Adhesion study of cultured human lens capsule cells on hydrophilic intraocular lenses coated with polyethylene glycol

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PURPOSE: To evaluate the adhesion of human lens capsule cells on hydrophilic acrylic intraocular lenses (IOLs) coated with polyethylene glycol (PEG).

SETTING: Department of Ophthalmology, Faculty of Medicine, Universidade Estadual Paulista–Botucatu, São Paulo, Brazil.

DESIGN: Experimental study.

METHODS: Human anterior lens capsules obtained during cataract surgery were cultured and seeded (200 cells/IOLs) in triplicates on the surface of a copolymer comprising hydroxyethyl methacrylate, ethyl methacrylate, and methyl methacrylate IOLs (Loflex) treated or not treated with PEG. After 26 hours, the number of viable adherent cells was estimated by counting in a hemocytometer.

RESULTS: The coating of hydrophilic acrylic IOLs with PEG was effective in inhibiting cell adhesion ($P < .05$). Cells showing 2 distinct morphologic patterns—epithelial and dendritic-like—were observed during the in vitro establishment of the cultures. A tendency toward greater adhesion of dendritic-like cells was observed in untreated IOLs compared with treated IOLs ($P = .095$).

CONCLUSION: Coating hydrophilic acrylic IOLs with PEG was effective in inhibiting cell adhesion. This treatment might play a role in posterior capsule opacification prevention.

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Posterior capsule opacification (PCO) is one of the most frequent late complications of cataract surgery,[1] with an incidence of 40% or more up to 10 years after cataract surgery with hydrophobic acrylic intraocular lens (IOL) implantation.[2,3] Treating PCO with a neodymium:YAG laser capsulotomy is not a risk-free procedure, and it has been associated with significant economic and social implications.[4,5]

The pathogenesis of PCO begins with the adhesion followed by proliferation and posterior migration of residual lens epithelial cells (LECs) on the surface of the IOL across the visual axis.[6]

Studies have focused on the prevention of this condition through the development of IOLs with new materials, designs, and coatings. At present, several types of IOL materials and designs are in use, with hydrophobic acrylic the most commonly used because of its stability[7] and material properties that permit a precise manufacturing process[8] related to the lowest incidence of PCO.[3,9,10]

Hydrophilic acrylic IOLs were used in the present study because of the development of an alternative to hydrophobic acrylic material that could efficiently prevent PCO and thus might reduce costs. The objective of the present study was to compare the adhesion capacity of human lens capsule cells to hydrophilic acrylic IOLs coated or not (control) with polyethylene glycol (PEG).

MATERIALS AND METHODS

Primary Cell Cultures

Anterior capsules were collected from patients having phacoemulsification cataract surgery at Botucatu Medical

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School, Universidade Estadual Paulista–Botucatu, São Paulo, Brazil. The capsules were removed after creation of a continuous curvilinear capsulorhexis during cataract surgeries. The study was approved by the institutional human research ethics committee. Only patients who provided informed consent were included in the study. Patients with other ophthalmic diseases were excluded.

The biopsies were maintained in Dulbecco's modified Eagle's medium (nutrient mixture F-12, Gibco, Life Technologies Corp.) containing 20% fetal calf serum (Cultilab), penicillin (100 IU/mL), gentamicin (40 μg/mL), and amphotericin B (2 μg/mL) in a 24-well plate at 37°C in a humidified environment containing 5.0% carbon dioxide (CO_2). The cell cultures were examined daily for the observation of morphology and cell behavior (adhesion, migration, and proliferation), and fresh medium was added every 3 or 4 days until proliferating cells reached semiconfluence with a satisfactory number of cells defined by the observation of cells with high mitotic activity occupying approximately two thirds of the area of the well. These cells were used for the experimental study of cell adhesion to IOLs. Because 2 patterns of cell proliferation were observed, 5 human lens capsule cell cultures of each proliferation pattern (epithelial and dendritic-like) were evaluated independently.

Intraocular Lens Treatment

Treatment consisted of coating hydrophilic IOLs consisting of a copolymer of hydroxyethyl methacrylate, ethyl methacrylate, and methyl methacrylate (Loflex) with PEG. This treatment was done at the Plasma Laboratory at Universidade Estadual Paulista–Sorocaba, São Paulo, Brazil, inside a glass reactor at a pressure of −0.0045 Torr by applying radiofrequency energy at a power of 5 to 15 W for 30 to 50 minutes. Sulfur hexafluoride was applied in the same reactor for 15 minutes at a pressure of −0.0045 Torr and 150 W to analyze the change in the hydrophilicity of the IOLs submitted to ionic discharge, verifying the Teflon effect on the surface of the IOLs in repelling proteins and macrophages. The IOLs were then submitted to dry-heat sterilization in an autoclave for 20 minutes at 120°C inside their original package. Before use, the IOLs were hydrated in 1 mL sterile phosphate-buffered saline (PBS) for 48 hours. The control group consisted of the same hydrophilic IOLs untreated with PEG.

