The neuronal endosomal-lysosomal system in Alzheimer's disease

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Robust activation of the neuronal lysosomal system and cellular pathways converging on the lysosome, such as the endocytic and autophagic pathways, are prominent neuropathological features of Alzheimer's disease. Disturbances of the neuronal endocytic pathway, which are one of the earliest known intracellular changes occurring in Alzheimer's disease and Down syndrome, provide insight into how β-amyloidogenesis might be promoted in sporadic Alzheimer's disease, the most prevalent and least well understood form of the disease. Primary lysosomal system dysfunction in inherited disorders is commonly associated with prominent neurological phenotypes and neurodegeneration. New studies now directly implicate lysosomal cathepsins as proteases capable of initiating, as well as executing, cell death programs. These and other studies support the view that the progressive alterations of lysosomal system function in Alzheimer's disease have broad relevance to the neurodegenerative processes occurring during the disease.

1. Introduction

Alzheimer disease (AD) is a complex neurodegenerative disorder characterized by a progressive and hierarchic decline in cognitive function. Neuropathologic alterations include neuronal cell loss, particularly in brain regions involved with memory and cognition, and extracellular deposits of the amyloid-β protein (Aβ) in the brain and the cerebrovasculature. The Aβ peptide is the major component of amyloid-β and the peptide most abundant in senile plaques of the brain parenchyma in patients with AD and individuals with Down syndrome (DS) [48], who invariably develop AD [60,106]. Another neuropathologic hallmark of AD is the presence of neurofibrillary tangles, primarily abnormal paired helical filaments composed mainly of the microtubule-associated protein tau, that accumulate within neurons as the disease progresses [34].

Most cases of AD are sporadic. However, a small proportion of cases, which are termed familial AD (FAD), are caused by genetic defects that are transmitted in an autosomal dominant fashion [42,68]. Worldwide, less than 0.1% of all AD cases are caused by one of several mutations in the amyloid-β protein precursor (AβPP), a broadly expressed membrane protein whose cellular function remains unknown [91]. Cleavage of AβPP at Lys15-Leu16 of Aβ gives rise to a large amino-terminal fragment called protease nexin II or secreted AβPP (AβPPs), which in some splice variants contains a Kunitz protease inhibitor domain and which has neurotrophic properties in various cell culture systems [63]. Alternative cleavages of AβPP gives rise to Aβ1-40 peptide and smaller amounts of Aβ1-42, the Aβ species which is most abundant in senile plaques. AβPP mutations causing FAD occur within or flanking the Aβ domain of AβPP. Some of these AβPP mutations have been shown to cause increased Aβ production, which has been viewed as support for the hypothesis that the production of amyloid-β is a seminal event in AD pathogenesis [90]. The majority of early-onset FAD cases (50–60%) are due to mutations in the presenilin 1 (PS1) gene. Although the normal biological function(s) of the multi-membrane spanning PS1 protein remains unknown, FAD-causing mutations are known to increase the intracellular production of Aβ1-42/43 relative to Aβ1-40 peptide in cell lines, transgenic animals, and humans [6,21,30,87], and recent data suggest that presenilin (PS) function is very closely linked to this cleavage event [92]. The remaining cases of early-onset FAD are associated with rare mutations

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in the closely related presenilin 2 protein (PS2) [85], as well as other yet to be identified genetic mutations. Mutant PS2 and PS1 proteins appear to have pro-apoptotic effects in some systems [107]. In addition to these genetic causes, the ε4 allele of the apolipoprotein (APO) E gene on chromosome 19 is a strong risk factor for late-onset AD [24]. Polymorphisms in a growing number of additional genes, including cathepsin D [76], LRP-1 [50,76,99,104], VLDL-R [110], Fe65 [44], α2-macroglobulin [5,56], bleomycin hydrolase [32,67] and interleukin 1 [37,70] are suspected of increasing the risk for AD.

