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Oxidative Stress as Genomically Mediated Neurodegeneration

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Abstract: It would be in terms of a neurodegenerative state that involves the cell as a series of pathway events that there would arise a further specific characterization of neuronal injury that finally resolves as irreversible transformation of such injury. Oxidative stress injury is a final common pathway event that paradoxically is initiated intraneuronally but that progresses largely as a microglially-mediated series of injuries to the neuron. The recognized validity of the use of the term neurodegeneration might derive from essential recognition of various stages in the injury to neurons that finally proves irreversible in terms of reactive oxidative stress. Neuroinflammation may thus arise as a second stage in the evolution of a given neurodegenerative state that would finally determine transformation to irreversible cell-death pathways. The specific recognition of any given neurodegenerative state might also be in terms of how neurons do actually transform with regard to injury induced by a final common endpathway of oxidative stress.

Key words: Oxidative, stress, mediated, neurodegeneration

INTRODUCTION

The pivotal and cyclical dynamics of oxygen availability and utilization would implicate an essential risk for reactive oxygen-radical production and toxicity. It would appear, in addition, that mitochondria are both targets and also effective mediators of significant oxygen-induced toxicity. In Leber's hereditary optic neuropathy, the most prevalent mitochondrial disorder, bioenergetics shape cell death pathways[1]. In a sense, perhaps, much of the nature of oxidative stress in terms of neurodegeneration might best be understood in terms of mitochondrial handling of oxygen especially as a mode of consumption of oxygen in the neuron. In addition, aggregation of modified proteins influence in particular proteasomal activity and protein turnover and may result from oxidative stress[2]. Abnormal copper homeostasis especially sensitizes the neuron to oxidative stress[3].

Oxidative stress might represent abnormal handling of oxygen that is primarily available to the cell and that is consumed via aberrant metabolic pathways as represented by states of neurodegeneration.

Metal protein interactions may be particularly implicated[4] through the action of redox transition metals[5].

Reactive oxygen radicals may reflect not only the primary neurodegenerative state but also effective mechanisms of induced neuronal injury.

It would seem that abnormal patterns of oxygen consumption might reflect the primary pathobiology affecting the cell, especially in neurodegeneration, involving especially genetic instability induced by oxidative stress as in ataxia telangiectasia[6].

A progressive form of injury to neurons that however survive may thus develop for a significant part of the disease course and as reflected in reactive oxygen-radical production in manganese neurotoxicity[7].

A condition such as Alzheimer's disease, Parkinson's disease, or amyotrophic lateral sclerosis might constitute a primary form of neuronal injury in a highly specific manner conducive to progression as a secondary compounding process of oxidative stress. In this way there may arise a mixed pattern of neurodegeneration and oxidative stress injury to neurons that determines overall disease progression. Proteasome disruption appears central to familial as well as sporadic neurodegeneration[8].

Progression and transformation of disease events in neurodegeneration may constitute oxidative stress injury that potentially involves dynamics of a disease as characterized clinically and pathologically.

Oxidative stress as neuronal compensatory mechanisms and as microglial elimination of neurons in alzheimer's disease: Oxidative stress injury in Alzheimer's disease may prove to be an end-pathway mechanism in inducing neurodegeneration. Oxidative free radical injury may be an immediate cause of neurodegeneration as both a specific and general phenomenon of neuronal involvement. Alpha-synuclein aggregation is a key event leading to neurodegeneration and may be associated with

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mitochondrial and proteasomal dysfunction[9] and also iron-associated toxicity[10].

Such a concept might indicate that microglial reactivity is mediated mainly by inducing reactive oxidative stress affecting injured neurons in various states of neurodegeneration. Oxidative alterations in Alzheimer's disease would constitute direct reflections and integral consequences of the effects of reactive microglia and of other cell components in leading to an end-pathway phenomenon in neuronal cell death. In such a process, amyloid beta-peptide appears to act as a source of free oxygen radicals in inducing neurodegeneration[11].

Senile plaques and neurofibrillary tangles would reflect impaired viability of neurons constituting an essential consequence of injury to the neuronal cell body or to its neurites.

Such a postulated compartmentalization of the neuronal injury as neurodegeneration would perhaps implicate a common endpathway event that is mainly reactive and induced by oxidative stress.

