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Genomic and Proteomic Pathophysiology of Pseudoexfoliation Glaucoma

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Abstract

PEX stems from a pathologic elastotic process involving the cross-linking gene lysyl oxidase-like-1 (LOXL1), and is associated with abnormal formation of elastic extracellular matrix. We previously described a protein sink model to explain PEX material deposition on the lens capsule and other intraocular surfaces. Recent research findings not only provide evidence to support this hypothesis, but also further our understanding of the fundamental disease process.

A key aspect of the pathogenic process is the compromise of blood-aqueous barrier integrity in PEXG. Decreased level of LOXL1 is associated with decreased elastin incorporation into elastic tissues, including the elastic lamina of blood vessels. This results in unincorporated elastin that is released as soluble elastin, and leakage of serum proteins, inflammatory cytokines, and extracellular matrix components into aqueous humor. This ultimately leads to aggregation and precipitation of large protein complexes, or PEX material, throughout intraocular surfaces as described in the protein sink model.

The pathologic PEX process also affects the biomechanical properties of elastic tissues, such as the trabecular meshwork, lens zonules, and lamina cribrosa. This may be part of the primary pathologic process with intrinsically altered extracellular matrix proteins. This fundamental change in the structural composition of these tissues may alter their rigidity, elasticity, and other biomechanical properties. This likely contributes to increased trabecular meshwork outflow resistance and high intraocular pressure, and mechanical injury to retinal ganglion cell axons at the lamina cribrosa, which are conducive to glaucoma. These pathophysiologic processes combined may underlie some of the clinical hallmarks observed in PEXG.

Keywords

Pseudoexfoliation; glaucoma; LOXL1; blood-aqueous barrier; trabecular meshwork; lamina cribrosa

Introduction

Glaucoma is a leading cause of irreversible blindness worldwide(1). Glaucoma is comprised of a number of conditions that result in neurodegeneration of the optic nerve, and is clinically diagnosed by structural changes of the optic nerve head associated with corresponding visual field deficits(2). Increased intraocular pressure (IOP) is a major modifiable risk factor for glaucoma and increased IOP may be associated with optic nerve pathology by decreasing tissue perfusion or causing mechanical damage of axons at the optic nerve head(3–8). Therefore, careful evaluation, monitoring, and treatment of elevated

IOP are critical for the care of individuals with glaucoma. Increased resistance to outflow is the main cause of elevated IOP. And although closed-angle glaucoma (CAG) is common, a normal outflow structure - as seen in open-angle glaucoma (OAG) - is the predominant case. This makes it often difficult to directly identify the cause of elevated IOP.

Pseudoexfoliation syndrome (PEXS) is characterized by an accumulation of fibrillar material in the eye and other tissues in the body. Pseudoexfoliation material (PEX) is observed throughout the anterior segment of the eye as white, fluffy appearing deposits on the zonules, anterior lens capsule, pupillary margin of the iris, cornea, and the irido-corneal angle(9). The 10-year cumulative probability of developing glaucoma (PEXG) in individuals with PEXS is about 15%(10). PEXG is the most common form of glaucoma in Scandinavian countries, and accounts for about 25% of all OAG - making PEXG the most common identifiable cause of OAG worldwide(10). The recognition and diagnosis of PEXS/PEXG at the slit lamp is critical for clinicians because PEXG has a poorer prognosis with a higher frequency and severity of optic nerve damage at time of diagnosis, worse visual field damage, poorer response to medications, more rapid and severe clinical course, more frequent necessity for surgical intervention, and higher rates of surgical complications compared to other forms of OAG(11, 12).

At the cellular level, PEX material arises from abnormal production of elastic fibers. Assembling normal elastic fibers is a complex cellular process, and perturbation of any step by the pseudoexfoliative process may result in altered composition, organization, deposition, and accumulation of PEX material(12–14). PEX thus affects tissues composed of elastic fibers, including blood vessel walls, the trabecular meshwork (TM), and lamina cribrosa. Indeed, PEX accumulation in the juxtacanalicular aspect of TM has long been thought to contribute to elevated IOP in PEXG(15, 16). But beyond the formation of PEX material, transcriptional and proteomic analyses demonstrate that these and other elastic tissues are abnormal, allowing us to better understand the disease process at the cellular level.

