UBIAD1, pathogenesis of schnyder's crystalline corneal dystrophy.

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Abstract

Schnyder's Crystalline Corneal Dystrophy (SCCD), also known as Schnyder's Corneal Dystrophy (SCD), is a rare autosomal dominant genetic disorder. The occurrence of SCCD is equal in both genders. SCCD is characterized by progressive corneal opacity, owing to aberrant accumulation of cholesterol and phospholipids in the cornea. A serial of SCCD affected families have been reported in the world, since it was first described in 1924. In 2007, the molecular basis of SCCD was illustrated by three different teams, respectively, and linked to UbiA prenyltransferase domain-containing 1 (UBIAD1). UBIAD1 was first named transitional epithelial response gene 1 (TERE1), which was isolated from the bladder mucosa and proved to be a tumor suppressor. More studies had demonstrated that UBIAD1 was a key enzyme which involved in vitamin K2 and CoQ10 biosynthesis at distinct organelles. Intracellular geranylgeranyldiphosphate (GGpp) molecules triggered the binding of UBIAD1 to 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMGCR) at Endoplasmic Reticulum (ER) membranes. The mutated UBIAD1 that caused SCCD was not able to bind GGpp, which resulted in the consistent binding of UBIAD1 to HMGCR at ER membranes. The long-term binding of HMGCR at ER membranes led to excess cholesterol biosynthesis and accumulation, finally, SCCD disease in cornea. Though the molecular basis and pathogenesis of SCCD had been clarified by efforts of couples of ophthalmologists and scientists around the world, more studies need to be done to better understand the working mechanism of UBAID1. Our review could guide effective diagnosis and treatment of SCCD for clinicians

Keywords: Corneal dystrophy, Visual loss, Phototherapeutic keratectomy, HMGCR degradation.

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Introduction

Schnyder's Crystalline Corneal Dystrophy (SCCD; MIM 121800) is a rare autosomal dominant genetic disorder that is characterized by progressive bilateral corneal opacity, owing to abnormal accumulation of cholesterol and phospholipids in the cornea, leading to visual loss and eventually blindness [1]. The occurrence of SCCD is equal in both genders. This inherited eye disease was first described by French ophthalmologists Van Went and Wibaut in 1924. And then, the Swiss ophthalmologist Schnyder clarified the clinical manifestations and genetic characteristics of this special corneal disease. Based on Schnyder's elucidation, this eye disease was named Schnyder's Crystalline Corneal Dystrophy (SCCD).

In the following years, a number of SCCD cases were reported around the world. The ophthalmologists also detected the phospholipids, free cholesterols and cholesterol esters in the blood sample, and found values of these biochemical indicators elevated compared with unaffected. They concluded that the etiology of SCCD was abnormal accumulation of cholesterol and phospholipids. Only half of SCCD cases presented crystalline deposits in their cornea, the famous American ophthalmologist Weiss et al suggested renaming the disease Schnyder Corneal Dystrophy (SCD).

To better understand the visual morbidity and surgical intervention of SCCD, Weiss et al. examined a batch of SCCD cases and the patients were divided into three categories on the basis of age for statistical analysis [2]:

- <26 years
- 26-39 years and
- ≥ 40 years

The clinical characteristics include:

- Early stage (<26 years), crystalline deposits in the center stromal epithelium.
- Middle stage (26-39 years), crystalline deposits continue to accumulate and appear to join together, forming a haze.
- Late stage (≥ 40 years), the degree of crystallization is increasing accompanied by aging, which leads to whole corneal opacity and blindness.

Up to now, the youngest SCCD patient found was a 17 month old and the occurrence age ranged from 2-81 years, with a mean age of 38.8 ± 20.4 years. The SCCD cases lose their vision gradually along with age, but they can obtain the vision through surgery. In clinic, the optimal therapeutic regimens to restore the vision were penetrating keratoplasty and phototherapeutic keratectomy operation.

Literature Review

The seeking of pathogenesis of SCCD lasts for decades after this eye disease was first been described in 1924. SCCD was a rare autosomal dominant genetic disorder which was uncovered and recognized as broad consensus. The molecular basis of SCCD obtained urgent attention around the world. More SCCD cases were reported and innovative methods were introduced to explore the DNA basis. In another study, Riebeling et al. reported a 66 year old woman and her son affected with SCCD. The woman also accompanied type IV hyper lipoproteinemia and hypercholesterolemia and her son had hypercholesterolemia with elevated LDL cholesterol levels. Microsatellite marker analysis demonstrated that D1S228 within the candidate interval of 1p34.1-p36 led to the observed SCCD. After then, Shearman et al. narrowed the SCCD locus to the 16 cm interval between D1S2663 and D1S228 microsatellite markers localized on 1p34.1-p36 through haplotype analysis in two large Swede-Finn families in central Massachusetts.

Similarly, Theendakara et al. collected 13 families from Finland, Germany, Turkey and the USA to refine candidate intervals correlated with SCCD and they narrowed the putative region to 1.58 Mbp through identity-by-state analysis. To further identify the genetic basis of SCCD, a batch of candidate genes (*CORT, CLSTN1, CTNNBIP1, DFFA, ENO1, GPR157, H6PD, KIF1B, LOC440559, LZIC, MGC4399, PEX14, PGD, PIK3CD and SSB1*) which localized at D1S2663 and D1S228 interval were analyzed through mutation screening in two SCCD affected pedigrees. Unfortunately, none of these candidate genes were linked to SCCD, but their work reduced the remaining positional candidate genes by half and led to the direct identification of the genetic basis of SCCD.

