Posterior Capsule Opacification: Experimental Review

Subjects: Ophthalmology

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Posterior capsule opacification (PCO) is the most common complication of cataract surgery. It causes a gradual deterioration of visual acuity, which would otherwise improve after a successful procedure. Despite recent advances in ophthalmology, this complication has not been eradicated, and the incidence of PCO can be as high as 10%.

posterior capsule opacification | experimental studies | cell cultures | tissue cultures | animal model of PCO

1.Introuction of Risk Factors

The development of PCO is influenced by patient-related factors, factors related to surgical technique, and the type of intraocular lens (IOL) implanted. Patient-related factors include young age, history of uveitis, glaucoma [1], arterial hypertension, metabolic disease, type of cataract (subcapsular), and injury [2][3][4]. These factors are known to increase the risk of PCO in the immediate postoperative period [4], but the mechanism of action has not been completely clarified. Some authors believe that diabetes may play a role in the promotion of PCO [5] while others have suggested that diabetes is a preventive factor [6]. Moreover, the data on PCO are inconsistent regarding sex distribution. The only IOL-related factors proved to be associated with PCO are a rounded edge and the phacoemulsification technique [7]. The geometry of the optic edge of the IOL is also important, as well as the shape and angulation of the haptics. PCO is much less likely to occur with IOLs that have a sharp posterior optic edge (360°). Mian et al., found that the frequency of posterior capsulotomies performed in patients with three-piece lenses was significantly lower than that in those with one-piece lenses [8]. Furthermore, thorough hydrodissection and aspiration of lens masses and polishing the posterior capsule reduce the occurrence of PCO, but increase the procedure time, which may increase the risk of surgical trauma. Incomplete LEC removal may lead to further proliferation of LECs within traumatized tissues, which exacerbates pro-inflammatory processes [9].

2. Treatment

The most common procedure performed to improve visual acuity that provides insight into the fundus of an eye with PCO is laser capsulotomy [10]. This procedure entails making an opening in the posterior capsule on the visual axis. Laser capsulotomy is accepted as a standard and effective treatment for posterior capsule opacification. It is an effective, quick and relatively easy outpatient procedure, but it can produce some complications. Recent studies

have not confirmed its association with retinal detachment, however it may be associated with complications, which range from mild short-term increase in intraocular pressure to visual impairment due to cystoid macular edema, or macular holes [11][12]. Trinavarat et al., noticed that laser capsulotomy may lead to IOL damage, subluxation, dislocation, and secondary glaucoma [13]. Moreover, laser capsulotomy is not compatible with the new generation of accommodative lenses, which require the presence of a lens capsule to function [14]. Laser treatment also places a significant financial burden on healthcare systems and is not widely available in developing countries. Therefore, the second course of action is to search for methods to prevent secondary cataracts. Until now, numerous in vitro and experimental animal studies have been conducted, but many have reported undesirable effects on the corneal endothelium [15][16]. Various trials of antiproliferative therapy have been performed in cells cultured in vitro and lens capsule models or in vivo (in rabbits, monkeys, and humans) [17][18][19][20]. Active agents are delivered to LECs via various carriers (including ophthalmic viscoelastic devices, drug delivery systems [DDSs], or slow-release implants) or can be delivered directly to the cell culture medium during in vitro experiments. Various techniques have also been developed for intraoperative application of pharmacological agents to lens cells, including adding them to infusion fluids, using devices that confine them in the capsular space, or coating the IOLs with the test substance [21].

