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Paradoxical roles for programmed cell death signaling during viral infection of the central nervous system

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Abstract

Programmed cell death (PCD) is an essential mechanism of antimicrobial defense. Recent work has revealed an unexpected diversity in the types of PCD elicited during infection, as well as defined unique roles for different PCD modalities in shaping the immune response. Here, we review recent work describing unique ways in which PCD signaling operates within the infected central nervous system (CNS). These studies reveal striking complexity in the regulation of PCD signaling by CNS cells, including both protective and pathological outcomes in the control of infection. Studies defining the specialized molecular mechanisms shaping PCD responses in the CNS promise to yield much needed new insights into the pathogenesis of neuroinvasive viral infection, informing future therapeutic development.

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Introduction

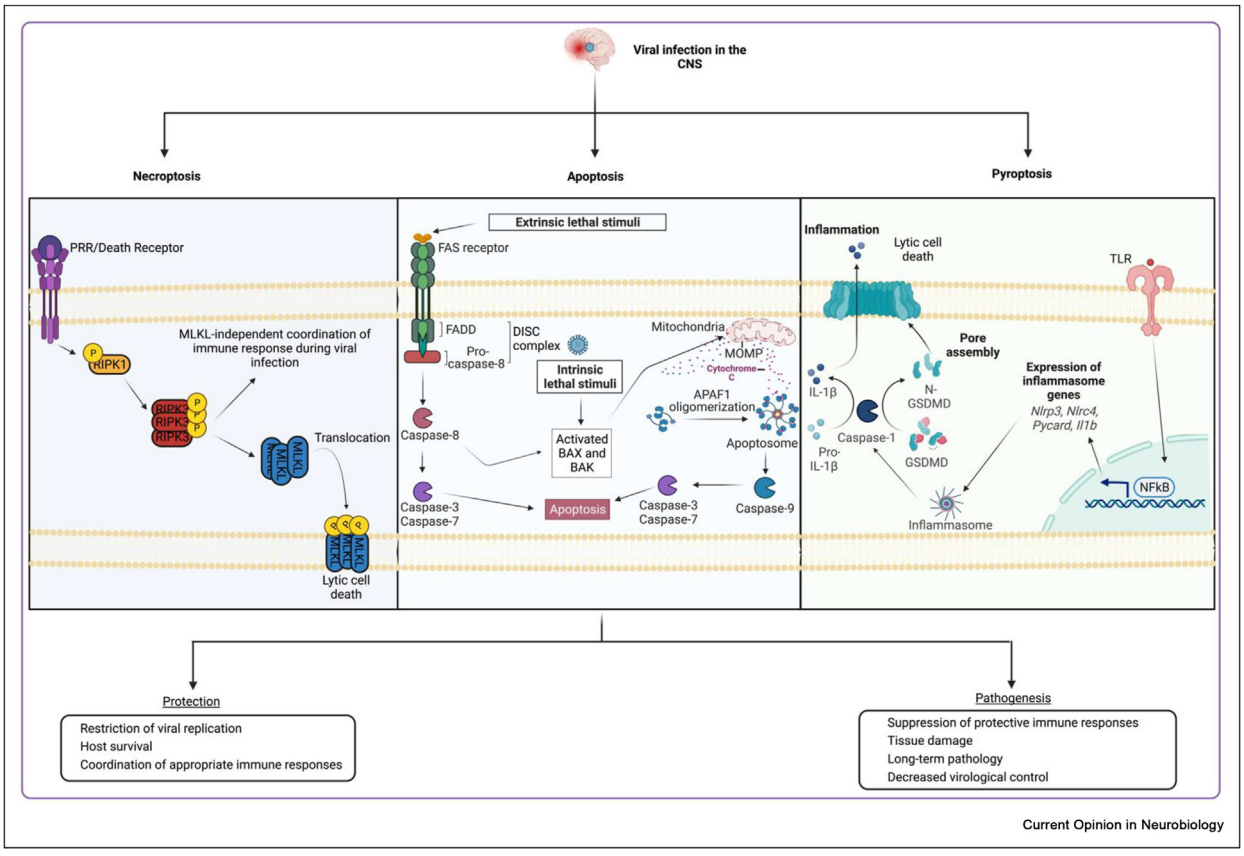
Programmed cell death (PCD) is a fundamental cell biological response to infection and injury. In the setting of viral infection, the primary purpose of PCD is thought to be the restriction of replication and dissemination by depriving viruses of the resources needed to propagate infection. However, a growing body of work has revealed that PCD signaling shapes the host response to infection in complex ways, including through regulation of both innate and adaptive immunity [1]. These impacts on host immune responses vary dramatically by the type of PCD signaling engaged during infection [2]. For example, nonlytic cell death (e.g. apoptosis) is thought to be relatively noninflammatory, but is a major effector mechanism of adaptive immunity; in contrast, lytic cell death (e.g. necroptosis and pyroptosis) is highly inflammatory due to the release of damage associated molecular patterns (DAMPs) and other immunogenic signals [3]. Given these diverse outcomes, the signaling that orchestrates PCD is tightly regulated by host cells, and viruses are under considerable selective pressure to evade and/or co-opt host PCD signaling to overcome PCD-mediated immune responses [4,5,6].

