributes to cognitive dysfunction by initiating neuroinflammatory cascades within key brain regions such as the hippocampus and prefrontal cortex (1), areas critically involved in learning, memory, and executive function. Necroptotic cell death results in membrane rupture and the release of damage-associated molecular patterns (DAMPs) (2), which act as endogenous danger signals. DAMPs stimulate the production of inflammatory mediators (3), including cytokines and chemokines; these mediators promote neural tissue infiltration by immune cells across the blood–brain barrier (4), amplifying the local inflammation within the neural tissue; activated microglia, astrocytes and peripheral immune cells respond to DAMPs and inflammatory signals, further propagating the inflammatory cascade (5). through the release of proinflammatory cytokines (6); persistent inflammatory signaling may lead to chronic neuroinflammation (7), which contributes to neuronal dysfunction and cognitive decline. Aging (8) and mTOR activation increase susceptibility to necroptosis and neuroinflammation; indeed, they are able to promote mitochondrial dysfunction (9), characterized by impaired ATP production and increased reactive oxygen species (ROS) generation, which enhance RIPK1/RIPK3-mediated necroptosis. This creates a feed-forward loop that sustains necroptosis and increases proinflammatory cytokine release (10), contributing to progressive cognitive decline.

with abnormal immune function.

Since increased RIPK3 or MLKL levels are not always indicative of necroptosis pathway activation [50], the activation of necroptosis in cases of cognitive impairment should be verified by analyzing the phosphorylation and post-translational modifications of RIPK1, evaluating the activation status of caspase-8, and detecting the presence of RIPK3 homodimers and MLKL oligomers.

However, despite autophosphorylated RIPK3 and phosphorylated MLKL are considered reliable prognostic biomarkers of necroptosis and can be detected in tissue sections, their biochemical detection in body fluids remains technically challenging; current methods for identifying necroptosis, such as immunofluorescence, immunoblotting, and biochemical analysis, are unsuitable for real-time monitoring [140]. Other common systemic biomarkers may be influenced by numerous confounding factors. Lactate dehydrogenase (LDH), for example, is a systemic biomarker of necroptosis; however, its elevated levels can also result from conditions such as liver diseases, anemia, heart attacks, bone fractures, muscle traumas, and cancers [140].

Presently, the primary approaches for necroptosis monitoring in blood samples could be represented by: (i) the detection of indirect markers of necroptosis, including HMGB1, IL-1, IL-33, cyclophilin A, LDH, and mitochondrial DNA; (ii) the measurement of specific markers associated with necrosome formation, including RIPK1, RIPK3, and MLKL mRNA or their respective proteins, which can be easily assessed and monitored using antibody-based methods. Additionally, the blood concentration and expression of PCD proteins, such as TNFR1, RIP1, and RIP3, provide valuable insights into their associations with changes in cognitive function of older individuals [140].

Currently, the main key questions related to the aging brain and cognitive decline include understanding the epigenetic mechanisms that regulate the expression of genes linked to necroptosis and cognitive impairment, as well as how these epigenetic changes interact with senescent physiology and environmental factors to regulate transcription. Epigenetic mechanisms, such as DNA methylation and histone modifications, alter chromatin structure and DNA accessibility. Furthermore, small non-coding RNAs, termed microRNAs (miRNAs), bind to mRNA to regulate translation.

Epigenome-wide DNA methylation studies have proven to be useful for identifying shared methylation status changes across various tissues, such as the brain and peripheral lymphocytes. Despite limited knowledge about the specific role of epigenetics in necroptosis of CNS cells, existing evidence strongly supports the crucial role of epigenetic mechanisms in memory formation, aging, and neurodegeneration [133]. A recent study employed whole-genome methylation association analysis to compare the differences in peripheral blood methylation profiles between patients with cognitive aging and those with late-stage mild cognitive impairment [150]. The study examined patients with early- and late-stage mild cognitive impairment, identifying numerous specific methylated biomarkers associated with cognitive decline and some of these biomarkers are related to immune function and inflammation [150].

A very useful approach to monitor older individuals may include the regular assessment of specific epigenetic changes linked to blood cytokine levels involved in neuroinflammation and cognitive impairment (Table 3) [151].

