Title:

Roadmap for the next decade of plant programmed cell death research

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Abstract/Summary

Programmed cell death (PCD) is fundamentally important for plant development, abiotic stress responses and immunity, but our understanding of its regulation remains fragmented. Building a stronger research community is required to accelerate progress in this area through knowledge exchange and constructive debate. In this Viewpoint, we aim to initiate a collective effort to integrate data across a diverse set of experimental models to facilitate characterization of the fundamental mechanisms underlying plant PCD and ultimately aid the development of a new plant cell death classification system in the future. We also put forward our vision for the next decade of plant PCD research stemming from discussions held during the 31st New Phytologist workshop, "The Life and Death Decisions of Plant Cells" that took place at University College Dublin in Ireland (14-15th June 2023). We convey the key areas of significant progress and possible future research directions identified, including resolving the spatiotemporal control of cell death, isolation of its molecular and genetic regulators, and harnessing technical advances for studying PCD events in plants. Further, we review the breadth of potential impacts of plant PCD research and highlight the promising new applications of findings from this dynamically evolving field.

Main body

How to describe an elephant?

Programmed cell death (PCD) research has gained considerable momentum in recent years, with a plethora of new datasets and experimental systems providing key insights into our understanding of molecular regulation of different PCD events in plants. Nevertheless, the existence of a core PCD machinery in plants is under debate and the sequence of events leading to controlled self-destruction of plant cells remains poorly characterised. These open questions, and ways to address them in the future, were the focus of the 31st New Phytologist workshop 'The Life and Death Decisions of Plant Cells' held in Dublin, June 14th and 15th, 2023. The workshop allowed participants, using a diverse set of model systems and approaches, and studying a range of different PCD contexts, to exchange ideas and compare their findings with colleagues. The issue of recommended plant cell death nomenclature and classification systems was also considered; however no unequivocal conclusion has been reached on the matter. This led to a stimulating discussion, evocative of the parable about the blind men and the elephant. In this ancient tale, a group of blind men investigate an elephant by touching a different part of its body, and consequently, each describes a different impression of the animal, comparing it to a snake, a rope, or a tree, depending on whether they touched the trunk, tail, or a leg, respectively. While each blind man is partly right, they will not be able to describe the elephant without finding a way of reconciling their individual observations. This is an excellent analogy to the critical need for knowledge and data integration across systems, experimental models, and investigated cell death scenarios in PCD research, as well as the importance of communication, but also debate, between researchers working in the field (Figure 1). The meeting "The Life and Death Decisions of Plant Cells" provided a small but important forum for such interactions, enabling discussion on triggers, biomolecular markers, subcellular and organellar control, signalling pathways and genes involved in the modulation of the PCD process. In this Viewpoint, we aim to maintain this momentum and include the broader community in the collective effort of integrating data on features of PCD in plants. To achieve this we provide a living document comparing observations across species and experimental models (Table 1). New entries can be continually submitted, and we invite all colleagues to join this attempt to "describe the (plant PCD) elephant" in more detail and from more perspectives. We are hoping that this initiative will inform the ongoing debate on how cell death programmes in plants should be classified and facilitate development of an updated nomenclature system akin to guidelines suggested for metazoan cell death pathways (Galluzzi et al., 2018). At the moment, some researchers favour PCD as a blanket term, that has been used historically to describe any active, genetically controlled cell death occurring in response to developmental, abiotic and biotic stimuli, as demonstrated by the early publications in the field (Lam et al., 2001, Lam, 2004, Beers, 1997, Greenberg et al., 1994). Other research groups follow classification of plant cell death based on the context in

which PCD is occurring (environmental – ePCD and developmental – dPCD) (Olvera-Carrillo et al., 2015) or adopt the recommendations of the Nomenclature Committee on Cell Death 2018 that distinguish PCD as a specific development-related subtype of genetically regulated cell death (RCD) (Galluzzi et al., 2018). Our discussions highlighted that the new nomenclature system for plant cell death pathways should consider issues such as the considerable environmental influences that often shape plant development and associated cell death events, as well as any effect of the proposed new nomenclature system on the communication and collaborative efforts between the plant and animal cell death communities. Furthermore, as our understanding of the mechanisms that orchestrate plant cell death expands, efforts defining subroutines of active cell death programmes in plants, similar to previously proposed classifications based on morphology (Mur et al., 2007, Reape et al., 2008, van Doorn et al., 2011) or key biochemical pathways, such as ferroptosis (Distéfano et al., 2017), will require integration of the large volume of new data and findings that have emerged over the last decade across the diversity of experimental systems. We believe that development of a nomenclature system capturing the plant cell death modalities should, as widely as possible, consult the broad community of scientists who are driving progress in this research area, and we hope that this Viewpoint article will lay the initial foundations of this process.

A vision for the next decade of plant PCD research.

Spatiotemporal, high precision study of PCD in plants

Recent findings and ongoing studies of plant PCD clearly highlight that plant cell death research has entered a new era, where we are gaining more high-level spatiotemporal insights into plant PCD processes and their regulation.

