Viewpoint

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Towards a molecular and structural definition of cell death

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Cell death contributes to tissue homeostasis and plays critical roles in inflammation and host defense. Our increasing understanding of the physiological importance of cell death underlines the need to more fully elucidate its underlying mechanisms in health and disease. Molecular and structural insight into the cell death apparatus could provide strategies to target the loss of cells in pathophysiological contexts. We asked experts studying a range of cell death types to share with us what they are most excited to tackle and what the field needs for progress.

Eli Arama: nonlethal caspase functions and caspase-independent cell death

Caspases, cysteine–aspartate proteases, are well known for orchestrating apoptosis, the primary form of programmed cell death acting during development and in response to injury. However, caspase activation does not always lead to cell death. Over the past two decades, numerous nonlethal caspase-dependent cellular processes (CDPs) have been identified, contributing to a range of physiological functions across different tissues and species. Meanwhile, growing evidence suggests that cell death can occur independently of apoptotic caspases, through more than a dozen distinct alternative cell death pathways (ACDs). This indicates that manipulating caspase activation as a therapeutic strategy for diseases such as cancer and neurodegenerative disorders may be more complex than previously thought.

For instance, although caspase activation might intuitively seem likely to suppress tumors by inducing cell death, evidence in certain cancers links increased levels of activated caspases to poorer survival rates. Although the reasons for this remain unclear, it may be due, at least in part, to the effects of CDPs. Moreover, as resistance to apoptosis is quite common in cancer cells, inducing ACDs could serve as a promising alternative to apoptosis-based therapies. It remains uncertain, however, which of the different ACD pathways would be most effective and have the least side effects, and how best to activate these pathways in vivo.

These challenges highlight significant gaps in our understanding of CDPs and ACDs. Although the number of identified CDPs has increased substantially, it remains unclear how many more are yet to be discovered. Furthermore, for most CDPs, the specific roles of caspases and the mechanisms by which cells cope with their lethal effects remain poorly understood. Compounding this, only a few ACD paradigms have been described in normal animal development, mostly in invertebrate models such as *Drosophila melanogaster* and *Caenorhabditis elegans*.

Why cells with the potential to induce apoptosis instead activate ACD pathways remains a mystery. One hypothesis that warrants further investigation is that ACDs and CDPs represent two sides of the same coin, with ACDs activated when caspase activity would otherwise lead to an undesirable cellular outcome through CDPs. To effectively combat many major diseases, it will be essential to address these knowledge gaps through extensive basic biology research, particularly in the context of whole organisms.

Katia Cosentino: decoding the structural logic of gasdermin pores in cell death

Cell death often hinges on a decisive event: membrane permeabilization. Members of the gasdermin (GSDM) family have emerged as central effectors of this process across multiple cell death modalities, notably pyroptosis and, increasingly, apoptosis. GSDMs undergo striking structural transformations from inert cytosolic precursors into pore-forming executioners. Upon proteolytic cleavage, GSDMs oligomerize at cellular membranes, forming pores that enable the release of pro-inflammatory molecules and initiate downstream signaling. Tight regulation of GSDM pores is essential to balance immune defense in infection and cancer while preventing pathological inflammation, underscoring the importance of a mechanistic understanding of their behavior.

However, the mechanistic principles governing pore formation remain poorly understood. Morphologically diverse GSDM assemblies — rings, arcs, slits and small oligomers — have been observed inserting into membranes. It is unclear whether these structures serve distinct functional roles in signaling and permeability or simply represent transient intermediates en route to mature pores. Currently, we lack tools to directly correlate structure with function, leaving a critical gap in understanding the sequence and significance of pore formation.

