Cell Death and Diseases of the Nervous System

细胞死亡与神经系统疾病

EDITED BY

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Cover illustrations: Background illustration is a portion of Fig. 256 from Ramon y Cajal's *Degeneration and Regeneration of the Nervous System*, first published in Spanish in 1913. The center illustration, courtesy of Vassilis E. Koliatsos, is a facial motor neuron undergoing apoptotic death after axotomy in the neonatal rat

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Foreword

It is an honor to be asked to write a foreword for this timely book, which assembles contributions from authorities working in the area of pathological nervous system cell death, and has been expertly edited by Vassilis Koliatsos and Rajiv Ratan. That the inappropriate demise of brain or spinal cord cells is at the root of many neurological diseases has been appreciated since the early days of microscopic neuropathology, but it has only been in the last decade or so that pervasive therapeutic nihilism has lifted. In the journey of medical progress, we have reached the shores of a marvelous new land.

Three major scientific thrusts in particular have converged to produce the press of ideas covered here. First, burgeoning information about the fundamental nature of central nervous system cell–cell signaling, both the fast signaling mediated by conventional neurotransmitters and the usually slower signaling mediated by neuromodulators and growth factors. A central theme emerging in recent years has been the duality of these signaling mechanisms, which serve the nervous system in health, but which can become the very mediators of neuronal or glial cell degeneration in disease settings. Glutamate-mediated neurotransmission and excitotoxicity have been the defining and best-studied examples, but many other examples have also emerged. Second, delineation of the molecular underpinnings of programmed cell death, and an appreciation of their awesome power. Cells in the nervous system share with other cell types a disconcerting readiness to self-destruct, which can be unleashed by the interruption of critical inputs, or by damage to vital structures. It has become clear in recent years how easily diseases of the nervous system can disturb the precarious suspension of programmed cell death that we call life. Third, development of animal models of neurodegenerative diseases. The most dramatic advantages have occurred in devising transgenic models of genetically driven diseases, but major refinements have also taken place in a variety of rodent or large animal models of ischemia or trauma. These models have made it possible to peer into the pathogenesis of brain or spinal cord cell loss as it occurs, to develop specific hypotheses about underlying mechanisms, and to determine whether specific experimental maneuvers can ameliorate this loss. Such neuroprotective maneuvers often represent unique, necessary tests of hypotheses, and, furthermore, can point the way toward the exciting prospect of developing therapeutic interventions in humans.

As Koliatsos and Ratan point out in their Preface, the biology of cell death has attracted unparalleled interest in recent years. Although no single book can cover this biology comprehensively, Parts I and II of *Cell Death and Diseases of the Nervous System* provide a good overview of mechanisms relevant to neuronal cell death. Building on this conceptual background, the heart of the book, Part III, places the theme of abnormal nervous system cell death in the context of a selected set of neurological and psychiatric diseases. Finally, Part IV looks into the future, with several chapters discussing the ap-

proaches that might be used to attenuate such abnormal cell death. As intended by the authors and editors, *Cell Death and Diseases of the Nervous System* should indeed be a useful guide to researchers or clinicians seeking a broad perspective on the field of pathological neuronal cell death. However, the field is moving quickly and new topics are coming into view with exciting regularity—insights into how nonneuronal cell death may differ from neuronal cell death, novel death mechanisms, new disease links and therapeutic strategies—so a sequel seems inevitable. Vassilis, Raj, I hope you have a chance to rest...

Dennis Choi, *MD, PhD*

Preface

One of our professors used to say that a preface serves its purpose only if written with the expectation that it is the only part of the book the reader will have time to study. This requirement implies a text that can capture the essence of the book in a nutshell. Unfortunately for editors of the book like *Cell Death and Diseases of the Nervous System*, the amount of information about cell death is enormous. On the other hand, asking questions about cell death represents a "Columbus egg"-type of paradox—it seems more a bypass than a solution to the problem. An enthusiast might argue that, since many problems in neurology are related to the death of neurons, cell thanatology is the science *par excellence* of clinical neurology. A cynic might respond that it is just a neuroscience written from the opposite—the bottom line—end. Whatever the epistemology of the topic, we have tried to present it for what it is: a useful concept for thinking about brain disease based on a good deal of common ground, but one also marked by several dilemmas. To those limitations we should add our—and the contributors'—biases and we can expect that every reader has his or her own (death is, after all, the *ultimate* event, and as such it tends to mobilize idiosyncratic responses).

