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Molecular genetics of age-related cataract

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Abstract

Advances in molecular biological and genetic technology have greatly accelerated elucidation of the genetic contribution to age-related cataract. Epidemiological studies have documented tendencies for cataracts to occur more frequently in relatives of cataract patients than in the general population, genetic studies have demonstrated contributory roles of some specific genes in age related cataract in small populations, and molecular studies have shown changes in expression of specific genes in cataractous lenses. Together, these studies are beginning to provide a conceptual framework for understanding age-related cataracts.

Keywords

Lens; Cataract; Genetics; Gene expression

1. Introduction

Cataract, most simply defined as opacity of the crystalline lens, results when the refractive index of the lens varies significantly over distances approximating the wavelength of the transmitted light (Delaye and Tardieu, 1983; Benedek, 1971). Variation in the refractive index over these distances can result from changes in lens cell structure, changes in lens protein constituents, or both. Cataracts are generally associated with breakdown of the lens microarchitecture. Vacuole formation can cause large fluctuations in optical density, resulting in light scattering. Light scattering and opacity also can occur if there are significant high molecular weight protein aggregates roughly 1000 Å or more in size. The short-range ordered packing of the crystallins, which make up over 90% of soluble lens proteins, is important in this regard; to achieve and maintain lens transparency, crystallins must exist in a homogeneous phase.

A variety of biochemical or physical insults can cause phase separation of crystallins into protein-rich and protein-poor regions within the lens fibers. The proteins either remain in solution or form insoluble aggregates or even crystals, any of which can result in light scattering (Pande et al., 2001). When mutations in crystallins are sufficient in and of themselves to cause aggregation they usually result in congenital cataract, while if they merely increase susceptibility to environmental insults such as light, hyperglycemic or oxidative damage they might contribute to age related cataract. Thus, congenital cataracts tend to be inherited in a Mendelian fashion with high penetrance, while age-related cataracts tend to be multi-factorial, with the likelihood of multiple genes and environmental factors influencing the phenotype. This makes them significantly less amenable to genetic and biochemical study. Finally, while

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the young human lens is colorless, a gradual increase in yellow pigmentation occurs with age (Lerman, 1980). As this pigmentation increases it can result in brunescent or brown cataracts.

2. Mendelian cataracts with adult onset

In addition to epidemiological evidence implicating genetic factors in age-related cataract, a number of inherited cataracts with post-infantile age of onset or progression of the opacity throughout life have been described. Mutations in BFSP2 can cause juvenile cataracts (Conley et al., 2000), the Marner and Volkmann cataracts can be progressive (Eiberg et al., 1995; Marner et al., 1989), mutations in aquaporin 0 (MIP) and γC-crystallin can cause progressive cataracts (Francis et al., 2000a; Ren et al., 2000), and the CAAR locus is linked to familial adult onset pulverulent cataracts (Heon et al., 2001). These all suggest that for at least some genes, a mutation that severely disrupts the protein or inhibits its function might result in congenital cataracts inherited in a highly penetrant Mendelian fashion, while a mutation that causes less severe damage to the same protein or impairs its function only mildly might contribute to age-related cataracts in a more complex multifactorial fashion. Similarly, mutations that severely disrupt the lens cell architecture or environment might produce congenital cataracts, while others that cause relatively mild disruption of lens cell homeostasis might contribute to age-related cataract.

The hyperferritinemia-cataract syndrome is a recently described disorder in which cataracts are associated with hyperferritinemia without iron overload (Beaumont et al., 1995). Ferritin L levels in the lens can increase dramatically. The molecular pathology lies in the Ferritin L iron responsive element, a stem loop structure in the 5′ untranslated region of the ferritin mRNA. Normally, this structure binds a cytoplasmic protein, the iron regulatory protein, which then inhibits translation of ferritin mRNA, which may exist in the lens at levels approaching that of a lens crystallin. Mutation of this structure and overexpression of ferritin by loss of translational control in the hyperferritinemia-cataract syndrome results in crystallization of ferritin in the lens, and other tissues as well. Ferritin crystals appear as breadcrumb like opacities in the cortex and nucleus. Ferritin cataract serves as an example that the presence of crystallin proteins at such high levels in the protein rich lens cytoplasm requires that crystallins or other proteins must be exceptionally soluble. This is emphasized by the occurrence of cataracts resulting from single base changes decreasing crystallin solubility but not stability (Kmoch et al., 2000).