Severe injury may involve particularly the neurites with direct involvement of the neuronal cell body at an early stage in the formation of the neuritic plaque. Such a phenomenon might possibly resemble a dying back process leading to plaque evolution. Diffuse Lewy body disease with its common overlapping features with Alzheimer's disease would be suggestive also of an exquisite susceptibility of the synaptic terminals to undergo degeneration. Platelet-Activating Factor (PAF) plays a role in synaptic plasticity and neurodegeneration. An interplay of PAF with oxidative stress and group I metabotropic glutamate receptors may be critically determinant in inducing neuronal cell death[12].

Such a postulated dying –back phenomenon starting from synaptic terminals would progressively spread proximally to involve the whole neurite as a reactive process and as compensatory pathways of attempted recovery on the part of the neuronal cell body.

Oxidative stress as an intraneuronal phenomenon would possibly be reflective of the enormous compensatory potential for neurons to salvage much of the neuronal and neuritic network.

Hence, perhaps, oxidative alterations in Alzheimer's disease within the neuron would reflect considerable attempts at compensation in cell recovery. Extraneuronal pathways of oxidative injury would be directed as terminal events in neuronal cell death that implicate components of the inflammatory response[13] and possibly also astrocytes[14]. A specialized form of extracellular matrix designated as perineuronal nets may surround and protect neuronal subpopulations from oxidative stress through local ion homeostasis[15].

Stereotyped patterns of neurodegeneraton further characterize individual attributes of neuronal cell injury: What is the possible role of genetic linkages as mutations/polymorphisms of the tau gene on chromosome 17 in association with frontotemporal dementia in the added general context of sporadic dementia cases?

One possibility would relate to a genetic association represented essentially by a form of susceptibility for the development of neurodegeneration that potentially implicates progression. In this way, overexpression of alpha-synuclein not only may participate in neuronal degeneration but may also increase the vulnerability of neurons to other potential neurotoxins[16].

Also, folate deficiency may potentiate other risk factors in neurodegeneration[17].

How might neurodegeneration as decreased viability of neurons within distinct neuronal networks be specifically predisposed to?

The distinctive occurrence of pronounced overlap of clinical and pathologic features between many different cases of dementia would classically develop as features of various neurodegenerative states ranging from the lobar type of frontotemporal dementias to Alzheimer's disease, Diffuse Lewy Body Disease and associated dementia in patients with amyotrophic lateral sclerosis. An important degree of variability in presentation clinically and pathologically of various cases of dementia may involve particularly patient age at presentation, rate of progression of the dementia and also as a pathologic involvement reflected for example in the number of Lewy bodies in the cerebral cortex.

The clinical and pathologic complex of dementia is so highly heterogeneous that there may exist a pathobiology affecting neuronal injury that is both progressive and possibly reactive to various different pathways of a transforming nature.

This would be reflected in the highly intricate integrative nature of neuronal networks that directly lead to diffuse and ill-defined features often characterizing clinical cases of evolving neurodegeneration.

The use itself of the term neurodegeneration is one that is defined by presently available methods of investigation and resolution of forms of neuronal injury.

Patterns of established pathobiology of involvement and evolution of the neuron might belie validity in presently available criteria in classifying and in distinguishing apparently distinct forms of neurodegeneration.

The use of the term neurodegeneration may on the other hand paradoxically account for certain innate attributes of the individual patient that are conducive to a final stereotyped pattern of neuronal injury. Such a

concept would modify such an essential neurodegenerative event as further characterized by parameters of extent of involvement anatomically and regionally in the cerebrum. Relative distribution, cortically and subcortically and the actual relationship of neurons to glia, might implicate involvement in dementia in terms of either tau inclusions or even as gliosis as seen in Pick's disease and other states of neurodegeneration.

Simple categorizing of types of neurodegeneration or dementia might be contrary to an integral approach to neuronal injury that evolves and progresses primarily as atrophy of cells. Innate attributes of susceptibility to neuronal injury as determined genetically or constitutionally would severely modify and determine the definitive characterization of the neurodegenerative process. In early onset familial Alzheimer's disease, mitochondrial abnormalities may result in increased neuronal susceptibility to oxidative stress and result in different apoptotic pathways[18].

Perhaps a stereotyped process as neurodegeneration of regional networks of neurons would account for also an individual variability in progression and distribution of lesions affecting patient genome. In such a manner, a stereotyped neurodegenerative state is subsequently modified as determined by individual patient susceptibility. Specific components of the respiratory chain, in particular, may be differentially susceptible to mitochondrial oxidative stress in the brain and such sensitivity might lead to neuronal cell death[19].

