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Primary lesion Multifocality and Dopaminergic Neuronal Cell Loss Involve Interacting Synaptic and Pre-Synaptic Disconnectivity Systems in Idiopathic Parkinson's disease

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Abstract

Dynamics of synaptic and pre-synaptic disconnectivity account for cellular injury linking neuroinflammation and oxidative stress to Lewy body inclusions and neuritic degeneration in dopaminergic and cortical neurons. The multistage pathologic lesion is evidenced by the multi-system manifestations seen clinically and the pathogenic factors that further support disease progression. Indeed, further to ongoing dopaminergic neuronal cell loss is the strict reactivity of microglia and astrocytes that provokes multi-dimensional spread as attested by the Braak staging system. In this sense, Idiopathic Parkinson's disease is a system pathway involvement that further progresses beyond simple neuronal cell loss in the substantia nigra zona compacta, Many pathogenic agonists such as mitochondrially induced oxidative stress and resulting neuroinflammatory pathways of induced injury secondarily reflect the formation of Lewy body inclusions. Mechanistic inter-dependence of integral synaptic and pre-synaptic disconnectivities allow for the sequestration of alpha-synuclein as intracellular inclusions and as agonist systems in their own right.

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Introduction

Classical loss of neurons in the substantia nigra, with accumulation of extracellular neuromelanin, is associated with intracellular crowding by Lewy bodies in many forms of Parkinsonism, particularly in the idiopathic, late-onset type of Parkinson's disease. Age is the number one risk in Parkinson's disease [1]. The various different genetic modulating agonists attest to mechanistic modes of pathogenesis linked especially to neuroinflammation and mitochondrial pathobiology. Particularly significant is overexpression of FAS-associated factor 1 and poly (ADP-ribose) polymerase 1 that acts as an axial system in death of dopaminergic neurons [2]. Astrocytes and microglia are implicated in the onset and progression dynamics of Parkinson's disease in terms of oxidative stress and reactive gliosis. Endoplasmic reticulum stress integrally contributes to disease pathophysiology [3].

Agonist Systems

A highly intriguing aspect of parkinsonism is the great variety of agonists implicated in death of dopaminergic neurons, including genetic factors that particularly target Complex I of the respiratory enzyme chain in mitochondria. Exosomes released from many biotypes

induce RNA uptake by neurons and subsequent modulation of target genes and repression of protein translation [4]. Specific kinetics of disease processes converge on the proteasome degradation pathway, thus linking pathophysiology of dopaminergic cell death with an acute accumulation of catabolic intermediates including metals such as free iron.

Operative Pathogenesis

Alpha-synuclein inclusions reflect faithfully the Braak staging progression of neuronal cell death that extends rostrally from the brain stem and potentially to various regions in the cortex. Lewy bodies consist mainly of presynaptic alpha-synuclein and ubiquitin with their subsequent aggregation [5]. Especially significant is the accumulation of Lewy bodies within neurites in dementia of Lewy body type that is linked to clinical dynamics of cognitive loss.

Environmental factors

Environmental conditioning of dopaminergic neurons is essential in terms of oxidative stress injury to neurons in general, and determine the relentless progression beyond the initial loss of neurons in the substantia nigra. Differential changes in selenotranscriptome are observed in different brain regions depending on critical profiling of selenoproteins [6]. Prefibrillar species of alpha-synuclein, rather than the deposits themselves, are toxic and may act as seeds to propagate disease between interconnected brain regions [7]. Genetic mutations and non-Mendelian factors such as polymorphisms in promoter regions of related pathogenic genes prove an essential spectrum of severity involving dopaminergic neuron cell death pathways. Pathways of mitochondrial dysregulation with reduced complex I activity, reactive oxygen species-induced DNA damage, bioenergetic failure and abnormal mitochondrial mitophagy and dynamics are implicated [8].

Neuromelanin quinone is itself an oxidation product of dopaminergic neuronal metabolism and exhibits similar features to an apoptotic loss of neurons. In this regard, it is particularly neuroinflammation that has been linked to parkinsonism in the post-encephalitic forms of the clinical disease spectrum.

Microglia

Microglial reactivity plays a central role in disease pathogenesis and includes subsequent gliosis. There is an association of a tauopathy in Parkinson's disease with other disease pathways such as those in Alzheimer's disease and dementia of Lewy body type. Chronic mild stress is implicated in neuroinflammatory disorders in Parkinson's disease [9]. The frequent spectral accumulation of lesions in Parkinson's disease seen clinically and pathologically indicates multi-system progression that spans various motor pathways, focal thalamic regions and multiple regions of the striatum, globus pallidus and subthalamic nucleus. Amyloid beta (molecular portion 25-35) results in intracellular nitrosative stress and chemical mutation of protein disulfide isomerase, an oxidoreductase chaperone in the endoplasmic reticulum [10].