Table 3
Epigenetic changes linked to blood cytokine levels involved in neuroinflammation and cognitive impairment.

Epigenetic changes	Cytokines with increased levels	Reference studies
DNA methylation Global hypomethylation (a decrease in the content of 5-methylcytosine in the genome)	IL-1β, TNF-α, IL-6, IL-8	Shinozaki G, et al., 2018 [152]
Histone modifications	TNF-α, IL-1β	Jiang W, et al., 2022 [153]
miRNA-155	TNF-a, IL-1β, IL-6, NOS	Cardoso AL, et al., 2012 [154]; Slota JA, et al., 2019 [155]
miRNA-204	TNF-a, IL-1β, IL-6,	Liu H, et al., 2021 [156]
miRNA-146a, miRNA-124, miRNA-31	TNF-α, IL-1β, IL-6, NF-κB	Fan W, et al., 2020 [157]; Slota JA, et al., 2019 [155]
miRNA195	TNF-α, IL-1β, IL-6, NF-κB, TRAF6	Slota JA, et al., 2019 [155]
miRNA221	TNF-α, IL-1β, iNOS (indirect effect)	Slota JA, et al., 2019 [155]

Notes: IL = interleukin; miRNA = microRNA; TNF=tumor necrosis factor; iNOS= inducible Nitric Oxide Synthase

4. Therapeutic strategies against necroptosis

4.1. Inhibitors of necroptosis mediators

Among the various drugs that influence the expression and/or the activity of necroptosis mediators, pharmacological inhibition of RIPK1, RIPK3, and MLKL represents one of the most promising strategies for the treatment of necroptosis-related diseases. It is important to keep in mind that in the necroptosis framework, RIPK1 is activated and autophosphorylated, subsequently recruiting RIPK3, which then activates MLKL through phosphorylation, leading to cell membrane permeabilization and finally necroptosis [158,159]. Inhibitors targeting these proteins have been explored for the treatment of some inflammatory conditions and viral infections [159,160]. The RIPK1 inhibitor Necrostatin-1 (Nec-1) served as the prototype compound establishing proof-of-concept for therapeutic targeting of necroptosis [161,162]. This led to the development of optimized derivatives, including GSK2982772, which showed dose linearity and target specificity in a phase I study [163]. It has subsequently been tested in phase II trials in patients with ulcerative colitis [164], psoriasis [165] and rheumatoid arthritis [164], showing a good safety profile but no significant efficacy.

RIPK3 inhibitors, such as GSK'840 and GSK'872, to the best of our knowledge, are still in preclinical development [166,167]; similarly, compounds targeting MLKL, such as necrosulfonamide, have demonstrated efficacy in animal models of inflammatory diseases [117].

At the brain level, considering the crucial role of RIPK1 and RIPK3 in mediating neuronal necroptosis, their inhibition might represent a promising therapeutic strategy in the neurodegeneration framework. Recent studies in AD animal models have demonstrated significant neuroprotection induced by specific necrostatins and inhibitors targeting RIPK1, RIPK3, or MLKL [30,168,169]; however, these molecules have not yet been evaluated in clinical trials. Currently, no drugs targeting necroptosis are approved for human use in clinical practice; natural compounds and medications with some preclinical potential in preventing cognitive impairment through modulation of necroptosis are reported in Table 4.

SAR443060 (DNL747), a selective, brain-penetrant RIPK1 inhibitor, demonstrated robust target engagement in three Phase I/Ib clinical trials in healthy volunteers and patients with AD and amyotrophic lateral sclerosis (NCT03757325, NCT03757351). In these studies, DNL747 distributed into cerebrospinal fluid after oral administration and achieved median peripheral target engagement (pRIPK1 inhibition in PBMCs) of 81.83% in AD patients and 65.92% in ALS patients at 50 mg twice daily for up to 28 days, with good safety and tolerability [170]. However, development was discontinued in 2020 due to dose-limiting toxicities observed only in long-term (3-month) preclinical studies in monkeys, including thrombocytopenia, anemia, and bleeding; these toxicities were compound-specific and not observed with other RIPK1 inhibitors [163,170,171]. Following SAR443060 discontinuation, a backup compound SAR443820 (DNL788) was advanced into clinical development; this compound is also a CNS-penetrant, selective RIPK1

Table 4
List of natural compounds and drugs targeting necroptosis and potentially effective in delaying or preventing cognitive impairment.

