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Review

Is aging part of Alzheimer's disease, or is Alzheimer's disease part of aging?

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Abstract

For 70 years after Alois Alzheimer described a disorder of tangle-and-plaque dementia, Alzheimer's disease was a condition of the relatively young. Definitions of Alzheimer's disease (AD) have, however, changed over the past 30 years and under the revised view AD has truly become an age-related disease. Most now diagnosed with AD are elderly and would not have been diagnosed with AD as originally conceived. Accordingly, younger patients that qualify for a diagnosis of AD under both original and current Alzheimer's disease constructs now represent an exceptionally small percentage of the diagnosed population. The question of whether pathogenesis of the "early" and "late" onset cases is similar enough to qualify as a single disease was previously raised although not conclusively settled. Interestingly, debate on this issue has not kept pace with advancing knowledge about the molecular, biochemical and clinical underpinnings of tangle-and-plaque dementias. Since the question of whether both forms of AD share a common pathogenesis could profoundly impact diagnostic and treatment development efforts, it seems worthwhile to revisit this debate.

Keywords: Aging; Alzheimer's disease; Amyloid; Dementia; Transgenic mice

At the opening of the twentieth century, Alois Alzheimer reported non-elderly demented individuals whose brains contained characteristic histopathologic features called plaques and tangles [3]. Shortly thereafter, Oscar Fischer recognized brains of elderly demented individuals also contained plaques [53]. In subsequent years, the medical community assimilated these observations so that the former situation was considered a disease and assigned a diagnostic eponym, Alzheimer's disease (AD) [105]. The latter situation was considered a normal part of aging, and for many decades hence syndromically referred to as senile dementia [4,18].

In the decades that followed, AD was a rather uncommon entity. Senile dementia, on the other hand, became increasingly prevalent as life expectancy increased. Whether or not a normal part of aging, the fact that senile dementia so adversely affected people's lives could no longer be ignored. In the second half of the twentieth century, expectations of what medical art and science could deliver were also growing. A case could be made that treating senile dementia was warranted. Up to this point, those dementing before the age of 65 had a disease, AD, and those after the age of 65 did not. The time to dispose of this arbitrary divide had come.

In a powerful and influential 1976 editorial, Katzman argued "Alzheimer disease and senile dementia are a single process and should therefore be considered a single disease" [93]. This justified making dementia syndrome research a national health priority and invigorated research into the phenomenon. Expanding the definition of AD to include those with senile dementia swelled the ranks of those diagnosed to such an extent it caused some to claim an "Alzheimerization" of dementia [1,178]. Today, AD is far and away the most commonly diagnosed dementia. When dementia overlap syndromes, such as mixed vascular-degenerative dementia are considered, the processes underlying AD (which can also drive changes of the cerebrovasculature) could be held to account for an even greater percentage of the overall dementia burden than it already is.

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Thirty years later, it is time to pay homage to the prescience of the Katzman editorial, as well as key observations leading up to it [16]. It is also time to reflect on the tremendous strides clinical and molecular neuroscience have made towards understanding both the original AD (as described by Alzheimer) and senile dementia. It seems reasonable to consider Katzman's 1976 editorial within the context of the clinical and scientific advances it helped spur. Finally, this review will attempt to discuss AD from a perspective of aging, operationally defined here as the aggregate of clinical and molecular changes that develop over the course of one's life, but which are not felt to represent an actual disease process.

1. Beta amyloid and the "Amyloidization" of Alzheimer's disease

If the field of dementia research has indeed experienced "Alzheimerization" in recent decades, then AD research can be further said to have undergone "amyloidization". Many investigators feel the key to understanding AD lies in deciphering the nature of the extracellular plaques seen in those with the disease. These plaques consist largely of an amyloid protein derivative called beta amyloid.

Amyloid proteins are beta-sheet proteins that can aggregate. When viewed by polarized light microscopy, following Congo red staining aggregations manifest a typical green birefringence pattern. Extracellular cortical plaques observed in persons with AD, elderly non-demented persons without clinical AD, dementia with Lewy bodies, non-demented persons following head trauma, temporal lobe epilepsy, the MELAS syndrome (mitochondrial encephalopathy, lactic acidosis and stroke), cerebrovascular disease and Down's syndrome largely consist of an amyloid protein called beta amyloid (Aβ) [5,83,92,107,126,136,153]. Beta amyloid, in turn, is a proteolytic degradation product of a larger protein called amyloid precursor protein (APP). Homozygous APP knock-out mice show early clinical and histologic sequellae (in the form of gliosis), which suggests APP is necessary for proper neuronal function and perhaps cerebral development [227]. Studies also demonstrate APP can influence a variety of cell processes [9,218]. Nevertheless, normal APP physiology remains poorly understood.