3. Pathophysiology

The breakdown of the blood-aqueous humor barrier during cataract surgery causes an immune response. Thereafter, epithelial-mesenchymal transition (EMT) occurs in cells in the lens capsule. The main cause of PCO after cataract surgery is migration and proliferation of LECs. The average number of LECs is approximately 4000–5000/mm^2, depending on patient age, with a significant decrease in density in those aged 80 years or older. LECs consist of a single layer of cuboidal-cylindrical cells attached to the posterior surface of the anterior lens capsule. A foreign body, such as an IOL, induces an inflammatory reaction, which includes multinuclear leukocytes, giant cells, and fibroblasts, in the anterior chamber in the immediate postoperative period [22][23]. It is worth noting that in animal studies (e.g., in mice from Melinda Duncan's lab) removal of the lens fiber core also induces the generation of fibrotic cells in the absence of insertion of an IOL. These cells produce cytokines, including transforming growth factor beta (TGF-β), interleukin-1, interleukin-6, basic fibroblast growth factor (bFGF), and tumor necrosis factor alpha (TNF-α), which activate transformation of LECs, proliferation, metaplasia around the equator of the anterior capsule, and migration toward the posterior capsule, leading to thickening and hypertrophy. This process is characterized by fibrosis and contraction reactions due to the activity of actin filaments [24]. Moreover, immunohistochemical studies have identified extracellular matrix (ECM), fibronectin, and collagen molecules on the surface of the IOL [25][26]. Collagen deposition on the IOL and capsule can cause clouding and edema in the posterior lens capsule [26].

The extent to which the IOL becomes coated by LECs depends on the material used in the IOL; its surface [26], optic shape, and diameter; mechanical properties of the haptics [25]; and implantation methods used [27]. The two types of PCOs are caused by two different types of epithelial cells. The first type of PCO involves anterior epithelial cells located in the central zone of the anterior capsule, which consist of LECs that are relatively inactive mitotically.

When stimulated, these cells are converted to myofibroblasts, causing fibrous metaplasia. Cells may also migrate toward the posterior capsule, where they proliferate and undergo hypertrophy and hyperplasia on the capsule surface, causing opacification [28]. The second type of PCO occurs when pluripotent cells gather around the equator of the capsule. When activated by interleukins, these cells migrate posteriorly. They do not undergo fibrosis but instead form large, balloon-shaped, or clustered Wedl or bladder cells. They undergo constant mitosis, proliferation, hypertrophy, and hyperplasia, creating clouding [29]. They can also participate in the formation of the fibrous form of PCO through the process of fibrous metaplasia, appearing as fibrous membranes. Metaplasia and inflammatory cells of the iris and ciliary body as well as fibrinous exudate also stimulate development of PCO [30]. Furthermore, the residual cortical fibers may regenerate, creating pathological clouding known as Soemmering's ring and Elschnig's pearls and is much more common than fibrotic PCO and is the main cause of a decrease in visual function after cataract surgery [26][27].

4. Cell and Membrane Mediators

In vitro research uses cells derived directly from human or animal lenses. These cells perfectly reflect the processes occurring during formation of PCO because of the original phenotype of the epithelium and their greater sensitivity to external factors. The proliferation and differentiation capacity of cultured LECs can be assessed using microscopy [21]. Alternatively, cells can be obtained by culture of a cell line; these cells are more stable and can provide information about cellular processes but do not completely reflect all processes occurring under actual biological conditions.

4.1. Inhibition of TGF-β

Given that TGF-β plays a key role in the formation of PCO, research efforts have focused on inhibiting its action. Sun et al. [31] performed a study in which they grew human lens epithelial (HLEB3) cells in vitro and stimulated them with TGF-β2. The cells then transformed into fibroblast-like cells and the bonds between them loosened, causing them to migrate (i.e., undergo EMT). Application of a SNAIL small interfering RNA polyclonal antibody released from a coated IOL inhibited the EMT process, mainly via inhibition of migration and adhesion of LECs.

Collison et al. [32] investigated the effect of an anti-TGF-β monoclonal antibody (CAT-152) on progression of PCO. In their experiment, ex vivo human lens capsules were incubated with various concentrations of TGF-β with or without CAT-152. Incubation of the lens capsule with TGF-β resulted in an increase in migration and differentiation of LECs, which, in turn, resulted in shrinkage of the capsule and formation of PCO. Addition of CAT-152 inhibited this process.

Yang et al. [33] evaluated the ability of pirfenidone to inhibit migration and differentiation of human LECs in vitro and concluded that pirfenidone inhibits TGF-β2-induced cell proliferation and migration, most likely by downregulating the TGF-β receptor (and Smad2, Smad3, and Smad4) in human LECs.