Careful regulation of PCD signaling is of particular importance in the central nervous system (CNS). Cell death is an especially costly response to infection in this organ system, as critical cell types, most notably neurons, are postmitotic and/or nonregenerative [7]. Beyond this, the cytoarchitecture of dendritic networks and myelin sheaths are not easily restored, even when cellular regeneration is possible [8,9]. Thus, CNS cells have evolved highly specialized mechanisms that suppress their susceptibility to PCD, and in some cases exhibit alternative outcomes of PCD signaling pathways that promote both nervous and immune function in the absence of cell death [10,11,12]. In cases where PCD does occur, many studies suggest that cell death in the CNS is more often harmful than helpful, driving deleterious neuroinflammation and tissue pathology [13,14,15]. Understanding the specialized regulation and outcomes of PCD signaling in the CNS is therefore a critical area of ongoing discovery, with particular relevance to CNS viral infection. We summarize the three major PCD modalities to be discussed in this review in Figure 1.

Apoptosis

The most conventional form of PCD is apoptosis, during which cells undergo a characteristic pattern of shrinkage, membrane blebbing, and chromatin condensation [16]. In contrast to other major PCD modalities, apoptosis does not result in plasma membrane degradation. Instead, cells fragment into "apoptotic bodies" that sequester intracellular contents and are cleared efficiently by phagocytic cells. While phagocytosis of apoptotic bodies does have immunologic consequences, including the facilitation of antigen presentation, this process is not generally regarded as "inflammatory" within the context of the immediate cellular microenvironment [2]. This feature

Figure 1



CNS infection elicits multiple PCD modalities, resulting in both protective and pathologic outcomes. Here, we summarize the three major PCD modalities discussed in this review: apoptosis, necroptosis, and pyroptosis. The major signaling and executioner molecules for each are shown and are discussed in text. All three modalities have been shown to have diverse and somewhat paradoxical outcomes in the setting of CNS viral infection. While PCD signaling can contribute to viral restriction and successful pathogen clearance, numerous studies have shown how PCD also contributes to immunopathology and long-term damage in the CNS. Understanding the molecular mechanisms that promote protective rather than harmful effects of host PCD responses will facilitate ongoing work to target these pathways for the treatment of CNS viral infection.

of apoptosis may, ostensibly, explain its relative frequency compared to other PCD modalities, particularly in the setting of development.

Apoptosis can occur downstream of two distinct pathways, termed "intrinsic" and "extrinsic." Both have relevance to CNS viral infection. As these pathways have been extensively reviewed elsewhere [2,17,18], we present only a general overview here. Intrinsic apoptosis is initiated by a variety of disruptions to cellular homeostasis that are common during infection, including DNA damage, reactive oxygen species (ROS)-mediated oxidative stress, endoplasmic reticulum stress, and others. These intrinsic stimuli initiate cell death signaling pathways that converge on the phenomenon of mitochondrial outer membrane permeabilization (MOMP) [19]. MOMP is mediated by two molecules of the B cell lymphoma 2 (BCL2) family: BCL2 associated X protein (BAX) and/or BCL2 antagonist/killer 1 (BAK). The pore-forming activity of BAX and BAK drives MOMP, stimulating the release of apoptotic factors from the mitochondria. One of these factors is cytochrome c-somatic (CYCS). CYCS, with the help of apoptotic peptidase activating factor 1 (APAF1), forms the apoptosome, which activates the initiator caspase 9. Caspase 9, in turn, catalyzes the proteolytic activation of executioner caspases, most notably Caspase 3. Executioner caspases proteolytically cleave a variety of cellular proteins, ultimately resulting in cellular demise [20].

Extrinsic apoptosis is triggered by a variety of external stimuli, including ligation of "death receptors," or loss of activation of "dependence receptors," which initiate apoptosis in the absence of their ligands [21]. In the context of viral infection, activated CD8 T cells are a common source of extrinsic apoptotic cues, including their display of Fas ligand (FASL), a protein related to the tumor necrosis factor (TNF) family of cytokines. Activation of the death receptor Fas on target cells leads to recruitment of the Fas associated death domain

protein (FADD), which further recruits procaspase 8, forming the death-inducing signaling complex (DISC). Enzymatic cleavage of procaspase 8 by DISC results in the active form of the initiator caspase 8, which in turn activates executioner caspases, driving apoptosis. CD8 T cells also mediate apoptosis in target cells through soluble factors such as perforin and granzyme. When bound to the plasma membrane of a target cell, perforin oligomerizes to form pore structures, allowing the diffusion of granzyme into target cell cytoplasm. Granzyme, in turn, exhibits protease activity capable of activating pro-apoptotic substrates, including BID and several caspases [22].

