

Anti-Amyloid- β Monoclonal Antibodies against Alzheimer's disease may be a potential breakthrough for cataract treatment

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Abstract

Cataracts are considered the underlying cause of blindness globally. When the average age of the earth's population is on the rise, cataract-induced blindness and visual dysfunction will increase dramatically. (1) Currently, the only viable treatment for cataracts is surgery, including removing the opaque lens and replacing it with an artificial one which has a huge impact on improving the patient's quality of life. Undoubtedly, cataracts have far-reaching repercussions for countries in terms of social and economic burdens, for example, the increasing rate of automobile accidents due to reduced visual acuity. (2) Nonetheless, due to the lack of facilities, ophthalmologists, and funds, surgery is not a choice in developing countries. (3) It should be noted that posterior capsular opacification is a common complication of cataracts, and sometimes, a second intervention is necessary. (4) This research has thrown up many questions in need of further investigation to find medications that restore full transparency of the lens.

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Introduction:

The opacification of the lens, called cataracts, is responsible for degrading visual acuity as a consequence of scattering the light as it passes through the lens. The ocular lens plays a pivotal part in focusing the light onto the retina, and its clarity is essential for visual acuity. In 2020, the prevalence of cataracts had been 15.2 million cases among over 50 years globally. It has been estimated by the year 2050, approximately 50 million people in the united states will suffer from cataracts. According to statistics, cataracts will increase with passing years.

Cataracts are considered the underlying cause of blindness globally. When the average age of the earth's population is on the rise, cataract-induced blindness and visual dysfunction will increase dramatically. (1) Currently, the only viable treatment for cataracts is surgery, including removing the opaque lens and replacing it with an artificial one which has a huge impact on improving the patient's quality of life. Undoubtedly, cataracts have far-reaching repercussions for countries in terms of social and economic burdens, for example, the increasing rate of automobile accidents due to reduced visual acuity. (2) Nonetheless, due to the lack of facilities, ophthalmologists, and funds, surgery is not a choice in developing countries. (3) It should be noted that posterior capsular opacification is a common complication of cataracts, and sometimes, a second intervention is necessary. (4)

The transparency of the lens depends mainly on the well-structured α , β , and γ crystallin proteins and their solubility over a lifetime. A cataract is formed as a result of protein aggregation within the lens

environment. (5) Uv radiation, deamidation, oxidation, and truncations have been characterized as key factors in the pathology of cataracts that covalent protein damages play a critical role in the accumulation of proteins. (6-8) There is a large volume of published studies that describe the role of protein destabilization and crystallin protein aggregation and thus formation of insoluble assemblies. (9-12)

There is a growing body of literature that recognizes the importance of amyloid-like structure in cataract pathology. (13-15) The accumulation of aggregated protein can be traced back to mutation, PTM (post-translational modification), the presence of naturally misfolded protein, and systemic amyloidosis. (16) It is now well established that cataracts are formed due to structural rearrangement within proteins that convert them into pathological species. High molecular weight complexes as a result of aggregation of crystallin lens, which led to the opacity of cataractous lenses and light scattering, is considered the main mechanism of cataract formation. (9)

On the other hand, the human eye and central nervous system (CNS) have similarities in terms of vasculature and embryological origin. (17-19), and also, there is a close resemblance between the blood-brain barrier and blood-retinal barrier and between Cerebrospinal fluid (CSF) and aqueous humour. (20) In addition, both the eye and brain show similar disease-specific pathological pathways. Recent evidence suggests that CNS disorders like stroke, multiple sclerosis (MS), Alzheimer's disease, and Parkinson's disease could be detected in the eye. (19) Several attempts have been made to identify the repeating units and same conformations in amyloid fibers in Alzheimer's, Parkinson's, and Huntington's diseases and also in cataracts by nuclear magnetic resonance (NMR), X-ray crystallography, and infrared (IR) studies. (21-23) With regard to the microscopic image, the primary difference between cataracts and other conformational diseases (abnormal folding in protein structure) lies in the size of aggregated particles. Large aggregates such as extracellular amyloid plaques found in AD and Lewy bodies have been detected in Parkinson's patients. By contrast, such aggregates have not been observed in cataracts. (24)

It should be noted that higher-order structure is considered the main cause of cataracts, as opposed to other conformational diseases, Alzheimer's, Parkinson's, and Huntington's, in which soluble oligomers pave the way for higher molecular weight aggregates and forming plaque.

