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PERSPECTIVES

Proposed Role for Internal Lens Pressure as an Initiator of Age-Related Lens Protein Aggregation Diseases

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Abstract: The process that initiates lens stiffness evident in age-related lens protein aggregation diseases is thought to be mainly the result of oxidation. While oxidation is a major contributor, the exposure of lens proteins to physical stress over time increases susceptibility of lens proteins to oxidative damage, and this is believed to play a significant role in initiating these diseases. Accordingly, an overview of key physical stressors and molecular factors known to be implicated in the development of age-related lens protein aggregation diseases is presented, paying particular attention to the consequence of persistent increase in internal lens pressure.

Keywords: lens, protein aggregation, cataract, presbyopia, oxidation

Introduction

The physiological lens is a major component of the optical system of the mammalian eye. It functions optimally during youth when its flexibility and optical clarity are uncompromised. In order for the lens to maintain optimal function, it must remain transparent with a stable, high refractive index (averaging somewhere between 1.41 and 1.43) despite insults that threaten it, such as continued UV exposure and oxidative stress.[1,2] The major proteins of the human lens responsible for maintenance of transparency and high refractive index are the Crystallin proteins.[3,4] Crystallin proteins are synthesized only once and never replaced due to the absence of protein turnover. As the crystallin proteins begin an aging process even before birth and continue to accumulate various oxidative insults throughout life, the task of preserving high transparency and stable refractive index becomes problematical. The literature attributes oxidative insults caused by UV exposure as the major cause of post-translational modifications leading to protein aggregation.[5,6] Protein aggregation of crystallins increases lens stiffness, a contributing factor to presbyopia and cataract, initiates light scattering[7] and, ultimately, reduces lens transparency which defines the condition known as cataract, all of which have a major impact on public health[5] 100% of humans who survive into their 5th decade will be affected by lens stiffness manifesting as presbyopia. In the US alone, incidence of age-related nuclear cataract (ARN) is around 40% in those aged 75 years or older.[8] Vision Loss due to cataract in the developing world remains ophthalmology's major unsolved problem[9] It is of interest that, while the most common type of cataract, ARN, occurs in an area of the lens which receives the highest lifetime exposure to UV, little scientific evidence exists showing UV plays a major role in inducing ARN.[10] Clearly, there is more to the process than is understood.

The biochemical process underlying age-related lens protein aggregation diseases occurs over time[11] yet the young eye has several defenses against oxidative damage that remains intact while the process ensues. The cornea has natural UV filters, a first line of defense, filtering out UV effectively to around age 40, yet damage to lens proteins begins years before these filters start to decline[12–16] In cortical cataract (cataract that occurs in the cortex or periphery of the lens), light-induced oxidation is attributed as a cause, yet the lens cortex is protected by the iris, eyelids, pupil and aperture.

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Also, Glutathione, the major natural lens antioxidant, is gradually depleted from the nucleus while levels in the cortex remain normal,[15,17–20] yet cortical cataract ensues even with Glutathione present. Because studies conclude it may only be after middle age that light promotes oxidation,[21] based on the available research it is unlikely oxidation acts alone in initiating and contributing to the progression of age-related lens protein aggregation diseases; parallel processes are strongly associated with the cascade of damage that ensues from oxidative insults.[22,23]

While the cause of age-related lens protein aggregation diseases is believed to be multifactorial, there is debate as to which factors other than oxidation are significant comorbidities. Periodic elevation in temperature of the eye over time, chemical exposure, pressure and osmotic changes have been suggested to contribute to the process.[24] As age-related lens protein aggregation diseases are a major cause of vision loss worldwide, and as the only treatment for cataract involves surgical removal of the opacified lens and its replacement with a prosthesis.[25,26] There is a significant unmet medical need for therapeutic treatments for age-related lens protein aggregation diseases. Developing effective treatments requires an understanding of all factors that contribute to the initiation and continuation of the process. Because of this, lens protein aggregation is a subject of intense biophysical research. This Perspective presents the need to identify root causes in order to pave the way to develop drug targets to confront age-related lens protein aggregation diseases and reduce the global burden.[25]