GSDMs also target multiple organelles, including plasma membrane, mitochondria and lysosomes, but the molecular and functional basis of this subcellular specificity remains unknown. Lipid specificity is necessary but insufficient; additional modulators such as local lipid metabolism, post-translational modifications and protein cofactors may influence membrane targeting and oligomerization. Mitochondrial localization is particularly intriguing. The mitochondrial membrane is already a critical hub in apoptosis, governed by permeabilization through BAX and BAK proteins. Whether GSDMs collaborate with, bypass or compete with BAX and BAK, and whether they serve distinct functions at this membrane, remain to be determined.

Another unresolved issue is what dictates the cellular outcome of GSDM pore formation: lysis or survival. In epithelial cells, pores

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may allow cytokine release without cell death, whereas in immune cells, pyroptosis dominates. It is likely that pore number, architecture and stability, as well as the lipid environment, influence these divergent outcomes.

Future progress will depend on developing biosensors and advanced imaging tools to visualize and manipulate functional GSDM pores with spatiotemporal precision. Building this structural framework will be essential to decoding the diverse roles and therapeutic potential of GSDMs across inflammation, immunity and cancer.

Peter E. Czabotar: unresolved mechanisms and therapeutic opportunities of the BCL-2 family in apoptosis

The discovery in the 1980s that BCL-2 inhibits apoptosis, and that its overexpression enables cancer cells to evade cell death, launched a new field focused on the molecular regulation of programmed cell death. Subsequent studies identified the broader BCL-2 family, with functional and structural studies uncovering a molecular network of interactions between opposing pro-survival and pro-apoptotic family members that ultimately governs the cell's apoptotic fate. However, despite decades of research and the successful development of therapeutics that target pro-survival BCL-2 family members, now used for cancer treatment, many aspects of apoptosis regulation remain poorly understood, and further opportunities exist to therapeutically target members of this protein family.

One major question is how executioner family members such as BAX and BAK form large pores during mitochondrial outer membrane permeabilization (MOMP), a pivotal step in the pathway. Although it is known that activated BAX and BAK homodimerize and likely assemble into toroidal pores comprising protein and lipid components, how they initiate membrane perforation, assemble to maintain pore integrity and can expand from small to large pores are still unclear. A BAX oligomer structure, published during this article's preparation, provides potential first clues to some of these questions while also opening new avenues to explore.

Additionally, the consequences of MOMP can vary. Classically, cytochrome *c* release leads to apoptosome formation and caspase activation, resulting in death. In some circumstances, however, transient pores may cause limited cytochrome *c* release, a phenomenon called sublethal MOMP, whereas in others, very large pores can release mitochondrial DNA and activate cGAS–STING signaling. The in vivo factors that determine these divergent outcomes are not well understood.

Other family members, such as BOK and tBID, may also mediate MOMP under certain conditions, but when and how they do so remains to be clarified. Another remarkable aspect of the family is that pro-survival and executioner proteins share the same structural fold, and the molecular basis of their opposing functions is unknown. The success of BH3 mimetics such as venetoclax demonstrates the druggability of this fold. A key challenge now is to translate this success to executioner proteins such as BAX and BAK, either to activate them in cancer or to inhibit them in diseases involving excessive cell death. Although the potential is great, achieving these goals will require deeper understanding of this complex pathway.

Boyi Gan: decoding the structural logic of cell sabotage and metabolic cell death

Over the past decade, several distinct forms of regulated cell death have emerged, each triggered by disruptions in cellular metabolism. Ferroptosis, characterized by iron-dependent lipid peroxidation, is the most studied. More recently, cuproptosis and disulfidptosis – triggered by copper overload and intracellular disulfide accumulation, respectively – have expanded this category. These pathways, often termed 'cell sabotage', differ fundamentally from 'cell suicide' pathways such as apoptosis, necroptosis and pyroptosis, which rely on defined signaling cascades and cell death executioner proteins.

These sabotage-type cell death pathways have enormous potential for treating diseases such as cancer and neurodegeneration. Yet a deeper understanding of their structural and molecular mechanisms is urgently needed to realize this promise.

