International Journal of Molecular Medicine and Advance Sciences 2 (1) : 109-114, 2006

Aberrant Neurofilament Trafficking and Membrane-Anchored Proteolytic Events Constituting Transformation of Senile Brain Atrophy to An Alzheimer Disease Process

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Abstract: A self-progressive neurodegenerative event of Alzheimer type would involve a distinctive process of increasing membrane proteolysis as the cause of neuronal cell death and of various aberrant attempts at dystrophic recovery. Indeed, a conceptual distinction of the Alzheimer process from senile brain atrophy might arise as a strict phenomenon of evolving protein-protein interactions and of various aberrant patterns of intracellular protein trafficking that mark out the Alzheimer neurodegenerative event as paradoxically both constitutional and possibly also of acquired nature. In terms, indeed, of a progressive phenomenon of atrophy of the brain that is neuronal in specific pathogenesis but also arising inherently as a neurodegenerative series of aberrant pathway attempts at recovery of injured neurons, a single event of degeneration would arise from proteolytic involvement of the neuronal cell body. It is in terms of such a postulated integral event of self-progressive proteolysis arising and evolving within neuronal membranes that there would be implicated not only ApoE isoforms but also Presenilin-1 and –2 as membrane-anchored molecules of progression in the Alzheimer process. Indeed, an integral neurodegenerative event of neuronal membrane processing would arise and proceed as a series of synaptic and neuritic dystrophic forms of activity specifically distinguishing the disorder from simple senile brain atrophy. It is perhaps in terms of quantitatively significant degrees of increased neuronal cell loss that Alzheimer disease would indeed constitute an active participation of various membrane-based transformations ranging from ubiquination to proteolysis to protein-protein interaction and lipid metabolism to Ca2 + /K + channeling as one constitutive Alzheimer process with added acquired dimensions.

Key words: Neurodegenerative, proteolytic, neurofilament, disease, membrane

INTRODUCTION

APO E NEURONAL EXPRESSION REFLECTS THE ALZHEIMER NEURODEGENERATIVE PROCESS IN TERMS OF ABERRANT ATTEMPTS AT NEURONAL RECOVERY

Apo E is a major plasma lipoprotein that functionally distributes cholesterol within cells in a manner whereby mobilization of such cholesterol in some way integrally involves its utilization in nonrecovery of neurons, not simply as neurons, but especially in terms of oligodendroglial and ependymal participation in possible neuronal recovery[1].

An essential interaction between Beta-amyloid deposits in the core of the senile plaque appears a fundamental aspect of blood flow and of transudation through a vessel wall as reflected in a rise of Apo E expression in neurons in the Alzheimer brain. Indeed, it might be valid to consider such Apo E expression as a mode of participation of neuronal reactions within a scheme of mobilization of cholesterol that constitutes secondarily dynamics of Beta-amyloid deposition in senile plaques. Cholesterol metabolism would promote tau phosphorylation and also the formation of Beta-amyloid-lipid particles as a cascade phenomenon[2].

In general, membrane lipid disturbances might account for many features of an Alzheimer process in terms of origin and progression of neurodegenerative pathways of dysfunctional membrane signaling and permeability[3].

That, for example, the Beta-amyloid deposits are basically deposits in the vascular wall related to the senile plaque core allowing or even promoting further accumulation of such Beta-amyloid might perhaps further its deposition; this might perhaps be analogous to different types of congophilic angiopathy that affect not only cerebral cortical vessels (as seen often in the

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occipital region) but also in small leptomeningeal vessels. Indeed, nonplaque amyloid appears increased in Alzheimer patients[4].

Such considerations would constitute an intricate participating role of the microcirculation in an overall abnormal process of cholesterol mobilization. Neuronal expression of Apo E would reflect an exogenous source of Apo E somehow converted to endogenous accumulation within neurons, and implicating glial cells as a series of neurodegenerative mechanisms of Alzheimer type.

Active participation of astrocytes, oligodendrocytes and ependymal cells would involve various mechanistic pathways of initiation and also of progression of neurodegeneration of Alzheimer type that contrast with the essential nonexistence of Apo E in normal neurons.

Even in terms that would actually constitute an active implementation of neuronal injury provoking progression of the neurodegeneration, Alzheimer process development might evolve as essential transformation leading to various multiple systems akin to such Apo E expression in neurons. In fact, disturbed proteolysis might be implicated in the generation of abnormal processing events and of accumulative phenomena in the Alzheimer process[5].

That Apo E expression in neurons is a recognized risk factor for sporadic late onset Alzheimer's might perhaps be a function of the late age onset of the neurodegeneative activity constituting a full series of trafficking defects intraneuronally and resulting in both active degeneration and various attempts at neuronal recovery. For example, presenilin-dependent proteolysis by gamma secretase appears to involve a dual pathway of cleavage of amyloid precursor protein and of CD44 as an adhesion molecule mediating nuclear signaling[6].

