*Immunology & Cell Biology* 2021; 1–6
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EDITORIAL

# The Australasian Cell Death Society (ACDS): celebrating 50 years of Australasian cell death research

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doi: 10.1111/imcb.12510

*Immunology & Cell Biology* 2021; 1–6

Australasian researchers, including those from Australia and New Zealand, have a rich history of medical innovation which has helped shape the world as we know it today. Between the textbook discoveries of penicillin by Sir Howard Florey, T-cell immunity by Professor Peter Doherty (together with Rolf Zinkernagel) and telomere functionality by Professor Elizabeth Blackburn, Australasian scientists have cemented their place as global leaders in health and medical research. Importantly, research aimed at understanding cell survival and cell death has long been integral to many of Australasia's most notable scientific breakthroughs. This Editorial, composed by members of the Australasian Cell Death Society (ACDS) committee, aims to celebrate the long and storied history of cell death research within Australia and New Zealand.

It was Australian pathologist John Kerr who first coined the term "apoptosis" (Greek for "falling off," in reference to the falling leaves from trees in autumn) to describe the unusual phenomenon of ordered cell death during acute liver injury in rats.[1,2] In a series of electron microscopy images, Kerr laid out the unique morphological features of apoptosis that are still referenced half a century later. These described an ordered process of cellular dismantlement that begins with nuclear and cytoplasmic condensation, and ends with the engulfment of apoptotic bodies by surrounding cells (Figure 1a).[2] While first considered a somewhat esoteric field of study, today the search term "apoptosis" generates nearly half a million hits in PubMed, an impressive accolade owing to its vital role in organism development, homeostasis and immune function, as well as its important influence in human disease.[3] Since John Kerr's landmark publication, the cell death field has expanded to now recognize at least twelve distinct forms of programmed cell death, including both intrinsic and extrinsic apoptosis, necroptosis, pyroptosis, ferroptosis, NETosis and autophagy-dependent cell death, to name a few.[4] To this day, Australasian researchers continue to make pivotal discoveries that define the complex biochemical processes of programmed cell death.

Since the late 1980s, researchers at the Walter and Eliza Hall Institute of Medical Research (WEHI) in Melbourne have investigated the proteins that regulate intrinsic apoptosis. Beginning with the breakthrough discovery of B-cell lymphoma (BCL)-2 as a novel oncogene promoting survival of B-cell leukemia,[5] WEHI researchers have continued to perform fundamental research aimed at understanding the molecular mechanisms of apoptosis. This includes studies on the prodeath apoptotic effectors,

