

## General Concepts of Neurodegeneration as Specificity of Mitochondrial Pathobiology of Neurons

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### Abstract

Dimensions of inclusion within the overall concept of neurodegeneration would appear to arise as inherent consequences of the high metabolic rates of neuronal patho-physiology that dimensionally characterizes the sub-set neuronal populations. It is valid to consider the essential neurodegenerative state as a highly inclusive pathobiologic state of response to neuronal injury that elicits multiple pathways of apoptosis.

It is within the spectral manifestations for further heightened susceptibility that disorders such as Alzheimer's, Parkinson's, Huntington's and also other disorders of the CNS would include also specific manifestations within the further contrasting specificities of disease states such as amyotrophic lateral sclerosis.

Hence, it is beyond specificity issues that the neurodegenerative state projects the overall dimensions of a generic cell injury within the strict confines of highly selective sub-type neuronal pathobiology in terms of the essential progressive manifestations of cell loss.

### Introduction

Age-related progression of neurodegenerative states is associated with the accumulation of mutant protein species in brain regions, including the development of intra-neuronal inclusion bodies within the nucleus and/or cytoplasm [1]. A combination of ATP and an excess of produced reactive oxygen species (ROS) has been proposed as central core phenomena leading to both inherited and sporadic forms of neurodegeneration; this would occur in a manner that would account for the wide range of phenotypic expression of such neurodegenerative multiple process. Neuronal hyper-excitability due to toxic effect exerted by astrocytes in patients with amyotrophic lateral sclerosis may enhance calcium influx and affect mitochondrial structure and physiology; ROS promote c-Abl signaling and thus induced apoptosis [2]. Mitochondrial dynamics, such as their architecture and connectivity through tethering and fusion/fission, besides movement along the cytoskeleton, may cause neurodegeneration; two mitochondrial fusion genes promote the development of Charcot-Marie Tooth type 2A and autosomal dominant optic atrophy [3]. Neurodegenerative states can arise particularly in cases of mutation in key members of the fission/fusion mechanistic pathways.

Mutations of glucocerebrosidase are regarded the most important genetic vulnerability factor for Parkinson's disease, with reduced enzyme activity increasing alpha-synuclein toxicity [4]. In such scenario, there appears to arise a variability of disease expression linked intimately to heteroplasmy, threshold effect and spectrum of both mitochondrial and nuclear mutations and deletions. [5]. Mutated PINK1 and PARK2/Parkin are implicated in familial Parkinson's disease and serve as a centrally operative trigger mechanism for autophagy of depolarized mitochondria [6]. Also, mitochondrial

protein deacetylation status enhances neuroprotection in bioenergetic, oxidative and excitatory stress [7].

### Potential for cellular interactions

There appears to arise a complex inter-potentiality that is crucial to the pathogenic effects of ATP depletion on the one hand and of excess ROS that is derived also from the variable degrees of dependence of various groups of neurons on oxygen demand. The innate immune response and inflammation are implicated in neurodegenerative states [8]. The B-cell lymphoma-2 protein family determines integrity of mitochondria in the setting of apoptotic insult [9]. Dysfunctional states are indeed the essential precursors of neurodegenerative disorders that account for the dementia, decreased cognition and the relentless demise of various subsets of neurons.

These neuronal subsets are specifically localized in highly restricted sites within the central nervous system, as evidenced in Alzheimer disease and Parkinson's disease; mitochondria are central to the pathogenesis of many neurodegenerative disorders [10]. A mechanistic connection appears to exist between extracellular beta-amyloid deposition and phosphorylation, missorting and aggregation of intracellular protein Tau in Alzheimer disease [11]. Ceramides may induce depolarization and increased permeability of mitochondria, increased production of ROS, cytochrome c release, Bcl-2 depletion and caspase-3 activation by modulating intracellular signaling of Akt/PKB and of mitogen-activated protein kinases [12].

