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Characterized Susceptibility to Apoptosis

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Abstract: Induced progression of a whole heterogeneous series of apoptotic pathways involved in various forms of neurodegeneration ranging from clinical dementia to selective neuronal subset depletion would implicate a realized form of evolving injury to nucleus and cell organelles such as mitochondria. Windows of susceptibility in the development of such injury might allow for the development of pathways of promoted transformation as best depicted in age-related dementia of possibly multifactorial type. One might indeed recognize dynamics of nuclear and mitochondrial membrane injuries that allow for further delineation of factors of evolving change that globally participate in subsequent progression. Etiologic and pathogenetic involvement of injury in the precipitation of apoptotic pathways might allow for a redefinition of injury to cells beyond simple concepts of induced effect. Moreover, progression might indeed allow for the subsequent delineation of events as borne out by the clearly defined schemes of prototypical events evidenced morphologically in terms of Alzheimer-type neurodegeneration or in the synucleinopathy of Idiopathic Parkinson's disease.

Key words: Apoptosis, heterogeneous, ftioligic , pathogenetic

PROAPOPTOSIS AS MEMBRANE AND CYTOSKELETAL INVOLVEMENT

A proapoptosis that is membrane progressive would incorporate an ischemic/hypoxic series of induced events that program an initiated event of protease inhibition or loss of such protease inhibition[1]. A dynamic give-and-take series of protease inhibition steps versus protease inhibitor loss would in various ways characterize a full spectrum of cell programmed death pathways ranging from membrane cytoskeletal to enzymatic and substrate modes of origin and progression as proapoptosis.

Such dynamic protease inhibitor loss would involve apoptosis as an actively programmed process in progression and paradoxically as a loss of actively induced programming in its onset. Onset and progression of apoptosis would appear antithetical in terms arising from insults affecting protease inhibitors and loss of such protease inhibitors.

AGGREGATED TAU AND ANTI-APOPTOSIS

Hyperphosphorylation of tau that specifically induces aggregation of tau as intracellular inclusions would constitute modes of intermolecular aggregation that operatively implicate such mechanisms of injury as oxidative stress[2]. Apoptosis appears an altogether alternative pathway of progression implicating a termination of evolving cell injury within contexts of neurodegenerative progression.

Neurodegeneration primarily would incorporate a realized system of progressive cell injury that is compounded by disrupted apoptotic pathways. Hence, a progression in neurodegeneration would be coupled with antiapoptotic pathways in inducing further evolving injury as exemplified by aggregation of phosphorylated tau.

MITOCHONDRIAL MEMBRANE PERMEABILITY BREAKDOWN

Interactions between apoptosis and various forms of cellular injury would directly and indirectly implicate permeability of mitochondrial membranes particularly to mediators as prototypically represented by caspase 3[3]. It might be significant to consider how oxidative stress is indeed primarily a result of effective generation of free oxygen radicals by oxidative phosphorylation specifically localized to the mitochondria. To further sublocalize various events that promote additional injury to the mitochondrial membrane there would be implicated lipid peroxidation as progressive membrane injury.

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Correlative interactions of apoptosis and oxidative stress injury would perhaps involve a mitochondrion that is progressively self-conducive in further promoting release of caspases into the cell cytoplasm. It is such extramitochondrial release that would permit the delineation of apoptosis beyond simple considerations of how injury does indeed arise in terms either of necrosis, infarction or neurodegeneration.

BEYOND APOPTOSIS IN INFLAMMATORY PROGRESSIVENESS

Inflammation appears a predetermining series of factors that interacts with hyperoxia in determining the onset and progression of various pathways of programmed cell death delineating thus a multitude of free oxygen radical-related forms of cell injury[4]. One might speak of how oxidative stress is a determining factor in the mediation of inflammatory effects even in terms unrelated to just concepts of cell injury. One might speak of how cells do respond reactively to various forms of development of cell injury that bypass inflammation but induce oxidative stress.

In a simple conceptual framework of progression of apoptotic cell death pathways that would at times appear to protect against a spreading perpetuation of injury at the inflammatory level, it might be significant to consider parameters of involvement as persistently active variables in hyperoxic exposure in lung tissue. One might schematically consider how a multitude of pathways would provide programmed cell injury that interactively promotes inflammatory progression beyond simple cell recoverability or progression of apoptosis.

IS APOPTOSIS A RESPONSE TO STRESSFUL NONINJURY?

Hyperoxia of alveolar epithelial cells and of bronchial epithelial cells appears to activate a programmed cell death pathway that is not apoptotic[5].