Compound	Mechanism of action	Population	Type of study	Study aims	Results
Rapamycin (sirolimus)	mTOR inhibition	Older adults with mild cognitive decline and early-stage AD	RCT, Early Phase I NCT04200911	CNS penetration, association with cognitive and functional status	Ongoing
Phenytoin + Megestrol	RIPK1 inhibition	Prevention of delayed memory associated with megestrol treatment	RCT Completed phase IV NCT02595723	Capacity of phenytoin to prevent megestrol-induced cognitive changes	Ongoing
LY3372689	Inhibits the phosphorylation of RIPK3	Older adults with early-symptomatic AD	RCT, Phase II, NCT05063539	Safety, tolerability, and efficacy in AD	Ongoing
Melatonin	RIPK3 inhibition	Mice with intracerebral hemorrhage	Preclinical study [173]	Protective effects against necroptosis surrounding the hematoma	Melatonin suppresses necroptosis by regulating the deubiquitinating enzyme A20
		Healthy subjects and patients with AD	Systematic review of RCTs [174]	Preservation or delay of cognitive impairment	Melatonin improves MMSE score in AD and especially in early-stage AD
Aucubin	RIPK1 inhibition	Lithium-pilocarpine-induced status epilepticus rat model	Preclinical study [175]	Protective effect against status epilepticus-induced changes	Aucubin decreases the number of apoptotic neurons, increases the number of survival neurons by inducing autophagy and inhibiting necroptosis.
Wogonin	RIPK1 and MLKL inhibition	Pilocarpine-induced status epilepticus murine model; Kainate-induced temporal lobe epilepsy rats	Preclinical studies [160, 176]	Protective effects against cognitive impairment	Wogonin mitigates microglia-mediated cognitive impairment and alleviates neuroinflammation
Scutellaria baicalensis	RIPK1 and MLKL inhibition	Okadaic acid-induced AD rat models; LPS-induced neuroinflammatory rat models	Preclinical studies [177, 178]	Protective effects against cognitive impairment	Scutellaria baicalensis improves cognitive function and mitigates memory deficits; Baicalin reduces microglia-associated neuroinflammation and cognitive changes
SAR443060 (previously DNL747)	RIPK1 inhibition	Healthy subjects and patients with multiple sclerosis and amyotrophic lateral sclerosis	RCT, Phase I NCT05795907 RCTs, Phase II, NCT05237284 NCT05630547	Evaluation of the safety, tolerability, pharmacokinetics, and pharmacodynamics	Ongoing
SAR443820 (DNL788)	RIPK1 inhibition	Healthy subjects and patients with amyotrophic lateral sclerosis and multiple sclerosis	Phase I RCT (NCT05630547) and Phase II RCTs (HIMALAYA, K2)	Improvement in amyotrophic lateral sclerosis and multiple sclerosis	Failed to meet primary endpoint

Notes: AD = Alzheimer's disease; CNS = central nervous system; LPS = lipopolysaccharide; MLKL = mixed lineage kinase domain-like protein; NCT = National Clinical Trial; RCT = Randomized Clinical Trial; RIPK1 = Receptor-Interacting Protein Kinase 1.