Although the genes causing the majority of FAD cases have been identified, the $>$ 80% of AD cases considered "sporadic" (SAD) are influenced by multiple genetic or environmental risk factors. While some of the structural brain changes in AD are becoming better understood, the metabolic antecedents of this pathology, particularly in SAD, are unclear. Altered processing of AβPP is considered a major event in the pathogenesis of AD, but what accelerates β-amyloidogenesis in SAD has not been identified. Moreover, although multiple cytotoxic cascades are suspected to contribute to the neurodegeneration, the mechanisms remain undefined. In this review, we focus on results from recent investigations in our laboratory and others showing the altered function in AD of two independent but interrelated cellular systems, the endocytic pathway and the lysosomal system. Both systems are critical to the processing of AβPP and other molecules of etiologic significance in AD. These studies indicate that abnormal activation of the endocytic pathway and lysosomal system in the early stages of AD leads to a continuum of progressive disturbances as the disease advances that may play a major role in β-amyloidogenesis and neuronal cell death.

2. The endosomal and lysosomal systems

The endosomal-lysosomal system is part of the cell's central vacuolar system (CVS) through which secretory and membrane proteins (and membrane lipids) are synthesized, modified, delivered to appropriate cellular compartments, and eventually degraded. This system, which is exceptionally well developed in neurons, consists of five major compartments: early endosomes, late endosomes, autophagic vacuoles, lysosomes, and residual bodies (Fig. 1). In the nervous system, the importance of the lysosomal system to proper cellular function is demonstrated by the 30 or so inherited human

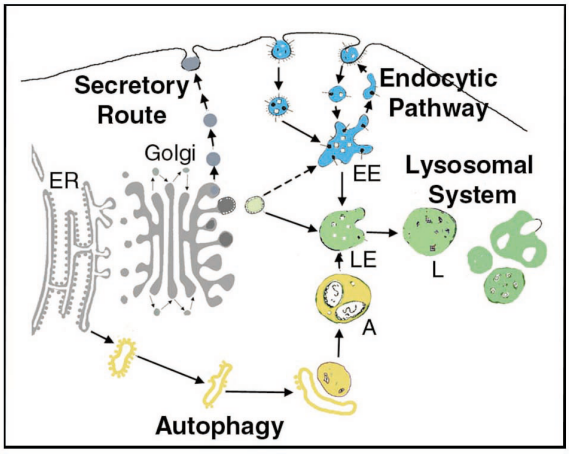

Fig. 1. This cartoon represents the neuron's central vacuolar system, which consists of a broad array of vacuolar compartments that link pathways of protein and lipid biosynthesis and degradation, cellular secretion, and internalization. These compartments in the secretory, endocytic, and lysosomal systems play a multifunctional role in the biosynthesis, sorting, processing, and degradation of many macromolecules. The endocytic and autophagic pathways intersect at the late endosome (LE), which receives material from the endocytic pathway via early endosomes (EE) as well as the autophagic pathway before directing this material to the lysosome (L). Autophagy begins with the sequestration of cytoplasm and cytoplasmic organelles within a vacuole, formed from membrane donated by the ER. This autophagic vacuole then fuses with a late endosome or possibly a lysosome. Newly synthesized acid hydrolases within the trans-Golgi network are introduced, via their interaction with the mannose 6-phosphate receptors and nascent vesicle budding, to late endosomes and lysosomes containing substrates for digestion. Undigested material accumulates within neurons in residual bodies. Figure reproduced with permission from [71].

disorders that involve defects in the synthesis, transport and/or function of lysosomal enzymes, where mental retardation, progressive cognitive decline and extensive neurodegeneration are among the most prominent phenotypic features. With the exception of these inherited lysosomal system disorders, however, prominent alterations of the endocytic pathway and lysosomal system such as those seen in AD are uncommon in neurodegenerative diseases. This underscores the distinctive nature of the neurodegenerative pattern in AD. While the endocytic pathway and the lysosomal system are part of a contiguous intracellular system, they also possess distinct biological functions. For this reason, alterations during AD in the endosomal pathway and the lysosomal system may have significant, although different, pathobiologic implications.

