Apoptosis: Programmed Cell Death

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MILESTONES

Kerr JFR, Wyllie AH, Currie AR:
Apoptosis: A basic biological phenomenon with wide-ranging implications in tissue kinetics.
British Journal of Cancer 1972, 26:239-257

John FR Kerr

In their landmark publication, Kerr, Wyllie and Currie proposed that in addition to necrosis – cellular death that is a passive consequence of injurious agents such as ischemia, toxins, chemical and physical injury – a second form of cell death existed with features of an active, inherently controlled process. They termed this other form of cell death apoptosis, a Greek word used to describe the "dropping off" or "falling off" of petals from a flower.

It had long been assumed that cells must be lost continuously from many normal tissues to balance cell division and that loss of cells accompanies atrophy and physiological involution of tissues and organs. The terms "necrobiosis" and "shrinkage necrosis" were sometimes used to refer to this "physiological cell death" which was more a concept than a characterized process. Pathologists had recognized a non-inflammatory form of lymphocyte cell death in thymus glands undergoing stress involution and in reactive germinal centers of lymph nodes and spleens. Pyknotic nuclear fragments within germinal center macrophages — so-called "tingible body macrophages" — were readily detected by light microscopy, but their genesis and significance were unknown. Embryologists were familiar with a non-inflammatory form of cell death that occurred during morphogenesis, such as when lumens develop in the solid anlagen of ducts and intestine, and when inter-digital webs are resorbed during embryonic development of fingers and toes. Endocrine pathologists recognized a non-inflammatory form of cell death in adrenal cortical cells following withdrawal of ACTH.

The work that led to the concept of apoptosis came from the doctoral studies of the Australian pathologist John Kerr. Working with a rodent model of ischemic-induced hepatic atrophy developed decades before by the American pathologist Peyton Rous, Kerr observed individual, scattered hepatocytes that contained small, round cytoplasmic masses and fragments of pyknotic chromatin. These were located in the non-necrotic liver adjacent to zones of experimentally-induced ischemic necrosis. Much was already known about the morphologic features of necrosis because it typically involves large zones of dead tissue visible to the unaided eye, thus making it easy to obtain samples for analysis. In contrast, the single cell changes present in apoptosis are microscopic lesions that typically occur in one percent or less of the cells. In a series of electron microscopic studies published beginning in 1965 Kerr showed that the small, round, cytoplasmic masses present in individual cells consisted of membrane-bound cellular fragments containing crowded, but structurally well-preserved organelles and remnants of pyknotic chromatin. These findings were distinctly different from the autolytic, degenerative, vacuolar changes seen in electron micrographs of necrotic cells. From a morphologic perspective, necrosis is conspicuous; apoptosis is subtle.

In 1970 Alistair Currie, an endocrine pathologist and Professor of Pathology at the University of Aberdeen became aware of Kerr's work and invited him to spend a sabbatical in Scotland investigating the cellular changes that occurred during adrenal cortical atrophy. Kerr joined Currie, and along with Andrew Wyllie, a Ph.D. student in Currie's lab, they found the same ultrastructural changes in adrenal atrophy that Kerr had described in the atrophic liver. Allison Crawford, a developmental biologist and Ph.D. student in the Aberdeen pathology department at that time, drew the group's attention to the extensive literature on "programmed cell death" that occurs during mammalian embryogenesis. Few outside of the field of developmental biology were aware of that literature and the published electron micrographs showing cellular changes during embryonic organogenesis that were the same as Kerr had observed in his liver model.

The application of electron microscopy by Kerr, Wyllie and Currie provided the resolving power to visualize the cellular changes that distinguished the two forms of cell death.

Apoptosis in normal tissues characteristically affects scattered single cells, thus limiting the opportunity for detection and investigation by microscopy. Certain physiological and pathological conditions increase apoptosis and these provided the models studied by Wyllie, Kerr and Currie. In a series of publications they described the evolution of apoptosis in normal neonatal rat adrenal cortex, in embryonic mesenchyme, in both human and animal neoplasms, in the adrenal cortex following ACTH withdrawal, and in various types of liver and adrenal injury. In every case the ultrastructural features were essentially the same. The authors designated the small, roughly spherical or ovoid cytoplasmic fragments as apoptotic bodies. The electron microscopy studies showed that the structural changes in apoptosis take place in two distinct stages: the first comprises the formation of apoptotic bodies, the second their phagocytosis and degradation by other cells, sometimes macrophages, sometimes parenchymal cells, sometimes both.

Subsequent studies by Kerr provided a possible explanation for the high mitotic rate, but paradoxically slow growth of certain malignant tumors, such as human basal cell carcinoma. As a surgical pathology fellow I was taught to ignore mitotic figures in assessing malignant tumors because they were unreliable predictors of tumor growth. At the time that was sound advice because trying to predict the growth properties of a tumor knowing its mitotic index but not its apoptotic index was like trying to predict the overall rate of a chemical reaction knowing only the forward rate, but not the backward rate.

The importance of the publication by Kerr, Wyllie and Currie[1] was that it presented an integrating concept that fundamentally changed thinking about cellular kinetics. The authors proposed – and provided supporting evidence – that cell death by apoptosis was a normal, intrinsically controlled, active process that occurred during physiological and pathological conditions and played a complementary but opposite role to mitosis in the regulation of animal cell populations. It is amazing that their ground-breaking publication was essentially ignored for more than a decade. Then, in the late 1980's publications from numerous laboratories began to describe some of the biochemical and molecular genetic mechanisms involved in apoptosis. During the 1990's the field underwent an explosive rate of growth and it was difficult to pick up a biology journal that did not have at least one article on apoptosis.

Many of the historic details of the research by Kerr, Wyllie and Currie that launched the current era of apoptosis research and led to the molecular genetic studies that followed in laboratories around the world are nicely covered in the article by Cummings, Winterford and Walker[2]. The 1972 publication by Kerr, Wyllie and Currie[1] is a prototype of a paradigm-changing article. The history of the discovery of apoptosis and the central role played by trainees working with seasoned mentors should be inspirational for graduate students and beginning investigators.

References

1. Kerr JFR, Wyllie AH, Currie AR: *Br J Cancer* 1972, 26:239-257
2. Cummings MC, Winterford CM, and Walker NI: *Am J Surg Pathol* 1997, 21:88-101