"Apoptosis: A Basic Biological Phenomenon with Wide-Ranging Implications in Tissue Kinetics" (1972), by John F. R. Kerr, Andrew H. Wyllie and Alastair R. Currie [1]

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"Apoptosis: A Basic Biological Phenomenon with Wide-Ranging Implications in Tissue Kinetics" (hereafter abbreviated as "Apoptosis") was published in the British Journal of Cancer in 1972 and co-authored by three pathologists who collaborated at the University of Aberdeen, Scotland. In this paper the authors propose the term apoptosis [4] for regulated cell death that proceeds through active, controlled morphological changes. This is in contrast to necrosis, a passive mode of cell death that results from uncontrolled cellular reactions to injury or stress. The journal article also suggests that apoptosis [4] plays crucial roles in various pathological and physiological conditions including the shaping of digits and the shrinking of vestigial organs in developing embryos.

Two fields of research have been instrumental in forming the concept of apoptosis [4]. Prior to the 1970s, embryologists had reported cell death in normal development, but the differences between regulated cell death and necrosis had not yet been specified. Around 1962, the first author of “Apoptosis,” Australian pathologist John Foxton Ross Kerr observed and recorded a seemingly well-controlled pattern of cell death while studying the pathology of liver atrophy for his PhD in pathology at the University College [5] Hospital Medical School, London. Using histochemical staining methods, Kerr saw small, round cytoplasmic masses with condensed chromatin [6] that emerged and disappeared outside necrotic zones in rat [7] livers under low blood supply. Kerr thought that his observations indicated a regulated process responsible for cellular loss in atrophying livers. He called this process shrinkage necrosis. After graduating in 1965, Kerr continued to study this curious mode of cell death in rat [7] livers using electron microscopy [6] and histological methods at the Department of Pathology of the University of Queensland, Brisbane, Australia.

In 1970, a second author of “Apoptosis,” Alastair Robert Currie, an endocrine pathologist based at the University of Aberdeen in Scotland, visited Brisbane as a Mayne Guest Professor in Pathology and met Kerr. Currie had noticed patterns of cell death in his study on carcinogenesis and endocrinology [9] and had observed cell fragments in the inner adrenal cortices of rats when they were exposed to low doses of the carcinogen polycyclic hydrocarbon 9,10-dimethyl-1,2-benzanthracene (DMBA). Currie’s newly enrolled PhD student Andrew H. Wylie had also detected similar cell fragments in the inner adrenal cortices of newborn rats depleted of adrenocorticotropic hormone [10] (ACTH). After viewing Kerr’s electron micrographs of ultrastructural changes in shrinkage necrosis, Currie invited Kerr to spend his upcoming sabbatical year at the Aberdeen lab to examine the cell fragments observed in rat [7] adrenal cortices. In 1971, Kerr arrived at Currie’s lab and met Wyllie. The trio thus embarked on a one-year collaboration:

In Aberdeen, Kerr helped to confirm that the cell fragments Currie and Wylie had observed in the adrenal cortices indeed resembled the cytoplasmic masses that he had seen in the injured rat [7] livers. They later found similar cell death phenomena in the regression of rat [7] breast carcinoma following removal of the ovaries. The confluence of ideas that led to the concept of apoptosis [4] was also catalyzed by a review of the literature on cell death in embryonic morphogenesis. Allison Crawford, a PhD student in Currie’s lab, pointed out the existence of extensive research in, as embryologists called it, programmed cell death. The relevant literature included Alfred Glücksmann’s 1951 review “Cell Deaths in Normal Vertebrate Ontogeny.” The three authors compared their electron micrographs to those published by other embryologists and confirmed that the regulated cell deaths recorded in development, and those observed under pathological conditions, had followed identical steps.

Based on converging evidence from studies in development and disease, Kerr, Currie, and Wyllie formally proposed that apoptosis [4] is a significant biological phenomenon for regulating cell populations. In “Apoptosis,” they define apoptosis [4] as an active, inherently programmed cell-deleting mechanism with distinct patterns of morphological change. They postulate that apoptosis [4] plays an opposite, but complementary role to mitosis [11] in regulating cell populations in multicellular organisms. The authors credit James Cormack, a professor of Greek at Aberdeen, for suggesting the Greek term apoptosis [4], which means “falling,” as leaves from a tree or petals from a flower.

Under the subheading “The Morphology of Apoptosis,” the authors describe the common morphological changes in apoptosis [4] with the aid of one diagram, four histological staining pictures, and twenty electron micrographs. They divide apoptosis [4] into two stages according to morphological characteristics. The first stage begins with the formation from the cells of what the
After summarizing the common morphology, the authors point out the wide distribution of apoptosis and its implications under the subheading "The Occurrence and Implications of Apoptosis." They argue for the importance of apoptosis, stating that the size of any cell population depends not only on the cell production provided by mitosis, but also on cell loss made possible by apoptosis. They review their own research and relevant literatures to support the thesis that apoptosis is ubiquitously instrumental in cell deletion in health, development, and disease. To stress the point that apoptosis is a reserved strategy for cell deletion in development, the authors enumerate the occurrence of focal apoptosis observed in embryonic processes such as the formation of limbs, interdigital clefts, and lumina in tubular structures, and the degeneration of phylogenetic vestiges. The relevance of apoptosis to disease is then summarized by highlighting the increased apoptosis observed in teratogenesis, malignant tumor growth, tumor regression, and injured tissues and organs.

Near the end of the paper, the authors offer a brief discussion of possible factors that might initiate apoptosis. Those factors include environmental stimuli such as steroid hormones and, as other researchers had speculated, intrinsic clocks within certain types of cells. In conclusion, the authors call for more extensive research into apoptosis, since many challenging questions remained.

For more than a decade after its initial publication, "Apoptosis" received little recognition. Indeed, very few researchers participated in the study of apoptosis in the 1970s. During the 1980s, however, many laboratories began to describe some biochemical and molecular aspects of apoptosis, leading to a rapid expansion of research that extended well into the 1990s.

Sources

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