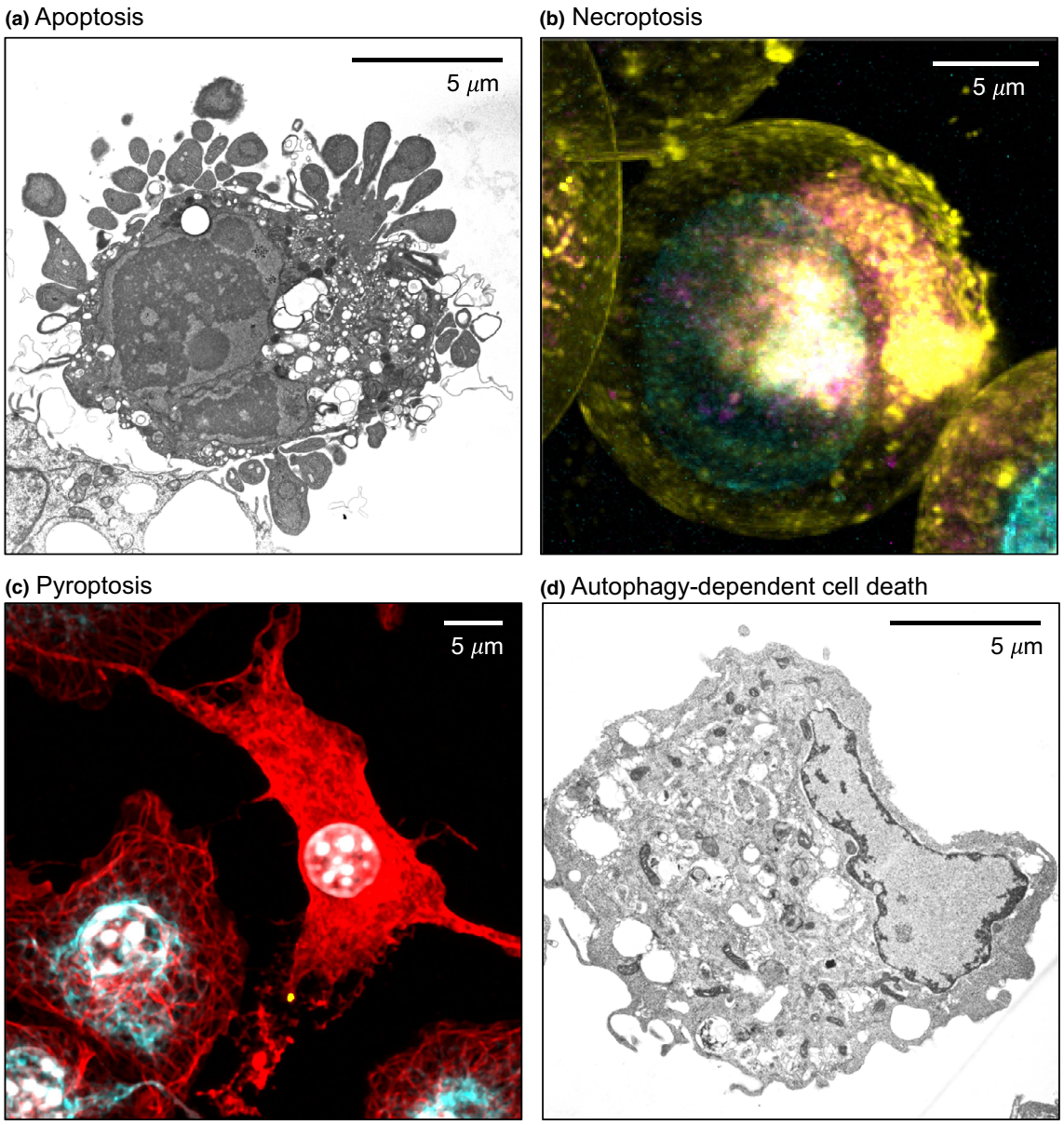


**Figure 1.** Examples of cell death studied in Australasia. **(a)** TEM of UV-irradiated apoptotic A431 cells (provided by Satoko Arakawa, Tokyo Medical and Dental University). **(b)** Lattice light sheet image of necroptotic HT29 cells following TSI treatment (yellow: Annexin V; magenta: mTagRFP–membrane fusion protein; cyan: TO-PRO-3; provided by Andre Samson, WEHI). **(c)** Confocal microscopy image of pyroptotic macrophages after LPS/nigericin treatment (gray: DAPI; yellow: ASC; red: alpha-tubulin; cyan: vimentin; provided by Caroline Holley, University of Queensland). **(d)** TEM of UV-irradiated Bax/Bak DKO MEFs undergoing autophagy-dependent cell death (provided by Satoko Arakawa). ASC, Apoptosis-associated speck-like protein containing a CARD; DAPI, 4′,6-diamidino-2-phenylindole; DKO, double-knockout; LPS, lipopolysaccharide; MEF, murine embryonic fibroblast; TEM, transmission electron microscopy; TSI, TNF, Smac mimetic and IDN-6556; UV, ultraviolet; WEHI, the Walter and Eliza Hall Institute of Medical Research.

BAX and BAK,[6–8] including key structural biology insights,[9–12] identification of the oncogenic transcription factor MYC,[13] therapeutic targeting of BCL-2 proteins in cancer[14–16] and the discovery of the BH3-only protein BIM,[17–20] including identifying its essential role in deleting self-antigen reactive lymphocytes.[21] Notably, deletion of self-antigen reactive lymphocytes is the cornerstone of the clonal selection theory that earned Australian Sir MacFarlane Burnet the Nobel Prize in Medicine and Physiology in 1960. This extensive portfolio

has paved the way for subsequent research that further delineates the mechanisms and downstream functions of intrinsic apoptosis, such as the release of cytochrome-*c*[22] and mitochondrial DNA,[23] the formation of apoptotic bodies[24] and crosstalk that enables proinflammatory cytokine release.[25]

