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Review

Research progress of lens zonules

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ABSTRACT

Background: The lens zonule, a circumferential system of fibres connecting the ciliary body to the lens, is responsible for centration of the lens. The structural, functional, and positional abnormalities of the zonular apparatus can lead to the abnormality of the intraocular structure, presenting a significant challenge to cataract surgery.

Main text: The lens zonule is the elaborate system of extracellular fibers, which not only centers the lens in the eye but also plays an important role in accommodation and lens immunity, maintains the shape of the lens, and corrects spherical aberration. The zonules may directly participate in the formation of cataract via the immune mechanism. Abnormal zonular fibers that affect the position and shape of the lens may play an important role in the pathogenesis of angle closure disease and increase the complexity of the surgery. Capsular tension rings and related endocapsular devices are used to provide sufficient capsular bag stabilization and ensure the safety of cataract surgery procedures. Better preoperative and intraoperative evaluation methods for zonules are needed for clinicians.

Conclusions: The microstructure, biomechanical properties, and physiological functions of the lens zonules help us to better understand the pathogenesis of cataract and glaucoma, facilitating the development of safer surgical procedures for cataract. Further studies are needed to carefully analyze the structure–function relationship of the zonular apparatus to explore new treatment strategies for cataract and glaucoma.

1. Introduction

The suspensory ligament of the lens (also known as the lens zonule) is a complex system of extracellular fibers, which is transparent in physiological state. Zonular fibers connect the crystalline lens to inner structures of the eye, mainly the ciliary body, and suspend the lens within the visual axis. In some cases, zonular fibers may be substantially weakened and broken, leading to lens tremor and subluxation, thus posing challenges to the surgical manipulation of the cataract. Therefore, clinicians often examine eyes for signs of zonular problems via a slit-lamp microscope before cataract surgery, such as iris tremor and shallow anterior chamber. However, these signs may be mild and are easily overlooked in the clinic. The dislocation of the intraocular lens is the main complication after intraocular lens implantation, which may be associated with zonular insufficiency.[1] Therefore, understanding the specific situation of the zonules can not only help avoid improper surgery but also reduce the incidence of intraoperative and postoperative complications.

In the era of refractive cataract surgery, the zonular apparatus plays a more important role in the accurate formulation of cataract surgery and stable postoperative vision. A deep understanding of the zonules seems of utmost importance. In this review, we summarized recent advances in the zonule's development, anatomy, biomechanical properties and functions, and the relationship between abnormal zonules and glaucoma and cataract to provide a reference for clinical work.

2. Development and structure of the lens zonules

Zonular fibers are similar to oxytalan (“acid enduring”) fibers[2] and are produced by the tissues flanking the zonule.[3–5] The zonule of the lens is mainly composed of proteins and polysaccharides. Zonular fibers are surrounded by a layer of proteoglycan, mainly chondroitin sulfate proteoglycan and hyaluronan (HA), to protect zonular fibers from the effects of proteases in the ocular medium. Studies of the lens zonule proteome reveal that human zonules are mainly composed of noncollagenous acidic glycoproteins, of which fibrillin 1 (FBN1) is the most abundant component.[3,6] Mutations of genes encoding zonular-related proteins may cause

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zonular abnormalities, which may lead to lens luxation, such as Marfan syndrome.[7] Hundreds of microfibrils are aggregated to produce large zonular fibers, which are similar to skeletal muscle.[8] Transmission electron microscopy has revealed the presence of a lateral association within zonular fibers.[9] This indicates that a possible correlation may exist among adjacent microfibers, and the viscoelastic behavior of the zonule probably depends on this interaction. Hence, we can better understand the physical properties of zonular fibers by determining the assembly of microfibrils and the contribution of specific proteins and polysaccharides, as well as the molecular composition of the cross-bridging structures.

