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Unfolded proteins and aggregates: The role of proteostasis in pseudoexfoliation pathology

Bushra Hayat,[1,2] Debasmita Pankaj Alone[1,2]

[1]National Institute of Science Education and Research, Bhubaneswar, Odisha, India; [2]Homi Bhabha National Institute, Training School Complex, Anushakti Nagar, Mumbai, India

Background: Proteostasis impairment is central to cellular dysfunction in protein aggregation disorders such as Alzheimer disease, Parkinson disease, and age-related macular degeneration. Pseudoexfoliation (PEX), a systemic age-related disorder and a leading cause of secondary glaucoma, is increasingly recognized as a protein aggregation disease. It is characterized by the deposition of pseudoexfoliative material (PEXM) in ocular tissues, leading to elevated intraocular pressure and optic neuropathy.

Objective: This review synthesizes current evidence on the role of proteostasis failure in PEX pathogenesis, with a focus on molecular mechanisms, stress response pathways, and potential therapeutic interventions.

Methods: We conducted a comprehensive literature review of studies examining proteostasis mechanisms in PEX. Emphasis was placed on cellular pathways regulating protein synthesis, folding, and degradation, including the unfolded protein response (UPR), ubiquitin–proteasome system (UPS), and autophagy, as well as environmental and aging-related triggers of proteotoxic stress.

Results: Evidence indicates that chronic proteotoxic stress, arising from aging, oxidative damage, and environmental influences, disrupts the proteostasis network (PN). Dysregulation of ER stress signaling, cytosolic stress responses, and protein degradation pathways contributes to the accumulation of misfolded proteins and extracellular matrix deposits in ocular tissues. These molecular alterations underlie disease onset and progression in PEX syndrome (PEXS) and PEX glaucoma (PEXG).

Conclusions: Proteostasis dysfunction plays a pivotal role in PEX pathogenesis by promoting protein misfolding, aggregation, and extracellular deposition. Targeting the proteostasis network, through modulation of stress responses and enhancement of degradation pathways, represents a promising therapeutic strategy for PEXS and PEXG.

Proteopathies refer to diseases caused by abnormal protein folding and aggregation. Non-native conformational changes in proteins, caused by destabilizing mutations, oxidative stress, or environmental factors, lead to the formation of intra- and extracellular deposits associated with cellular dysfunction [1]. The proteostasis network comprising molecular chaperones, the unfolded protein response (UPR), the ubiquitin-proteasome system (UPS), and autophagy, plays a crucial role in maintaining protein quality control by preventing misfolding and degrading toxic aggregates [2-4]. Disruption of this network is central to many aggregation-related disorders, including Alzheimer disease (AD), Parkinson disease (PD), and Huntington's disease (HD) [3,5,6].

Pseudoexfoliation (PEX; OMIM: 177650) is an age-related systemic disorder that shares proteotoxic characteristics with other protein aggregation diseases. Clinically, PEX is characterized by flaky, whitish fibrillary pseudoexfoliative material (PEXM) that accumulates in both ocular and extraocular tissues [7]. Intraocularly, PEXM deposits on the anterior lens capsule (central and mid-peripheral zones), iris, ciliary body, corneal endothelium, zonules, and trabecular meshwork with particulate material detectable near Schlemm's canal [8]. Extraocular deposits and related elastotic changes have been reported in conjunctiva, skin, and certain visceral tissues, supporting the concept of PEX as a systemic elastotic/proteopathy [9-11]. The early stage of PEXM deposition is termed pseudoexfoliation syndrome (PEXS). As PEXM builds up, it obstructs aqueous humor outflow, elevating intraocular pressure (IOP) and leading to pseudoexfoliation glaucoma (PEXG), a severe form of secondary glaucoma that accounts for 20%–60% of open-angle glaucoma cases worldwide [8,12]. Figure 1 illustrates PEXM accumulation in the anterior segment, contributing to increased IOP and progressive optic nerve damage.

In addition to its ocular manifestations, PEX is also associated with systemic conditions, including cardiovascular disorders, hypertension, and cerebrovascular diseases,

Correspondence to: Debasmita Pankaj Alone, Molecular Genetics and Epigenetics Laboratory, School of Biological Sciences, National Institute of Science Education and Research (NISER), P.O. Jatni, Khurda 752050, Odisha, India, ORCID: 0000-0003-4809-925X; Phone: (91) 6742494204; FAX: +916742494004; email: debasmita@niser.ac.in

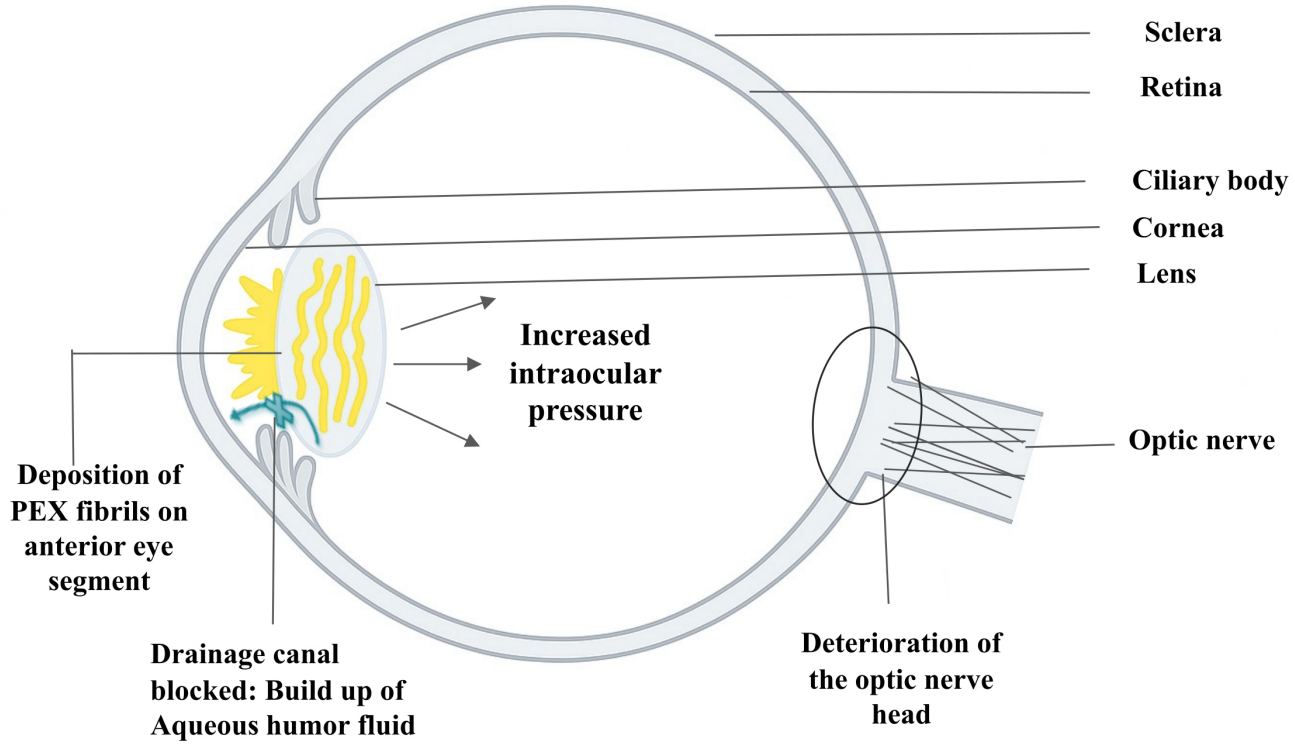

Figure 1. Schematic representation of pseudoexfoliation pathology in the human eye. Yellow fibrillar deposits on the anterior lens capsule and pupillary margin represent PEX material, which can obstruct aqueous humor outflow, leading to increased intraocular pressure and subsequent glaucomatous optic nerve damage. The diagram illustrates key ocular structures involved in the disease process. Outline of the eye adapted from OpenClipart.

suggesting that proteotoxic stress may have systemic implications [13-18]. Globally, PEX affects 60–70 million people, with prevalence peaking in older populations. It is particularly common in certain ethnic populations, reaching 20%–25% in Iceland and 0.69%–22.1% across Indian cohorts [19-22].