In parallel to this significant body of work detailing the regulation of intrinsic apoptosis, Australasian researchers have also made an impressive contribution to our understanding of extrinsic death receptor signaling. After the international discovery of the death-inducing ligands, Fas ligand (FASL) and tumor necrosis factor (TNF), Australasian findings indicated that two distinct apoptotic pathways existed, as Fas-induced death was found to be independent of BCL-2.[26] Since this discovery, Australasian research has continued to expand our knowledge of extrinsic apoptosis. Key studies include those on TNF receptor signaling,[27,28] TNF receptor-associated protein with a death domain (TRADD),[29] Mind Bomb-2 (MIB2),[30] and inhibitor of apoptosis proteins,[31–33] including the crucial discovery of the inhibitor of apoptosis protein antagonist Smac/DIABLO.[34] Australasian researchers have also detailed the intersecting apoptotic pathways during T- and natural killer-cell killing,[35,36] and discovered the novel apoptotic effector protein, caspase-2,[37] among many other ground-breaking publications on extrinsic cell death.[38–42]

In addition to apoptosis, Australasian researchers have also pioneered our understanding of alternative cell death modalities. In Adelaide, fundamental research investigating cell death mechanisms in *Drosophila*[43–46] uncovered a unique caspase-independent pathway known as autophagy-dependent cell death (Figure 1d).[47,48] At WEHI, the pseudokinase mixed-lineage kinase domain-like (MLKL) was shown to form pores in the plasma membrane and cause another caspase-independent form of cell death called necroptosis (Figure 1b).[49,50] Recent studies have now detailed important structural and functional insights into the regulation of MLKL activity and processes that drive cell death.[51,52] Australasian research has also focused on other key necroptotic regulators, including receptor-interacting protein kinase 1 and 3 (RIPK1 and RIPK3), and highlighted their critical roles in inflammation and human disease.[53–55] In addition, Australasian researchers working internationally have uncovered extensive plasticity and crosstalk between apoptotic and lytic modes of cell death such as necroptosis.[54,56–59]

At the University of Queensland, Australasian researchers have made seminal contributions to the field of inflammasomes and pyroptotic cell death (Figure 1c). These include detailing how the pyroptotic effector caspase-1 is regulated,[60] inflammasome-mediated crosstalk between pyroptosis and apoptosis,[61] and the discovery of inflammasome-driven NETosis.[62] Crucially, many studies have now highlighted the critical role of inflammasome signaling and pyroptosis in disease.[63–66] Broadening the implications of dysregulated cell death in disease, work performed in Melbourne has also revealed the novel connection between extrinsic apoptotic and necroptotic cell death and inflammasome signaling.[42,67]

These discoveries have revolutionized our understanding of basic cell biology, revealing the complex interlocking mechanisms controlling cell survival and death. In addition to maintaining homeostasis, cell death is also implicated in a wide number of conditions, including cancer, autoimmune, neurodegenerative, inflammatory and infectious diseases.[68–70] Given this close association between cell death and disease, Australasian cell death research has also had an immense impact on human health. The most notable example showcasing the translation from basic cell death research to the clinic is the development of Venetoclax. Building on their foundational studies from the 1980s,[5,71,72] researchers at WEHI, in collaboration with industry partners AbbVie and Genentech (Roche), designed and developed the first "BH3 mimetic" to target the prosurvival protein BCL-2.[14] Also known by the moniker ABT-199, the drug Venetoclax is now approved for the treatment of chronic lymphocytic leukemia and acute myeloid leukemia[73–75] in the European Union, the United States and Australia. Furthermore, teams at WEHI, The Alfred Hospital and the Australian Centre for Blood Diseases were involved in the identification of the anti-apoptotic BCL-2 family member, MCL-1, as an attractive target for cancer therapy.[76] As such, the French pharmaceutical company Servier has developed the first specific MCL-1 inhibitor that is in clinical trials for acute myeloid leukemia and other blood cell–derived malignancies in Melbourne and many other parts of the world.[15] These are just some of the many Australasian success stories where basic research has led to drug development and improvement of patient outcomes on a global scale. With the abundance of Australasian cell death groups currently investigating models of disease and therapeutic development,[77–81] we can expect to see many more pioneering Australasian studies being translated into the clinic.

