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Featured Article

DNA damage-associated oligodendrocyte degeneration precedes amyloid pathology and contributes to Alzheimer's and dementia

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Abstract

Introduction: In looking for novel non-amyloid-based etiologies for Alzheimer's disease, we explore the hypothesis that age-related myelin loss is an attractive explanation for age-associated cognitive decline and dementia.

Methods: We performed a meta-analysis of data in the National Alzheimer's Coordinating Center database accompanied by quantitative histopathology of myelin and oligodendrocytes (OLs) in frontal cortices of 24 clinically characterized individuals. Pathological findings were further validated in an Alzheimer's disease mouse model and in culture.

Results: Myelin lesions increased with cognitive impairment in an amyloid-independent fashion with signs of degeneration appearing before neuronal loss. Myelinating OLs in the gray matter showed greater vulnerability than those in white matter, and the degenerative changes correlated with evidence of DNA damage. Similar results were found in myelinating OL cultures where DNA damage caused aberrant OL cell cycle re-entry and death.

Discussion: We present the first comprehensive analysis of the cell biology of early myelin loss in sporadic Alzheimer's disease.

Keywords: Myelin; Oligodendrocyte; Dementia; DNA damage; Amyloid plaques

1. Introduction

Sporadic Alzheimer's disease (AD) is a dementing illness that is associated with the appearance of β-amyloid (Aβ) peptide deposits, phosphorylated tau protein aggregates, synaptic loss, and neuroinflammation [1]. To offer an explanation of this complex condition, it has been proposed that the amyloid abnormalities drive a cascade of events that leads to the other pathological features [2]. Indeed, CSF amyloid changes are found a full 15–20 years before the onset of dementia (DEM), appearing as early as the mid-fifties [3]. Yet, while the amyloid cascade hypothesis has become the dominant AD model, the recent failures of clinical trials based on this model have stimulated a search for alternative hypothesis for this multifactorial disease in addition to the amyloid cascade [4,5]. Observations, primarily from magnetic resonance imaging (MRI), have suggested that loss of myelin represents one such alternative.

The natural history of myelination across the human life span closely tracks cognitive capacity [6,7]. Cortical myelin, particularly in frontal lobes, does not fully mature in humans until their late-thirties [8,9]. Afterward, myelination regresses, and this naturally occurring age-related loss is accelerated in AD [10]. While myelin is associated mostly with white matter (WM), myelination of axons begins and ends in gray matter (GM). This is significant as GM (intracortical) myelin is the brain feature that is most highly correlated with decline in cognitive performance in healthy humans as they age [6,11–13]. Indeed, it is thought that the GM portions of myelinated axons are the main determinants of axon conduction velocity [14]. Myelin loss, like tangles of phosphorylated tau, is not likely to be AD specific as it

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occurs in a wide spectrum of amyloid-free neurological diseases. For example, in multiple sclerosis, patients with severe cortical demyelination have DEM symptoms that highly resemble those of AD, despite the virtual absence of amyloid plaques and tangles [15,16]. Myelin loss is, therefore, a strong correlate of cognitive decline in the aging brain and as such deserves our attention as a contributor to the etiology of AD [17].

A second attractive candidate as an age-associated contributor to the AD process is the loss of genomic integrity. DNA damage may be one of the most powerful drivers of aging, particularly in brain [18–20]. Human mutations in DNA repair genes (e.g., Cockayne syndrome), virtually all cause premature aging. Like neurons, oligodendrocytes (OLs) accumulate DNA damage with age, and in DNA repair mutants, myelin abnormalities appear as part of the premature aging syndrome [21]. We recently proposed that the accumulation of unrepaired DNA drives age-related losses of OLs and myelin and that this process potentially contributes to the loss of cognition in AD and other DEMs [17]. One of the ways in which DNA damage exerts its influence is through the process of cell cycle regulation. Our laboratory and others have shown that DNA damage in postmitotic neurons can drive aberrant cell cycle re-entry and that in AD this is followed by neuronal degeneration [22–25]. A similar involvement of ectopic neuronal cell cycling in neurodegeneration is found in conditions such as ataxia-telangiectasia [26,27], and others [28]. As mature OLs (mOLs) are also permanently postmitotic [29], we set out to ask whether DNA damage in these cells might have the same effects.

Earlier studies suggested that myelin degradation in sporadic AD or its mouse models is the direct consequence of amyloid pathology [10,30,31], but these findings are difficult to reconcile with the timing of myelin loss in normal aging cerebral cortex, which is detected as early as the mid-forties [6,8,32]. Our central hypothesis is that myelin degradation is one of the earliest structural changes in the sporadic AD brain and is driven by age-associated DNA damage, independent of amyloid plaque formation. Here, our findings from MRI meta-analysis, histopathological observations of human autopsy material, longitudinal studies of mouse AD models as well as OL cell culture not only support this hypothesis but also offer an alternative explanation and pathway to sporadic AD in addition to and beyond the amyloid cascade.

2. Method and materials

2.1. NACC-MRI data sets

A cross-sectional data set of a longitudinal study cohort was obtained from the National Alzheimer's Coordinating Center (NACC). This is a database with standardized research data from 39 Alzheimer's centers in the United States [33] (http://www.alz.washington.edu/). A summary data set of MRI scans of 507 subjects from one of the centers was analyzed. The analysis protocol is summarized in Supplementary Methods, and the demographic details of the subjects are listed in Supplementary Table S1.

2.2. Human brain tissue

Postmortem brain tissue was obtained from the National Institutes of Health NeuroBioBank at The University of Maryland and the Human Brain and Spinal Fluid Resource Center, CA with approvals from the Tissue Access Committee of NeuroBioBank and The Hong Kong University of Science and Technology human research committee. Subjects with amyloid plaque–free DEM, AD, and age-matched normal controls (NCs) were requested; any cases with parkinsonian disorder or depression were excluded. A total of 24 subjects meeting the search criteria were obtained. All tissues were from left frontal cortex that had been frozen without prior fixation and stored at −80°C. The demographics and neuropathological characteristics of the subjects are listed in Supplementary Table S2. Tissue Tek medium-embedded frontal cortices were cryosectioned at 16 μm and stored at −80°C until use.

2.3. Animals

A colony of R1.40 transgenic mice (B6.129-Tg[APPSw] 40Btla/Mmjax) was established from mice, originally purchased from The Jackson Laboratory. The mice carry a 650 kb insert from a yeast artificial chromosome clone that contains the full genomic copy of the human APP gene with the familial AD Swedish mutation (K670M/N671L) [34]. Our R1.40 colony is maintained by backcrossing hemizygous animals to wild type mice of the C57BL/6J genetic background. Hemizygote mice were used for the reported studies. All animal experiments were conducted with license from the Government of Hong Kong SAR and were approved by the Animal Ethics Committee of the Hong Kong University of Science and Technology. Mice were maintained in the Animal and Plant Care Facility at the Hong Kong University of Science and Technology, and all procedures comply with the guidelines of the institution and the Department of Health, Government of Hong Kong.

2.4. Histopathology and immunohistochemistry of tissue sections

Mice were deeply anesthetized by Avertin (1.25% tribromoethanol, Sigma, 375 mg/kg, I.P.) and sacrificed using transcardial saline perfusion delivered with a peristaltic pump. The right brain was isolated by dissection and post-fixed in paraformaldehyde (4%) for 24 hours. The tissue was then cryoprotected in sucrose (30% w/v) for 48 hours before embedding for cryosectioning. Sagittal 10 μm sections were cut beginning at the midline and kept at −80°C until use. For human tissue, the frozen sections