Indeed, a dichotomous pathway of cell death progression that is non-necrotic might help redefine nonapoptosis as a series of attempts at recovery of the injured cell exposed to stress. Indeed, the secretion of NF-kappaB might help clarify a situation whereby a cell exposed to stress does not undergo apoptosis. One might consider apoptosis as a failed attempt at recovery from cell stress in a manner that would merge with an endstage pattern of cell death approaching cell necrosis.

The question of considering tumors as an example phenomenon of suppressed apoptosis might at some point have to take into account various aspects of a syndromic manifestation of cell death that occurs under stress but in the essential absence of progressive cell injury. It is in this regard that one might consider apoptosis as a heterogeneous phenomenon of nonrecovery from stressful events that are noninjurious as far as organelle function is concerned.

ADENOMAS AND PREMALIGNANT TRANSFORMATION

Neovascularization of hyperplastic islet cells would appear to contradict a basic premise implicating angiogenesis in tumor cell progression. Such neovascularization would concern primarily hyperplastic groups of cells rather than neoplasms[6]. One might speak of hyperplasia as both a benign proliferation of islet cells and also as a premalignant predisposition leading generally to neoplasia.

In considering such aspects of a proliferation of islet cells as hyperplasia in terms of loss of apoptotic activity there would develop a variable susceptibility that progresses as either pure hyperplasia or as a pure neoplastic process. Variant cellular proliferation would be distinct from either hyperplasia or neoplasia in terms essentially of non-precarcinogenesis.

EXTRA-AND INTRA-CYTOPLASMIC FACTORS OF INFLUENCE

Herniation of the inner mitochondrial membrane through gaps in its outer membrane might be reminiscent of an increased pressure gradient generated within the mitochondrion itself as an intra-cytoplasmic flux phenomenon[7]. One might speak of the increased caspase activity of such affected mitochondria as an essential phenomenon evolving in terms of influx or efflux of enzymatic mediators in apoptotic cell death pathways.

Increased intramitochondrial pressure generation and herniation of inner membrane would have to be coupled with an essential breakdown at multiple focal points of the outer membrane, reminiscent of enzymatic action in its own right. Hence, it would appear that both extramitochondrial intracytoplasmic and intramitochondrial enzymatic release are responsible for increased onset of caspase activity that subsequently provokes apoptotic cell death pathways to develop and progress.

PREVENTION OF SPREAD OF INJURY TO NEIGHBORING CELLS

Nonspecificity of endonucleases for apoptotic cell death pathways would perhaps be suggestive of

supersidiary or superimposed systems of redundant apoptotic control pathways variably designated as initial fragmentation events and subsequent oligomerization of nuclear DNA strands[8].

A concept of enumeration of double strand breaks of nuclear DNA might be classically associated with a progressive sequence of DNA damage that broadly involves subsequent steps in DNA cleavage and oligomerization. Apoptosis might prove inevitable in spite of absent oligomerization of DNA double strands or in terms of enumeration of the double strand breaks.

Apoptosis might be considered as simply a mechanism limiting cellular progressive transfer and as prevention of metabolic and genetic injury to neighboring cells in transfer dynamics or infection. Ischemically injured cells might also constitute possible transfer systems of influence reflected in active pathways of apoptotic prevention of cellular injury to adjacent cells.

CELL APOPTOTIC INJURY VERSUS APOPTOTIC CELL DEATH

A concept of inevitable apoptosis might refer specifically to irreversible injury to cellular nucleus or DNA whereby initial steps in fragmentation of the DNA are self-progressive[9]. One might refer to mitochondrial damage as prior or subsequent consequence in progressive cellular injury of apoptotic type. In fact, one might speak of apoptotic cell injury in contradistinction from simple consequences of a cellular injury that is non-necrotic. Indeed, perhaps recognition of apoptosis as a series of sequential steps might help account for various lesions that inter-relate; DNA fragmentation is initially a self-progressing step in apoptotic injury versus apoptotic cell death.

VARIABLE CLINICAL EXPRESSION OFFRONTO-TEMPORAL NEURODEGENERATION

Neuropathology cannot definitively determine the clinical presence of neurodegenerative disease of frontotemporal type and would be suggestive of a variable phenomenon of expression of lesions arising directly from involvement of different neuronal subsets[10].

A selective vulnerability of neurons to frontotemporal dementia might be associated with how such dementia assumes dimensions of clinical involvement independent of neuropathologic manifestations of progression. It might be reasonable to consider how a full array of pathologic lesions may be variably expressed clinically as different manifestations of a core process of frontotemporal dementia.

Only in terms of a frontotemporal dementia arising as a consequence of neurodegeneration can one further conclude that such degeneration is subsequently progressive as clinical manifestations of variable severity of the demented state.