Like PEX, several neurodegenerative disorders involve the accumulation of misfolded protein aggregates, which progressively deposit in aging tissues. Amyloids in Alzheimer, drusen in age-related macular degeneration (ARMD), and Lewy bodies in Parkinson resemble PEX deposits in their composition and age-related progression [23-26]. PEX-affected eye tissues show abnormal expression of lysyl oxidase like-1 (LOXL1), clusterin, complement factors, amyloid peptides, and components of the ubiquitin-related proteins, highlighting shared mechanisms of proteotoxic stress [9,27-30].

Molecular pathophysiology of PEX: Proteomic and ultrastructural studies suggest PEXM is a complex aggregate of extracellular matrix (ECM) and elastic-fiber proteins such as fibrillin-1, elastin, vitronectin, transforming growth factor β1 (TGF-β1) or its binding proteins, and laminin together with regulators of elastogenesis such as LOXL1 and fibulin family member [9,27,31]. Additional components include molecular chaperones (Clusterin), small heat shock proteins (α-Crystallins), intermediate filament proteins (vimentin), complement components, ubiquitin-related proteins, and proteoglycans within PEX deposits [9,10,32-35]. Thus, PEXM represents not just ECM overproduction but a hybrid aggregate of structural ECM proteins, misfolded peptides, and extracellular chaperones. LOXL1 has emerged as a key factor in PEXM formation. Risk variants and dysregulated expression impair elastin cross-linking and elastic fiber assembly, leading to aberrant microfibrillar networks [9,36,37]. Expression patterns vary with disease stages; upregulated in the lens capsule and ciliary body of PEXS, and then reduced in advanced PEXG, suggesting progressive destabilization of the ECM. However, other studies have found reduced LOXL1 expression even in the early PEXS stage in tissues such as the lamina cribrosa, peripapillary sclera, and lens capsule [37-40]. In parallel, oxidative and age-related stress can promote misfolding or abnormal modification of ECM proteins such as fibrillin-1, elastin, and fibulin-5 [9,41-43].

These findings support the view of PEX as a proteopathy, implicating both elastotic degeneration and proteostasis failure in disease pathogenesis. Such extracellular aggregation is closely linked to defects in the intracellular proteostasis machinery.

Given the accumulating evidence linking protein aggregation disorders with cellular stress responses, it is crucial to explore how proteostasis failure contributes to PEX pathology. This review examines the interplay of cytosolic and endoplasmic reticulum (ER) mediated UPR, UPS, and autophagy in PEX, exploring how their dysregulation drives disease progression. The following section explores the components of this network and their role in PEX pathogenesis.

Proteostasis and its role in PEX pathogenesis: Emerging evidence underscores proteostasis failure as a central factor in PEX pathogenesis. Stress responses, such as the UPR, are activated by ER stress, while protein degradation mechanisms, including the UPS and autophagy, are compromised. Impaired UPR signaling, reduced proteasome activity, defective autophagosome–lysosome fusion, and chronic oxidative stress have all been reported in PEX-affected tissues [29,35,44,45]. These failures compromise the clearance of misfolded or damaged proteins, allowing them to escape degradation and be secreted or shed into the extracellular space, where they co-assemble ECM components and chaperones to form persistent deposits. Although disruptions in UPR, UPS, and autophagy have been identified, the precise mechanisms underlying their interplay in PEX remain unclear.

Proteostasis, or protein homeostasis, is maintained through a dynamic network of mechanisms that regulate protein folding, quality control, and degradation to ensure cellular health. This proteostasis network (PN) involves molecular chaperones, signaling pathways such as the UPR, and degradation systems including the UPS and autophagy [46,47]. When proteotoxic insults occur, such as during oxidative stress or protein overload, the UPR is activated to handle misfolded ECM proteins such as fibrillin-1 and elastin, while UPS and autophagy provide secondary clearance mechanisms [9,29,47]. The UPR is further categorized based on the subcellular location of the stress: cytosolic UPR and endoplasmic reticulum UPR (ER-UPR). Figure 2 illustrates the key components of the proteostasis network.

These systems often act in tandem. The coordinated regulation of these pathways is essential for maintaining the integrity of the proteome. However, in PEX, these systems, along with other cytoprotective pathways, are markedly dysregulated [29,30,42,44,45,48]. Chronic ER stress in the anterior segment of PEX eyes has been linked to oxidative damage and inflammatory responses, further exacerbating proteostasis imbalance [49-51]. Reduced proteasome activity, downregulated proteasome maturation protein (POMP), and defective ubiquitin-conjugating enzymes compromise protein clearance [29,42]. Additionally, patient-derived fibroblasts exhibit impaired autophagosome–lysosome fusion, leading to defective protein degradation [44,45].

The UPS and molecular chaperones act in coordination to maintain intracellular protein homeostasis. Clusterin (CLU) is a multifunctional chaperone with critical roles in both intracellular and extracellular proteostasis. As an extracellular chaperone, CLU assists in protein folding, stabilizes misfolded proteins, regulates adhesion, and targets proteins for degradation. Elevated CLU levels in the aqueous humor, tears, and lens capsules of PEX patients, along with strong immunoreactivity in PEX fibrils, underscore its involvement [30,33,34,48,52]. Genetic studies have identified several CLU variants associated with PEX in diverse populations [30,53]. Beyond genetic variation, epigenetic modifications of CLU have also been implicated in disease causation and progression [54]. Dysregulated CLU expression and impaired chaperone activity may promote excessive fibril formation, contributing to PEX material accumulation. While CLU is protective under physiologic conditions, pathological overaccumulation may promote fibril formation or exert cytotoxic effects, depending on the CLU-to-substrate ratio [55]. These findings establish CLU as a central maladaptive factor in the extracellular proteostasis imbalance of PEX.

Disruptions of proteostasis, particularly the ER-UPRs' inability to resolve misfolded protein accumulation, are hallmarks not only of PEX but of several neurodegenerative and protein aggregation disorders. Studies in familial neurodegenerative diseases have linked mutations in PN components to proteostasis failure, underscoring the critical role of this network in disease pathogenesis [56]. Overall, proteostasis failure, including dysregulated UPR, defective UPS and autophagy, and maladaptive chaperone activity underpins the molecular pathogenesis of PEX. These disruptions parallel mechanisms in neurodegenerative diseases, reinforcing the concept of PEX as a systemic protein aggregation disorder [29,35,45,49,57].

Understanding the integrated roles and dysfunction of the PN in PEX is critical for identifying novel therapeutic targets aimed at restoring protein homeostasis and halting disease progression. In the following section, we explore the cytosolic UPR and its regulation of heat shock proteins (HSPs) in the context of PEX pathogenesis.

Cytosolic unfolded protein response (UPR): Cells activate adaptive mechanisms such as the heat shock response (HSR)

to maintain proteostasis under proteotoxic stress. The hallmark of HSR is the activation of heat shock factors (HSFs), particularly heat shock factor 1 (HSF1), which upregulates the expression of HSPs. HSPs act as molecular chaperones, stabilizing and refolding misfolded proteins, facilitating protein degradation, and alleviating proteotoxic stress [58]. Based on molecular weight, HSPs are classified into families such as HSP27, HSP40, HSP60, HSP70, and HSP90, as well as the small heat shock proteins (e.g., α-Crystallins).

