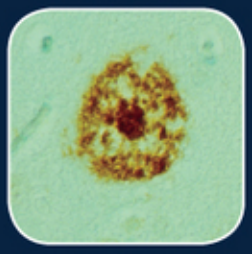

NEURODEGENERATION

the molecular pathology of dementia and movement disorders

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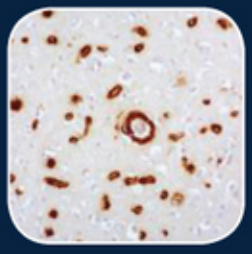

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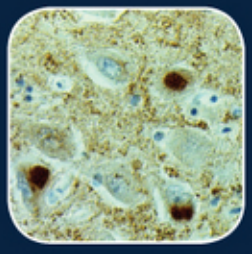

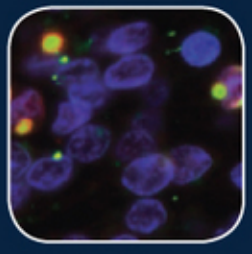

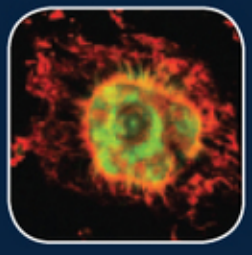

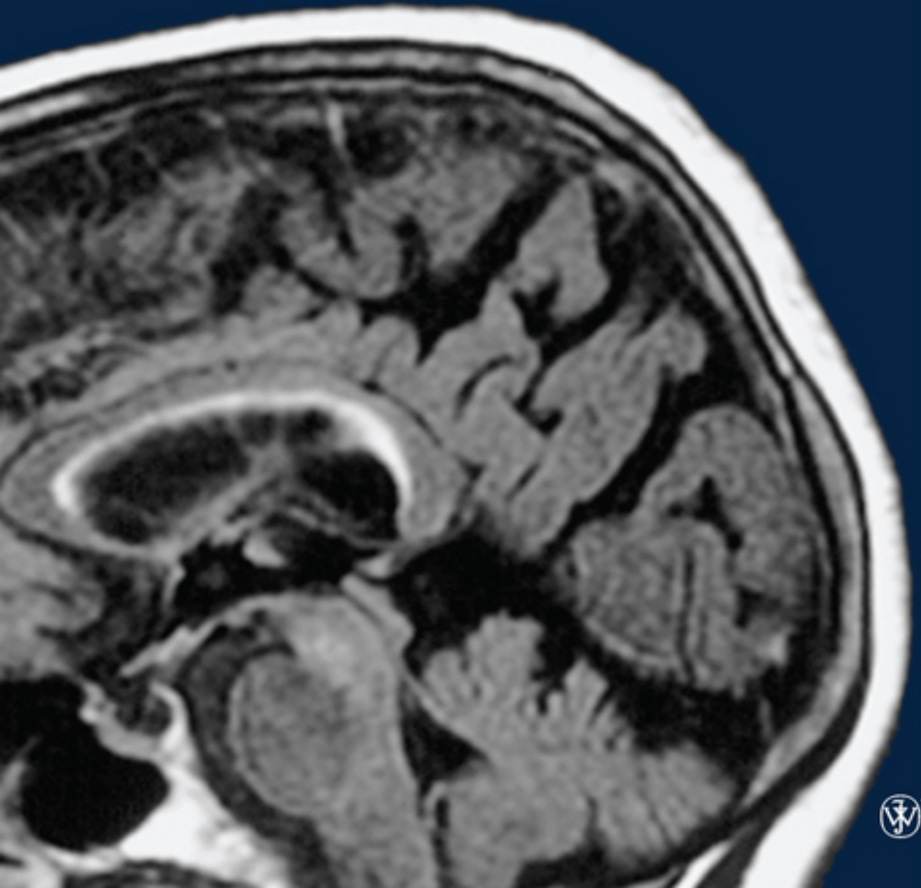

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Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders

Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders

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SECOND EDITION

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Preface

One of the major roles of the International Society of Neuropathology (ISN) is to promote world-wide education and research in the pathology of neurological disease for the enhancement of care and treatment of patients. As the interface between neuropathology and other scientific and clinical disciplines became increasingly blurred, a series of books on the "Pathology and Genetics" of neurological disease was initiated by Dr Paul Kleihues to promote mutual understanding and collaboration.

The first book in the series was on *Brain Tumours* (1997); that is now in its fourth edition as the *WHO Classification of Tumours of the Central Nervous System*, edited by David N. Louis, Hiroko Ohgaki, Otmar D. Wiestler and Webster K. Cavenee and published by WHO Press (2007). A further four books were published by ISN between 2001 and 2005 with Yngve Olsson as Series Editor: *Structural and Molecular Basis of Skeletal Muscle Diseases,* Volume Editor George Karpati (2002); *Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders,* Volume Editor Dennis Dickson (2003); *Developmental Neuropathology* , Volume Editors Jeffrey A. Golden and Brian Harding (2004); *Pathology and Genetics of Cerebrovascular Diseases,* Volume Editor Hannu Kalimo (2005). Each volume brought together expertise from multiple international authors writing in a standard format that allowed readers to navigate the different chapters with ease. These features led to the considerable success of the series.

Publication of the "Pathology and Genetics" series has entered a new phase with a new publisher and a new Series Editor. As publisher of the very successful ISN Journal *Brain Pathology,* Wiley-Blackwell has been appointed to publish the ISN book series. Following wide international consultation, a second edition of *Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders* was selected as a priority for publication with Dennis Dickson and Roy Weller as Volume Editors. This reflects the considerable and momentous advances that have occurred in the field of neurodegeneration since the publication of the first edition. Many of the authors from the first edition have been retained and every chapter has been rewritten and thoroughly updated. The format that is familiar to readers of the first edition has also been retained but new sections have been added to reflect advances in the field. In its multidisciplinary approach, the volume concentrates on pathology, genetics, molecular biology and biochemistry in relation to clinical aspects of neurodegenerative disease, imaging and the new therapies that are on the horizon. There is some overlap between volumes in the series, such that vascular dementia is covered in the previous book on cerebrovascular diseases.

I would like to thank Dennis Dickson as Volume Editor for establishing the structure of the current book on neurodegeneration and for inspiring the authors. Our thanks go to the 96 authors who put so much effort and expertise into ensuring the high quality of the text and illustrations. Sadly, one author, Mark Smith, died in a road accident at the end of 2010 but will be remembered through his contribution to this book.