Such multi-regional involvement in Parkinson's disease is evidence for the onset and progression of basic cellular nature linked to a proteasomal malfunctioning In this regard, further pathogenic dimensions indicate a cellular loss that extends to involve neuronal pathways in multi-focal manner. This may account for misfolded alpha-synuclein that impairs tight junction protein expression of the cerebral endothelium [11].

Braak staging of cell loss and of Lewy body inclusion involvement allows for a disease progression that is multi-systemic in its dimensional spread beyond dopaminergic neuronal systems. Interestingly, alpha-synuclein expression has been characterized as a virus inhibitor between the peripheral and central nervous system, involving a putative viral restriction factor mode of action [12].

Disease Spread

Disease spread is anatomically a selective predisposition that strictly characterizes the interacting pathways of the neuronal cell body on the one hand, and neurites and synaptic pathology on the other. In this regardmm, the endo-lysosomal system dysfunction is

also implicated [13]. The focal dopaminergic loss of neurons in the substantia nigra pars compacta relate to basal ganglionic pathways linked to involvement of cortical neurons in end-stages of the disease.

Connectivity issues

An exquisite inter-dependence exists between multi-system alpha-synuclein inclusions and attests to possible association of dementia with multiple motor pathways along a neuro-axis spanning basal ganglia and cortex. Neuro-inflammation arise in a context of further dimensional spread involving cell proteasomal pathogenesis.

A putative bystander mode of lesion spread is central to dopaminergic neuronal cell loss that precipitates complex dynamics of neuronal loss. Prolonged retention of the Miro, an outer mitochondrial membrane protein, may account for mitophagy as central pathophysiology in Parkinson's disease [14]. Such contextual conditioning of disease involvement and spread include genetic factors that significantly modify clinical and pathologic features of the disease evolution. Differential evolutionary dynamics attest to the emergence of a gain of function phenomenon integral to modulated neuronal susceptibility. Neuroinflammation is critical in pathogenesis and may suppress Src/phosphatase and tensin homologue deleted on chromosome 10 (PTEN)/Akt signaling [15].

Complexity of Pathogenesis

Complexity in the anatomic structuring of modulated motor pathways involves multifocal pathogenesis in Idiopathic Parkinson's Disease. Various specific losses of neuronal groups range in number and degree of severity. An incremental neuronal cell loss in dopaminergic pathways is evidence for neurotransmitter insufficiency. Incremental progression is reflected in the emergence of cortical Lewy body disease in these patients.

Mitochondrial oxidative pathways are implicated in several genetic lesions linked to parkinsonism as illustrated by mutations in Parkin and Pink1 genes. Interactions between mutations of genes SNCA, Parkin, DJ-1 and leucine-rich repeat kinase 2 and the environmental toxins such as pesticides, herbicides, illicit drugs and heavy metals are critical in shared pathogenesis [16].

Neuronal cell loss

Overall characterization of dopaminergic neuronal injury in parkinsonism implies a extra-pyramidal selectivity linked to cell synaptic disconnectivity and further compounded by proteasomal loss of function. Increased gut permeability and altered gut microbiota can affect many pathways involved in Parkinson's disease and their control may significantly modulate disease course [17]. Indices of reactivity to injury involve microglial and macrophage over-activity as neuroinflammatory disorders induce especially prior loss of neuronal connectivity and subsequent dopaminergic neuronal cell loss.

Loss of connectivity of neurons contrasts with a spreading phenomenon of neuronal subset involvement that amplifies the neuronal cell loss in the substantia nigra and as further expressed in terms of an accumulation of alpha-synuclein Lewy inclusion bodies. Over-expression of hyaluronan and proteoglycan binding linked protein 2 are a prominent finding in the substantia nigra of patients with Parkinson's disease [18]. Alpha-synuclein fibrillization is a system dynamics focused on the essential lack of dopamine synthesis and neurotransmission.

Determinants of precipitation of alpha-synuclein are therefore a proto-type of the essential evolution of a dopaminergic neuronal dis-contectivity inherently arising as neuroinflammation and oxidative stress injury of neurons.

Concluding remarks

A highly significant and accentuated feature of Parkinson's disease of idiopathic type is the distribution of accumulating alpha-synuclein inclusion bodies that essentially pre-dates neuronal cell loss

In a real sense, the targeted modality that dominates the cellular injury is the primary involvement of disconnectivity pathways as well indicated by the Braak staging system of lesions in Idiopathic Parkinson's disease. It is in terms beyond neuronal cell loss that laevo-dopa administration often ameliorates clinical features such as bradykinesia and rigidity of skeletal muscle.

Further to proteasomal pathophysiology, dynamics of active pathogenesis in Idiopathic Parkinson's disease may involve an evolutionary course and an outcome as essential system multi-focality of lesions. In such context, microtubule dynamics and tau protein are implicated in loss of cytoskeletal homeostasis leading to abnormal trafficking along dendrites and axons in Parkinson's disease [19]. Distribution and re-distribution of parameters of cellular injury are inherent pathogenic indices for progression of a disease that primarily targets connectivity parameters centered on dopaminergic neurons of the substantia nigra pars compacta.

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