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Developmental Dimensions of Autophagy and Lysosomal Reactivities In Alzheimer Disease

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Abstract: It would appear that pathways of impaired autophagy are inherently conducive to co-localization of neurofilaments, with the formation of neurofibrillary tangles and with synapse loss. Indeed, intracytoplasmic amyloidogenesis might, in specific ways, be a component system in production of both synapse loss and neuronal cell death largely in terms of the etiologic cause of the amyloidogenesis as a prototype of cellular degeneration in its own right. It might perhaps be relevant to consider how synapse loss and neuronal cell death would implicate reactivity of lysosomes that affects the metabolic activity of neurons. A low neuronal metabolic rate would inherently affect trafficking systems and also the production of a variable response to different insults ranging from neurotrophin factor lack to ischemia primarily evolving as phenomena centered on cerebral cortical neurons. Impaired autophagy implicating abnormal lysosomal activation would promote the accumulation of ubiquinated endproducts of neuronal metabolism with the appearance of phosphorylated neurofilament aggregates and granulovacuolar degeneration. Interpretative assessment of neuronal inclusion body phenomena in selected neuronal subsets might implicate a failed central pathway mechanism promoting the development of neurodegeneration. Indeed, it is in terms of primary lysosomal disease that major neuropathologic lesions in Alzheimer's disease would be conducive to subsequent slowly progressive neurodegeneration as a selective neuronal subset phenomenon. It might be significant to recognize amyloidogenesis as a reflected consequence of such lysosomal involvement beyond simple considerations of directly involved proapoptosis or cell cyclical activity but within a strict context of impaired turnover events affecting cell organelles in particular.

Key words: Alzheimer disease, autophagy, lysosomal, reactivities

SYNAPTIC LOSS LEADS TO AXONAL TRANSPORT DYSFUNCTION AND NEURONAL APOPTOSIS

Neuronal cell death appears a consequence of events that progress largely as axonal and dendritic developmental changes and synaptic loss[1]. A proapoptotic environment in Alzheimer's disease might constitute a largely impaired autophagic phenomenon[2,3]. Synaptic loss would constitute a leading cause of neuronal apoptosis in a manner allied to cell organelle dysfunction and as reflected in abnormal kinesin with accumulation of lysosomes, degenerating mitochondria and neurofilaments in dystrophic terminals. In particular, mTOR and p70S6K, which modulate cell growth, proliferation and autophagy, constitute antiapoptotic mechanisms that are altered in Alzheimer's disease[4]. In terms of synaptic loss, pathways of consequence arise as an intermediate form of cell change that damages recoverability from insults ranging from relative trophic factor lack to ischemia of cortical neurons and oxidative stress[5]; such cell change is possibly related to re-entry into the cell cycle[6].

It is perhaps with regard to derived damage to the synapse that summation of injury would result in an evolving neuronal cell death pathway of Alzheimer type associated epigenetically with senile plaque and neurofibrillary tangle formation. Intracellular beta-amyloid accumulation would affect adversely subcellular compartments and potentially contribute to neuronal cell injury[7].

Presenilin mutations would damage lysosomes in a manner synergistic to the action of beta-amyloid[8]. The potentially neuroprotective role of autophagy appears impaired in dystrophic neurites in particular, with consequent abnormal turnover of intracellular organelles[9].

PERMANENT NEURONAL PHENOTYPE IN HYPERPHOSPHORYLATION-INDUCED TRANSCRIPTION FAILURE

Hyperphosphorylation of tau appears a system of progression involved in abnormal localization of cdc2/B1 cyclin activities leading to decreased transcription of m RNA[10]. A fundamental defect inducing mitotic activity

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of permanent neuronal phenotypes would perhaps induce a neurodegenerative cascade of events.

This would implicate hyperphosphorylation particularly of RNA Polymerase II that subsequently induces further protein hyperphosphorylation in the cytoplasmic subcompartment of mitotically initiated permanent neurons. The lysosomal protease cathepsin D would block production of precursors in the formation of neurofibrillary tangles[11]. Cathepsins are implicated in the initiating and executing of cell death pathways involving in particular primary lysosomal dysfunction[12].