Finally, who will benefit from reading this book on neurodegeneration? Our aim was to provide succinct and well-ordered chapters for instant access to the concepts and many of the details of the pathology and genetics of neurodegenerative disease to further the multidisciplinary interests of pathologists, clinicians and neuroscientists involved in research and in the diagnosis and care of patients with neurodegenerative disease. We trust that our aspirations will be fulfilled.

Roy O. Weller
Series Editor

List of Abbreviations

1C2	antibody to the expanded polyglutamine repeat segment of TBP
3-NP	3-nitropropionic acid
5-HT	5-hydroxytryptamine (serotonin)
5-HIAA	5-hydroxyindolacetic acid
8-OHG	8-hydroxydeoxyguanosine
17-AAG	17-allylamino geldanamycin
αSyn	α-synuclein
AA	amyloid associated
Aβ	amyloid β
Aβ40	Aβ isoform of 40 amino acids
Aβ42	Aβ isoform of 42 amino acids
ABC	ATP-binding cassette
ABri	amyloid-Bri
ABriPP	amyloid-Bri precursor protein
ACE	angiotensin-converting enzyme
ACE-1	angiotensin-converting enzyme 1 (protein)
AChE	acetylcholinesterase
AD	Alzheimer's disease
ADan	amyloid-Dan
ADanPP	amyloid-Dan precursor protein
ADCA	autosomal dominant cerebellar ataxia
ADom	autosomal dominant
ADPath	Alzheimer's disease pathology
aFTLD-U	atypical frontotemporal lobar degeneration with ubiquitinated inclusions
AGD	argyrophilic grain disease
AGE	advanced glycation endproducts
AIDS	acquired immunodeficiency syndrome
AIF	apoptosis-inducing factor
ALP	autophagy-lysosomal pathway
ALS	amyotrophic lateral sclerosis
ALSbi	ALS with behavioral impairment
ALSci	ALS with cognitive impairment
ALS-PD	amyotrophic lateral sclerosis parkinsonism/ dementia complex of Guam
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANG	angiogenin
AOPD	adult-onset Parkinson's disease
AOS	apraxia of speech
apoE	apolipoprotein E (protein)
APOE	apolipoprotein E (gene)
APOJ	apolipoprotein J (gene)
APP	β-amyloid precursor protein
AR	androgen receptor, autosomal recessive
ARSACS	autosomal recessive spastic ataxia of Charlevoix and Saguenay
ArG	argyrophilic grains
ARJP	autosomal recessive juvenile parkinsonism
ASM	acid sphingomyelinase
Atg	autophagy-associated protein
ATP	adenosine triphosphate
AV	autophagic vacuole
AVED	ataxia with isolated vitamin E deficiency
BASE	bovine amyloidotic spongiform encephalopathy
BCSG1	breast cancer-associated protein 1
BDNF	brain-derived neurotrophic factor
BI	basophilic inclusion
BIBD	basophilic inclusion body disease
BN	ballooned neuron
bp	base pairs
BSE	bovine spongiform encephalopathy
bvFTD	behavioral variant frontotemporal dementia
CA	hippocampal pyramidal cell sector (cornu ammonis)
CAA	cerebral amyloid angiopathy
CAB	calbindin
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CAMCOG	Cambridge Cognition test battery
CAP	caudate-accumbens-putamen
CB	coiled bodies
CBD	corticobasal degeneration
CBGD	corticobasal ganglionic degeneration
CBS	corticobasal syndrome

CBP	CREB-binding protein
CCA	cerebellar cortical atrophy
CDK	cyclin-dependent kinase
CDR	Clinical Dementia Rating
CEI	cholinesterase inhibitor
CERAD	Consortium to Establish a Registry of Alzheimer's Disease
ChAT	choline acetyltransferase
CHMP2	charged multivescicular body protein 2B gene
CI	confidence interval
CJD	Creutzfeldt–Jakob disease
CLU	clusterin (gene)
CM	center median
CNS	central nervous system
COMT	catechol-o-methyl-transferase
CPEB	cytoplasmic polyadenylation element-binding protein
CR	Congo red
CR1	complement component (3b/4b) receptor 1 (gene)
CREB	cAMP-responsive element-binding protein
CSF	cerebrospinal fluid
CST3	cystatin C (gene)
CT	computed tomography
CWD	chronic wasting disease
CXCL8	interleukin 8 (gene/protein; alternative name of IL-8)
CXCR2	chemokine (C-X-C motif) receptor 2
CysC	cystatin C (protein)
DAT	dopamine transporter
DBS	deep brain stimulation
DLB	dementia with Lewy bodies
DLDH	dementia lacking distinctive histopathology
DM	diabetes mellitus
DMX	dorsal motor nucleus of the vagus nerve
DN	dentate nucleus/dystrophic neurites
DNA	deoxyribonucleic acid
DOPAC	3,4-dihydroxyphenyl acetic acid
DRAM	damage-regulated autophagy modulator
DRG	dorsal root ganglion
DRN	dorsal raphe nucleus
DRPLA	dentatorubropallidoluysian atrophy
DUB	deubiquitylating enzyme
DWI	diffusion-weighted imaging
EAAT-2	excitatory amino acid transporter 2
ECL	enhanced chemoluminescence
EEG	electroencephalography
EL	encephalitis lethargica
ELISA	enzyme-linked immunosorbent assay
EM	electron microscopy
EMG	electromyography
eNOS	endothelial nitric oxide synthase
EOAD	early-onset Alzheimer's disease
EOAH	ataxia with oculomotor apraxia and hypoalbuminemia
EOFAD	early-onset familial Alzheimer's disease
EOPD	early-onset Parkinson's disease
ER	endoplasmic reticulum
ERAD	ER-associated degradation system
ESES	electrical status epilepticus during slow-wave sleep
fALS	familial amyotrophic lateral sclerosis
FBD	familial British dementia
fCJD	familial Creutzfeldt–Jakob disease
FDC	follicular dendritic cell
FDD	familial Danish dementia
FDG-PET	2-deoxy-2[F-18]fluoro-D-glucose positron emission tomography
FENIB	familial encephalopathy with neuroserpin inclusion bodies
FFI	fatal familial insomnia
FLAIR	fluid attenuation inversion recovery
FRDA	Friedreich's ataxia
frda	frataxin gene
FSE	fast spin echo
FSH	follicle-stimulating hormone
FTD	frontotemporal dementia
FTDP	frontotemporal dementia and parkinsonism
FTDP-17T	frontotemporal dementia and parkinsonism linked to chromosome 17 caused by *Tau* mutations
FTL	ferritin light chain
FTLD	frontotemporal lobar degeneration
FTLD-FUS	frontotemporal lobar degeneration with FUS pathology
FTLD-MND	frontotemporal lobar degeneration with motor neuron disease type inclusions
FTLD-ni	frontotemporal lobar degeneration with no inclusions
FTLD-tau	frontotemporal lobar degeneration with tau pathology
FTLD-TDP	frontotemporal lobar degeneration with TDP-43 pathology
FTLD-U	frontotemporal lobar degeneration with ubiquitinated inclusions
FTLD-UPS	frontotemporal lobar degeneration with UPS pathology
FUS	fused in sarcoma
FUS	fused in sarcoma gene
GAA	guanine-adenine-adenine
GAB2	GRB2-associated binding protein 2 (gene)
GABA	γ-amino butyric acid
GABAA	γ-amino butyric acid A
GAD	glutamate decarboxylase
GBA	glucocerebrosidase/acid β-glucosidase
GCI	glial cytoplasmic inclusion
GDNF	glia-derived neurotrophic factor
GFAP	glial fibrillary acidic protein
GFP	green fluorescent protein

