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Review Article

Molecular-Genetic Markers of Cataract

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Abstract

Despite the high effectiveness of surgical treatment, access to it remains limited in many regions of the world, which makes the search for biomarkers for early diagnosis relevant. Furthermore, a deep understanding of the molecular basis of cataract is necessary for the development of preventive and pharmacological approaches capable of slowing disease progression.

Molecular-genetic studies of cataract have developed in two main directions: the study of Mendelian hereditary forms and the search for genetic variants predisposing to age-related cataract.

Key Words: crystallins; heterogeneous disease; molecular-genetic

Introduction

Age-related eye diseases – age-related macular degeneration, cataract and glaucoma – are the main causes of irreversible vision loss and blindness worldwide [3,5]. Among them, cataract occupies a leading position: according to the World Health Organization, about 17 million people suffer from blindness due to cataract, with the vast majority of them being over 50 years of age [3]. The disease manifests as opacification of the lens, which occurs because proteins lose stability, aggregate into large aggregates and begin to scatter light, as well as due to disruption of the lens fiber structure [1].

Cataract is a multifactorial disease involving both genetic and environmental factors [4,10]. Proven risk factors include older age, female sex, smoking and hereditary predisposition [4]. Heritability estimates in family and twin studies reach 58%, indicating a significant contribution of genetic components [4]. According to the age of manifestation, cataract is classified into congenital, infantile, childhood, presenile and age-related forms [2,10]. Morphologically, nuclear, cortical, posterior subcapsular, zonular, polar, total and membranous forms are distinguished, with different types possibly having partially overlapping but not identical etiologies [20].

Despite the high effectiveness of surgical treatment, access to it remains limited in many regions of the world, which makes the search for biomarkers for early diagnosis relevant [4,12]. Furthermore, a deep understanding of the molecular basis of cataract is necessary for the development of preventive and pharmacological approaches capable of slowing disease progression [2].

Genetic architecture of cataract

Molecular-genetic studies of cataract have developed in two main directions: the study of Mendelian hereditary forms and the search for genetic variants predisposing to age-related cataract [18].

To date, at least 59 genes have been identified whose mutations cause Mendelian hereditary forms of primary cataract, as well as more than 200 genetic diseases associated with secondary cataract [19]. Among the genes responsible for congenital cataract, the largest proportion is accounted for by crystallins, which comprise about one third of all cases [21]. Crystallins constitute up to 90% of all lens proteins and provide its transparency and high refractive index [15]. Mutations in crystallin genes, such as CRYAA, CRYAB, CRYBB2 and CRYGD, lead to disruption of protein packing and formation of aggregates that scatter light [6]. Depending on the specific gene and type of mutation, opacities may be localized in different zones of the lens – from the nucleus to the cortical layers [7]. They may manifest as nuclear, lamellar, total or polymorphic cataract [8].

Mutations in connexin genes, primarily GJA3 and GJA8, also account for a significant proportion of hereditary cataract etiology [9]. These proteins form gap junctions between lens cells, providing intercellular communication and maintenance of ion and metabolite homeostasis [10]. Disruption of this exchange leads to local changes in osmolarity and secondary opacification [11]. In addition, mutations have been identified in genes of membrane proteins and transporters, such as MIP and LIM2, as well as in genes of transcription factors HSF4 and PITX3, which regulate lens development [16].

Oxidative stress as a key mechanism of pathogenesis

Age-related cataract is considered in the modern literature as a result of long-term exposure to environmental factors against a background of genetic predisposition determining vulnerability to oxidative stress [2].

Despite the diversity of risk factors in different types of cataracts, oxidative damage is a common pathogenetic link [4].

With age, a diffusion barrier forms in the lens, which impedes the entry of small molecules, including the key antioxidant glutathione [8]. This creates conditions for the accumulation of reactive oxygen species and oxidative damage to proteins, lipids and DNA [16]. Damaged proteins lose their native conformation, undergo aggregation and form light-scattering structures characteristic of cataract [1].

During oxidative stress, a cascade of signaling pathways (MAPK/ERK and MAPK14) is triggered, which release the NRF2 factor from its bound state with its inhibitor KEAP1 [6]. Released NRF2 translocates to the nucleus, where it binds to the MAF protein and activates genes responsible for antioxidant defense and damage repair [7]. Among them are genes of enzymes that neutralize reactive oxygen species (catalase, glutathione peroxidase, superoxide dismutase), as well as enzymes involved in detoxification of toxic oxidation products [4,20]. An additional regulator of this process is the CITED2 protein [2,9]. Thus, NRF2 is the main regulator of the cellular protective response to oxidative stress, and disruptions in this system increase the risk of developing age-related cataract [11].

An important aspect is also the role of mitochondrial dysfunction [12]. Mitochondria are the main source of reactive oxygen species in cells, and with age the efficiency of the respiratory chain decreases, which exacerbates oxidative stress [10,21]. Among the molecular pathways associated with age-related cataract, the most significant are the tricarboxylic acid cycle and the mitochondrial electron transport chain [14]. The importance of these processes is confirmed by the fact that mitochondrial dysfunction is consistently identified among the major pathogenetic disorders [15]. This explains why many of the antioxidant drugs being developed are aimed at protecting mitochondria [11,19]. In hyperglycemia leading to diabetic cataract, an increase in superoxide levels in mitochondria is also observed [13,18].

Finally, when a combination of environmental stress factors against a background of genetic predisposition leads to the development of oxidative stress, the CDKN2A gene is activated [8, 19]. As a result, two different proteins are formed from this gene – p16INK4 and p14ARF [10]. The latter stabilizes the TP53 protein, which can not only induce apoptosis but is also directly associated with age-related cataract [21].