A key gap lies in how metabolic perturbations – lipid peroxides, copper or disulfides – translate into cell death. In cell suicide pathways, this process is executed by pore-forming proteins such as BAX and BAK, mixed lineage kinase domain-like (MLKL) or GSDMs. By contrast, no analogous executioners have been identified for ferroptosis, cuproptosis or disulfidptosis.

In ferroptosis, despite extensive CRISPR screening, no terminal effector proteins have been conclusively found, suggesting that lipid peroxides may directly compromise membrane integrity and trigger cell death. However, the molecular details of how lipid peroxides disrupt membranes at the structural level remain elusive.

For cuproptosis, copper-loaded agents such as elesclomol cause depletion of Fe–S cluster proteins and aggregation of lipoylated mitochondrial proteins. But whether these events causally drive cell death is an open question – especially in the absence of defined downstream cell death executioners.

Similarly, disulfidptosis appears to stem from disulfide-induced cytoskeletal collapse. However, the full complement of molecular players involved in this form of cell death and whether they form a dedicated cell death machinery both remain unclear.

Elucidating the structural logic and execution mechanisms of these cell death pathways will not only deepen our mechanistic understanding but also uncover novel markers and therapeutic strategies for diseases in which metabolism-linked cell death is dysregulated.

Elizabeth Hartland: cell stress, cell death and what it means for host–pathogen interactions

Cell stress responses are intimately linked to cell death pathways. Cell stress signaling strives to restore cellular homeostasis, but if the stress is severe or cannot be resolved, the cell dies. In the context of infection, this can provide immune protection by abolishing the host replicative niche, and some pathogens actively block cell stress signaling to prolong host cell survival. Paradoxically, however, other pathogens induce cell stress to promote cell homeostasis and preserve a niche for replication. Hence, the outcome of stress signaling during infection can be cell type and pathogen specific.

More recently, cell stress responses have been linked to the initiation of inflammatory signaling and immunometabolism, especially in innate immune cells such as macrophages, providing a direct connection with the innate

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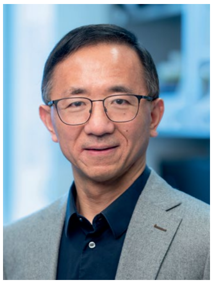
immune response. The links between cell stress and the cell-intrinsic immune mechanisms that restrict pathogen replication deserve further attention to understand the benefits to host and pathogen.

Cell death and inflammation are major drivers of tissue damage and symptomatic disease, yet how cell stress from pathogen invasion influences different modes of cell death during infection, such as apoptosis, pyroptosis and necroptosis, is not well understood. Better knowledge of the intersection of cell stress, cell death and the innate immune response could help shape approaches that limit damage from infection, drive efficient clearance of the pathogen, and safeguard cell and tissue integrity for more rapid recovery.



Xuejun Jiang: many faces of ferroptosis

Ferroptosis is a process of cell death driven by iron-dependent phospholipid peroxidation. Unlike apoptosis and several other regulated cell death modalities whose occurrence requires the activation of certain executing molecules, ferroptosis, or rather phospholipid peroxidation, can be considered a natural consequence of cellular metabolism. As such, ferroptosis normally needs to be suppressed by a variety of safeguard mechanisms, but when these mechanisms are suppressed or overwhelmed in one way or another, cells die by ferroptosis.

As ferroptosis is an emerging field, there remain numerous intriguing and potentially fundamental questions about it, ranging from whether it has any physiologically beneficial function, and how it functionally interacts with processes such as metabolism and immunity, to how it impacts diseases. Although the jury is still out about whether ferroptosis has physiologically beneficial functions, evidence for its involvement in various pathologies, including cancer and ischemic organ injuries, has been quite compelling. The conventional wisdom is that the better we understand the mechanisms of ferroptosis, the better chance we will have to identify its physiological function, if any, and to develop ferroptosis-based therapeutics.