Lovastatin also has the potential to inhibit TGF-β [34]. The mechanism of action of lovastatin involves blocking RhoGTPase, which stimulates the TGF-β-dependent conversion of LECs. In a study performed using a porcine model, LECs were pre-treated with lovastatin and then incubated with TGF-β for 24 h. Unlike the control group, the lovastatin group showed no increase in mRNA expression and protein production of LEC's, or increased collagen contractility. These findings suggest that lovastatin could be considered for the prevention of PCO [34].

Kubo et al. described the roles of TGF and fibroblast growth factor (FGF)-2, their relationship to tropomyosin in regulation of EMT in lens capsule cells, and the development of PCO [35]. They identified two types of TGF-β-dependent differentiation of LECs, with or without FGF-2, based on research performed in mice and rats. The first type led to differentiation of cells in the lens capsule toward tropomyosin-positive myofibroblasts showing epithelial-to-myofibroblast transition (EMyoT) morphology without the presence of FGF-2. The second type differentiated into fibroblastic tropomyosin-negative cells induced by FGF-2 with simultaneous administration of TGF-β2. Increased expression of tropomyosin may be associated with the progression of EMyoT in mice, PCO in rats, and healing of LECs in mice. Tropomyosin is an important marker of PCO and constitutes a therapeutic target in the wound healing process and in neoplastic invasion. Further investigation of the mechanism by which tropomyosin is regulated will provide valuable insights into its inhibitors and introduce new methods of treatment and prevention of EMT-dependent diseases.

Hypoxia-inducible factor (HIF)-1α is degraded after cataract surgery due to an increase in pO_2. TGF-β2, in turn, increases the activity of HIF-1α in cells after cataract surgery. Nahomi and Nagaraj evaluated the role of HIF-1α in EMT mediated by TGF-β2 in cultured FHL124 human LECs [36]. TGF-β2 was shown to increase the concentration of HIF-1α during EMT in FHL124 cells, while an attempt to increase HIF-1α expression using a prolyl hydroxylase inhibitor did not induce EMT in these cells. Moreover, KC7F2, an HIF-1α protein translation inhibitor, inhibited TGF-β2-mediated EMT in FHL124 cells. These findings indicate that HIF-1α has a significant role in TGF-β2-mediated EMT of LECs, which may be important in prevention of PCO.

Taiyab et al., evaluated the interaction between β-catenin (involved in non-canonical signal transduction) and Smad3 (required in canonical signaling) in TGF-β-induced EMT regulation using an ex vivo rat lens model [37]. Lens cells were tested to show the interaction between the three TGF-β-dependent EMT pathways using alpha-smooth muscle actin (α-SMA). In their study, inhibition of the Smad3 pathway protected against translocation of β-catenin into the nucleus and loss of E-cadherin from cell–cell contacts as well as blocked TGF-β-dependent EMT in lens cells. Inhibition of β-catenin and Smad3 reduced the amount of TGF-β receptor mRNA present. The results of that study indicated a close relationship between interaction in the β-catenin/Smad3 line and regulation of the EMT process in the lens and could lead to development of an agent for the prevention and treatment of PCO.

4.2. Disruption of Cell Adhesion

Mibefradil is a T-type antagonist of the calcium channels present in cell membranes. As a non-selective calcium channel blocker, it causes depolarization of cell membranes. Moreover, it reduces the expression of integrins, resulting in inhibition of proliferation and induction of apoptosis. Its use in the prevention of PCO is based on the

hypothesis that it inhibits the pathways mediating cell adhesion. The effect of mibefradil dihydrochloride was tested in primary human LECs obtained after cataract surgery and in a human lens cell line (HLE-B3) [38]. During the surgical procedure, fragments of the lens present on the anterior capsule were collected and cultured for 1–2 weeks. They were subsequently separated from the capsule and transferred to a growth medium. Next, the cells were treated with the drug for 24 h. The earliest signs of mibefradil-induced apoptosis of human LECs were observed after 4 h of incubation. These signs were accompanied by a significant reduction in cell size and initiation of apoptosis by phosphatidylserine switch in the plasma membrane. DNA fragmentation in the cell nucleus and fragmentation of cytoskeletal actin were observed. Apoptosis is correlated with inhibition of integrin expression, decreased proliferation, and depolarization of cell membranes. This research suggests that depolarization of the human LEC membrane and inhibition of integrin expression leads to a decrease in cell adhesion and apoptosis, which may inhibit development of PCO. Inhibition of integrins prevents LECs from adhering to the lens capsule and leading to PCO.