The ACDS was established in 2021 to harness the long history of Australasian cell death research illustrated in this Editorial, and to support the next generation of upcoming scientists. The overriding goal of the ACDS is to create a supportive cell death community where national and international collaboration can flourish. By facilitating connectivity and communication between early, mid- and senior career researchers, the ACDS aims

to build upon the Australasian reputation as global leaders in cell death research. The ACDS recognizes the barriers that upcoming scientists face, such as scarce and highly competitive funding, and strives to support the professional development of its junior members through Career Development Awards, networking and seminar opportunities as well as exposure through the easily accessible Cell Death Researcher Database. The ACDS was the vision of postdoctoral scientist Dr Georgia Atkin-Smith (ACDS President) and is led by a committee of enthusiastic PhD students and postdocs from across Australasia. The society pays tribute to the Pioneers of Australasian cell death research, Professor Andreas Strasser, Professor Sharad Kumar, Professor Suzanne Cory, Associate Professor Ruth Kluck, Professor Jerry Adams, Professor Peter Colman, Professor David Vaux and Dr Kim Newton, who have been appointed as Honorary Members to provide strategic oversight. Many of Australasia's most notable cell death findings were made possible through strong collaborations with international researchers. As such, the ACDS is honored to welcome Professor Shigekazu Nagata to its Pioneer Board, as the society strives to further strengthen its ties between Australasia and Japan. In addition to its Pioneers, the ACDS showcases inspirational leaders in the cell death field as Luminaries, who hail from the WEHI, Peter MacCallum Cancer Centre, Monash University, the Hudson Institute of Medical Research, La Trobe University, the Olivia Newton John Cancer Research Institute, The University of Adelaide, The University of Queensland, The University of Otago (Te Whare Wānanga o Ōtākou) and Genentech.

Given the long and distinguished history of cell death research in Australasia, the ACDS is excited to celebrate its 1-year anniversary by endorsing a Virtual Australasian Cell Death Issue of *Immunology & Cell Biology* (ICB) that includes works by Pioneers, Luminaries and emerging leaders in the field.

## ACKNOWLEDGMENTS

We thank the following for providing the microscopy data presented in Figure 1: (a, d) Satako Arakawa (Tokyo Medical and Dental University), (b) Andre Samson, Niall Geoghegan and Ying Zhang (WEHI) and (c) Caroline Holley (University of Queensland). We also thank Andreas Strasser for his constructive oversight to this Editorial and the ACDS Sponsors (WEHI, Abacus DX, Promega and Thermo Fisher Scientific) for their financial support.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## REFERENCES