A recent seminal study demonstrated that genetic polymorphisms in lysyl oxidase-like 1 (LOXL1) play an important role in the pathogenesis of PEXG(17). LOXL1 encodes an enzyme that catalyzes the cross-linking of elastin polymers. We review data showing that abnormal tissue expression or function of LOXL1 contributes to abnormal elastic fiber production, abnormal precipitation of elastic microfibril and extracellular matrix components on intraocular surfaces (protein sink model), and abnormal biomechanical properties of elastic tissues, such as the TM and lamina cribrosa(13, 14). These processes are particularly conducive to glaucoma because they affect aqueous production, outflow resistance, and the structural support of the optic nerve. Other mutations and polymorphisms that affect elastic fiber composition and formation are speculated to similarly contribute to development of PEXG, as well as other forms of glaucoma(18). Taken together, the findings reviewed here are not only expanding our understanding of PEXG, but may also help us better understand the eye’s regulation of IOP and the pathogenesis of glaucoma.

Genetic predisposition

In a recent landmark genome wide association study (GWAS), three single nucleotide polymorphisms (SNPs) in the lysyl oxidase-like protein 1 (LOXL1) gene were identified to be significant genetic risk factors for the development of PEXG in a Scandinavian population(17). One SNP (rs1048661) is in a non-coding intron and is hypothesized to affect the post-transcriptional regulation of LOXL1 mRNA expression levels. The other two SNPs (rs1048661 and rs3825942) are in protein coding exons, and may impact LOXL1 protein function. These two high risk SNPs carry a ~2.5-fold increased risk of developing PEXG compared control, although approximately 25% of their general population is homozygous for the highest risk haplotype. Taken together, these two high risk SNPs were present in over 99% of their PEXG cohort(17).

Many other studies have since confirmed the association of SNPs in LOXL1 and PEXG on other populations (refer to the review article by Allingham et al in this issue for more information on the genetics of PEXG). Here, we focus on the role LOXL1 and other disease-associated genes have on the pathophysiology of PEXG.

PEX material composition

Intraocular PEX material is most frequently visualized on the iris pupil margin and the anterior lens capsule. PEX material is deposited on the lens capsule surface in a bullseye-like configuration from iris-capsular rubbing during iris excursion in changing light conditions. In fact, the *sine qua non* for diagnosis of PEXS is identification of PEX deposits on the lens capsule by slit lamp examination after dilation of the iris. Nevertheless, PEX material is also found on the iris pupillary border, irido-corneal angle, vitreous, corneal endothelial surface, and other ocular surfaces.

PEX material composition has been studied by immunostaining and differential proteomic analysis of anterior lens capsules removed during routine cataract surgery from PEXS/PEXG and non-glaucoma patients(13, 19–21). Proteomic analysis demonstrates that PEX material composition can be categorized into: (a) elastic fiber, (b) basement membrane, and (c) blood-derived components (table 1). The presence of fibrillin, elastin, tropoelastin, LOXL1, and other elastic fiber components is a strong indicator of an elastotic process, or in other words, a degeneration of elastic fibers with ectopic deposition of elastic fiber components. Interestingly, a number of complement factor proteins are also present in PEX deposits. This suggests that either the abnormal eye tissue elastotic process drives the recruitment of inflammatory mediators, complement factors, and other serum proteins into the aqueous humor, or that an underlying inflammatory process associated with a weakening of the blood-aqueous barrier allows an abnormal leak of such proteins into the aqueous humor.