The detailed mechanism of cytosolic UPR is schematically represented in Figure 3, which shows that under unstressed conditions, HSF1 exists in an inactive, monomeric state bound to HSP70 or HSP90. Upon exposure to proteotoxic stress, such as misfolded protein aggregation, HSF1 dissociates from this complex, undergoes trimerization, nuclear translocation, and post-translational modifications, and binds to heat shock response elements (HSREs) upstream of heat shock gene promoters. This process upregulates the transcription of genes involved in protein folding, degradation, and trafficking, thereby alleviating cellular stress and maintaining proteome stability [59,60]. Once the required levels of molecular chaperones are reached, HSF1 is negatively regulated through feedback binding to HSP70 or HSP90, thus ending the HSR [61,62]. Although this regulatory

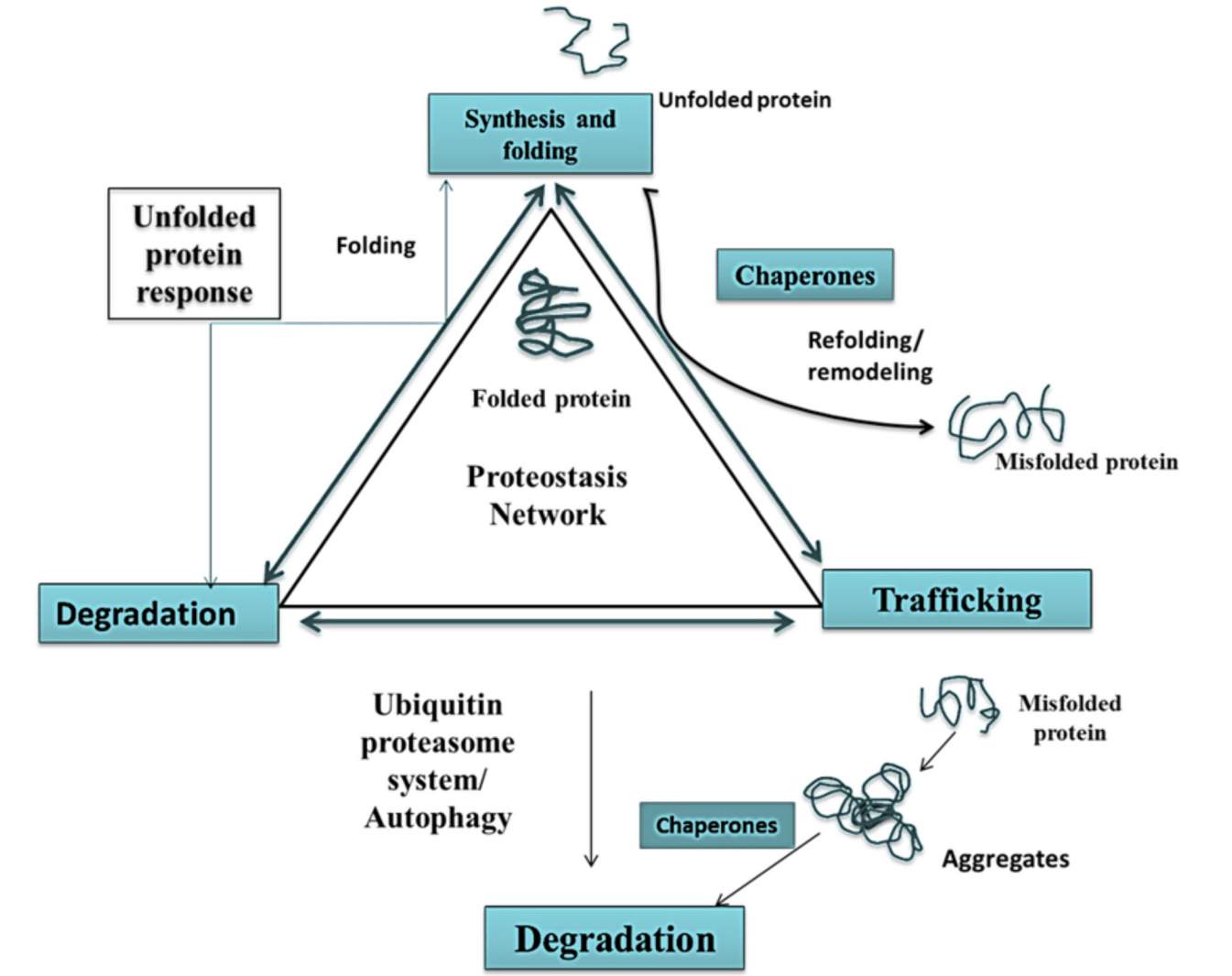

Figure 2. Schematic representation of proteostasis network components. Protein homeostasis is maintained by integrating major branches of the PN: (i) protein synthesis, the folding factors responsible for the folding of newly synthesized proteins; (ii) the unfolded protein response (UPR) pathways that resolve stress by inducing stress response elements, (iii) The chaperone pathways for remodeling of misfolded proteins and protein disaggregation, and (iv) The pathways of protein degradation by the ubiquitin proteasome system and autophagy [3,58,93,106,116].

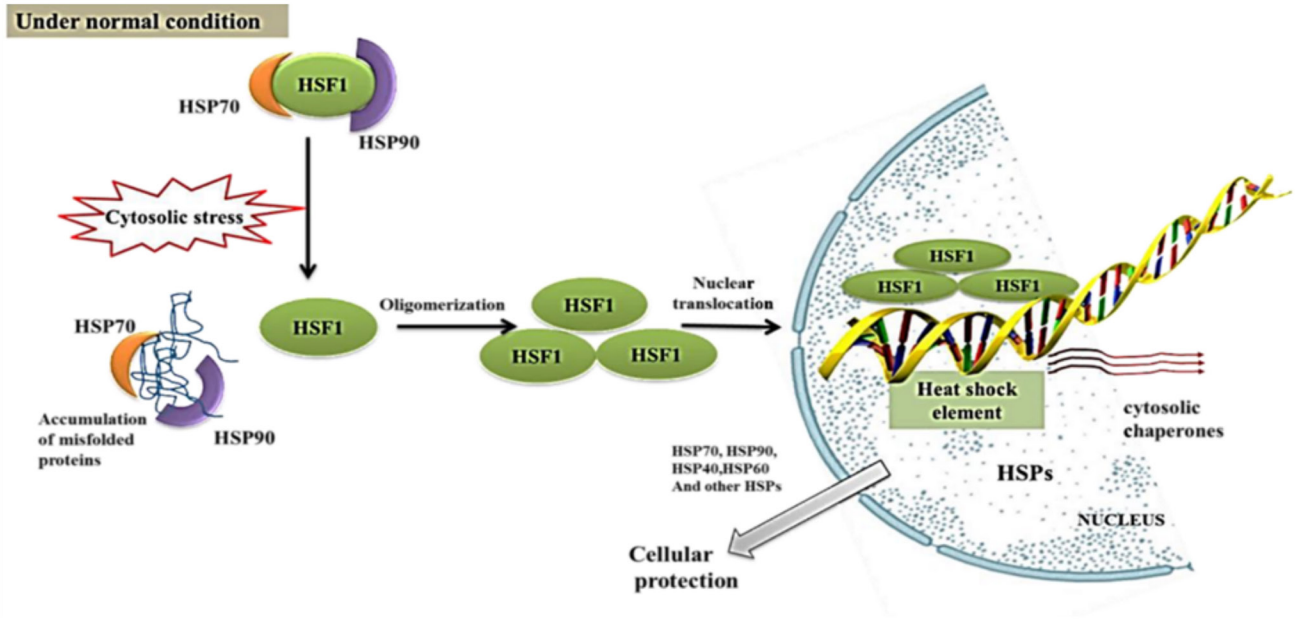

Figure 3. Diagrammatic representation of cellular stress responses. Under unstressed conditions, heat shock factor-1 (HSF-1) remains in a complex with heat shock protein 70 (HSP70) and heat shock protein 90 (HSP90). When the cell is challenged with stress, HSF-1 dissociates from the complex, undergoes post-translational modification and trimerization, and translocate to the nucleus. It binds to the heat shock element in the promoter and activates the expression of cytosolic chaperones, thus providing cellular protection [52-55].

feedback loop is well established, evidence suggests it may be dysregulated in PEX, contributing to persistent proteotoxic stress and disease progression.

HSPs are constitutively expressed and play a vital role in preventing protein aggregation, acting as key modulators of neurotoxicity in various neurodegenerative diseases, including AD, PD, and HD. Studies suggest that HSPs such as HSP90, HSP70, and HSP32 facilitate amyloid beta (Aβ) clearance by inducing cytokine production and enhancing Aβ degradation via the Toll-like receptor-4 (TLR4) pathway in AD [63]. Additionally, elevated autoreactivity of HSPs has been observed in the sera of ARMD patients compared to controls, suggesting their involvement in ARMD pathogenesis [64]. Transcriptomic and genetic studies highlight a strong association of HSFs and HSPs with PD [65]. Moreover, dysregulated HSF1 expression has been reported in conditions like HD and polyglutamine-induced neurodegeneration [66,67]. Notably, activating HSF1 in diseased mouse models has been shown to disrupt aggregate formation, underscoring its crucial role in preventing pathological protein accumulation [68]. Thus, cytosolic stress responses are essential for protein quality control, and their impairment has been implicated in various protein misfolding disorders, including PEX.