GFT	glial fibrillary tangle
GHAI	granular hazy astrocytic inclusion
GNI	glial nuclear inclusion
GlcCer	glucosylceramide
GP	globus pallidus
gPD	genetic prion disease
GPe/GPi	external/internal globus pallidus
GRN	progranulin gene
GSK-3β	glycogen-synthase-kinase 3β
GSS	Gerstmann–Sträussler–Scheinker syndrome
Guam PDC	parkinsonism-dementia complex of Guam
GVD	granulovacuolar degeneration
GWAS	genome-wide association study
HADC	histone deacetylase
HD	Huntington's disease
HE, H&E	hematoxylin and eosin
Het-s	heterokaryon incompatibility protein
HF	hereditary ferritinopathy
hGh	human growth hormone
HMW	high molecular weight
hnRNP	heterologous ribonucleoprotein
HSD	Hallervorden–Spatz disease
HSP	heat shock protein
HTT	huntingtin
HuGENet	Human Genome Epidemiology Network
HVA	homovanillic acid
IB	inclusion body
IBMPFD	inclusion body myopathy with Paget's disease of the bone and frontotemporal dementia
IBZM SPECT	[^{123}I]iodobenzamide single photon emission computed tomography
ICAM1	intercellular adhesion molecule 1
iCJD	iatrogenic Creutzfeldt–Jakob disease
IDE	insulin degrading enzyme
IFC	inferior frontal cortex
IFT74	intraflagellar transport 74 gene
IGF-1	insulin-like growth factor-1
IHC	immunohistochemistry
IL8	interleukin 8 (gene/protein)
ILBD	incidental Lewy body disease
ILOCA	idiopathic late-onset cerebellar ataxia
INAD	infantile neuroaxonal dystrophy
iNOS	inducible nitric oxide synthase
IPD	idiopathic Parkinson's disease
IR	immunoreactive
ISEL	*in situ* end labeling
ISF	interstitial fluid
ITM2B	integral membrane protein 2B
JHD	juvenile Huntington's disease
JNK	c-Jun N-terminal kinase
LB	Lewy body
LBD	Lewy body disease
LBHI	Lewy body-like hyaline inclusions
LC	locus coeruleus
LCCA	late cortical cerebellar atrophy
LD	linkage disequilibrium
LDL	low-density lipoprotein
LDLR	low-density lipoprotein receptor (gene/protein)
L-dopa	levodopa
L-ferritin	light subunit of holoferritin
LH	luteinizing hormone
LHRH	luteinizing hormone-releasing hormone
LMN	lower motor neuron
LN	Lewy neurite
LOAD	late-onset Alzheimer's disease
LRP-1	low-density lipoprotein receptor-related protein-1
LRRK2	leucine-rich repeat serine/threonine-protein kinase 2
M	methionine
MAF	minor allele frequency
MAO	monoamine oxidase
MAP	microtubule-associated protein
MAPT	microtubule-associated protein tau
MBP	myelin basic protein
MCI	mild cognitive impairment
MED	male erectile dysfunction
MERRF	myoclonus epilepsy associated with ragged-red fibers
MHC	major histocompatibility complex
MIBG SPECT	[^{123}I]metaiodobenzylguanidine single photon emission computed tomography
MIM	Mendelian Inheritance in Man
MJD	Machado–Joseph disease
MM	methionine/methionine
MMSE	Mini Mental State Examination
MND	motor neuron disease
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MR	magnetic resonance
MRC CFAS	Medical Research Council Cognitive Function and Aging Study
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRS	magnetic resonance spectroscopy
MSA	multiple system atrophy
MSA-C	multiple system atrophy, cerebellar variant
MSA-P	multiple system atrophy, parkinsonian variant
MSN	medium spiny neurons
mTOR	mammalian target of rapamycin
MUNE	motor unit number estimate
M/V	methionine/valine
MWM	Morris water maze
NA	nucleus accumbens
NAC	non-amyloid component
NACP	non-amyloid plaque component
NAD	neuroaxonal dystrophy
NAIP	neuronal apoptosis inhibitory protein
NBIA1/2	neurodegeneration with brain iron accumulation type 1/2
NBM	nucleus basalis of Meynert

