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Pro-Mitosis as Selective Neuronal Apoptosis in Amyotrophic Lateral Sclerosis.

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Abstract: It is perhaps significant that any attempt at responsive mitotic activity on the part of neurons as permanent phenotypes might result in injury and loss of cells. Programmed cell death might inherently constitute a component system at promitosis that involves activity on the part of the neuron to enter the cell cycle. It might be in terms of reactivity to inflammation, to trophic factor lack, to ischemia, or to the generation of and exposure to, numerous or varied toxins, that neurons of the anterior spinal horn, brain stem and precentral motor cortex would evolve as promitosis or as induced attempts at mitosis. Promitosis would constitute a susceptibility to cell death in the evolving exposure and development of cell cyclical activity that stresses and damages permanent phenotypic attributes of the neuron. A reactivity on the part of a neuron of specific physiologic category or subclass in amyotrophic lateral sclerosis would induce persistent cell loss that is characterized as aborted cell cyclical activity and as subsequent programmed cell death. Superoxide dismutase activity and its mutant forms would highlight such susceptibility to evolving neuronal injury and stress that is generated as both induced promitosis and as subsequent programmed cell death in the course of repeated attempts at entry into the cell cycle.

Key words: Amyotrophic pro-mitosis neuronal apoptosis

INTRODUTION

Neurofilament triplet stoichiometry in evolving neuronal injury in als: A heterogeneous group of biologic processes appears to be incompletely expressed as motor neuronal loss in Amyotrophic Lateral Sclerosis (ALS)[1]. A decrease in NFL with preservation of NFM and NFH neurofilaments in lateral spinal neurons of cervical spinal cord of ALS patients appears an expression in failed processing consequent to protein dysregulatory synthetic pathways[2]. Such synthetic dysregulation would constitute events borne out from processes that initially characterized that particular cell as a motor neuron developmentally[3]. Developmental evolution of stoichiometric organization of neurofilament triplets would be expressed as incorporation of cytoskeletal structural subunits in a reaction to various stimuli ranging from infection to oxidative stress. The Golgi apparatus of neurons, in particular, would participate in attempted mitosis and in generation of microtubules that maintain cell organelle integrity [4]. Increased free radicals and decreased efficiency of reparative/degradative mechanisms would contribute to neuronal injury by affecting proteolysis and other processing pathways[5].

Astrocytic responses to neuronal pathophysiology in ALS: Oxidative stress as induced motor neuronal injury would arise as a reactivity in the course of astrocytic and inflammatory cell responses[6].Calcium-induced mitochondrial permeability appears particularly implicated[7]. Inflammatory cells would induce proliferative reactions on the part of astrocytes that result in neuronal injury as induced by increased oxidative stress. A terminal proinflammatory state develops as revealed by specific gene characterization[8]. Astrocytes would prove a derived phenomenon in consequence to both neuronal and inflammatory cell responses that evolve as astrocytic rather than neuronal pathophysiology. Fibroblast growth factor-1 of astrocytic origin may help prevent apoptosis of neurons in response to injury[9].

Astrocytes define neuronal injury in ALS: A phenomenon of zinc buffering action coupled with a role of Zn in Cu/Zn Superoxide Dismutase (SOD) action as an antioxidant might implicate dynamics of a disease process primarily limiting pathogenesis to astrocytic responses and subsequent neuronal injury[10].

Mutant SOD1 toxicity might increase susceptibility to stressful stimuli in inducing neuronal injury[11]. Astrocytes would respond in terms of S100 A6 functionality borne out in terms of a astrogliosis to defined neuronal injury. It is also significant that neurons, in turn, participate fully in the development of an astropathy that evolves subsequent to neuronal oxidative injury.