Lamellar and polymorphic cataracts have been associated with missense mutations in the MIP gene. One mutation, E134G, is associated with a non-progressive congenital lamellar cataract, and the second T138R is associated with multifocal opacities that increase in severity throughout life. When expressed in *Xenopus laevis* oocytes, both of these mutations appear to act by interfering with normal trafficking of MIP to the plasma membrane and thus with water channel activity (Francis et al., 2000b). In addition, both mutant proteins appear to interfere with water channel activity by normal MIP, consistent with the autosomal dominant inheritance of the cataracts.

3. Age-related cataracts

While congenital cataracts can be particularly threatening to vision, and up to one half of all congenital cataracts are inherited, they affect relatively few individuals in comparison to age-related cataracts, which are responsible for just under half of all blindness worldwide (Congdon et al., 2003). Even in technologically advanced industrial nations, cataracts cause a significant fraction of blindness. The Baltimore Eye Survey in Maryland, USA found that cataract is the leading cause of blindness in African-Americans and of visual impairment in all races (Tielsch et al., 1990). Cataract surgery is the most frequently performed surgical procedure in the United States (Javitt, 1993), and because of its demographics, it has been estimated that delaying the

development of cataract by ten years would decrease the need for cataract surgery by about 45% (Kupfer, 1987). Age-related cataract is associated with a number of environmental risk factors, including cigarette smoking, obesity or elevated blood glucose levels, corticosteroid exposure, exposure to ultraviolet light, and alcohol consumption.

In age-related cataracts the lens presumably develops reasonably normally during infancy and remains clear in childhood. Then, by somewhat arbitrary definition, at some time after 40 years of age, detectable opacities begin to form in the lens. As mentioned above, these opacities almost certainly result at least in part from the cumulative damage of environmental insults on lens proteins and cells. Lens proteins are known to undergo a wide variety of alterations with age, and many of these are accelerated in the presence of oxidative, osmotic, or other stresses, which are also known to be associated with cataracts. Susceptibility to these alterations may be exacerbated by barriers to movement of small molecules between the central lens nucleus and the metabolically more active epithelium (Truscott, 2003). In the case of lens crystallins, these alterations include proteolysis, an increase in disulfide bridges, deamidation of asparagine and glutamine residues, racemization of aspartic acid residues, phosphorylation, nonenzymatic glycosylation, and carbamylation (summarized in Hejtmancik, et al., 2001). Many of these changes are increased in cataractous lenses and can be induced in vitro or in model systems by stresses analogous to those epidemiologically associated with cataracts (Dickerson et al., 1995; Davies et al., 2001; Spector, 1995). In contrast, some changes do not appear to be implicated in cataractogenesis and may even serve to protect crystallins from harmful modifications (Lapko et al., 2003).

The lens crystallins form one obvious target for this accumulated damage, although they are certainly not the only one. Thus, as the β- and γ-crystallins slowly accumulate damage over the lifetime of an individual, they would loose the ability to participate in appropriate intermolecular interactions, and even to remain in solution. As these crystallins begin to denature and precipitate, they are bound by the α-crystallins, which have a chaperone-like activity (Horwitz, 1992). Binding by α-crystallins maintains solubility of βγ-crystallins and reduces light scattering, but the α-crystallins appear not to renature their target proteins and release them into the cytoplasm, as do true chaperones. Rather, they hold them in complexes that, while soluble, increase in size as additional damaged protein is bound over time until they themselves begin to approach sizes sufficient to scatter light. Eventually, it seems likely that the available α-crystallin is overwhelmed by increasing amounts of modified βγ-crystallin and the complexes precipitate within the lens cell, forming the insoluble protein fraction that is known to increase with age and in cataractous lenses (Carver et al., 1996).

Whether proteins in age related cataracts become insoluble as a result of complete or partial denaturation, or whether they simply become less soluble due to modifications that leave their protein folds largely intact, is not currently known. More highly studied Mendelian cataract models support both denaturation, as is seen in the association of some severe crystallin mutations with cataracts (Ren et al., 2000), and simple insolubility with maintained protein folds as is seen in other cataracts (Pande et al., 2000). Classically, it was believed that insoluble proteins in the lens became insoluble because they were denatured. There is a large body of data showing that insoluble protein in the aged cataractous lens not only is denatured and crosslinked, but that a fraction exists as relatively short peptides cleaved from larger proteins. There are even suggestions that this denatured protein exists as amyloid, although it would, at least initially, be intracellular, and there is little evidence that it causes precipitation of normal protein from the lens fiber cell cytoplasm. However, it seems likely that the presence of large amounts of unstable or precipitated crystallin, or other protein, does damage to the lens cell and eventually contributes to cataracts not only directly through light scattering by protein aggregates but eventually also through disruption of cellular metabolism and damage to the

cellular architecture. This is clear from numerous mouse models of cataracts resulting from crystallin mutations (Graw and Loster, 2003).