Environmentally-induced PCD: One of the model systems that has recently provided advances in our understanding of finely-tuned PCD regulation is the hypersensitive response (HR). HR occurs when recognition of pathogen attack leads to a rapid cell death in the cells surrounding the zone of pathogen invasion, preventing the spread of (hemi-)biotrophic pathogens, and contributes to local and systemic defence signalling (Heath, 2000, Mur et al., 2007). Time- and zone- dependent multi-omic approaches have proven a powerful tool for dissecting the molecular networks controlling HR and the formation of boundaries between cells that stay alive and their dying neighbours. In *Arabidopsis thaliana* (hereafter referred to as Arabidopsis), transcriptomic assays have revealed spatio-temporal differences in genes and biological processes regulated in the cells undergoing HR and in the surrounding living tissue, and have consequently defined robust transcriptional *in vivo* cell death markers (Salguero-Linares et al., 2022). Similarly in maize, a combination of transcriptomic, proteomic, and degradomic analyses of dying cells identified time-dependent gene reprogramming and has defined general-

and trigger specific- cell death markers (Barghahn et al., 2023). These data underpinned the basis for the mechanistic exploration of new molecular functions involved in life and death decisions, as well as the initiation and execution of cell death. Moreover, *in vivo* imaging techniques are currently being explored as tools to study the dynamics and zonation of HR (Betsuyaku et al., 2017) and the use of genetically encoded biosensors will allow researchers to closely monitor particular processes such as proteolysis or follow changes in redox homeostasis and small molecule fluxes [e.g. Ca^{2+}; (Fernández-Fernández et al., 2019)]. Cell suspension cultures are another well-established model for studying PCD in plants, which have been recently used in combination with multi-omic approaches to generate new insights into the regulation of cell death and survival decisions in plant cells. The homogenous cell suspension facilitates precise monitoring of PCD rates induced by a broad range of stimuli, thus offering an opportunity to specifically sample cells undergoing PCD. Burke et al. (Burke et al., 2023) compared the transcriptional response to three different PCD-inducing treatments used in combination with three cell death inhibitors; this enabled inference of core- and stimuli- specific gene regulatory networks and isolation of putative transcriptional regulators of PCD that were not previously explored in the context of cell death. Importantly, this study highlighted that, depending on the treatment used to induce cell death, cell cultures can mimic PCD induced by biotic interactions, abiotic stress, and even developmental programmes, and in this way facilitate comparisons between cell death occurring in different contexts. Furthermore, Schwarze et al. (Schwarze et al., 2023) combined the use of Arabidopsis cell suspension culture with cellular fractionation and proteomic profiling to identify proteins released from plant mitochondria upon PCD induction, and to characterise changes in cytosolic protein abundance associated with early stages of PCD. Ease of repeated sampling of cell suspension cultures, and the homogeneity of the observed response, can powerfully support studies aiming to achieve fine resolution of transcriptional and proteomic patterns associated with different stages of PCD. In the near future, single cell approaches will almost certainly provide us with even higher resolution of dynamic spatio-temporal transcriptome maps during ePCD events.

Developmental PCD: Significant spatiotemporal insights into molecular and cellular processes associated with developmental PCD were provided by studies using the Arabidopsis root cap model (Kumpf and Nowack, 2015). Root cap cells undergo highly organised and temporally coordinated PCD to regulate root cap organ size in balance with cell division (Fendrych et al., 2014). As this PCD occurs at the periphery of the growing root tip, it is amenable to a number of analytical approaches, including live-cell imaging (Fendrych et al., 2014), single-cell transcriptomics (Minne et al., 2022), and pharmacology (Dubreuil et al., 2018), as well as cell-type specific gene editing by CRISPR (Decaestecker et al., 2019, Bollier et al., 2021). This model system has facilitated resolving gene regulatory networks (Fendrych et al., 2014, Huysmans et al., 2018, Feng et al., 2023), hormone signalling (Xuan et al., 2016), and autophagy (Feng et al., 2023) involved in developmentally controlled PCD. More

recently, the root cap system has been used to analyse the sequence of cellular processes during PCD execution (Wang et al., 2023). Established core events like vacuolar breakdown and plasma membrane permeabilization for non-membrane permeable dyes such as propidium iodide (PI) occurred late in the execution process and were preceded by cellular calcium influx, cytosolic acidification, mitochondrial disintegration, and the breakdown of the nuclear envelope and endoplasmic reticulum (ER) (Wang et al., 2023). Interestingly, despite plasma membrane permeability to PI, the leakage of used reporter proteins to the apoplast was not observed, reminiscent of the situation in animal apoptosis (Zhang et al., 2018). Though it cannot be excluded that the sequence and type of subcellular processes are specific to root cap cell death, the system provides an excellent framework to formulate and test hypotheses to understand the molecular processes of PCD execution *in planta*. Another model system facilitating high precision studies of developmental PCD is provided by leaf perforation formation of lace plant (Gunawardena et al., 2004). Here, the cell death begins in the centre of areas known as areoles, between transverse and longitudinal veins, and continues outwards, stopping four to five cells from the vascular tissue, creating a gradient of living cells surrounding an area of dying cells. The order of cellular events that occur during lace plant PCD was established using a long-term live cell imaging technique (Wertman et al., 2012). Indeed, the accessibility and predictability of PCD during lace plant leaf development, combined with laser capture microdissection-based sampling, recently facilitated comparisons of transcriptional profiles of cells at different stages of PCD and living cells from the non-PCD zone (Rowarth et al., 2021). The spatiotemporal predictability of lace plant PCD also makes it a good subject for computational modelling approaches, used extensively in developmental biology from the molecular to tissue level (Sharpe, 2017). While anthocyanins, reactive oxygen species (ROS), and auxin were all implicated in the control of lace plant leaf PCD (Denbigh et al., 2020, Dauphinee et al., 2017), their exact roles and interactions remain elusive, and are currently subject to computational modelling with the aim of providing a plausible explanation for the underlying mechanisms involved (unpublished data – Sophie Tattrie, Gunawardena's lab). Finally, the Papaver self-incompatibility-induced PCD (SI-PCD) system provides another excellent model to study PCD and provide spatio-temporal insights in the signalling network involved. SI triggers a Ca^{2+}-dependent signalling network that rapidly inhibits pollen tube growth and later culminates in PCD in incompatible pollen, thus preventing self-fertilisation (Wang et al., 2018). The Papaver SI-PCD system has been transferred to Arabidopsis and is fully functional in both reproductive and vegetative cells (Lin et al., 2015, Lin et al., 2020). This engineered 'poppydopsis' system facilitates a broad diversity of genetic approaches (Wang et al., 2020b) and thus represents a powerful resource to test new hypotheses and elucidate genetic components and cellular events involved in and leading to PCD in plants. For example, use of genetically encoded fluorescent probes identified a link between SI-induced ATP depletion and cytosolic acidification (Wang et al., 2022), the latter being required for execution of PCD (Bosch