ISCHEMICALLY INDUCED TROPHIC FACTOR INSUFFICIENCY IN ALZHEIMER DISEASE

A decreased trophic factor effect on CA1 hippocampal cortical neurons as represented by decreased expression of hippocampal cholinergic neurostimulating peptide precursor protein (HCNP) mRNA might account for evolving Alzheimer Disease neurodegeneration linked inherently to a possible array of accompanying ischemic injury to neurons in general[13].

A system of concurrently evolving neuronal injury as typified primarily by cortical ischemia might evolve as subsequent trophic factor insufficiency and as decreased HCNP and decreased levels of Brain Derived Neurotrophic Factor.

An accompanying increase in expression of Nerve Growth Factor would indicate compensatory systems of response primarily aimed at recovery from ischemically-induced trophic factor insufficiency in Alzheimer disease.

DYSFUNCTIONAL CYCLICAL ACTIVITY OF NEURONS

Re-entry of neurons into the cell cycle appears to constitute a basic scheme of progression of neurodegeneration in Alzheimer disease that is linked to factors such as ischemia and astrocytic proliferation as responses to adjacent deposits of Beta-amyloid[14].

Lysosomal dysfunction possibly contributes to protein accumulation, blockage of axonal/dendritic transport and synaptic loss. Phosphorylation of eukaryotic initiation factor-2 alpha (e IF2 alpha) terminates global protein translation and induces apoptosis. Autophagy is regulated by e IF2alpha kinase[15]. A compensatory mechanism otherwise operates[16].

The hyperphosphorylated neurofibrillary tangles would evolve in terms of how such neuronal injury develops consequent to inhibited nuclear cyclical activity.

A disrupted cell cycle activity pattern might perhaps implicate hyperphosphorylation of tau and of other intracytoplasmic proteins leading eventually to neurodegeneration. The ribosomal S6 protein kinase p70 S6 kinase modulates cell-cycle progression, cell size and cell survival and would modulate upregulation of tau translation in neurofibrillary tangle formation[17].

DYSFUNCTIONAL AXONAL TRANSPORT AND SYNAPSE LOSS

Decreased synaptophysin immunoreactivity and synapse loss would progress concurrent with various other parameters of neurodegeneration primarily characterized as insufficient trophic effect[18]. Indeed, synapse maintenance would constitute a true functional correlate of neuronally induced events maintaining functionality of neuronal events in the cerebral cortex.

A dichotomy between progressive neuronal cell loss and synapse loss might be best resolved as a dystrophy of axons that progresses both as dysfunctional axonal transport and as decreased neuronal viability.

NEURONAL CONNECTIVITY AND AXONAL TRANSPORT AS VIABILITY ISSUES

Synaptic dysfunction would evolve as axonal neurofilament injury largely characterized as deposition of neurofibrillary tangles in the cell body[19]. Paired helical filament-tau is not phagocytosed by lysosomes and may constitute a source of granulovacuolar degeneration[20,21]. Lysosomal degeneration and neurodegeneration of Alzheimer type might simply constitute different phases of a cellular injury primarily centered on evolving dysfunctional transport mechanics and intracellular amyloidogenesis[22,23]. Autophagy in particular may be related to abnormal degradative pathways in recycling and turnover of neuronal cytoplasmic constituents[24]. Upregulation of glycohydrases and of Ras are early markers of Alzheimer disease[25].

In this sense, both axonal transport failure and synaptic failure would constitute manifestations of an evolving defect in message transfer that directly implicates neurodegeneration as a basic system of failed maintenance of such neurofilament transfer.

Neurofilament transport mechanics might correlate with synaptic transmissibility evolving as both trophic sufficiency and neuronal viability dynamics of connectivity.

DYSTROPHIC NEURITES IMPLY FAILED SYNAPTIC TRANSMISSION AND SYNAPTIC LOSS

The transformation from physiological nonamyloidogenic processing to amyloidogenic senile plaque formation appears a concurrent development to the formation of dystrophic neurites and to synaptic loss[26]. Beta-amyloid is an interactive series of reactivities

based on m RNA transfer from neuronal dendrites to the senile plaque milieu. Cleavage and propagation mechanics of amyloid processing would involve particularly susceptibility for progression to a state of neuronal cell loss as an induced first stage of synaptic transport failure and as subsequent dystrophic neurite formation. Indeed, dystrophy of neurites would be reflected inherently in a failed transport system in synaptic transmission.