PEX material is also found throughout the human body including the heart, liver, kidney, gall bladder, and cerebral meninges(22, 23). Systemic PEX material is often found in the periphery of blood vessels and may originate from fibroblasts and muscle cells(12). Proteomic analysis of serum from PEXG shows elevated levels of elastic fiber proteins such as vitronectin and fibulin compared to control patients(24, 25). Interestingly, the levels of

various complement factors and other immune-related proteins are also elevated in the serum of PEXG patients, but not significantly greater to those in serum from primary open angle glaucoma (POAG) patients(24). Also, apolipoproteins, complement factors, and other cytokines have been connected with other diseases of aging including age-related macular degeneration, atherosclerosis, cardiovascular disease, and Alzheimer's disease(24). This suggests that inflammatory mediators are not specific to the pathophysiology of PEXG, but rather may be a common feature of various diseases of aging including glaucoma.

The structure of PEX deposits has been studied by electron microscopy (EM). Elastic microfibrils and other protein components involved in elastic fiber formation are hypothesized to form the core of PEX deposits(14). Fibrillin-1, a key component of elastic microfibrils, is a large glycoprotein that can interact with many basement membrane proteins(14). Also, fibulin-5, another component of elastic microfibrils, can directly bind LOXL1(26). Thus, basement membrane and aqueous humor proteins likely bind the core via such proteins, and thereby create large PEX protein complexes that precipitate and accumulate throughout intraocular surfaces(13, 14). What drives the deposition and aggregation of elastic fiber proteins throughout the anterior segment of PEXS/PEXG eyes is unclear and why this is associated with aging and is not a constant process present at birth or in young individuals with genetic susceptibility is unknown.

The pathogenesis of PEX deposits is believed to be a stress- or inflammatory-induced elastosis associated with changes in the expression of elastic microfibril components(12). Indeed, compared to controls, individuals with PEXS have increased intraocular expression of fibrillin-1, LTBP-1 and LTBP-2, LOXL1, and other elastic microfibril components(27, 28). In fact, the expression of LOXL1 in the cilliary processes of PEXG eyes seems to increase in early disease followed by a reduction in late disease, compared to controls(27). It is unclear why there is an increase in LOXL1 and elastic fiber gene transcription in early disease, but risk SNPs in LOXL1 may alter the timing or efficacy of LOXL1 expression affecting the fidelity of elastin polymer cross-linking in affected individuals(17, 27). Another possibility is that risk polymorphisms in LOXL1, particularly those found in exonic regions, ultimately affect the function of LOXL1 protein. Such changes could potentially alter assembly or cross-linking, leading to extracellular matrix elastotic changes and formation and deposition of PEX material(14, 29).

Genetic polymorphisms that affect expression of other disease-associated genes may also play an important role in onset, progression, or severity of disease. Clusterin is a protein chaperone molecule known to prevent aggregation and precipitation of mis-folded proteins. Clusterin is significantly downregulated in anterior segment tissues and reduced in aqueous humor of PEX eyes(30). Decreased levels of clusterin may therefore promote aggregation of proteins around the PEX elastic microfibril core, thereby leading to the formation of PEX deposits, through a process we describe as protein sink(13). Further analyses of current GWAS data, or additional genetic studies, may help reveal SNPs in clusterin or other disease-associated genes that contribute to the pathogenesis of PEXS/PEXG.

The changes in gene expression that occur in early disease may be regulated by inflammatory cytokines, oxidative stress, hypoxia, or breakdown of the blood-aqueous

barrier. Regardless of the inciting process, an important mediator appears to be transforming growth factor beta type 1 (TGF-β1). TGF-β1 transcription is upregulated both in aqueous and anterior segment tissues of PEX eyes, and TGF-β1 regulates LOXL1, clusterin, complement factors, and other genes whose products are found in PEX material. Moreover, TGF-β1 itself associates with PEX deposits via its binding proteins LTBP-1 and -2(31–33). Therefore, environmental and genetic factors that drive expression of TGF-β1 may induce the elastotic process leading to PEX material formation and deposition in genetically susceptible individuals.