An abnormally induced neuronal response might in general terms implicate an integral role for the Apo E neuronal expression as possibly self-propagated deposition of Beta-amyloid in senile plaques. Indeed, aberrant neuritogenesis would itself tend to evolve as a source of continuing neurodegeneration in Alzheimer's. Beta-amyloid as a stimulus for such aberrant neurogenesis would perhaps integrally constitute the true nature of an Alzheimer process that underlies its progressiveness as a series of mechanistic attempts at recovery of the injured neurons. However, senile plaques might contribute not only to characterization of the Alzheimer neurodegeneration but also to various transforming pathways of induced neuronal non-viability per se. In this sense, especially, unfolded protein responses and endoplasmic reticulum-associated protein degradation pathways would implicate Presenilin-1 gene mutations in mechanisms of inhibited proteolysis by the ubiquitin-26S proteosome system as seen in early onset Familial Alzheimer disease[7].

A SINGLE END-PATHWAY OF ONSET, PROGRESSION AND PERSISTENCE OF ALZHEIMER DISEASE ACTIVITY AS VARIOUS PRIMARY PATHOGENETIC SYSTEMS OF PATIENT PREDISPOSITION

A central problem in trying to understand implications of the E4 allele of the apolipoprotein E in the late onset Alzheimer process is that the Apo E genotype might actively contribute not only to the essential disease process but especially to quantitative differentiation of the Alzheimer process from the senile brain atrophy.

Such a process might implicate protein oxidation and oxidized Apo E5 participation in inefficient recycling of Beta-amyloid lipid[8]. It is in terms specifically related to progression of neuronal damage that one might possibly link specific neuronal membrane lipid pathways of degradation to fundamental aspects of the Alzheimer process evolving in a distinctively persistent and progressive fashion. In this regard, amyloid precursor protein proteases clearing would involve axonal vesicular trafficking and signaling pathways determining developmental cellular activity[9].

It is therefore perhaps useful to consider the E4 allele of Apo E as directly reflecting a series of mechanisms that permit stimulatory disease-related factors to evolve within a context of neuronal damage. Such a concept would perhaps help distinguish the Alzheimer process as a series of disease-related factors that contrast with simple brain aging and senile brain atrophy.

Actual induction of the Alzheimer disease process would not only involve increasing persistent progression of the neurodegeneration but also transformation of such events as different modes of precipitating onset.

Intramembranous and juxtamembranous proteolysis would implicate cell fate determination pathways, regulatory growth responses and even sterol regulation as key cellular signaling pathways as implicated particularly in Alzheimer's disease[10].

The neurodegeneration in Alzheimer's might be compatible with a multitude of actively progressing pathways[11], and with a single series of pathways steps including gamma secretase activity[12] that dominantly determine disease onset, progression and persistence in a manner distinct from simple senile brain atrophy. Nicastrin and presenilins would functionally constitute a multimeric complex involving gamma secretase activity as intramembranous proteolysis of Notch and Amyloid

precursor protein[13]. Subsequent intranuclear translocation of a cleaved amyloid precursor protein fragment would perhaps interfere with transcription[14].

MEMBRANE-BASED PROTEOLYTIC ACTIVATION IN PROTEIN-PROTEIN ACTIVATION AND IN FOLDING/UNFOLDING AS AN ENDPATHWAY IN ALZHEIMER'S DISEASE

An evolving system of proteolysis that involves protein-protein interactions that is membrane-based might revolve around fundamental protein folding and unfolding events[15].

Also, endoplasmic reticulum stress would induce protective chaperone induction and translational expression-such mechanisms would be impaired in cases of presenilin-1 initiation and contribute to apoptosis of neurons[16]. Calpain, a Ca2 + dependent protease, may be regulated by presenilins[17].

Indeed, there would ultimately develop abnormal patterns of cell and organelle/system signaling that are translated as neurodegenerative activity. The possible forms of membrane damage accompanying such membrane-based proteolysis and subsequent folding/unfolding would constitute progressive proteolysis in terms of persistent ubiquination and proteosome activity. Increased production of the 42-residue Beta-amyloid peptide would also be involved in such a process[18].

Persistent ongoing activity of a proteolytic pathway has been demonstrated for intramembranous gamma-secretase proteolysis of amyloid precursor protein at the Amyloid Beta 40 and Amyloid Beta 42 cleavage sites. This would in different ways remain activated as a possible endpathway for neurodegeneration that is related to membrane-based injury or protein-protein interactive type.

