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Review Article

The role of LncRNAs in the development of cataracts

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ABSTRACT

The prevalence of eye diseases worldwide is dramatically increasing and represent a major concern in underdeveloped and developed regions, especially sight threatening diseases. Ocular diseases, previously associated with a higher depression risk, also impose a substantial economic burden on affected families and society, thus the importance of early detection and accurate treatment in order to avoid and prevent blindness should be emphasized. Cataract, a clouding (opacification) in the normally transparent of lens which leads to a decrease in vision, is most commonly due to aging but may also be present at birth and occur due to trauma or radiation exposure. With the increasing population of elderly people and cataract patients in China, the social burden of cataract is a big challenge at present and will continue to be a challenge in the future. Genetics have been shown to play an important role in the occurrence of eye diseases, with the detection of a numbers of specific gene mutations. LncRNAs have emerged as a novel class of regulatory molecules involved in numerous biological processes and complicated diseases, however the proper connections and pathways they may use to influence the susceptibility to developing cataracts have not yet been completely elucidated. In this review, we focus on the lncRNAs characteristics and its regulation, and summarize these results from separate, independent, cataract-related studies in addition to discussing possible pathways by which lncRNAs might contribute to the development of cataract.

1. Introduction

A cataract is a clouding (opacification) in the normally transparent of lens which leads to a decrease in vision. In healthy unclouded lens, light is able to pass through to the retina, allowing us to see detail. Around 40 year old of age, the proteins in the lens start to break down and clump together, which leads to the development of a cloudy area on the lens.[1] It often develops slowly and can be uni or bilateral, the symptoms include blurry or double vision, faded colors,halos around light, photophobia, and nyctalopia.[2] Poor vision caused by cataracts may also result in an increased depression risk and adverse events including falls and fractures.[3,4] Cataracts are most commonly due to aging but may also be present at birth and occur due to trauma or radiation exposure.Biological aging is the most common cause of cataracts but other https://en.wikipedia.org/wiki/Cataract - cite_note-WHOPri-4 risk factors include diabetes, smoking tobacco, prolonged exposure to ultraviolet radiation, skin diseases, injury, infection, smoking, and genetic factors.[5]

Cataracts are the leading cause of reversible blindness and 33% of visual impairment worldwideremains a severe public health challenge worldwide, especially in China.[6] With the increasing population of elderly people and cataract patients in China, the social burden of cataract is a big challenge at present and will continue to be a challenge in the future.[7] Therefore, it is critical to explore the potential risk factors for ARC from an epidemiological perspective to determine the mechanism

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for the formation of cataracts and a potential method for cataract prevention.Surgery is needed only if the cataracts are causing problems and generally results in an improved quality of life.[8] Cataract surgery is not readily available in many countries, which is especially true for women, those living in rural areas, and those who do not know how to read.[9] It is the cause of approximately 5% of blindness in the United States and nearly 60% of blindness in parts of Africa and South America.[9] Blindness from cataracts occurs in about 10 to 40 per 100,000 children in the developing world, and 1 to 4 per 100,000 children in the developed world.[10]

The transparency of lens tends to deteriorate with ultraviolet radiation, oxidative stress, age and many other toxic factors, eventually resulting in the development of cataract.[11,12] Increased proteolysis, alteration of cell cycle, DNA damage, changes in growth and differentiation of lens epithelial cells are the main morphological and functional changes occurring during the process of cataract development.[13] Accumulating evidence reveals that gene expression in the lens epithelium is significantly altered during cataract formation. For instance, metallothionein IIA, osteonectin and adhesion related kinase are up-regulated in cataractous lenses relative to transparent lenses,[14–16] whereas many ribosomal proteins and protein phosphatase 2A are down-regulated in cataractous lenses relative to transparent lenses.[17,18] Metallothionein IIA participates in metal binding and detoxification. Osteonectin is a calcium-binding protein, which serves as a key regulator of cell growth. Decreased protein synthesis, a pathological process involved in the development of cataract can be the result of reduced expression of ribosomal proteins.[11]