NCI	neuronal cytoplasmic inclusion
NDD	neurodegenerative diseases
NE	norepinephrine
NEP	neprolysin
NF	neurofilament
NF-H	neurofilament heavy subunit
NF-κB	nuclear factor kappaB
NF-L	neurofilament light subunit
NF-M	neurofilament medium subunit
NFT	neurofibrillary tangle
NI	nuclear inclusion
NIA	National Institute on Aging
NIBD	neurofilament inclusion body disease
NIFID	neuronal intermediate filament inclusion disease
NII	neuronal intranuclear inclusion
NINDS-SPSP	National Institute of Neurological Disorders and the Society for Progressive Supranuclear Palsy
NM	neuromelanin
NMDA	N-methyl-D-aspartate
NMI	nuclear membrane indentation
NNI	neuronal nuclear inclusion
NP	neuritic plaque
NPC	Niemann-Pick type C disease
NPDPSC	National Prion Disease Pathology Surveillance Center
NREM	non-rapid eye movement
NSE	neuron-specific enolase
NT	neuropil thread
OMIM	Online Mendelian Inheritance in Man
OPC	olivopontocerebellar
OPCA	olivopontocerebellar atrophy
OR	odds ratio
OS	oxidative stress
P_0	peripheral nerve myelin zero
PAC	P1-derived artificial chromosome
PAF	pure autonomic failure
PAGF	pure akinesia with gait failure
PAS	periodic acid-Schiff
PB	Pick bodies
PBP	progressive bulbar palsy
PCA	posterior cortical atrophy
PCD	programmed cell death
PCR	polymerase chain reaction
PD	Parkinson's disease
PDC	parkinsonism-dementia complex
PDD	Parkinson's disease dementia
PEP	postencephalitic parkinsonism
Per	peripherin
PET	positron emission tomography
PET blot	paraffin-embedded tissue blot
PF	parafascicular
p-FTAA	pentameric formic thiophene acetic acid
PGBD1	piggyBac transposable element derived 1 (gene)
PGC-1	proliferator-activated receptor gamma coactivator-1
PGRN	progranulin
PH-8	phenylalanine hydroxylase
PHF	paired helical filament
PIB	Pittsburgh compound B
PICALM	phosphatidylinositol binding clathrin assembly protein (gene)
PiD	Pick's disease
PINK1	PTEN-induced putative kinase 1
PK	proteinase K
PKAN	pantothenate kinase-associated neurodegeneration
PLAN	*PLA2G6*-associated neurodegeneration
PLS	primary lateral sclerosis
PMA	progressive muscular atrophy
PMCA	protein misfolding cyclic amplification
PME	progressive myoclonus epilepsy
Pmel17	melanocyte protein 17 precursor
PML	promyelocytic leukemia protein
PMP-22	peripheral nerve myelin protein 22
PNFA	progressive non-fluent aphasia
pNFP	phosphorylated neurofilament protein
PNS	peripheral nervous system
PRNP	prion protein gene
PrP	prion protein
PrP^{C}	cellular prion protein
PrP-CAA	prion protein cerebral amyloid angiopathy
PrP^{Dis}	disease-associated prion protein
PrP^{res}	protease-resistant (disease-associated) prion protein
PrP^{Sc}	scrapie prion protein
PSD	pseudoperiodic synchronous discharges
PSEN1	presenilin 1
PSEN2	presenilin 2
PSP	progressive supranuclear palsy
PSPr	protease-sensitive prionopathy
PSWC	periodic sharp-wave complex
PVM	perivascular macrophage
RBD	rapid eye movement sleep behavioral disorder
RBP	RNA-binding proteins
RCL	reactive center loop
REM	rapid eye movement
RIP	receptor interacting protein kinase
RNA	ribonucleic acid
RNP	ribonucleoprotein complexes (aka RNA granules)
ROS	reactive oxygen species
RS	Richardson's syndrome
SAA	serum amyloid A protein
sALS	sporadic amyotrophic lateral sclerosis
SBMA	spinobulbar muscular atrophy
SCA	spinocerebellar ataxia/atrophy
SCD	spinocerebellar degeneration
sCJD	sporadic Creutzfeldt–Jakob disease

SCNA	α-synuclein gene
SD	spongiform degeneration, semantic dementia
SDS	Shy–Drager syndrome
SDT	senile dementia with tangles
Serpin	serine proteinase inhibitor
SERPINA	clade A serpin peptidase inhibitor
SETX	senataxin
SF	straight filaments
sFI	sporadic fatal insomnia
siRNA	small inhibitory ribonucleic acids
SMA	spinal muscular atrophy
SMN	survival motor neuron
SN	substantia nigra
SND	striatonigral degeneration
SNpc	substantia nigra pars compacta
SOD	superoxide dismutase
SOD1	copper/zinc superoxide dismutase
SORL1	sortilin-related receptor (gene)
SorLA	sortilin-related receptor (protein)
SP	senile plaque/substance P
SPECT	single photon emission computed tomography
SPECT rCBF	single photon emission computed tomography regional cerebral blood flow
ST	straight tubule
STN	subthalamic nucleus
Sup35	yeast suppressor 35
TARDBP	transactive response DNA binding protein gene
TBP	TATA binding protein
TCS	transcranial sonography
TDP-43	transactive response DNA binding protein with M_r 43 kDa
TF	transferrin (gene/protein)
TFG	tau-positive fine granule
TGF	transforming growth factor
TH	tyrosine hydroxylase
TNF-α	tumor necrosis factor α (protein)
TNK1	tyrosine kinase, non-receptor 1 (gene)
TTR	transthyrethin
TSE	transmissible spongiform encephalopathy, turbo-spin echo
TUNEL	terminal deoxynucleotidyl transferase dUTP nick end labeling
Ub	ubiquitin
ub-ir	ubiquitin-immunoreactive
UCH	ubiquitin carboxyl-terminal hydrolase
UMN	upper motor neuron
UPR	unfolded protein response
UPS	ubiquitin-proteasome system
UTR	untranslated region
V	valine
VAMP	vesicle-associated membrane protein
VAPB	vesicle-associated membrane protein
vCJD	variant Creutzfeldt–Jakob disease
VCP	valosin containing protein gene
VEGF	vascular endothelial growth factor
VEN	von Economo neurons
VH	visual hallucinations
VLDL	very low-density lipoprotein
VMAT2	vesicular monoamine transporter
VTA	ventral tegmental area
VV	valine/valine
WHO	World Health Organization

1 Introduction: Basic Mechanisms of Neurodegeneration

1 Introduction to Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders

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Introduction

Neurodegenerative diseases share the common property of neuronal loss of specific populations of neurons, encapsulating the concept of selective vulnerability. Neuronal loss in many of these conditions involves anatomically related functional systems, such as the extrapyramidal and pyramidal motor systems or the higher order association and limbic cortices. The particular system affected determines the clinical presentation; in fact, the distribution of the pathology is more predictive of the clinical presentation than the molecular nature of the pathology, as illustrated in tauopathies and frontotemporal degenerations. It remains one of the major unattained goals of modern research on the degenerative diseases to determine the molecular basis for selective vulnerability.

While much of the focus in research on neurodegeneration is directed to neurons, the role of glia in neurodegenerative disorders is also increasingly recognized [1]. Glia, especially astrocytes, display reactive changes as a part of virtually every neurodegenerative disorder. More recently, oligodendroglia and astrocytes have been implicated in fundamental abnormalities of multiple system atrophy [2] and several of the tauopathies [3].