and Franklin-Tong, 2007). The highly complex, hierarchical signalling events involved in SI-PCD are well suited for a systems biology approach: modelling the interactions of various components of SI-PCD may facilitate subsequent examination of these complex and important biological responses in qualitative and quantitative terms.

The studies listed above represent only a handful of examples showing that both established and new models for studying PCD, when combined with multi-omics technologies, a diversity of genetic tools, and computational modelling approaches, can collectively inform our understanding of plant cell death as a highly dynamic process involving complex signalling networks. Many of these models are particularly suitable for investigating the role of cell-to-cell communication in life and death decisions in plants. As previously highlighted, integration of a large volume of recent data across these models is one of the challenges ahead, but also an exciting opportunity to understand the details of regulation of cell death processes operating in plants with unprecedented accuracy.

Friend, foe or both? - Fine-tuning the regulators that balance cell death or survival outcomes.

Much progress has also been made in terms of exploring the often complex relationships between plant PCD and other pathways. For example, autophagy is emerging as a critical mediator of the balance between cell survival and cell death, rather than simply operating as a pro-survival or pro-death response. In plants and other organisms, autophagy can contribute to cell survival during stress, attenuating cell death by clearing intracellular damage and preventing toxicity (Nelson and Baehrecke, 2014, Guan et al., 2019, Zhu et al., 2019). However, a role for autophagy in the execution of cell death pathways has also been established, depending on the conditions and cell type. For example, in Arabidopsis root caps, autophagy is involved in the timely cell death of columella cells, but not of the distal root cap cells (Feng et al., 2022). In Arabidopsis, autophagy can play a positive or negative role in PCD regulation (Xu et al., 2017, Kacprzyk et al., 2014, Coll et al., 2014), and in maize it is activated at both cell survival and cell death stages of a prolonged ER stress response (Srivastava et al., 2018). Likewise, during perforation formation in the lace plant leaves, autophagy plays a dual role in promoting cell survival in non-PCD cells and mediating timely cell death in PCD cells (Rowarth et al., 2023). Future high-resolution studies and modelling approaches will continue to elucidate the link between plant PCD and other pathways that, as demonstrated by the example of autophagy, may be dependent on the PCD context, stage of PCD, timing or intensity of cell death-inducing stimuli. Similarly, studies deciphering the roles of proteases previously linked to plant PCD (Salguero-Linares and Coll, 2019, Stael et al., 2023, Chichkova et al., 2010, Ge et al., 2016, Hatsugai et al., 2015, Lampl et al., 2013) are required, as in many cases it remains unclear whether they act as executioners or alternatively function as signalling molecules that carefully control the cell

death initiation. To date, understanding the function of individual proteases in plant PCD has been hampered by the fact that knocking out individual proteases often results in modest, if any, phenotypes, indicating a high degree of genetic redundancy. However, with the advent of CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) technology the community has started addressing this problem by creating higher-order protease mutants (Shen et al., 2019). An example that was thoroughly discussed during the Workshop in Dublin was that of metacaspases, proteases that have been extensively studied as plant PCD regulators since their discovery more than two decades ago (Uren et al., 2000). Based on their structural resemblance to animal caspases, metacaspases have been often postulated as "caspase-like" or "apoptotic-like" proteins. However, their substrate specificity is certainly not caspase-like (Vercammen et al., 2004, Minina et al., 2020) and a growing body of evidence suggests that at least some of the metacaspases that have been characterised to date participate in stress responses and may be mainly stress sensors rather than cell death executioners. For example, the type II metacaspase AtMC4 is activated upon wounding, generating a signalling peptide essential for the response to this type of stress (Hander et al., 2019). In turn, the type I metacaspase MC1 participates in clearance of harmful protein aggregates formed as a result of proteotoxic stress, a function conserved from fungi to plants (Lee et al., 2010, Hill et al., 2014, Ruiz-Solaní et al., 2023, Coll et al., 2014). On the other hand, both Arabidopsis MC3 and Chlamydomonas CrMCA-II have been shown to be involved in drought and heat stress tolerance, respectively, independently of their catalytic activity (Pitsili et al., 2023, Zou et al., 2023). Collectively, despite the fact that metacaspases may have evolved from the same ancestor as caspases, current evidence indicates that they are not simply executioner caspases in the context of PCD and that they could instead function, or have additional, context-dependent roles, as pro-survival proteins. Accumulating evidence in non-plant fields also supports the idea that other cell death proteins may also have non-lethal roles (Arama et al., 2021). These examples highlighted that nuanced aspects of cell death regulation in plants require further exploration across experimental systems, cell death modalities and stages.