Indeed, the progression of neurodegenerative disorders is a result of a panoramic range of insults that arise especially within scenarios of specific and non-specific targeting of various mutant proteins to the mitochondria. Multiple mitochondrial diseases are associated with ROS-induced injuries; thus, enhanced inducible nitric oxide synthase

and nitric oxide production, decreased respiratory complex activity, impaired electron transport and opening of the permeability transition pores are implicated in mitochondrial dysfunction [13]. In various ways, the inherent biology of mitochondrial metabolic pathways accounts for the exhibited dimensions of insult that are translated as excess release of a wide variety of highly apoptogenic molecules from this organelle form. Hypoxia promotes hippocampal neurodegeneration and impaired memory [14].

### Unitary projections

Dimensions of sporadic neurodegenerative states arise as a possibly unitary series of sequential steps that bear out the spectral manifestations of neuronal injury that is essentially progressive. Oxidative stress is associated with mitochondrial dysfunction in aging and neurodegeneration; mitochondria are responsible for the generation of ROS and are also their main target [15]. Alzheimer disease is related to early deficits in regional glucose uptake in the brain, regional brain atrophy and oxidative stress [16]; following a metabolic insult, neurons conserve energy with activation of mitophagy/autophagy and fusion/fission. Prolonged fission leads to mitochondrial degradation and protein release [17]. ROS are an integral scenario of the mitochondrial electron transport mechanisms that impair in essential manner the respiratory activity of specific subtypes of neuronal groups that morphologically and metabolically are highly distinctive. Glutamate and mitochondria are important in oxidative stress underlying neurodegeneration [18]. Peroxisomal and mitochondrial dysfunction is intertwined through redox modulation, and together with defective proteostasis are principal pathogenic mechanisms in Alzheimer's and Parkinson's disease [19].

Neuronal demise is an essential dysfunctionality of various, highly individualized forms of instability states that especially implicate depletive energy supply to neurons. The gradual morphologic degeneration of mitochondria within endothelial cells, pericytes and perivascular astrocytic processes can be seen electron-microscopically in Alzheimer disease [20].

Mitophagy is central to mitochondrial quality control, and is involved in the activated cellular stress response, including aging and neurodegeneration [21]; ubiquitin-ligation plays a major role in mitophagy, particularly when mediated by PINK1 and PARK2/Parkin [22].

MicroRNAs modified by mitochondria are likely to contribute to post-transcription regulation of gene expression related to mitochondrial functions [23]. The release of highly apoptogenic molecules from mitochondria attest to the evolutionary history of progressive injury to neurons, and mitochondrial homeostasis is fundamental to qualitative cellular parameter control [24]. The highly selective targeting of various subsets of neurons in mitochondrial disease in general accounts for the projected dimensions of a dualism of energy crisis and of the general array of apoptogenic molecules that, in an overall manner, are respiratory-insufficiency mediated. An interactive series of links exists between Parkinson's disease genes involved in mitochondrial function and neuroinflammation [25].

Synaptosomal bioenergetic defects appear related to early Alzheimer disease [26]. Loss of nicotinamide adenine dinucleotide affects multiple metabolic pathways, targeting the electron transport chain and ATP production [27]. The activity of poly (ADP-ribose) polymerase1 increases under conditions of oxidative stress and leads to

the accumulation of ADP-ribose polymers and NAD (+) depletion, leading to induced energy crisis [28].

### Selectivity of neurodegeneration

The selectivity of mitochondrial neurodegeneration pathways allows for the primary variability in expression of a dynamic threshold series of effects as those resulting from susceptibility of genes when neurons are exposed to environmental toxins such as MPTP in parkinsonism. Histone deacetylases are emerging drug targets in neurodegeneration [29].

The overall phenomena of neuronal cell death pathways are vast arrays of molecularly induced processes of accumulation and depletion that arise within system biology of mitochondrial pathophysiology. Programmed cell death is implicated in aging-associated mitochondrial dysfunction and neurodegeneration [30]. Deficits of respiratory enzymes, reduced calcium influx, mitochondrial DNA defects and apoptotic proteins, and impaired mitochondrial membrane potential promote severe energy deficit, with pro-neurodegeneration progression in the aging brain [31]. The resulting neuronal cell loss also arises as mitochondria-related secondary end-results that further enhance the instances of primary mitochondrial DNA mutations, deletions and depletions, as seen in classical mitochondrial diseases of multi-systemic states of disease. Excitotoxicity is mediated by activated glutamate receptors with increased  $Ca^{2+}$  influx and mitochondrial  $Ca^{2+}$  overload [32].