Sureshkumar et al. [14] tested the ability of drugs that rapidly inhibit the actin cytoskeleton network to prevent PCO in the human lens capsule. Two agents were used, namely, H-7, a broad-spectrum serine-threonine kinase inhibitor, and latrunculin (LAT)-B, a macrolide isolated from the sea sponge *Latrunculia (Negombata) magnifica*; both agents are less toxic than ethylenediaminetetraacetic acid (EDTA) and the antimetabolites that act in a similar fashion [39]. These substances differ slightly in their mechanism of action in that H-7 reduces focal cell adhesion, damages cell membranes, and causes relaxation of fibers, whereas LAT-B damages direct intercellular connections. In their study, Sureshkumar et al. [14] tested 48 human eye lens capsules that were collected 24 h postmortem. After extracapsular cataract extraction was performed, the bags were incubated in three types of solutions. The cells were then observed with photographic documentation for 28–30 days. In the control group, opacities formed on the lens capsule, leading to shrinkage of the capsule on days 3–5, which became more marked at the end of the observation period. No free or dead cells were observed in the surrounding fluid. In the group incubated with H-7, no PCO was detected during the observation period, whereas in the liquid medium, drifting free cells were visible (probably LECs that could not adhere to the capsule). Inhibition of growth of LECs on the capsule occurred at each drug concentration used. In the LAT-B group, the results varied according to concentration used. LECs were visible at a dose of 2 µM, some were visible, and some were not at a dose of 5 µM, and none were observed at a dose of 10 µM. There were no visible free cells floating in the medium in any subgroup. The differences in efficacy between the substances tested suggest that focal cell adhesion has a greater role than intercellular junctions in the formation of PCO. However, H-7 also inhibited wound healing in a rat cornea model [40], which would be an undesirable effect during postoperative recovery.

4.3. EGFR as a Potential Target for Prevention of PCO

The epidermal growth factor receptor (EGFR) is of interest to researchers because it activates cascades that play a key role in the formation of PCO [41][42]. Stimulation of this receptor activates the tyrosine kinase cascade, which alters gene expression and increases cell activity and growth. Erlotinib and gefitinib are EGFR inhibitors that were registered and approved by the US Food and Drug Administration in 2003 and 2004, respectively, for the treatment

of locally advanced or metastatic non-small cell lung cancer in combination with cisplatin and other cytostatic agents, and for advanced pancreatic cancer in 2007 [43].

The potential role of EGFR inhibitors in the prevention of PCO has been tested in vitro in human LECs (an HLE-B3 cell line) and spontaneously immortalized fetal cell line (an FHL-124 cell line) [40][41]. Their impact on the ability of these cells to proliferate, migrate, spread, and contract was investigated. At the same time, ex vivo observations were performed on human lens capsules. Cataract surgery was performed on the eyes of cadaveric donors 24 h postmortem. Pairs of collected anterior lens capsules were tested: one was incubated with a gefitinib/erlotinib solution and the other served as a control. Migration capacity was assessed as the ability of crystal violet-stained HLE-B3 cells to pass through a membrane with 8 µm pores and spread. PCO fundamentally involves proliferation of multiplied cells from the equator of the anterior lens capsule to the visual axis, which causes decrease in visual acuity. Both EGFR inhibitors decreased chemotactic migration, proliferation, and contractility of lens cells in vitro. In both cell culture and donor tissues, the migration of gefitinib-treated cells was prolonged from an average of 5.8 days to 10.6 days. Although no cytotoxicity was observed, these agents may cause trichomegaly, trichiasis, dysfunctional dry eye syndrome, and corneal ulceration with long-term oral administration.