Evaluation of Cell Adhesion

The experiment was performed in triplicate with 3 treated IOLs and untreated IOLs tested per case. When the cells reached semiconfluence, the cultures were washed 3 times with PBS and trypsinized (Versene trypsin, Instituto Adolfo Lutz). Next, the cell suspensions were centrifuged and adjusted to a concentration of 1 cell/mL × 10^4 cells/mL. The IOLs were placed in 24-well plates, and 20 μL of the 1 cell/mL × 10^4 cells/mL cell suspension were added to the surface of each IOL (200 cells/28.26 mm^2). The plates were then transferred to a humidified incubator and maintained at 37°C in a 5.0% CO_2 atmosphere during 2 hours for cell adhesion. After this period, a nutrient medium with 20% fetal calf serum was added to each well. The culture plates were again transferred to the incubator and maintained for 24 hours at 37°C in a 5.0% CO_2 atmosphere. The nutrient medium was discarded, and the IOLs were carefully washed 2 times with PBS to remove unadhered cells. Finally, the IOLs were trypsinized and the cell suspension obtained was centrifuged. The pellets were resuspended and stained with trypan blue, and cells were counted in a hemocytometer in triplicate by the same expert observer (M.M.H.V.). To evaluate the reliability of the results, remaining unadhered cells on the supernatant of each culture wells were also counted.

Statistical Analysis

The data were analyzed by the nonparametric Mann-Whitney *U* test. A *P* value less than 0.05 was regarded as statistically significant.

RESULTS

Anterior lens capsules from patients having cataract surgery with a mean age of 68.6 years ± 15.54 (SD) (range 41 to 89 years) were cultured as explants, and 2 morphologic distinct patterns were observed in cultured cells. The cells growing in vitro showed a round morphology, as expected for epithelial cells, detaching from the capsule and proliferating (Figure 1, *A*). Alternatively, dendritic-like cells that first proliferated throughout the capsule and then migrated to the culture plate were also observed in several cases. When subcultured, these cells greatly increased in size, releasing dendritic prolongations (Figure 1, *B* and *C*).

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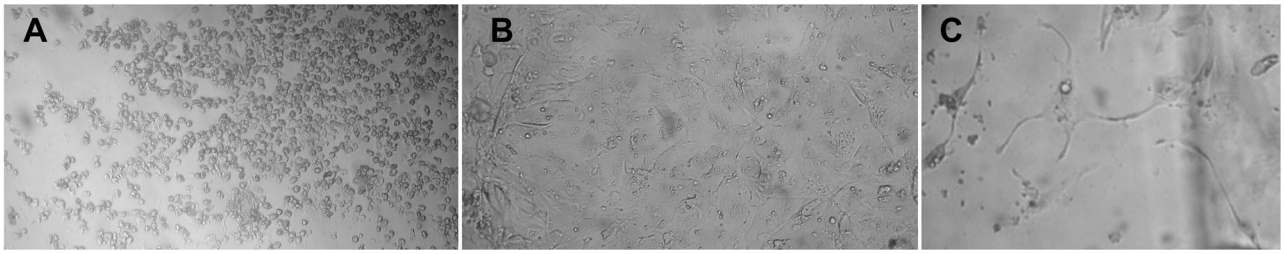

Figure 1. Human lens capsule epithelium specimens were obtained during cataract surgery and cultured in vitro. Distinct morphologic patterns were observed after establishment of cell cultures from anterior capsule biopsies: epithelial round morphology (*A*) and dendritic-like cells (*B* and *C*, for details of confluent and nonconfluent growing of dendritic-like cells) (bright-field phase contrast microscopy; original magnification ×10, ×20, and ×40).

To evaluate the adhesion properties of these human lens capsule cells, 5 cultures of each morphologic cell type were used in the study. In general, cell adhesion was lower for IOLs treated with PEG than for untreated control IOLs ($P < .05$) (Figure 2, *A*). When the morphologic differences were considered, it was observed that dendritic-like cells showed a trend toward adhering less to treated IOLs than to IOLs untreated with PEG ($P = .095$). The same tendency was not observed in the epithelial human lens capsule cells group ($P = .421$) (Figure 2, *B*). The count of unadhered cells remaining in the supernatant of each triplicate confirmed the results of the corresponding count of adhered cells in IOLs (Figure 2, *C*).