The mammalian lens has a separate and distinct internal pressure than intraocular pressure (IOP). In young mouse lenses internal lens pressure is around 340 mmHg and in elderly mouse lens pressure almost doubles.[27] This increase occurs linearly over time, yet very little research suggest it as having a significant impact on the structure and function of lens crystallins or and other lens proteins responsible for maintaining lens function and homeostasis such as gap junction proteins. As pressure in tissues elsewhere in the body has been shown to lead to precipitation and aggregation of proteins, cross-linking and other factors implicated in protein aggregation diseases[20,28–34] it appears to have been largely overlooked as a factor in age-related lens protein aggregation diseases. I present an argument suggesting linearly increasing internal lens pressure is a contributor to stiffening, light scattering and opacification that characterize age-related lens protein aggregation diseases; that this pressure plays a significant yet understated, even overlooked factor in the multifactorial process behind initiation and progression of these diseases.

Lens Crystallin Proteins: Architecture, Stress and Damage

Crystallins are the predominant structural proteins of the lens.[35] Their short-range ordered packing into a dense homogeneous phase is decisive for lens transparency.[25] Lens nuclear proteins have the greatest longevity of any human proteins. They are synthesized only once and never replaced due to the absence of protein turnover.[25] Lens crystallins must maintain an ordered and stable architecture despite the ongoing onslaught of insults they endure throughout a lifetime including continued UV exposure and other oxidative stress.[1,2] In fact, they begin an aging process even before birth and continue to accumulate various insults throughout life.[25] As lens fiber cells lack ribosomes and other organelles, the lens is not anatomically capable of repairing or replacing damaged crystallins.[25,36,37] Unfortunately, the high crystallin concentrations needed to attain the glass-like refractive index required for the eyes optical system are conducive to an environment suitable for protein aggregation.[25] Protein aggregation increases with age[38] as once soluble lens proteins become insoluble (precipitate), leading to deterioration of lens architecture, lens stiffness (presbyopia), changes in refractive index, optical aberrations and, ultimately, opacity (cataract).[39,40] Folding and unfolding of the crystallins is required to maintain lens transparency.[41] There are three major types, α-Crystallin, β-Crystallin, and γ-crystallin.[25,42,43] In their healthy form, crystallins are non-cross-linked and fold and unfold without being modified by oxidation. However, in response to stresses such as mutations, proteolysis, increase in disulfide bridges, glycosylation, phosphorylation, carbamylation, scission of tryptophan indole rings, deamidation of asparagine and glutamine, and racemization of aspartic acid residues,[25,36,37] crystallins often lose their native folds and tend to denature and aggregate.

Chaperone molecules protect lens proteins from damage during folding and unfolding.[24,25] α-Crystallin, a member of the heat shock family of proteins (HSPs), is a chaperone molecule.[44,45] During cataractogenesis, α-crystallin becomes a water-insoluble cross-linked aggregate, resulting in a decrease of lens chaperone activity.[12] As longevity of crystallin proteins is correlated with long-term retention of folded structure and is attributed to efficient capture and refolding by chaperones,[42] protection provided by α-Crystallin against oxidative insult declines. The exhaustion of α-crystallin

chaperone, a nonrenewable protein resource, is likely to be the limiting factor in causing almost all age-related cataracts.[25] Currently, all proposed models of lens opacification include structural modifications within the crystallins.[46]

Post Translational Modifications of Lens Crystallin Proteins

Precipitation of lens proteins occurs secondary to chemical modifications known as post-translational modifications (PTMs). Proteins of mature fiber cells (MF) do not turnover, thus the lens nucleus contains the oldest proteins. Given the extreme age of nuclear crystallin proteins, a variety of PTMs accumulate.[47,48] PTMs lead to presbyopia and cataract.[49] The major lens PTMs include disulfide bonding, methionine oxidation, deamidation, phosphorylation, and proteolysis.[20,48,50–53] Deamidation is a chemical reaction in which an amide group in the side chain of amino acids asparagine or glutamine is removed or converted to another functional group. Deamidation is the most common PTM affecting the human lens.[52,54] Phosphorylation, the attachment of a phosphate group to a molecule or an ion, is the most common PTM of the α-crystallins.[54,55] Crystallin proteolysis, the enzymatic breakdown of proteins or peptides into amino acids, is significantly increased in cataract as compared with young lenses.[56–58]