1. Kerr JF. A histochemical study of hypertrophy and ischaemic injury of rat liver with special reference to changes in lysosomes. *J Pathol Bacteriol* 1965; **90**: 419–435.
2. Kerr JFR, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *Br J Cancer* 1972; **26**: 239–257.
3. Singh R, Letai A, Sarosiek K. Regulation of apoptosis in health and disease: the balancing act of BCL-2 family proteins. *Nat Rev Mol Cell Biol* 2019; **20**: 175–193.
4. Galluzzi L, Vitale I, Aaronson SA, *et al*. Molecular mechanisms of cell death: Recommendations of the Nomenclature Committee on Cell Death 2018. *Cell Death Differ* 2018; **25**: 486–541.
5. Vaux DL, Cory S, Adams JM. Bcl-2 gene promotes haemopoietic cell survival and cooperates with c-myc to immortalize pre-B cells. *Nature* 1988; **335**: 440–442.
6. Hockings C, Alsop AE, Fennell SC, *et al*. Mcl-1 and Bcl-x L sequestration of Bak confers differential resistance to BH3-only proteins. *Cell Death Differ* 2018; **25**: 719–732.
7. Alsop AE, Fennell SC, Bartolo RC, *et al*. Dissociation of Bak α 1 helix from the core and latch domains is required for apoptosis. *Nat Commun* 2015; **6**: 6841.
8. Willis SN, Fletcher JI, Kaufmann T, *et al*. Apoptosis initiated when BH3 ligands engage multiple Bcl-2 homologs, not Bax or Bak. *Science* 2007; **315**: 856–859.
9. Uren RT, O'Hely M, Iyer S, *et al*. Disordered clusters of bak dimers rupture mitochondria during apoptosis. *Elife* 2017; **6**: e19944.
10. Westphal D, Dewson G, Menard M, *et al*. Apoptotic pore formation is associated with in-plane insertion of Bak or Bax central helices into the mitochondrial outer membrane. *Proc Natl Acad Sci USA* 2014; **111**: E4076–E4085.
11. Czabotar PE, Westphal D, Dewson G, *et al*. Bax crystal structures reveal how BH3 domains activate Bax and nucleate its oligomerization to induce apoptosis. *Cell* 2013; **152**: 519–531.
12. Dewson G, Kratina T, Sim HW, *et al*. To trigger apoptosis, Bak exposes its BH3 domain and homodimerizes via BH3: groove interactions. *Mol Cell* 2008; **30**: 369–380.
13. Adams JM, Gerondakis S, Webb E, Corcoran LM, Cory S. Cellular myc oncogene is altered by chromosome translocation to an immunoglobulin locus in murine plasmacytomas and is rearranged similarly in human Burkitt lymphomas. *Proc Natl Acad Sci USA* 1983; **80**: 1982–1986.
14. Souers AJ, Leverson JD, Boghaert ER, *et al*. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. *Nat Med* 2013; **19**: 202–208.
15. Kotschy A, Szlavik Z, Murray J, *et al*. The MCL1 inhibitor S63845 is tolerable and effective in diverse cancer models. *Nature* 2016; **538**: 477–482.
16. Mason KD, Vandenberg CJ, Scott CL, *et al*. *In vivo* efficacy of the Bcl-2 antagonist ABT-737 against aggressive Myc-driven lymphomas. *Proc Natl Acad Sci USA* 2008; **105**: 17961–17966.

