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Editorial

Green death: revealing programmed cell death in plants

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With the advent of agriculture, plants have been essential to the wellness of our society and the sustainability of our planet's ecosystem for the past 10 000 years. Their potential new use as renewable biofactories to transition our economy from fossil fuel-based resources ensures that advances in plant biology will be critical if we are to continue to sustain human development while minimizing impacts on global climate. Understanding fundamental processes that govern plant development, evolution and environmental responses is essential to usher in this new era of plant domestication for energy and novel products.

The programmed nature of plant cell death was demonstrated experimentally in the 1980s and 1990s by studies of spontaneous cell death mutants[1] and the discovery that heterologous expression of certain transgenes can deregulate cell death.[2] Many of these earlier studies were summarized in a special volume of *Plant Molecular Biology* published in 2000. In the decade since then, the field of plant programmed cell death (PCD) has begun to mature. Although much of the work in this field has drawn heavily on comparative analyses using paradigms derived from animal systems, especially those of the apoptotic pathways, distinctive features and adaptive characteristics that correlate to the lifestyle of plants are also beginning to be recognized. Several highly conserved or more distantly related components have also been revealed genetically to regulate PCD across eukaryotes.[3–10] In a few cases, it has become possible to join these components into pathways.[11] Unlike metazoans, however, single-gene mutations in most of these PCD components are viable and their effects on cell death induction and execution are usually quantitative in nature. These observations are thus consistent with the view that plant PCD pathways involve combinatorial modules to insure their proper control under a constantly changing environment that is superimposed on internal developmental cues.[12] In this view, the sessile nature of plants favors an indeterminate mode of development where stem cells are generated in various parts of the body, while the physical fixation and isolation of individual cells restricts the range of pathways (e.g., engulfment of dead cells) that can be deployed to assist in PCD. On the other hand, the lack of an inflammatory system responding to the debris generated from a dying cell may also have opened new possibilities of using a dying or dead cell's content for novel functions such as long distance signaling.

To fully unravel the complex cell death mechanisms in plants, we thus believe that one needs to critically examine the particular PCD morphotype being studied and seek to integrate cellular observations with genetic and biochemical approaches. It is in this spirit that we considered this an opportune time to publish a series of reviews presenting cutting edge knowledge about individual molecular components or pathways of plant PCD. Apart from seven reviews on specific aspects of cell death, this issue incorporates the first classification of plant cell deaths.[13] Similar to animal cell death classification,[14] this document establishes a nomenclature of plant cell death morphologies and proposes unified criteria for their definition.

Hypersensitive response (HR)-associated cell death activated under pathogen attack is an integral part of plant immune systems and one of the most dramatic manifestations of PCD in plant biology. Whether mechanisms regulating HR cell death in plants and inflammatory cell deaths in animals (pyroptosis and necroptosis) are evolutionarily conserved is discussed by Coll *et al.*[15] In particular, the authors present a recently discovered type I metacaspase-dependent regulatory module that translates immune receptor-mediated recognition of pathogens into downstream activation of cell death. This module is reminiscent of caspase-dependent regulation of immune response in mammals.

Understanding of the homeostatic role of autophagy, a major catabolic process in eukaryotic cells, is just beginning to emerge in plant biology. Hofius *et al.*[16] have made a systematic analysis and attempted to reconcile contradictions among the recent studies on the involvement of autophagy in disease resistance and HR cell death. In these studies, knockout of the same *ATG* (AuTophaGy) genes led to opposing effects on the progression of cell death, depending on the pathosystem and age of the infected tissue. The authors explain why pleiotropic impact of defective autophagy on the physiology of the whole plant may in turn affect cell death and disease resistance.

Being encased in a rigid polysaccharide cell wall, plant cells nevertheless can exhibit dynamic changes in their size and

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shape even after they have received cell death signal. These changes go along with intracellular disassembly, and both processes are mediated through remodeling of microtubules and microfilaments. Smertenko and Franklin-Tong[17] describe and compare structural alterations in the cytoskeleton occurring during PCD in diverse model systems. The authors analyze how drug-assisted perturbations of microtubules and actin filaments affect progression of PCD and come to conclude that cytoskeletal changes are important in cellular signaling that controls initiation and execution of PCD in plants. They finally draw the models correlating cytoskeletal dynamics with other cell death processes.

