Review Article
Pathogenesis of stromal corneal dystrophies

Zenan Lin[1*], Lili Lang[1*], Qi Zhang[2*], Qian Li[1], Yi Shi[1], Jie Chen[1], Cheng Peng[1], Hongping Cui[1]

[1]Department of Ophthalmology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai 200120, China; [2]School of Clinical Medicine, Nanjing Medical University, Nanjing 211166, China. *Equal contributors.

Abstract: Corneal dystrophies (CDs), with lesions mainly appearing in the stroma, are defined to be stromal CDs. In recent years, growing knowledge about stromal CDs is uncovered thanks to the great advances in the technical fields, such as high-definition optical coherence tomography (HD-OCT) and whole genome sequencing. However, most of the new findings are presented separately and not systematized. Here we summarize and analyze the proposed hypotheses of the potential etiology of each type of stromal CDs, aiming to present more comprehensive and precise etiological pathways.

Keywords: Stromal corneal dystrophies, pathogenesis, pathology, histology, gene mutation

Introduction

Corneal dystrophies (CDs) are a group of commonly-occurring primary and progressive corneal diseases. Depending on the anatomical sites of the lesions, CDs can be classified into 4 subtypes: (1) Epithelial and subepithelial CDs (e.g. Anterior basement membrane dystrophy and Meesman's epithelial dystrophy), (2) Epithelial-stromal TGFBI CDs (e.g. Granular corneal dystrophy, Lattice corneal dystrophy), (3) Stromal CDs (e.g. Macular dystrophy, Schnyder corneal dystrophy, Fleck dystrophy, and Congenital hereditary stromal dystrophy), and (4) Endothelial CDs (e.g. Fuch's dystrophy, Congenital hereditary endothelial dystrophy, and Posterior polymorphous dystrophy). However, the knowledge about CDs is really rare for a long period. Despite their enigma, our knowledge about CDs has been expanded greatly in recent years due to the advances of gene sequencing technique and ophthalmological examination (e.g. confocal microscopy and high-definition optical coherence tomography). A growing number of mutations in UBIAD1 (UbiAprenyltransferase domain-containing protein 1), SLRP (small leucine-rich proteoglycan), PIP5K3 (Type III Phosphoinositide 5-kinase), CHST6 (carbohydrate 6-sulfotransferase) and other genes that may result in CDs have been reported. There are some hypotheses about the etiology of CDs depending on their experimental findings. However, these hypotheses are seemingly separated from each other and the detailed mechanism of CDs remains poorly understood. In clinic, we diagnosed some stromal CDs and manage to analyze and systemize the research advances on stromal CDs and elucidate their causes in a more succinct, comprehensive and systemic manner, which may benefit our understanding of stromal CDs [1].

Central cloudy dystrophy of François (CCDF)

CCDF, first reported in 1955 [2], is characterized by polygonal cloudy gray stromal opacities separated by relatively clear lines tocreate aleather-like crocodile in the central cornea. The posterior stroma part of CCDF has larger and more numerouslesions than the anterior part, withoutaffecting the corneal endothelium or epithelium [3]. CCDF very likely has an autosomal dominant pattern [4]. Similar corneal opacities located at either the peripheral or central cornea in the deep stromal layer are known as "posterior crocodile shagreen" and reported to be an age-related corneal degeneration [5].

CCDF has been rarely studied because its corneal opacities usually do not impair the visual acuity. Thus, the patients may remain unaware of CCDF for a long time [6]. Though the cause of

CCDF is poorly understood, there is a case whose right cornea has a mosaic appearance similar to CCDF patients. This 73-year-old woman, with infection-induced blindness in the right eye since age 15, had flat right anterior chamber and low IOP. After investigation, it was proposed that the tension relaxation of Bowman's layer may lead to the insertion of many prominent anterior stromal collagen lamellae into Bowman's layer, which results in a mosaic appearance of cornea [7, 8] However, the clinical characteristics of the case may restrict the applicability of this hypothesis.

Schnyder's central crystalline dystrophy (SCCD)

SCCD (OMIM 121800) has an autosomal dominant inherited pattern and was first described by Schnyder and Van Went. SCCD is characterized by bilateral clouding of the central cornea, arcuslipoides and/or visible crystalline depositions of cholesterol in the stroma. Phospholipid, unesterified cholesterol and cholesterol ester aggregate in the corneal stroma. Gene analysis of SCCD shows that the mutations may localize at 1p34.1-p36 interval and several candidate genes were proposed [9]. Some systemic findings such as hypercholesterolemia and hyperlipidemia are associated with SCCD.