4. Genetic epidemiology of age-related cataracts

There is increasing epidemiological evidence that genetic factors are important in the pathogenesis of age-related cataract (McCarty and Taylor, 2001). In 1991, the Lens Opacity Case Control Study indicated that a positive family history was a risk factor for mixed nuclear and cortical cataracts (Leske et al., 1991), and the Italian American cataract study group supported a similar role for family history as a risk factor in cortical, mixed nuclear and cortical, and posterior subcapsular cataracts (1994b). In 1994, the Framingham Offspring Eye Study showed that individuals with an affected sibling had three times the likelihood of also having a cataract (1994a). The Beaver Dam Eye Study examined nuclear sclerotic cataracts using sibling correlations and segregation analysis. While a random environmental major effect was rejected by this study, Mendelian transmission was not rejected, and the results suggested that a single major gene could account for as much as 35% of nuclear and up to 75% or cortical cataract variability (Heiba et al., 1995). Most recently, the twin eye study demonstrated significant genetic influence of age-related cortical cataract, with heritability accounting for 53–58% of the liability for age-related cortical cataract (Hammond et al., 2001). This hereditary tendency was consistent with a combination of additive and dominant genes, with dominant genes accounting for 38–53% of the genetic effect, depending on whether cataracts were scored using the Oxford or Wilmer grading systems. Similarly, genetic factors were found to account for approximately 48% of the risk for nuclear cataract (Hammond et al., 2000).

5. Molecular and biochemical characteristics of age-related cataract

Galactosemic cataracts provide an interesting example of mutations severely affecting a gene causing congenital cataracts while milder mutations contribute to age-related cataracts. Deficiencies of galactokinase, galactose-1-phosphate uridyl transferase, and severe deficiencies of uridine diphosphate 1–4 epimerase cause cataracts as a result of galactitol accumulation and subsequent osmotic swelling. The latter two are also associated with vomiting, failure to thrive, liver disease, and mental retardation if untreated, while the cataracts in galactokinase deficiency are isolated. Interestingly, galactosemic cataracts initially are reversible both in human patients and in animal models. In 2001 a novel variant of galactokinase, the Osaka variant with an A198V substitution, was shown to be associated with a significant increase in bilateral cataracts in adults (Okano et al., 2001). It results in instability of the mutant protein and is responsible for mild galactokinase deficiency leaving about 20% of normal levels. This variant allele frequency occurs in 4.1% in Japanese overall and 7.1% of Japanese with cataracts. The allele was also present in 2.8% of Koreans but had a lower incidence in Chinese and was not seen in blacks or whites from the United States. This and other GALK1 variants appeared to be absent from Northern Italians with age related cataract, suggesting that the genetic contributions cataract might vary in different populations (Maraini et al., 2003).

The GALK1 results fit in well with the known influence of hyperglycemia on age-related cataract. That these cataracts result from polyol accumulation is suggested by work in galactosemic dogs and transgenic and knockout mice. Dogs have aldose reductase levels similar to those in humans and when stressed readily develop sugar cataracts that are prevented by aldose reductase inhibitors. Mice, which have very low aldose reductase activity in the lens, are naturally resistant to sugar cataracts, either galactosemic or hyperglycemic. However, upon transgenic expression of aldose reductase, mice readily develop cataracts, especially when galactokinase or sorbitol dehydrogenase is deleted (Lee et al., 1995). Consistent with these animal data are the recent findings that susceptibility to cataracts as a diabetic complications

in humans is associated with specific allele Z of the microsatellite polymorphism at 5′ of the aldose reductase gene (Lee et al., 2001).

As mentioned above, the epidemiology of cataracts strongly implicates oxidative stress, and especially photo-oxidation, as risk factors for age-related cataracts. This suggests that key enzymes of metabolic pathways maintaining the reducing environment of the lens might be candidates for involvement in age-related cataracts. One such candidate that has shown inconclusive results is glutathione S-transferase, with studies showing increased, unchanged, and decreased risk for age-related cataracts with the null allele of glutathione S-transferase M in different populations (Sekine et al., 1995; Alberti et al., 1996; Juronen et al., 2000; Hao et al., 1999). It is possible that glutathione S-transferase P might show a stronger effect on risk of age-related cataracts, since it is the most prevalent glutathione S-transferase in the lens. Thioltransferase (glutaredoxin) has been shown to increase in response to oxidative stress in immortalized human lens epithelial cells (Raghavachari et al., 2001), and would also represent a reasonable gene for consideration. As with glutathione S-transferase, however, this might be complicated by the occurrence of more than one form in the lens.

