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Cataracts: Role of the unfolded protein response

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Summary Many cataracts are caused by unfolded protein aggregates in highly oxidized lenses, but the underlying mechanisms of their formation are poorly understood. A literature search has shown that many cataractogenic stressors are also endoplasmic reticulum (ER) stressors, which induce the unfolded protein response (UPR) in a wide range of cell types. Since the lumen of the ER is highly oxidized, ER stressors might generate unfolded protein aggregates, which activate the UPR leading to the production of reactive oxygen species (ROS) in lens epithelial cells (LECs). ROS decrease the amount of free glutathione from whole lenses and elicit a more oxidized environment, where unfolded protein aggregates are formed and grown to large protein aggregate particles to scatter light. Recently, we have shown that ER stressors, homocysteine, tunicamycin, Ca^{2+} ionophore (A23187), and glucose deprivation induce the UPR in LECs. Here we hypothesize the cataractogenic stressors induce ER stress, initiate the UPR and ROS production in LECs with or without apoptosis and eventually resulted in cataracts.

Introduction

The pivotal role of the endoplasmic reticulum (ER) in the life of cells has been known for several decades, but the part it plays in the progression of human diseases has only recently been appreciated. Although many causes of cataracts have been identified, the underlying mechanisms of initiation of cataract formation are poorly understood. It is increasingly evident that a few common pathways are shared in the responses to multiple, seemingly divergent stresses. A number of recent reports support idea that multiple intracellular stress pathways converge into a single event: the unfolded protein response (UPR). The UPR is induced by unfolded protein aggregates in the ER (ER stress) [1–3].

The ER is a principal site for protein synthesis and is the location where the vast majority of secreted, glycosylated, modified, and lipid proteins are folded into their tertiary and quaternary structure. The lumen of the ER is a highly oxidized compartment and the concentration ratio of reduced glutathione (GSH):oxidized GSH (GSSG) is 3:1, whereas in the cytosol the ratio is 100:1 [4]. Only those proteins that are properly folded are formed into oligomers and are transferred to the Golgi complex for further modification. Otherwise, Bip/GRP78, a central sensing protein in the ER, binds to improperly folded proteins, which are subsequently degraded by ubiquitin [2,4,5]. If this response is not capable of removing unfolded

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protein aggregates, the cells are able to activate death pathways that include the production of ROS and an activation of multiple caspases. The basic mechanisms of the UPR induced by ER stress and enzymes involved in the UPR were recently elsewhere reviewed in depth [2,3]. We shall here describe multiple cataractogenic stressors inducing the UPR in the lenses.

Decades of study on cataract formation have shown that a wide variety of stressors induce cataracts [6—10]. Interestingly, all types of known cataracts are associated with a significant loss of free glutathione (GSH) [9,11,12] and the generation of a highly oxidized environment, where unfolded crystallin aggregate particles are formed and grow to larger than 5×10^7 Da to scatter light [13].

Similar chemical interactions must be provoked by cataractogenic stressors in the highly oxidized lumen of the ER, generating unfolded protein aggregates. Recent reports show that the ER produces a significant amount of ROS, where electrons are generated from the formation of disulfide bonds, and oxygen molecules serve as the terminal electron acceptor [14—16]. This electron transfer then leads to the production of ROS and ultimately to the oxidation of GSH. In addition, deprivation of GSH induces dysfunctional mitochondria, which further generate ROS [17]. Thus the UPR may generate significant levels of ROS from the ER and mitochondria.

The UPR induced by ER stress may be a common cellular basis for cataract development

Careful examination of the different stressors involved in cataractogenesis overwhelmingly shows that these stressors also induce ER stress and activate the UPR in various cell types.

Oxidative imbalance: Decades of studies have shown that oxidative insults induce cataract formation in the lens [11,18]. Rat lenses cultured in 0.5—25 μM of H_2O_2 induce neither cataract nor apoptosis [19]; by contrast, LECs exposed to 1000 μM of H_2O_2 underwent necrosis [20]. Our preliminary study showed that Bip/GRP78 was elevated and cell death was increased in human LECs treated with between 30 and 50 μM of H_2O_2 for 24 h, suggesting that a certain concentration of oxidative stress may induce the UPR. In contrast, deprivation of oxygen induces cataracts [21] and UPR dependent apoptosis [22,23]. Thus, appropriate oxygen tension is essential for cell survival and lack of oxygen induces the UPR in LECs which may be associated with cataract formation.

Glucose imbalance: Diabetic complications induce anterior and posterior sub-capsular cataracts [24,25]. Several papers reported that hypoglycemia induces the UPR in various cell types [26,27] presumably by inhibiting N-linked protein glycosylation in the ER. In the lens, osmotic and oxidative stresses are reported to contribute to cataract development at higher glucose levels [10,28]. Deprivation of glucose induces reversible cataracts [29,30], and an acute cataract has been observed in diabetics when the blood glucose has been brought down very rapidly [31,32]. In addition, ischemia (deprivation of glucose, oxygen, and various factors) induces the UPR [22,23,33] and sub-capsular and nuclear cataracts [34].

Ca^{2+} imbalance: Although Ca^{2+} plays numerous functional roles, intralumenal Ca^{2+} storage is important for the generation of Ca^{2+} signals as well as for the correct folding and post-translat ional processing of proteins entering the ER after synthesis. Influx of Ca^{2+} into LECs treated with Ca^{2+} ionophore (A23187) induces the UPR [1,5,35] and cataract formation [36], while a hypo- or hyper-Ca^{2+} environment causes LEC death and cataract [37].