4.4. In Vitro Research Involving Photodynamic Therapy

Culturing human tissue is the model closest to in vivo conditions and can provide information on migration, proliferation, and differentiation of LECs [21].

Photodynamic therapy with bacteriochlorin has been studied as a potential method for prevention of PCO. Bacteriochlorin is obtained from the photosynthetic bacterium *Rhodospirillum rubrum* and acts as a photosensitizing agent [44]. Both photodynamic therapy and bacteriochlorin are safe when used separately but have a damaging effect on cells when combined in the presence of oxygen. This treatment strategy has been successfully used in the treatment of skin cancer, esophageal and bladder cancer, and non-cancerous diseases, such as arteriosclerosis and rheumatoid arthritis [45].

In a study by Fisher et al. [45], 106 human eyes were collected ex vivo and subjected to extracapsular cataract extraction. In the experimental group, bacteriochlorin was administered at concentrations of 50, 25, 12.5, 10, 6.25, 3.12, and 1.6 µg/mL for 10, 8, 6, 4, or 2 min with irradiation using laser diode light at a wavelength of 760 nm for periods of 12, 10, 5, or 2 min. Control groups were treated with bacteriochlorin only or light only. After 7 days of tissue culture, LECs underwent histological evaluation. In the experimental group that was incubated with 10 µg/mL bacteriochlorin for 10 min followed by irradiation for 15 min, proliferation activity and cell growth on the lens capsule was completely inhibited. After 7 days, no formation or growth of LECs was observed. The cell nuclei did not show staining or chromatin condensation. However, there were visible signs of apoptosis, and the cytoplasm showed signs of severe disorganization. These features were also observed, but to a lesser extent, in cells exposed to lower concentrations of bacteriochlorin and irradiation for a shorter period. In the control groups, LECs developed as a compact layer and contained heterochromatin-packed and euchromatin-packed nuclei and a well-differentiated cytoplasm with many cell organelles. The toxicity of bacteriochlorin to corneal endothelial cells and

the ciliary body, as well as the duration of therapy, have yet to be established. Furthermore, the treatment period was extended by 25 min because this is the optimal application of both treatments. Bacteriochlorin could be administered as an intraoperative injection with application of light occurring after surgery.

4.5. Ex Vivo Tests with Heat Shock Protein 90

Heat shock protein (HSP)90 is known to be involved in the regulation of cell proteostasis in the presence of pathological factors. However, its role in PCO is not known. Li et al. [46] investigated the potential therapeutic use of HSP90 in PCO using an LEC line and an ex vivo rat lens capsule. Protein expression in response to application of tanespimycin (17-AAG), an HSP90 inhibitor, was assessed by immunoblotting and real-time polymerase chain reaction (RT-PCR) and apoptosis by the TdT-mediated dUTP nick-end labeling method. Tanespimycin was found to suppress the proliferation of LECs and to inhibit the viability of the LECs remaining in the capsule. Moreover, tanespimycin induced apoptosis, which was characterized by an increase in reactive oxygen species levels, apoptotic DNA damage, and activation of caspase-3 and caspase-9. HSP90 has been reported to play a role in regulation of the EGFR and TGF-β receptor (TGFR) signaling pathways. Inhibition of HSP90 by tanespimycin led to the destabilization of EGFR and inhibition of TGF-β-mediated phosphorylation processes [40][41]. These data suggest that stimulation of HSP90 protects the cells remaining in the epithelium of the lens capsule from oxidative stress and is also involved in the regulation of cell proliferation, EMT, and migration of rat LECs through the EGFR and TGFR signaling pathways. Therefore, treatment with tanespimycin suppresses PCO and may be a candidate agent for prevention of PCO [40][41].

While in vitro studies are valuable, not all pathways of proliferation and migration, or contraction of the lens capsule are reproducible under laboratory conditions. Moreover, PCO in humans and laboratory animals may be stimulated to different degrees postoperatively depending on the operative course [47]. Therefore, in vivo tests are required.

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