17. O'Connor L, Strasser A, O'Reilly LA, *et al*. Bim: a novel member of the Bcl-2 family that promotes apoptosis. *EMBO J* 1998; **17**: 384–395.
18. Bouillet P, Metcalf D, Huang DCS. Proapoptotic Bcl-2 relative Bim required for certain apoptotic responses, leukocyte homeostasis, and to preclude autoimmunity. *Science* 1999; **286**: 1735–1738.
19. Puthalakath H, O'Reilly LA, Gunn P, *et al*. ER stress triggers apoptosis by activating BH3-only protein Bim. *Cell* 2007; **129**: 1337–1349.
20. Puthalakath H, Huang DCS, O'Reilly LA, King SM, Strasser A. The proapoptotic activity of the Bcl-2 family member Bim is regulated by interaction with the dynein motor complex. *Mol Cell* 1999; **3**: 287–296.
21. Bouillet P, Purton JF, Godfrey DI, *et al*. BH3-only Bcl-2 family member Bim is required for apoptosis of autoreactive thymocytes. *Nature* 2002; **415**: 922–926.
22. Kluck RM, Bossy-Wetzel E, Green DR, Newmeyer DD. The release of cytochrome c from mitochondria: a primary site for Bcl- 2 regulation of apoptosis. *Science* 1997; **275**: 1132–1136.
23. McArthur K, Whitehead LW, Heddleston JM, *et al*. BAK/BAX macropores facilitate mitochondrial herniation and mtDNA efflux during apoptosis. *Science* 2018; **359**: eaao6047.
24. Poon IKH, Chiu YH, Armstrong AJ, *et al*. Unexpected link between an antibiotic, pannexin channels and apoptosis. *Nature* 2014; **507**: 329–334.
25. Vince JE, De Nardo D, Gao W, *et al*. The mitochondrial apoptotic effectors BAX/BAK activate caspase-3 and -7 to trigger NLRP3 inflammasome and caspase-8 driven IL-1β activation. *Cell Rep* 2018; **25**: 2339–2353. e4.
26. Strasser A, Harris AW, Huang DCS, Krammer PH, Cory S. Bcl-2 and Fas/APO-1 regulate distinct pathways to lymphocyte apoptosis. *EMBO J* 1995; **14**: 6136–6147.
27. Vince JE, Wong WWL, Khan N, *et al*. IAP antagonists target cIAP1 to Induce TNFα-dependent apoptosis. *Cell* 2007; **131**: 682–693.
28. Rickard J, Anderton H, Etemadi N, *et al*. TNFR1-dependent cell death drives inflammation in Sharpin-deficient mice. *Elife* 2014; **3**: 3464.
29. Anderton H, Bandala-Sanchez E, Simpson DS, *et al*. RIPK1 prevents TRADD-driven, but TNFR1 independent, apoptosis during development. *Cell Death Differ* 2019; **26**: 877–889.
30. Feltham R, Jamal K, Tenev T, *et al*. Mind bomb regulates cell death during TNF signaling by suppressing RIPK1's cytotoxic potential. *Cell Rep* 2018; **23**: 470–484.
31. Dueber EC, Schoeffler AJ, Lingel A, *et al*. Antagonists induce a conformational change in cIAP1 that promotes autoubiquitination. *Science* 2011; **334**: 376–380.
32. Mace PD, Linke K, Feltham R, *et al*. Structures of the cIAP2 RING domain reveal conformational changes associated with ubiquitin-conjugating enzyme (E2) recruitment. *J Biol Chem* 2008; **283**: 31633–31640.
33. Jost PJ, Grabow S, Gray D, *et al*. XIAP discriminates between type I and type II FAS-induced apoptosis. *Nature* 2009; **460**: 1035–1039.
34. Verhagen AM, Ekert PG, Pakusch M, *et al*. Identification of DIABLO, a mammalian protein that promotes apoptosis by binding to and antagonizing IAP proteins. *Cell* 2000; **102**: 43–53.