2.1. The endocytic pathway

In neurons, the endocytic pathway internalizes and processes extracellular nutrients and trophic factors;

recycles, modifies, and degrades receptors and other integral membrane proteins after neurotransmitter release; and directs information to intracellular biosynthetic pathways [22] (Fig. 1). Endocytosis enables neurons to modify or degrade molecules from the cell surface in intracellular compartments through a series of vesicular budding and fusion events. Early endosomes are the first major sorting station of the endocytic pathway and receive endocytosed materials from the cell surface for recycling, sorting, or transport to late endosomes and lysosomes [22]. The highly regulated trafficking of vesicles among these CVS compartments to their intended destination is controlled by a family of monomeric GTPases called Rab proteins [7,74,113]. While the turnover of internalized proteins and lipids was originally thought to be limited to lysosomes, it is now known that some acid proteases are present in early endosomes and are capable of modifying endocytosed materials. Although all lysosomal enzymes have acidic pH optima, many are active, albeit more unstable, at physiologic pH. Even those with the most acidic optima, e.g. cathepsin D, can cleave certain substrates at neutral pH. Therefore, although the lysosome is considered primarily a terminal degradative compartment, "lysosomal" acid hydrolases in other less acidic compartments, like early and late endosomes, may carry out limited proteolysis to generate new functionally important proteins or peptides.

2.2. Abnormalities of the endocytic pathway in Alzheimer's disease

Early endosomes have a special relevance to AD pathogenesis. Many of the genetic modifiers of AD risk encode proteins that depend on endocytosis for their function. The most established genetic risk factor for SAD, apolipoprotein E (Apo E), its receptor on neurons (LRP), another LRP ligand (α-2-macroglobulin), and the very low density lipoprotein receptor all are molecules that traffic through early endosomes as they bring cholesterol or other ligands into the cell. ApoE mediates the endocytosis of cholesterol into neurons [59] and has antioxidant and growth-promoting properties on cells [38,54]. ApoE also interacts with Aβ, thereby influencing its endocytosis/clearance [81], ability to aggregate [105,108], and neurotoxicity [49, 66] – effects that may all be relevant to AD pathogenesis.

The endocytic pathway is also responsible for the internalization and initial processing of cell surface AβPP. The generation of both Aβ1-40 and Aβ1-42 in endosomes is well established [39,52,94,98]. First, cultured cells stably transfected with wild type AβPP, the AβPP Swedish mutation, or AβPPswe/V717L (Indiana) mutations combined with deletion of the AβPP C-terminal endocytic targeting signal show a decrease in Aβ1-40 secretion and in the ratio of Aβ42/Aβ40, suggesting a decrease in Aβ42 production [98]. Mutagenesis of the internalization signal also reduced both Aβ40 and Aβ42 secretion [80]. Second, the expression of the dominant negative dynamin mutant that prevents endocytosis in the same transfected cell lines decreases ratios of secreted Aβ1-42/Aβ1-40 for all three AβPP constructs [98]. Third, cell models using chimeric forms of AβPP that retain AβPP in the ER, or direct AβPP trafficking to the lysosome or the cell surface indicate that production of Aβ1-40 occurs mainly in the endocytic pathway, but that Aβ1-42 was produced both in the ER/cis-Golgi apparatus and in the endocytic pathway [94].

The convergence in early endosomes of many etiologically important molecules in AD is noteworthy in light of recent findings that an apparent activation of the endocytic pathway is the earliest cellular pathology yet demonstrated in AD. Our previous studies of sporadic AD showed that neuronal early endosomes in AD brain can be as much as 32-fold larger in volume than in control brain and that total endosomal volume per neuron was on average 3-fold larger in AD cases compared to normal controls [15] (Fig. 2). These endosomal changes preceded clinical symptomatology and appeared before substantial amyloid-β accumulated in the brain [12]. Enlarged endosomes are seen in neurons from adults with DS and in some cortical neurons in infants and third trimester fetuses with DS, decades before the first evidence of extracellular amyloid-β deposition [12].