The lens zonules are transparent and covered by the iris. Consequently, it is difficult to observe the zonules even under microsurgical vision and mydriatic conditions. New imaging methods, such as ultrasound biomicroscopy (UBM), heip in visualizing the zonule.[10] UBM has shown the anterior movement of lens zonules during accommodation and with aging lens.[11] Pigments are often seen on the lens zonules during dilation. This may contribute to increased pigment deposition of the trabecular meshwork, and heavy amounts of pigment may contribute to intraocular pressure elevation. Meanwhile, detailed morphological studies, which are based on transmission and scanning electron microscopy, have expanded our understanding of the zonule. Zonular fibers span the space between the lens equatorial edge and ciliary body tip (about 1.07–0.65 mm).[12] However, how the zonules of the lens bridge the gap between the lens and the ciliary body is not clear.

The suspensory ligament of the lens has a complex and precise structure. Three groups of zonular fibers can be differentiated in terms of structure and function, and work together to maintain the fine function of the zonular apparatus together. The posterior zonules arise from the gulfs of the pars plana and cover the pars plana epithelium. These zonular fibers run forward to the valleys and lateral walls of the ciliary, where they are fixed within the zonular plexus. In the area of the zonular plexus, the posterior zonules are attached and mingle with the anterior zonules.[13] From there, the anterior zonules are divided into the posterior and anterior zonular tines. These zonules form the anterior and posterior zonular tines attached to the posterior and anterior aspects of the equatorial lens capsule, respectively. Also, some fiber bundles move to the lens equator directly. Therefore, the zonules can be roughly categorized into the anterior, posterior, and equatorial tines based on different anchor positions on the surface of the lens capsule.[12]

Among the ciliary processes, some finer fibers separate from the main fiber bundles, and run in the opposite direction of the main fiber bundles, and are attached to the ciliary processes, forming short “tension fibers”.[12] The zonular plexus is firmly attached to the curvature vertex of the main fiber bundles by the tension fibers that act as a fulcrum.

The third group of zonules is the vitreous zonules, including a group of anterior, intermediate and posterior vitreous zonules. These zonules are connected to the vitreous membrane.[14,15] One set of zonules (called the anterior vitreous zonules) attaches the zonular fibers to the anterior hyaloid membrane the Wieger’ s ligament. In the middle of the pars plana, a crack exists between the vitreous membrane and the pars plana zonules. The crack is bridged by zonular fibers called the intermediate vitreous zonule. Each intermediate vitreous zonular fiber moves forward and forms a fork with tines inserted into the zonular plexus on either side of the ciliary process. Posteriorly, each intermediate vitreous zonular fiber splits into a number of fine fibers and becomes part of the vitreous membrane. Finally, a multilayered sponge-like ring is formed, called the posterior vitreous zonule, at the site of vitreous attachment to the posterior pars plana. These vitreous-related fiber bundles likely act as a shock absorber, play a role in ensuring the synchronous movement of the lens, zonule, ciliary body, and vitreous humor and assist in the smooth movement of the lens during accommodation.[15,16]

3. Biomechanical properties of the lens zonules

The zonular tension plays an important role in the stable and centered position of the intraocular lens after cataract surgery. It is difficult to measure the mechanical properties of the zonule directly. Therefore, the zonule, ciliary body, lens, and sclera are usually measured as a unit. We need to only measure the change in fiber length (the strain) in response to a given stretching force (the stress) to calculate Young's modulus of the zonule. If the stress and the strain have a linear relationship, the ratio between the stress and the strain is called Young's modulus (with units of mN/mm^2 or kPa). Many studies measured the mechanical properties of zonular fibers. A previous study showed that the tension resistance of the zonular fibers decreased with age.[17] Fisher[18] indirectly estimated the force exerted on the lens and zonules by comparing the changes in lens thickness during the stretching of anterior eye sections and the lens spinning experiments. He found Young's modulus as 350 kPa, which did not vary with age. Van Alphen and Graebel[19] measured the tensile force by treating the lens, zonular fibers, and ciliary body as a single unit. They used a two-arm stretching device with one force sensor and determined Young's modulus as 1000 mN/mm^2 for 20-year-old donor eyes and 1500 mN/mm^2 for 60-year-old donor eyes. Michael et al.[20] stretched the samples that were divided into eight parts and connected to eight equally spaced hooks to avoid circumferential tension. The measured Young's modulus ranged from 270 to 340 kPa. The elastic modulus of the zonules reported from these studies was in the range of 200–1500 kPa, which was similar to the modulus of elastin-containing fibers (300–1200 kPa).[21]