PRESERVATION OF NEURONS AND SYNAPSES IN NORMAL BRAIN AGING

Developmental neuronal survival and synaptogenesis appear to constitute outcome parameters that determine whether pathology of Alzheimer type evolves as microglial and astrocytic reactivity or whether neurodegeneration is halted as normal brain aging proceeds[27]. Apoptotic astrocytes may characterize white matter degeneration in Alzheimer disease[28]. It would appear that normal aging constitutes preservation of neurons and of synapses from the scavenging and proinflammatory action of microglia and from astrocytic reactivity responses. Autophagy would constitute a multifunctional pathway implicated in apoptosis, removal of damaged organelles and tissue specific functions[29]. Neuronal and synaptic preservation would then evolve as an integral process in the face of trophic insufficiency of brain aging.

RETROGRADE TRANSPORT OF NEUROTROPHINS

Retrograde transport of neurotrophins would involve a reactive response on the part of the parent neuron that ensures survival maintenance mechanisms of synapses and responsiveness to a variety of injuries[30].

One might speak of dynamics of involvement that participate in the development of defective transport of such neurotrophins within a context of evolving injury of the neuronal cell body. The ability of ceramide to physically alter membrane formation and fusion may seriously compromise normal endocytic trafficking[31]. Therefore, neurodegeneration as a generic process would constitute the evolving insufficiency of neurotrophins in the face of developing injury to the neuron integrally based on soma and synapse interactivity. Upregulation of lysosomal enzymes could be responsible for enhanced GM1 ganglioside catabolism in Alzheimer disease fibroblasts[32].

NEUROTROPHIN RECEPTIVITY AND PARAMETRIC NEURONAL RECOVERY

Nerve Growth factor receptors appear to constitute an evolving system of responsive adaptation to neuronal injury based largely on retrograde transport of activated endosomes along axons and dendrites[33]. It might be realized that pathways arising in terms of effective replacement of neurotrophic influence in the aging brain would naturally implicate attempts involving resolved, intensely focused injury and response to such injury.

A primary disturbance in neurotrophic receptivity would concurrently progress with defective utilization of transport systems of delivery of neurotrophins. Alzheimer disease might realistically constitute a means for progressive injury to neurons to recover largely as supporting pathways involving neurotrophin receptivity.

REDUCED METABOLIC RATE OF ALZHEIMER TYPE

A reduced metabolic rate would accompany progression of Alzheimer dementia in a manner linked to decreased blood glucose utilization by the involved neurons[34]. An increase in size of the Golgi apparatus in initial stages of the disease would constitute a compensatory mechanism inherently associated with subsequent progression of a disease process as manifested by decrease in size of the Golgi apparatus in patients with Apo E epsilon 4 genotype. Proteasome dysfunction develops with formation of aggresomes and sequestration of beta-catenin; this latter colocalizes with gamma-tubulin and vimentin. Apoptotic cell death develops due to accumulation of phospho-beta catenin affecting the Wnt signaling pathway and as a presenilin-1-interacting protein[35].

AN INDEX OF ALZHEIMER DISEASE ACTIVITY AS INCREASED PRO-NGF LEVELS

A progressive rise in pro-NGF with dementia progression of Alzheimer type might specifically correlate not only with compensatory attempts at neuronal recovery but especially with a tendency for replacement of lost neurotrophic action by mechanistic neuronal survival pathways[36].

Improved neurotrophic attempts at recovery of neurons might reflect a real need for sustained discharge

of neuronal impulses related to progression of the primary disease process itself.

BETA-AMYLOID DEPOSITS ACCOMPANY LYSOSOMAL INJURY AND IMPAIRED AUTOPHAGY

Impaired lysosomal function of neurons appears linked particularly to impaired autophagy as involved in intracellular neurotransmitter turnover[37]. Intermediate-filament containing ubiquinated inclusions may mark neuronal attempts at cellular degradation in eliminating pathogenic insults[38]. Familial Alzheimer disease associated with presenilin mutations is related to increased beta-amyloid deposition.