Alterations of early endosome morphology and levels or distributions of specific markers of early endosomal function strongly suggest that the neuronal endocytic pathway is activated and likely involves increased rates of endocytosis and endosome recycling [12]. The use of rab5 as a specific endosomal marker has shown that neuronal endosomes in AD brain are increased in size and volume – a morphologic change known to be associated with increased endocytic pathway activation, particularly internalization [9,35] (Fig. 2). The observation that inheritance of the APOE ε4 allele accentuates endocytic abnormalities in AD [12] suggests that genetic susceptibility for AD is linked mechanistically to endocytic pathway alterations, and possibly to β-amyloidogenesis. For example, rab4 is known to

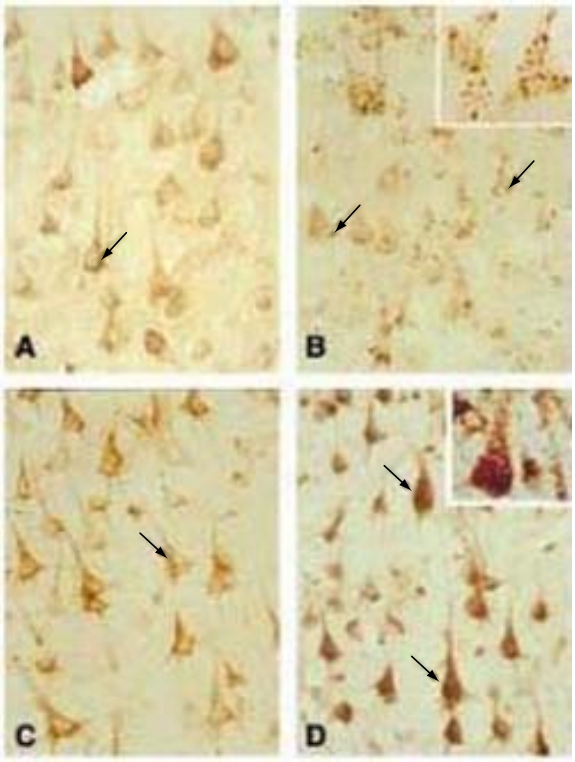

Fig. 2. Endocytic pathway and lysosomal system alterations in AD. Early endosomes in cortical neurons immunolabeled with an anti-rab5 antibody (A and B, arrows) show the striking increase in size of these compartments in the AD brain (B and B inset) compared with those of control (A). Alterations in early endosomes appeared at early stages of AD and were widespread in the AD brain. Endosomal volume in the AD cases was on average 3-fold greater than in normal control – a morphologic change consistent with increased endocytic pathway activation. Cortical neurons of normal human brain contain numerous lysosomes that are immunoreactive for the lysosomal hydrolase cathepsin D (C, arrow). Early alterations of the lysosomal system are prominent in normal appearing pyramidal neurons from a patient with AD (D, arrows) and include increased numbers of hydrolase-positive compartments, particularly at the base of the cell soma (D and D inset).

stimulate endosomal recycling vesicles when overexpressed in cells [19,26,102]. Rab4 immunoreactivity within small vesicles in lamina III pyramids from the pre-AD brains is elevated, implying greater activity of endosomal recycling to the cell surface. In addition, rabaptin 5 and EEA1, downstream effector proteins associated with rab 5 [93,97], which are involved in vesicle membrane fusion and docking, are also altered in AD brain. Overexpression of rabaptin 5 in transfected cells results in enlargement of early endosomes and increased numbers of transferrin receptor-positive vesicular compartments [9,27,35], which are morphological changes consistent with increased endocytosis [9,27, 35]. Immunocytochemical labeling of sections from early stage AD brains ("possible AD") with antibodies to rabaptin 5 and EEA1 detected early endosomes that, like the rabaptin 5-transfected cells, were morphologically identical to swollen endosomal profiles labeled with rab5 [12]. Interestingly, endosomes are normal in size in the brains of individuals with FAD caused by mutations of PS1 or PS2, which exhibit abundant amyloid-β deposition [12]. Thus activation of neuronal endocytosis in SAD is not a consequence of Aβ overproduction or amyloid-β deposition. The findings in PS FAD parallel other recent findings that, unlike sporadic AD and DS, PS-FAD is also not influenced by APOE genotype [43,101] and that PS mutations may promote Aβ generation and disease progression mainly via non-endocytic routes [64] which might not be expected to be influenced by apo E.