DNA damage (radiation insults) has been produced by irradiation of the eye with most regions of the electromagnetic spectrum from γ-rays to microwaves [6]. Posterior subcapsular cataracts (PSC) have been produced by irradiation of the eye with γ-rays or X-rays [6,38—40]. Death of peripheral LECs appears to be associated with development of lens opacity. Dividing cells are more susceptible to X-rays, which may also explain why very young animals are more susceptible to X-ray cataracts than older animals. DNA damage beyond that which is repaired is known to induce cataract and cell death in animals [41,42] and the UPR [43—45].

Metal ions: Lead, copper, and mercury induce cataracts [46], the UPR and cell death. Methylmercury is known to bind thiol groups and be incorporated into proteins, which may generate unfolded protein aggregates [47]. Copper and lead induce depolarization of the mitochondria membrane [48] and lead induces the UPR by direct binding to Bip/GRP78 [47,49].

Selenium is an essential trace element, but at high concentrations it induces nuclear cataract in various animals, which display ionic imbalances, Ca^{2+} accumulation, calpain induced apoptosis, lens opacification, and LEC death [50]. In selenite injected rat lenses, apoptosis occurs in 7—8% of epithelial cells in the germinative zone [51] and the UPE is induced [52].

Homocystinuria is also highly associated with cataract formation [53,54]. Homocysteine interacts with proteins through a disulfide bond, and resulting modified protein aggregates are recognized in the ER and induce the UPR. A prolonged exposure to higher levels of homocysteine induces UPR dependent apoptosis [55,56].

Tunicamycin blocks the glycosylation of many glycoproteins, which generates unfolded proteins that are recognized by the ER and induce the UPR [5], LEC death, and sub-capsular opacity within 48—72 h in culture [1].

Naphthalene cataracts: Cortical cataracts have been produced in animals by feeding them large doses of naphthalene. The auto-oxidized toxic agent appears to be 1,2-naphthoquinone, which in turn can react with the thiol groups of glutathione and lens crystallins [57]. Recently, naphthalene/quinone has been reported to induce ER stress and apoptosis [58,59].

Deficiency cataracts: Amino acid and vitamin deficiencies lead to cataract formation [60]. A lack of tryptophane has been most often implicated in cataract [60,61] and also induces the UPR [45]. Riboflavin deficiency is the only vitamin deficiency which has produced cataract consistently in animals for several decades [62,63], and its deficiency has also been reported to induce the UPR and apoptosis in Jurkat cells [64,65]. A novel conserved flavin adenine dinucleotide (FAD) dependent enzyme (Ero1p) directly interacts with FAD to oxidize protein disulfide isomerase (PDI), which then subsequently oxidizes the folding protein directly, therefore riboflavin deficiency results in a striking defect in oxidative protein folding [66].

Malnutrition: Chronic diarrhea [67], which is common in some tropical countries, and anorexia nervosa [68,69] are associated with cataracts and probably generate deprivation of essential amino acids (such as tryptophane) and riboflavin, and induce dehydration, acidosis, and increased plasma urea concentration, which can induce carbamylation.

Viral infection: Herpes, retrovirus, and rubella induce cataracts [70—73]. Viral proteins in the ER activate the UPR [74]. Chronic hepatitis B virus infection induces oxidative stress and DNA damage and results in UPR induced apoptosis [75—77]. Retrovirus infection also induces Bip/GRP78 and the UPR [78]. Alpha virus induces the UPR and cell death [79]. Expression of viral protein such as viral E7 gene [80] or RB gene, a tumor repressor gene [81] in transgenic mice induce cataract, but we do not know whether the UPR is induced in these animals. Furthermore, prion protein is also known to induce the UPR [82].

Nitric Oxide (NO): NO is speculated to induce cataract [83] and reported to induce the UPR [84] in macrophages.

U18666A: A cholesterol biosynthesis inhibitor induces subcapsular cataracts in animals and increases the risk of cataract in humans [85—88]. Several reports indicated that U18666A induces Ca^{2+} activated proteolysis, protein modification, lipid peroxidation, and loss of junction. It is apparent that apoptosis is induced in LECs shortly after being treated with U18666A [88], and two recent papers showed that the suppression of cholesterol apparently induces the UPR [89,90].

Toxic cataracts: Over-dose of ethanol induces cataracts [6]; acetaldehyde, a major metabolite of the alcohol, is able to bind to proteins and induce the UPR [91]. Methionine sulphoximine induces anterior and peripheral cataracts [92] and ER stress [93]. Dinitrophenol induces cataract in various animals and man [94] and also induces the UPR [95]. 3-Aminotriazole induces posterior cataracts [96] and the UPR [15].

To date, no information is available whether the following cataractogenic stressors induce the UPR; allopurinol, diquat, hyperglycemia, hyperbaric tank, uremia (carbamylation), mutant proteins in the ER, phenothiazines, or steroids.

In conclusion, it is not surprising that many cataractogenic stressors are also ER stressors, which induce similar chemical interactions in the highly oxidized lumens of the ER and induce unfolded protein aggregates in the lens. The unfolded protein aggregates induce the UPR, which induces ROS production with or without induction of apoptosis [1]. The UPR may play a central role in the initiation and progression of many types of cataract formation. The prevention of cataracts would entail the removal of any ER stressor in daily life.

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