Despite years of research on SCCD, its exact genetic mechanism still needs to be elucidated. The mutated gene responsible for SCCD is localized in the 1p34.1-p36 interval and several candidate genes were proposed, such as fatty-acid-binding protein 3 (FABP3), cytidine 5'-triphosphate synthetase (CTPS), sterol carrier protein 2 (SCP2), collagen type VIII alpha-2 polypeptide (COL8A2), UDP galactose-4-epimerase (GALE) and UBIAD1 [9]. Among them, the most commonly reported one is UBIAD1. To date, mutations of UBIAD1 have been identified in more than 28 unrelated families with SCCD [10-13]. UBIAD1 mutations are mainly found in exons 1 and 2, and form a discrete transcript encoding protein with a predicted prenyltransferase domain and up to eight transmembrane spanning regions. It was proposed that UBIAD1 could compensate for the para-hydroxybenzo-ate-polyprenyltransferase/coenzyme Q2 reductase (COQ2) in a ubiquinone pathway, which has secondary effect on cholesterol metabolism. Thus, UBIAD1 mutations may lead to abnormal accumulation of cholesterol and

phospholipids in the cornea through the cholesterol metabolism pathway [14, 15]. UBIAD1 may also be involved in apoE prenylation that is indispensable for trafficking and function of newly-synthesized apoE protein, which participates in mediating the solubilization and removal of cholesterols from cells. Due to the relationship to apoE protein, UBIAD1 mutations also can result in cholesterol deposition in the corneas of SCCD patients [16].

Congenital stromal corneal dystrophy (CSCD)

CSCD (OMIM 610048), which is uncommonly seen, has clinical manifestations including the bilateral diffused corneal cloudiness of flake-like whitish opacities within the stroma. The aberrant deposition occurs shortly after birth and progress with age. Some patients also have strabismus or nystagmus. The outcomes of the penetrating keratoplasty in early childhood are mostly good [17]. CSCD is reportedly the only human disease associated with the mutated gene of decorin, a small leucine-rich proteoglycan (SLRP) [18].

Decorin, which belongs to class I SLRP, has 12 leucine-rich repeats (LRRs) in the central domain [19-22]. Three frame-shift gene mutations (c.947delG; c.967delT; c.941delC) are associated with CSCD, and all of them locate in the C-terminus of decorin [23-26]. These gene mutations can lead to identical truncations of decorin lacking a 33 amino acid segment that includes the "ear" repeat, which is a specific feature for SLRPs participating in the protein folding of decorin and ligand recognition [22]. Mutant decorins were retained in the endoplasmic reticulum (ER) and could not be transferred to the Golgi apparatus, which is an indispensable step for thesecreations ofdecorin to the stromal matrix [18]. The accumulation of mutant decorins in ER leads to ER stress, which in normal conditions is an important pathway for degradation of unfolded proteins with ubiquitin-proteasome. However, if the ER stress is too strong, the keratocytes may reprogram and lose their functions of secreting appropriate extracellular components including SLRPs, thus damaging the stromal structure. Nevertheless, stromal structure is disturbed due to the lack of the C-terminal truncated decorins within the stromal matrix, because decorinsare able to bind to collagen fibrils as well as other extracellular components such as fibronectin,

thrombospondin and tenascin which contributes to the architectural stability of the corneal lamellae [27].

Posterior amorphous corneal dystrophy (PACD)

Posterior amorphous corneal dystrophy (OMIM 612868) is an uncommon corneal dystrophy, which has an autosomal dominant hereditary pattern. It is characterized by the opacification of the posterior corneal stromal lamella partially or completely, flattening of the corneal curvature, and decreased corneal thickness. Some patients may also have iridocorneal adhesions, iris atrophy, iris coloboma, and corectopia [28, 29]. Its pathogenesis remains still unclear. According to Anthony J. Aldave et al. and Michelle J. Kim et al., the gene mutations of PACD are reported to locate within a 3.5 Mb interval region on chromosome 12q21.33, which includes 26 genes. Among them 4 SLRPs encoding genes, lumican (LUM), decorin (DCN), keratocan (KERA), and epiphycan (EPYC) are thought to be candidate genes [30, 31]. Similar to the CHSD, the gene mutations may disturb the function of SLRPs, which play an important role in the collagen fibrillogenesis and matrix assembly, resulting in the appearance of corneal opacification.

Francois-neetens fleck corneal dystrophy (FCD)

Francois-Neetens FCD (OMIM 121850) is a rare disease first described in 1956 [32]. The slit-lamp reveals that flat, bilateral and gray-white oval or round opacities are distributed throughout the corneal stroma [33]. FCD occursat early age but progresses slowly without great impair on the visual acuity [34]. FCD is caused by PIP5K3 mutations with an autosomal dominant inherent pattern [35, 36].