Epigenetic regulation: long non-coding RNAs as a connecting link

Traditional genetic markers – mutations and polymorphisms – explain only a small proportion of the hereditary predisposition to age-related cataract [2]. Even mutations in genes that are not themselves associated with antioxidants ultimately lead to oxidative stress, especially if they affect mitochondria [4]. This has led researchers to turn to epigenetic mechanisms and, in particular, to the active study of long non-coding RNAs, which in the last decade have come to be regarded as key regulators of the pathogenesis of age-related eye diseases [1-5].

Long non-coding RNAs are transcripts longer than 200 nucleotides that do not code for proteins but actively participate in the regulation of gene expression at the transcriptional, post-transcriptional and epigenetic levels [1-6]. They affect proliferation, migration, apoptosis, angiogenesis and immune cell responses [19]. In pathological conditions, including glaucoma, cataract, diabetic retinopathy and eye tumors, the expression of lncRNAs in ocular tissues and cell lines changes, confirming their significant role in the development and progression of these diseases [4, 8]. These non-coding RNAs have been shown to affect important cellular processes, including angiogenesis, inflammation, cell proliferation and apoptosis, which play a key role in the development and progression of eye diseases [19].

Among all long non-coding RNAs, the most studied in the context of eye diseases is MALAT1 [20]. The transcript of the MALAT1 gene is about 7000 base pairs in length, and its expression is comparable to that of highly active genes, such as β-actin [21]. MALAT1 is expressed in most human tissues, but mostly in the lungs and pancreas [1]. This gene has also been implicated in the etiology and development of neurodegenerative retinal diseases [3].

In addition to MALAT1, the lncRNA H19 is being actively studied in the pathogenesis of cataract and has been proposed as a marker of age-related cataract [5]. H19 regulates oxidative stress and apoptosis in lens cells, and its level correlates with the severity of opacification [6]. Furthermore, the role of lncRNAs NEAT1 and MEG3 in the pathogenesis of age-related eye diseases has been described in the literature, although their specific role in cataract requires further study [7].

Recent evidence indicates differences in the patterns of epigenetic modifications of lncRNAs, in particular m6A methylation, between congenital and age-related cataract [13-16]. In the age-related form, the level of such modifications is significantly higher, which reflects differences in epigenetic regulation [9]. At the same time, the final pathological processes – protein aggregation and lens opacification – are common to both forms [10].

The regulatory activity of lncRNAs in cataract is closely linked to the mechanisms of oxidative stress and apoptosis [11]. For example, MALAT1 affects the level of TP53 protein through binding to miR-125b [12]. Since TP53 controls apoptosis, this mechanism links changes in lncRNA expression to lens cell death, which exacerbates opacification [10,16]. As a result, a vicious circle arises: oxidative stress damages proteins, alters lncRNA expression, and the latter, in turn, weakens antioxidant defense, making cells even more vulnerable [14].

Thus, based on the presented data, three levels of molecular markers of cataract can be distinguished, which reflect the continuous spectrum of disease causes and link different pathogenetic mechanisms into a single picture [2]. The first level consists of structural mutations in genes of crystallins, connexins and membrane proteins, responsible mainly for congenital and childhood forms of cataract [4]. These mutations lead to primary defects in the structure of lens proteins, making them prone to aggregation regardless of external factors [6]. The second level is represented by polymorphisms in genes of antioxidant defense and metabolism, which determine predisposition to age-related cataract through disruption of the cellular response to oxidative stress [9]. These polymorphisms do not themselves cause the disease, but create a favorable background for its development under the influence of environmental factors [10]. The third level includes epigenetic markers – lncRNAs and their post-transcriptional modifications, which integrate signals from the genetic background and environmental factors and modulate the expression of target genes, including both structural lens proteins and components of the antioxidant system [15].

Regardless of the level of the primary lesion, the final pathogenetic pathway of cataract is the same – disruption of antioxidant defense and aggregation of lens proteins [2]. In congenital forms, mutations create proteins that are initially prone to aggregation [4]. In age-related cataract, oxidative stress damages proteins and weakens defense systems through epigenetic mechanisms [16]. Thus, lncRNAs act in this scheme as molecular sensors, linking different levels of regulation and ensuring the transition from predisposition to disease manifestation [15].

The developed three-level model has direct clinical significance and opens up opportunities for creating a multi-stage strategy for predicting the risk of cataract development [12]. For individuals with a family history of cataract and early manifestation, sequencing of crystallin and connexin genes is advisable to identify structural mutations [11, 20]. For older individuals without obvious hereditary burden, analysis of polymorphisms in antioxidant defense genes in combination with determination of oxidative stress markers in biological fluids is more informative [5, 9]. Finally, determination of lncRNA levels, such as H19 and MALAT1, in non-invasive samples (e.g., tear fluid or buccal epithelium) can serve as an integral indicator of the current state of the

antioxidant system and the risk of opacification progression, which will allow timely preventive measures to be prescribed [20].

Conclusion

Cataract is a heterogeneous disease based on both genetic and epigenetic mechanisms [2, 15]. Monogenic forms are mainly associated with mutations in structural lens genes, while age-related cataract is caused by a complex interaction of polymorphisms of antioxidant defense genes and environmental factors, realized through epigenetic regulatory networks [1-5]. In recent years, increasing evidence points to a key role of long non-coding RNAs as integral regulators of pathogenesis, linking genetic predisposition to the cellular stress response [16]. Studying the functions of lncRNAs in aging eye tissues is important for the development of medicine aimed at preserving vision in elderly patients [1-12].

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