Cell death in biology and pathology

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Preface

The subject of cell death includes several seemingly diverse fields of inquiry, and there is to date no common source of information for the researcher or advanced student. Dispersion of the information on the subject also hinders the development of a theoretical or historical sense of the significance of cell death as a biological phenomenon. This book is an attempt to collate the thrust of current research on cell death and also to point out the direction of future lines of research.

Cell death may be accidental or induced or may be genetically programmed (Chapter 1). As a matter of principle, programmed cell death should be regarded as a mechanism for survival rather than destruction. It is a paradox that cell death is intimately involved in the birth and development of life as we know it, occurring during the formation of eggs and sperm and at many vital stages during embryological development (Chapter 2), and forming the basic mechanism underlying morphogenesis and metamorphosis (Chapter 3). It exerts a balancing or homeostatic function in relation to tissue kinetics and may be an important factor in the control of size and shape in normal tissues, organs, appendages and whole organisms (Chapter 4). Cell death is also an important element in the control of abnormal growth such as tumours (Chapter 6) and many therapeutic agents exploit this factor to induce regression.

An understanding of the mechanisms of cell death is fundamental to an understanding of cell biology. Genetically programmed cell death may involve differential gene activity, differential synthetic activity in terms of enzymes and proteins and finally, differential cell lysis or destruction (Chapters 5, 9 and 13). All these steps are controlled in ways which we are now only beginning to understand.

Cell death is of considerable medical significance (Chapters 6, 8, 10, 11 and 12) and is of obvious import to pathologists who have to interpret histological patterns of cell death. This book deals with the causes of induced cell death (Chapter 7) including disease and also outlines recent techniques for demonstrating cell death (Chapter 13).

It is evident that cell death can be broadly classified into two categories: lysis or coagulative necrosis, in which cells osmotically swell and rupture: and apoptosis or related forms of physiological cell death, in which the cell undergoes more elaborate conversions before succumbing (Chapters 1, 2, 3, 10, 11, 13). The mechanisms of the latter are neither as obvious nor as well understood as are those of the former, but substantial progress has been made in the last few years, and the field is burgeoning.

It is clear that lysosomal enzymes often play a role in the destruction of the cytoplasm, but very few authorities feel that they initiate the process (Chapters 1, 2, 3, 5-8, 12, 13). The cells show many forms of damage, and sometimes even complete destruction, before lysosomes become a dominant part of the environment. What initiates the process is still unclear, although in several instances it appears that the death of a cell may arise from any one of several pathways (Chapters, 10, 11). It is rather interesting that evolution has chosen to achieve the same goal by different means. Apparently no one point is exceptionally or preferentially vulnerable, though a common pathway, such as permeability of the plasma membrane to calcium (Chapter 7), might currently be too subtle for routine identification. Factors which affect membrane stability and which induce membrane bending can lead to blebing, cell fragmentation and death. Thus, more work on the changing chemistry of the plasma membrane in relation to environmental fluctuations would be welcomed.

Space requirements and the major orientation of the book forced the exclusion of several very interesting topics: an evolutionary treatment of the advantages of cell death as a means of eliminating vestigial organs or embryonic scaffolding; or consideration of the merits of body sculpting by cell death rather than cell growth. These ideas have been thoughtfully examined by the founders of the field, to whom reference is made in many chapters. It appears that if cell death can be evoked as a physiological command, then it is far less expensive to change shape by cutting away than by adding. It is presumably easier to call forth existing genes, such as those regulating catabolism, than to eliminate genes for particular structures – especially if the tissues destined for evolutionary loss serve as scaffolding for other tissues.

Finally, there are vast areas that deserve to be considered but which are excluded from this work, either because of the immenseness of the field or lack of information. Destruction of cells by chemotherapeutic agents or by viruses are areas of great interest, but most of the literature focusses on the behaviour of the virus rather than the host cell, and the literature relating to the invocation of self-destruction pathways by the host cell remains diffuse. Also, in spite of several excellent studies in the field (see especially Chapters 8, 9, and 11) the relation of nuclear control to cytoplasmic destruction is not well understood. The discussions emphasize our need to know to what extent cytoplasmic destruction is a spontaneous, perhaps physico-chemical, response to specific conditions, to what extent it is brought about by prior restrictions on nuclear activity, and to what extent it is a direct result of specific gene function.

These and several other questions need to be resolved, but it is gratifying to see how similar are the thoughts from the different fields. The latent unanimity is itself justification for presenting this work at this time, and we hope that our effort will serve to stimulate, provoke, and crystallize the thoughts on the subject.

R. A. L., New York, March, 1981

I. D. B., Cardiff, March, 1981

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R.A.L.