PIP5K3 is a large 41-exon gene (189 kb) that encodes a predicted 2098-aa protein. The PIP5K3 protein is a kinase, PIKfyve, which can phosphorylate phosphatidylinositol (PtdIns) 3P to PtdIns (3, 5) P2. Because PtdIns 3P and PtdIns (3, 5) P2 appear at the external membrane of endosomes at different stages, they very likely play a role in the metabolism of endosome formation [37]. PIP5K3 regulates the transport of endosome-to-trans-Golgi network (TGN) retrograde and interacts with p40, an RAB9 effector implicated in retrograde traffic from the late endosome [38, 39]. This mechanism could be mediated through a putative role of PtdIns (3, 5) P2 in membrane fission as suggested in wild-type yeast, where PtdIns (3, 5) P2 levels increase upon hyperosmotic shock and lead to vacuolar fragmentation [40, 41]. The gene mutations of PIP5K3 may cause the PIKfyve truncation before the formation of protein structure, resulting in inactivation. Both maintenance of mammalian cell morphology and endocytic membrane homeostasis require enzymatically active phosphoinositide 5-kinase PIKfyve. The inactiveness of PIKfyve disturbs the homeostasis of the endosomes of keratocytes, which are pivotal in the substance secretion into the extracellular matrix, resulting in the clinical manifestations [36].

Macular corneal dystrophy (MCD)

MCD (OMIM 217800) is very rare and has an autosomal recessive inheritance pattern [42]. MCD occurs in early years of life with superficial gray-white lesions located in the central cornea. The opacities spread to the periphery to affect the entire corneal stroma. Corneal thinning is also a characteristic manifestation of MCD [43]. MCD patients may suffer severe visual impairment [44]. MCD is reportedly caused bygene mutations at CHST6, which encodes corneal N-acetyl glucosamine 6-O-sulfotransferase (C-GlcNAc6ST), an enzyme that transfers sulfate to the unsulfatedkeratan chains on lumican [45]. MCD is classified into subtypes I and II, depending on the absence or presence of keratan sulfate (KS) in the serum. A third subtype, type IA with KS present in the keratocytes but absent in the cornea and the serum, wasfound in MCD patients from Saudi Arabia [44].

Several missense mutations, insertions and nonsense mutations in CHST6 were detected in MCD I patients, while deletions and/or rearrangements in the upstream region as well as missense mutations in CHST6 were found in MCD II patients [46]. CHST6 gene mutations affect keratocytes, which secrete most of abnormal depositions of unsulfatedkeratan sulfate proteoglycans (KSPGs) [47]. The unsulfated KSPGs are less water-soluble than the fully-sulfated KSPGs due to the smaller polarity of the keratan sulfate glycosaminoglycan (GAG) chain in the absence of sulfate esters. The

unsulfated KSPGs may also eliminate their degradation by keratocytes [48]. The KS detected in the serum of MCD II patients very likely results from the KSPG degradation in cartilage, but the detailed mechanism is still poorly understood.

Pre-descemet's corneal dystrophy (PDCD)

PDCD, or Deep filiform dystrophy, was first described and called as cornea farinata in 1923. Depending on the colors under direct and indirect slit-lamp illumination, PDCD can be classified into 4 subtypes: Deep filiform dystrophy, Deep punctiform dystrophy, Polychromatic dystrophy, and corneal farinata [49]. However, little research is done in PDCD so far due to low prevalence. Fine morphological opacities appear in the posterior stroma, andthe lesions are composed of lipids [50]. PDCD is age-related, but the pathology remains poorly understood [51]. The clinical manifestations are usually asymptomatic without impair in the visual acuity. PDCD usually occurs in the fourth to seventh decade.

Histopathologic examination of one PDCD patient demonstrates that the pathologic findings are limited to the keratocytes of the posterior stroma [52]. The keratocytes are cytoplasmic vacuoles containing lipid-like materials, which consist of fibrillogranular and electrondense lamellar inclusions under electron microscopy. No extracellular deposition of similar material was noted. These findings suggest that the accumulated materials are most likely lipofuscin, a degenerative pigment that accumulates in aged cells [51].

Conclusion

Stromal corneal dystrophies (CDs) are characterized by the aberrant depositions mainly in the stroma. Most of them are caused by the gene mutations in UBIAD1, SLRP, PIP5K3, and CHST6. The mutant genes (CHST6) can directly cause structural damage to the aggregated substances leading to theirlower ability of degradation and dissolution in water in MCD patients. UBIAD1 encodes proteins participating in the cholesterol metabolism through interaction with COQ2 and apoE. Thus, the mutant UBIAD1 could cause cholesterol deposition in the cornea, a characteristic of SCCD. The decorin encoded by mutant SLRP will be retained in the Endoplasmic Reticulum (ER), leading to decorin deficiency and then structural abnormality in the extracellular matrix. Moreover, the aggregation of aberrant decorin in ER may also cause keratocyte dysfunction and cornea homeostasis disturbance, resulting the clinical manifestations of CSCD and PACD. In FCD patients, mutant PIP5K3 may affect the endosome formation in keratocytes, resulting in the dysfunctions of intracellular-to-extracellular substance transport and eventually damage both the keratocytes and extracellular matrix.

We try to systemize the new findings in recent years and present more understandable pathophysiological pathways of stromal CDs. However, more investigations are needed to elucidate the etiology perfectly and find out new treatment methods.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hongping Cui, Department of Ophthalmology, Shanghai East Hospital, Tongji University School of Medicine, 150 Jimo Road, Pudong New District, Shanghai 200120, China. Tel: 86-13671900868; E-mail: hpcui@vip.163.com

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