Although the mean age of both morphology types did not differ in this study, 2 patients from the dendritic-like group were 41 years old and 49 years old, while only individuals older than 60 years were found in the epithelial group.

DISCUSSION

The pathogenesis of PCO has been subject of extensive research in pathophysiology and molecular biology.[11,12] It is believed that the velocity of capsule contraction and the extent of capsule fibrosis reflect the responsiveness of anterior LECs to the biochemical properties of the optical material. Anterior capsule fibrosis after cataract surgery seems to be a response to capsule damage and to a foreign body, in this case the IOL. Concerning this process, the recruitment of anterior LECs for tissue repair and fibrosis production has been shown to be significantly inhibited with the use of hydrophobic acrylic and second-generation silicone IOLs with a square-edged design.[11] Recent studies to identify the best biomaterial have focused on IOL treatments that are able to potentiate the inhibition of cell adhesion, such as IOL coating with fibronectin,[13] alkylphosphocholines,[8] and the polymerization of the hydrophobic acrylic IOL surface with PEG, a hydrophilic polymer that reduces protein deposition and cell adhesion.[14–16]

Several factors are related to the formation of PCO, and alternative IOL shapes and materials are being tested in an attempt to prevent or reduce this condition. It is believed that hydrophobic acrylic and second-generation silicone prevent PCO by permitting intimate contact between the anterior and posterior capsules and the IOL, forming a physiologic barrier that inhibits cell migration through the phenomenon of contact inhibition.[17,18] These materials are much more effective than poly(methyl methacrylate) (PMMA). However, an in vitro study[19] found better adhesion and proliferation of human LECs on hydrophobic acrylic IOLs than on PMMA or silicone IOLs.

Although PCO is a multifactorial process that involves factors ranging from the surgical technique, IOL material or design, and postoperatively administered medications[20,21] to predisposing conditions of the patient,[12] the present study analyzed the response to hydrophilic acrylic IOLs coated with PEG in an attempt to prevent or minimize the adhesion of LECs to IOLs. Polyethylene glycol is a high-molecular-weight hydrophilic polymer that firmly adheres to the surface of the IOL; as a consequence, the remnant molecule is free to move, thus impairing the deposition of protein material and inflammatory cells.[14–16]

Because the use of cell lines for the study of PCO is controversial and the cell lines could not be representative of individual variability, primary cultures were therefore chosen in the present study. In addition, care was taken to use one half of the cell samples with epithelial morphology and one half with dendritic-like morphology because the latter probably corresponds to epithelial cells undergoing transdifferentiation to activated myofibroblasts which, theoretically, have a higher adhesion capacity.[12,22,23]

Two patients in the dendritic-like group were 41 years old and 49 years old, while in the epithelial group all were older than 60 years, Even though the mean age did not differ between both morphology types, this could suggest that younger individuals

