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Prospects of imaging retinal amyloid beta using fluorescent probes for early diagnosis of Alzheimer's disease

Xinyuan Hu

Westminster School, London, SW1P 3PB, United Kingdom

lillie.hu@westminster.org.uk

Abstract. Alzheimer's Disease is the most common cause of dementia amongst older adults, affecting more than 55 million people globally. Identifying accessibility concerns for conventional methods used for diagnostics, this review focuses on an alternative approach detecting amyloid beta in the retina. The utility of this biomarker is yet to be verified due to the low number of in vivo studies in AD patients, as well as the need for further investigation on the subtle differences between cerebral and retinal patterns of amyloid deposition. However, this approach has shown great promise as recent in vivo studies of larger sample sizes are conducted. Exemplifying the applications of curcumin, this paper also examines current methodologies in rAβ research and evaluates the outlook of chemically modifying fluorescent probes for oligomeric selectivity.

Keywords: Alzheimer's Disease, Retinal Amyloid Beta, Curcumin, Amyloid Beta Oligomers

1. Introduction

Early intervention of Alzheimer's Disease (AD) has proved significant in slowing down the progression of the disease. While primary interventions such as genetic risk factors for AD remain elusive to the general population, the ongoing race to identify biomarkers before the onset of symptoms has led to the development of technologies such as Cerebral Spinal Fluid (CSF), Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) [1]. However, they are commonly invasive, costly, technically complicated, and sometimes involve radioactive tracers, factors which limit their availability in many healthcare settings and populations. Retinal imaging of AD biomarkers has gained a lot of attention in the past decade for its comparatively low cost and wide accessibility. The retina seems to fit the criteria for being a good alternative to whole-brain imaging for the linkages and parallel pathways between the retina and the CNS, as well as the neuroretina's accessibility for non-invasive optical imaging [2-5].

The National Institute on Aging and the Alzheimer's Association (NIA-AA) published a research framework in 2018 which proposed the A/T/N system for diagnosis of AD. It places an emphasis on three biomarkers: amyloid beta (Aβ) plaques, tau pathology, and neurodegeneration. The presence of Aβ plaques is deemed necessary for clinical diagnosis of preclinical AD. An extensively researched indicator is the Cerebral Spinal Fluid (CSF) Aβ42 (or the Aβ42/Aβ40 ratio), an alloform of Aβ which is associated with greatest neurotoxicity and tendency for aggregation [6-8]. Aβ has been one of the most extensively studied AD biomarkers and has been found in the retina of AD patients as early as 2003 [9]. Moreover, while cerebral Aβ deposition can happen as early as 15-20 years before clinical

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manifestations of AD, AD transgenic mice models suggest that retinal Aβ are detected even earlier [10-12]. The problem is that these transgenic AD mice all rely on mutations of familial AD-associated genes, obscuring the interpretation of their biological relevance [13]. Having an extremely limited amount of research systematically targeting patients *in vivo*, it still cannot yet be determined whether retinal Aβ can serve as an effective diagnostic tool. It becomes evident that the biggest obstacle in justifying this biomarker is the difficulty of carrying out large-scale, population-wide *in vivo r*etinal screening of Aβ [12, 14-16].

This review aims to assess the use of retinal amyloid beta (rAβ) as a diagnostics biomarker for preclinical AD. Another focus of this review would be the current and future developments of safe, precise fluorescent probes for *in vivo* rAβ screening in AD patients.

2. Retinal Amyloid B as A Biomarker

2.1. Aβ Oligomers

Amyloid beta is formed when Amyloid-Beta Precursor Protein (APP) is cleaved by β and γ-secretase. The monomeric form of amyloid beta plays various essential physiological roles in the brain, including improvement of memory, protection of the blood brain barrier (BBB), and even antimicrobial properties. The dysregulation of peptide folding leads to the formation of one of the key hallmarks of AD pathology: senile plaques composed of Aβ fibrils surrounded by a halo of amyloid beta oligomers (AβOs). Insoluble fibrillar amyloid-beta is seen as having low toxicity and has even been postulated as an *in vivo* strategy for removing soluble amyloid-beta. On the other hand, the soluble AβOs are the most toxic form of the protein. This is a key idea in the oligomer cascade hypothesis (supplanting the original Amyloid Cascade Hypothesis), and it explains that the AβOs are most directly correlated to the Alzheimer's pathogenesis, causing synaptic dysfunction, selective neuronal cell death, inflammation, and oxidative damage. Notably, the AβOs triggers the formation of the other key hallmark of AD pathology (neurofibrillary tangles, NFTs) in the cascade by promoting the hyperphosphorylation, intracellular aggregation, and extracellular propagation of tau [17-23].

