CELL STRUCTURE AND FUNCTION 28: 3–9 (2003)
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REVIEW

The Role of Apaf-1 in Programmed Cell Death: From Worm to Tumor

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ABSTRACT. **Apoptosis or programmed cell death is an important process to eliminate unnecessary or hazardous cells. Apaf-1, a mammalian homologue of CED-4 of *C. elegans,* is the essential adaptor molecule in the mitochondrial pathway of apoptosis. Mice lacking Apaf-1 show accumulation of neurons in the developing central nervous system due to reduced apoptosis. Apaf-1-deficient cells are remarkably resistant to various apoptotic stimuli. Apaf-1-mediated apoptosis plays a role in the prevention of tumorigenesis. However, Apaf-1-independent cell death pathways are also indicated. In this review, we will summarize what has been learned about the role of Apaf-1 by biochemical and genetical approaches.**

Key words: Apaf-1/apoptosis/mitochondria/caspase/cytochrome *c*

In the year 2002, three scientists were awarded the Nobel Prize in Physiology or Medicine for their discoveries concerning the genetic regulation of organ development and programmed cell death. Robert Horvitz, one of the three laureates, characterized the key genes controlling cell death by using the roundworm *Caenorhabditis elegans* as an experimental system. He also showed how these genes interacted with each other during the cell death process and that corresponding genes existed in higher species. These discoveries are of significance not only for the understanding of the cell death mechanism on a molecular basis but also for the medical research on the pathogenesis of various diseases.

The body of any multicellular organisms consists of different cell types. In human body, for instance, there are about 10^{14} cells with hundreds of cell types, all of which originated from the single fertilized egg. Thus, during the embryonic and fetal development, large numbers of cells are generated by cell division. Even in an adult human, numerous cells are created every day. In parallel with this process of cell increase, large numbers of cells die through a controlled "suicide process" referred to as programmed cell death (PCD). First observed during amphibian metamorphosis, PCD has been discovered to occur in many developing tissues (for review, see Clarke and Clarke, 1996) and studies have revealed how important PCD is during animal development and in the maintenance of homeostasis. PCD serves many functions including sculpting structures to form the proper shapes of organs by removal of cells, deleting unneeded structures, and adjusting the number of cells that are overproduced. Elimination of dangerous or injured cells, such as virus-infected cells or cells with gene mutation, is also an important function of PCD (reviewed in Jacobson *et al.*, 1997). As one can well imagine, failure of PCD may cause various problems and diseases due to the accumulation of unnecessary and/or harmful cells.

Spectacular progress has been made in past years in understanding the molecular mechanisms of PCD. The role of the mitochondria, which generate cellular energy as a form of ATP by oxidative phosphorylation, in apoptosis came into focus when studies revealed that several mitochondrial proteins, which reside in the intermembrane space of mitochondria, are released and activate the cell death program at the early phase of apoptosis (see the detailed review by Wang, 2001). Amongst these mitochondrial proteins, cytochrome *c* (Cyto *c*), a component of the mitochondrial electron transfer chain, is translocated into the cytoplasm in response to a variety of apoptotic stimuli (Kluck *et al.*, 1997; Yang *et al.*, 1997; Bossy-Wetzel *et al.*, 1998). By reconstitution experiments with cell free extracts, Cyto *c* has been shown to trigger the activation of a group of

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Abbreviations: PCD, programmed cell death; Cyto *c*, cytochrome *c*; CARD, caspase-recruitment domain; ES cells, embryonic stem cells; EF, embryonic fibroblasts; PNS, peripheral nerve systems.