If is, for example, the central role of Beta-amyloid core deposits in senile plaque evolution as related to both adhesion and subsequent dystrophic neuritic growth response that a series of reactions would implicate progressive proteolysis. Persistent proteolysis might strictly distinguish the Alzheimer process in a manner based on persistently activated pathways involving cell membranes as a neurodegenerative process. Aberrant preservation of membrane components subsequent to activated mechanisms would involve signal translocation to other subcompartments of the neuron; these would be based on phenomena that, as protein-protein interaction and folding/unfolding of such protein molecules, effectively characterizes the Alzheimer process as distinct from simple senile atrophy of the brain.

Notch receptor signaling would constitute effective tissue processing and proper cell-fate determination arising from intramembranous cleavage activity analogous to that of gamma secretase proteolysis of amyloid precursor protein in Alzheimer disease[19].

INAPPROPRIATE TROPHIC EFFECT IN SYNAPTIC LOSS AND IN DYSTROPHIC NEURITOGENESIS OF ALZHEIMER TYPE

An essential developmental process of enhanced cortical synaptogenesis would progress in APPv717F transgenic mice in a manner associated with early hippocampal atrophy and with subsequent decrease in synaptic density, concurrent with aging of these transgenic mice. This aspect of neurodegenerative atrophy that is directly related to a developmental phenomenon might perhaps be associated with amyloidogenesis as enhanced neuritogenesis and of synaptogenesis resulting subsequently in synaptic loss and in aberrant synaptic dystrophy. Such a phenomenon of progressively induced synaptogenesis and of neuritogenesis would directly provoke eventual overall synaptic loss in terms of abnormally maintained trophic effects. Such an overall scheme might progressively deteriorate as a series of attempts at neuritogenesis leading to aberrant morphogenesis. In fact, the dystrophic features of neuritogenesis would help account for much of the decrease in synaptic density observed with aging of the APPv818F mice[21].

Such features would, in various ways, implicate neuritogenesis as an abnormal sustainment of trophic effect provoking synaptic loss in Alzheimer's disease. It would, in addition, perhaps account for integration of a dystrophic neuritogenesis as a concurrent process component in terms of an accelerating trophic effect depletive process. The Beta-amyloid deposits might constitute both a consequence of such catabolism of synapses and also a source for stimulation of dystrophic neurogenesis. Synthetic routes for Beta-amyloid would correspond to similar aspects of release of the intracellular domain of mutated amyloid precursor protein. However, gamma secretase activity preferentially processes amyloid precursor protein rather than implicate nuclear signaling in cases of APP mutation[22].

DELAYED TERMINATION OF Ca2 + /K + CHANNELINGINFLUENCINGPROTEIN-PROTEIN INTERACTION IN CASES OF MUTANT PRESENILIN-1

Facilitation of intracellular Ca2 + entry subsequent to membrane depolarization might constitute a system of

activation of calcium ion channels that is related to a persistent opening state of the ion Ca2-channel, once opened[23].

Such a system involving a delay in closing of Ca2 + channels might be related to larger medium and late after-hyperpolarization developing subsequent to delayed termination of calcium ion elimination.

The role played by mutants of human Presenilin-1 in delayed closure of Ca2 + ion channeling might relate to a biophysical defect in the coupling of depolarization and of subsequent hyperpolarization of the membrane with actual ionic flux of Ca2 +. Indeed, voltage-dependent K + channels and increased levels of intracellular Ca2 + would rise above usual levels within a system that functions or malfunctions as degrees of activation of both Ca2 + and K + channels.

Presenilin-1 as a membrane-anchored protein molecule of unknown function influencing protein trafficking with regard to the endoplasmic reticulum, and the Golgi apparatus, might also be associated with the plasma membrane via influences on ionic channels. This would account for the spatial paradox involving protein-protein interactions and influences exerted by delayed termination of Ca2 + /K + channeling[24] .

MULTIGENIC ETIOLOGY AND PATHOGENESIS AS MULTIPLE CONTRIBUTORS IN SPECIFIC CHARACTERIZED PATTERNS OF ALZHEIMER NEURODEGENERATION

Non-Mendelian inheritance, as a strict pattern of inheritance, and as multi-gene biology, would constitute a plethora of effects involving functional genomics beyond simple interactions between individual genes[25]. In the regard, estrogen replacement therapy would reduce the risk for sporadic Alzheimer disease in postmenopausal women[26].

In terms of a multi-alleleic involvement in the pathogenesis of neurodegeneration[27], fixed stereotyped forms of neurodegeneration such as Alzheimer's, Parkinson's and amyotrophic lateral sclerosis would be suggestive genomic influences in pathogenesis that distinguish familial from sporadic forms of a strictly integral neurodegenerative event. The similar processing events occurring intramembranously, for both amyloid precursor protein and Notch, might effectively redefine Alzheimer disease as a specific disturbance of cell fate determination[28,29].