Harnessing new technologies and tools to advance our understanding of plant cell death.

Studying plant PCD with high spatiotemporal resolution and dissecting the details of finely tuned regulation of cell death processes will be supported by the increasing accessibility of new technologies, especially if they are applied to the range of model systems available for studying PCD in different contexts.

For example, single-cell transcriptomics approaches have started to open up new possibilities in biological research in recent years. Single-cell RNA-sequencing (scRNA-seq) holds great potential to detect the rapid gene expression changes during cell death induction and the early stages of plant PCD. While transcriptional regulation is only one element of PCD control, it has been shown to play decisive roles in both

developmental and stress-induced PCD processes (Cubría-Radío and Nowack, 2019, Burke et al., 2020). Interestingly, in the context of developmental PCD in Arabidopsis, scRNA-seq has revealed that only a handful of cells express late PCD-associated genes (Olvera-Carrillo et al., 2015, Wendrich et al., 2020). As such, scRNA-seq approaches can become invaluable in identifying the gene regulatory networks that orchestrate the preparation for PCD *in planta*.

Beyond the transcriptional level, more advanced and dedicated proteomics approaches (e.g. redox proteomic, N-terminomics and degradomics) will provide more insights on the intricate networks involved in plant cell death (Huang et al., 2023, Demir et al., 2022, Rowland et al., 2022). Post-translational oxidative modifications, phosphorylation, and certainly protein cleavages and degradation, can provoke rapid alterations or termination to the functionality of either signaling or structural proteins. Therefore, the implementation of innovative proteomics workflows and the use of more advanced mass spectrometry technologies will certainly further advance our knowledge in this area. For example, very little is known regarding possible proteolytic cascades activated during plant PCD, and it would be highly beneficial to systematically identify the substrates of the cell death proteases that actively take part in the process. For this identification, an N-terminal-based degradomics approach could be employed, comparing the *in vivo* population of non-canonical N-termini between two experimental setups, with one set-up missing the protease activity of interest, either by inhibition or mutation. In the absence of the protease, the N-termini missing or with a significantly reduced abundance, will point to candidate substrates that can be subjected to further validation. Techniques based on positive enrichment or negative enrichment of N termini that have been used to study plant proteases include Combined Fractional Diagonal Chromatography (COFRADIC) (Gevaert et al., 2003), Terminal Amine Isotopic Labeling of Substrates (TAILS) (Huesgen and Overall, 2012), and High-efficiency undecanal-based N termini enrichment (HUNTER) (Weng et al., 2019). COFRADIC, TAILS and HUNTER have all produced interesting results for groups investigating protease substrates in plants (Tsiatsiani et al., 2013, Willems et al., 2017, Pitsili et al., 2023), but more research is needed specifically in the context of PCD. Such degradomics techniques have limitations linked to detection threshold and protein cleavage redundancy. Therefore, it might be advantageous to additionally use Proximity-dependent biotinylation labelling techniques such as Turbo ID (Mair et al., 2019). Proximity labelling can identify protease partner proteins, as shown for phytaspase (Teplova et al., 2021) and in principle, some protease partners could be substrates, depending on how protease-substrates interact. Systematically identifying protease substrates during plant PCD with support of the above-described approaches is a much-needed step to fully understanding the function of the candidate cell death proteases.

Finally, genome editing using CRISPR technology has revolutionised life sciences in recent years, with the field of plant PCD being no exception. Interestingly, CRISPR not only enables us to generate single or higher-

order mutants in an efficient and targeted fashion, but also can be used to generate knock-outs in a tissue-specific or inducible manner (Decaestecker et al., 2019, Wang et al., 2020c, Bollier et al., 2021). Such conditional approaches will be particularly suitable for investigating the function of key PCD genes that might lead to pleiotropic phenotypes or even lethality when mutated.

Plant PCD research: implications for the future

The recent advances in our understanding of plant PCD necessitate highlighting the breadth of the potential applied impact of studying plant PCD, as well as innovative ways to translate this knowledge from the lab to the field and beyond. Knowledge generated on the molecular mechanisms and cellular events that lead to PCD may be applicable to many agriculturally relevant developmental and defence related cell death events in crops. In addition, in the future it could be used to selectively target and activate PCD pathways in weeds without affecting crop plants, thereby decreasing further herbicide use whilst maintaining yield. Another example of the applied potential of PCD research is deepening our understanding of Papaver SI-PCD that, considering its proven transferability over a large phylogenetic distance, will open opportunities for its exploitation in agricultural systems, for example in the production of F1 hybrids. While discussing agriculturally relevant applications of plant PCD research, a few key points were made regarding studying PCD in the context of a diversity of conditions faced by a plant in its environment. Firstly, plants exhibit a spectrum of responses to environmental stresses, ranging from acclimation to cell death, depending on the stress level. The climate change-associated increasing frequency and intensity of extreme weather conditions leading to heatwaves, droughts and soil waterlogging suggests that cell death inducing levels of abiotic stresses experienced by plants will be reached more often, underscoring the need to strongly integrate PCD research into crop improvement strategies. Secondly, the environmental factors faced in the field may have a considerable effect on developmental cell death programmes. Finally, while lab-based experiments are generally performed under controlled conditions with imposition of a single stress or PCD inducing stimuli, in the field plants encounter multiple simultaneous stresses that can lead to distinct responses (Zandalinas and Mittler, 2022). As an example, mutants in autophagy-related genes are more sensitive to stress combinations than to individual stresses (Balfagón et al., 2022). Likewise, research on metacaspases may lead to increased potential to develop new plant varieties that are more resilient to the increasingly volatile weather conditions linked to climate change. For example, the metacaspase AtMC3 is involved in modulating vascular plasticity in response to drought (Pitsili et al., 2023) and overexpressing this protease results in plants that are more tolerant to drought with no apparent negative effects on growth

or yield. As different stresses elicit both common and distinct pathways for regulation of programmed cell death (Burke et al., 2023), the coordination of cell death pathways in response to combinations of stresses, and to adverse conditions outside the laboratory, will be an exciting area for future studies and an excellent way to validate the impact of findings on how plant PCD is controlled in real-world scenarios.