Cytosolic UPR dysregulation in pseudoexfoliation: Increasing evidence indicates that dysregulation of cytosolic proteostasis pathways plays a key role in PEX pathogenesis. Studies by Zenkel et al. and Hayat et al. reported the upregulation of key molecular chaperones, including HSP40 and HSP60, respectively, in various ocular tissues affected by PEXS, such as the iris, ciliary processes, and lens capsule [29,35]. Similarly, another study reported upregulation of HSP27 in the aqueous humor of PEXG patients [69]. In parallel, data sets from our group have reported deregulated expression of additional chaperones, DNAJB1 (Hsp40 subfamily B, member 1), and DNAJB11 (Hsp40 subfamily B, member 11), in the lens capsule of PEXS individuals, while HSP90 levels remain unchanged in the LC of PEXS subjects [29,70]. Importantly, HSF1, a master heat shock response regulator, has also been implicated in PEX pathogenesis. Padhy et al. reported a significant increase in HSF1 expression in the lens capsule and conjunctiva of PEXS patients, further supporting the role of proteotoxic stress in disease severity [71]. Additionally, mass spectrometry analysis identified the presence of small heat shock protein Crystallin alpha A (CRYAA) within pathogenic PEX deposits, reinforcing the involvement of chaperones in PEX pathology [32]. These findings highlight the essential role of molecular chaperones in mitigating

proteotoxic stress, reinforcing their involvement in PEX progression and their potential therapeutic significance.

Interestingly, HSP70 levels demonstrate tissue-specific regulation. In the lens capsule, HSP70 is significantly downregulated; in contrast, aqueous humor from PEXS patients shows increased HSP70 levels compared to controls [70,72]. Moreover, Hayat et al. identified that the HSP70 expression in the lens capsule is epigenetically silenced through hypermethylation [70]. Such methylation-driven downregulation may impair its cytoprotective role, leading to proteostasis failure and contributing to PEX pathogenesis. Conversely, the increased HSP70 levels in the aqueous humor may reflect a compensatory extracellular response to heightened proteotoxic stress in the anterior chamber. This upregulation could result from the active secretion of HSP70 by stressed ocular cells, serving as a defense mechanism to mitigate protein aggregation and maintain extracellular proteostasis. This divergence suggests a complex and compartmentalized regulation of HSP70 in PEX, reinforcing its potential role in disease progression and as a therapeutic target for restoring proteostasis.

Collectively, these findings point to a potential breakdown in the canonical HSF1-HSP70 feedback inhibition loop. Findings from our laboratory show upregulation of HSF1 alongside downregulation of HSP70 in the lens capsule of PEX patients, suggesting persistent or maladaptive activation of HSF1 in the absence of sufficient chaperone feedback. This uncoupling may drive sustained stress signaling, ineffective protein clearance, and progressive proteotoxic stress in PEX. Supporting this, previous studies have also reported elevated stress marker levels in PEX aqueous humor [72]. Further research into the molecular mechanisms governing the HSR may uncover new therapeutic strategies to mitigate proteotoxic stress and restore proteostasis in PEX. While the cytosolic UPR plays a frontline role in alleviating proteotoxic stress, persistent protein misfolding can overwhelm cellular defenses, leading to ER stress.

Endoplasmic reticulum stress and unfolded protein response (UPR) modulation: ER triggers the stress response signaling pathways collectively called ER-UPR to cope with the accumulation of unfolded or misfolded proteins. ER-UPR is regulated through a signaling cascade from three sensor proteins: inositol-requiring enzyme 1 (IRE1), activated transcription factor 6 (ATF6), and Protein kinase RNA-like ER kinase (PERK; Figure 4). All three sensors relieve ER stress and restore protein homeostasis either by attenuating protein translation, upregulating the expression of chaperones that facilitate protein folding, or by clearing the abnormally folded proteins by autophagy and the ER-associated degradation (ERAD) pathway. However, in case of an overwhelming burden, the UPR promotes cell death [73]. Activated IRE1, an endonuclease, splices out a specific region from X-box binding protein 1 (XBP1), which then codes for the XBP1 protein. XBP1 is a transcription factor that binds to ER stress response elements (ERSE) of UPR stress genes, including glucose-regulated proteins (GRP), and activates their expression required for combating ER stress [74]. On the other hand, activated PERK phosphorylates elongation factor 2α (eIF2α) and blocks overall translation in the cell [75]. Further, ATF6 also acts as a transcription factor and binds to the ERSE sequence of ER stress genes like CCAAT-enhancer-binding homologous protein (CHOP), protein disulfide isomerase (PDI), and GRP proteins [76]. PDI maintains the native structure of ER proteins while CHOP acts as a pro-apoptotic protein and plays a major role in ER stress-induced apoptosis.

ER-UPR dysfunction is a hallmark of neurodegenerative diseases, where chronic stress leads to neuronal loss. In PD, α-synuclein aggregates physically interact with ATF6, inhibiting its processing and impairing ERAD gene upregulation, thereby sensitizing neurons to apoptosis [77]. Similarly, dysregulation of IRE1 and PERK pathways in AD exacerbates tau phosphorylation and amyloid beta (Aβ) accumulation, further driving neurodegeneration [78]. Amyotrophic lateral sclerosis (ALS) and HD also exhibit persistent ER stress, characterized by abnormal activation of PERK-eIF2α and CHOP, leading to protein synthesis shutdown and neuronal apoptosis [56,79]. The role of ER stress in ocular diseases is well established. In glaucoma, failure of the UPR resulting in activation of the PERK/ATF4/CHOP pathway contributes to retinal ganglion cell (RGC) apoptosis, which is a major factor in normal-tension glaucoma [80,81]. Studies in a *Drosophila* MYOC-induced ocular hypertension model, as well as genetic associations of baculoviral inhibitor of apoptosis protein containing 6 (BIRC6) and protein disulfide isomerase A5 (PDIA5) with primary open-angle glaucoma (POAG), further support the role of UPR dysfunction in glaucoma pathogenesis [82,83]. Given that ER-UPR impairment is linked to both neurodegenerative disorders and glaucoma, similar mechanisms may likely contribute to the progression of pseudoexfoliation.

ER stress dysregulation in pseudoexfoliation: Emerging research has deepened our understanding of the relationship between ER stress and PEX. Chronic ER stress, characterized by the accumulation of misfolded proteins, activates the UPR pathways. While the UPR initially serves a protective role, prolonged activation can exacerbate protein aggregation and cellular dysfunction [80,84]. Studies have reported the upregulation of ER-related stress markers in many