35. Sutton VR, Davis JE, Cancilla M, *et al*. Initiation of apoptosis by granzyme B requires direct cleavage of Bid, but not direct granzyme B-mediated caspase activation. *J Exp Med* 2000; **192**: 1403–1413.
36. Schuster IS, Wikstrom ME, Brizard G, *et al*. TRAIL$^+$ NK cells control CD4$^+$ T cell responses during chronic viral infection to limit autoimmunity. *Immunity* 2014; **41**: 646–656.
37. Kumar K, Kinoshita M, Noda M, Copeland N, Jenkins N. Induction of apoptosis by the mouse Nedd2 gene, which encodes a protein similar to the product of the *Caenorbabditis elegans* cell death gene ced-3 and the mammalian IL-1β-converting enzyme. *Trends Genet* 1994; **10**: 350.
38. Vince JE, Pantaki D, Feltham R, *et al*. TRAF2 must bind to cellular inhibitors of apoptosis for tumor necrosis factor (TNF) to efficiently activate NF-κB and to prevent TNF-induced apoptosis. *J Biol Chem* 2009; **284**: 35906–35915.
39. Anderton H, Rickard JA, Varigos GA, Lalaoui N, Silke J. Inhibitor of apoptosis proteins (IAPs) limit RIPK1-mediated skin inflammation. *J Invest Dermatol* 2017; **137**: 2371–2379.
40. Haas TL, Emmerich CH, Gerlach B, *et al*. Recruitment of the linear ubiquitin chain assembly complex stabilizes the TNF-R1 signaling complex and is required for TNF-mediated gene induction. *Mol Cell* 2009; **36**: 831–844.
41. Silke J, Hawkins CJ, Ekert PG, *et al*. The anti-apoptotic activity of XIAP is retained upon mutation of both the caspase 3- and caspase 9-interacting sites. *J Cell Biol* 2002; **157**: 115–124.
42. Lawlor KE, Khan N, Mildenhall A, *et al*. RIPK3 promotes cell death and NLRP3 inflammasome activation in the absence of MLKL. *Nat Commun* 2015; **6**: 6282.
43. Dorstyn L, Colussi PA, Quinn LM, Richardson H, Kumar S. DRONC, an ecdysone-inducible *Drosophila caspase*. *Proc Natl Acad Sci USA* 1999; **96**: 4307–4312.
44. Colussi PA, Quinn LM, Huang DCS, *et al*. Debcl, a proapoptotic Bcl-2 homologue, is a component of the *Drosophila melanogaster* cell death machinery. *J Cell Biol* 2000; **148**: 703–714.
45. Quinn L, Coombe M, Mills K, *et al*. Buffy, a *Drosophila* Bcl-2 protein, has anti-apoptotic and cell cycle inhibitory functions. *EMBO J* 2003; **22**: 3568–3579.
46. Dorstyn L, Read S, Cakouros D, *et al*. The role of cytochrome c in caspase activation in *Drosophila melanogaster* cells. *J Cell Biol* 2002; **156**: 1089–1098.
47. Denton D, Shravage B, Simin R, *et al*. Autophagy, not apoptosis, is essential for midgut cell death in Drosophila. *Curr Biol* 2009; **19**: 1741–1746.
48. Daish TJ, Mills K, Kumar S. Drosophila caspase DRONC is required for specific developmental cell death pathways and stress-induced apoptosis. *Dev Cell* 2004; **7**: 909–915.
49. Murphy JM, Czabotar PE, Hildebrand JM, *et al*. The pseudokinase MLKL mediates necroptosis via a molecular switch mechanism. *Immunity* 2013; **39**: 443–453.
50. Hildebrand JM, Tanzer MC, Lucet IS, *et al*. Activation of the pseudokinase MLKL unleashes the four-helix bundle domain to induce membrane localization and necroptotic cell death. *Proc Natl Acad Sci USA* 2014; **111**: 15072–15077.