Antioxidation Protection in the Lens

Extensive oxidation of lens proteins begins at the lens fiber cell membrane.[16,47,59] Glutathione, the major natural lens antioxidant, is vital for maintenance of transparency.[13] Glutathione, which exists in unusually high concentration in the lens, detoxifies oxidants formed by UVA.[60] Since corneal UV filters decrease at approximately 12% per decade, increasing amounts of UVA reach nuclear proteins of older lenses, forming reactive species which bind to proteins. Glutathione intercepts reactive species, minimizing damage. A barrier or bridge forms in the middle of the lens around middle-age restricting Glutathione from reaching the center of the lens, leaving proteins in this region susceptible to oxidation and PTMs.[50,60] The genesis of age-related lens protein aggregation diseases may be traced to the onset of this barrier.[61] A decrease in levels of Glutathione is a typical finding associated with nearly all experimental cataract.[28,50,62,63]

Lens Stress: Physical Forces Which Misfold Proteins

The initiators of age-related lens protein aggregation diseases are what misfolds proteins, not what oxidizes them once misfolded. It is proposed that some "stressors" acting over time unfolds proteins, increasing susceptibility to damage by oxidation that is an initiator of age-related lens protein aggregation diseases (Figure 1).

A review of literature suggests that increases in eye temperature lead to heat-based denaturing of lens proteins as a stressor contributing to the course of age-related protein aggregation diseases.

Heat

The absorption of infrared radiation by the lens results in development of cataracts.[64] Goldman argues absorption of radiant energy by the iris conducting heat to the lens is responsible for cataracts.[65–69] Studies suggest temperature of the anterior chamber varies by several degrees depending upon climate, with incidence of ARN greater in areas of higher temperature. However, structures anterior to the lens regulate temperature. Heat is absorbed by iris melanin and conducted away by iris blood circulation,[70,71] conducted away by tear film evaporation, eyelid blood flow and minimized

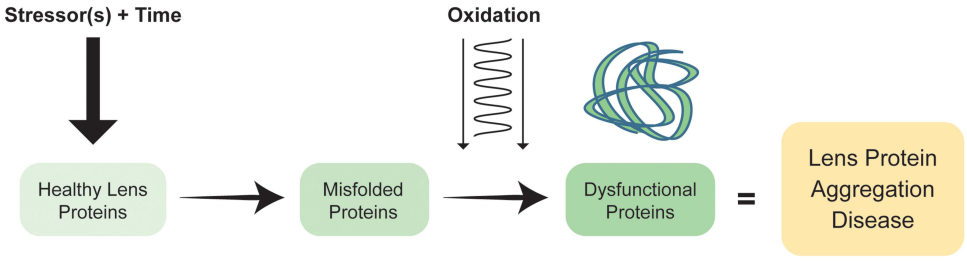

Figure 1 Schematic representation highlighting the role stressors play on the lens: over time, certain stressors initiate protein misfolding leading to dysfunctional proteins and the disease state.

by reduction of the eye's aperture through squinting and pupil regulation during high luminance situations. Also, natural convection of aqueous in the anterior chamber maintains temperature of the eye close to other body organs when subjected to thermal disturbance.[69,72]

Studies show exposure to even extreme heat causes minimal increases in eye temperature. Although few workers in an iron mill wore protection against heat, most were observed to "screw their eyelids up", reducing corneal area exposed to radiant energy.[69,73,74] While a radiation source of 1500 °C was responsible for increases in lens temperature of only 1–2 °C.[52] A temperature increase of 1–2 °C is no more than what occurs in a normal eye when body-core temperature and ambient temperature are significantly above 37 °C.[69]

Based on these findings, researchers hypothesized if heat-induced denaturation of crystallin is not due to short-term exposure to high temperature, perhaps it is due to lower levels of elevated eye temperature over longer periods of time,[65,75] yet the chaperone function of α-crystallin markedly improves with an increase in temperature,[76] sufficiently compensating for the narrow range of temperatures to which the human eye is exposed.