An example that reinforces the necessity of studying developmental PCD processes in the context of specific environmental conditions is senescence-associated cell death. Senescence is finalis ed by PCD of all cells of the plant organ (Rogers, 2015). Plant senescence and associated remobilisation of nutrients is critical to crop production especially in cereals (Havé et al., 2016). Critically, senescence requires live cells for the remobilisation and hence there is a carefully orchestrated balance between senescence and eventual cell death. Understanding the regulators of this balancing act has progressed through developments in omics and use of model plants (Woo et al., 2018) with new layers of regulation continuing to emerge including epigenetic reprogramming (Rogers, 2022). However, senescence is not only a developmental programme but also a response to adverse environmental conditions and therefore understanding the tipping point between life and death will be critical for sustained crop production in the face of environmental uncertainty. Even beyond harvest, cell death continues to play a part in food security. Shelf life of fresh produce and cut flowers is dependent on delaying cell death through reduced temperatures of storage and modified atmospheres to slow down metabolism and reduce the senescence and cell death promoting effects of ethylene (Rogers et al., 2023, Zhang et al., 2022). Even in the cow rumen, plants respond to the adverse conditions by switching on stress responses, a specific form of senescence (Hart et al., 2022), and altering the expression of cell-death related genes, and this has important effects on the nutritional value of forage grass. Thus, how cell death is regulated even after harvest has important implications for food security and needs to be carefully considered. Another emerging future area for exploring PCD mechanisms extends not only beyond the confines of the laboratory, but in fact also beyond plant growth on Earth. Spacecraft and non-Earth planetary surface environments present a diverse array of relatively understudied stressors, underlining the critical need to unravel plant developmental responses and stress resilience strategies. This need is highlighted within the recent NASA decadal survey (National Academies of Sciences and Medicine, 2023), which describes ‘Plants in Space’ as one of 11 key focus areas for the next decade of space research. This will require testing how PCD signalling pathways operate in space habitat, that is characterised by distinct stressors such as microgravity or galactic cosmic rays. In addition to future

352 experiments investigating modulation of PCD in space environments, this can be probed using the Open
353 Science resources, such as NASA's GeneLab (Berrios et al., 2020), providing comprehensive access to 64
354 multi-omic plant datasets from space experiments as well as user friendly analytical tools. The platform
355 has already been harnessed by (Choi et al., 2019) to identify spaceflight-associated induction of genes
356 associated with PCD modulation in Arabidopsis, such as *BAG6* (Wang et al., 2020a) and heat shock
357 proteins (Rowarth et al., 2019, Qi et al., 2011), and general repression of peroxidase transcripts that
358 indicate altered redox homeostasis (Kolupaev et al., 2019), suggesting that it is likely that space habitat
359 may have a significant effect on PCD-associated signalling.

360 It is also becoming increasingly clear that plant PCD research may lead to applications that extend
361 beyond plant growth and food production, such as in medicine and production of novel therapeutics.
362 For example, anthocyanins extracted from lace plant, previously shown to modulate the balance
363 between cell survival and cell death in this model species, were recently demonstrated to induce
364 apoptosis in breast cancer cells, but not in the normal mammary cell line (Gunawardena et al., 2021).
365 The underlying mechanism/s responsible for cell death induced by anthocyanins in cancer cells is
366 currently under investigation. Likewise, metacaspase AtMC1, initially studied mainly in the context of
367 plant PCD, has been shown to efficiently degrade aggregated cytotoxic proteoforms (Ruiz-Solaní et al.,
368 2023). Progressive protein aggregation is associated with major neurodegenerative pathologies, such as
369 Alzheimer's disease, Parkinson's disease, and Huntington's disease, in addition to being a hallmark of
370 ageing. Therefore, AtMC1 based solutions may inform therapies targeting these harmful insoluble
371 aggregates, yet again underscoring the potential of cross-disciplinary knowledge exchange when the
372 field of plant PCD is considered. Both in Plasmodium and Trypanosoma parasites, metacaspases -being
373 absent in humans- were studied as potential drug targets. Structural information of plant metacaspases
374 and identification of small molecule inhibitors might therefore be important to battle human pathogens,
375 including those triggering neglected diseases (Stael et al., 2023, Yadav et al., 2023). Finally, the ability to
376 manipulate PCD levels in plant suspension cultures using a diversity of approaches (as demonstrated by
377 (McCabe and Leaver, 2000) or (Burke et al., 2023)) may have implications for plant cell-culture based
378 biotechnology and promote the use of plant cell suspension cultures as attractive bioprocessing
379 platforms for production of secondary metabolites, natural plant products and recombinant proteins.
380 The importance of translational biology in PCD is also highlighted by findings from animal systems
381 informing applications in plants. For example, studying the ER stress and untranslated protein response
382 (UPR) in animal models has led to the identification of chemical chaperones that prevent proteins from

being misfolded and aggregating *in vitro,* and their subsequent use for academic research and clinical trials (He and Moreau, 2019). Among those chemicals is 4-phenylbutyric acid (4-PBA), which has been used for probing and alleviating ER stress in yeast and plants (Watanabe and Lam, 2008, Yang et al., 2016, Mai et al., 2018). In agreement with its ER stress-resolving activity, 4-PBA was found to abrogate Arabidopsis HR cell death with no apparent effect on avirulent bacteria (Cacas and Champion, 2017). Further work unexpectedly revealed a potent fungicidal activity for this molecule, associated with a broad range of cryptogamic diseases that could potentially be targeted (Cacas et al., 2023).