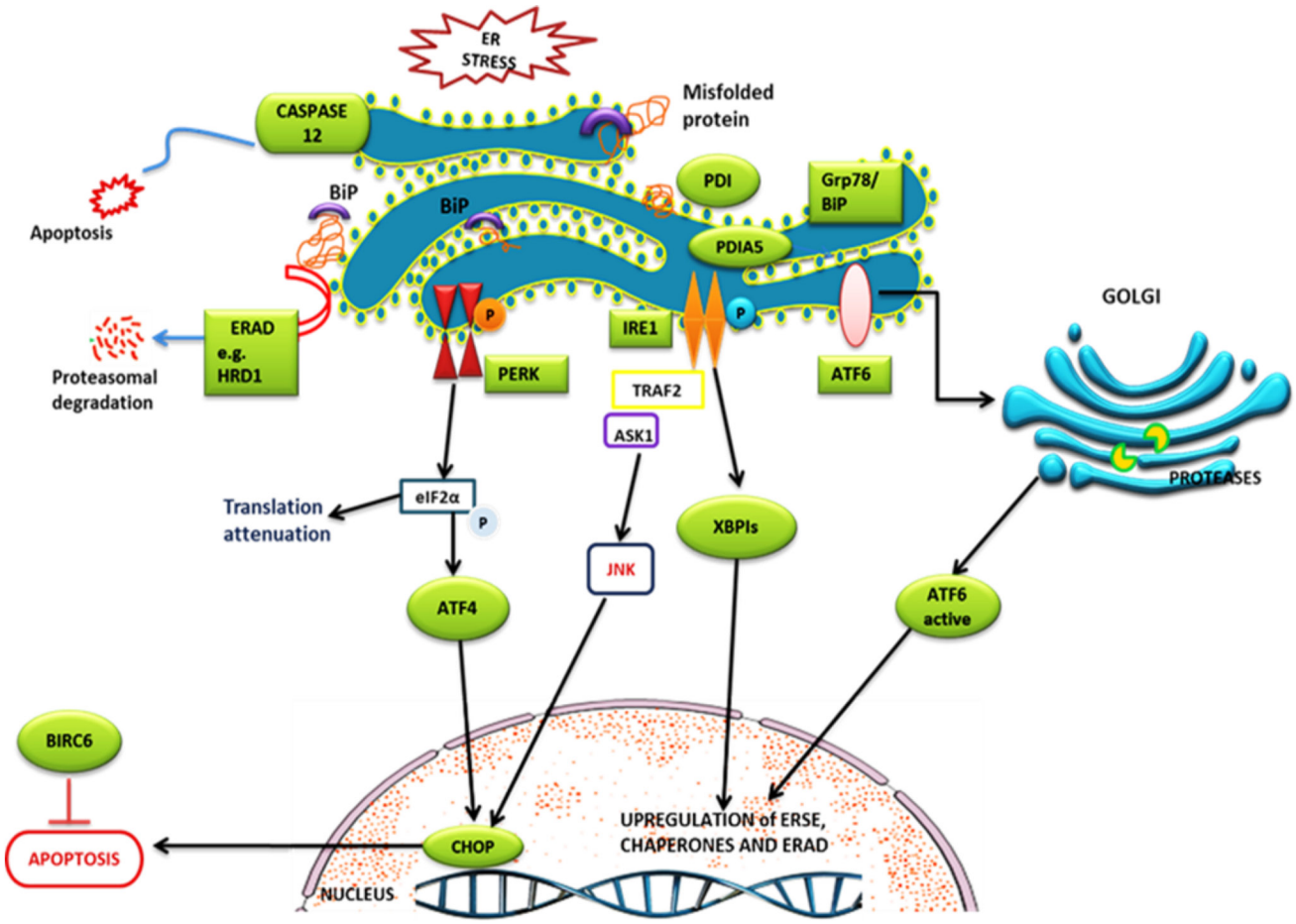

Figure 4. Schematic representation of the UPR signaling pathway. The unfolded protein response (UPR) is activated by the accumulation of misfolded proteins in the endoplasmic reticulum (ER) and is mediated by three key branches: inositol-requiring enzyme 1 (IRE1), activated transcription factor 6 (ATF6), and Protein kinase RNA-like ER kinase (PERK), all regulated by glucose-regulated proteins 78/Binding protein (GRP78/BiP). Upon ER stress, GRP78 dissociates from these sensors, leading to their activation. PERK phosphorylates elongation factor 2α (eIF2α), temporarily halting global protein synthesis to reduce ER burden. IRE1 splices X-box binding protein 1 (XBP1) mRNA, producing a transcription factor that enhances protein folding and processing, while ATF6 translocate to the Golgi for cleavage into its active form, upregulating ER stress genes like GRP78. Anti-apoptotic factors, baculoviral inhibitor of apoptosis protein containing 6 (BIRC6) and HRD1 (Synoviolin) facilitate the degradation of pro-apoptotic proteins, promoting cell survival. However, prolonged ER stress leads to activation of JNK via IRE1 and PERK, triggering caspase-dependent apoptosis, while CCAAT-enhancer-binding homologous protein (CHOP) and CASPASE12 further contribute to cell death [81-85]. The cell organelles template was adapted from Biorender.com, Toronto, Canada.

neurodegenerative conditions [85-87]. In the context of PEX, specific molecular alterations have been identified. For instance, downregulation of an apoptosis regulator, growth arrest and DNA damage-inducible gene 153 (GADD153) also known as DNA Damage-Inducible Transcript 3 (DDIT3) or C/EBP Homologous Protein (CHOP), has been reported in PEX eyes. This downregulation suggests a reduced cellular capacity to respond to ER-associated cell death, potentially contributing to the accumulation of protein aggregates in the extracellular space [35]. Genetic studies have further explored the association between ER stress-related genes and PEX. Single nucleotide polymorphisms (SNPs) in genes involved in reducing ER stress, such as BIRC6 and PDIA5, have been investigated in PEXG individuals, which demonstrated an association between the BIRC6 gene and PEXG [83].

The mechanisms leading to proteostasis impairment in PEX and the impact of ER stress on protein degradation pathways are being actively explored. Recent studies have examined the expression of UPR genes in lens capsules, conjunctiva, and peripheral blood samples from PEX individuals, revealing striking differences in local tissue and systemic responses. In tissue samples, particularly those from the lens capsules of PEXS patients, there is a significant upregulation of UPR-related genes [29]. This includes protein

folding and assembly genes, such as Heat Shock Protein Family A Member 5, (HSPA5), and Calnexin (CANX), XBP1, EIF2AK3, DDIT3, and HSPA5. Increased levels of ER chaperones suggest an active attempt to alleviate ER stress by promoting misfolded protein degradation via the ERAD pathway [88,89]. A study by Zhu et al. proposes that ER-UPR initially upregulates protective genes to restore homeostasis [90]. Additionally, genes associated with translation inhibition, like Eukaryotic Translation Initiation Factor 2 Alpha Kinase 3/PERK (EIF2AK3) were found to be upregulated, indicating translation inhibition as an adaptive response to ER stress. Genes involved in apoptosis execution, such as Caspase 12 (CASP12), and those involved in protein degradation and anti-apoptosis, like Synoviolin 1 (SYVN, also known as HRD1) were also upregulated.

Wang et al. have confirmed a direct correlation between activation of the PERK-dependent UPR signaling pathway upon ER stress conditions and glaucoma pathogenesis showing that ER stress triggers apoptotic cell death both in trabecular meshwork stem cells (TMSCs) and TM cells [91]. Marked upregulation of the GRP78, spliced X-box binding protein 1 (sXBP1), and CHOP in TM cells compared to TMSCs further highlights UPR involvement in disease progression [91]. This upregulation suggests an active response to ER stress within the ocular tissues, aiming to manage misfolded proteins through mechanisms like the ERAD pathway. Among all candidate genes, SYVN1 emerged as a key UPR component highly upregulated in PEXS and PEXG-affected lens capsules, reinforcing its role in ERAD-mediated protein homeostasis [29].

In contrast to the upregulation observed in ocular tissues, UPR genes were significantly downregulated in peripheral blood samples from PEX patients at all disease stages [92]. Genes involved in protein degradation and ER stress regulation, such as VCP-interacting membrane protein (VIMP), EIF2AK3 (PERK), protein disulfide isomerase A3 (PDIA3, also known as ERP57), and glucosidase II alpha subunit (GANAB), exhibited reduced expression levels. Additionally, the study notes that most ERAD response elements were significantly downregulated in PEXG compared to ocular hypertension (OHT), suggesting that protein-folding regulatory mechanisms become more compromised as the disease progresses. This suggests a systemic decline in UPR activation as the disease progresses, which may reflect impaired regulatory controls over protein folding in peripheral circulation [92].

These contrasting findings highlight the complexity of UPR activation in PEX. While ocular tissues demonstrate a robust UPR activation to counteract ER stress, systemic responses in peripheral blood suggest a declining ability to manage protein misfolding. This disparity underscores the need for further research to delineate how tissue-specific and systemic UPR mechanisms contribute to PEX pathogenesis. Additionally, identifying key regulatory points in these pathways may provide potential therapeutic targets for preventing or slowing PEX progression. Chronic ER stress not only disrupts protein folding but also interferes with cellular degradation mechanisms, including the UPS and autophagy. The following section explores how dysfunction in these pathways contributes to PEX pathology.

Defective protein degradation pathways: Maintaining proteostasis relies on two primary intracellular degradation systems: the ubiquitin-proteasome system (UPS) and autophagy. These pathways operate in a coordinated manner to eliminate misfolded, aggregated, or damaged proteins, particularly those arising from oxidative stress, mitochondrial dysfunction, impaired calcium homeostasis, or other upstream disruptions that trigger ER stress thereby preserving cellular homeostasis and preventing proteotoxic stress [93,94]. Disruptions in these systems can lead to pathological protein accumulation, a hallmark of PEX pathogenesis. This observation aligns with previous findings from our laboratory and others, which have reported elevated total protein levels in PEX individuals compared to controls [30,95,96]. These studies suggest that impaired protein degradation may contribute to the excessive accumulation of proteins in PEX-affected individuals. A schematic representation in Figure 5 illustrates the interplay between the UPS and autophagy in maintaining cellular homeostasis under ER stress.