inhibitor that was optimized to reduce off-target toxicity. In a first-in-human Phase I study in healthy adults (NCT05795907), it demonstrated dose-proportional pharmacokinetics, a cerebrospinal (CSF)-to-unbound plasma concentration ratio between 0.8 and 1.3, and a maximum median peripheral RIPK1 inhibition of approximately 90%, confirming high target engagement and good tolerability without serious adverse events [171]. The compound subsequently progressed to Phase II trials in amyotrophic lateral sclerosis (HIMALAYA; NCT05237284) and multiple sclerosis (K2, NCT05630547), but both studies failed to achieve their primary endpoints; more specifically, in the first trial, SAR443820 did not significantly improve the amyotrophic lateral sclerosis Functional Rating Scale-Revised (ALSFRS-R) scores compared to placebo; in the multiple sclerosis trial, no significant changes were observed in serum neurofilament light chain levels, a biomarker of axonal degeneration. Collectively, these data demonstrate that while SAR443060 and SAR 443820 achieve potent and sustained RIPK1 inhibition with favorable CNS pharmacokinetics, translation of target engagement into clinical efficacy has not yet been achieved. These findings raise critical questions about the therapeutic window of RIPK1 inhibition and whether monotherapy is sufficient to alter the trajectory of established neurodegenerative disease [172].

Rapamycin (also named sirolimus) has been demonstrated to regulate necroptosis by inhibiting mTOR. This latter activates necroptosis through various mechanisms: the main one is the mTOR-induced downregulation of autophagic processes by means of degradation of ubiquitinated RIPK3, thus altering the interaction between RIPK1 and RIPK3 [59]. In other words, mTOR inhibits autophagy and promotes necroptosis; therefore, a mTOR inhibitor like rapamycin could be a promising strategy to counteract necroptosis and necroptosis-related neuroinflammation. Nevertheless, an open-label phase I clinical trial, NCT04200911, has failed to demonstrate the capacity of orally administered rapamycin to engage its target in CSF in older adults with MCI and mild AD dementia. Furthermore, several neuroinflammatory and neurodegeneration biomarkers significantly increased after treatment, thus questioning the possible efficacy of rapamycin in the AD field [179, 180].

Another drug, phenytoin, is clinically used as an anticonvulsant; it may prevent necrosome formation and partially inhibit RIPK1, with possible beneficial effects on cognitive performance [181]. Accordingly, a completed randomized controlled crossover study reported that pre-administration of phenytoin attenuated delayed declarative memory performance associated with megestrol treatment [182,183].

Additionally, O-GlcNAcylation of RIPK3 has been shown to inhibit RIPK3 phosphorylation and its interaction with RIPK1, thereby further inhibiting the activation of necroptosis. In this regard, LY3372689 (Formulaic Ia), an orally active O-GlcNAcase (OGA) enzyme inhibitor, is currently undergoing a Phase II clinical trial to evaluate its safety, tolerability, and efficacy in participants with early symptomatic AD [184].

Melatonin, an endogenous hormone secreted by the pineal gland, is inversely associated with age and cognitive deficits [174]. Interestingly, melatonin supplementation has been shown to inhibit endothelial

necroptosis by blocking RIPK3-mediated signaling [185]. Further studies have shown that melatonin supplementation can suppress microglial RIPK3-mediated necroptosis [173], suggesting potential benefits for improving cognitive function [174].

Furthermore, some natural compounds, such as aucubin and wogonin, might also delay aging-related cognitive decline by inhibiting RIPK1 activity, although their efficacy in individuals with cognitive disorders has not yet been documented [175,186,187].

5. Conclusions

In summary, necroptosis seems to play a pivotal role in the context of age-related cognitive disorders, both inducing neuronal death and neuroinflammation that in turn facilitates neurodegenerative processes, thus fueling a vicious circle.

Elevated levels of necroptosis markers such as RIPK3 and MLKL have been consistently observed in the aging brain and in neurodegenerative disorders, supporting a potential mechanistic role that warrants further investigation to clarify causality. Preclinical studies using genetic or pharmacologic inhibitors of necroptosis have shown neuroprotective and cognitive benefits, suggesting a mechanistic role. However, definitive causal links in humans remain to be firmly established, and more translational research is required to bridge this gap. Specifically, some questions still remain unanswered: (1) In the neurodegeneration field, what is the "primum movens": necroptosis or neuroinflammation? In other words: how much is necroptosis a cause and how much is it a consequence of neuroinflammation? (2) Can we consider necroptosis a hallmark of normal aging? If yes, is there a standardizable threshold that accurately distinguishes between "physiological" and pathological necroptosis? (3) What is the role of necroptosis in each neurodegenerative disease both at qualitative and quantitative level? For instance, does necroptosis have the same importance in PD and in AD pathophysiology? (4) Is necroptosis a modifier of the trajectory of neurodegenerative diseases? In other words: can necroptosis contribute to explaining the interindividual variability characterizing the natural history of neurodegenerative diseases?