Similar to the role of the cytoskeleton in sensing and transducing death signals being evolutionarily conserved, the importance of endoplasmic reticulum (ER) in initiating calcium level-mediated cell death is confirmed in all eukaryotes including plants. Although most components of ER stress-induced cell death found in animals are missing in plants, Bax inhibitor-1 (BI-1) is a common cell death suppressor in both kingdoms. Ishikawa *et al.*[18] update our understanding of the role of BI-1 in plant biology. The authors perform in-detail genetic and molecular analyses to characterize the functions of plant BI-1 and putative BI-1-containing protein complexes both in the maintenance of ER homeostasis and in the related anti-cell death pathways. In line with this analysis, the authors propose a model of plant BI-1 function in stress-induced PCD that suggests the ER as an integration point for multiple cellular stress response pathways.

It has long been debated whether plants have proteases functionally similar to initiator and effector caspases acting during apoptosis. Although various plant proteases were suggested to have this role, it is still difficult to favor any of them because very little is known about their proteolytic targets *in vivo*. Among these proteases, metacaspases are the closest relatives and putative ancestors of caspases. Tsiatsiani *et al.*[19] illuminate different aspects of metacaspase biology, stretching the scope beyond cell death to include emerging roles of metacaspases in cell proliferation and stress response. Critical analysis of substrate specificity and other biochemical properties of metacaspases is connected to the practical recommendations on how to measure and inhibit metacaspase activity by taking into account their arginine/lysine specificity. These recommendations should help in preventing further misapplication of caspase-specific probes in metacaspase research.

It appears that during plant evolution a number of proteolytic pathways have evolved and they are either physiologically or biochemically similar to those mediated by mammalian caspases. Apart from arginine/lysine-specific metacaspases, there are three types of aspartate-specific proteolytic enzymes shown to mediate PCD in plants, including subtilisin-like serine proteases, vacuolar processing enzymes (VPEs) from the legumain family and proteasome subunit PBA1. Vartapetian *et al.*[20] describe the role of a subset of subtilisin-like proteases, called saspases and phytaspases, in abiotic and biotic stress-induced cell deaths. An intriguing feature of these proteases is their constitutive activation in the living cells and export to the apoplast, where they wait for cell death stimulus to enter the cell. The authors discuss physiological significance of this phenomenon and its possible molecular regulation.

VPEs reside in vacuoles, the property that follows from their name. Lytic vacuoles execute developmental PCD in plants and perform a similar function in many examples of HR cell death.[13] Hara-Nishimura and Hatsugai[21] distinguish two different ways for how plants use lytic vacuoles during execution of PCD: the destructive way and the non-destructive way. Although the destructive way implicates VPEs and is activated to kill intracellular pathogens or to clean up intracellular contents during development, the non-destructive way requires caspase-like activity of the proteasomal subunit PBA1 and is used by plants to combat bacterial pathogens that accumulate in the apoplast. The authors focus on the analysis of the mechanisms of the two different ways of vacuole-mediated cell death in plant defense against pathogens.

We think this collection of critical reviews should be an invaluable resource as a guide to the plant PCD community and plant biologists in general. In addition, comparative analyses of cell death mechanisms in plants, animals and fungi will provide an evolutionary framework for understanding PCD function and control in various biological systems. This cross-feeding of information will help to define the essential cell death 'engine' that is common in all eukaryotes, and may help provide clues for discovering new PCD regulators in the different kingdoms. As we begin to gather the pharmacological and genetic tools to manipulate cell death in plants, it is likely that applications in areas such as improved biomass and wood production, disease and stress resistance, and plant reproduction will begin to emerge. These advances should have great impact on agriculture and forestry, which in turn would help our planet cope with the ever-increasing demand for food and renewable materials.

Conflict of Interest

The authors declare no conflict of interest.

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