

# Apoptosis in Embryonic Development

Apoptosis, or programmed cell death, is a mechanism in embryonic development that occurs naturally in organisms. Apoptosis is a different process from cell necrosis, which is uncontrolled cell death usually after infection or specific trauma. As cells rapidly proliferate during development, some of them undergo apoptosis, which is necessary for many stages in development, including neural development, reduction in egg cells (oocytes) at birth, as well as the shaping of fingers and vestigial organs in humans and other animals. Sydney Brenner, H. Robert Horvitz, and John E. Sulston received the Nobel Prize in Physiology or Medicine in 2002 for their work on the genetic regulation of organ development and programmed cell death. Research on cell lineages before and after embryonic development may lead to new ways to reduce or promote cell death, which can be important in preventing diseases such as Alzheimer's or cancer.

Karl Vogt observed the phenomenon of apoptosis in Neuchâtel, Switzerland, in 1842, but Vogt did not use the term apoptosis. Vogt noticed in midwife toad (*Alytes obstetricans*) embryos that cells in the notochord, a cartilaginous skeletal structure, disappeared and were replaced by cells of the vertebrae. Although Vogt documented that some cells disappeared during development, he did not focus his research on that phenomenon. Researchers did not give apoptosis very much attention until 1885 when Walther Flemming, who worked at the University of Kiel in Kiel, Germany, used more advanced staining techniques on the cell nucleus to observe what he called chromatolysis, the diminishing of nuclear material in dying cells. Chromatolysis is part of the process of apoptosis, but Flemming's research was overshadowed until biologist Alfred Glücksmann, who worked at the Strangeways Research Laboratory in Cambridge, England, published a review on cell death literature in 1951.

In his review, Glücksmann hypothesized that for an organism to grow and develop, cell death must occur. At the time of Glücksmann's review, many scientists interpreted dead cells as metabolic byproducts of cells undergoing mitosis, or cellular replication. Glücksmann presented evidence from past embryological research that described planned cell death as an aspect of normal development. Glücksmann's hypothesis remained largely unnoticed for more than twenty years. However, John F. Kerr, Andrew H. Wyllie, and Alastair R. Currie, pathologists working at the University of Aberdeen in Aberdeen, Scotland, referenced Glücksmann's review as motivation to develop their own research on apoptosis in 1972.

Kerr had first studied cell death in 1965 when he noticed atrophy, or shrinkage, in rat liver cells under an electron microscope. Kerr noticed that the shrinkage was distinct from necrosis due to trauma, which normally causes the cell to rupture and release its contents. A few years later, Kerr and his colleagues noted common patterns involved in cell death related to their research and recorded in previous experiments and reviews, including Glücksmann's work. Kerr and his team framed their research focus as about programmed cell death, a concept that Richard Lockshin and Carroll Williams at St. John's University New York City, New York, had used in 1964. Kerr and his colleagues coined the term apoptosis to describe programmed cell death. They claimed that cell death from apoptosis was not accidental, and that it followed the same pattern in both developing and developed cells. With their 1972 article, Kerr and his team brought the idea of apoptosis to greater scientific attention.

Kerr, Wyllie, and Currie's research clarified the process of apoptosis as a series of specific steps, later verified by other researchers. First, cells undergoing apoptosis begin to shrink in size and lose physical connections with neighboring cells. Second, the chromatin, or the combination of DNA and protein within the cell nucleus, condenses and enzymes begin to fragment the chromatin

within the cell. Third, the cell membrane bulges irregularly, or blebs. Fourth, the nucleus collapses and breaks into fragments containing pieces of chromatin, while the cell continues to bleb. Fifth, the cell breaks into several smaller membrane bodies that contain various cellular fragments, called apoptotic bodies. Lastly, white blood cells, also called phagocytes, or neighboring cells engulf the apoptotic bodies and break them down. The organism suffers no major injury as a result.

After Kerr, Wyllie, and Currie published their research, scientists accepted apoptosis as a mechanism in cellular development and began to study its significance in development and disease. For example, since the 1970s Sydney Brenner in Berkeley, California, Robert Horvitz in Cambridge, Massachusetts, and John Sulston in Cambridge, England, conducted much of their early research on the nematode *Caenorhabditis elegans* (*C. elegans*). Through diagrams of cell lineages and careful documentation, Brenner, Horvitz, and Sulston predicted when cell death would occur, and they identified some of the genes involved in the regulation of cell death. In particular, Horvitz noted that *C. elegans* neurological development included a large amount of apoptosis, with 105 of the 131 programmed cell deaths occurring in neural cells. Brenner, Horvitz, and Sulston received the Nobel Prize in Physiology or Medicine in 2002 for their work in genetic regulation of organ development and programmed cell death.

Research conducted after Brenner, Horvitz, and Sulston published their findings on *C. elegans* reinforced the theory that programmed cell death through apoptosis is essential for development in animals. In 1993, scientists working with Horvitz found that a gene in mice was very similar to the gene that codes for an enzyme that causes cell death during development in *C. elegans*. The research showed that the apoptosis observed in *C. elegans* also occurs in mammals.

In 1997, Michael Jacobson and researchers at the MRC Lab of Molecular Biology in Cambridge, England, outlined the importance of cell death in animals in the article "Programmed Cell Death in Animal Development". Jacobson and colleagues claimed that the primary functions of apoptosis are to sculpt the organism by deleting unwanted structures, controlling the number of cells, and eliminating nonfunctional, harmful, abnormal, or misplaced cells. Absence of apoptosis can include malformations of digits, decreased neurological function, malformations of the heart, or even cancer. For example, soft tissue cells between the fingers and toes undergo apoptosis in order to separate the digits from each other during development. The proper formation of heart loops also relies on the process of apoptosis.

In his article "The Apoptotic Oocyte," Gary Wessel from Brown University in Providence, Rhode Island, discusses the role of apoptosis in human females. Human female oocytes undergo apoptosis during development and after birth. Scientists estimate that seven to eight million oocytes are formed in the fetus, which are reduced to about 100,000 oocytes at birth, and then only a few hundred at the onset of menopause.

Apoptosis occurs not only during embryonic development, but also after birth. In humans for example, brain cells undergo apoptosis prior to and following birth to eliminate excess brain cells and streamline nerve impulses. Apoptosis also occurs in some cells that the body identifies as cancerous to prevent the spread of the cancer and kill the cancerous cells. However, unregulated apoptosis can cause disorders, such as Alzheimer's disease and amyotrophic lateral sclerosis, which is a motor neuron disease.

## Sources

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