Let's just zoom in on a very specific and not-so-grand mechanistic question concerning certain aspects of phospholipid peroxidation, which is presumably the end stage of ferroptosis but also relevant to inflammation and cell signaling, among other processes. The substrates of phospholipid peroxidation are phospholipids with polyunsaturated fatty acyl chain, or PUFA-PLs. Limiting the availability of PUFA-PLs can obviously render the cell more resistant to ferroptosis induction, which is how certain cancers evade ferroptosis. Strikingly, sometime a modest decrease of PUFA-PLs in a cell can make it exquisitely resistant to ferroptosis induction, a scenario that defies simple quantitative interpretation. One way to explain this quantitative conundrum is to consider that there might be specific microdomains on the cell membrane that are enriched with PUFA-PLs and serve as the 'designated' sites of phospholipid peroxidation and eventual membrane rupture.

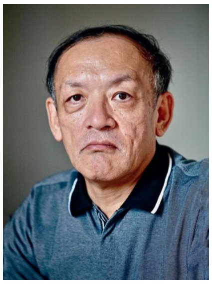
To test this hypothesis, new tools, such as lipidomic analysis with subcellular resolution, need to be developed. Both these new tools and the membrane microdomain hypothesis may be highly relevant to broader research in cell biology, beyond cell death or ferroptosis.

Jonathan C. Kagan: reversing cell death

How reversible are the pathways of cell death once they have been initiated? In human society, stories of near-death experiences have fascinated people since antiquity. This fascination derives, in part, from the belief that once a death process has begun, there is no turning back. The rare stories in which humans live healthy lives after a near-death experience violate our morbid assumption that death pathways are irreversible.

This same concept can be considered at the cellular level. We know that cells have several activities to prevent cell death from being initiated, with notable examples being enzymes that repair damaged DNA, refold damaged proteins and degrade dysfunctional organelles. In the absence of these repair, recycling or degradation enzymes, cellular damage is more likely to initiate some form of death pathway. Such cellular activities can be considered the molecular equivalent of human efforts to exercise and eat healthy foods, meaning that they operate to prevent the initiation of death processes. But do pathways exist that act to stop a death pathway, once initiated? We have less understanding of such potential processes.

Understanding how far down a death pathway our cells can proceed, and still reverse course to return to health, would be novel knowledge that could illuminate novel regulatory mechanisms. I propose that, akin to the way that reverse transcriptase demonstrated the reversibility of the original central dogma of molecular biology, whereby the path from DNA to RNA to protein was considered unidirectional, death pathways may also emerge as reversible. Stated differently, and in homage to the famed poet Dylan Thomas, I wonder if cells rage against the dying of the light. Perhaps they do.



Shigekazu Nagata: cell death by efferocytosis

In 1972, Kerr, Wyllie and Currie described a unique form of cell death characterized by distinct morphological features, introducing the term apoptosis. This programmed process involves nuclear condensation and fragmentation, along with the maintenance of plasma membrane integrity. In the final phase, apoptotic cells are recognized and engulfed by macrophages, which digest them through lysosomal degradation. Unlike necrosis — which involves membrane rupture and the uncontrolled release of intracellular contents — apoptosis was proposed to follow a genetically regulated pathway. Subsequent studies revealed that apoptosis is also defined by DNA fragmentation into nucleosomal units, now considered a hallmark of this controlled cell death process.

Meanwhile, Bretscher and colleagues (1971) had demonstrated the asymmetric distribution of phospholipids in the plasma membrane, with phosphatidylserine (PtdSer) localized primarily to the inner leaflet. Around the same period, it was observed that red blood cells exposing PtdSer on their surface were efficiently cleared by macrophages. This led to the hypothesis that externalized PtdSer functions as an 'eat me' signal. In 1992, it was confirmed that apoptotic cells expose PtdSer, thereby facilitating their recognition and clearance by phagocytes.