Studies that suggest a relationship between age of onset of presbyopia and increase in ambient temperature[66,77] failed to account for the concomitant increase in UV that occurs at latitudes approaching the equator.[70,75] One study reported a positive relationship for cataract formation with increasing UV, latitude, and average hours of sunlight, however no relationship was found for increasing temperature.[78]

α-crystallin, a HSP, was identified in the lens subsequent to identification in cardiology where it was known to protect from heat shock.[79] This may have led to the assumption that heat stress was a cause of age-related lens protein aggregation diseases. But HSP is a misnomer as HSPs protect crystallin protein misfolding from heat[79] and other stresses including cold,[80] UV,[81] tissue remodeling,[82] and pressure.[83]

Cumulative Exposure to UV

The literature reports cataracts appearing after exposure to UV in atomic bomb irradiation,[84] whole-body irradiation,[85,86] microwave,[87] laser,[88] x-ray[89] and UV radiation.[90,91] UV radiation, especially UVB, is an important risk for cortical cataracts,[90,92–94] however, there is no evidence UVB is associated with ARN[95–102] Based on available evidence, the following conclusions are drawn about exposure to UVB and cataract. (1) Exposure to UVB can cause lens opacities. (2) There is limited evidence exposure to solar UVB causes cortical opacities in humans. (3) Nuclear cataracts are not causally associated with exposure to solar UVB but there is an association between UVB and cortical opacities.[100,103] The nucleus is directly along the visual axis and is exposed to UVB at a much higher amount than the cortex, yet UVB is implicated in cortical cataracts, not nuclear. If UVB cannot be implicated in cataract formation in the region of the lens receiving the most exposure to UVB and heat variations are not significantly at play, then some other stressors must contribute to initiation of age-related lens protein aggregation diseases.

Internal Lens Pressure

Once proteins fold, various conditions pose a threat to their integrity. Temperature, pressure, osmotic changes and chemicals interfere with protein folding.[24] Specifically, pressure has been shown to lead to precipitation and aggregation of proteins, cross-linking and other factors implicated in age-related lens protein aggregation diseases.[19,28–34] Under high pressure, proteins are penetrated by water.[82] Studies have shown hyperbaric oxygen accelerates aging in the nuclear region of the guinea pig lens, causing loss of cytoskeletal proteins, damage to plasma membranes and formation of protein disulfides.[40,104,105] Such modifications are similar to those that occur in the nuclei of aging human lenses.[106]

Lipid membranes are extremely sensitive to pressure. Protein oxidation in the lens has been shown to initiate at the lipid membrane. Products of lipid oxidation in the lens increase with both age and development of cataract. Studies show that membrane derangement occurs in human cataractous lenses, indicating lipid oxidation and/or changes in the lipid membrane may be a cause of lens opacification (Figure 2).[106]

Sources Responsible for Elevating Internal Lens Pressure

The space between fiber cells is the interstitium, and fluid present within is interstitial fluid. Interstitial fluid circulates through the lens. An intracellular gradient of hydrostatic pressure drives fluid from center towards surface epithelial cells,

pushing outwards against the lens capsule.[107] Mathematically, hydrostatic pressure is the change in volume divided by the change in pressure; the more fluid that filters into the interstitium, the greater the volume of the interstitial space (V_i) and the hydrostatic pressure within that space (P_i). In young human lenses, the intracellular hydrostatic pressure gradient ranges from ~340 mmHg in central fiber cells to 0 mmHg in surface cells, increasing with age.[27]

Water within the lens exists in two states; free water (water not bound to crystallin proteins) and bound water (water bound to crystallin proteins). During accommodation, liquid water is expulsed from its bound state with lens crystallin, becoming free water, decreasing osmotic pressure[99,108] and moving from the lens to the surroundings, increasing lens osmolarity. As the ability to accommodate is lost, internal lens pressure increases causing the free-to-bound water ratio to decrease. The ability of the lens to respond reversibly to pressure decreases along with the decrease in accommodation, and, when accommodation is lost, an increase in free water ensues.[108] Thus, with no remaining accommodation, the lens is fixed in its unaccommodated, compressed configuration with lower tendency for water movement out of the interstitium and a higher internal pressure. With aging, the ability of the lens to compensate for increased hydrostatic pressures decreases.[109] When a response to pressure is irreversible, released water accumulates in lakes (Syneresis) witnessed in incipient and mature cataract. Total water content is much higher in cataractous lenses than normal lenses.[109]