Although apoptosis is recognized as a fundamental innate immune response to infection, growing evidence suggests that apoptosis can be counterproductive in the setting of CNS viral infection. Neuronal apoptosis is a hallmark of CNS viral infection and is likely a major source of disease pathogenesis and mortality [23,24]. For example, genetic ablation of caspase 3 extends host survival and improves clinical disease signs during West Nile virus (WNV) encephalitis [25]. Notably, while *Casp3*$^{-/-}$ mice exhibited markedly reduced neuronal apoptosis, they exhibited no change in CNS viral burden, suggesting that neuronal apoptosis does not serve to restrict viral replication. Mice lacking *Casp8* similarly show no deficit in virologic control of WNV in the CNS [26]. In the setting of Japanese encephalitis virus (JEV) encephalitis, blockade of protein kinase R-like endoplasmic reticulum kinase (PERK)-mediated apoptosis signaling similarly reduced neuropathology and ameliorated host mortality following infection [27]. Most strikingly, interventions that limit the infiltration of cytotoxic effector cells during the peak of flavivirus encephalitis have been shown to greatly reduce apoptosis in resident CNS cells, and these manipulations extend host survival and improve disease outcomes [28,29]. Together, these findings suggest that neuronal apoptosis is not a critical determinant of virologic control in the CNS, and that interventions that spare neurons from cell death may limit long-term pathology without compromising CNS immune function.

Beyond a direct role in neuropathogenesis, apoptosis has also been shown to have counterproductive effects on CNS viral clearance by suppressing key antiviral immune responses. For example, recent work has shown that neuroinvasive herpes simplex virus-1 (HSV-1) infection results in apoptosis primarily in microglia, key resident immune cells in the CNS [30]. Prevention of microglial apoptosis via pharmacologic inhibition of apoptotic caspase signaling promoted microglial survival, resulting in more robust type-I interferon (IFN) responses, decreased CNS viral burden, and improved disease outcomes. These findings suggest that, while apoptosis may serve a purpose in removing infected cells, the death of key effector cells may blunt the overall neuroimmune response to infection, paradoxically resulting in decreased virologic control throughout the CNS. The death of infected microglia and other key glial cell types, such as astrocytes, may also remove their contributions to tissue homeostasis, including nutrient import, waste clearance, and neurovascular regulation, resulting in enhanced neuropathogenesis [24,31].

Finally, apoptosis may promote worse disease outcomes during CNS viral infection via direct anti-inflammatory activity [13]. Upon engulfment of apoptotic cells, phagocytes have been shown to secret anti-inflammatory metabolites [32] and cytokines, including IL-10 [33]. This response is generally critical for immune homeostasis but may be counterproductive in the setting of active CNS infection. For example, IL-10 has been shown to suppress efficient viral clearance in the CNS, as *Il10*$^{-/-}$ mice exhibit enhanced viral burden and accelerated mortality following neuroinvasive WNV infection [34]. Similarly, increased IL-10 expression has been shown to delay viral clearance and enhance demyelination in a model of neuroinvasive coronavirus infection [35]. IL-10 was also shown to be dispensable for virologic control in a model of alphavirus encephalitis [36]. However, in this study, IL-10-deficient animals experienced enhanced immunopathology, including accelerated paralysis and mortality. Other reports have similarly underscored the important immunoregulatory function for IL-10 during neuroinflammation [37], including important roles in the modulation of glial cell activation during CNS infection [38]. Although these studies provide some clues as to the potential roles for apoptosis-mediated cytokine production by phagocytes during CNS viral infection, this idea has not been carefully tested to date (to our knowledge). Future work carefully defining the cell type- and disease stage-specific functions for immunoregulation by apoptotic cells in the infected CNS are therefore warranted.

Necroptosis

In contrast to the conventional, non-lytic PCD modality of apoptosis, several other major forms of PCD employ various means of plasma membrane permeabilization [39,40]. Necroptosis, or programmed necrosis, is one such PCD modality. During the initiation of necroptosis, a variety of immunologic stimuli, including pattern recognition receptor (PRR) and death receptor signaling, induce the formation of a "necrosome" complex. The defining feature of this complex is the oligomerization and activation of the protein receptor interacting protein kinase-3 (RIPK3), which phosphorylates the executioner protein mixed lineage kinase domain-like pseudokinase (MLKL) [41]. Activated MLKL traffics to the plasma membrane, disturbing its integrity and driving osmotic lysis and cell death [42]. Cellular lysis results in the release of cytoplasmic DAMPs into the extracellular environment, which is

potently immunogenic. Necroptotic cells also undergo a burst of *de novo* production of inflammatory mediators [43,44] which, intriguingly, may go on for some time after loss of plasma membrane integrity [45]. Thus, necroptosis is generally regarded to be a highly inflammatory form of PCD.

Notably, many recent reports have identified roles for necroptosis and RIPK3 signaling in the inflammatory pathogenesis of neurodegenerative disorders and CNS trauma [46,47,48]. However, roles for this pathway during CNS viral infection have not been as thoroughly explored. Studies to date suggest that necroptosis may not be a common response to neuroinvasive infection, and that when it does occur, necroptosis may promote immunopathology without meaningful impacts on pathogen control. For example, mice infected with JEV exhibit robust upregulation of MLKL in neurons, which is correlated with an increased appearance of propidium iodide^{+} necrotic CNS cells following infection [49]. However, necroptosis does not appear to restrict JEV infection in the CNS, as both *Ripk3*$^{-/-}$ and *Mlkl*$^{-/-}$ mice exhibit diminished clinical signs of disease, enhanced survival, and decreased neuroinflammation following infection [49,50]. CNS viral burden was actually decreased in *Ripk3*$^{-/-}$ animals, concomitant with increased expression of IFN-stimulated genes (ISGs) [50]. These findings suggest that, rather than serving a protective function, necroptosis is actually a driver of severe disease during JEV encephalitis.