The UPS in protein degradation: The UPS serves as the major pathway for the selective degradation of short-lived, misfolded, or damaged proteins in the cytoplasm and nucleus. It operates through a two-step process: ubiquitination and proteasomal degradation [97,98].

Ubiquitination involves a hierarchical enzymatic cascade where the E1 ubiquitin-activating enzyme initiates the process, followed by the E2 ubiquitin-conjugating enzyme transferring activated ubiquitin, and finally, the E3 ubiquitin ligase catalyzing the covalent attachment of ubiquitin to target proteins [99]. Proteasomal degradation occurs when polyubiquitinated proteins are recognized and degraded by the 26S proteasome, a large multi-subunit complex. The 20S core particle harbors proteolytic sites responsible for substrate degradation through chymotrypsin-like, trypsin-like, and caspase-like activities, while the 19S regulatory particle unfolds polyubiquitinated proteins and facilitates their translocation into the 20S core for degradation [100].

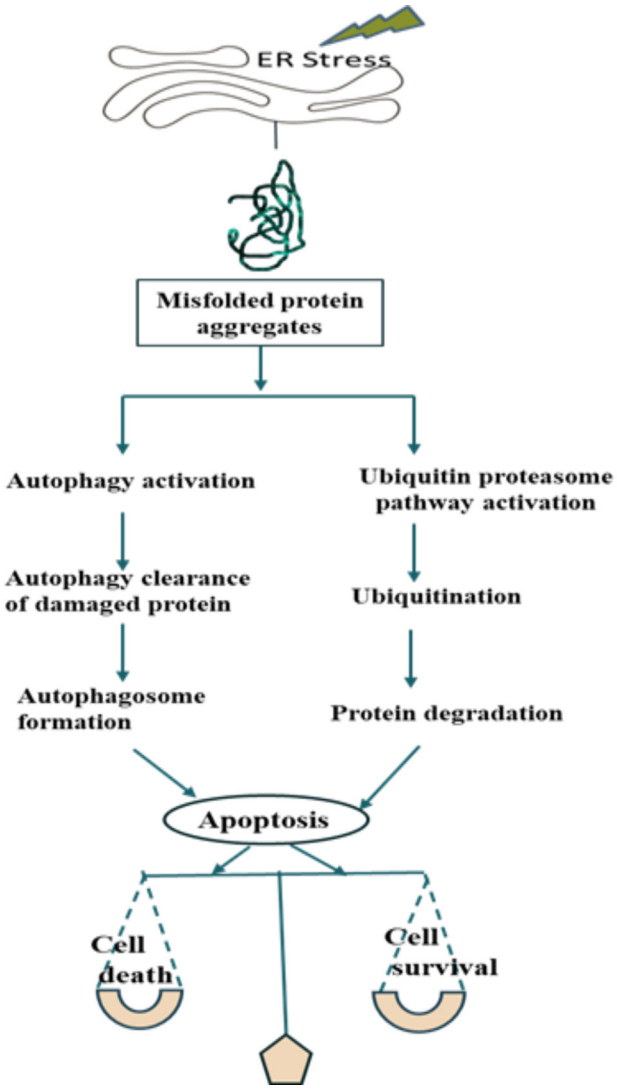

Figure 5. Interplay between ER stress, mitophagy, and proteostasis pathways. ER stress triggers the recruitment of mitophagy-related proteins, leading to the activation of degradation pathways. The ubiquitin proteasome system (UPS) primarily targets misfolded proteins for degradation via the proteasome, whereas autophagy facilitates the clearance of larger cellular components, including dysfunctional mitochondria, through lysosomal degradation. The balance between these two systems is crucial for cellular survival, as an imbalance may contribute to pathological conditions.

Extensive studies have shown that proteasomal activity declines with aging, reducing the ability to clear misfolded proteins and contributing to pathological protein aggregation [101-103]. In neurodegenerative diseases, this impairment plays a key role in disease progression. In AD, ubiquitinated tau aggregates block the 19S proteasomal recognition site, leading to inefficient degradation and a proteasomal traffic jam [104,105]. Similarly, β-amyloid (Aβ) aggregates directly inhibit 26S proteasome function, preventing the clearance of toxic proteins [106,107]. In PD, α-synuclein aggregates bind and impair proteasome function, exacerbating neuronal toxicity [108,109]. Additionally, in HD, expanded polyglutamine (polyQ) stretches in mutant huntingtin inhibit proteasomal activity, resulting in intracellular protein accumulation [110,111]. Beyond neurodegeneration, UPS impairment is evident in ocular diseases, including glaucoma and PEXS.

Dysfunction of the UPS in PEX: Recent genetic and molecular studies have linked UPS dysfunction to PEX pathogenesis. While there are no direct reports linking ubiquitin B (UBB) overexpression to PEX, evidence suggests increased ubiquitin protein conjugates and enhanced ubiquitin conjugation activity in response to oxidative stress in lens epithelial cells [112]. However, contradictory findings suggest proteasome impairment in PEX tissues. Zenkel et al. reported a reduction in ubiquitin-conjugating enzymes UBE2A/B in the iris and ciliary processes of PEX eyes [35]. Aung et al. found downregulation of proteasome maturation protein (POMP) and transmembrane protein 136 (TMEM136) in iris and ciliary body tissue of PEXS eyes when compared to age-matched controls [113]. However, it was also reported that POMP was upregulated in lens capsular epithelial cells from PEXS patients [114]. Our study revealed reduced expression

of proteasome subunits 26S proteasome non-ATPase regulatory subunit 1 (PSMD1) in PEXS and proteasome subunit alpha type-5 (PSMA5) in both PEXS and PEXG individuals. Chymotrypsin-like proteasome activity was significantly decreased in the lens capsules of PEXS patients compared to non-PEX controls, indicating reduced capacity for ubiquitin-mediated protein degradation. Elevated mRNA expression of UBB and accumulation of ubiquitinated proteins further confirm UPS dysfunction in PEX pathogenesis [29].

Autophagy: The secondary degradation pathway: Autophagy serves as a complementary protein degradation system to the UPS, primarily responsible for clearing long-lived proteins, organelles, and aggregated proteins. It is a multi-step process involving phagophore initiation, autophagosome formation, and autolysosome formation, where the autophagosome fuses with lysosomes for degradation [115,116]. Dysfunctional autophagy has been implicated in various age-related neurodegenerative diseases, where defective clearance of misfolded proteins contributes to pathogenesis [117]. In AD, defects in autophagosome-lysosome fusion lead to the accumulation of autophagic vesicles containing β-amyloid and tau aggregates, further exacerbating neurotoxicity [118]. Mutations in PINK1 and Parkin disrupt mitophagy, leading to the accumulation of dysfunctional mitochondria and increased oxidative stress in PD [119,120]. HD is also associated with defective autophagy, where mutant huntingtin impairs autophagosome formation, resulting in the accumulation of toxic aggregates [121]. Autophagy dysfunction is also implicated in ocular diseases, including glaucoma, cataracts, ARMD, diabetic retinopathy, and PEX [122-125]. Defects in lysosomal function result in the accumulation of non-degradable materials, increasing oxidative stress and protein misfolding [126].

Autophagy impairment in PEX pathogenesis: Recent evidence suggests that autophagy dysfunction contributes to PEX by promoting the accumulation of abnormal ECM protein deposits. Fibroblasts from PEX patients exhibit impaired autophagosome-lysosome fusion, leading to excessive intracellular protein aggregation [44,45]. PEX-derived Tenon's fibroblasts show larger vacuoles filled with debris and impaired autophagosome clearance [45]. Bernstein et al. confirmed autophagy dysfunction in PEXG fibroblast cells, documenting defects in lysosomal and autophagosome positioning [125].

Beyond general autophagic impairment, mitochondria-specific autophagy (mitophagy) has also been implicated in PEX pathogenesis. PINK1 (PTEN-induced kinase 1) and Parkin, key mediators of mitophagy, help construct ubiquitin chains on the outer mitochondrial membrane, initiating the mitophagy cascade [127,128]. A recent study by Dilara A. et al. demonstrated a significant increase in PINK1 mRNA and protein expression in the anterior capsule lens epithelial cells (LECs) of PEXS patients, suggesting mitochondrial dysfunction compared to controls [129]. These findings are consistent with previous research indicating a decline in mitochondrial membrane potential and a rise in depolarized mitochondria in PEX [45]. Additionally, elevated Parkin protein levels, as detected through immunohistochemistry, further support the activation of mitophagy in PEXS indicating a coordinated PINK1-Parkin response to mitochondrial stress [129].