The other glial cells that play a role in virtually all neurodegenerative disorders are microglia. Microglia are cells of the mononuclear phagocytic system that respond to virtually all forms of cellular injury. They are also the cells linked to neuroinflammation, a term used to refer to innate immune responses in the brain characterized by activated microglia, but sparse or no blood-borne leukocytes. Neuroinflammation has been studied most extensively in Alzheimer's disease (AD) [4] and Parkinson's disease (PD) [5], but is common to virtually all neurodegenerative disorders.

Molecular classification of neurodegenerative disorders

Most textbooks on neurodegenerative disorders have used a classification scheme based upon either the clinical syndromes or the anatomical distribution of pathology. In contrast, this book takes a different approach by using a classification based upon molecular mechanisms, rather than clinical or anatomical boundaries. Major advances in molecular genetics and the application of biochemical and immunocytochemical techniques to neurodegenerative disorders have generated this new approach. Throughout most of the current volume, diseases are clustered according to the proteins that accumulate within cells or in the extracellular compartments or according to a shared pathogenetic mechanism, such as trinucleotide repeats that are a feature of specific genetic disorders.

β-amyloid

The most common of the neurodegenerative disorders is AD, in which mutations in the amyloid precursor protein (*APP*) gene or genes related to APP metabolism strongly implicate amyloid in the pathogenesis of AD [6]. In addition to β-amyloid deposits, AD is also associated with neurofibrillary degeneration characterized by accumulation of aggregates of the microtubule-associated protein tau within vulnerable neurons. Although there may be some common factors in the pathogenesis of all amyloidoses, neurodegenerative disorders associated with accumulation of amyloids other than β-amyloid, such as familial British dementia (FBD), are discussed separately. Similarly, the primacy of prion protein in Creutzfeld–Jakob disease (CJD) warrants its consideration in the context of other transmissible spongiform encephalopathies rather than in association with the β-amyloidoses.

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Tau

In addition to AD, neurofibrillary pathology is present in a range of disorders. While previously considered a relatively non-specific response of neurons to diverse insults, this view has changed with the discovery that mutations in the tau gene (*MAPT*) cause frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17T) [7]. Disorders in which abnormalities in tau are considered to play a critical role in disease pathogenesis have been referred to as tauopathies [8]. This group of disorders includes both genetically determined and sporadic conditions, including FTDP-17T, Pick's disease, progressive supranuclear palsy, Guam Parkinson dementia complex, argyrophilic grain disease and others.

α-Synuclein

The second most common neurodegenerative disorder is PD, which has long been associated with Lewy bodies in vulnerable neurons. The discovery of mutations in the gene for α-synuclein (*SNCA*) in familial PD [9] and the later recognition that α-synuclein was the major structural component of Lewy bodies [10] raised α-synuclein to the level of a major class of diseases. Biochemical and structural alterations in α-synuclein have been detected in several disorders in addition to PD, including dementia with Lewy bodies, pure autonomic failure and multiple system atrophy.

Trinucleotide repeats

Huntington's disease (HD) is one of the most extensively studied hereditary neurodegenerative diseases. The discovery that the mutations in the gene encoding huntingtin (*HTT*) lead to expansion of a trinucleotide repeat, specifically CAG, in the coding region of *HTT* [11] revealed a common molecular mechanism for a group of disorders that are grouped in this book as the trinucleotide repeat diseases [12]. Not all trinucleotide repeat diseases are associated with CAG repeats and not all of the repeats are in the coding region of the gene. Moreover, the range of clinical and pathological phenotypes in trinucleotide repeat disorders is wide. Nevertheless, these disorders have a shared genetic signature that now warrants their current grouping. Future research may eventually disclose pathomechanisms that will provide a more rational basis for subclassification of these disorders.

Prions

A common theme for many of the degenerative disorders is the formation of abnormal conformers of normal cellular proteins that have an increased tendency to aggregate and to be transmissible from cell to cell [13]; the prion disorders are the archetypal example of conformational disorders. There are few differences between the pathogenic and normal cellular form of PrP besides conformation, yet this is sufficient to lead to a fulminant and invariably fatal neurodegeneration. Prion diseases, like many of the other neurodegenerative disorders, include sporadic and familial forms. Even the sporadic forms may have a genetic predisposition, specifically polymorphisms in the prion protein gene (*PRNP*) [14].

TDP-43 and FUS

Since the first edition of this book, major advances have been made in the discovery of common molecular mechanisms between frontotemporal lobar degenerations (FTLD) and motor neuron disease or amyotrophic lateral sclerosis (ALS) [15]. Specifically, the major protein that accumulates in the most common forms of FTLD and ALS is the RNA/DNA binding protein, TDP-43. Mutations in the gene for TDP-43 (*TARDBP*) cause some forms of familial ALS, while other genes are implicated in FTLD, such as the genes for progranulin (*GRN*) and valosin containing protein/p97 (*VCP*) [16]. In addition to FTLD and ALS, TDP-43 has also been detected in other disorders [17], where it appears to be a secondary disease process, not dissimilar to α-synuclein pathology (Lewy bodies) that can occur in the setting of a range of other disorders, especially AD [5]. Evidence that RNA/DNA binding proteins are fundamental to this group of disorders is derived from the study of another member of the protein family, i.e. FUS/TLS [18]. This protein is mutated in rare forms of familial motor neuron disease, and FUS protein accumulates in neuronal inclusions in rare forms of FTLD that are negative for TDP-43 pathology [19]. Interestingly, most cases of FTLD associated with inclusions enriched in intermediate filaments (neuronal intermediate filament inclusions disease – NIFID [20]) also have FUS pathology. These advances now provide a rational basis for grouping these disorders.

Shared mechanisms in neurodegenerative disorders

Despite their clinical and pathological diversity, many of the neurodegenerative disorders share certain fundamental disease processes, including oxidative stress and programmed cell death, as well as disorders of protein aggregation or protein degradation, or both. These topics are the focus of chapters in the first part of this book. Programmed cell death is an attractive mechanism to explain selective vulnerability of neuronal populations since most neurodegeneration is not associated with influx of blood-borne inflammatory cells, as is the case with other types of tissue damage, such as necrosis. The molecular pathways involved in activation of apoptosis fall in two categories – intrinsic and extrinsic. The extrinsic pathway is triggered by extracellular ligands and their cell surface receptors, while intrinsic pathways act through changes in mitochondrial permeability, thus linking mitochondria to both oxidative stress and cell death mechanisms. Mitochondria are one of the major sources of reactive oxygen species generated as byproducts of oxidative phosphorylation. Accumulation of reactive oxygen species and the cellular defenses against oxidative stress are implicated in a number of neurodegenerative disorders.