6. Experimental approaches to age-related cataracts

In addition to genetic epidemiological studies, a number of direct experimental approaches have provided insight into the genetics of age-related cataract. One approach has been to identify those gene products that show a substantial increase or decrease in cataractous lenses at the level of mRNA (Zhang et al., 2002). This approach does not directly identify genes that, when mutated, cause or contribute to cataract, as do the more direct genetic studies described above. Importantly these studies suffer from the limitation that they do not distinguish those genetic alterations that cause cataract from those resulting from the presence of cataract. In addition, mRNA levels tend to be measured in lens epithelial cells, while in age-related cataracts, with the exception of posterior subcapsular cataracts, the opacities tend to occur in the nuclear or cortical fiber cells. Thus, the gene expression changes examined in this approach most likely reflect responses of lens epithelial cells to the presence of underlying cataract.

The lens epithelium is an ideal tissue for this type of analysis since it is the first part of the lens exposed to insults that are likely to be involved in cataract and damage to the epithelium or its enzyme systems can cause cataract. The lens epithelium contains the majority of protective, metabolic, osmotic and other regulatory systems of the lens. It is the only part of the lens that contains nuclei and is therefore capable of responding to cataract or cataract-associated insults through altered gene expression. Considerable evidence suggests that the lens epithelium is capable of communicating with the underlying fiber cells providing a basis for its responding to the presence cataract (Rae et al., 1996; Bassnett et al., 1994).

By examining gene expression changes in the lens epithelium this approach identifies genes that belong to protective, metabolic or regulatory networks that are activated or inhibited as a result of cataract formation. These genes may or may not be directly affected by cataract or cataract-associated insults in the lenses in which they were identified. However, it is reasonable to hypothesize that if cataracts or the stresses that cause them induce or retard the expression of these genes, mutations in these genes might then contribute to cataract formation. Thus, genes identified in this fashion are certainly candidates for the more direct genetic analysis described above.

The identified genes form an interesting and rather surprising group. These genes have been identified by differential display RT-PCR differential display and more recently DNA microrray analysis. For instance, the mRNAs encoding metallothionein IIa (Kantorow et al., 1998b) and osteonectin (Kantorow et al., 1998a) (also known as SPARC, secreted acidic protein rich in cysteines) are increased, while those for protein phosphatase 2A regulatory

subunit (Kantorow et al., 1998b) and some ribosomal proteins including L21, L15, L13a, and L7a are decreased (Zhang et al., 2002). These findings are consistent with induction of metallothionein by lens epithelia in the face of oxidative and perhaps toxic stress in the presence of divalent cations, and also with a protective role for SPARC. Although the function of SPARC, which also binds calcium, is less well understood, it is known to increase in the face of cellular injury and to be involved in cellular growth and growth factor control. Similarly, the decrease in protein phosphatase 2A regulatory subunit is consistent with decreasing cell division in the lens epithelia, while decreasing ribosomal proteins would be expected in the face of the corresponding decreases in protein synthesis. That these reactive proteins might cause cataracts if aberrantly expressed is supported by the occurrence of cataracts in mice lacking SPARC (Gilmour et al., 1998). In addition to the above transcripts, transglutaminase, an enzyme implicated in the cross-linking of fibronectin and other extracellular matrix proteins, is increased in anterior polar cataracts (Wan et al., 2002) as is the transforming growth factor beta inducible gene betaig-h3 (Lee et al., 2000) while ADAM9, a disintegrin and metalloproteinase (Lim et al., 2002) is decreased.