PEX and aqueous humor formation

Increased resistance to aqueous outflow is well described in eyes with PEX; however, it is unclear whether increased aqueous secretion occurs in some PEX eyes as well. The A3 adenosine receptor, a member of a family member of G-protein coupled receptors, is overexpressed in the non-pigmented ciliary epithelium of PEX eyes with or without glaucoma(34). Because A3 adenosine receptors regulate aqueous secretion and IOP(35, 36), dysregulation of A3 adenosine receptors may be associated with the development of high IOP and PEXG, especially in association with ischemia or oxidative stress(13). However, studies aimed at evaluating IOP show a similar rate of aqueous production in PEX eyes (if not slower) compared to control eyes(37, 38). These apparently contradicting findings may have several explanations. Aqueous humor production is a very dynamic process, and the rate of aqueous humor production may vary throughout the course of disease. Another explanation is that outflow resistance influences the rate of aqueous production and vice versa, so determining an absolute rate of aqueous humor production may be very difficult. Therefore, it is unclear whether rate of aqueous secretion in PEX eyes is affected in pre, early, or late stages of PEXG.

The composition of aqueous humor is clearly altered in PEX eyes. Breakdown of the blood-aqueous barrier and leakage of serum from iris vessels has been demonstrated to occur in PEX eyes(13, 25, 39, 40). This is associated with an abnormal accumulation of serum proteins and extracellular matrix components in aqueous humor, as well as changes in pH, osmolality, and reactive oxygen species related to increased oxygen content in the aqueous humor of PEX eyes. Indeed, recent proteomic analyses of aqueous from PEX eyes demonstrated the presence of clusterin, extracellular matrix proteins, complement factors, hemoglobin, immunoglobulins, and other proteins(13, 25). This supports the notion of a protein sink model where altered aqueous humor proteins in PEX eyes create a permissive molecular environment for abnormal aggregation of multiple proteins leading to formation of PEX deposits. It is yet to be determined whether some of these molecules abnormally found in aqueous humor and PEX deposits, such as TGF-B and other cytokines, also trigger pathologic changes in the function of other tissues bathed by aqueous humor such as the lens, corneal endothelium, and TM.

These findings suggest that vascular changes and breakdown of the blood-aqueous barrier could be a key feature of the elastotic process that defines PEX. Indeed, fibrillin, elastin, LOXL1, and many of the genes implicated in the disease are expressed throughout the eye including the vasculature(14). Effects on the vasculature may also explain the presence of

PEX deposits throughout the body, although disease has only been demonstrated in the eye – PEXG. “Knockout” or loss of LOXL1 expression is sufficient to cause loss of elastin in iris vessels, leakage of serum into aqueous, and formation of PEX-like cataracts(41). This study shows that lack of LOXL1 protein alone is sufficient to cause some PEX-like ocular pathology, although it does not capitulate human PEXG especially because PEX deposits are not observed in LOXL1 knockout mice. This may reflect the complexity of diseases of aging such as PEXS/PEXG that involve sophisticated interactions between different genetic and environmental factors. As mentioned above, polymorphisms in other modifier genes are likely to influence the ultimate disease phenotype. Similarly, specific environmental factors likely contribute to onset, rate, and severity of the disease. (See Pasquale et al in this issue on gene-environment interactions in PEXS.)

An elastotic process affecting vascular integrity may also explain an association between PEXS and cardiovascular disease(42). Recent studies suggest that individuals with coronary artery ectasia, cerebrovascular disease, aortic aneurysms, or peripheral vascular disease more frequently have PEXS/PEXG after ophthalmologic examination(43–47). Notwithstanding the growing evidence, some studies have failed to identify an association between PEXS/PEXG and cardiovascular disease, and there is no evidence of increased mortality in individuals with PEXG(48–52). To date, there is no evidence from a multi-center, randomized clinical trial for a clear association between PEX and systemic disease, nor a clear benefit from an evaluation by a primary care physician.