### ATP depletion and ROS

Particularly relevant is the depletion of ATP that is linked to a budding and dynamic turnover of mitochondria that in turn is inherent to the mobility, fusion and fission processes of organelle functionality and dysfunctionality.

Increasing evidence links mitochondrial dysfunction arising from inherited mitochondrial DNA load or mitochondrial proteomic deficit, to Parkinson's disease [33]. The mobility of mitochondria is especially evidenced in neural and axonal pathways in the distal portions of the axon that pre-synaptically depend on large amounts of metabolic energy provision central to ion fluxes in neurotransmission across synapses.

Significant is the heteroplasmy of mitochondrial DNA that strictly characterizes the various percent constitution of mutated and wild-type DNA within organs, tissues and especially within the single cell. Neurons constitute a highly susceptible target for such heteroplasmy of mitochondrial DNA in view especially of the acute dependence of such cell-type on provision of constantly evolving oxygen supplies. Abnormal mitochondrial dynamics and quality control underlie dysfunction in the pathogenesis of Parkinson's disease [34].

HIV proteins released from infected cells induce neuro-cognitive disorders possibly by altering mitochondrial fission/fusion in neurons [35].

### Target multi-specificity

A multiplicity of targets of injury in mitochondria-linked neurodegenerative states is a core state of involvement that ranges from neuronal injury to the evolving damage to skeletal myofibers and the peripheral neuropathy. Peroxisome proliferator-activated receptors regulate inflammation and multiple other pathways, inducing neurodegeneration [36]. Such pathways of involvement are reinforced

by the inherent patterns of neuronal axonal tracts that constitute the CNS. Enhancement of mitochondrial oxidative phosphorylation via alternative mitochondrial electron transfer may protect against neurodegeneration [37]. Performance phenomena of instability therefore are a result of determined performance of emerging dysequilibrium as evidenced by cortical neurons and as further proposed by such systems as the spino-cerebellar tracts and the spinal axonal pathways in both sensory and motor systems. Activated microglia secrete pro-inflammatory and neurotoxic factors including Tumor Necrosis Factor alpha and thus initiate apoptosis and neurodegeneration [38]. Both TNF-induced oxidative stress and inflammation interact to promote neurodegeneration by inducing the activation of ROS- and nitrogen species-producing enzymes [39].

### Neuro-transmission

The involvement of maternal transmission of mitochondrial DNA mutations in the ovum is a fundamental phenomenon of manifestations that range from hereditary modes of expression and also sporadic neurodegenerative states that promote a segregation series of patterns for further progression that result also in male affliction.

### Inclusive dimensions

Dimensions of inclusivity for further DNA damage is an expression of a range of dynamic performance in metabolic processing that allows for electron leakage from the respiratory electron transfer pathways centered within the mitochondrial sub-compartments of neurons. Cytochrome c released from mitochondria is often detected after acute or chronic insults involving neurodegeneration and including Alzheimer disease [40]. The exclusive manifestations of neurodegeneration within the essential nervous system belies a multi-system involvement that classically affects the endocrine organs and renal tubules as specified by the ubiquitous participation of mitochondria in terms of system biology of these organelles.

Specificity in dimensional manifestations includes the release of highly apoptogenic molecules that implicate mitochondria as central hub in the constitutional dysfunctionality in actively programmed cell death. Glycation with the production of advanced glycation end products is implicated in cases of neurodegeneration such as Alzheimer's disease [41]. Derivative consequences of the intrinsic pathways of apoptosis lead to the further participation of such pathways with many molecular systems of effective consequence as evidenced by high degrees of susceptibility of neuronal sub-sets to specific environmental toxins. Microglia has recently been recognized as ROS producers in tauopathies, involving with tau hyperphosphorylation a vicious circle central to neurodegeneration [42].