Given the putative role of necroptosis in neurodegeneration, finding answers to these and other questions might improve the clinical management of neurogenerative diseases. Currently, no necroptosis-targeting therapies are approved for clinical use in neurodegenerative diseases. However, several promising candidates, including RIPK1 and RIPK3 inhibitors, as well as mTOR and MLKL modulators, are under investigation. Some obstacles hinder the implementation of efficacious necroptosis-targeting therapies in the neurodegeneratione field. First, drugs have to be able to precisely engage their molecular targets, with null or scarce off-target side effects; second, drugs have to cross the BBB; third, the modulation of necroptosis may potentially impact PANoptosis and other forms of PCD, with very uncertain final effects on body and brain homeostasis.

Diagnostic advances, including more reliable detection of phosphorylated necroptosis mediators and epigenetic biomarkers, could enhance our ability to identify patients most likely to benefit from such therapies. However, in this regard, there are significant challenges that should be addressed. First, necroptosis is a dynamic process that changes over time that can be modulated by several mechanisms beyond neurodegeneration, both acute and chronic and it is unknown how much more harmful a chronic increase is than an acute elevation of necroptosis levels, as well as it is unknown whether a low-grade chronic necroptosis activation or a strong acute necroptosis induction is more dangerous; therefore, in real-life setting, according to the current state of knowledge, it is not easy to give the correct interpretation of necroptosis biomarker levels both for diagnostic and prognostic purposes. Second, the implementation of necroptosis biomarkers in routine clinical practice is still hampered by the lack of standardization. Third, it is still not clear what the precise impact of normal aging is on necroptosis levels and, therefore, the usefulness of age-based cut-offs for necroptosis biomarkers is unknown.

Future research should aim to (1) validate specific biomarkers of necroptosis in accessible biological fluids, (2) clarify the temporal dynamics of necroptotic activity during disease progression, and (3) test the therapeutic efficacy and safety of necroptosis inhibitors in well-designed clinical trials targeting age-related cognitive decline. A deeper mechanistic understanding of necroptosis and its interplay with systemic inflammaging may ultimately pave the way for novel, personalized strategies to preserve cognitive function in the aging population. Therefore, future studies in the neurodegeneration field should clarify whether necroptosis biomarkers can be implemented for risk stratification and/or diagnosis and/or prognosis and/or disease monitoring, as well as whether necroptosis-targeted therapies can be exploited in different age-related neurological disorders.

In conclusion, the present review has summarized the current state of the art regarding the link between necroptosis, neuroinflammation and neurodegeneration. Given the current wide heterogeneity of the literature on this topic, we could not perform a systematic review and meta-analysis; therefore, the choice of included references was based on our personal evaluation of the relevance of the papers and, therefore, it might be biased. This represents the main limitation of our work.

We hope that findings from future large clinical trials focused on necroptosis-targeting drugs will be summarized by rigorous meta-analysis to give clear insights into the potential of this therapeutic strategy to counteract age-related cognitive decline.

CRediT authorship contribution statement

Leonardo Biscetti: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Maria Elsa Gambuzza:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Maria Princiotto:** Writing – review & editing, Visualization. **Jacopo Sabbatinelli:** Writing – review & editing. **Fabiola Olivieri:** Writing – review & editing, Supervision. **Marco Fiorillo:** Writing – review & editing. **Chiara Chinigò:** Writing – review & editing. **Lucia Muglia:** Writing – review & editing. **Annalisa Cozza:** Writing – review & editing. **Alessia Beccacece:** Writing – review & editing. **Guido Gembillo:** Writing – review & editing. **Giuseppe Bruschetta:** Writing – review & editing. **Edlin Villalta Savedra:** Writing – review & editing. **Fabrizia Lattanzio:** Writing – review & editing, Supervision. **Andrea Corsonello:** Writing – review & editing, Supervision. **Luca Soraci:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Conceptualization.

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Data availability

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