PEX and outflow resistance

PEX deposits are commonly found at the pupil margin of the iris and the anterior lens capsule of PEXG patients. These deposits are thought to be carried by aqueous convection currents and accumulate in the TM, contributing to elevated IOP and development of PEXG(15, 16). Interestingly, the amount of PEX deposited on the anterior lens capsule doesn’t always correlate with severity of glaucoma. However, the severity of PEXG appears to correlate with the amount of PEX material in the TM. PEX material accumulates in the TM approximately 3-fold greater in the TM of PEXG compared to PEXS eyes. Also, greater extent of PEX deposition correlates with greater IOP and greater degree of glaucomatous damage. Within TM, deposits mostly localize to the deeper- uveal and juxtacanalicular layers, as well as the endothelial surface of Schlemm’s canal in advanced PEXG. This raises the question of whether PEX material in TM is extrinsic (arising from aqueous currents) or intrinsic i.e. arising from with the TM.

Some evidence exists to support the suggestion that PEX material in TM arises from production of abnormal elastic fibers within TM. *In situ* PEX material production is supported by EM data showing increased secretory organelles and mitochondria, thickening of the plasma membrane, and organization of fibrils on the surface of trabecular cells in PEXG eyes(16). In healthy TM, the extracellular matrix associated with trabecular cells is comprised of tightly organized elastin beams coated with collagen(53). LOXL1 cross-links elastin and collagen and is expressed in multiple ocular tissues including TM(27), and may therefore play an important role in the formation of normal TM extracellular matrix. Lack of LOXL1 in mice leads to abnormal elastin fiber deposition and PEX-like material, similar to

the pathology observed in TM of PEXG eyes. This supports not only that PEX material can be produced within TM, but also that PEX material is possibly produced because of abnormal elastin polymerization in TM as part of the primary disease process. Therefore, increased TM resistance may result not just from TM outflow channels clogged with PEX deposits, but also from a dysfunction of TM, which regulates IOP.

Discovering the set of genes involved in the formation of PEX material and their expression profiles in the eye will greatly help us understand how each tissue is affected in PEXG. For example, regulation of LOXL1 expression varies from tissue to tissue within the eye, and throughout the course of disease in PEXS/PEXG(27). This may allow for disparate elastosis and PEX formation in different ocular tissues, and may also explain why the amount of PEX deposits visible on the anterior capsule may not always correlate with PEX accumulation in TM and severity of PEXG(13, 14, 54).

LOXL1-positive PEX material is also found in other outflow structures including Schlemm's canal, the periphery of intrascleral aqueous collector channels, aqueous veins, and episcleral veins, and suprachoroidal space(27). It is therefore possible that PEX eyes have increased resistance at a structural level posterior to TM as well as within the uveo-scleral outflow pathway. This may help explain why PEXG is an aggressive form of OAG with higher baseline IOP at diagnosis, greater spikes in IOP, and is associated with more rapid progression of optic nerve damage.

PEX and optic nerve damage

The pathophysiology of PEXG is also speculated to increase risk and rate of progression of glaucomatous optic nerve damage independent of IOP(55). For example, despite similar baseline IOP, a greater rate of conversion to glaucoma is reported from ocular hypertension to PEXG than to POAG(56). Also, untreated patients with PEXG progress faster than those with POAG or normal tension glaucoma (NTG)(57). Some of this risk is thought to arise from structural changes in lamina cribrosa leading to increased damage of retinal ganglion cell axons(58, 59). The extracellular matrix of lamina cribrosa is composed of elastic fibers, and significant elastosis is observed in PEXG eyes(58). Although these changes can result from chronic elevation in IOP, the extent of elastosis observed in PEX eyes is significantly greater to that observed in other forms of glaucoma. This suggests that these optic nerve head associated changes are part of the primary PEX pathophysiologic process, not elevated IOP(59).