As discussed later, early endosome function is also influenced by lysosomal system activation, which is associated with the increased content of cathepsins in early endosomes and elevated levels of the cation-dependent, 46 kDa mannose 6-phosphate receptor (MPR46) that targets hydrolases not only to lysosomes but to early endosomes [95,96]. Notably, one of the cathepsins elevated in early endosomes, cathepsin D, has been shown to have β and γ-secretase activity toward model peptides, recombinant AβPP and the C-100 fragment of AβPP [20,29,31,58]. Other cathepsins also indirectly influence Aβ formation [4,57,68, 86,98]. Because the identification of specific hydrolases involved in constitutive Aβ production is still not complete, these studies raise the possibility that under pathologic circumstances, proteases not normally involved in constitutive Aβ formation become abnormally routed to cellular compartments within which they directly or indirectly contribute to Aβ production. Supporting this hypothesis are recent studies showing that when MPR46 expression in fibroblasts is increased by transfection, "lysosomal" hydrolases are partly redirected to early endosomes, as seen in AD brain, and Aβ secretion is substantially increased in the absence of changes in total levels or half-lives of AβPP [62].

2.3. Organization of the lysosome

The lysosomal system is a group of acidic vesicular organelles, including lysosomes, late endosomes, Golgi-derived vesicles containing newly synthesized hydrolases that are targeted to late endosomes, and residual bodies containing indigestible material such as ceroid and lipofuscin (Fig. 1). Over 80 hydrolytic

enzymes reside in lysosomes. Among them are the cathepsins, proteases with varying peptide bond specificities. The activity of these proteases can generate either smaller functional proteins/peptides or inactive peptide fragments that are ultimately degraded to amino acids and transported into the cell's cytosol. The proteins of the lysosome are synthesized on rough ER associated polyribosomes and transported through the Golgi apparatus. The majority of hydrolases destined for the major acidic compartments of the CVS are modified in the ER-Golgi intermediate compartment and cis-Golgi by the addition of one or more mannose 6-phosphate residues to their N-linked carbohydrate trees [53,78]. This signal is then recognized in the trans-Golgi network (TGN) by one of two integral membrane receptor molecules, the mannose 6-phosphate receptors (MPR), which deliver the lysosomal hydrolase via shuttle vesicles to late endosomes. The MPR then recycles back to the TGN. Vesicular transport of macromolecules to the lysosomal systems for degradation occurs along numerous pathways. The most prominent of these are the previously discussed heterophagy (receptor-mediated endocytosis, pinocytosis, phagocytosis) and autophagy, which deliver extracellular and intracellular constituents, respectively.

Autophagy is the process by which cells digest their own cytoplasmic contents, both to provide materials for new synthesis and to turnover organelles such as mitochondria [89]. Autophagy begins with a rate-limiting sequestration of cytoplasm in a membranous organelle of unknown origin and composition but believed to be derived from ER membranes (Fig. 1). The double-membrane vacuole that is formed (the autophagosome) fuses with a prelysosomal compartment – likely to be the late endosome. Whereas non-lysosomal protein degradation in cells is relatively constant, autophagic degradation may account for 0–4% of the cell's protein per hour, depending on the cell's metabolic needs. In many cells, the rate of autophagy responds by negative feedback to the concentration of cytoplasmic amino acids [73]. Lysosomal activity, in part via autophagy, is considered a key mechanism for controlling cell volume [73], and is likely to be relevant to cell shrinkage as a feature of the AD brain and as an antecedent of neurodegeneration.