Oxidative stress-induced injury as the second and final stage in cell death: What is the pathogenic role of oxygen-induced stress in precipitating neuronal cell death?

Is it a universal aspect of death of a cell type particularly characterized by requirements for high delivery of oxygen during health? An accumulative event of oxidative injury within neurons might reflect a sudden cessation in the effective utilization of the oxygen due to impaired cellular metabolism. Post-translational modification of brain proteins as oxidative reactions may be especially implicated in diseases such as Alzheimer's[20].

Cessation of metabolic activity of the neuron might reflect not only impaired utilization but also abnormal delivery of oxygen to that cell.

It is perhaps this latter abnormal delivery of oxygen to neurons that would account for oxygen-induced toxicity as an essential second phase in the progression of a potentially wide variety of neuronal forms of injury that somehow provokes the onset of cascade-type events. Interruption of this final series of steps in neurodegeneration might salvage the neuron in terms of delay in cell death.

Exposure to oxidative stress might in essentially help redefine phenomena of cell death in terms of the generation of a possible second phase in cell injury. It may very well prove true that oxidative stress constitutes a universal state of reactivity that is independent of actual forms of initial cellular injury but that subsequently transform as specific attributes of a cascade-type series of pathways, as postulated in Alzheimer's disease[21].

In the same way that availability of oxygen is central to the survival and physiology of the cell, it is also central to the definitive establishment of pathways of final cell injury promoting irreversible transformation and cell death.

It is perhaps the irreversible form of such an injury to the cell that would in some way account for subsequent establishment of a final reactive stage of oxygen-mediated injury that transforms the cell.

Neurodegeneration integrally reflects patient genomic attributes: One central problem in neurodegenerative states relates to the definitive delineation of a specific pathologic entity. What constitutes such a defined variant as a novel form of neurodegeneration? Is it perhaps the patient's genetic code that ultimately determines the intrinsic biology of the neurodegenerative process afflicting that patient, as proposed for example with L-glutamate neurotoxicity [22] through deficiency of high-affinity glutamate transporter dEAATI? It is perhaps relevant to consider a neurodegenerative process simply as an initial event or series of events in the final subsequent establishment of a cascade-type series of pathways leading to cell death as determined by both environmental and genetic factors[23].

Underlying oxidative stress may be protected against by overexpression of the Drosophila melanogaster gene sniffer in preventing neuronal apoptosis induced by oxygen[24].

The actual process of evolution of a neurodegenerative process might account for distinctive features affecting the cell and determining onset and progression of the final cell-death pathway. Presenilin 1 gene plays a role in nitric oxide synthase activation in neurons and may confer resistance to oxidative stress on neurons in a calcium/nitric oxide-dependent manner[25].

The essential evolution of a degenerative process is one that identifies attributes involving the individual patient. This peculiar attribute of neurodegeneration would be an essential phenomenon in its own right but one that involves forms and modes of adoption by the neuron and nervous system in further characterizing the

disease process in that patient. Thiamine deficiency may induce abnormalities in oxidative metabolism in releasing neuronal inflammatory signals that activate microglia, astrocytes and endothelial cells[26].

In this manner, the patient's genome would distinctively characterize the neurodegenerative process as one that finally transforms neuronal viability in terms also of reactive injury as mediated by oxidative stress.

Genetic disorders of copper homeostasis may be associated with neurodegeneration as seen in Menkes' and Wilson's diseases[3].

In this manner, mode of progression of the neuronal injury would constitute a determining parameter in finally defining distribution and nature of the injury to cells. In this manner, neurodegeneration following spinal cord injury implicates altered cellular redox status, activated transcription factors and induced proinflammatory genes[27].

Dynamics of imbalance in the evolution of processes of neuronal injury would account for events that induce neuronal loss. Such imbalance may be predisposed to by genetic factors as in early onset Parkinson's disease[28]. Strict categorization of an Alzheimer disease process would hence depend on such patterns of neuronal cell loss that eventually predetermine development also of reactive injury mediated by microglia and neuroinflammation.

It is the particularly wide variety and range of genetic information that resides in the central nervous system that would render neurodegeneration a prime example of an evolving expression of the genomic constitution of that individual patient.

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