

## Preface

Who would have believed it?! Mitochondria, the powerhouses of cellular life, are also the motors of cell death. Few would have accepted this even 5 years ago. Now it is one of the hottest topics in biomedical research. In July 1998 the Biochemical Society devoted its annual symposium at Sheffield University to Mitochondria and Cell Death. Reflecting the increasing interest in this topic from pharmaceutical companies, the symposium was sponsored by SmithKline Beecham, Glaxo-Wellcome, Janssen, Pfizer and Merck, Sharpe & Dohme. This book is derived from that symposium, and it is intended to present the latest research and thinking on this subject from some of the key researchers in the field.

Several different lines of research have converged on the mitochondrion and its role in cell death. These fields are: (i) mitochondrial permeability transition; (ii) apoptosis; (iii) neurodegeneration and excitotoxicity; (iv) mitochondrial DNA diseases; (v) free radicals and nitric oxide; and (vi) hypoxia/ischaemia.

(i) In the presence of excess calcium and/or oxidants mitochondria undergo a 'permeability transition' to a state of much higher permeability to all low-molecular-mass solutes. This transition involves the opening of a pore, which is blocked by cyclosporin A, and is implicated in hypoxic/ischaemic and oxidant-induced damage to tissues. Chapters 15 and 16 present the latest research on the molecular nature of this pore. Chapters 1 and 17 review its role in apoptosis and necrosis. Chapter 8 discusses its role in brain damage.

(ii) Apoptosis is a form of programmed cell death executed by cysteine/aspartate proteases, the caspases. Mitochondria can trigger apoptosis by releasing cytochrome *c* and other components into the cytosol, and this may be one of the major routes by which apoptosis is controlled. Chapters 1, 3, 7 and 17 discuss the mitochondrial control of apoptosis, and its role in cell death.

(iii) There is increasing evidence for mitochondrial dysfunction in neurodegenerative diseases, in particular Parkinson's disease and Huntington's disease (reviewed in Chapters 5, 9 and 10). The neurotransmitter glutamate can, in certain conditions, kill neurons, a process known as 'excitotoxicity'; the involvement of mitochondria in this type of neuronal death is discussed in Chapters 4 and 6.

(iv) Mutations of mitochondrial DNA can result in muscular and neurological disease. Chapter 11 examines the role of primary DNA mutations in causing cell dysfunction, and Chapter 10 discusses the role of secondary abnormalities of mitochondrial DNA in neurodegeneration.

(v) Mitochondria are major cellular sources of the reactive oxygen species, and these oxidants can in turn inhibit the mitochondrial respiratory chain, induce the permeability transition and mutate mitochondrial DNA. Mitochondria are also targets for nitric oxide and reactive nitrogen species, as discussed in Chapters 2, 5 and 10. Cytotoxic levels of nitric oxide are produced during inflammation, and may contribute to inflammatory, ischaemic and neurodegenerative diseases. Septic shock is the disease where nitric oxide overproduction is best characterized, and is discussed specifically in Chapter 14.

(vi) Hypoxia causes an acute inhibition of mitochondrial respiration, but hypoxia/ischaemia and reperfusion also cause secondary damage to mitochondria, which may lead to cell death. The mechanisms of such damage and death are discussed in Chapters 2, 13, 14 and 15 for the heart, Chapters 4, 6, 8 and 12 for the brain, and Chapter 17 for the liver.

Of course, these lines of research and the cellular processes they describe interact in many ways in the pathophysiology of real diseases, and the problems of measurements *in vivo* of the role of mitochondria in initiating cell death are discussed in Chapter 12. Disentangling these multiple interactions between mitochondria and cell death will provide experimental challenges for the next decade at least. We hope that this book will contribute to unravelling these complexities, and stimulate further breakthroughs in this exciting field.

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