2.4. Abnormalities of the lysosomal system in alzheimer's disease

Independently of alterations in the endocytic pathway, prominent activation of the lysosomal system occurs early in AD and develops in virtually all neurons within cell populations that are potentially vulnerable to the disease process, preceding the development of neurofibrillary pathology. These lysosomal system disturbances, however, probably occur after disturbances of endocytosis are evident [12]. Lysosomal system activation is represented by an increase in the number and density of lysosomes and increased gene expression and synthesis of all classes of lysosomal hydrolases, including cathepsins, as demonstrated by various investigators [3,13,69] (Fig. 2). Expression of neuronal MPR46, but not the cation-independent 215 kDa MPR, is also elevated, which partly explains the abnormally increased trafficking of cathepsins to early endosomes [15] described earlier and the increased release of cathepsins into the CSF [88]. In early-onset FAD caused by mutations of PS1 and in transgenic mice overexpressing the PS1 L146M mutation, activation of the lysosomal system is accentuated beyond that seen in SAD [61]. Lysosomal system activation progressively worsens as neurons become metabolically compromised [16]. Cathepsin D mRNA levels are particularly elevated in CA1 pyramidal neurons containing neurofibrillary tangles relative to their tangle-free neighbors [11].

While AD-related alterations of the lysosomal system far exceed those accompanying normal aging, age-related changes are appreciable and may also be relevant etiologically given that advanced age is a major risk factor for AD. In normal aging, brain levels of the aspartyl protease, cathepsin D, increase [36], but, unlike in early AD, levels of several lysosomal cysteine proteases decrease (Nixon, unpublished data). These changes are accompanied by progressive accumulation of lipopigment and ceroid in residual bodies [72]. Inhibiting cysteine protease activity markedly increases cathepsin D, which is normally degraded by cysteine proteases, and induces ceroid lipofuscinosis similar to that in aging brain [1,2,47], indicating that aging-related alterations of lysosomal function likely involve an altered balance of cathepsins and inefficient degradation of substrates.

In AD, at more advanced stages of degeneration, intact neurons display striking accumulation of hydrolase-positive residual bodies despite continued lysosomal system upregulation suggesting a superimposition of gradual lysosomal dysfunction. As AD progresses, the lysosome also becomes an important target of disease-related cytotoxic factors. One of these factors is Aβ1-42, which disrupts lysosomal membrane integrity as it accumulates, exacerbating aging-related

increases in lysosomal membrane fragility [112]. Oxidized lipoproteins that are endocytosed and trafficked to the lysosome have similar toxic effects on neurons, which are believed to be mediated by free-radical damage. As neurons or their processes begin to degenerate, lysosomal compartments and their hydrolases are released into the extracellular space [14,16] and appear at abnormally elevated levels in the CSF [88]. These acidic compartments or their component enzymes persist in brain in association with deposits of amyloid-β [16–18].

The connection between the lysosomal system and the development of AD is strengthened by additional recent genetic evidence. An exonic polymorphism of the cathepsin D gene (ala to val at position 224, exon 2), which is associated with increased pro-cathepsin D secretion and altered intracellular maturation when expressed in cell lines [100], is over-represented in an Alzheimer population (11.8%), compared to non-demented controls (4.9%) [76,77]. Carriers of this gene had a 3.1 fold increased risk of developing AD than non-carriers. Moreover, the increased risk for AD conferred by the APOE ε4 allele (3.9 fold) was additive to the effect of the cathepsin D polymorphism (odds ratio for APOE ε4 plus cathepsin D polymorphism = 19.0). Although this initial report on a small population was not confirmed in a second small study [65], the original finding has now been replicated in a larger cohort [77]. In addition, cystatin C, an intralysosomal inhibitor of cysteine proteinases, has also recently been shown to be a candidate susceptibility gene for AD [25]. This is particularly intriguing in light of the interrelationship between cysteine protease inhibition, cellular aging, cathepsin D elevation, and neurodegeneration discussed earlier.