Conclusions: Improving our knowledge of plant PCD will have a significant breadth of implications ranging from better understanding of fundamental biological processes operating in plants, to development of innovative solutions to grand challenges in plant science and beyond. Technical advances and newly available resources and data are already contributing to progress in this area and will be further enhanced by data integration and the growth of a stronger research community. Both the early career scientists and principal investigators attending the 31st New Phytologist workshop in Dublin agreed that it is an exciting time to be a plant PCD researcher, and the meeting created an appetite for holding larger conferences open to all members of the plant PCD community. We are looking forward to future opportunities for exchanging ideas and discussing different aspects of the life and death decisions of plant cells.

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Authors contributions

All co-authors attended the 31st New Phytologist workshop in Dublin, and subsequently contributed to development of concepts and ideas proposed in this Viewpoint article. JK, RB, ANG and PFMC came up with the idea for the workshop and formed the meeting organising committee. JK drafted the first version of the manuscript, that was further developed and approved by all authors. Other authors listed are early career researchers in alphabetical order (LA, MC, SBT, HV), followed by principal investigators in alphabetical order (DCB, MB, NB, JLC, NSC, PG, KK, MKN, HJR, FVB).

Conflict of interest statement

Authors declare no conflict of interest.

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Figures

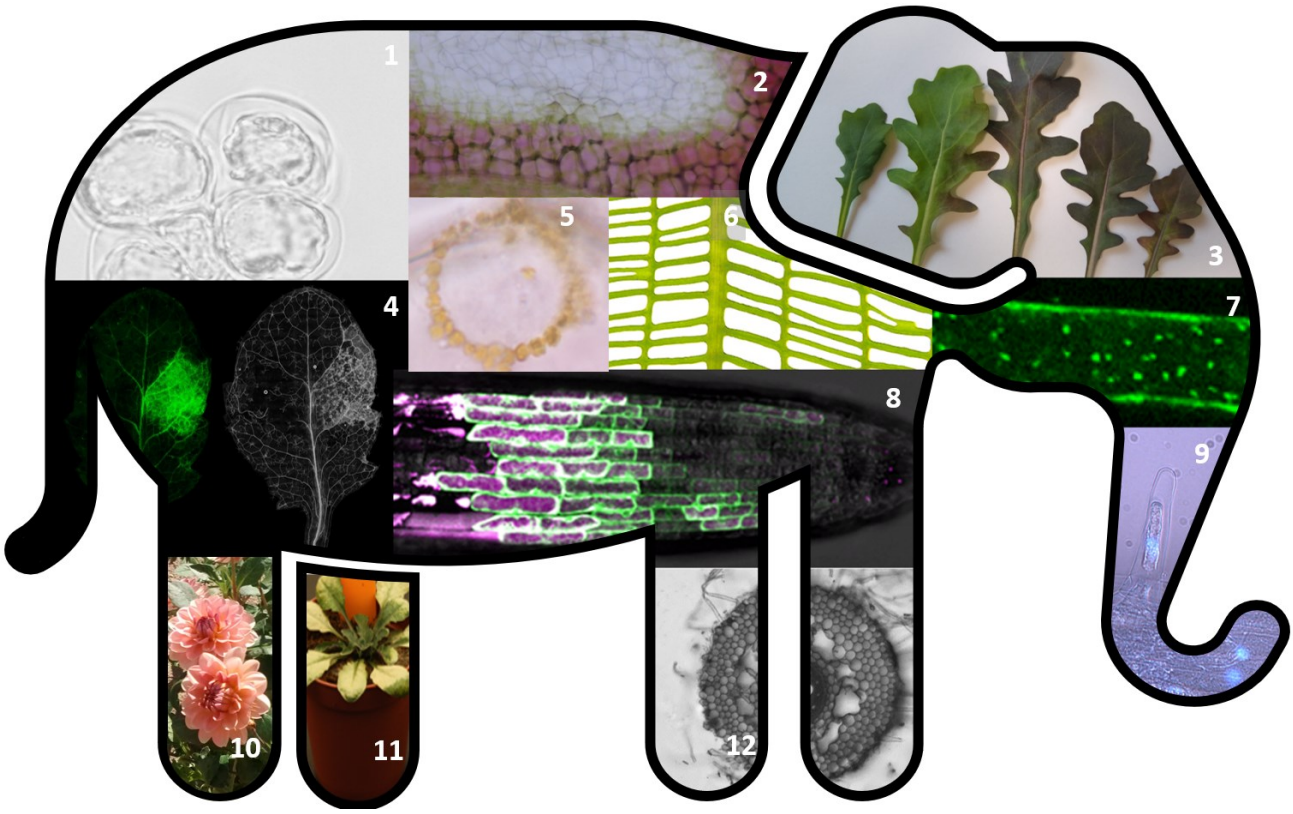


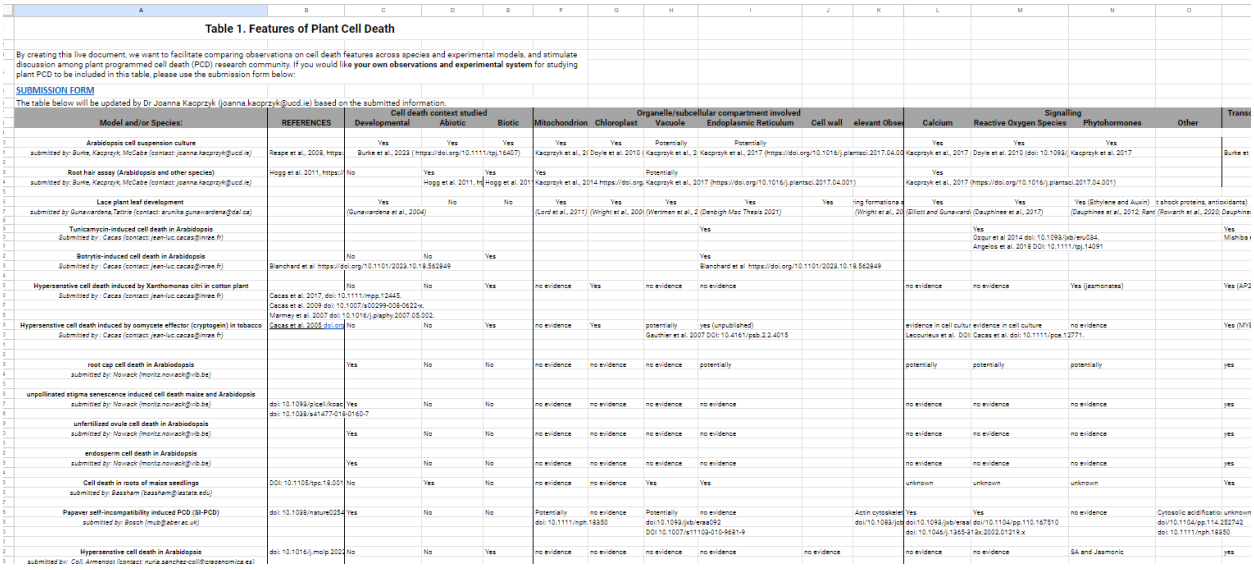
Figure 1. How to describe the plant PCD elephant? Images of PCD research highlight the diversity of experimental systems used by participants of the meeting in Dublin. Integration of data across the systems, communication and debate will underpin the progress in the field, lead to better understanding of the cell death pathways operating in plants, and support the development of an agreed cell death nomenclature and classification systems. Image credits: 1. *Arabidopsis thaliana* suspension cells that have undergone PCD induced by heat treatment (J. Kacprzyk), 2. Lace plant window stage leaf close up (A.N. Gunawardena). 