Moreover, Shi et al.[22] employed a pull-up assay that exerted a uniform stretch across all zonular fibers to measure the biomechanical properties of the zonule in the mice. The force generated in the mouse zonule decreased with time, indicating that the zonular apparatus behaved as a viscoelastic rather than as an elastic element. The structural changes at a molecular or cellular level underly these observed mechanical and physiological changes. The viscoelasticity of the zonule is still to be determined. Whether viscoelasticity reflects the deformation of individual microfibers or the collective behavior of microfiber bundles within the fiber is still not clear. Therefore, it is necessary to better understand the interaction between neighboring microfibrils and the influence from internal and external factors to the fibers on their mechanical properties so as to accurately simulate the viscoelasticity of the zonule. Careful analysis and quantification of mechanical properties of zonular fibers would be beneficial to improve the accuracy of the accommodation model.

4. Function of the lens zonules

The zonular apparatus centers the lens on the visual axis and transmits the forces generated by the ciliary muscle to the lens. The zonular fibers presumably work together to ensure that the lens, zonule, ciliary body, and vitreous humor function as an integrated unit during accommodation. A previous study showed that the most anteriorly located zonules (MAZ) originated from the valleys and lateral walls of the most anterior pars plicata near the transition into the iris.[23] A dense nerve fiber plexus and mechanical receptors existed near the anchoring region of the MAZ. The afferent nerve terminals at MAZ were connected to the intrinsic nervous network of the ciliary muscle and to the autonomic ganglion outside the eye, which might assist in fine and rapid refocusing.[16] Similarly, the vitreous zonules also generated the fast and smooth alterations required for the fine regulation of focusing.[15]

The term “immune privilege” is coined to describe sites of the body in which the introduction of foreign antigens does not elicit an inflammatory immune response, such as the eyes, brain, placenta, and testes.[24] As an immune-privileged tissue, the lens is protected by anatomic barriers to prevent vision damage caused by immunogenic inflammation. However, it has been shown that immune cells can surveil the avascular lens to maintain lens homeostasis. In response to cornea wounding, immune cells that surveilled the lens traveled from the vascular-rich ciliary body along the zonule fibers to the lens surface, and some even traveled through the lens capsule.[25] Further, the resident immune cells of the lens were progenitors of myofibroblasts, which were associated with fibrosis and posterior capsule opacification (PCO).[26] The ciliary body/ciliary zonule pathway was a potential source of lens-resident immune cells to provide a mechanism for replenishing depleted populations of resident immune cells of the lens in adult animals.[27] Hence, these findings supported that the zonules acted as a conduit for immune cells and directly participated in the immune response of the lens. There still remains much to learn about the function of zonules in lens immunity, the knowledge of which might help in investigating the pathogenesis of cataract and PCO, especially in autoimmune diseases such as diabetes and uveitis.