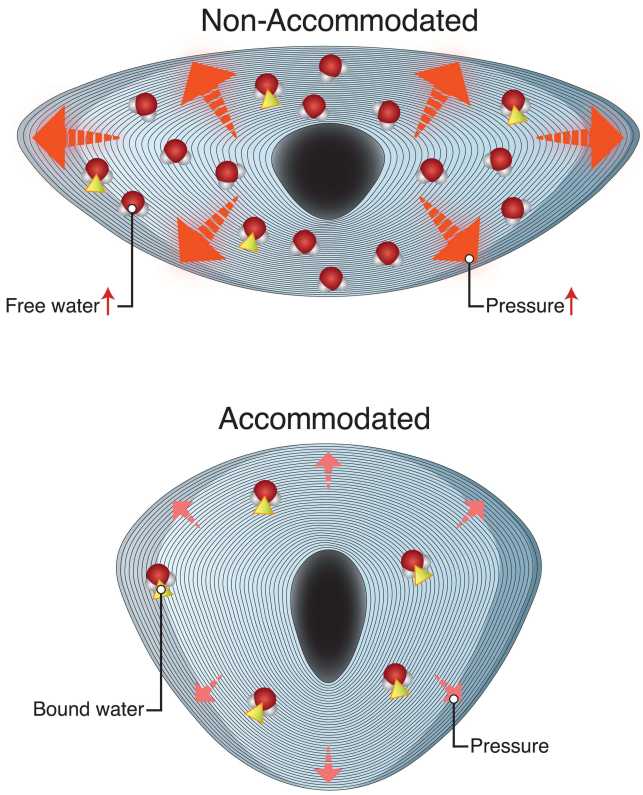

Figure 2 Representation of an accommodated and unaccommodated lens. Bottom figure – accommodated lens with most water molecules existing in the bound state. Top figure – unaccommodated lens fixed in its compressed configuration trapping free water within interstitium resulting in higher internal pressure.

Compression via Constraint of the Lens Capsule

The lens, confined by an elastic capsule, exists in a state in which small increases in fluid volume lead to large increases in pressure. Large increases in tissue interstitial pressure can lead to tissue damage and cellular death.[109] The lens capsule is a strong basement membrane[110] capable of shaping the lens and its curvature through accommodation.[111] It completely encloses the lens.[112–115] The elastic modulus of the capsule must be sufficiently higher than the lens substance to allow forces applied by the ciliary muscles to mold the lens shape. In fact, it is approximately two thousand times higher than the lens cortex and nucleus it surrounds.[111,116,117]

During accommodation, zonules apply stress with both parallel (stretching) and perpendicular (compressive) components. These stresses are transformed into a uniform stress approximately perpendicular to the lens surface. The transition from unaccommodated to accommodated state, includes a reduction of stresses perpendicular to the lens surface.[118,119] Under uniaxial load, capsular elastic moduli at 10% strain increase with age until approximately age 35. Once the age of 35 has been exceeded capsule load is maximized.[120] Continual production of lens fiber cells in the environment constrained by the capsule, fixed in a contained volume, contributes to continually increasing crowding and compaction. Fluidic changes combined with increasing pressure from the production of proteins in a confined space increase hydrostatic pressure, and consequently, the syneretic process increases resistance within the lens. Over time, lens stiffness[121] and elastic modulus[116] increase resulting from the continual accession of fiber cells.[122] As the elastic modulus of the lens substance increases, more force must be transmitted through the capsule to mold its shape. This is thought to be the primary cause of Presbyopia.[118,119]

Pressure Triggers Oxidative Damage of Gap Junctions

Gap junctions are intercellular channels that mediate direct cell-to-cell transfer of ions and metabolites.[122,123] The lens, lacking blood vessels, must use non-vascular mechanisms to move nutrients and waste products into and out of fiber cells in the lens center. This is achieved in part by an extensive network of gap junctions that join cells of the lens into an ionic and metabolic syncytium. In the lens, hundreds of gap junctions come together to form Gap Junction Channels (GJCs).[124–127] GJCs are composed of the protein connexin and found in arrays called plaques. GJCs allow small molecules to pass directly between cytoplasm of two connected cells.[128–130]

