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# 1 Introduction: Basic Mechanisms of Neurodegeneration

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# 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.

### $\beta$ -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  $\beta$ -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  $\beta$ -amyloid, such as familial British dementia (FBD), are discussed separately. Similarly, the primacy of prion protein in Creutzfeldt–Jakob disease (CJD) warrants its consideration in the context of other transmissible spongiform encephalopathies rather than in association with the  $\beta$ -amyloidoses.

## 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.

## $\alpha$ -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  $\alpha$ -synuclein (*SNCA*) in familial PD [9] and the later recognition that  $\alpha$ -synuclein was the major structural component of Lewy bodies [10] raised  $\alpha$ -synuclein to the level of a major class of diseases. Biochemical and structural alterations in  $\alpha$ -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  $\alpha$ -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  $\alpha$ -synuclein.

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