What is cell death? What is death in general? Ignoring for the moment the philosophical response, this question brings painful memories to clinicians—neurologists in particular—who in certain cases have gone through a multiple test protocol for brain stem reflexes and even used EEG recording to diagnose a patient's death based on the permanent functional silence of the nervous system. This, of course, is already too late for the clinician-therapist. It is of interest that the diagnosis of cell death in tissues is as equally involving as the diagnosis of a patient's death. In fact, we have just begun to develop techniques to determine neuronal death in tissues beyond any reasonable doubt. But again, by the time the diagnosis is established, it is too late to intervene. It is much more useful, at least from the viewpoint of therapeutic interventions, to think in terms of irreversible injury or decision point, i.e., the stage at which the neuron commits itself to a self-destructive process—in the case of programmed cell death or apoptosis—or the stage in which the accumulated damage inflicted upon the neuron by extrinsic agents is incompatible with organelle function or maintenance of the membranous compartments. This point of no return should be the operational definition of cell death and the target phenomenon of investigations aiming at prevention or treatment of disease.

There is very little doubt that, in recent years, the biology of cell death has attracted unparalleled interest. Although the current fad is an overdue response of the biomedical community to a relatively small number of seminal observations made by pioneer scientists, the recent massive recruitment into the field of talented, ambitious investigators has contributed significant advances to our understanding of cell death mechanisms. What is more important for the clinic, the previous progress in understanding has led to recom-

mendations of ways to combat cell death—indeed, some of them employed by nature to regulate the physiological cell death that occurs during development. Based on the latter, one can argue that directly targeting cell death, instead of "upstream" causes, in treating neurological illness is not cracking the Columbus egg, but hitting the beast at the head with a smart—even convenient—weapon. On the other hand, precisely because nature uses cell death as a regulatory process, we must be cautious in assuming that cell death is always negative, or bad, for the organism; this may be naive, even in the case of disease. Nerve cells out of network or loaded with abnormal organelles and aberrant metabolites represent unproductive consumers of space and energy. Even worse, they are carriers of pathologic burdens potentially spreadable to neighboring healthy tissues in the form of transmissible agents, amyloidogenic foci recruiting nearby processes, or inflammatory triggers inviting phagocytic cells that may lyse innocent bystanders.

Capturing the excitement in the scientific community is definitely one of the causes of this book. Another cause that needs underlining is our commitment to the presentation of the great ideas in the field, rather than mere accounts of a series of high-tech experiments. The first of these commitments does not originate simply in the need to give appropriate credit to the innovators. It is primarily the result of our belief that this is the only secure way to promote the important, i.e., persisting, issues. It is pertinent here to state that we agree with Ron Oppenheim who has commented that the study of cell death in the nervous system is not a recent endeavor. Regardless of its popularization by rebaptizing the issues with molecular nomenclature—coinciding with the disappointment that the features of neurons that were the focus of attention in the last two decades have not been of great therapeutic utility—the field of cell death has been a busy and rewarding venture for a few faithful investigators for almost twenty years. The molecular era has helped popularize and rejuvenate the field, though the underlying ideas are quite old. In *Cell Death and Diseases of the Nervous System*, we have tried to underline the permanent and at the same time pass on the excitement about current and future discoveries.

Although it is usually difficult to trace precisely the developments that lead to major shifts in scientific directions, it can be argued that an underlying reason for refocusing on the bottom line—the death of neurons—is a continued frustration in the end-of-century Neurology after multiple waves of exacting science with very limited clinical gains. This tradition begins with the astute and highly replicable bedside observations in the Charcot era, then moves to the structural revolution with Nissl and Ramon y Cajal, continues on with the lesion-and-deficit experiments in the first half of the century and the connectional and single unit recording era in the 60s, then with the recent transmitter era in the 70s and 80s, which prepared what has been called the molecular movement, and is currently experiencing the cognitive revolution. Although most of the above approaches have yet to speak their last word, clinicians remain eager for treatment tools.