Such beta-amyloid deposits would correlate with impaired lysosomal autophagy in a manner marking dynamics of deposition of the amyloid and as insufficient neurotrophic effect. Increased autophagic vesicles appear a significant source of cleavage of amyloid precursor protein, thus implicating the endosomal-lysosomal system in Alzheimer disease progression[39].

Amyloid precursor protein, presenilin, nicastrin and gamma-secretase all colocalize in the lysosomal membrane[40]. Only in terms of such progression of the lesion in Alzheimer disease would there develop a susceptibility characterizing dynamics of beta-Amyloid deposition.

OVERLAPPING INDICES IDENTIFY THE ALZHEIMER DISEASE PROCESS

Neurofibrillary tangles appear reliable markers of Alzheimer-type dementia in late stages of the disease as evidenced by moderate to marked numbers of tangles in the cerebral cortex[41]. Neuritic plaques, even if modest in number, appear more reliable markers of stages of the Alzheimer disease process.

Both neurofibrillary tangles and senile plaques consist of overlapping indices of an integral disease process largely characterized as synaptic loss and as subsequent neuronal cell death.

TANGLE FORMATION INDUCES SYNAPSE PATHOLOGY AND SUBSEQUENT AMYLOIDOGENESIS

Neurofibrillary tangle formation constitutes an intracellular series of events linked in multiple ways to a primarily intracellular accumulation of Beta-amyloid[42].

It is in terms of actively induced processes ranging from neurofilament hyperphosphorylation to the generation of tau isoforms pathologically conducive to co-localization that there would subsequently evolve amyloidogenesis as senile plaques and extracellular beta-amyloidosis. Early activation of the endosomal-lysosomal system might act as a link between altered amyloid precursor protein processing, defective membrane proteins and apolipoprotein E function in Alzheimer's disease[43].

Programmed neuronal cell death would account for a neuronal cell loss primarily linking neurofibrillary tangles to loss of synapses and variably affected trafficking along neurofilaments.

PRIMARY LYSOSOMAL DEGENERATION

A neurodegenerative cascade pathway of events would be suggestive of an abnormal primary degradation step in Alzheimer's disease linked to a defect in cell organelle turnover.

It is significant that lysosomal defects and impaired autophagy would account for a failed turnover of metabolic endproducts. The selective vulnerability of neuronal subsets in Alzheimer's disease would relate to phosphorylated neurofilament, senile plaque formation and amyloidogenesis implicating in particular lysosomal activity of microglia neuronal injury and also impaired autophagy and lysosomal reactivity.

Primacy of lysosomal pathology in neurodegeneration would perhaps arise as a reflection of identifiable consequences of provoked injury pathways in response to inclusions such as seen particularly in neurodegeneration. Beyond even the recognition of neuroinflammation or of subsequent neuronal cell death, there might arise a primary evolving susceptibility to impaired metabolic processing in ubiquination and proteasome trafficking. Such a postulated susceptibility to neuronal injury might imply a range of lysosomal reactivities encompassing autophosphorylation and hyperphosphorylation as ongoing ubiquination and amyloidogenesis of cell membrane constituents.

Cell cyclical activity and proapoptosis might mark attributes of primacy of lysosomal pathology in Alzheimer's linked to evolving systems of accumulation of inclusion body constituents. Paired helical tau filaments, in particular, are a component pathway of distributon arising as a consequence of proteasome dysfunction.

Proteasomes are representative pathways of modes of participation of various other cellular organelles in the trafficking and post-processing elimination of

endproducts. Susceptibility of neurons would implicate cells triggered to respond to injury as a common endpathway of abnormal accumulative phenomena of reactivity and dysfunction.

MEMBRANE INJURY

Lysosomal reactivity associated with oxidative stress and impaired autophagy might constitute modes of progression of brain atrophy relative to significant injury to cell membranes in particular. Cell organelles would constitute a prime target to a series of representative steps in the evolution of injury to cell membranes calling into operation activated lysosomal processing. An impaired autophagy in the face of such membrane injury would represent a final common pathway in the realization of such injury as synapse loss and deposition of beta-amyloid.