2.2. In/Ex vivo studies investigating retinal amyloid β vs cerebral manifestations of Alzheimer's Disease

While rAβ has yet to be validated for clinical use for preclinical AD diagnosis, several studies over the last few years show significant correlation between the increase of toxic rAβ and the progression of AD pathologies in the brain.

A comprehensive ex vivo study comparing retinal proteome signatures in mild cognitive impairment (MCI) and AD patients to those with normal cognition (NC) reported a significant correlation between increase in levels of Aβ42 and intraneuronal Aβ oligomers (AβOi) to the severities of brain Aβ pathology. The researchers analyzed the age- and sex- matched postmortem retinas and brains from 86 human donors who had undertook a cognitive evaluation less than 1 year prior to death. The severity of brain pathologies were determined by assessing the Aβ plaque burden, amyloid angiopathy and many other biomarkers, while sandwich ELISA assays and mass spectrometry were conducted to determine the specific amount of rAβ42 burden after peroxidase-based and fluorescence-base immunostaining. This burden was shown to have increased five- and nine- fold respectively in MCI and AD patients compared to the NC group, suggesting a strong correlation of rAβ42 to disease progression. Furthermore, retinal cross sections were labelled with the ScFvA13 immunoreactive dye, and the AβOi burden showed a statistically significant increase in MCI and AD patients, especially in the superior-temporal-F (ST-F) subregion of the retina. Notably, the rAβ abnormalities were characterized to be distributed mostly in the peripheral subregions and the inner retina, suggesting a regional focus for imaging technologies [24].

A recent *in vivo* study shows modest correlation between amyloid PET SUVr in the brain and retinal spot count (number of retinal Aβ plaques), but like many other *in vivo* studies, were limited to a very small sample size (n=4) [25].

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2.3. Questions about Retinal Aβ

The truth is: despite showing great promise in finding a 'strong correlation' for a potent diagnostic biomarker, the underlying mechanism of retinal Aβ deposition has not been adequately explored.

The retinal pigment epithelium (RPE) is a monolayer of pigmented cells that forms the outer layer of the Blood Retinal Barrier (BRB). One possible mechanism for Aβ deposition in the retina is through the production of Aβ by RPE cells, which have been shown to express APP [26]. Even though researchers have shown Aβ plaques could be detected in the retina in early-preclinical stages of AD, most studies employ transgenic mice models (TgAPP/PS1 mice) or examined postmortem tissue [25, 27-29]. Whether this theory could be confirmed by *in vivo* studies for humans remains uncertain. Furthermore, how the production of Aβ by the retina affects/is affected by cerebral manifestations of AD is not well understood. Another possible mechanism is that membrane transporters found on the RPE can catalyze the transport of Aβ monomers into the retina, for example, P-glycoproteins is shown to actively transports Aβ40 and Aβ42 across the BBB which has a similar structure as the BRB [30, 31].

Furthermore, retinal Aβ has been suggested to be closely associated with the progression of other retinal degeneration diseases, namely age-related macular degeneration (AMD) and glaucoma [15, 32-33]. Varying levels of Aβ has been detected in the retinal ganglion cells (RGC) and RPE of patients with glaucoma and AMD, respectively, i.e. Aβ immunoreactivity was seen in 30%-40% of soft drusen in AMD patients [15, 26, 34, 35]. As a result of the shared biomarker, the effects of Aβ on both cerebral and retinal neurons are strikingly comparable in the case of Aβ-amyloidosis [36]. In primate models, lower levels of vitreous Aβ associated with glaucoma were found to be associated with lower cognitive function, like in AD pathology [37, 38]. The highly interconnected relationship between the AD, AMD, and glaucoma inevitably raises questions for diagnostic accuracy of rAβ.

To understand how this overlap affects diagnostics, a clear line (or rather, a Venn diagram) needs to be drawn to distinguish the mechanisms of Aβ accumulation in the retina as well as rAβ distribution between AD, AMD, and glaucoma. Mice models as well as limited number of small-scale *in vivo* studies show that in AD, Aβ is distributed throughout the retinal layers, including within and surrounding neurons and the cells that support them [25,28, 39]. This provides hope for distinguishing the Aβ for glaucoma (found concentrated in the ganglion cell layer, GCL) [40, 41], and Aβ for AMD (mostly found on the RPE) [15, 34, 35, 42]. Longitudinal investigations will also be required to evaluate whether retinal Aβ burdens persist over time and how these deposits evolve in the diseases' progression [32].

3. In Vivo Fluorescent Probes For rAβ

The structure of amyloid beta plaques found in the retina resemble that of cerebral amyloid beta plaques, having the same alloforms (Aβ42 and Aβ40), and a similar range of sizes (5μm to 20μm) [32]. *In vivo* observation of rAβ in transgenic mice models is a comparatively mature procedure [43], whereas the poor transferability for human rAβ seems mostly concerns of invasiveness and efficient delivery of probes across the BRB. Several studies have successfully obtained images of human rAβ *in vivo* using fluorescent curcumin agents with optical coherence tomography (OCT) and scanning laser ophthalmoscope (SLO) technologies.