Considerably more is known about APP processing (see Fig. 1) [192]. Proteolysis by an enzyme or enzymes called alpha secretase(s) can occur 83 amino acids from APP's intracellular carboxyl terminal. Alternatively, proteolysis by enzymes called the beta secretases (BACE) cut 99 amino acids upstream of the APP carboxyl end. An enzyme complex, the gamma secretase, further processes the remaining carboxyl end of alpha secretase (C-terminal fragment α; CTFα) or beta secretase (C-terminal fragment β; CTFβ) digested APP. This complex consists of the following proteins: presenilin 1 or presenilin 2, nicastrin, APH-1 and PEN2 [47]. Gamma secretase proteolysis does not uniformly occur at a single amino acid, although proteolysis either 57, 59 or 61 amino acids up from the APP carboxyl terminus is most common. A second gamma secretase cut also occurs 50 amino acids from the APP carboxyl end, which generates a 50 amino acid (from the APP carboxyl end) degradation product called the amyloid intracellular domain (AICD) [156].

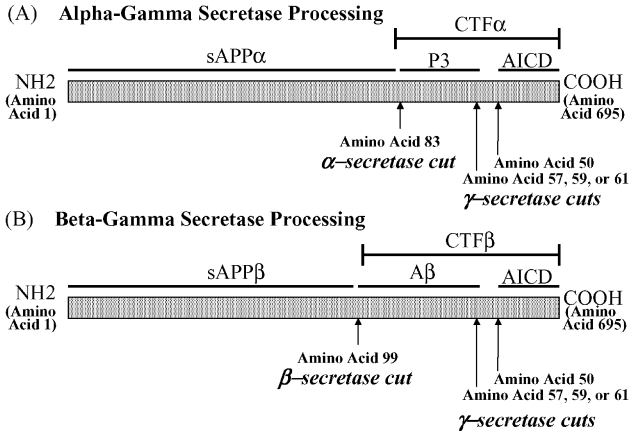

Fig. 1. APP processing by the alpha, beta and gamma secretases. Note the amino acid positions of the APP protein itself are numbered starting from the amino end, while the sites where secretases cut APP indicate the number of amino acids upstream from the APP carboxyl end. Only the key neuronal 695 amino acid isoform of APP is shown. CTF, C terminal fragment; sAPP, soluble APP; AICD, amyloid intracellular domain.

Initial data suggested AICD protein translocates to cell nuclei and regulates gene transcription via a process functionally reminiscent of Notch-mediated transcription regulation [27,42,100,189,215]. As first reported, the phenomenon involved binding of the AICD to specific cytoplasmic "adaptor proteins" (Fe65, Jip1b) followed by subsequent binding of the resulting complex to a histone acetytransferase (Tip60) inside the nucleus [27,100,215]. It was further proposed that via this mechanism AICD protein facilitated creation of a feedback loop through which APP protein status could modulate transcriptional activation of the *APP* gene itself [215]. It is important to note, though, the story of how APP protein status regulates gene expression is still unfolding. Recent data indicate AICD control of Tip60 may not involve nuclear translocation or even membrane release of the AICD fragment [28], or that APP itself may activate Tip60 through a gamma-secretase independent pathway [75].

Following sequential alpha and gamma secretase proteolysis, in addition to the AICD two other main APP degradation products are produced. The peptide flanked by the alpha and gamma secretase cuts is a 3 kDa fragment called p3. The much longer amino terminal portion persisting upstream of the alpha secretase cut is titled soluble APPα (sAPPα). sAPPα appears to act as a trophic factor [144]. Beta-gamma secretase processing precludes sAPPα production, creating instead a long amino-end fragment called sAPPβ. The 40–42 (although it can be 38–43) amino acid segment directly created by beta and gamma secretase proteolysis is the beta amyloid peptide.