The organization of the material in the book follows a logical scheme designed to guide the study of the clinician-scientist. However, in keeping with our commitment to the presentation of ideas, the underlying thread is historical. The neuronal death chronicle starts with observations on the death of Rohon-Beard cells in developing skates by Beard at the end of the previous century and the experiments of Kallius, Ernst, and Glucksman during the third decade of this century. However, it was Hamburger and Levi-Montalcini who promoted the phenomenon of neuronal death to its present prominence as a major

regulator event during development and who provided an adequate conceptual framework for its understanding. The historical importance of the studies of these two pioneer investigators becomes evident in Hamburger's confession that, to a neurobiologist of the Spemman school (Spemman was Hamburger's mentor), *regressive* (death) phenomena during the *progressive* process of development would hardly be conceivable. It is interesting, though, that few people in the neuroscience community paid attention to these historical developments, even after the issue was reintroduced in the scientific literature by Hamburger and a few other investigators in the 70s (*see* chapter by Burek and Oppenheim in Part I). At the same time, other pioneer investigations were being made in the invertebrate nervous system using the convenient tiny roundworm *C. elegans*, adding up to the discovery of a strict genetic program leading to a predictable death of 50% of neurons during development (the case *par excellence* of programmed cell death). The dynamics of this *instructive* process are very different from those working in the *selective* death of neurons during vertebrate development, but the underlying molecular details may be exactly the same. At about the same time (70s and 80s), pioneering observations were being made also in tumor cells and lymphocytes, with the discovery of the major morphological subtypes of dying cells (apoptosis and necrosis) (*see* chapters by Clarke and by Pittman and colleagues in Part I).

Despite the previous remarkable discoveries, neuroscientists were absorbed in their long honeymoon with the neurotransmitters in what can be characterized as the most influential single period in the history of neuroscience, because of its implicit promises for therapy through links with pharmacology. Our obsession with transmitters, and the shapes and sizes of different classes of neurons, in the 70s and 80s led to the simplistic notion that cells not responding to phenotypic probes (Nissl stains, immunocytochemistry, *in situ* hybridization), were practically dead. Only approximately 20 years after neurochemical transmitter research had become the predominant approach in neuroscience, we began to separate dedifferentiation from death. Another symptom of this neglect was that a crucial theory published by Stan Appel in the heyday of the transmitter era linking neurodegenerative disease with developmental neuronal death, although widely cited, was not useful in guiding research. In our defense, we did have an unambiguous way of labeling dead neurons *in situ* and we had no particular desire to occupy ourselves with hard-to-substantiate concepts.

Bob Horvitz's presentation to the broader neuroscience community of the experience with the *C. elegans* at the annual meeting of the Society for Neuroscience in Phoenix in 1989 had a major impact on an audience already excited by the prospect of treating neuronal degeneration with molecules naturally employed to combat cell death (*see* chapter by Hilt and colleagues in Part IV). These molecules (trophic factors) had made a remarkable appearance in 1989 with the discovery of the NGF family and the cloning of CNTF, the first cytokine with effects on the nervous system (*see* chapter by Koliatsos and Mocchetti in Part IV). It is perhaps the concept of cell death most linked in scientists' minds to the notion of substances with therapeutic potential, despite the fact that the prototypical trophic factor NGF was a direct product of developmental neurobiology and, indeed, the conceptual offspring of the same team of scientists who first studied embryonic neuronal death 35 years ago.

A remarkable development was the cloning of the genes *ced-3* and *ced-4,* which instruct cell death, as well as the gene *ced-9*, which prevents cell death in the *C. elegans* (*see* chapter by Royal and Driscoll in Part II). The mammalian proto-oncogene *bcl-2*, initially characterized by its ability to prevent death in myeloid precursors deprived of trophic factors, has been shown to have 23% nucleotide identity with *ced-9*, whereas the mammalian interleukin-1 beta-converting enzyme (ICE) gene is homologous to *ced-3*. These developments facilitate understanding the findings in mammalian systems in light of the rich experimental record on *C. elegans* and raise the possibility of discovering specific compounds to combat cell death, including neuronal cell death (*see* chapter by Rosen and Casciola-Rosen in Part I).

The recent discovery of 11 different missense mutations of the principal free radical scavenger, superoxide dismutase 1 (SOD1), in patients with familial ALS has brought to the fore the free radical theory of neuronal cell death (*see* chapter by Rabin and Borchelt in Part III). Exciting new mechanisms have been proposed for the interaction of free radicals, calcium, and the toxic messenger, nitric oxide, in keeping with the basic idea of multiple converging pathways for neuronal death, as suggested by Dennis Choi in the 1990 Dahlem workshop on neurodegenerative diseases (*see* chapters by Dykens and by Leist and Nicotera in Part I). In the meantime, tumor biology has continued to provide clues about coupled regulation of cell proliferation and death, a still evolving concept that may be especially pertinent to postmitotic, terminally differentiated cells like neurons (*see* chapter by Freeman in part I).