Previous studies revealed that several extracellular matrix and signaling proteins could promote the movement of immune cells in the zonule proteome.[3,28] For example, tenascin C supports the adhesion of immune cells via its binding with Toll-like receptor 4,[29] Microfibril-associated glycoprotein-1 connects the active form of transforming growth factor β (TGF-β) to fibrin,[30] and TGF-β is associated with cell migration.[31] The lymphatic vessel endothelial hyaluronan receptor-1(LYVE-1) is a hyaluronic acid receptor, which maintains a connection with the matrix during cell migration.[32] Logan et al.[33] found that the link of the LYVE-1 ectodomain with the ciliary zonules is enhanced in the eyes of N-cad$^{\Delta lens}$ mice, which supported the role of the zonules in the migration of immune cells from the ciliary body to the lens. Therefore, comprehending the mechanism of fibrin, TGF-β and their related molecules in promoting the migration of immune cells along the zonules can deepen our understanding of cataract formation and lens fibrosis, as well as provide a potential therapeutic target for cataract and PCO.

The tension forced by the ciliary muscle through the zonules affects the hydrostatic pressure gradient in the lens via activating the regulated water channel.[34] As regulating intracellular hydrostatic pressure gradient in the lens can alter the water content and the gradient of refractive index, zonules may also play a role in the correction of spherical aberration.[34,35] Gao et al.[36] found that, in the senile lens, the continuous stimulation of transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential vanilloid 4 (TRPV4) by the zonules may lead to changes in lens pressure and water distribution, causimg some aging alterations of the lens, such as presbyopia or cataract. When aquaporin 5 knockout lenses are organ cultured under hyperglycemic conditions, they are more prone to osmotic swelling compared with wild-type lenses.[37] This abnormal fluid transport may cause increased lens size and anterior displacement of zonules in patients with diabetes. These changes in the eyes of diabetic patients might lead to glaucoma due to increased iridolenticular contact, rubbing, and pigment liberation. Thus, the regulation of the zonules provides insights into how dysfunction of lens water transport can result in cataract and glaucoma.

Furthermore, the abnormality of lens size probably is secondary to the abnormality of the zonular structure, rather than the defect independent of lens growth. FBN1 and latent TGF-β-binding protein 2 (LTBP2) encode two major genes for the components of the zonule, which are closely related to microspherophakia (an unusually small and spherical lens).[38,39] A study indicated that the tensile strength of the zonule was diminished in LTBP2-deficient mice.[22] In the mouse experiment, the FBN1 deletion was associated with the diminished tensile strength of the zonule and the increase in globe size.[40] The weakened zonules cannot provide adequate tension to the lens, which may cause changes in the size and shape of the lens.

5. Zonular abnormality and angle closure glaucoma

The European Glaucoma Society guidelines indicated that lens-related abnormalities are one of the mechanisms in angle closure glaucoma (ACG).[41] The abnormal zonules may account for the forward movement of the lens and the anterior displacement of the iris lens diaphragm, resulting in the closure of the anterior chamber angle, and hence promoting the occurrence of ACG.[42] In the eyes with pseudoexfoliation syndrome, the zonules are often frayed and broken due to the accumulation of pseudoexfoliation material on the zonular fibers.[41] Abnormal zonular attachment to the lens or ciliary body may result in the anterior displacement of the lens, which may lead to the secondary angle closure.[43] Salimi et al.[44] found that patients with ACG had a higher prevalence of zonular instability (7.3%) compared with the general population. Another case–control study analyzed the proportion of zonular abnormality (undiagnosed before surgery) in patients with ACG by observing the intraoperative signs of the zonular instability. The prevalence of zonulopathy was evidenced among 46.2% of the eyes compared with the general population, and a majority of the eyes of acute ACG had abnormal zonules.[45] These results revealed that the zonular abnormality might play a major role in the pathogenesis of ACG, especially in acute ACG. Enes Toklu et al.[46] reported that compared with patients who underwent the partial pars plana vitrectomy, those who underwent the complete pars plana vitrectomy (with vitreous base shaving) had a significantly deeper anterior chamber. Considering the anatomical proximity of the vitreous base to the zonules, the zonules may play an important role in the pathogenesis of glaucoma by altering the depth of the anterior chamber, and the role of vitreous zonules in the glaucoma pathogenesis may be greater than that of other zonules.