Although cataracts are divided into cortical and nuclear cataracts, there has been no reliable evidence regarding different biochemical processes or etiologies. (9)

Numerous factors seem to be involved in the age-related cataract, and its etiology is complex.

Background:

There are a variety of examples illustrated that a drug was originally developed for one specific disease, showed indication to other diseases mainly owing to have overlap mechanism to some extent. For instance, the amyloidophilic compound cpd-B is a case point that was initially developed for the treatment of cataracts but showed activity against Prion disease. (25)

In a study conducted by Chemerovski-Glikman et al. suggested that Rosmarinic acid can restore the transparency of the lens due to its amyloid destabilization effect and remolding lentic protein aggregate. They have developed ex vivo assay for screening anti-cataract medications. They found that Rosmarinic acid completely restores the clarity of the human cataractous lens in ex vivo and delays cataract formation in selenite-induced cataracts in the newborn rat model. (26) Previous studies have reported that Rosmarinic acid also able to bind to oligomers of A β and alpha-synuclein by interfering with protein aggregates in neurodegenerative disease. (27-28)

A large and growing body of literature has investigated the examination of the opaque lens as a sign of Alzheimer's disease. A much debated question is whether amyloid beta in the brain leads to cataracts or amyloid assemblies in the lens form as a process of aging process and has its own pathway.

In 2003, Goldstein et al. initially detected A β protein precursor (A β PP) in postmortem human lens specimens diagnosed with AD. Although they demonstrated that the accumulation of A β in the lens has its own

molecular mechanism, a major problem in the study is that they used cadaveric human lens samples. The present results are significant in at least one major respect, identifying the A β protein precursor in the lens. (29)

In 2010, Moncaster and colleagues examined the lens of patients with Down syndrome (trisomy 21); Chromosome 21 contains the gene responsible for encoding A β PP. A positive correlation was found between a high incidence of bilateral cataracts and accumulation of A β in the lens in patients with Down syndrome. (30-31)

In a study conducted by Kerbage et al., a fluorescent ligand that binds to A β aggregates was used along with a laser scanning device called SAPHIRE system to examine human lenses. They realized that the fluorescent signature of ligand-bound A β in the thickest supranuclear in the AD patients was twice as much as in the control group. (32)

The authors also performed a similar experiment in 2015. They utilized fluorescent ligand eye scanning (FLES) system by measuring the fluorescent signature of Aftobetin hydrochloride, which is bound to A β to distinguish between a group of healthy control (n=20) and potential AD patients (n=20). Compared to Amyvid PET (brain imaging), the FLES data illustrated better predictions of clinical diagnosis than those of A β PET. (33)

Although, these results differ from some published studies (Michael, 2014; Ho, 2014; Williams, 2017). (34-36) These contradictory results are justified by variations in staining methods, fixation techniques, use of monoclonal antibodies with the different antigen-binding sites, and lack of secondary analytical methods. (37)

The positive link between the formation of cataract and Alzheimer's disease is clarified by genome-wide association studies which were conducted by Jun et al. They analyzed lens cataractous lens imaging from 1249 patients and proposed that genetic variability in Catenin Delta 2 gene play a significant role in cortical cataracts with AD-related brain changes. (38)

As mentioned above, the most striking result to emerge from the data is that A β depositions are the same characteristics of Alzheimer's disease and cataracts.

While some researchers have attempted to develop anti-cataract medications based on their inhibitory effect on the aggregation of misfolded lentic proteins, such results were unsatisfactory.

In 2015, Zhao L. *et al* . reported that lanosterol could reduce cataract severity in a canine model and decrease crystallin proteins' aggregation in vitro. (39)

Makley, L. N. et al. (2015) showed that 25-hydroxycholesterol could reverse the aggregation of α -crystalline in vitro and restore the clarity of the lens in an age-related cataract to some extent. (40)

This research has thrown up many questions in need of further investigation to find medications that restore full transparency of the lens.

The hypothesis is that, design screening libraries include anti-amyloid- β monoclonal antibodies, which currently are in the clinical trials for Alzheimer's disease to identify their potential ability to restore full transparency of the lens.