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I.D.B.

Contents

Introduction

The death of cells is a phenomenon often mentioned, the importance of which is recognized, and which attracts the attention of researchers in numerous fields of the biological sciences. In searching through the literature, one finds the term referenced as a keyword in papers deriving from the separate fields of pathology, neurology, development, genetics, radiation, teratology, immunology and oncology, bacteriology and aging. In spite of the interest, however, several problems become apparent to anyone who takes the time to try to understand the process and mechanism of cell death: the term may refer to several different phenomena; the vast majority of papers in the area note the existence of dead cells without further analysis of mechanism or causality, and there exists no comprehensive treatise attempting to provide guidelines or a source of comparison or unification. Indeed, I feel the time is ripe for such a treatise.

The first and most obvious difficulty is that there is, to our knowledge, no adequate definition as to what constitutes a dead cell. For those seeking to recognize, in histological sections, dark condensed cells or fragments of cells, with dense compacted chromatin, lysed completely extruded cells or dark condensed cells residing within vacuoles of phagocytes, there is no particular problem: surely these cells are dead – although the questions of why they condense, lyse, or are attacked by phagocytes do not seem to have been examined closely. It is more difficult to cope with the question if one is seeking to understand how cell death occurs: is a cell dead because it has ceased to synthesize DNA? Neurons may live more than a century in a post-mitotic state. Is a cell dead because it has ceased to synthesize RNA? In many systems the death of a cell may be prevented by inhibition of RNA synthesis. In some experimental systems, such as developing embryos, metamorphosing insects and involuting thymocytes, cells can be shown to follow a programme toward their own death, the programme being reversible by specific experimental manoeuvres up to a specific time before the cell can be seen to deteriorate rapidly; should an operational definition be employed to define cell death as a point of experimental irreversibility?

Although several authors suggest different definitions, our initial assumption will be that the most accurate judgement is based on the cytology of the cell. Accordingly, it will be most useful to imagine that a cell is dead when the nucleus condenses or lyses. Presumably this event correlates with the final cessation of

DNA synthesis, if the cell was previously capable of synthesizing DNA, or with the cessation of synthesis of RNA. Condensation of the nucleus occurs simultaneously or nearly simultaneously with the collapse of membrane permeability barriers in at least one insect system (Lockshin and Beaulaton, 1979); otherwise, the question seems not to have been greatly explored, and gross biochemical analyses, such as synthesis or lack of synthesis of total RNA, cannot at present be considered to be sufficiently precise to permit their use as definitions.

Such biochemical analyses may ultimately prove to be of value in studies involving metamorphosing animals, although, even in these models, tissue heterogeneity and lack of synchrony may well limit the usefulness of definitions based on such phenomena. For those studying random isolated instances of cell death, as occurs in cell turnover or at higher frequency in many pathological conditions, or the gradual dropout of cells from cultures of fibroblasts, at present only the histological definitions seem sufficiently precise, although radioautographic analysis of certain synthetic events may prove of value. Nevertheless, we may almost certainly assume that unequivocal cytological alteration is secondary to the event we should properly term as cell death and which we would like to understand. Our excuse for accepting cytological alteration operationally is that, as our expertise in the subcellular location and characterization of the alteration increases, the alteration will help us to define the border.

That our definitions remain in this unsatisfactory state derives in part from the lack of focus in the field. In spite of the outstanding efforts of Glücksmann (1951) to classify and organize the field, the excellent review by Saunders (1966) and a further effort to develop a theme by Lockshin and Beaulaton (1974) most authors view the death of cells as a landmark or end point for experiments directed toward other goals, and many are unaware of studies or interpretations deriving from distantly related fields. We hope that this book will bring together some of these ideas so that, even if ultimately our guesses, predictions and themes prove to be wrong, we at least can provide a starting point.

The second reason for the unsatisfactory state of our definitions can best be described in tabular form. Although many authors mention cell death in passing or by using other terms, one can get a general picture of the field by compiling a list of those who have considered the phenomenon of sufficient importance to include it in a title or keyword. A rough and personal classification of such articles, based on a computer search which turned up 668 items from 1871 to 1978, is shown in Table 0.1; some references are included under more than one category. Of the types of tissue examined, and especially recently, those dealing with mammalian neural and circulatory tissue lead the list by far; most represent observations of cell death in embryonic tissues such as sympathetic ganglia, either under normal conditions or when deprived of a source of nerve growth factor; or they are observations of loss of cells in aging animals. The majority of papers dealing with cell death in the circulatory system referred to acute anoxic death of cardiac muscle in simulations of infarcts; and, under the rubric 'connective tissue', most of the studies referred to the death of fibroblasts in long-term culture, or immunological