One consequence of cellular oxidative stress is post-translational modification (e.g. nitration) of proteins. These proteins take on abnormal properties that may lead to changes in their solubility and promote aggregation. Aggregation of abnormal conformers

of neuronal and glial proteins is increasingly recognized as a common mechanism of a number of neurodegenerative disorders, as noted for prion protein. The role of protein–protein interaction, protein aggregation and changes in structural properties suggests that abnormal conformation of proteins is critical to aggregation and inclusion formation. Accompanying protein aggregation and accumulation are usually evidence of aberration of the normal cellular mechanisms for protein degradation. In addition to the actions of cellular and extracellular proteinases, two major pathways exist for protein degradation that involves cellular organelles adapted for this purpose – lysosomes and proteasomes. Much current research in neurodegenerative disease is focused on the role of ubiquitin proteasomal system in basic cellular processes as well as in disease. Lysosomal pathways, particularly autophagy, may also be involved in a number of neurodegenerative disorders and interaction of the two processes is increasingly recognized.

In addition to these major disease mechanisms, Part 1 also includes an overview of recent advances in genetics, which underpins the molecular classification of disease that is the basis for the organization of the book. Chapter 7 is a review of some of the animal models most widely used to study human neurodegenerative diseases, particularly related to amyloid, tau and α-synuclein.

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2 Cell Death and Neurodegeneration

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Introduction

Neurodegenerative diseases (NDD) are characterized by progressive neurological dysfunction that is typically associated with neuron loss in selected areas of the nervous system. Given the limited neurogenic capacity of the adult nervous system, neuronal cell death marks an irreversible and catastrophic phase of the neurodegenerative process. Tremendous scientific effort has been focused on defining the cellular and molecular pathways regulating neuron death as this may lead to the discovery of novel therapeutic interventions that could halt or slow down NDD progression.

Definition

Three major morphological types of cell death have been described in NDD: apoptotic, necrotic and autophagic [1]. *Apoptosis* is characterized by chromatin condensation, nuclear fragmentation, and cytoplasmic blebbing [2]. Apoptosis has been implicated in many NDD and is the most extensively investigated form of cell death in the nervous system [1]. *Necrotic cell death* is characterized by cell and organelle swelling or rupture of cell membranes accompanied by spillage of intracellular contents [3]. Necrosis is usually considered to be an accidental (i.e. non-programmed) form of cell death and is commonly observed after trauma or infection [4]. However, necrosis has also been reported in Parkinson's (PD), Alzheimer's (AD), and Huntington's (HD) diseases, and in amyotrophic lateral sclerosis [5]. The molecular mechanisms that initiate necrotic cell death in NDD are not well understood, but may include excitotoxicity, intracellular Ca^{2+} increase, and ATP depletion [6]. *Autophagic cell death* is characterized by accumulation of autophagic vacuoles (AVs) concomitant with markers of apoptosis or necrosis [7]. There is a growing awareness of a possible role for autophagic cell death in NDD. Most recently, research has focused on understanding the interplay between these death pathways, particularly between apoptosis and autophagy.

Apoptosis in neurodegenerative diseases

Apoptosis is a highly regulated process that can be activated by receptor-mediated (extrinsic) or mitochondria-mediated (intrinsic) pathways that converge at cleavage-dependent activation of aspartate-specific effector caspases (caspases-3, 6, and 7). Once activated, effector caspases cleave many cellular components, leading to degradation of DNA and cytoskeletal proteins and causing nuclear fragmentation, degradation of subcellular components, and collapse of the cytoskeleton (Fig. 2.1A). Apoptosis allows a cell to die without affecting the viability of neighboring cells and tissues [8].

Loss of selective neuronal cell populations is a feature of most NDD; therefore, the possibility of apoptosis-associated molecules and processes being responsible for NDD pathogenesis has received significant attention. Implication of apoptosis as a general cell death mechanism in NDD has largely been supported by evidence from animal models and tissue culture studies, while investigations on human postmortem brain have yielded conflicting results [9]. However, identifying apoptotic neuron death in autopsied human brain can be difficult since neurodegenerative processes represent chronic brain demise, while apoptotic cell death can be executed within a few hours [10]. Nevertheless, elevated levels of protein and mRNA of several caspases were found in postmortem AD brains [9]. Caspases-3 and -6 have also been implicated in the generation of cleavage-mediated toxic species of amyloid precursor protein and AD pathology [11,12], and elevated levels of activated caspases-3 and -6 have been detected in neurites of AD patients where they co-localize with

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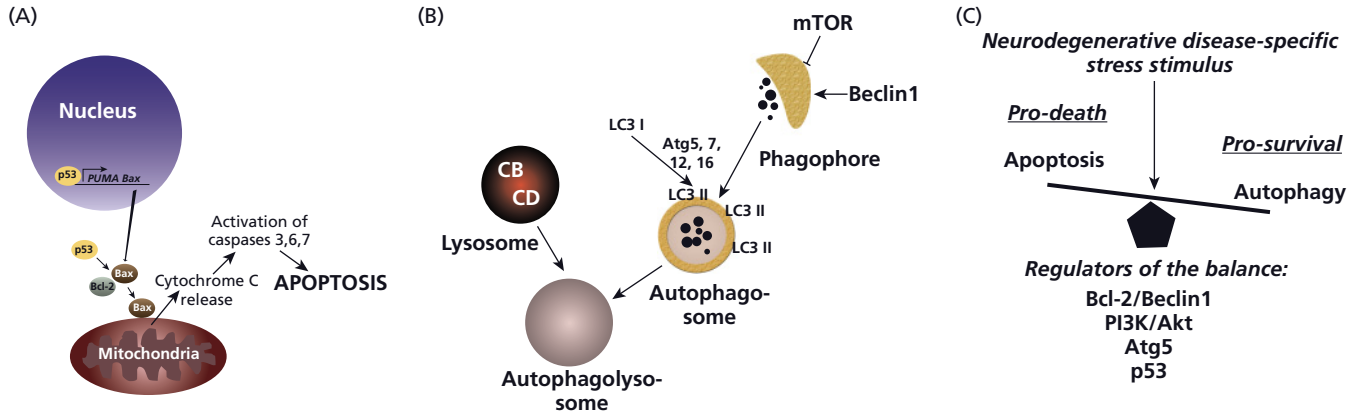