In addition to necroptosis, other recent work has shown that RIPK3 signaling in the brain has outcomes distinct from its canonical function in promoting MLKL-dependent cell death. In models of neuroinvasive WNV and Zika virus (ZIKV) infection, mice bearing global or forebrain neuron-specific deletion of *Ripk3* exhibited dramatically increased susceptibility to encephalitis, including accelerated and enhanced mortality [26,51]. Strikingly, however, infection of *Mlkl*$^{-/-}$ mice resulted in no change to any clinical, virologic, or immunologic parameter of disease, suggest that RIPK3 serves a critical neuroprotective function during WNV and ZIKV infection that is independent of MLKL and necroptosis. Instead of promoting cell death, neuronal RIPK3 signaling drove a complex transcriptional program that induced a number of antimicrobial responses, including the recruitment of peripheral leukocytes to the CNS [26] and the remodeling of neuronal metabolism to restrict viral replication [51]. These findings identified a previously unknown diversity in the outcomes of RIPK3 activation in neurons and may reflect a unique adaptation of a major cell death pathway in a highly sensitive, post-mitotic cell type [10].

Pyroptosis

Pyroptosis is another form of lytic PCD that is strongly associated with inflammation. In its canonical form, pyroptosis is initiated by protein complexes termed "inflammasomes" that sense a variety of pathogenic stimuli, including DAMPs and microbial PAMPs [52]. Multiple inflammasomes have been described, including those consisting of Nod-like receptors (NLRs), DNA receptor Absent in Melanoma 2 (AIM2), and the Pyrin receptor. Activated inflammasomes recruit the adapter protein apoptosis-associated speck-like protein containing a CARD (ASC), facilitating the cleavage and activation of caspase-1. Active caspase-1 then cleaves and activates the inflammatory cytokines interleukin (IL)-1β and IL-18, as well as the executioner molecule gasdermin D (GSDMD). Processed GSDMD forms pore structures in the plasma membrane, allowing the escape of inflammatory mediators, as well as eventual lysis and further DAMP release [53]. Noncanonical signaling via capsases-4, 5, and 11 can also activate GSDMD-mediated pyroptosis [54]. Whichever pathway is engaged, pyroptosis has been shown to be highly immunogenic, serving critical functions in pathogen control [55,56,57].

Like necroptosis, pyroptosis has been implicated as a driver of neuroinflammation in a broad variety of CNS disease states involving sterile inflammation [58]. However, roles for pyroptosis during CNS infection remain relatively poorly understood. To date, studies suggest that inflammasome activation and IL-1 cytokine signaling are important determinants of viral restriction for multiple neuroinvasive viruses, although the specific role for GSDMD-mediated cell death and/or the relative contributions of CNS versus peripheral cell types is unclear. For example, mice lacking pyroptotic signaling elements, including NLRP3 (*Nlrp3*$^{-/-}$), ASC (*Pycard*$^{-/-}$), and caspase-1 (*Casp1*$^{-/-}$) exhibit enhanced mortality and failure of virologic control in the CNS following subcutaneous WNV infection [59,60]. Similar observations have been reported in mice lacking IL-1R (*Il1r*$^{-/-}$) or in those treated with IL-1R neutralizing antibodies [59,61,62]. However, mice lacking these molecules universally show no change in disease outcomes following intracranial infection with WNV, suggesting that pyroptotic signaling is primarily required for virologic control outside of the CNS, and that this lack of peripheral control results in worsened CNS disease. While *in vitro* studies suggest that flavivirus infection may be able to induce pyroptosis in CNS cell types [63,64], direct evidence of GSDMD-mediated pyroptotic cell death has not been reported in the CNS *in vivo* in a model of flavivirus encephalitis, to our knowledge. The use of mouse genetic systems and other advanced tools to selectively modulate pyroptotic signaling in resident cells of the CNS is therefore needed to clarify the specific contributions of pyroptosis during flavivirus infection.

In contrast, CNS-specific roles for pyroptotic signaling during HIV infection are somewhat better defined.

Microglia are major CNS targets of HIV infection, even in patients whose infection is otherwise well controlled by antiretroviral therapy [65,66]. Multiple HIV proteins have been shown to induce inflammasome signaling, caspase-1 activation, and IL-1 β release in microglia [67,68,69,70]. However, the resultant neuroinflammation from this signaling does not appear efficacious to eliminate chronic HIV infection in the CNS. Instead, pyroptotic signaling in microglia drives immunopathology and neurotoxicity, contributing to the chronic neurodegeneration observed in many people living with HIV (PLWH) [71,72]. Recent work also suggests that HSV-1 infection can induce microglial pyroptosis, resulting in deleterious neuroinflammation during HSV-1 encephalitis [73]. These findings suggest that pyroptosis may be a common source of immunopathology during CNS viral infection and, therefore, may represent a promising target for therapeutic development [15,58]. However, further mechanistic work is needed to define the beneficial contributions, if any, of pyroptotic signaling by resident CNS cells to antiviral neuroimmune function.