Although Dilara et al. also reported a reduction in p62 (also known as SQSTM1) gene expression in PEXS anterior capsule LECs, though the change was not statistically significant, as assessed by quantitative RT–PCR [129]. p62 is a multifunctional protein that not only serves as a marker of the autophagosome degradation phase but also plays roles in oxidative stress and NF- κB signaling pathways [130,131]. Thus, reduced p62 expression might indicate active autophagic degradation but only if autophagosome formation is concurrently elevated. Complementing this, they also observed increased LC3B protein levels in PEXS lens capsule tissue via immunohistochemistry (IHC), indicating increased autophagosome formation [129]. LC3, particularly its lipidated form LC3-II, is a critical marker of autophagosome membranes and is often used to assess autophagy at the protein level [132]. These findings underscore the relevance of mitophagy-related genes and proteins such as PINK1, Parkin, and LC3B in PEX pathogenesis.

It is important to note that many autophagy-related genes, including p62, often do not exhibit significant changes at the mRNA level, making protein-based analyses such as western blotting or IHC more reliable for evaluating autophagy dynamics. The observed discrepancy between p62 gene expression and LC3B protein level in PEX may thus reflect different stages of the autophagy process or tissue-specific regulatory mechanisms. Together, these findings highlight the need for integrated mRNA and protein-level assessments to accurately interpret autophagy status in PEX pathogenesis.

At the genetic level, recent research has explored the potential role of autophagy-related gene polymorphisms in PEX pathogenesis. A study investigating ATG16L1, ATG2B, and ATG5 polymorphisms in a Spanish population examined their role in PEXS and PEXG [133]. ATG16L1, a key regulator of autophagosome formation, interacts with ATG5 and ATG12 in the autophagic complex [134]. The T300A variant of ATG16L1, previously associated with Crohn's disease, was investigated for its potential role in PEX [135]. ATG2B, recruited later in autophagosome formation, and ATG5, essential for autophagosome expansion, were also analyzed.

However, no significant differences were found in allelic or genotypic frequency distributions of these genes between PEX patients and controls. While these polymorphisms do not appear to be major contributors to PEX susceptibility, the role of autophagy dysregulation in PEX pathogenesis remains evident [133]. Additional studies are necessary to explore other autophagy-related genes and their involvement in PEX progression.

The UPS and autophagy are interconnected degradation pathways, and their impairment is a key feature of PEX pathogenesis. While UPS dysfunction leads to reduced proteasomal degradation and increased ubiquitinated protein accumulation, autophagy impairment contributes to defective lysosomal clearance of ECM deposits. This dual impairment results in proteostasis failure, exacerbating oxidative stress, ECM accumulation, and disease progression in PEX and PEXG. To consolidate current evidence, Table 1 summarizes epidemiologic and molecular studies that have examined proteostasis-related markers in PEXS and PEXG, highlighting consistent findings of dysregulated clusterin, impaired UPS/UPR function, and incomplete autophagy across tissues and cohorts. Together, these abnormalities create a proteostasis imbalance, promoting progressive protein accumulation and cellular stress, as seen in neurodegenerative diseases and PEX and point to potential therapeutic strategies aimed at restoring proteostasis. Understanding these pathways could offer potential therapeutic targets for mitigating disease progression in PEX and related neurodegenerative disorders.

Potential therapeutic targets for PEX: Current therapies for pseudoexfoliation syndrome (PEX) primarily focus on lowering intraocular pressure (IOP) through medications such as beta-blockers, selective alpha2-agonists, prostaglandin analogs, and sympathomimetics. When medical management is insufficient, surgical interventions like laser trabeculoplasty (LTP), trabeculectomy, or glaucoma drainage device (GDD) implantation are considered [136-139].

However, currently no pharmacological strategies are available to prevent PEX, and its etiology remains poorly understood despite extensive research. Although numerous molecules, genes, and disrupted stress response pathways have been identified, no single causal factor has been pinpointed. This highlights the need for novel therapies targeting cellular stress pathways, particularly ER stress and proteostasis mechanisms. Targeting UPR pathways like PERK (EIF2AK3), IRE1, and ATF6 can help restore protein-folding homeostasis and reduce ER stress [140]. Elevated PERK expression in the lens capsule of PEX patients indicates heightened ER stress, making PERK inhibition a potential therapeutic approach. Given the differential PERK expression—increased in the lens capsule but decreased in blood cells, localized ocular delivery may be preferable to minimize systemic effects. Preclinical ocular-specific studies are needed to confirm its efficacy and safety. PERK activation leads to apoptosis and DNA damage in TM cells [141]. The PERK inhibitor LDN-0060609 has shown potential in enhancing cell viability, reducing DNA damage, and restoring cell morphology under ER stress conditions [142]. Lowering lysosomal pH, a strategy explored in ARMD treatment, may also benefit PEX [143]. Sigma-1 Receptor (S1R) Agonists; (+)-Pentazocine alleviates endoplasmic reticulum (ER) stress, oxidative stress (OS), and apoptosis in lens epithelial cells, suggesting its potential for slowing cataract progression [144]. Given that similar mechanisms of ER stress and oxidative damage are involved in TM cells and other ocular tissues affected by PEX, S1R agonists could help reduce stress-induced damage and slow disease progression in PEX. Additionally, they could be used in combination with agents targeting ER stress, proteostasis, or IOP to enhance therapeutic outcomes. Reducing PEXM protein accumulation can help limit aggregate formation [145,146]. Emerging experimental approaches include magnetic phage display, microRNA therapies, gene therapy, stem cell therapy, and nanotechnology-based interventions [147-150]. These strategies aim to restore protein synthesis, folding, and degradation balance, thereby preventing cellular damage and supporting ocular health in PEX and PEX-associated glaucoma.

Conclusion and future perspectives: This review highlights the pivotal role of proteostasis components, specifically the UPR, UPS, and autophagy in the pathogenesis of PEXS and its progression to PEXG, an aggressive form of glaucoma. As illustrated in Figure 6, cellular stress triggers such as oxidative and ER stress activate proteostasis mechanisms, including chaperones, UPR, UPS, and autophagy. These interconnected pathways form the proteostasis network, which maintains cellular homeostasis under normal conditions. However, dysregulation of proteostasis mechanisms marked by HSR/UPR failure, defective UPS and autophagy pathways, and PEXM accumulation underpins the molecular basis of PEX pathogenesis. This results in excessive extracellular matrix deposition, increased intraocular pressure, optic neuropathy, and disease progression. Understanding the disruption of these interconnected pathways provides valuable insights into the molecular mechanisms underlying PEXM deposition and disease progression.

Targeting the complex interplay between UPR, UPS, and autophagy presents promising opportunities for therapeutic intervention. Future studies should prioritize functional analyses to validate the causal role of proteostasis impairment

Table 1. Summary of epidemiologic and molecular studies on proteostasis-related markers in pseudoexfoliation syndrome (PEXS) and pseudoexfoliation glaucoma (PEXG).