### Parameters of consequence

Parameters of consequence are progressive in a manner inherently arising from the natural history of apoptogenic stimuli. Loss of receptivity of neurons is a cardinal manifestation of neuronal pathobiology in terms of sequential promotion of the neuronal injury. In an essential manner, the specific subsets of neurons are manifestations of the progressiveness of the cellular injury, on the one hand, and for specificity of the neuronal involvement that participates in highly permissive manner in the paradoxical parametric manifestations of neurodegenerative states. Methionine metabolism is

linked to mitochondrial defects in respiration and may have important implications in neurodegeneration in multiple sclerosis patients [43].

The further promotional dimensions of neurodegeneration are inherently sporadic within the further scenarios of inherited disorders that enhance the overall characterization of disease states ranging from Alzheimer disease to Parkinson's and to Huntington's disease and amyotrophic lateral sclerosis. It is inherent consequence of neuronal cell loss that the dimensions for promotional recruitment for further subsets of neurons progress as evidenced by the downhill clinical course of neurodegenerative states. Both endoplasmic reticulum-mitochondria stress and protein conformational disorders interplay as a common mechanism in various neurodegenerative conditions [44].

### Dynamics of progression

It is important to consider the overall dynamics of progression of neuronal pathobiology as central core pathogenesis in neurodegeneration. There is uncoupling of expression of mitochondria-related genes in Alzheimer disease [45]. This arises from the active participation of various toxic gains of function as evidenced by various aspects of superoxide dismutase over-expression in some familial forms of amyotrophic lateral sclerosis. Inflammation regulates Bax expression that subsequently contributes to neurodegeneration of nigrostriatal dopaminergic neurons [46]. The over-activity of many neuronal sub-sets in various patho-physiologic states is shown especially in terms of mitochondrial pathobiologies as portrayed by the relentless course of neurodegenerative states in general.

Disruptions in lipid homeostasis (synthesis and degradation) appear implicated in the development of some cases of Parkinson's disease [47].

The question of specific patho-physiologic states appears paradoxically stable manifestations in such disease progression, regardless of the essential dynamics of neuronal metabolic and respiratory electron exchange. Mitochondrial deregulation leads to metabolic reprogramming as an initial step to maintain neuronal integrity in Alzheimer disease, thus providing a link between aging and sporadic Alzheimer disease [48]. It is within scenarios for further self-promotion of neuronal injury that a core pathway effect arises as system pathology of exclusive neuronal pathobiology without significant threshold variability in terms of systemic manifestations. Lack of cytokine interferon-beta signaling leads to spontaneous neurodegeneration in the absence of neurodegenerative disease-inducing mutant proteins [49].

### Neuronal toxicity

Toxicity of neurons emerges as central form of affliction in neurodegeneration that is inherent as neuronal spectra for lowered threshold effects and that are further promoted in terms of the significant participation of ATP depletion within scenarios of ROS over-generation.

### Conclusion

The overall characterizations of neuronal injury allow for paradoxical permissiveness in susceptibility of neuronal subsets within the specific scenarios of proposed strict homeostasis that have evolved and allowed for neuronal specialization leading to essential sub-set pathophysiology. The pathogenesis of dimensional spread of pathogenic molecular pathways is evidenced in the multiplicity of

apoptogenic pathways of recruitment of specific sub-sets of neurons as specific pathobiology.

The detailed portrayal of neurodegeneration as re-capitulation of the system cell biology of mitochondria strictly characterizes the nature and also mutability of the essential neurodegenerative state.

The highly variable manifestations of many states of neurodegeneration may not be classifiable in terms of classic forms for such pathobiology but paradoxically allow for flux promotion of neurodegenerative states as substrates for further progression. Permissive mutability is evidenced by high rate and metabolic repertoire of individual neurons within systems of sub-set diversity of response to neuronal injury, as further indicated by variable cell receptivity.

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