Conclusions

The field of PCD has enjoyed a recent explosion of interest and new discovery in the biomedical sciences. The discovery of new PCD modalities, such as necroptosis and pyroptosis, has revolutionized our understanding of the ways in which cell death shapes the immune response to pathogens. As always, however, interactions between the immune system and the CNS often defy traditional paradigms. The recent work we have reviewed here highlights the difficulty of balancing the antimicrobial benefits of PCD with its potential for eliciting deleterious inflammation and long-term tissue damage. This balance is particularly fraught in the CNS, wherein appropriate immune responses are essential for viral clearance and host survival, but in which cell death often comes at a heavier cost than that faced in other, more regenerative tissues. As our understanding of the molecular underpinnings of PCD grows, new opportunities emerge to define the specialized ways that PCD signaling operates during neuroinvasive infection, including the unique features these pathways may display across distinct CNS cell types and regions. The ongoing description of ever more unique and complex forms of PCD, including ferroptosis [74], cuproptosis [75], and others highlights the potential for new discovery in the study of cell death in the CNS. This work holds tremendous promise as a new frontier in neuroimmunology and may yield important advancements in the treatment and prevention of viral encephalitis and other infectious diseases of the brain and spinal cord.

Author contributions

Both authors contributed to the writing and editing of the manuscript.

Conflict of interest statement

Nothing declared.

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References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest

1. Bedoui S, Herold MJ, Strasser A: **Emerging connectivity of programmed cell death pathways and its physiological implications**. *Nat Rev Mol Cell Biol* 2020, **21**:678–695.
2. Snyder AG, Oberst A: **The antisocial network: cross talk between cell death programs in host defense**. *Annu Rev Immunol* 2021, **39**:77–101.
3. Frank D, Vince JE: **Pyroptosis versus necroptosis: similarities, differences, and crosstalk**. *Cell Death Differ* 2019, **26**: 99–114.
4. Hofmann K: **The evolutionary origins of programmed cell death signaling**. *Cold Spring Harbor Perspect Biol* 2020:12.
5. Jorgensen I, Rayamajhi M, Miao EA: **Programmed cell death as a defence against infection**. *Nat Rev Immunol* 2017, **17**: 151–164.
6. Verdonck S, Nemegeer J, Vandenabeele P, Maelfait J: **Viral manipulation of host cell necroptosis and pyroptosis**. *Trends Microbiol* 2022, **30**:593–605.
7. Franjic D, Skarica M, Ma S, Arellano JI, Tebbenkamp ATN, Choi J, Xu C, Li Q, Morozov YM, Andrijevic D, *et al.*: **Transcriptomic taxonomy and neurogenic trajectories of adult human, macaque, and pig hippocampal and entorhinal cells**. *Neuron* 2022, **110**:452–469 e414.
8. Franklin RJM, Frisen J, Lyons DA: **Revisiting remyelination: towards a consensus on the regeneration of CNS myelin**. *Semin Cell Dev Biol* 2021, **116**:3–9.
9. Sofroniew MV: **Dissecting spinal cord regeneration**. *Nature* 2018, **557**:343–350.
10. Daniels BP, Oberst A: **Outcomes of RIP kinase signaling during neuroinvasive viral infection**. *Curr Top Microbiol Immunol* 2020:1–20.
11. Hollville E, Romero SE, Deshmukh M: **Apoptotic cell death regulation in neurons**. *FEBS J* 2019, **286**:3276–3298.
12. Unsain N, Barker PA: **New views on the misconstrued: executioner caspases and their diverse non-apoptotic roles**. *Neuron* 2015, **88**:461–474.
13. Heckmann BL, Tummers B, Green DR: **Crashing the computer: apoptosis vs. necroptosis in neuroinflammation**. *Cell Death Differ* 2019, **26**:41–52.
14. Yuan J, Amin P, Ofengeim D: **Necroptosis and RIPK1-mediated neuroinflammation in CNS diseases**. *Nat Rev Neurosci* 2019, **20**:19–33.
15. Hu Y, Wang B, Li S, Yang S: **Pyroptosis, and its role in central nervous system disease**. *J Mol Biol* 2022, **434**, 167379.
16. Hacker G: **The morphology of apoptosis**. *Cell Tissue Res* 2000, **301**:5–17.
17. Hacker G: **Apoptosis in infection**. *Microb Infect* 2018, **20**: 552–559.
18. Strasser A, O'Connor L, Dixit VM: **Apoptosis signaling**. *Annu Rev Biochem* 2000, **69**:217–245.
19. Green DR: **The mitochondrial pathway of apoptosis: Part I: MOMP and beyond**. *Cold Spring Harbor Perspect Biol* 2022:14.

20. McComb S, Chan PK, Guinot A, Hartmannsdottir H, Jenni S, Dobay MP, Bourquin JP, Bornhauser BC: **Efficient apoptosis requires feedback amplification of upstream apoptotic signals by effector caspase-3 or -7**. *Sci Adv* 2019, **5**, eaau9433.

21. Lossi L: **The concept of intrinsic versus extrinsic apoptosis**. *Biochem J* 2022, **479**:357–384.

22. Voskoboinik I, Whisstock JC, Trapani JA: **Perforin and granzymes: function, dysfunction and human pathology**. *Nat Rev Immunol* 2015, **15**:388–400.