DEVELOPMENT OF APOPTOTIC POTENTIAL IN ALZHEIMER'S

A defect in maturation of neuronal subsets in terms particularly of migration of these cells through white matter and towards the cerebral cortex might be associated with defective apoptotic activity[11]. Such defective apoptosis would relate to how developmental immaturity of such cells in fact constitutes a mechanism of failure of development for apoptotic activity linking it to ectopic neurons in white matter.

Alzheimer's disease might constitute a substrate for evolving developmental defects linking immaturity in neuronal migration to immaturity of apoptotic activity arising directly from such ectopic displacement of the neurons in the white matter. One might speak of a derangement in developmental survival of neurons that is associated with presenilin mutations.

TRANS-SYNAPTIC TROPHIC INNERVATION

Retrograde trans-synaptic influence on presynaptic neurons appears to specifically implicate cell adhesion molecules and pore formation mediating the transfer of both molecularly based phenomena of membrane conformation and also secretory trophic factors[12]. An integral combination of both types of influence would induce either potentiation or depression of the presynaptic neuron and also of adjacent neurons within a radius up to 100 um in diameter field. It appears significant that trans-synaptic modulation appears a parallel phenomenon of anterograde and retrograde transfer that cooperatively induces a dual neuronal pathway incorporating the trans-synaptic cleft structure.

A model consisting primarily of the dense synaptic structure might help elucidate both anterograde and retrograde transmission influences that account for fundamental trophic phenomena of potentiation of innervation at the neuromuscular junction.

NONRESPONSIVENESS TO NERVE-GROWTH FACTOR

Neurotrophic action appears primarily to arise as a function of recoverability of cells from a variety of lesions

ranging from ischemia to specific forms of neurodegeneration[13]. It might be significant that neuronal cell injury progresses in terms of how such cells in fact do produce neurotrophic factors such as Nerve Growth Factor (NGF).

A tight coupling of cell injury to NGF and basic Fibroblast Growth Factor production might entail the evolution of patterns of cell response based primarily on neurotrophin production rather than on specific types of cell injury as applicable to neurodegenerative states in particular. Neurodegeneration might arise in terms that primarily involve nonresponsive neurons to various neurotrophic factors such as NGF.

REDUCED RNA-MEDIATED SYNTHESIS AND IMPAIRED DNA REPAIR

Appropriate activation of cell cycle activity via an influence of cdc appears instrumental in a generalized phosphorylation phenomenon affecting particularly the transcriptional regular RNA polymerase II[14]. Such phosphorylation appears central to an evolving process involving reduced RNA levels in cells and decreased protein synthesis.

It might be significant to recognize cell cycle activity as a cardinal regulatory mechanism in cell protein synthetic processes that directly determine viability of neurons in general. Neurodegenerative states might arise and progress largely in terms of such decrease in RNA-mediated protein synthesis that depletes the cells particularly in the ability to repair DNA damage.

VASCULAR HYPERPERMEABILITY IN COTTON WOOL PLAQUE FORMATION

Cotton wool plaques appear as eosinophilic balls without a central amyloid core and are associated with nonreactive microglia[15]. In terms of a pathogenesis primarily arising as a deposition of material from hyperpermeable vessels as with a congophilic related disorder, such cotton wool plaques might mark sites of collected hyperpermeable vessels in Alzheimer's disease. Hyperpermeability of the wall of groups of blood vessels may correlate possibly with oxidative stress injury to neurons and neuropil in the further evolution of neurodegeneration of Alzheimer type, irrespective of the familial or sporadic nature of the primary disorder.

NEURODEGENERATION AS A DISORDER OF PROTEIN MOLECULAR ASSEMBLY

Tau filament toxicity appears a toxic influence irrespective of fibrillogenesis[16].

Indeed, one might speak of an accumulative phenomenon of aggregation primarily concerned with evolving responsiveness of neurons as a primary event in neurodegeneration of tauopathy type. In a more broad sense, one might speak of a neurodegeneration that induces protein molecular aggregation as reflected in tau molecular filament aggregation and in neurofibrillary tangle formation. In this sense, also, neurodegeneration might be characterized as a disorder of protein assembly within neurons.

OXIDATIVELY TRANSFORMED ALPHA-SYNUCLEIN AS NONSPECIFIC ATTRIBUTES OF NEURONAL PATHOPHYSIOLOGY

A potential conversion of labile to proteinase-resistant alpha-synuclein might redefine synucleinopathies as an inhibited proteolysis of a range of protein products including alpha-synuclein itself[17]. One might view tissue localization of abnormal synuclein as an expression of how disease processes affect neurons as regional cellular subsets. Oxidatively transformed synuclein would perhaps best account for modes of progression of alpha-synucleinopathies involving either the brain stem, hippocampus, or cortex, irrespective of actual attributes of specific neuronal physiology or pathophysiology.