Thanks to extensive research, the molecular and structural underpinnings of apoptosis are now well understood. Because of its immunologically silent nature, apoptosis has long been considered an ideal mechanism for eliminating tumor cells. However, therapies

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designed to induce apoptosis — such as death receptor agonists or survival pathway inhibitors — often come with serious side effects. Moreover, because apoptosis involves the activation of DNases, incomplete execution may result in genomic instability, potentially promoting tumor progression.

To harness cell death more effectively, targeted immunotherapies such as checkpoint inhibitors and CAR-T cells exploit apoptosis with high specificity, allowing T cells to discriminate between malignant and healthy cells. Building on this concept, novel strategies could involve non-inflammatory clearance of resistant cells. For instance, designing cell-permeable peptides that inhibit flippases in cancer or senescent cells could lead to persistent PtdSer exposure, marking them for macrophage-mediated removal even if they evade apoptosis — offering a promising direction for future therapies.

Kate Schroder: how cell corpses shape immunity from beyond the grave via pyroptosis

The life of an organism relies on the timely birth and death of its cells. Moreover, it is crucial for cells to die not only at the right time, but also in an appropriate manner. Pyroptosis is a mode of inflammatory cell lysis triggered by members of the GSDM pore-forming family. Pyroptosis shapes immune responses in vivo, but our understanding of the underlying mechanisms remains rudimentary.

Pyroptotic cell death is often instructed by inflammasome signaling. Here, activated caspases (such as caspase-1, -4, -5 or -11) cleave gasdermin D (GSDMD) to unmask its pore-forming activity that induces cell lysis. Concomitantly, the cell releases mediators (cytokines and alarmins) that elicit immune signaling in neighboring cells. These pathways culminate in immune system activation, including programs to engage the adaptive arm of the immune system. Although inflammasome-dependent cytokines (interleukin-1β (IL-1β) to IL-18) have been extensively studied, the full suite of alarmins generated during pyroptosis, and their functions in immune regulation, remain poorly defined. Thus far, most studies have concentrated on the soluble alarmins (such as ATP, HMGB1 and IL-1α) released by pyroptotic macrophages.

Emerging studies are revealing that the pyroptotic corpse itself has biological functions that continue beyond the cell lifespan. For example, neutrophils signaling via the caspase-4–caspase-11 inflammasome extrude their chromatin to form a neutrophil extracellular trap — a web-like structure that entraps bacteria, prevents bacterial dissemination and thus contributes to antibacterial defense. In another recent discovery, pyroptotic cells assemble F-actin-rich filopodia minutes before they undergo plasma membrane rupture. These filopodia persist at the edges of pyroptotic corpses after cell lysis, stimulate the extracellular F-actin receptor CLEC9A on incoming dendritic cells and induce the upregulation of antigen-presentation mechanisms for adaptive immunity.

It is likely that such studies of how pyroptotic corpses posthumously instruct antimicrobial defense, innate immunity and adaptive immunity have merely scratched the surface. Drug candidates that suppress pyroptosis to prevent inflammation, or induce pyroptosis to destroy tumor cells, are currently under development. For the field to fully harness the potential benefit of modulating pyroptosis in the clinic, a key remaining challenge will be to define the full suite of immunomodulatory and antimicrobial functions of pyroptosis-liberated alarmins and pyroptotic corpses.

Liming Sun: the unknown mechanism of MLKL in necroptosis — a major gap in understanding lytic cell death

MLKL was identified as the membrane-disrupting executioner of necroptosis even before GSDMD was recognized as the effector of pyroptosis. Yet, intriguingly, our structural understanding of the GSDM family has advanced much faster. The pore-forming architecture of GSDMD and its caspase-dependent activation mechanism are now well defined. By contrast, despite years of study, the structural and mechanistic details of MLKL activation and membrane engagement remain unclear.