Until 2007, Orr et al., Weiss et al. and Yellore et al. firstly, indicated that UbiA prenyltransferase domain containing 1 (UBIAD1), was the causal gene responsible for SCCD, independently [3-5]. In their studies, Weiss et al. and Yellore et al. also confirmed that the loci of UBIAD1 associated with SCCD were located on chromosome short arm 1, region 36 [4,5]. After decades, the pathogenesis of SCCD was finally elucidated and linked to the UBIAD1 gene. SCCD affected cases were analyzed and more UBIAD1 point mutations were explored, and among all these mutations, N102S was the most proved and been known as hotspot in UBIAD1 associated SCCD. To date, we have investigated 28 point mutations of UBIAD1 that cause SCCD through a literature research. Similarly, the occurrence of SCCD is higher in European and North American countries compared with other countries and regions associated with this gene defect, including Asia and Africa. Prevalence of SCCD is also reported in the Chinese Han and Japanese populations. After years of efforts by generations of scientists and ophthalmologists, the genetic basis of SCCD was elucidated and proved linked to UBIAD1, which participates in cholesterol synthesis and storage intracellular. Their work, therefore, provided molecular targets and references for SCCD treatment and drug development for this rare heredity eye disease.

UBIAD1, also known as transitional epithelial response gene 1 (TERE1), was obtained from the human bladder mucosal extracted RNA through reverse transcription. UBIAD1 expresses two transcripts (1.5 and 3.5 kb), which are widely present in various human tissues but absent or down-regulated in bladder muscle-invasive cell carcinoma. Though the length of these two transcripts was different, they both encoded UBIAD1 protein. The causal reason of these two transcripts may be due to alternative splicing in mRNA maturation. These two transcripts were deposited in NCBI with accession numbers AF117064 and NM_013319. McGarvey et al. indicated a 61% reduced expression of the UBIAD1 transcriptome in prostate cancer cells. When UBIAD1 was transferred and expressed in prostate cancer cell lines LNCAP and PC-3, the cell proliferation rate was reduced by 80%, indicating that UBIAD1 was a potential tumor suppressor in urinary system.

The UBIAD1 gene encodes a prenyltransferase containing 338 amino acids, with a molecular weight of 36.83 kDa. Nakagawa et al. indicated that UBIAD1 could catalyze the synthesis of menaquinone-4 (MK-4) from the conversion of deuterium-labeled vitamin K derivatives in human cells [6]. Their results for the first time proved that UBIAD1 was an MK-4 biosynthesis enzyme in human, which largely broaden the knowledge. An orthologous protein of UBIAD1 in *Drosophila melanogaster*, was *Heix* (*Heixuedian*), composed of 359 amino acids with a molecular weight of 39.22 kDa. Heix converts menadione to vitamin K2 in *Drosophila* [7]. A black dot phenotype lymphoma was detected in the 3rd to 4th instar larvae in *Drosophila* when Heix mutated.

UBIAD1 localizes at the mitochondria and converts vitamin K1 to K2 (MK-4), which is a significant cofactor in eukaryotic blood coagulation and an electronic carrier. When Heix is mutated, mitochondria dysfunction arises. Vitamin K2 is necessary and sufficient for electron transport in *Drosophila* mitochondria, supplementation with vitamin K2 rescues mitochondrial dysfunction.

To further broaden UBIAD1 function, Mugoni et al. used zebrafish to investigate intracellular roles of the UBIAD1 ortholog gene, *Barolo* (*Bar*) [8]. The zebrafish cardiovascular system fails in development, after Bar is mutated. The causal reason resulted from oxidative stress and ROS-mediated cell damage. Mugoni et al. found that UBIAD1 is a non-mitochondrial localized prenyltransferase and it catalyzed CoQ10 synthesis on the Golgi membrane. Reduced expression of UBIAD1 in vascular cells could decrease antioxidant CoQ10 cytoplasmic content, resulting in Reactive Oxygen Species (ROS)-mediated lipid peroxidation. Further study also demonstrated that UBIAD1 regulates ROS levels and the redox status in vertebrate cardiovascular system. Therefore, increasing oxidative stress causes heart and vascular cell apoptosis, as well as cardiovascular system failure when UBIAD1 is deficient.

When UBAID1 mutates, cholesterols and lipids accumulate abnormally in the cornea, causing SCCD disease, indicating that UBIAD1 is involved in lipid metabolism in cells.

Schumacher et al. demonstrated that sterols stimulate UBIAD1 binding to HMG CoA reductase, which is a cholesterol biosynthetic enzyme and subject to sterol-accelerated, Endoplasmic Reticulum Associated Degradation (ERAD) augmented by the non-sterol isoprenoid geranylgeraniol [9]. Geranylgeraniol then inhibits UBIAD1 binding of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMGCR) that promotes reductase degradation and transport of UBIAD1 from the ER to Golgi. HMGCR is an important rate-limiting enzyme in the cholesterol and non-sterol isoprenoid biosynthetic pathway, which is regulated by cholesterol feedback. The mutation in UBIAD1 results in a conformation change of this protein, thereby inhibiting the binding of GGpp to UBIAD1 mutants, which prevents HMGCR degradation and dissociation of UBIAD1, thus contributing to consistent synthesis and accumulation of cholesterol *in vivo*.

Conclusion

These results indicated that SCCD associated mutants impede its ER-to-Golgi transport and stabilize its interaction with HMGCR. The disturbed transport then increases cholesterol biosynthesis, causing excess accumulation of cholesterol in the cornea and, eventually, SCCD. The present review clarified the pathogenesis and functions of the SCCD associated gene UBIAD1, therefore guiding effective diagnosis and treatment of the inherent eye disease.

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