Very important observations have been made, in the last few years, by exposing neurons to various types of injury in vitro and in vivo, under conditions modeling human disease, in which investigators challenge ideas originating in general cell biology against the peculiarities of the nervous system. These models of neurological disease (especially animal models) are the best tools we have to test the clinical significance of more fundamental observations from cell lines or nonneuronal cells (*see* chapters by Elliot and Snider, Olney and Ishimaru, and O'Hearn and Molliver in Part II). The introduction of altered genes—especially genes known to cause familial forms of neurologic disease—into the genome of experimental mammals promises to revolutionize our ability to look into the mechanisms and to test drugs preclinically for the treatment of neurologic diseases. These transgenic animals—principally mice—have already provided excellent naturalistic models for such devastating diseases as ALS (*see* chapter by Rabin and Borchelt in Part III) and prion diseases (*see* chapter by Borchelt in Part III) and represent superb tools for the study of the principal mechanisms associated with other diseases, such as amyloidogenesis in Alzheimer's disease (*see* chapter by Koliatsos and Mocchetti in Part IV). Transgenic mice can also be used to examine the crucial issue of the interaction between genetic vulnerability and environmental triggers in the pathogenesis of neurologic disease (*see* chapter by Elliot and Snider in Part I).

The advent of *in situ* methods to label dying (apoptotic) neurons in tissues has allowed direct observations of neuronal death in the human brain. These observations will help clarify pathogenic mechanisms and, possibly, to redirect or redefine our therapeutic targets in various diseases of the nervous system (*see* chapters by Vornov, Shin and Lee, Dietrich, Back and colleagues, Wood, Burke, Ross and colleagues, and Gelbard in Part III). On the other hand, the progressive introduction of neurobiological tools to the neuropathological study of the human brain has reinvigorated a field that has been rather lim-

ited in its ability to explain mechanisms of human neurologic disease. This renaissance of neuropathology is founded not only on the availability of tools that can be used for labeling phenomena that occur *in situ* (*see* chapter by Ross and colleagues in Part III), but also on the application of systems neuroscience, principally the result of physiological and anatomical investigations on nonhuman primates or the combinations of molecular and systems approach (*see* chapter by Braak and Braak in Part III). The emergence of what has been called by some "smart neuropathology" may be especially helpful for a better understanding of the most elusive diseases of the nervous system, such as schizophrenia (*see* chapter by Arnold in Part III).

Continued work on animal models of neurological disease, combined with more specific observations on the brains of patients using imaging or tissue technique, will allow the development of specific ways to combat neuronal cell death, either with small molecules that can be given systematically (*see* chapters by Koliatsos and Mocchetti, Tymianski, Bar-Peled and Rothstein, and Ratan in Part IV) or larger peptides for intrathecal administrations (*see* chapter by Koliatsos and Mocchetti in Part IV). Targeting mechanisms of cell death for therapeutic interventions is becoming a realistic and powerful approach, supported by a constantly expanding and increasingly innovative biotechnology.

Some of our editorial principles: Our book primarily targets the clinician-scientist and the graduate student of biology and neuroscience, but also hopes to refresh the memory and reinforce the commitment of established basic scientists. We have placed a great emphasis on the teaching function of the book. This function is best served through the presentation of informed views (rather than dogmas or single findings) in a simple, clear, and diagrammatic fashion. The topics were also selected with the previous function in mind. Conscious of the fact that no book can compete with scientific journals, we have also decided not to reproduce the style and content of excellent topical volumes on the subject of cell death. Our hope is that *Cell Death and Diseases of the Nervous System* will remain the definitive reference on neuronal cell death for the clinician-scientist for several years to come.

In keeping with its teaching function, we have tried to make ours a user-friendly book. We have edited to ensure uniformity in the quality and mode of presentation, as well as a logical progression from one topic to another, and have provided extensive cross-referencing. Because of our strong emphasis on human disease, the overall schematic should facilitated the readers' understanding and treatment of neurological illness. In the chapters that cover the basic sciences (the first two parts of the book), there is a concluding passage on the implications for human disease. This is realized in detail in the clinical chapters, where the various authors comment on models pertinent to the diseases they discuss. For the sake of simplicity and uniformity, we have discouraged halftone illustrations, whereas a large number of line diagrams were included. The result, we sincerely believe, is one of the best organized and user-friendly books on clinical neuroscience a reader can find today.

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