23. Peng BH, Wang T: **West Nile virus induced cell death in the central nervous system**. *Pathogens* 2019, **8**.

24. Soung A, Klein RS: **Viral encephalitis and neurologic diseases: focus on astrocytes**. *Trends Mol Med* 2018, **24**: 950–962.

25. Samuel MA, Morrey JD, Diamond MS: **Caspase 3-dependent cell death of neurons contributes to the pathogenesis of West Nile virus encephalitis**. *J Virol* 2007, **81**:2614–2623.

26. Daniels BP, Snyder AG, Olsen TM, Orozco S, Oguin 3rd TH, Tait SWG, Martinez J, Gale Jr M, Loo YM, Oberst A: **RIPK3 restricts viral pathogenesis via cell death-independent neuroinflammation**. *Cell* 2017, **169**:301–313 e311.

27. Wang Q, Xin X, Wang T, Wan J, Ou Y, Yang Z, Yu Q, Zhu L, Guo Y, Wu Y, *et al.*: **Japanese encephalitis virus induces apoptosis and encephalitis by activating the PERK pathway**. *J Virol* 2019, **93**.

28. Daniels BP, Jujjavarapu H, Durrant DM, Williams JL, Green RR, White JP, Lazear HM, Gale Jr M, Diamond MS, Klein RS: **Regional astrocyte IFN signaling restricts pathogenesis during neurotropic viral infection**. *J Clin Invest* 2017, **127**: 843–856.

29. Szretter KJ, Daniels BP, Cho H, Gainey MD, Yokoyama WM, Gale Jr M, Virgin HW, Klein RS, Sen GC, Diamond MS: **2'-O methylation of the viral mRNA cap by West Nile virus evades ifit1-dependent and -independent mechanisms of host restriction in vivo**. *PLoS Pathog* 2012, **8**, e1002698.

30. * Reinert LS, Rashidi AS, Tran DN, Katzilieris-Petras G, Hvidt AK, Gohr M, Fruhwurth S, Bodda C, Thomsen MK, Vendelbo MH, *et al.*: **Brain immune cells undergo cGAS/STING-dependent apoptosis during herpes simplex virus type 1 infection to limit type I IFN production**. *J Clin Invest* 2021:131.

This study demonstrates that microglia infected with HSV-1 undergo apoptosis, thereby removing an important source of type I interferon production during HSV encephalitis. This work highlights a novel mechanism by which death of resident CNS cells diminishes the capacity of the brain to adequately restrict viral infection.

31. Waltl I, Kalinke U: **Beneficial and detrimental functions of microglia during viral encephalitis**. *Trends Neurosci* 2022, **45**: 158–170.

32. * Medina CB, Mehrotra P, Arandjelovic S, Perry JSA, Guo Y, Morioka S, Barron B, Walk SF, Ghesquiere B, Krupnick AS, *et al.*: **Metabolites released from apoptotic cells act as tissue messengers**. *Nature* 2020, **580**:130–135.

This study profiles the apoptotic "secretome," describing previously unknown metabolites released from apoptotic cells. These metabolites have potent anti-inflammatory properties, suggesting that apoptosis may exert several overlapping mechanisms of immunosuppression.

33. Chung EY, Liu J, Homma Y, Zhang Y, Brendolan A, Saggese M, Han J, Silverstein R, Selleri L, Ma X: **Interleukin-10 expression in macrophages during phagocytosis of apoptotic cells is mediated by homeodomain proteins Pbx1 and Prep-1**. *Immunity* 2007, **27**:952–964.

34. Bai F, Town T, Qian F, Wang P, Kamanaka M, Connolly TM, Gate D, Montgomery RR, Flavell RA, Fikrig E: **IL-10 signaling blockade controls murine West Nile virus infection**. *PLoS Pathog* 2009, **5**, e1000610.

35. de Aquino MT, Kapil P, Hinton DR, Phares TW, Puntambekar SS, Savarin C, Bergmann CC, Stohlman SA: **IL-27 limits central nervous system viral clearance by promoting IL-10 and enhances demyelination**. *J Immunol* 2014, **193**:285–294.

36. Kulcsar KA, Baxter VK, Greene IP, Griffin DE: **Interleukin 10 modulation of pathogenic Th17 cells during fatal alphavirus encephalomyelitis**. *Proc Natl Acad Sci U S A* 2014, **111**: 16053–16058.

37. Burmeister AR, Marriott I: **The interleukin-10 family of cytokines and their role in the CNS**. *Front Cell Neurosci* 2018, **12**: 458.

38. Puntambekar SS, Hinton DR, Yin X, Savarin C, Bergmann CC, Trapp BD, Stohlman SA: **Interleukin-10 is a critical regulator of white matter lesion containment following viral induced demyelination**. *Glia* 2015, **63**:2106–2120.

39. Kayagaki N, Kornfeld OS, Lee BL, Stowe IB, O'Rourke K, Li Q, Sandoval W, Yan D, Kang J, Xu M, *et al.*: **NINJ1 mediates plasma membrane rupture during lytic cell death**. *Nature* 2021, **591**:131–136.