Alzheimer's disease might actually co-occur with a Parkinson's disorder within a system that is based on individual hereditary traits determining both cognitive defect and Parkinsonism as a seemingly integral neurodegenerative event. Indeed, such an association of Alzheimer's with Parkinson's might assume various forms of combination relative to progression. An apparently finite form of progression towards affliction patterns of neurodegeneration would characterize the temporal lobe dementia with Parkinsonism associated with chromosome 17 on the one hand, and the development of cortical Lewy bodies in patients with cognitive disorder, on the other.

A full resolution of the problem of Alzheimer's would implicate a neurodegenerative event dependent on specific foci of involvement of neurons in the CNS. Also, it would appear that intrinsic attributes of neurodegeneration would relate especially to combined neuronal body and axonal involvement determining a dendritic participation. Formation of neurofibrillary tangles, in particular, together with dystrophic neuritogenesis, would perhaps specifically integrate the Alzheimer pathology as a single neurodegenerative event.

The essential concept of ongoing pathology in the etiopathogenesis of Alzheimer's would have to be modified in terms particularly of an essential setting of multiple potential pathways of possible subsequent evolution, as in terms relative to apolipoprotein profile, estrogen/menopausal status, vascular/ischemic processes, and amyloid deposition. Also, in particular, proteases implicated in Notch receptor activation would follow pathways of activity closely analogous to those of gamma-secretase cleavage of amyloid precursor protein[30]. Indeed, a scheme of evolving effect that fluctuates not only in terms of degree of dementia, but also in terms of the nature of essential neurodegenerative activity in that particular patient, might specifically characterize the Alzheimer process as distinct from simple senile process of brain atrophy.

A multigenic etiopathogenesis in Alzheimer's would implicate multiple pathways as a paradoxically centrally integral neurodegenerative event.

NEURONAL CYTOSKELETAL DETERMINATION OF TRAFFICKING DYNAMICS REFLECTED IN PRESENILIN 1 AND 2 AGGREGATION

The essential membrane anchorage of Presenilin 1 and 2 as polytopic membrane associated aspartyl proteases[31] might induce the aggregation of molecules that in some way would be involved in interconversion between Presenilin 1 and Presenilin 2 protein forms[32]. Such considerations would be significant in terms of the catalytic subunit role of Presenilin in intramembranous cleaving activity of the gamma secretase complex[33]. Presenilin 1 and 2 as highly homologous proteins might involve an essential membrane-related event that in

possibly different ways would determine Presenilin-1 and Presenilin-2 especially in molecular aggregation events as an ongoing process of potentially abnormal transport and of abnormal accumulation; these would essentially characterize the primary Alzheimer process. Also, Notch signaling would implicate an associated pathway of specific cell fate determination induced by Presenilin cleavage of Notch receptor[34].

Membrane-associated accumulative aggregation of Presenilin 1 and 2 would constitute a phenomenon in some way inter-related with endoplasmic reticulum subcompartments and possibly also with the Golgi apparatus. Also, Glycogen synthase kinase-3 beta, in a context of Presenilin-dependent gamma-secretase cleavage of amyloid precursor protein, would promote amyloid plaques and also phosphorylation of tau protein[35].

Particularly significant is the interaction of the endoplasmic reticulum with the cytoskeleton of the cells in a process implicating Presenilin 1 and 2. Association of Presenilin 1 with accumulation of Beta-amyloid precursor-like protein 1 and TrkB (which are affected by loss of Presenilin 1 activity) might implicate intracellular trafficking involved in accumulative aggregation of Presenilin 1 and 2 within the neuronal body, particularly as a function of the cytoskeleton. Presenilin-1 would act also as a negative influence on signaling systems via the Wnt/beta-catenin pathway.

INTRANEURONAL TRAFFICKING OF TAU INTERACTING WITH PRESENILIN IN TAU ISOFORM EXPRESSION

Essential shifts in Tau isoforms might operate as functions of neurofilament trafficking and link up with Presenilin membrane anchorage in an overall phenomenon that permits both active and passively dynamic processes of accumulation of aggregation and of hyperphosphorylation of Tau subsequent to its accumulation[36].

The strict compartmentalization of different isoforms of Tau, especially within axons and neurites as noted normally, or within the neuronal somas as seen particularly in Alzheimer's disease, might constitute a dynamism reflecting accumulation and also regeneration of new tau isoforms at sites of accumulated Tau isoforms. The generation of longer isoforms of Tau associated with the formation of Tau spheroids in spinal cord axons in cases of an experimental hindlimb abnormality, might constitute a self-amplified production of more of the same Tau isoform that does not just implicate a simple passive phenomenon.

An integral process that allows Tau filament generation to acquire true biologic attributes beyond simple physical accumulation[37] might implicate isoform identity of the Tau filament as an expression of specific generative processes linked directly to biology of neurofilament trafficking arising from membrane-anchored proteins such as Presenilins.

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