Although the above findings have provided interesting insight into the potential roles of individual genes in age-related cataract, they do not provide sufficient gene representation to identify clusters of related genes whose collective gene expression changes could elucidate those lens functional pathways altered in age-related cataract. In order to identify these pathways, recent studies have sought to identify the full complement of gene expression changes that occur in the lens epithelium upon cataract formation at the genomic level using DNA microarrays (Ruotolo R et al., 2003; Hawse et al., 2003). These approaches have now identified hundreds of genes whose expression levels are increased or decreased in the epithelia of age-related cataracts. Although mention of the individual genes are beyond the scope of this review, many of the identified gene expression changes are consistent with those identified in the differential display studies highlighted above. Some specific examples of increased genes include SP1 required cofactor for transcriptional regulation, osteomodulin, chloride channel 3, Na + K + transporting polypeptide beta 1and Ca ++ transporting ATPase. Some examples of genes decreased in cataract include alpha A-crystallin, multiple glutathione peroxidases, multiple ribosomal subunits, HSP 27, Na + /K + ATPase and transketolase. More than two thirds of the identified genes are decreased in cataract suggesting loss of gene expression as consequence of lens damage. Functional clustering of the identified genes suggests that the genes increased in cataract tend to be associated with transcriptional control, ionic and cytoplasmic transport, protein salvaging pathways and extra-cellular matrix components while transcripts decreased in cataract tend to be associated with protein synthesis, defense against oxidative stress, heat shock/chaperone activity, structural components of the lens and cell cycle control. Many of the identified genes and their associated pathways are consistent with previously identified lens functions believed to play major roles in cataract while others point to novel cataract-associated processes.

Another approach towards identifying genes belonging to regulatory or metabolic pathways that might be important in age-related cataracts has been to examine mRNAs whose expression is modified in lens cells subjected to oxidative stress (as described above, a large body of experimental and epidemiological evidence implicates oxidative, and especially photo-oxidative, stress in age related cataract). In one study, those genes whose expression is altered in cultured human SRA04/01 cells treated with hydrogen peroxide were identified (Goswami et al., 2003). In this study global acute gene responses to H_2O_2 treatment of cells were separated from those arising from apoptosis, necrosis and serum induction and the resulting genes functionally categorized. This approach identified over 1000 genes that acutely respond to peroxide stress. Many of these genes fell into categories previously associated with oxidative stress in the lens and other systems including those encoding DNA repair proteins, antioxidant defense systems, molecular chaperones, protein biosynthesis and trafficking/degradation

proteins. Some specific examples previously shown to be important for oxidative stress include glutathione-S-transferase, thioredoxin reductase B and peroxiredoxin. Some of the identified genes including HSP40 and ORP150 are better known to respond to other forms of stress. Interestingly, many of the genes identified in this study also are differentially induced in actual cataract epithelia as described. One of these called ARK tyrosine kinase is believed to be a major upstream activator of the stress response in many cell types (Sheets et al., 2002).

The second approach towards identifying genes that respond to oxidative stress has involved the extended treatment of SV-40 transformed αTN4-1 mouse lens cells with H_2O_2 followed by the selection of cells that resisted peroxide insult and subsequent identification of those genes whose overexpression allowed them to adapt to H_2O_2 treatment. Both differential display RT-PCR and DNA microarray analysis have been employed in this approach. The genes identified by differential display RT-PCR are predominantly antioxidant and cellular defense enzymes including catalase, which increased 14-fold. Reticulocalbin increased 6-fold, while glutathione peroxidase, ferritin, and αB-crystallin each increased 2-fold. αA-Crystallin mRNA levels decreased to one fifth of baseline, while mRNAs for aldose reductase and mitochondrial enzymes showed no change (Carper et al., 2001). The H_2O_2 immortalized cells have also been examined by DNA microarray analysis (Spector et al., 2002a) and compared to a second SV-40 transformed αTN4-1 cell line conditioned to survive both H_2O_2 and t-butyl hydrogen peroxide (TBHP) stress (Spector et al., 2002b). Interestingly similar genes were identified by to be altered when these cell lines were compared including catalase, multiple glutathione-S-transferases, NAD(P)H menadione oxidoreductase 1 and ferritin light chain. Like the acute H_2O_2 genes discussed above, many of the genes identified in this analysis are also differentially expressed in actual cataract epithelia providing further evidence for a major role for oxidative stress in age-related cataract.

7. Summary

Significant inroads are being made into understanding the genetics of human congenital cataracts, and the first initial insights are opening up for age-related cataracts. It has been estimated that there might be as many as 40 genes contributing to congenital cataracts in the mouse, and it would be reasonable to assume a similar number in humans. As our understanding of congenital and age-related cataracts increases, the relationship between their genetic causes becomes correspondingly more approachable. This is important for the study of age-related cataracts, because delineation of their genetics is much more difficult, due to their complex inheritance and late onset. Understanding the genetics of these cataracts is of paramount importance in order to guide development of a medical therapy that will prevent or delay their onset, lessening their burden on the aging population and the requirement for large numbers of surgical procedures.

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