The elastic fiber network of lamina beams in PEX is disorganized and fragmented and is associated with formation of PEX aggregates(55). There is also decreased expression of LOXL1 gene as well as elastin, fibrillin-1 and fibulin-4 in lamina cribrosa of PEXG eyes. Moreover, LOXL1 protein, normally localized in the cytoplasm of astrocytes associated with elastic fibers, accumulates with PEX aggregates co-localized with elastin, fibrillin-1, and fibulin-4(55). Interestingly, no change is observed in collagen expression or organization, or in the macroscopic architecture of lamina cribrosa in PEX eyes. Taken together, this suggests that the biomechanical properties such as compliance or stiffness - rather than overall structure - of lamina cribrosa is affected in PEX eyes. Of note, LOXL1

also accumulates in the blood vessel walls of pre-laminar capillaries and retrobulbar short posterior ciliary arteries suggesting that axonal damage could also result from vascular pathology in the optic nerve head(55). Indeed, mechanical and vascular injury at the optic nerve head are not mutually exclusive processes, and both affect axoplasmic flow in retinal ganglion cell (RGC) axons leading to RGC glaucomatous degeneration.

Optic nerve damage and progression could also result from pathology in the ganglion cell and inner plexiform layers (GCL and IPL, respectively) of the retina. Recent studies have shown an accumulation of complement factors in the IPL during early glaucoma(60–63). This complement accumulation may lead to pruning of the RGC dendrites and RGC dysfunction in early disease(63–65). Moreover, a recent GWAS showed that SNPs in complement factor C7 are associated with POAG(66). Therefore, the breakdown of the blood barrier in PEX, together with increased levels of complement factors, TGF-B, and other cytokines in PEXG may potentially lead to degeneration of RGCs independent of IOP. Interestingly, LOXL1 protein is found in the IPL and GCL of healthy eyes(67); it would be interesting to see if the vasculature supplying the inner retina is also altered in PEX eyes.

Taken together, there is no evidence to establish a causative relationship between changes in lamina cribrosa and IOP-independent glaucomatous damage in PEXG. Nevertheless, this research work helps explain why PEXG is more aggressive than other forms of OAG, and sheds light on the biochemistry and biomechanics of elastic tissue and its relationship with glaucomatous damage.

Conclusion

Clinically observed PEX deposits in intraocular surfaces may represent the “tip of an iceberg” of a more fundamental disease process affecting the organization of elastic fiber networks. In the eye, this results in abnormal biomechanical and biochemical properties of many tissues including the trabecular meshwork and lamina cribrosa, and may also produce zonular fragility. PEX also results in compromised blood-aqueous barrier integrity in the ciliary body and iris, resulting in abnormal aqueous composition and PEX material formation and deposition. These molecular and pathophysiologic events may underlie uncontrolled IOP, glaucoma, lenticulo-zonular complex weakness, surgical complications, and higher rates of postoperative inflammation seen in PEXG.

Understanding the function and regulation of LOXL1 and other genes implicated in PEX have helped elucidate molecular pathways involved in axonal support at the lamina cribrosa, aqueous production, outflow, and control of IOP. Further research will further help us better understand not only PEX, but also glaucoma at the molecular level, and may lead to development of diagnostic tools and treatments for affected individuals.

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Table 1

Capsular PEX deposit protein composition by proteomic analysis(19)

Elastic Fiber Components
Fibrillin-1
Elastin
Tropoelastin
Microfibril associated glycoprotein (MAGP-1)
Emilin
LOXL1
Basement Membrane and Extracellular Matrix Components
Fibronectin
Vitronectin*
Fibulin-2*
Laminin
Heparan sulphate
Amyloid P
Versican
Syndecan-3
Blood-Derived and Immune-related proteins
Hemoglobin A2
Clusterin
Complement factor C1q
Complement factor C3c
Complement factor C4c
Latent transforming growth factor b (TGF-β) binding proteins (LTBP-1 and LTBP-2)

* Proteins found in greater concentration of serum from PEXG compared to control patients(24)