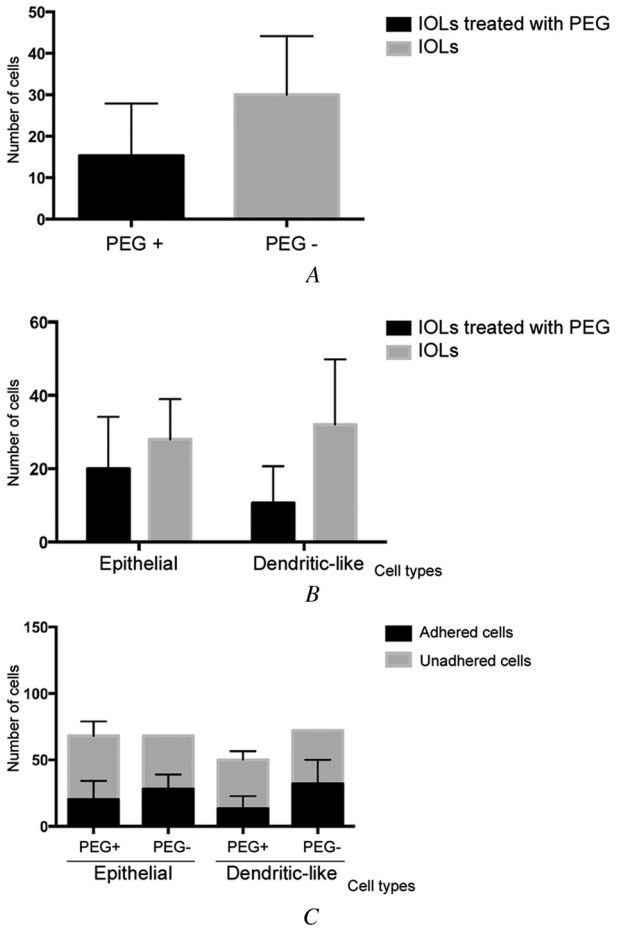

Figure 2. Cell adhesion assay on IOLs treated or not with PEG (PEG+ and PEG−, respectively). After in vitro proliferation, 200 cells were seeded on IOLs in triplicates. *A*: General comparison of cell adherence on treated IOLs and untreated IOLs ($P < .05$). *B*: Adherence assay of cells classified according to the morphologic pattern: epithelial or dendritic-like cells (for epithelial cells, $P = .421$ PEG+ versus PEG− IOLs; for dendritic-like cells, $P = .095$ PEG+ versus PEG− IOLs). *C*: Comparison of cell count between adhered cells to IOLs and unadhered cells remaining in the culture supernatant (IOLs = intraocular lenses; PEG = polyethylene glycol).

have a greater chance of developing transdifferentiation to activated myofibroblasts.

Significantly lower cell adhesion was observed for hydrophilic acrylic IOLs treated with PEG than for untreated IOLs. In another study using cell lines cultures,[14] coating hydrophobic acrylic IOLs with PEG successfully inhibited PCO in rabbit eyes during the first 7 weeks after surgery only. The present study was developed in parallel with an experimental study by the Veterinary Ophthalmology Sector of the Universidade Estadual Paulista using the same hydrophilic IOLs with PEG treatment in rabbit eyes.[24] That study evaluated PCO over 1 to 24 weeks after phacoemulsification with IOL implantation using image-analysis PCO software system (POCOman).[24,25] This study found an reduction in the intensity of PCO in the first weeks of evaluation with the treated IOLs. However, at the end of the experimental period, the severity of PCO was similar in the groups receiving IOLs coated or IOLs not coated with PEG, a finding that can be explained by the high potential of the rabbit lens for proliferation/regeneration.[26–30] However, this characteristic makes the rabbit appropriate as a PCO experimental model, allowing the study of capsular bag changes in a relativity short period of time because 6 to 8 weeks approximately corresponds to 2 years in human eyes[28] and 24 weeks would be 8 years in human eyes, a reasonable period considering that PCO develops before this time.

In general, cell adhesion was lower for IOLs treated with PEG than for untreated control IOLs ($P < .05$). This can be explained by the better distribution of the variability when considering the total cells regardless of their morphologic type, which enhanced the sensitivity of the statistical test. As expected, the adhesion comparison between the 2 types of cells (epithelial and dendritic-like) in the control group and treated group showed a higher tendency toward adhesion for dendritic cells ($P = .421$ versus $P = .095$, respectively). However, the count of remaining cells that did not adhere to the IOL showed fewer dendritic-like cells even in the supernatant medium; thus, the statistical significance of the general cell adhesion could be explained by both morphologic cell types, not just by the probably higher adhesion of the dendritic-like cells.

To our knowledge, no study has used cells with different phenotypes in primary cultures, an approach that permits one to test the capacity of different IOL materials to prevent the adhesion of human lens capsule cells already transdifferentiated into activated myofibroblasts, and the 2 cell patterns could reflect the intrinsic characteristics of each individual. That could explain why some patients develop severe PCO with capsule contraction and others with the same technique and same IOL model never develop any type of PCO.

Further studies are needed to access the transparency and immunogenicity of the treated IOLs and determine whether modifications in the method of IOL coating with PEG can potentiate the inhibition of cell adhesion to the surface of IOLs as well as how prolonged their time of action is. In addition, it would be important to evaluate the correlation between cell morphology and the patient's postoperative evolution of PCO as well as the association between patient age and the morphology of the cultured cells.

In conclusion, the coating of hydrophilic acrylic IOLs with PEG was effective in inhibiting cell adhesion, and this treatment might play a role in PCO prevention.

WHAT WAS KNOWN

- Better IOL biomaterial is still being studied in an attempt to prevent PCO with cost-effective strategies.

WHAT THIS PAPER ADDS

- Coating with PEG in hydrophilic acrylic IOLs inhibited human lens capsule cell adhesion on the IOL surface ($P < .05$).
- New studies are necessary to identify the origin of the dendritic-like cells and to study the association with PCO.

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