PARKINSONIAN NEURODEGENERATION AND FREE OXYGEN RADICALS

Free oxygen radical-induced injury to dopamine-containing neurons of the zona compacta substantia nigra appears an axial mechanistic pathway leading directly to the evolution of various forms of possible cellular outcome[18]. It is perhaps in understanding the full spectrum of cellular forms of involvement as neurodegeneration that one might better delineate Parkinson's disease as a further step in progression of free oxygen radical-induced injury.

Large neurons with increased content of iron involve secondarily bound neuromelanin. Neurodegeneration in Parkinson's is indeed a series of lipid peroxidation and protein oxidation pathway steps in promoting even more iron deposition and free oxygen radical-induced injury.

A vicious circle of promoted injury to neurons in the substantia nigra would best account for a particular tendency for neurodegeneration that induces even further degeneration. This would relate to lipid and protein chemical participation in both production and further extension of injury as induced by free oxygen radicals.

Neurodegeneration would prove a form of self-sustained progression of endogenous free oxygen radical generation associated with promoted self-progressive injury to neurons and to melanin-bound iron accumulation.

NEURONAL ADAPTABILITY TO ACTIVATED NEURODEGENERATION PATHWAYS

Neuroinflammation appears a system of injury that affects aging and related phenomena of neuronal degeneration[19]. Aging may not only prove a susceptibility window for the development of neurodegeneration but may act in the precipitation of the neurodegenerative process that is activated as an on/off mechanism of progression or nonprogression.

In terms relative to a switching on of mechanistic activation of neuroinflammation as primarily a process of neuronal injury and loss, one might speak of aging as a process whereby such activation responds to various parameters of active participation.

Lipid peroxidation would appear one particular aspect of increased susceptibility to disease onset that is distinct from subsequent strict considerations of how that activated disease process progresses. Activated disease processes of neurodegeneration would relate solely to dynamics of onset of the disease process irrespective of whether subsequent disease process is relentlessly progressive or relapsing/remitting or even a chronic system of increased susceptibility to various injurious agents.

Activated systems of neuronal susceptibility would subsequently progress in terms largely of activation of the neurodegeneration as an initial pathway of subsequent dynamics of potential progression or evolution. Neurodegeneration would evolve as a susceptibility whose progression clinically and pathophysiologically is largely related to activation of pathways subsequently evolving in this or other direction related to neuronal injury or adaptability.

PROTEIN MOLECULAR MISFOLDING AND ACCUMULATION

A spectrum of interactivity between neuronal intranuclear inclusions and coiled bodies and also promyelocytic leukemia protein would appear to arise as part of the CAG repeat expansions in neurodegenerative states[20].

Multiple molecular aggregates would interact not simply as an ubiquitination-proteasome system of degradation of protein but especially as dynamic interactivities inherent to inclusion body formation in the nucleus. One would perhaps consider how intranuclear protein aggregation arises as a progressive accumulation that is based on intermolecular interactivity. Indeed, there would seem to develop aggregation as specific reactive patterns based on dynamics of intranuclear transport pathways. Capsular molecular aggregation around intranuclear inclusions might constitute the prime molecular mechanism for molecular interactivity; such interactivity would prove an accumulative phenomenon involving protein molecular targeting and also activation of various clearance mechanisms in yielding progressive neuronal injury and disease.

A whole series of systems progressing as various pathways of accumulation, deposition and aggregation of molecules would prove not only possible consequences of protein molecular misfolding but also possible subsequent interference with intranuclear transport as part of such aggregation deposition as accumulative events.

CONCLUSION

It appears significant that apoptosis is a derived consequence of different forms of injury to cells that evolve as subsequent progression of such injury. In terms of a dual involvement with increasing age of neurodegeneration and also an increased susceptibility to tumorigenesis, one might relate cell apoptosis as a mechanistic pathway of transforming type. It is especially in view of neuronal cell subset loss that globally progresses as focal groups of apoptotic cells that Alzheimer's disease and other clinically distinct types of neurodegeneration implicate a phenomenon of selectivity characterizing heterogeneous systems of induced apoptotic cell death. Neurodegeneration would prove an outcome phenomenon in the introduction and subsequent progression of lesions affecting cell membranes and nucleus or mitochondria. Only in terms of suborganelle dysfunctionality can a variety of progressive steps appear significant in the pathogenesis of a lesion that is neurodegenerative and cell depletive in different phases of the disease.

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