Maintenance of metabolic activities of interior cells of the lens depends on this network of GJCs.[131–134] An electrical gradient carried predominantly by Na^+ flows into the lens and through extracellular spaces.[134,135] The gradient drives Sodium (Na^+) and Calcium (Ca^+) into fiber cells, through them, and outward cell to cell via GJCs. Flow is concentrated in the equatorial region of the lens where fibers are differentiating and is termed coupling conductance. Central to age-related changes in the lens is a reduction in fiber cell gap junction coupling conductance,[27] presumably due to oxidative damage to lens connexins.[136,137] As fiber cell connexins are sensitive to oxidative damage, a downregulation of gap junction coupling with age causes depolarization of the intracellular voltage and increases in intracellular concentrations of Na^+ and Ca^+. Depolarization and increased intracellular Na^+ concentration reduce the transmembrane driving force of fiber cell membrane Na^+-dependent transporters. Collectively, these effects compromise systems that protect intracellular proteins and allow increased oxidative damage to crystallins. This down regulation impacts all factors involved with lens circulation.[27] There is an approximate 50% decrease in junctional coupling observed during lens fiber maturation.[138]

As coupling conductance decreases, forces that drive lens circulation must increase to maintain circulating fluxes. This includes increases in intracellular hydrostatic pressure, diffusion for Na^+, and voltage gradient. With age there is a reduction in the fiber cell transmembrane electrochemical potential for Na^+ entry. Consequently, Na^+ influx decreases and since it drives water flow out of the lens, water flow decreases, increasing gradients for intracellular Na^+ concentration, voltage, and hydrostatic pressure.[27,139] Since hydraulic conductivity depends on the number of open GJCs, reduced hydraulic conductivity and increased lens radius with age both cause intracellular hydrostatic pressure, p_i, to increase.[27]

Intracellular hydrostatic pressure in the lens is expected to vary in proportion to the group of parameters:[12]

$a^2 j_{Na}/N_j$ where j is the average density of fiber cell transmembrane influx of sodium (moles/cm), N_j is the number of open GJCs per area of fiber cell to cell contact (cm^{-2}), and a is the lens radius (cm).[140]

Based on this formula and knowing the number of open GJCs per area of fiber cell to cell contact decreases with age we can deduce that hydrostatic pressure in the lens increases with age.

A study[27] presents compelling data demonstrating that, in mouse lenses in which gap-junction coupling is increased, central pressure is lower, whereas if gap-junction coupling is reduced, central pressure is higher but surface pressure always remains zero. Thus, reduction in gap junction coupling is a direct cause of age-related increase in intracellular hydrostatic pressure in the nucleus of the lens.[137] Further, their data indicate that the gap junction coupling in differentiating fibers (DF) and MF decreases with age, indicating the total number of open GJCs also decreases with age. Reduced hydraulic conductivity and increased radius with age both cause intracellular hydrostatic pressure to increase with age.[27]

Intralenticular Circulation, Conductance, and Calcium Homeostasis

Gap junction coupling of interior fiber cells to surface cells is an essential component of Ca^{2+} homeostasis. At the surface, Ca-ATPase and Na/Ca exchange transport out of the lens. This sets up circulation of Ca^{2+}, where the path to surface depends on the presence of gap junctions.[141] The MF deep within the lens do not have Ca-ATPase activity or Na/Ca exchange to transport Ca^{2+} out, yet are permeable to Ca^{2+}, hence Ca^{2+} is continuously leaking into these cells.[139] Ca^{2+} accumulates in MF until diffusion to the surface balances equilibrium. A loss of gap junction coupling cuts off the MF zone from this circulation. With time, ion gradients in uncoupled cells dissipate, intracellular Ca^{2+}increases, proteolysis of cytoplasmic proteins (crystallin and connexins) occurs[128] and denatured proteins aggregate and form light-scattering elements responsible for nuclear opacity.[142,143] Several studies show a correlation between elevated Ca^{2+} and cataracts.[144–147]

It is hypothesized that this system creates a well-stirred intracellular environment in which active transport by peripheral cells maintains a homeostatic environment for cells in the MF zone. The appearance of cleaved connexins between the peripheral shell of DF and the inner core of MF has been correlated to a change in coupling conductance. Loss of coupling cuts off the MF zone from this circulation.[143] I suggest the loss of coupling conductance cutting off the MF zone is the cause of the Glutathione Bridge, suggested as one of the major factors in cataractogenesis.