The non-coding region of the genome has recently been recognized to possess a crucial functional importance in normal development and physiology and this discovery has focused increasing attention on its potential to contribute towards diverse disease aetiology.[19] LncRNAs are define as transcripts with a size ranging from 200 to 100 000 nucleotides, structurally resembling mRNA and presenting little to no protein-coding potential and can be classified into several types according to their genonic locations. Although the vast majority of lncRNAs are situated in the nucleus,[20] however, a substantial minority (nearly 15%) are present in the cytoplasm.[21] LncRNAscan be classified as sense or antisense, the former comprising of those that overlap withprotein-coding genes, and the later comprised those that are antisense transcribed toprotein-coding genes. If the promoter and transcript are situated in proximity and also in a head-to head orientated fashion, the lncRNA is then said to be bidirectional.[22–24] Many studies reported important regulatory roles for LncRNAs in multiple biological processes, including cell lineage commitment, stem cell maintenance, and cellular phenotype differentiation.[25–27] Transcriptional regulation may be influenced by LncRNAs via several modes such as decoy, signal, guide and scaffold.[28] They might also as signals in response to multiple stimuli, participate in recruiting corresponding complexes in order to directly or indirectly silence or activate the expression of a gene.[29–31] In addition, some lncRNAs may affect gene expression through post-transcriptional events, lncRNAs also participate in the modification process post-translation.[32] Nonetheless, several lncRNAs have been implicated in various diseases such as neurodegenerative diseases,[33–36] multiple tumors and cancers,[37–45] and common ocular diseases such glaucoma,[46] and diabetic retinopathy,[47] among others, the proper connections and pathways they may use to influence the susceptibility to developing cataracts have not yet been completely elucidated.

In this article, we aim to demonstrate implication of lncRNAs in cataracts development by summarizing results from separate, independent studies.

2. II- LncRNAs in cataracts

2.1. βB1-crystallin (CRYBB1) and βB2-crystallin (CRYBB2)

Close to half of all cases of congenital cataracts are reportedly caused by genetic mutations,[48] a dozen genes have successfullybeen associated with the development of the condition[49] such as membrane transport protein genes, cytoskeletal protein gene, crystallin genes and transcription factor genes. Crystallins, composed of α, β and γ, represent ocular lens'structural proteins, and are necessary for normal lens transparency and refractive power preservation.[50] Initially thought to be only present in the lens, however their expression have been detected in various tissues.[51,52] α-crystallins act as small heat-shock proteins; whereas functions of βγ-crystallins is not completely elucidated. β- and γ-crystallins share a common core protein structure with two similar domains, each composed of characteristic key-motifs.[53–55] Characterized as oligomers, β-crystallin family actually comprises basic (β$B1$, β$B2$, β$B3$) andacidic (βA3/A1, βA2, βA4) proteins.[56] Basic β-crystallins possess both N-terminal and C-terminal extensions, whereas acidic β-crystallins have only N-terminal extensions.[57]

The discovery of multiple mutations mostly in Chinese families suggests important role played by CRYBB1 in congenital cataract. CRYβA3/A1-Crystallin Knockout was not only linked to the development of nuclear cataract but is also suspected to induce impairedlysosomal cargo Clearance and calpain activation. Homozygous CRYBB1 deletion mutation underlies autosomal recessive congenital cataract whereas missense mutation S228P and nonsense mutation (p.Q223X) have been previously associated with autosomal dominant congenital cataract.Additionally, the CRYBB1 mutation (c.347T>C), CRYBB2 mutation (c.355G>A) are novel in patients with congenital

cataract.[58–61]

βB2-crystallin (CRYBB2) is highly expressed in the postnatal lens cortex and linked to the development of cataracts, hinting at the alteration of gene expresssion in the lens epithelium during the development of cataract.Reports about the effect of CRYAA and CRYBA1/CRYBA3's downregulation and the upregulation of the receptor tyrosine kinase adhesion-related kinase (ARK) in a mouse model of age-related cataracts were made bySheets et al.[62] Furthermore, metallothionein-IIA, osteonectin and ARK were also proved to becomparatively upregulated in cataractous lenses.[14–16] Additionnaly, genes such as GCS1, and POLR2E were also found to be extensively downregulated n cataractous lens.[63] Crystallins, indexing CRYBB2 in particular, are suspected to be able to primarily act as lens' structural proteins.[64] The relative CRYBB2 protein expression was demonstrated to change markedly during the first year of life,[65] suggesting that CRYBB2 serves a contributive function in lens development. Moreover, targeted knockout (KO) of CRYBB2 in mice has been demonstrated to induce age-related[66] and congenital cataracts;[67] however, its functional significance is not yet known.

Yin and al. tried to analyze lncRNAs and mRNAs by performing expression profiling on CRYBB2 knockdown-induced cataracts and non-treated mice. Their results showed a total of 329 differentially expressed in lncRNAs CRYBB2 KO group mice lenses (A total of 149 lncRNAs identified to be upregulated, 180 lncRNAs were found downregulated).[68]

2.2. MIAT

MIAT, also known as Gomafu in human or Rncr2 in mouse, is a lncRNA initially identified in 2000 as a susceptibility locus for myocardial infarction patients,[69] located at 22q12.1, highly expressed in retinal precursor cells and highly conserved in placental mammals.[70,71] It also shows a deregulation in multiple diseases such as neuroendocrine prostate cancer, non-small-cell lung cancerdiseases, diabetic cardiomyopathy and neuropathy, chronic chagas disease, chronic lymphocytic leukemia , schizophrenia, ocular neovascularizations, bone disease and ischemic stroke.[71–74]