3. Senescence in rocket leaves (H.J. Rogers). 4. Hypersensitive response cell death triggered by *Pseudomonas syringae* carrying the effector AvrRpm1 in *Arabidopsis thaliana* (Nerea Ruíz-Solaní from N.S. Coll's lab). 5. Chloroplasts forming a ring around the nucleus in the lace plant during the mid to late stages of PCD (S.B. Tattrie from A.N. Gunawardena's lab). 6. Lace plant fenestrate mature leaf with perforations formed via PCD (A.N. Gunawardena). 7. GFP-ATG8e labelled autophagosomes in an *Arabidopsis thaliana* root cell (D.C. Bassham). 8. Developmentally controlled programmed cell death at the edge of the root cap in *Arabidopsis thaliana* (M. K. Nowack). 9. Root hair that has undergone PCD in *Arabidopsis thaliana* (Johanna Schwarze from J. Kacprzyk's

lab). 10. Dahlia flowers as a model for studying petal senescence associated PCD (H. J. Rogers). 11. PCD phenotype of catalase deficient plant (F. Van Breusegem). 12. PCD mediated formation of aerenchyma in barley roots under waterlogging conditions (Orla Sherwood from J. Kacprzyk's lab).

Tables

Table 1. Features of Plant Cell Death. By creating this live document, we want to facilitate comparing observations on cell death features across species and experimental models, and stimulate discussion among plant programmed cell death (PCD) research community. If you would like your own observations and experimental system for studying plant PCD to be included in this table, please use the submission form included. The table below will be updated by Dr Joanna Kacprzyk (joanna.kacprzyk@ucd.ie) based on the submitted information.

Note: Below a screenshot of Table 1 is provided. Table 1 is a live online document that will remain open for submissions from the members of plant PCD research community, available at: https://shorturl.at/dxHU8



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SUBMISSION FORM

The table below will be updated by Dr Joanna Kacprzyk (joanna.kacprzyk@ucd.ie) based on the submitted information.