Pressure Effects on Cytoskeletal Proteins

The cytoskeleton of lens proteins may play an important role in Ca^{2+}-induced transparency loss. At moderately increased Ca^{2+} levels, opacification occurs without major degradation of intracellular proteins and may be the result of Ca^{2+}-stimulated interactions between the membrane-cytoskeletal network and crystallins and may even be reversible.[142] Pressure has been shown to accelerate age-related loss of nuclear cytoskeletal proteins.[148] Furthermore, pressure has been pinpointed as a cause of the disulfide cross-linking of MIP26 and cytoskeletal proteins spectrin and vimentin, implicated in cataracts.[106]

Conclusions

There is little conclusive literature indicating that UV plays a major role in inducing ARN,[16] and its possibly after middle age that light even begins to promote lens oxidation.[10,14] Cataract forms in areas of the lens blocked from exposure to short-wavelength light, eliminating it as a cause of cortical cataracts. The literature indicates oxidative processes taking place in the nucleus are not present in the cortex yet cataracts still form. As nuclear Glutathione decreases, Glutathione levels in the outer cortex remain normal yet cortical cataracts still form.[17–20] Furthermore, UV damages only misfolded proteins, thus plays an intermediate role in the formation of age-related lens protein aggregation diseases; it is not an initiator of misfolding. The literature indicates that heat-stress is an unlikely initiator of age-related lens protein aggregation diseases. Research has established that increased pressure shifts proteins toward dissociation, and dissociated proteins are implicated as contributing to the formation of presbyopia and cataracts,[90] and pressure converts proteins into partially folded segments,[32,149–154] exposing them to oxidative damage. This leads to precipitation, aggregation, cross-linking and other factors implicated in the progression of age-related lens protein aggregation diseases.[20,28,31,33,106]

Evidence is presented proposing the barrier that forms in the middle of the lens in middle age impeding Glutathione from protecting the lens nucleus[50,60] is suggested to be a direct result of linear increasing internal pressure of the lens with age.

Lens stiffening, opacification, water and Ca^{+} accumulation leading to distension of intracellular spaces, plasma membrane disruption, increased levels of disulfide bonding, decreased levels of soluble proteins, and loss of nuclear cytoskeletal proteins[106,148] seen in cataract are likely influenced by linearly increasing internal lens pressure, not heat stress.

The number of open GJCs decreases with age causing hydrostatic pressure to increase, decreasing sodium influx leading to trouble moderating the increase in hydrostatic pressure.[27,139] Also, at the point where the lens has lost all ability to accommodate, it is fixed in its compressed configuration with lower water movement out of the interstitial spaces creating higher internal pressure.[109] With age, an increase in free water ensues[108] and in the lens, small increases in fluid volume lead to large increases in pressure leading to tissue damage and cellular death.

In summary, the continual production of lens cell fibers in the environment constrained by the lens capsule contributes to continual crowding and compaction. These changes generate pressure and resistance leading to increased stiffness, elastic modulus, increased light scattering, and a less pliability decreasing the ability of the lens to accommodate[116,118] an

attribute of presbyopia. As pressure mounts, metabolic activity is compromised distorting lens architecture causing further light scatter, refractive changes, ultimately contributing to sclerosis and opacification of cataract.

It is proposed a root cause of age-related lens protein aggregation diseases is constant increasing internal lens pressure, which, over time, interrupts healthy folding and unfolding of lens proteins, disrupts lens fluid circulation and eliminates pathways for Ca^{2+} to leave the lens, increasing opportunities for oxidation to trigger PTMs that gradually contribute to age-related lens protein aggregation diseases.

Disclosure

Dr Alan Glazier reports patent 17/537,088 pending to Unassigned Licensee, patent 17/666,424 pending to Unassigned Licensee, patent 17/713,691 pending to Unassigned Licensee, and patent 17/718,673 pending to Unassigned Licensee. The author reports no other conflicts of interest in this work.

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