Figure 2.1 Balance between apoptosis and the autophagy-lysosomal pathway dictates the fate of neurons affected by neurodegenerative disease-specific stress stimuli. Proapoptotic proteins such as p53 can initiate apoptosis either by directly affecting mitochondrial membrane permeability and cytochrome C release or by inducing transcription of other proapoptotic proteins (A). The autophagy-lysosomal pathway (ALP) supplies neurons with energy and metabolic building blocks by recycling outlived or damaged organelles and protein aggregates (B). Therefore, the ALP is thought to serve a prosurvival function under stressful conditions. However, a number of proapoptotic regulators can jeopardize the integrity of the ALP and tip the balance towards cellular demise (C). CB, Cathepsin B; CD, Cathepsin D.

protein aggregates [13,14]. A proapoptotic member of the Bcl-2 family of proteins, Bax, has been implicated in apoptosis induction and disease progression in HD and PD [9]. However, it is still not known if neurological dysfunction observed in NDD such as AD, PD, and HD is a direct consequence of apoptotic neuron death or of neuronal dysfunction occurring prior to frank neuron loss.

Regulation of cell death and survival by the autophagy-lysosomal pathway

Many NDD are accompanied by accumulation of protein aggregates [15]. These diseases are collectively termed proteinopathies [16]. This group includes PD, HD, and AD in which protein aggregates are primarily cytosolic and/or extracellular. Protein aggregates are thought to be formed as a result of toxic gain of function mutations or modifications. It is debated whether soluble monomeric aggregation-prone proteins, their oligomers or larger aggregates are most toxic [17]. However, in general, the protein's capacity to aggregate correlates with its toxicity (although not necessarily with the aggregates themselves). Two main systems are responsible for clearance of proteins in cells: the ubiquitin-proteasome system (UPS) (see Chapter 5) and the autophagy-lysosomal pathway (ALP) [18].

The principal function of the ALP is to regulate intracellular energy balance by recycling outlived and/or damaged cellular components such as protein complexes and organelles. Three major types of autophagy have been defined: macro-autophagy (hereafter simply referred to as "autophagy"), micro-autophagy, and chaperone-mediated autophagy. Autophagy is initiated by generation of a double-membrane phagophore, which surrounds the cellular components targeted for degradation, forming an AV [19]. Autophagy initiation is regulated in part by the activation of mammalian target of rapamycin (mTOR) which inhibits autophagy input by affecting interactions between autophagy-associated proteins (Atgs) regulating AV formation [20]. For autophagy to be completed, the cargo of AVs has to be degraded and this is achieved by fusion of AVs with lysosomes (Fig. 2.1B) [20].

Increasing evidence indicates that autophagy plays a critical role in protein aggregate clearance and regulation of neuron death in a number of NDD [21]. Although many proteins associated with proteinopathies (such as α-synuclein and huntingtin) are partially dependent on the UPS for their clearance, autophagy becomes the route of degradation for aggregate-prone proteins, their oligomers and aggregates that cannot be efficiently cleared by the proteasome. The dependence of proteins on autophagy for their clearance correlates with their propensity to aggregate [22,23]. For instance, inhibition of autophagy has a much smaller effect on the clearance of wild-type huntingtin exon 1 fragment or wild-type α-synuclein than on the clearance of the mutant aggregate-prone species [22,23].

The pivotal role of autophagy in clearance of aggregate-prone proteins and their aggregates is further supported by studies in mice lacking neuronal expression of *Atg5* or *Atg7*, genes responsible for AV formation and initiation of autophagy. These mice die as young adults and show striking neurodegenerative and neurological phenotypes, including accumulation of protein aggregates that increase in size and number with age, and neuron loss in cerebrum and cerebellum [24,25]. Chronic metabolic insufficiency, such as that induced by the mitochondrial inhibitor rotenone, has also been shown to cause a decline in ALP activity and its ability to degrade aggregated protein species [26]. Therefore, accumulation of aggregated proteins in NDD can also be explained by a decreased ability of neurons undergoing metabolic stress, as was reported in some PD models, to induce autophagy sufficient to clear these protein inclusions [9].

Inhibition of autophagy

Inhibition of autophagy completion resulting from altered lysosomal function has also been associated with neurodegeneration [27]. For instance, deficiency in cathepsin D, an aspartic lysosomal protease, leads to extensive neuron death and is accompanied by accumulation of autophagosome/autolysosome-like bodies containing ceroid lipofuscin [28]. Mice with combined deficiency of cathepsins B and L, lysosomal cysteine proteases, die during the first 4 weeks of life; these animals manifest massive cell death of selected neurons in the cerebral cortex and cerebellum. Neurodegeneration is accompanied by accumulation of lysosomal bodies and by axonal enlargements, indicators of impaired degradation capacity of the ALP in these mice [27].

Discovery of a mutation in the *ATP13A2* gene encoding a lysosome protein causing familial early-onset PD further highlights the importance of the ALP in NDD. *ATP13A2* encodes a lysosomal ATPase, a group of proteins involved in the maintenance of the acidic environment of the lysosomal lumen, which is crucial for proper functioning of lysosomal proteases [29]. Interestingly, elevated levels of *ATP13A2* expression have also been detected in the brains of sporadic PD patients, suggesting a potential role for this protein and proper lysosomal functioning in idiopathic PD [29]. Furthermore, lysosomal function has been shown to decline with age in the human brain and thus, diminished autophagy completion may contribute to age-related NDD [30].

A prosurvival or prodeath role for autophagy

Although accumulation of AVs has been observed in affected neurons in a number of NDD such as PD and AD and numerous models of these diseases, there is ongoing debate as to whether autophagy plays a prosurvival or prodeath role in NDD [21]. Indeed, autophagy is best known for its homeostatic role in mediating bulk degradation of cytoplasm and organelles and degradation of aggregate-prone proteins and damaged organelles, such as mitochondria. These findings are often used to support the argument that autophagy has a prosurvival function [9]. However, autophagy, as a cleansing and recycling mechanism, can only be effective if lysosomal degradation of AVs is accomplished [27]. Therefore, a combination of factors that impair AV formation and degradation or overactivate AV formation relative to the degradative reserve of the cell can lead to "cell death with autophagy" which some investigators argue may be a more precise term than autophagic cell death [31].