3.1. Using Curcumin in vivo

In 2008, curcumin's minimal toxicity in humans was established by a series of phase I and II trials in cancer patients, even at high doses of 12 g/day [44]. Retinal amyloid was first studied in AD patients *in vivo* in 2011, where researchers first used the spice-derived curcumin as a labelling technique for rAβ. Subjects were administered curcumin through intravenous injections daily, as well as two hours before examination. Sets of filters specific to curcumin fluorescence was applied to a retinal imaging microscope named The Micron II [12]. A recent study uses fundus autofluorescence (FAF) techniques and OCT to study retinas of patients who took curcumin (500mg of Curcumin Meriva supplements daily for two months). The autofluorescence detects accumulations of lipofuscin levels in dysfunctional layers of RPE which indicate neurodegeneration. OCT is used to identify the layer of defect. Researchers also

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demonstrated that retinal tau could also be stained by curcumin, possibly due to its conformational properties [45].

Notably, curcumin has also received attention for its neuroprotective effects against neurodegenerative diseases for its anti-amyloid, antioxidant, and anti-inflammatory characteristics. It is shown to decrease nitric oxide concentrations, which protects the brain from lipid peroxidation. Several studies have demonstrated that curcumin can help prevent the production of amyloid A1-42 oligomers and the disaggregation of the produced fibrils. Inc clinical trials, curcumin has also demonstrated antiproliferative and apoptotic action against brain cancers [46-48].

3.2. Curcumin and its Scaffolding – Chemical Modifications

As established in section 1.1, the ideal probe for rAβ would not only have properties suitable for pharmacokinetics, a high bioavailability, and a high fluorescence intensity, but should also have a special affinity for Aβ oligomers. Current forms of curcumin simply bind to hydrophobic sites on β-sheets in fibrils and oligomers and lack higher selectivity [49]. Various chemical modifications of curcumin structures have been investigated to address this issue.

CRANAD-3 was the first form in the curcumin scaffold to be capable of detecting the soluble oligomers of amyloid beta along its fibrillar and monomeric forms. The stereohindrance of this molecule was further altered to produce CRANAD-102 in 2017, which showed considerable selectivity for the soluble Aβ over insoluble Aβ. This probe was demonstrated to be able to monitor the changes in concentration of soluble Aβ in vivo transgenic mice models [50, 51].

Oligomers could be distinguished from the monomers of Aβ for having a triangular protein cavity, as well as exposed Phe19 and Val36 residues [52, 53]. The PTO-41 probe was designed to have a V-shaped wedge allowing insertion into this cavity as well as forming hydrophobic interactions with the residues. To resolve the then issue of higher lipophilicity of the molecule, a hydroxyethyl group was incorporated. The resulting is shown to have a relatively faster elimination, decent BBB permeability, as well as appropriate emission wavelengths for near-infrared imaging, for *in vivo* diagnosis [54].

Unfortunately, the enhancement of one desired trait may degrade another [55, 56]. Not only is the most crucial limitation of curcumin's low bioavailability yet to be resolved, traits such as its poor water solubility, poor stability in solution, as well as the intestinal first-pass and hepatic metabolism calls for further research [57]. This does not suggest it is impossible for the ideal AβO-specific fluorescent probe to be invented through further modifications, however, although the probes described above should be validated for its relative efficacies in the context of the BRB before clinical applications.

4. Conclusion and Future Directions

To conclude, significant challenges persist, demanding a multitude of further *in vivo* research to validate the efficacy, safety, and reproducibility of the utilization of rAβ in diverse patient populations. The reason for high heterogeneity across studies have been commonly identified as a lack of methodological harmonization. Globally, it is imperative to establish standardized protocols in researching rAβ to promote data comparability and reliability across studies. By navigating these obstacles with determination and innovative methodologies, we may unlock the potential of this approach, offering hope for very early AD detection with this non-invasive, cost-effective target. The utilization of fluorescent probes for imaging rAβ also harbors significance potential, with the possibility to be used in conjunction with new drug delivery technologies, e.g. nanobodies. The lead of curcumin research provides a framework which opens opportunities to explore other candidate probes, including but not limited to anti-Aβ an antibody, BODIPY, etc.

In the future, leveraging machine learning algorithms and artificial intelligence techniques to analyze fluorescence images could also aid in the development of automated and accurate diagnostic tools for early Alzheimer's disease detection, ensuring broader accessibility and cost-effectiveness to ultimately transform the landscape of dementia care.

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