2.5. Lysosomal system dysfunction as an antecedent to neurodegeneration in alzheimer's disease

Although caspases and calpains have received the greatest attention as key players in the execution of apoptosis and necrosis, respectively [23,103], lysosomal dysfunction has long been linked to degenerative phenomena [82]. Recently, cathepsins have been strongly implicated as a trigger of apoptosis. Cathepsin D is an essential mediator in HeLa cells of apoptosis induced by interferon, Fas/APO-1 or TNF-alpha, and cathepsin D induces or promotes apoptosis when overexpressed [28,79]. Cathepsin D gene transcription is activated directly by p53 binding to the cathepsin D promoter during apoptosis [109]. Inhibiting cathepsin D transcription or cathepsin D activity blocks apoptosis induced in caspase-inhibited PC12 cells deprived of trophic factors [45]. Several other cathepsins have also been implicated in apoptosis [46]. Mice deficient in cystatin B, an endogenous cytosolic inhibitor of cysteine proteases [10], exhibit a loss of cerebellar granule cells, apparently by apoptosis [79].

Additional evidence suggests that when lysosomal membrane stability is compromised, leakage of cathepsins into the cytosol induces apoptosis or a mixed apoptotic/necrotic pattern in various cell systems [8,33,41, 84], providing support for deDuve's original notion of the lysosome as a potential "suicide bag". Recent studies suggest that hydrolase leakage from lysosomes may initiate cell death by mechanisms upstream from the caspase-mediated cascade, rather than being an endpoint of this cascade. In cardiomyocytes [75] or fibroblasts [83], the release of cathepsin D from lysosomes into the cytosol, induced by the redox-cycling quinone naphthazarin, precedes release of cytochrome c, loss of the mitochondrial transmembrane potential, and apoptosis associated changes in morphology [83]. Direct lysosomal photo-damage in mouse leukemia cells initiates a similar cascade [51]. Ceramide, an intracellular signal that mimics the transducing effects of various exogenous stimuli causing apoptosis, binds to and activates cathepsin D [40].

These findings highlight the early role of cathepsins in certain forms of cell injury leading to apoptosis and suggest tantalizing connections between these findings and AD based on several recent observations. One involves the cytotoxic mechanism of Aβ1-42, which is taken into neurons by endocytosis and delivered to lysosomes. Relative to Aβ1-40, internalized Aβ1-42 is slowly degraded and therefore accumulates in lysosomes [112]. Lysosomal accumulation of Aβ1-42 is followed by leakage of lysosomal enzymes into the cytosol, which precedes morphological evidence for cellular toxicity [112]. Cerebrovascular disease and cerebral ischemia, which are known risk factors for AD, may compound these effects on the lysosomal system. In CA1 pyramidal neurons of monkeys subjected to transient ischemia, cathepsin B levels increased and some cathepsin B was redistributed to the cytosol hours or days before the loss of these neurons [111]. Inhibiting cathepsin B activity immediately after ischemia afforded substantial neuroprotection. The development of plaque lesions and endothelial injury in arteriosclerosis involves, in part, loss of lysosomal membrane integrity mediated by the uptake of oxidized LDL [33, 55] and may also have relevance as an additive insult in AD pathogenesis.

3. Conclusion

Prominent alterations of the endocytic pathway and lysosomal system, which we and others have identified in AD, are an uncommon morphological pattern in neurodegenerative diseases. The endocytic pathway is a unique crossroad in the trafficking of molecules key to AD pathogenesis and to Aβ generation. The upregulation of endocytosis implied by morphologic and biochemical findings in the AD brain represent a possible basis for accelerated β-amyloidogenesis in the more than 90% of all AD cases that develop in the absence of a causative gene mutation. Robust activation of the lysosomal system occurs in all neurons of at-risk populations, beginning before degenerative phenomenon are evident and progressively worsening as neurons become metabolically compromised. Lysosomal system activation is accentuated in PS-linked FAD and is reproduced in transgenic mouse models of AD. Increased autophagic degradation may contribute to the exacerbated lysosomal system response in PS-based AD. Chronic activation and/or late dysfunction of the lysosomal system reduces cell survival and could promote cell injury leading to neurodegeneration. New data implicating cathepsins in apoptosis and other forms of cell death have rekindled interest in lysosomal system dysfunction as a potential pathogenic mechanism in AD-related neurodegeneration. Further investigation of these cellular pathways, the roles of which are as yet still poorly understood in AD, should facilitate an understanding of how endocytic pathway activation and lysosomal system dysfunction could promote AD and may identify new molecular targets for early diagnosis and therapy.

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