Chaperone functionality of heat shock proteins is an astrocyte-derived attribute: Heat shock proteins constitute a chaperone system that protects against injury, particularly of oxidative type[12,13]. It would appear that variable trafficking dynamics of heat shock proteins would constitute patterns of neuronal susceptibility as induced by oxidative stress as exerted by astrocytes. Mutant SOD1 aggregation would induce mitochondria dysfunction with potentially toxic interactivity with heat shock proteins, thus promoting apoptosis[14] . Astrocytes might account for a variable response to oxidative injury in terms both of a neuronal cell and as other systems such as inflammatory cells, macrophages and endothelial cells[15]. Free radicals released from activated microglia would initiate motoneuron injury through selective susceptibility of AMPA/kainate receptors to glutamate[16].

Astrocytes progress in an interactive manner with neuronal cell loss in ALS: DNA single end double strand breaks constitute an astrocytic attribute contributing to progression of the ALS process[17]. Neuronal injury and cell death evolve in the presence of increased PARP protein but without increased PARP m RNA. Such a phenomenon would simply indicate evolving differences in response both to injury to astrocytes and to neurons. Nitric oxide challenge to neuronal cells in particular might ultimately result in apoptosis[18].

An astocytically mediated form of injury to neurons would be associated with further astrogliosis secondary to evolving neuronal cell loss. Reactive astrocytes in ALS express inflammatory markers including cyclooxygenase (Cox-2) and nitric oxide synthase, to produce nitrotyrosine and to downregulate the glutamate transporter EAAT2[19].

A permissive role in protein rna flow in determining axonal flow: RNA flow of information through nuclear pores might involve protein-RNA transfer that regulates in particular axonal flow of impulses[6].

Such a phenomenon might implicate a gain of adverse function that results in a neuropathologic lesion determining subsequent evolution of motor neurons as target cells in amyotrophic lateral sclerosis. The mitochondrion/apoptosome pathway might be the main mechanism leading to death of proneural and neural cells[21]. Loss of predetermined neuronal fate might predispose to a decycling of protein RNA flow between nucleus and cytoplasm that further promotes motor neuronal loss. It might be significant that the permissive role of protein molecules in variable response of neurons is one tied up principally with pathophysiology of axonal flow. Also, restrained differentiation and integration of neural stem cells into mature neuronal networks would involve genetic and epigenetic mechanisms[22].

Progression of subtype gaba receptor loss as a familial trait in als pathophysiology: GABA A receptor m RNA constitutes a representation of events that trigger the emergence of neurodegeneration as depicted by motor neuronal loss of ALS type[23].

It is perhaps significant that the development of lesions in a motor neuron is essentially a result of a realized pathway of progression as further reflected in GABA A receptor subunit loss. Only insofar as receptor subtype evolves as lesions affecting neurons is it also possible to recognize a pure motor neuronal lesion in ALS patients and as familial cases of the disease.

Aggregation dynamics as a disease attribute of als progression: Inclusion body neurofilament aggregation might be best characterized as a distinguishing parameter in axonal neurofilament dysfunction that is structurally reflected in aggregation as an ongoing event of predetermined dynamics[24]. Aggregation of SOD1 would contribute significantly to neuronal cell death, particularly in familial cases of ALS[25]. One might view disturbances in neurofilament aggregation as a phenomenon derived from a selective predilection for skein formation and for disturbed recognition of antigenic sites as induced by stable tubule-only polypeptide proteins.

Astrocytic responsiveness critically compromises neuronal viability in ALS: Neurodegenerative progression in amyotrophic lateral sclerosis would arise mainly as a reactive pattern to a whole heterogeneous group of possible insults to the neuron[26]. Oxidative and endoplasmic reticulum- induced stress causing caspase-12 activation are involved in neuronal death and disease progression in ALS[27]. Particularly significant appears a concurrent response on the part of adjacent astrocytes that would compromise, from an initial time of tissue and cellular injury, any neuronal viability. Within a dynamic context of evolving reactivity, the progressive loss of neuronal viability would be best reflected in oxidative stress. Also, insufficient vascular endothelial growth factor appears a risk factor in ALS[28].

Programmed cell death: Programmed cell death implicates a point of no return in the evolution of a near-terminal cell reactivity that predetermines the fate not only of a cell but that of other cell types as an integral tissue process[29]. A motoneuron-restricted cell death pathway would be mediated by neighboring cells in ALS[30].

