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Unraveling the Role of Lipid Metabolism in Alzheimer's Disease

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Imagine the heartbreak of being unrecognizable to your spouse after 40 years of marriage or losing the capacity to remember one's only child—such are the features salient in the latter course of Alzheimer's dementia. Given that Alzheimer's Disease (AD) is estimated to affect up to 40 % of North Americans over the age of 85, it constitutes a substantial obstacle to healthy aging.[1,2]

Upon finishing her post-doctorate work with Dr. Michael Hayden at the University of British Columbia, Dr. Cheryl Wellington began investigating the link between neurodegenerative disease and lipid disorders. Given that the most important genetic risk factor for AD is apolipoprotein E (apoE), which is a major cholesterol carrier in the brain, Dr. Wellington set out to further investigate the relationship between cholesterol metabolism and AD.

One of the major neuropathological hallmarks of AD is the presence of amyloid plaques within the brain parenchyma and cerebral blood vessels. The plaques are deposits of Aβ peptide, a by-product of amyloid precursor protein that is continuously produced and then cleared from the brain. With aging, it is hypothesized that the clearance and degradation of Aβ become less effective. Dr. Wellington's lab has shown that the clearance rate of Aβ is strongly affected by how much lipid is carried on apoE.[3]

The natural function of apoE is to distribute lipids among various cell types in the brain, a function that is critical for repairing damaged neuronal membranes. The cholesterol transporter ABCA1 acts to move excess lipids from the cell surface to apoE. In humans, the polymorphic *apoE* gene is present in three different allelic isoforms (2,3, and 4), and *apoE4* has been shown to increase the risk of developing AD with each inherited copy. At least 50 % of patients with AD possess at least one *apoE4* allele.[3]

In accordance with ethical guidelines for preclinical research, Dr. Wellington has used murine models of AD to show that the whole degradation pathway of the Aβ peptide slows down in the absence of ABCA1. The mice deteriorate cognitively and develop more amyloid deposits in their brains. Dr. Wellington has also shown that lipid saturation of apoE can be increased by using genetic modifications or small molecule compounds that increase ABCA1 activity. This results in more rapid degradation of Aβ peptides and less amyloid formation. "This gives us the ability to possibly provide novel therapeutic strategies for Alzheimer's disease that can augment therapies being developed to slow the

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production of Aβ," says Dr. Wellington.[3]

Despite her progress she emphasizes that our ability to treat or prevent the illness is nascent and that we must not overlook the influence of other factors that do affect overall risk. Intriguingly, what is good for the heart is good for the brain. She explains that "the biggest piece of advice I always give to the general public is never stop exercising; that's probably one of the best things that you can do to promote healthy aging from the cardiovascular, metabolic, and neurologic perspectives."[3]

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University of British Columbia Conference on Dementia 2011

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On January 29, 2011, The University of British Columbia partnered with the Clinic for Alzheimer's Disease and Related Disorders at UBC Hospital (CARD-UBCH) to host Dementia 2011. Speakers included Jean Blake, CEO of Azheimer Society of BC, and Dr. Lynn Beattie, medical director at CARD-UBCH. The objective of this conference was to inform the public on Alzheimer's Disease (AD) diagnostic techniques, current treatments, and future treatments. AD affects 25–45 % of persons over the age of 85, and this percentage is projected to increase as the geriatric population grows. One of the event's focuses was in AD diagnostics, which is currently undergoing substantial review. AD can only be diagnosed upon post-mortem examination, leading to frustration and uncertainty over the appropriate course of treatment for patients.

Current AD diagnostic techniques primarily include assessment of medical history, cognitive examination, and neuroimaging. The Mini Mental Status Examination (MMSE) is an especially important cognitive exam to conduct; the MMSE tests a patient's cognitive capacity through a series of basic questions and tasks. It has high sensitivity but only moderate specificity, occasionally resulting in false positive diagnoses. Part of the difficulty in using the MMSE is that it is a highly subjective test and depends on the age and educational level of the patient. Magnetic resonance imaging (MRI) has also been a useful diagnostic tool, especially when considering the decrease in hippocampal volume. However, a decrease in hippocampal volume is common in many forms of dementia other than AD and therefore does not provide a definitive diagnosis. This is problematic because many AD treatments are most effective when implemented at early stages of the disease. Furthermore, a compounding problem is that the most advanced diagnostic tools are restricted to urban areas resulting in inaccessibility for rural populations.

A relatively newer diagnostic tool used in clinical trials measures the ratio of beta amyloid 42 (Aβ-42) to phosphrylated tau (p-tau) protein as biomarkers in the cerebrospinal fluid (CSF). Biomarkers are measurable biological substances which indicate the presence or absence of a particular disease state. Studies have indicated that Aβ-42 concentration diminishes as AD progresses while p-tau concentration increases with disease severity. Therefore, when the biomarkers are used together, clinicians can accurately assess both disease severity and stage.

The most promising solution is to develop a non-invasive, accessible, and accurate technique such as blood testing which would detect AD at an early stage. Although this field of research is still in its infancy, recent reports have found possible blood biomarkers which could lead to definitive AD diagnosis. AD diagnostics has progressed significantly in the past decade. Looking forward, physicians will increasingly rely on biomarkers found in the CSF and blood plasma to diagnose AD and hopefully to provide patients and their families with some peace of mind.

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