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 Huntingdon'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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Abbreviations

AIF	apoptosis-inducing factor
ALS	amyotrophic lateral sclerosis
AM	acetoxymethyl ester
ANT	adenine nucleotide translocase
BAPTA	bis-(*o*-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetra-acetic acid
BKA	bongkrekic acid
BOLD	blood-oxygenation-level-dependent
CAT	carboxyatractyloside
CBF	cerebral blood flow
CBV	cerebral blood volume
CNS	central nervous system
CS	citrate synthase
CsA	cyclosporin A
CyP	cyclophilin
cyt *c*	cytochrome *c*
DCD	delayed Ca^{2+} de-regulation
DOG	2-deoxyglucose
DWI	diffusion-weighted imaging
EPR	electron paramagnetic resonance
FRDA	Friedreich's ataxia
GAPDH	glycyceraldehyde-3-phosphate dehydrogenase
GST	glutathione S-transferase
Hb	deoxyhaemoglobin
Hb-NO	nitrosyl haemoglobin
HbO_2	oxyhaemoglobin
HD	Huntington's disease
HEt	hydroethidine
HLA	human leucocyte-associated antigen
ICD	immediate Ca^{2+} de-regulation
IL	interleukin
IMM	inner mitochondrial membrane
iNOS	inducible nitric oxide synthase
JC-1	5,5′,6,6′-tetrachloro-1,1′,3,3′-tetraethylbenzimidazolo-carbocyanine
KSS	Kearns–Sayre syndrome
LHON	Leber hereditary optic neuropathy
LVDP	left-ventricular developed pressure

MELAS	mitochondrial encephalopathy, lactic acidosis and stroke-like episodes
MERRF	myoclonus epilepsy with ragged red fibres
MPP^+	1-methyl-4-phenylpyridinium ion
mPT	mitochondrial permeability transition
MPTP	1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
mtDNA	mitochondrial DNA
NIRS	near-infrared spectroscopy
NMDA	*N*-methyl-D-aspartate
NOS	nitric oxide synthase
3-NPA	3-nitropropionic acid
PCr	phosphocreatine
PD	Parkinson's disease
PDH	pyruvate dehydrogenase
PEG	poly(ethylene glycol)
PheArs	phenylarsine oxide
PPIase	peptidylprolyl *cis–trans* isomerase
PT	permeability transition
PTPC	permeability transition pore complex
PUFA	polyunsaturated fatty acid
R123	rhodamine-1,2,3
RCR	respiratory control ratio
Ref	reference laboratory diet
ROS	reactive oxygen species
RR	Ruthenium Red
RRF	ragged red fibre
SOD	superoxide dismutase
TBH	t-butylhydroperoxide
TH	tyrosine hydroxylase
TMRM	tetramethylrhodamine methyl ester
TNFα	tumour necrosis factor-α
VDAC	voltage-dependent anion channel (mitochondrial porin)