Fas-mediated apoptosis involves the activation of p38MAP kinase and of neuronal nitric oxide synthase[31]. It is beyond just cell death that amyotrophic lateral sclerosis proves an indeterminate progression of insults to cell neuroprotective measures.

It is perhaps in realizing aspects of neuronal survival that one would recognize ALS as a system of progression allied to neuronal recoverability in the face of a programmed execution of cell death pathways that is beyond just classic apoptotic pathways. Both wildtype and mutant SOD1 binds to antiapoptotic protein Bcl-2[32].

Selectivity in motoneuron degeneration in ALS: A genetic defect might increase susceptibility to an environmental neurotoxin in ALS[33] and would orchestrates a multifactorial etiopathogenesis[34]. Misfolding of mutant superoxide dismutase molecules would focally operate in primarily targeting motoneurons in anterior spinal horns and precentral gyrus[35]. A process of aggregosome generation in some way would result in a toxic gain of function in terms of a chronic neurodegeneration and also loss of function of CREB-binding protein as central events[36].

Integral tissue participation in such toxic gain of function of mutant SOD1 might implicate in particular astrocytes that promote variable progression as aggregosome and misfolding events.

Apoptosis generates oxidative stress: Neuronal apoptosis would constitute a universally operative pathway inducing cell loss linked to mediators such as prostate apoptosis response-4 protein (Par-4)[37]. Indeed, one might view oxidative stress as integral to apoptotic pathways whereby toxic gain of function implicates apoptosis. Nitric oxide and peroxynitrite induce mitochondrial damage to the electron transport chain, affecting particularly neurons[38]. Multiple molecular pathways for programmed cell death emanate from mitochondria[39,40]. Viewing apoptotic pathway activity in oxidative stress might better explain a relative susceptibility of motoneurons in an ALS disease process primarily inducing severe neurodegeneration. Par-4 is enriched in synaptosomes and the synapse might be a crucial cellular site promoting neuronal cell death in motor neuron disease[41].

Neuronal promitosis induces apoptosis of neurons: Cyclin-dependent kinases that normally regulate cell cycle progression may be implicated in neuronal apoptosis as induced by various insults[42]. Neurofilament inclusions in motoneurons in ALS patients appear related to p38 mitogen-activated protein kinase in a manner linking neuronal apoptosis to possible attempts at neuronal mitosis[43]. It seems reasonable to consider how neuronal cell mitosis is a stimulus for both apoptosis and oxidative stress linking these to a defect in the astrocytic EAAT2 transporter of glutamate. Excitotoxicity might be viewed as an overall characterization of events incorporating diverse events ranging from neuronal apoptosis and mitosis to formation of phosphorylated neurofilament inclusions within neurons.

Neuronal promitosis as reflected in astrogliosis and glutmate receptor expression: Glutamate receptor Type I expression and astrogliosis appear linked to progression of the ALS disease process in a manner conducive to neuronal apoptosis progression[44]. Mitotic activity of astrocytes in the spinal anterior horns of ALS patients might develop concurrently with progression of neuronal apoptosis as a distinct neuronal promitosis in reactive development.

Oxidative stress in ALS patients might specifically reflect such a distinct promitosis in terms both of the astrogliosis and as metabotropic glutamate receptor Type I expression. Possible Ca^{2+} influx through atypical AMPA receptors might lead to misfolding of mutant SOD1 protein and eventual neuronal cell death[45].

Nucleic/cytoplasmic uncoupling: Ubiquinated intranuclear and intracytoplasmic inclusions in patients with frontotemporal dementia of motor neuron type might extend to involvement in ALS patients as defective transport from cytoplasm to nucleus[46]. Protein nitration appears implicated in aggregation phenomena and accompanying cell death[47]. It would further appear that neuronal loss correlates with a predisposition to ubiquinated inclusions that links neurodegeneration to a biophysical accumulative event isolating nucleus from protein-synthesizing pathways in the cytoplasm.

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