Some ocular characteristics may play an essential role in angle closure caused by abnormal zonules. Kwon et al.[47] compared the preoperative ocular characteristics of eyes with and without underdiagnosed zonulopathy in glaucoma, suggesting that eyes with longer axial length, shallower anterior chamber, and higher lens vault often had abnormal zonules. Xing et al.[42] demonstrated that the shallower anterior chamber (<1.25 mm) and thicker lens (>5.13 mm) might be powerful predictors of lens zonula relaxation in patients with acute ACG. Another study showed that the shallower the anterior chamber depth (ACD) of patients with ACG, the greater the risk of zonular abnormality. All patients with ACG with ACD <1.9 mm were complicated with abnormal zonules. ACD differences between two eyes and ACG types were related risk factors for zonular abnormality.[45] These studies suggested that clinicians should consider the possibility of zonular abnormality during cataract surgery for eyes with ACD <1.25 mm, lens thickness >5.13 mm, longer axial length, and higher len s vault among eyes with a history of ACG attack. In the clinic, it is difficult to determine the zonular stability in eyes with ACG before surgery. Further studies are needed to find more accurate methods to evaluate the preoperative and intraoperative abnormalities of the zonules.

Moreover, the long anterior zonule (LAZ) trait may be a risk factor for higher intraocular pressure in open-angle and narrow-angle patients for unknown reasons. During slit-lamp examination, the LAZs are observed as fine, radially oriented fibers on the anterior capsule, extending more central than usual along the anterior lens surface.[48] A significant correlation was found between LAZ and mild elevated intraocular pressure,[49] suggesting that the existence of LAZ might increase the risk of glaucoma. Khurana et al.[50] found that angle closure was present in more than half the eyes with LAZ, and most of these eyes had primary angle closure diseases. Eyes with LAZ also had a thicker lens, shallower anterior chamber and a shorter axial length as compared with controls. The pigment dispersion occurred in the older patients but the mechanism for this dispersion wasn't clear.[51] Newman et al.[52] speculated that these older patients may have had long anterior zonule associated pigment dispersion. These findings implied that the LAZ trait might have a potential relationship with elevated intraocular pressure.

Recent studies suggested that the LAZ might present with at least two phenotypic varieties. Most cases with unknown etiology and prevalence possibly of about 2% have been reported in female patients mostly aged more than 50 years, hyperopic, and without retinal degeneration.[53] Another phenotype may be detected at a young age, which has an association with late-onset retinal degeneration (L-ORD).[54] The patients with L-ORD have a serine 163 arginine (S163R) substitution in the complement 1q tumor necrosis factor–related protein 5 gene (C1QTNF5/CTRP5).[55] The physiological mechanism of elevated intraocular pressure caused by these different LAZs is still unclear. Given the potential correlation between LAZ and glaucoma, a great deal of research is needed to further explore the LAZ characteristics.

6. Zonular abnormality and cataract

Zonular instability can increase the complexity of cataract surgery. Lin et al.[56] analyzed the risk factors for structural changes intraoperatively, and the detection rate of the Berger space in patients with a high risk of zonular weakness (60.7%) was significantly higher than that in patients without this risk factor (33.0%). The result revealed that phacoemulsification could damage the vitreo-lenticular interface structure, especially in eyes with abnormal zonules, resulting in the intraoperative entrance of fluid and particulates to the Berger space. The zonular abnormality not only increases the risk of intraoperative and postoperative complications, such as vitreous prolapse, capsular rupture, intraocular lens dislocation, and uveitis, but also reduces the success rate of the surgery.[44] The common risk factors for zonular abnormality include posterior polar cataract, pseudoexfoliation syndrome, small pupils, axial length greater than 26 mm, previous trauma, and history of intravitreal injection.[57]

It is often difficult to determine the zonular instability preoperatively on slit-lamp examination. The preoperative signs of zonular problems include iris tremor, shallow anterior, displacement of the lens equator and asymmetry in the anterior chamber depth or axial length compared with the contralateral eye.[58] The intraoperative abnormality of the zonule can be identified at all steps of the cataract surgery procedure. The anterior capsule wrinkles, difficulty with lens rotation after multiquadrant hydrodissection, and excessive movement or instability of the capsular bag during nuclear disassembly or cortical clean-up can be the signs of zonular abnormality.[43,44] These signs may be mild and partial, and are easily overlooked in the clinic.