40. De Schutter E, Cappe B, Wiernicki B, Vandenabeele P, Riquet FB: **Plasma membrane permeabilization following cell death: many ways to dye!** *Cell Death Dis* 2021, **7**:183.

41. Orozco S, Oberst A: **RIPK3 in cell death and inflammation: the good, the bad, and the ugly**. *Immunol Rev* 2017, **277**:102–112.

42. Samson AL, Zhang Y, Geoghegan ND, Gavin XJ, Davies KA, Mlodzianoski MJ, Whitehead LW, Frank D, Garnish SE, Fitzgibbon C, *et al.*: **MLKL trafficking and accumulation at the plasma membrane control the kinetics and threshold for necroptosis**. *Nat Commun* 2020, **11**:3151.

43. Zhu K, Liang W, Ma Z, Xu D, Cao S, Lu X, Liu N, Shan B, Qian L, Yuan J: **Necroptosis promotes cell-autonomous activation of proinflammatory cytokine gene expression**. *Cell Death Dis* 2018, **9**:500.

44. Yatim N, Jusforgues-Saklani H, Orozco S, Schulz O, Barreira da Silva R, Reis e Sousa C, Green DR, Oberst A, Albert ML: **RIPK1 and NF-kappaB signaling in dying cells determines cross-priming of CD8(+) T cells**. *Science* 2015, **350**:328–334.

45. Orozco SL, Daniels BP, Yatim N, Messmer MN, Quarato G, Chen-Harris H, Cullen SP, Snyder AG, Ralli-Jain P, Frase S, *et al.*: **RIPK3 activation leads to cytokine synthesis that continues after loss of cell membrane integrity**. *Cell Rep* 2019, **28**: 2275–2287 e2275.

46. Zhao W, Liu Y, Xu L, He Y, Cai Z, Yu J, Zhang W, Xing C, Zhuang C, Qu Z: **Targeting necroptosis as a promising therapy for alzheimer's disease**. *ACS Chem Neurosci* 2022, **13**: 1697–1713.

47. Jayaraman A, Reynolds R: **Diverse pathways to neuronal necroptosis in Alzheimer's disease**. *Eur J Neurosci* 2022.

48. Salvadores N, Court FA: **The necroptosis pathway and its role in age-related neurodegenerative diseases: will it open up new therapeutic avenues in the next decade?** *Expert Opin Ther Targets* 2020, **24**:679–693.

49. Bian P, Zheng X, Wei L, Ye C, Fan H, Cai Y, Zhang Y, Zhang F, Jia Z, Lei Y: **MLKL mediated necroptosis accelerates JEV-induced neuroinflammation in mice**. *Front Microbiol* 2017, **8**: 303.

50. * Bian P, Ye C, Zheng X, Luo C, Yang J, Li M, Wang Y, Yang J, Zhou Y, Zhang F, *et al.*: **RIPK3 promotes JEV replication in neurons via downregulation of IFI44L**. *Front Microbiol* 2020, **11**:368.

This study shows that RIPK3 signaling is detrimental during Japanese Encephalitis virus infection through the suppression of interferon-stimulated gene expression. The authors show a suprising immunosuppressive effect of RIPK3 signaling in the CNS, which appears to involve MLKL-dependent necroptosis.

51. * Daniels BP, Kofman SB, Smith JR, Norris GT, Snyder AG, Kolb JP, Gao X, Locasale JW, Martinez J, Gale Jr M, *et al.*: **The Nucleotide sensor ZBP1 and kinase RIPK3 induce the Enzyme IRG1 to promote an antiviral metabolic state in neurons**. *Immunity* 2019, **50**:64–76 e64.

This study demonstrates that RIPK3 signaling is protective during neuroinvasive Zika virus infection. In this context, RIPK3 does not engage necroptosis, but rather promotes a transcriptional program that remodels neuronal metabolism to restrict infection.

52. Xue Y, Enosi Tuipulotu D, Tan WH, Kay C, Man SM: **Emerging activators and regulators of inflammasomes and pyroptosis**. *Trends Immunol* 2019, **40**:1035–1052.

53. Orning P, Lien E, Fitzgerald KA: **Gasdermins and their role in immunity and inflammation**. *J Exp Med* 2019, **216**: 2453–2465.

54. Wright SS, Vasudevan SO, Rathinam VA: **Mechanisms and consequences of noncanonical inflammasome-mediated pyroptosis**. *J Mol Biol* 2022, **434**, 167245.

55. Briard B, Malireddi RKS, Kanneganti TD: **Role of inflammasomes/pyroptosis and PANoptosis during fungal infection**. *PLoS Pathog* 2021, **17**, e1009358.

56. Booty LM, Bryant CE: **Gasdermin D and beyond - gasdermin-mediated pyroptosis in bacterial infections**. *J Mol Biol* 2022, **434**, 167409.

57. Tate MD, Mansell A: **An update on the NLRP3 inflammasome and influenza: the road to redemption or perdition?** *Curr Opin Immunol* 2018, **54**:80–85.

58. McKenzie BA, Dixit VM, Power C: **Fiery cell death: pyroptosis in the central nervous system**. *Trends Neurosci* 2020, **43**: 55–73.