Co-ordination between apoptosis and autophagy

Based on our growing awareness of multiple prosurvival and prodeath pathways, it seems likely that a single death pathway may not be solely responsible for neuron loss in the context of NDD (Fig. 2.1C). Instead, multiple prosurvival and cell death mechanisms may interact to determine neuron fate [9]. Also, inhibition of one pathway of cell death may not prevent neuron loss but instead, may recruit alternative death mechanisms, e.g. inhibition of caspase activation may prevent apoptosis but stimulate autophagic or necrotic cell death [32]. Therefore, increased research interest is aimed at determining the interactions between apoptotic and autophagic death pathways.

There is a growing list of apoptosis regulators interacting with autophagic machinery. For instance, Beclin1/Atg6, a protein involved in regulation of AV formation and autophagy induction, has a Bcl-2 homology domain (BH-3-domain) and has been shown to interact with prosurvival members of the Bcl-2 family of proteins. Bcl-2 and Bcl-X_L can bind to Beclin1, preventing it from interacting with the complexes involved in AV formation, and in turn inhibit autophagy [33]. Therefore, the ratio of Bcl-2 to Beclin1 is an important determinant of whether a cell will activate the prosurvival autophagic pathway and/or a death-inducing apoptotic program.

Pathways regulating induction of autophagy can also activate pathways that affect apoptosis. For instance, PI3K/Akt-mediated phosphorylation of Bad, a BH3-only member of the Bcl-2 family, leads to its dissociation from Bcl-2, thus allowing Bcl-2 to sequester proapoptotic Bcl-2 family proteins such as Bax and prevent them from inducing apoptosis. Akt also antagonizes the transcriptional activity of a number of proapoptotic transcription factors, such as p53, which results in inhibition of proapoptotic gene expression and promotion of cell survival [32]. Atg5, involved in AV formation and LC3I to LC3II conversion, can also influence apoptotic signaling pathways. Atg5 can be cleaved following various apoptotic stimuli, forming an N-terminal product that translocates to the mitochondrial membrane, interacts with Bcl-X_L, and promotes apoptosis. At the same time, Atg5 cleavage leads to autophagy inhibition, as a pool of available Atg5 necessary for AV formation is decreased [32,34].

Recently, p53, a well-studied regulator of neuron apoptosis, was reported to also modulate autophagy [35]. Interestingly, the effects of p53 on autophagy appear to be dependent on its intracellular localization. Nuclear p53 can stimulate autophagy by inducing transcription of damage-regulated autophagy modulator (DRAM), a novel protein believed to localize to the lysosomal membrane, or by inhibiting mTOR activity [35,36]. On the other hand, cytoplasmic p53 was shown to inhibit autophagy induction by activating mTOR [35]. A number of studies have reported elevated protein and mRNA levels of p53 in postmortem NDD brain tissue and in a number of PD and AD animal and cell culture models, suggesting that p53 may be involved in regulation of neuron loss in these pathologies [37,38].

Future directions

The tremendous scientific interest in apoptotic and autophagic cell death mechanisms and their involvement in NDD has produced significant advances in our understanding of the cellular and molecular processes controlling neuron life and death. Despite the fact that numerous questions remain about the precise role of these pathways in human NDD, there is no disputing that a dead neuron is a dysfunctional neuron. Future

investigations are necessary to devise strategies for restoring function to injured neurons before they become committed to death, regardless of the death pathway(s) being activated.

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3 Oxidative Stress and Balance in Neurodegenerative Diseases

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Definition

Oxidative damage is a major feature of the cytopathology of a number of chronic neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease. The original concept of oxidative stress promoted by Denham Harmon has been used to indicate an excess of oxygen free radicals that breach oxidant defenses with consequent detriment. By this definition, detection of damage resulting from reactive oxygen species is indicative of oxidative stress [1,2]. Reactive oxygen species are a by-product of cellular oxidative metabolism and are generated in the mitochondria during oxidative phosphorylation with production of molecules with unpaired electrons such as superoxide ($O_2^{\cdot}$).

Superoxide is a short-lived molecule that is reduced by the family of superoxide dismutases (SODs) to generate hydrogen peroxide (H_2O_2). Reduction of H_2O_2, for example through the action of redox-active cations such as iron and copper, generates a hydroxyl radical (•OH), which can oxidize proteins, lipids, and nucleic acids.

Nitric oxide is another short-lived species with limited toxicity that is produced by a family of nitric oxide synthases. After interaction with superoxide, nitric oxide forms peroxynitrite (ONOO-), which is another powerful reactive species that can lead to damage of cellular macromolecules through nitration or generation of additional free radicals. Cells have evolved an elaborate array of antioxidant defenses, including SOD, glutathione reductase and catalase (Figure 3.1).

Detection of cellular oxidative damage

Cellular oxidative damage can be detected in a variety of ways. Widely used markers of oxidative damage to lipids include 4-hydroxynonenal and isoprostanes, to nucleic acids include 8-hydroxy-2'-deoxyguanosine, and to proteins include nitration and glycation [3]. Indirect evidence of cellular oxidative stress is increased expression of molecules involved in oxidant defense, such as heme oxygenases, SODs, glutathione transferases, catalase, and glucose-6-phosphate dehydrogenase. It is important to note that neurons displaying signs of oxidative stress are not necessarily succumbing to oxidative stress, but may be adapting by way of oxidant defenses. These findings suggest that neurodegenerative disorders where oxidative stress is postulated to play a role, such as Parkinson's disease and AD, are associated with mechanisms that maintain a balance between oxidative stress and adaptation to this stress, reflecting the ability of living systems to dynamically regulate their defense mechanisms in response to oxidants. Therefore, mere evidence of oxidative damage does not necessarily indicate cell death by way of oxidative stress, given that the cell may have successfully increased endogenous cellular defenses sufficiently to compensate for the increased flux of reactive oxygen responsible for the damage. It does, however, indicate that the normal balance between the production and defense reduction of oxidative stress has been challenged.

Consequences and mechanisms of cellular oxidative damage

Evidence suggests that cells that fail to compensate for oxidative stress enter apoptosis, which in turn leads to death within hours [4,5]. This is particularly germane to the discussion of degenerative diseases that have a course of years. Those cells experiencing increased oxidative damage, by their continued existence, testify to their increased compensatory response to reactive oxygen.

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