Model and/or Species:	REFERENCES	Cell death context studied			Organelle/subcellular compartment involved						Signalling				Transc
		Developmental	Abiotic	Biotic	Mitochondrion	Chloroplast	Vacuole	Endoplasmic Reticulum	Cell wall	elevant Obse	Calcium	Reactive Oxygen Species	Phytohormones	Other	
Arabidopsis cell suspension culture *submitted by: Burke, Kacprzyk, McCabe (contact: joanna.kacprzyk@ucd.ie)*	Reape et al., 2009, https:	Yes Burke et al., 2023 (https://doi.org/10.1111/tpj.16407)	Yes	Yes	Yes Kacprzyk et al., 2(	Yes Doyle et al. 2010 (	Potentially Kacprzyk et al., 2	Potentially Kacprzyk et al., 2017 (https://doi.org/10.1016/j.plantsci.2017.04.00			Yes Kacprzyk et al., 2017	Yes Doyle et al. 2010 (doi: 10.1093/	Yes Kacprzyk et al. 2017		Burke et
Root hair assay (Arabidopsis and other species) *submitted by: Burke, Kacprzyk, McCabe (contact: joanna.kacprzyk@ucd.ie)*	Hogg et al. 2011, https://	No Hogg et al. 2011, ht	Yes Hogg et al. 201	Yes Yes Kacprzyk et al., 2014 https://doi.org			Potentially Kacprzyk et al., 2	Potentially Kacprzyk et al., 2017 (https://doi.org/10.1016/j.plantsci.2017.04.001)			Yes Kacprzyk et al., 2017	(https://doi.org/10.1016/j.plantsci.2017.04.001)			
Lace plant leaf development *submitted by Gunawardena,Tatiire (contact: anuhka.gunawardena@dal.ca)*		Yes (Gunawardena et al., 2004)	No	No	Yes (Lord et al., 2011)	Yes (Wright et al., 200	Yes (Wernmen et al., 2	Yes (Denbigh Mac Thesis 2021)	Yes	ring formations a (Wright et al., 20	Yes (Elliott and Gunawardi	Yes (Dauphinee et al., 2017)	Yes (Ethylene and Auxin)	t shock proteins, antioxidants) (Dauphinee et al., 2012, Rent	(Rovarsh et al., 2020, Dauphine
Tunicamycin-induced cell death in Arabidopsis *Submitted by : Cacas (contact: jean-luc.cacas@inrae.fr)*								Yes				Yes Caqur et al 2014 doi: 10.1093/jxb/eru034. Angelos et al. 2016 DOI: 10.1111/tpj.14091			Yes Mishba
Botrytis-induced cell death in Arabidopsis *Submitted by : Cacas (contact: jean-luc.cacas@inrae.fr)*	Blanchard et al https://doi.org/10.1101/2023.10.18.562849	No	No	Yes				Yes Blanchard et al https://doi.org/10.1101/2023.10.18.562849							
Hypersensitive cell death induced by Xanthomonas citri in cotton plant *Submitted by : Cacas (contact: jean-luc.cacas@inrae.fr)*	Cacas et al. 2017, doi: 10.1111/mpp.12445. Cacas et al. 2009 doi:10.1007/s00299-008-0622-x. Marmey et al. 2007 doi: 10.1016/j.plaphy.2007.05.002.	No	No	Yes	no evidence	Yes	no evidence	no evidence			no evidence	no evidence	Yes (jasmonates)		Yes (AP2
Hypersensitive cell death induced by oomycete effector (cryptogein) in tobacco *Submitted by : Cacas (contact: jean-luc.cacas@inrae.fr)*	Cacas et al. 2005 doi.org	No	No	Yes	no evidence	Yes	potentially Gauthier et al. 2007	yes (unpublished) DOI:10.4161/psb.2.2.4015			evidence in cell cultur Lecourieux et al. DOI	evidence in cell culture Cacas et al. doi: 10.1111/pce.12771.	no evidence		Yes (MYB
root cap cell death in Arabidopsis *submitted by: Nowack (moritz.nowack@vib.be)*		Yes	No	No	no evidence	no evidence	no evidence	potentially			potentially	potentially	potentially		yes
unpollinated stigma senescence induced cell death maize and Arabidopsis *submitted by: Nowack (moritz.nowack@vib.be)*	doi: 10.1093/plcell/koac doi: 10.1038/s41477-018-0160-7	Yes	No	No	no evidence	no evidence	no evidence	no evidence			no evidence	no evidence	no evidence		yes
unfertilized ovule cell death in Arabidopsis *submitted by: Nowack (moritz.nowack@vib.be)*		Yes	No	No	no evidence	no evidence	no evidence	no evidence			no evidence	no evidence	no evidence		yes
endosperm cell death in Arabidopsis *submitted by: Nowack (moritz.nowack@vib.be)*		Yes	No	No	no evidence	no evidence	no evidence	no evidence			no evidence	no evidence	no evidence		yes
Cell death in roots of maize seedlings *submitted by: Basaham (basaham@iastate.edu)*	DOI: 10.1105/tpc.19.001	No	Yes	No	no evidence	no evidence	Yes	Yes			unknown	unknown	unknown		Yes
Papaver self-incompatibility induced PCD (SI-PCD) *submitted by: Bosch (mub@aber.ac.uk)*	doi: 10.1038/nature025	Yes	No	No	Potentially doi: 10.1111/nph.19350	no evidence	Potentially doi:10.1093/jxb/eraa092 DOI:10.1007/s11103-012-9681-9	no evidence		Actin cytoskelet doi/10.1093/jxb	Yes doi:10.1093/jxb/eraa doi:10.1046/j.1365-313x.2002.01219.x	Yes doi/10.1104/pp.110.167510	no evidence	Cytosolic acidificatio doi:10.1104/pp.114.252742	unknown doi:10.1111/nph.19350
Hypersensitive cell death in Arabidopsis *submitted by: Cell Armenpost (contact: nuria.sanchez-coll@crag-cenomica.es)*	doi: 10.1016/j.molp.2022	No	No	Yes	no evidence	no evidence	no evidence	no evidence	no evidence		no evidence	no evidence	SA and Jasmonic		yes