Proteostatic markers	Study specimen	Sample size*	Role in PEX pathogenesis	References
Clusterin (CLU)	Cornea, Trabecular Meshwork, iris, lens, ciliary processes, aqueous humor (AH)	20 PEXS 20 PEXG 28 Controls	Clusterin deficiency in anterior segment tissues of PEX eyes; strong binding to PEX deposits and relative increase in AH of PEXG. Deficiency may impair proteostasis and promote PEXM deposition.	Zenkel et al., 2006
	Aqueous Humor (AH)	16 PEXS 18 PEXG 21 Controls	Study emphasizes genetic association; higher deposition in LC of PEXG eyes, augmenting extracellular protein accumulation.	Padhy et al., 2014
	Lens capsule (LC)	11 PEXS 09 PEXG 12 Controls		
	Blood	19 PEXS 18 PEXG 20 Controls	3′-UTR polymorphisms and promoter hypomethylation jointly dysregulate clusterin, impairing proteostasis in PEXS/PEXG.	Kapuganti et al., 2023b
	Lens capsule	6 PEXS 3 PEXG 6 Controls		
Heat shock proteins (HSP27, HSP40 and HSP60)	Ciliary processes and Iris tissue	6 PEXS 6 PEXG 6 Controls	Alterations in cellular cytoprotective mechanisms in anterior segment tissues of PEX eyes.	Zenkel et al., 2007
Ubiquitin conjugating enzymes (UBE2A/2B)				
Heat shock factor 1 (HSF1)	Lens capsule	11 PEXS 10 PEXG 21 Controls	An upregulated HSF1 mRNA levels indicate proteotoxic stress in anterior eye tissues of PEXS-affected patients.	Padhy et al., 2017
	Conjunctiva	09 PEXS 09 PEXG 21 Controls		

Proteostatic markers	Study specimen	Sample size*	Role in PEX pathogenesis	References
Synoviolin (SYVN1)	Lens capsule	22 PEXS, 19 PEXG, 31 Controls	PEX is marked by upregulation of ER stress markers, but failure of proteasome degradation leads to impaired proteostasis and apoptotic cell death.	Hayat et al., 2019
Calnexin (CANX)		20 PEXS, 17 PEXG, 28 Controls		
Proteasome subunits (PSMD1 and PSMA5)		08 PEXS, 07 PEXG, 10 Controls		
Ubiquitin B (UBB)		11 PEXS, 04 PEXG, 17 Controls		
HSP40 (DNAJ family members)		08 PEXS		
HSP60 (HSPD1)		06 PEXG		
Caspase 12 (CASP12)		14 Controls		
Eukaryotic translation initiation factor 2-alpha kinase 3 (EIF2AK3)				
Heat shock protein family A member 1A (HSPA1A/ HSP70)	Lens capsule	19 PEXS	Decreased expression of HSP70 correlates with hypermethylation of CpG islands in PEXS individuals.	Hayat et al., 2020
		16 PEXG		
		19 Controls		
	Aqueous humor	31 PEXS	HSP70 levels in the aqueous humor of patients with PEXS was found to be higher than those in the controls.	Güler M et al., 2020
		30 Controls		
VCP-interacting membrane protein (VIMP)	Peripheral blood	17 PEXS	Downregulation of UPR genes across all stages of PEX is a key pathogenic driver, linking impaired proteostasis with progression to glaucoma.	Rao et al., 2020
EIF2AK3 (PERK)	mononuclear cells	11 PEXG		
Protein disulfide isomerase A3 (PDIA3)	(PBMCs)	11 Controls		

Proteostatic markers	Study specimen	Sample size*	Role in PEX pathogenesis	References
Glucosidase II alpha subunit (GANAB)				
PTEN-induced kinase 1 (PINK1)	Anterior capsule	19 PEXS	Findings support the concept that impaired but activated mitophagy is a key pathogenic mechanism in PEX progression.	Dilara et al., 2025
Parkin	lens epithelial cells	20 Controls		
SQSTM1 (p62)				
Microtubule-associated protein				
1A/1B-light chain 3 B (LC3B)				

*Sample sizes vary depending on assay. Values reflect pooled data across experimental approaches within each study (qRT-PCR, IHC, protein assays, etc.).

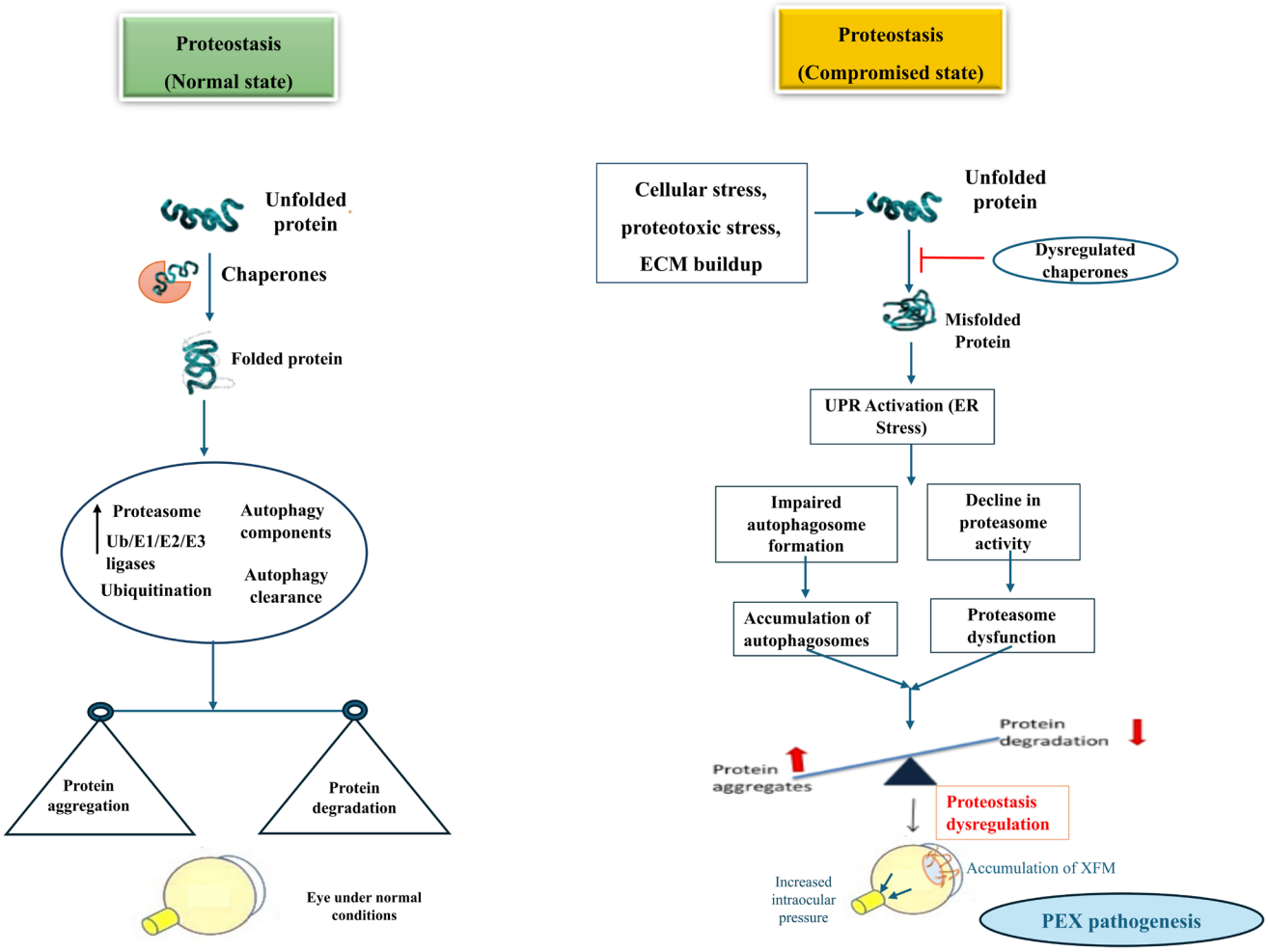

Figure 6. Mechanisms of proteostasis dysregulation and pathogenesis in pseudoexfoliation. Normal State: In a healthy cellular environment, the ubiquitin proteasome system (UPS) and autophagy function in a coordinated manner to degrade misfolded or damaged proteins, preventing their accumulation. The equilibrium between protein synthesis and degradation maintains proteostasis, ensuring proper cellular function. Compromised State in PEX Pathogenesis: Under pathological conditions, such as PEX, impairments in protein degradation pathways result in proteostasis dysregulation. Dysfunctional UPS and autophagy lead to the accumulation of extracellular matrix (ECM) proteins and intracellular protein aggregates. This proteotoxic stress contributes to increased oxidative damage, mitochondrial dysfunction, and cellular stress, ultimately driving PEX pathogenesis. Red arrows highlight the points of dysregulation in the degradation pathways, leading to proteostasis imbalance. The tilted scale depicts the imbalance, symbolizing the shift toward protein aggregation and ECM accumulation, hallmarks of PEX pathology.

and identify specific molecular targets. Additionally, research into the genes regulating proteasome maintenance and their involvement in PEX could pave the way for precision medicine approaches to mitigate disease severity and progression.

By elucidating the mechanisms of proteostasis dysregulation, this review sets the stage for the development of novel therapeutic strategies aimed at restoring cellular homeostasis and preventing the vision-threatening consequences of PEX at later stages. Collaborative efforts combining molecular research, genetic studies, and therapeutic innovations are essential to advance the understanding and management of PEXS and PEXG.

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