51. Hildebrand JM, Kauppi M, Majewski IJ, *et al.* A missense mutation in the MLKL brace region promotes lethal neonatal inflammation and hematopoietic dysfunction. *Nat Commun* 2020; **11**: 3150.
52. Davies KA, Tanzer MC, Griffin MDW, *et al.* The brace helices of MLKL mediate interdomain communication and oligomerisation to regulate cell death by necroptosis. *Cell Death Differ* 2018; **25**: 1567–1580.
53. Rickard JA, O'Donnell JA, Evans JM, *et al.* RIPK1 regulates RIPK3-MLKL-driven systemic inflammation and emergency hematopoiesis. *Cell* 2014; **157**: 1175–1188.
54. Newton K, Wickliffe KE, Dugger DL, *et al.* Cleavage of RIPK1 by caspase-8 is crucial for limiting apoptosis and necroptosis. *Nature* 2019; **574**: 428–431.
55. Lalaoui N, Boyden SE, Oda H, *et al.* Mutations that prevent caspase cleavage of RIPK1 cause autoinflammatory disease. *Nature* 2020; **577**: 103–108.
56. Newton K, Wickliffe KE, Maltzman A, *et al.* RIPK1 inhibits ZBP1-driven necroptosis during development. *Nature* 2016; **540**: 129–133.
57. Newton K, Dugger DL, Wickliffe KE, *et al.* Activity of protein kinase RIPK3 determines whether cells die by necroptosis or apoptosis. *Science* 2014; **343**: 1357–1360.
58. De Almagro MC, Goncharov T, Newton K, Vucic D. Cellular IAP proteins and LUBAC differentially regulate necrosome-associated RIP1 ubiquitination. *Cell Death Dis* 2015; **6**: e1800.
59. Newton K, Wickliffe KE, Maltzman A, *et al.* Activity of caspase-8 determines plasticity between cell death pathways. *Nature* 2019; **575**: 679–682.
60. Boucher D, Monteleone M, Coll RC, *et al.* Caspase-1 self-cleavage is an intrinsic mechanism to terminate inflammasome activity. *J Exp Med* 2018; **215**: 827–840.
61. Sagulenko V, Thygesen SJ, Sester DP, *et al.* AIM2 and NLRP3 inflammasomes activate both apoptotic and pyroptotic death pathways via ASC. *Cell Death Differ* 2013; **20**: 1149–1160.
62. Chen KW, Monteleone M, Boucher D, *et al.* Noncanonical inflammasome signaling elicits gasdermin D–dependent neutrophil extracellular traps. *Sci Immunol* 2018; **3**: eaar6676.
63. Masters SL, Gerlic M, Metcalf D, *et al.* NLRP1 inflammasome activation induces pyroptosis of hematopoietic progenitor cells. *Immunity* 2012; **37**: 1009–1023.
64. Yu CH, Davidson S, Harapas CR, *et al.* TDP-43 triggers mitochondrial DNA release via mPTP to activate cGAS/STING in ALS. *Cell* 2020; **183**: 636–649. e18.
65. Rashidi M, Simpson DS, Hempel A, *et al.* The pyroptotic cell death effector gasdermin D is activated by gout-associated uric acid crystals but is dispensable for cell death and IL-1β release. *J Immunol* 2019; **203**: 736–748.
66. Bierschenk D, Monteleone M, Moghaddas F, *et al.* The Salmonella pathogenicity island-2 subverts human NLRP3 and NLRC4 inflammasome responses. *J Leukoc Biol* 2019; **105**: 401–410.
67. Conos SA, Chen KW, De Nardo D, *et al.* Active MLKL triggers the NLRP3 inflammasome in a cell-intrinsic manner. *Proc Natl Acad Sci USA* 2017; **114**: E961–E969.
68. Hotchkiss RS, Strasser A, McDunn JE, Swanson PE. Mechanisms of disease: Cell death. *N Engl J Med* 2009; **361**: 1570–1583.
69. Czabotar PE, Lessene G, Strasser A, Adams JM. Control of apoptosis by the BCL-2 protein family: implications for physiology and therapy. *Nat Rev Mol Cell Biol* 2014; **15**: 49–63.
70. Jorgensen I, Rayamajhi M, Miao EA. Programmed cell death as a defence against infection. *Nat Rev Immunol* 2017; **17**: 151–164.
71. Strasser A, Whittingham S, Vaux DL, *et al.* Enforced BCL2 expression in B-lymphoid cells prolongs antibody responses and elicits autoimmune disease. *Proc Natl Acad Sci USA* 1991; **88**: 8661–8665.
72. Strasser A, Harris AW, Cory S. bcl-2 transgene inhibits T cell death and perturbs thymic self-censorship. *Cell* 1991; **67**: 889–899.
73. Wei AH, Strickland SA, Hou JZ, *et al.* Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a phase Ib/II study. *J Clin Oncol* 2019; **37**: 1277–1284.
74. Wei AH, Montesinos P, Ivanov V, *et al.* Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood* 2020; **135**: 2137–2145.
75. Wei AH, Roboz GJ, Kantarjian HM. Harnessing the therapeutic value of venetoclax: a breakthrough therapy in acute myeloid leukemia. *J Clin Oncol* 2021; **39**: 2742–2748.
76. Kelly GL, Grabow S, Glaser SP, *et al.* Targeting of MCL-1 kills MYC-driven mouse and human lymphomas even when they bear mutations in p53. *Genes Dev* 2014; **28**: 58–70.
77. Lee EF, Clarke OB, Evangelista M, *et al.* Discovery and molecular characterization of a Bcl-2-regulated cell death pathway in schistosomes. *Proc Natl Acad Sci USA* 2011; **108**: 6999–7003.
78. Stutz MD, Allison CC, Ojaimi S, *et al.* Macrophage and neutrophil death programs differentially confer resistance to tuberculosis. *Immunity* 2021; **54**: 1758–1771. e7.
79. Pearson JS, Giogha C, Mühlen S, *et al.* EspL is a bacterial cysteine protease effector that cleaves RHIM proteins to block necroptosis and inflammation. *Nat Microbiol* 2017; **2**: 16258.
80. Coll RC, Hill JR, Day CJ, *et al.* MCC950 directly targets the NLRP3 ATP-hydrolysis motif for inflammasome inhibition. *Nat Chem Biol* 2019; **15**: 556–559.
81. Speir M, Lawlor KE, Glaser SP, *et al.* Eliminating *Legionella* by inhibiting BCL-XL to induce macrophage apoptosis. *Nat Microbiol* 2016; **1**: 15034.