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Cell Death in Us and Others

Pierre Golstein

Although there have been scattered reports on the topic of cell death for more than a century, the 20,000 publications on this topic within the past 5 years reflect a shift from historically mild interest to contemporary fascination. In normal animal development, cell death is involved not only in sculpting shapes but also in optimizing functions, for instance, in the immune or central nervous systems. Defects in cell death therefore result in major developmental abnormalities. Cell death also plays a role in the adult, for example, by contributing to proper turnover of cells in the skin or gut. More generally, tight coupling of cell death and cell multiplication ensures in many tissues a constant, controlled flux of fresh cells, which are crucial to the preservation and optimal functioning of the adult organism. Although cell death and renewal in an organism contrast with the apparent overall integrity of the organism, they are, in fact, required for this integrity. Defects in the coupling of cell death and multiplication result in pathologies such as tumors or functional deficiencies.

[Cell death] is invading not only the minds of many biologists but also many fields of biology.

Our current understanding of the elaborate course of events within a dying cell is dominated by two major observations. First, from a molecular point of view, as initially shown in the nematode *Caenorhabditis elegans*,* cell death is the outcome of a programmed intracellular cascade of genetically determined steps. This cascade is centered on the activation of a class of cysteine proteases called caspases (see the five papers in this issue on caspases and other important molecules and subcellular structures involved in cell death). Second, from a morphological point of view, in animals this cascade leads to apoptosis,† a given set of traits in dying cells that reflects the systematic dismantling of key cellular components. Phagocytosis then completes the elimination of dead cells. Inhibitors of caspase activation have already been shown to inhibit abnormally occurring cell death in several models of pathological situations, raising cautious optimism about possible therapeutic applications.

However, the paradigmatic caspase-dependent cascade leading to apoptosis is now being challenged by several instances of apparently caspase-independent (and sometimes nonapoptotic) cell death. It is therefore becoming important to find good experimental models for, in particular, caspase-independent cell death. Phylogenetics may help.

In effect, cell death occurs in many places along the phylogenetic tree other than in animals. Apart from the sheer joy of discovery, investigation of cell death in other organisms may reveal phenomenological convergence or molecular conservation and then yield invaluable comparative information. Plants and animals show how the common theme of cell death can be accommodated very differently, depending on specific constraints. For instance, the partial disposal of dead plant cells occurs by vacuolar autophagy instead of heterophagy, and plant cell death often leaves remains that play a structural role. A number of plant resistance genes, which control local cell death and thus limit the spread of pathogen infection, show some similarity to genes involved in animal cell death. Emerging models of cell death, possibly simpler and more experimentally and genetically tractable than most animal models, include the yeast *Saccharomyces*, which can be induced to die in spite of a glaring lack of caspase genes; the fungus *Podospora*, in which genetically controlled cell death is observed when strains of different origin confront one another; and the slime mold *Dictyostelium*, an early, conditional multicellular organism that shows developmental cell death.

Thus, cell death cuts across a wide range of organisms. The process is invading not only the minds of many biologists but also many fields of biology. Cell death is thus becoming better understood from a fundamental point of view even as socially beneficial applications appear closer.

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*H. M. Ellis and H. R. Horvitz, *Cell* **44**, 817 (1986). †J. F. R. Kerr, A. H. Wyllie, A. R. Currie, *Br. J. Cancer* **26**, 239 (1972).