A recent study performed lncRNA microarray on cataractous and transparent lens and identified 38 differentially expressed lncRNAs, including 21 up-regulated and 17 down-regulated among which MIAT's expression level was significantly higher in cataractous lens. Further investigations on MIAT expression level on aqueous humor and whole blood collected from healthy controls, cataract, glaucoma and PVR patients in order to verify their early findings. The results showed that MIAT is significantly up-regulated in the plasma and aqueous humor of cataract patients, but not in other patients with glaucoma, PVR.[75,76] Oxidative stress is considered an important risk factor for the development of age-related cataract because lens cells are constantly exposed to reactive oxygen species including hydroxyl radical (·OH), free radicals superoxide (O2·−), H2O2 and hypochlorous acid (HClO).[13,16] Accumulated products of oxidative stress is present in cataract patients and may explain why they possess an higher MIAT expression level compared to the matched controls. The viability and proliferation ability of human lens epithelial cells could be reduced by oxidative stress, whereas they were showed to be further decreased when subjected to a MIAT's knockdown, implying that an increased MIAT level is possibly a response against oxidative stress. Opacification of posterior capsule is the main complication of cataract surgery. Following the insult of surgery, residual lens epithelial cells rapidly grow at the equator and under the anterior lens capsule. These cells proliferate and migrate onto the posterior capsule.[77,78] The response of lens epithelial cells can be considered a wound healing reaction resulting from the activation of inflammatory cells and production of cytokines and growth factors after surgery.[79] The above findings suggest that MIAT might potentially be used as a specific biomarker in early detection of cataract.

2.3. lncRNA H19

LncRNA H19, is a transcript from the H19/IGF2 gene, and located at 11p15.5 locus. Its expression in very high in fetus but tends to decrease progressively after birth, and these favorable characteristics enable its function as a genetic biomarker.[80] It actually regulates various biological processes by acting as a ceRNAthat released the miRNA's targets via the competition for miRNA to influence the related protein factors.[81] LncRNA H19 has been found to be implicated via different signaling pathways in many kinds of tumors, and its mutation in mouse zygotes lead to prenatal lethality, suggesting a important role in normal growth and development.[82–84] and prompting new research paradigm to further understand intrinsic mechanisms of lncRNAs.[85]

MicroRNAs (miRNAs) are the most frequently studied class of the non coding RNAs, and possess a length of ~22 nucleotides (nt). They participate in the mediation of post transcriptional gene silencing via controlling the translation of mRNA into proteins.[86,87] Specifically expressed in lens, previous researches have tried to decipher the regulating role of miRNAs in HLECs function[88,89] and found out that in some cases, miRNAs level decreased in cataractous lens cells from rats.[90] Cheng and al. recently used sequencing technology aiming to identify and compare expression of lncRNAs in age-related cataracts and further explore the oxidative damage repair mechanism. In their experiment, more than 50 lncRNAs were differently expressed, among which lncRNA H19 was up-regulated at early age-related cataract development and ultra violetirradiation-

induced oxidative damage model cells, whereas miRNA 29a expression decreased in the three types of early ARC and in HLECs exposed to UVB irradiation.[91] Reactive oxygen species accumulation oxidative stress by inducing damage to the DNA can lead to the age related cataract development.[13] human thymine DNA glycosylase plays an important role in aberrant BER pathway of oxidatively damaged DNA .These data indicate that lncRNA H19 could be a useful biomarker of early age-related cataract and deciphering the proper relation between lncRNA H19 and miR-29a may represent a target for age-related cataract treatment.

3. Conclusion

III characteristics and regulation, and tried to discuss potential pathways by which $\beta B1$-crystallin (CRYBB1), $\beta B2$-crystallin (CRYBB2), MIAT, LncRNA H19 may contribute to the development of cataracts. However, further researches and investigations are needed to discover vast number of cataract-associated lncRNAs, their characteristics and expression patterns, and decipher pathways of their involvement and role in the pathogenesis of this potentially blinding condition. We stress that this article creates a paradigm for future studies of lncRNAs in the early determination and monitoring of the evolution of cataract and may prove to be useful for early determination of whether a patient with a suspected lncRNAs should receive prioritized treatment to help slow the progression of the condition, and subsequently avoid blindness, and retain quality of life.

4. Contributorship Statement

Involved: in conception, design (CY), literature search and writing of the manuscript (CY); supervision (CY), critical reading (CY, DVK), approval of the final proofs of the article (CY, DVK).

5. Competing Interests

The authors have declared that no competing interest exists.

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8. Conflict of Interest

None.

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