This discrepancy reflects more than just experimental challenges — it points to fundamentally different membrane-disruption strategies. Unlike GSDMD, which requires proteolytic cleavage by caspases to expose its pore-forming domain, MLKL does not rely on cleavage for activation. Overexpression of full-length GSDMD is inert (that is, it has no effect on cell death), whereas overexpression of MLKL — or its upstream phosphorylation by RIPK3 — is sufficient to trigger necroptotic cell death. This distinction underscores the fact that MLKL follows a unique activation logic and likely uses a distinct physical mechanism to damage membranes.

So far, no defined pore-like structure formed by MLKL has been observed. How MLKL interacts with the lipid bilayer — whether it oligomerizes, embeds into the membrane or exerts its effects through transient, dynamic interactions — remains unclear. These unknowns highlight a major conceptual gap in our understanding of necroptosis, and of membrane-lytic cell death more broadly.

Moving forward, structural and biophysical investigations — focusing on phosphorylation-driven conformational changes of MLKL and its real-time behavior at the membrane — will be critical. Unraveling how MLKL executes necroptosis will not only clarify the distinctions between cell death pathways but may reveal entirely new principles of regulated necrosis.

Daichao Xu and Junying Yuan: towards defining cell death type–specific biomarkers

Apoptosis and necroptosis are two fundamental types of programmed cell death mechanisms that can be activated to promote cell death in development, during host defense and in disease conditions. The activation of caspases, such as caspase-3 and caspase-8, defined by specific proteolytic cleavages provides the biomarkers for apoptosis. The activation of RIPK1, RIPK3 and MLKL, as marked by their specific phosphorylation events, provides the biomarkers for the activation of necroptosis. In addition, the caspase-mediated cleavage of GSDMs, such as GSDMD, provides the biomarker for pyroptosis. The biomarkers for the different forms of cell death are highly valuable for evaluating the occurrence of different forms of programmed cell death in vivo, particularly in human pathological samples, as they provide evidence for the possible involvement of particular form of cell death and therefore suggest the value of testing the effects of related inhibitors to treat specific disease condition.

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In addition to the programmed cell death mechanisms mentioned above, cells may also die passively as a result of stress, through processes such as ferroptosis, cuproptosis and disulfidptosis. Ferroptosis can be induced by excessive lipid peroxidation, which can be the result of depriving cells of the essential precursor glutathione. However, whereas excessive lipid peroxidation can induce ferroptosis, lipid peroxidation can result from certain reversible metabolic processes and is not necessarily indicative of cell death. Cuproptosis is a form of passive cell death due to proteotoxic stress from excess accumulation of copper ion in mitochondria. Disulfidptosis is characterized by the collapse of the cytoskeleton due to disulfide bond accumulation, specifically within the actin cytoskeleton. For these passive cell death pathways, no specific biomarkers or death executors have thus far been identified. This lack of specific biomarkers or death executors makes it difficult to assess their possible causative roles in pathological conditions.

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Competing interests

P.E.C. is an employee of the Walter and Eliza Hall Institute, which has an agreement with Genentech and AbbVie, and receives milestone and royalty payments related to Venetoclax. Employees of the Walter and Eliza Hall Institute may be eligible for financial benefits related to these payments. P.E.C. receives such a financial benefit as a result of previous research related to Venetoclax. X.J. is an inventor on patents related to autophagy and cell death, and he holds equity of and consults for Exarta Therapeutics and Lime Therapeutics. J.C.K. receives compensation from and holds equity in Corner Therapeutics, Larkspur Biosciences, MindImmune Therapeutics and Neumora Therapeutics. None of these relationships impacted this study. K.S. is a co-inventor on patent applications for NLRP3 inflammasome inhibitors which have been licensed to Inflazome, a company acquired by Roche. K.S. served on the Scientific Advisory Boards of Inflazome (Ireland), Quench Bio (USA) and Novartis (Switzerland). All other authors declare no competing interests.