Observed dynamics and parametric reconstruction of events in the development of an Alzheimer neuropathologic lesion would call into question any relative interaction between Beta-amyloid and cell membranes as acutely precipitated lesions. It might be significant to reconsider beta amyloidogenesis as a recurrent event in evolving cell organelle and plasmalemmal injury borne out by a set of factors related to oxidative stress and reperfusion injury and of a series of cascade events of mitochondrial and lysosomal origin. One might refer to resolution of injurious events largely in terms of modes of development of cell organelle dysfunction and of reconstitutive events in the face of such injury.

Lysosomal reactivity as a primary event in cascade pathway development might specifically reconstitute the membrane as both organelle and cellular biologic processing of lipid bilayers. In a real sense, the essential distinction of Alzheimer pathophysiology from successful brain aging largely rests on a developmental series of consequence to cell membrane reconstruction in the face of such bilipid layer injury. One might perhaps recognize primacy of lysosomal reactivity in terms of degrees in the evolving distinction from neuronal injury due to such diverse factors as ischemia, hypoglycemia, or excitation injury.

In terms, therefore, directly derived from reconstitution of cell organelles and cell membranes in a repeated series of injuries to cells, it is perhaps significant that a developmental pathway of neuronal cell loss is itself modified to account for pathobiologic evolution of proapoptotic stimulation and for consequences of subsequent injury as borne out by neurofibrillary tangle formation and amyloidogenesis.

DEVELOPMENTAL PROGRESSION

Conceptual generalization of events in Alzheimer disease appears to implicate a realized formalization of such events linked inherently to a directly derived substitutive step in processing of metabolic substrates by given neuronal subsets. In a sense, one might recognize the express production of metabolic endproducts derived from exogenous source that subsequently implicate progressive neurodegeneration. Indeed, realized pathways of cascade type imply a substitution of pathways by others that evolve as an amplified series of steps in promoting further progression. Such a system is itself indicative of modes of implied participation of events that further define Alzheimer disease as a restricted form of neurodegeneration in its own right.

Alzheimer disease would constitute a mode of development of lesions that concurrently are promoted by a series of underlying developmental steps in further characterized neuronal pathobiologic injury.

The hippocampal and neocortical distribution of lesions attests to a directly evolving consequence to neurodegeneration of Alzheimer type that is linked to how neuronal subsets themselves are developmental characterizations of possible subsequent injury.

It is in defining such terms of neuronal subset injury that an endogenously arising series of transformation steps would implicate the characterization issues of neuropathobiology in Alzheimer disease. A view of strict causation in Alzheimer disease would simply constitute modes of localized effect of the neurodegeneration that is primarily of cascade type progression.

Reconstituted pathways in the evolution of neuronal injury might arise as defects in the evolving subsequent steps in cellular development. Evolving consequences of derived injury might implicate a delay followed by the development of cell loss as constitutive and also as evolving pathobiologic attributes of neurodegeneration.

DIMENSIONS OF PREDILECTED INJURY

Dimensions of neuronal subset susceptibility are selective indices of how Alzheimer disease proceeds beyond just considerations of individual cell neuropathology. There appears to evolve a series of determining steps in the developmental characterization of such selective neuronal susceptibility that promotes specific lysosomal reactivity. In such terms, it is significant that hippocampal and neocortical substrates for disease progression indicate progression to endstage

disease irrespective largely of age of onset of the disease process.

The severity of disease marks out a distinctive characterization of progression linked only to duration of disease activity. In this sense, an early onset in development of the Alzheimer disease process indicates a possible correlation with other active components induced by such systems as autophagy and lysosomal reactivity.

A primary distinction in the evolution of the disease would refer to how lysosomes are targeted as sites of predilected progression. Deterministic parameters of such progression might imply a reconstitution of events as characterizing neuronal cell injury in developmental terms.

One might speak of lysosomal initiation of a series of steps in determining subsequent susceptibility to injury borne out by diverse pathways inducing abnormal cell membrane and organelle turnover. Such constitutive turnover dynamics might strictly redefine the Alzheimer disease process beyond just pathobiology indices of etiology type.

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