59. Ramos HJ, Lanteri MC, Blahnik G, Negash A, Suthar MS, Brassil MM, Sodhi K, Treuting PM, Busch MP, Norris PJ, *et al.*: **IL-1beta signaling promotes CNS-intrinsic immune control of West Nile virus infection**. *PLoS Pathog* 2012, **8**, e1003039.

60. Kumar M, Roe K, Orillo B, Muruve DA, Nerurkar VR, Gale Jr M, Verma S: **Inflammasome adaptor protein Apoptosis-associated speck-like protein containing CARD (ASC) is critical for the immune response and survival in west Nile virus encephalitis**. *J Virol* 2013, **87**:3655–3667.

61. Durrant DM, Daniels BP, Klein RS: **IL-1R1 signaling regulates CXCL12-mediated T cell localization and fate within the central nervous system during West Nile Virus encephalitis**. *J Immunol* 2014, **193**:4095–4106.

62. Durrant DM, Robinette ML, Klein RS: **IL-1R1 is required for dendritic cell-mediated T cell reactivation within the CNS during West Nile virus encephalitis**. *J Exp Med* 2013, **210**: 503–516.

63. Yamaoka Y, Matsunaga S, Jeremiah SS, Nishi M, Miyakawa K, Morita T, Khatun H, Shimizu H, Okabe N, Kimura H, *et al.*: **Zika virus protease induces caspase-independent pyroptotic cell death by directly cleaving gasdermin D**. *Biochem Biophys Res Commun* 2021, **534**:666–671.

64. Fares M, Gorna K, Berry N, Cochet-Bernoin M, Piumi F, Blanchet O, Haddad N, Richardson J, Coulpier M: **Transcriptomic studies suggest a coincident role for apoptosis and pyroptosis but not for autophagic neuronal death in TBEV-infected human neuronal/glial cells**. *Viruses* 2021, **13**.

65. Boucher T, Liang S, Brown AM: **Advancing basic and translational research to deepen understanding of the molecular immune-mediated mechanisms regulating long-term persistence of HIV-1 in microglia in the adult human brain**. *J Leukoc Biol* 2022.

66. Borrajo A, Spuch C, Penedo MA, Olivares JM, Agis-Balboa RC: **Important role of microglia in HIV-1 associated neurocognitive disorders and the molecular pathways implicated in its pathogenesis**. *Ann Med* 2021, **53**:43–69.

67. * He X, Yang W, Zeng Z, Wei Y, Gao J, Zhang B, Li L, Liu L, Wan Y, Zeng Q, *et al.*: **NLRP3-dependent pyroptosis is required for HIV-1 gp120-induced neuropathology**. *Cell Mol Immunol* 2020, **17**:283–299.

This study demonstrates that the HIV-1 viral protein gp120 activates NLRP3-dependnet pyroptosis and inflammation in microglia. This microglial pyroptosis promotes chronic neuroinflammation along with neurotoxicity and other CNS damage associated with neuroHIV.

68. Mamik MK, Hui E, Branton WG, McKenzie BA, Chisholm J, Cohen EA, Power C: **HIV-1 viral protein R activates NLRP3 inflammasome in microglia: implications for HIV-1 associated neuroinflammation**. *J Neuroimmune Pharmacol* 2017, **12**: 233–248.

69. Walsh JG, Reinke SN, Mamik MK, McKenzie BA, Maingat F, Branton WG, Broadhurst DI, Power C: **Rapid inflammasome activation in microglia contributes to brain disease in HIV/AIDS**. *Retrovirology* 2014, **11**:35.

70. Chivero ET, Guo ML, Periyasamy P, Liao K, Callen SE, Buch S: **HIV-1 tat primes and activates microglial NLRP3 inflammasome-mediated neuroinflammation**. *J Neurosci* 2017, **37**:3599–3609.

71. Lunemann JD, Malhotra S, Shinohara ML, Montalban X, Comabella M: **Targeting inflammasomes to treat neurological diseases**. *Ann Neurol* 2021, **90**:177–188.

72. Jin X, Zhou R, Huang Y: **Role of inflammasomes in HIV-1 infection and treatment**. *Trends Mol Med* 2022, **28**:421–434.

73. * Hu X, Zeng Q, Xiao J, Qin S, Wang Y, Shan T, Hu D, Zhu Y, Liu K, Zheng K, *et al.*: **Herpes simplex virus 1 induces microglia gasdermin D-dependent pyroptosis through activating the NLR family Pyrin domain containing 3 inflammasome**. *Front Microbiol* 2022, **13**, 838808.

This study shows evidence that HSV-1 can activate the NLRP3 inflammasome in microglia, resulting in GSDMD-dependent lytic cell death. This was associated with deleterious neuroinflammation and severe clinical disease in a rodent model of HSV-1 encepthalitis.

74. Jiang X, Stockwell BR, Conrad M: **Ferroptosis: mechanisms, biology and role in disease**. *Nat Rev Mol Cell Biol* 2021, **22**: 266–282.

75. Tsvetkov P, Coy S, Petrova B, Dreishpoon M, Verma A, Abdusamad M, Rossen J, Joesch-Cohen L, Humeidi R, Spangler RD, *et al.*: **Copper induces cell death by targeting lipoylated TCA cycle proteins**. *Science* 2022, **375**:1254–1261.