At present, the absence of effective methods to objectively assess the zonular stability poses unique challenges to cataract surgery. Therefore, it is necessary to find effective evaluation methods for abnormal zonules to avoid postoperative and intraoperative complications.

As the zonular abnormality may lead to lens capsule tearing, we should pay close attention to the abnormal zonules during capsulorhexis. The capsule tears radially along the fiber due to zonular insufficiency. Recent research revealed that the LAZs frequently reduced the size of the anterior capsule's zonule-free zone[49] compared with the normal anterior lens surface. If zonular fibers are inevitably cut during capsulorhexis, it may increase the risk of capsular tearing.

In patients with abnormal zonules, the capsulorhexis should be started from a place far away from the zonulopathy area to avoid puncturing of the capsule. Further, it is advantageous to apply femtosecond laser-assisted capsulotomy (FLACS) in eyes with zonular abnormality, as it does not involve additional stress to the remaining zonules.[59] If a radial capsule tear occurs, the tear should be reoriented to the center to return to the required circumferential path. Little's rescue techniques[60] have been widely used to rescue the torn anterior capsule, in which the capsulorhexis is unfolded into its natural position and then pooled circumferentially backward and then centrally. If necessary, the second corneal incision can be made at the position that allows traction. Moreover, the use of two micro capsulorhexis forceps in a hand-over-hand technique is useful in patients with severe zonulopathy.[61] Adjunctive devices, such as the capsule tension ring and the capsular tension segment for scleral suture fixation, can be used alone or in combination based on the severity of zonular weakness to provide capsular support during surgery.[62,63] Further, when the zonules are seriously injured, alternative methods of lens fixation must be considered, such as suture fixation to the sclera.[64]

7. Conclusions

The lens zonule plays an important role in rapid refocusing and lens immunity, maintaining lens shape and correcting spherical aberration. Changes in the composition, structure and biomechanical properties of the zonule provide insights into the pathogenesis of cataract and glaucoma. However, much remains to be learned about the function of zonule-associated proteins and the interaction between neighbouring microfibrils. Further studies are needed to fully understand the structure-function relationship of the zonular apparatus and to explore the potential therapeutic target for cataract and PCO. Furthermore, zonular abnormalities may pose a challenge to surgical manipulation of the cataract. Therefore, clinicians should consider the possibility of zonular abnormalities during cataract surgery. Further studies need to focus on finding more accurate methods to assess preoperative and intraoperative zonular abnormalities.

Study approval

Not applicable.

Author contributions

The authors confirm contribution to the paper as follows: HZ and QZL conceived and designed the study; YYP searched references of the study; YYP selected the references; YYP wrote the original paper; HZ and QZL re-wrote the final paper and submitted the paper. All authors have read and approved the manuscript.

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Abbreviations

ACD	Anterior chamber depth
ACG	Angle closure disease
FBN1	Fibrillin 1
FLACS	Femtosecond laser-assisted capsulotomy
HA	Hyaluronan
LAZ	Long anterior zonule
L- ORD	Late-onset retinal degeneration
LTBP2	Latent transforming growth factor beta binding protein 2
LYVE-1	Hyaluronan receptor-1
MAGP1	Microfibril-associated glycoprotein-1
MAZ	Most anteriorly located zonules
PCO	Posterior capsule opacification
TGF-β	Transforming growth factor β
TRPV1	Transient receptor potential vanilloid 1
TRPV4	Transient receptor potential vanilloid 4

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