Pathology of the Iridocorneal-Endothelial Syndrome

The ICE-Cell

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Purpose. The iridocorneal-endothelial (ICE) syndrome is characterized by glaucoma, corneal failure, and iris destruction. Specular photomicroscopy of the corneal endothelium in this disease shows a population of abnormal cells named ICE-cells. Comparison between ultrastructural examination and specular photomicroscopy demonstrates that the histologic equivalent of ICE-cells are cells with an epithelial phenotype. The authors have studied the differentiation markers expressed by ICE-cells using an ultrastructural immunocytochemical technique.

Methods. Seven keratoplasty specimens from patients with the ICE syndrome were examined by scanning and transmission electron microscopy and light and electron microscopic immunocytochemistry. Comparison was made with three normal corneas. Immunocytochemical studies were performed with monoclonal antibodies to broad-spectrum cytokeratins, cytokeratins 3, 5/8, 8/18 and 19, vimentin, and epithelial membrane antigen.

Results. ICE-cells were morphologically similar to epithelial cells and expressed the same profile of differentiation markers as did normal limbal epithelial cells.

Conclusions. ICE-cells may arise from an embryologic ectopia of ocular surface epithelium. Alternatively, these findings are consistent with a metaplastic stimulus resulting in a profound change in the phenotype of normal corneal endothelial cells. Invest Ophthalmol Vis Sci. 1995; 36:2592-2601.

The iridocorneal-endothelial syndrome (ICE syndrome) is a disease of the ocular anterior segment characterized by a "hammered-silver" appearance of the corneal endothelium, corneal failure, glaucoma, and iris destruction. Specular photomicroscopy of the corneal endothelium has contributed greatly to our understanding of the ICE syndrome. Legacie, 1-5 These studies have demonstrated a population of abnormal cells named ICE-cells. 4 ICE-cells are said to be unique to this disease and are observed in every patient except those whose corneal edema is sufficiently severe as to preclude examination. 4 ICE-cells are larger and more pleomorphic than normal, and their specular reflex shows "light–dark reversal"; the cell surface is dark instead of light, often with a central light spot, and the intercellular borders are light instead of dark. In some patients, the normal endothelial mosaic is replaced completely by ICE-cells (total-ICE) while in others some areas of the endothelium are occupied by ICE-cells and the remainder by normal cells (subtotal-ICE). 4

Ultrastructural studies of the endothelium of ICE syndrome keratoplasty specimens have shown a population of cells with epithelial features such as desmosomes, tonofilaments, and microvilli. 5-14 Ultrastructural examination of corneas shown by specular photomicroscopy to have a subtotal ICE pattern of cell distribution 5,12,13 demonstrates that these epithelial cells are the histologic equivalent of the ICE-cell; cells that are morphologically similar to those of normal corneal endothelium are the histologic equivalent of the normal cells seen by specular photomicroscopy alongside ICE-cells.

The results of studies on the expression of differentiation markers by the endothelial cells of corneas
Characteristics of the ICE-Cell

TABLE 1. Clinical Details of Patients With the ICE Syndrome

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<th>Patient/Cornea Number*</th>
<th>1</th>
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</tr>
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</table>

*One cornea was available from each patient.
†Age at which surgery was undertaken.
Uni = unilateral disease; Bi = bilateral disease; PK = penetrating keratoplasty; Redo PK = repeat penetrating keratoplasty.

with the ICE syndrome have varied. Cytokeratins (CKs) were identified in three corneas; in two corneas, CKs were absent; and in one cornea, vimentin was identified and CKs were absent. These inconsistencies may have arisen from the light microscopic immunocytochemical techniques that were used because the resolution attained by light microscopy is insufficient to distinguish between the different endothelial cell types in this condition.

In the current study, we used an ultrastructural immunocytochemical technique to investigate the differentiation markers expressed by the ICE-cells and normal cells of ICE syndrome corneal endothelium. The differentiation marker profiles of these cellular populations were compared with those of normal corneal tissues.

MATERIALS AND METHODS
Criteria for Inclusion of Patients With the ICE Syndrome

Patients were included in the study when they had clinical signs and specular photomicroscopic appearances typical of the ICE syndrome (Table 1). All had the "hammered-silver" appearance of the corneal endothelium, peripheral irido-corneal synechiae, and various combinations of corneal edema—sometimes at normal or minimally elevated intraocular pressure—glaucoma, and signs of iris disease such as atrophy and nodules. Specular photomicroscopy showed subtotal-ICE (i.e., ICE and normal cells were present) in all patients included in this study, except for patient 7 who had total-ICE (i.e., only ICE-cells were seen).

To avoid the inadvertent inclusion of patients with disorders such as posterior polymorphous dystrophy or Fuchs' endothelial dystrophy, subjects were excluded if any one of the following criteria applied: onset at 10 years of age or younger; family history of a similar disorder; widespread guttate or vesicular-geographic lesions of the corneal endothelium; any preceding major ocular disorder, surgery, or penetrating/severe trauma (except filtering surgery necessitated by the ICE syndrome process itself). Bilateral disease is well documented and was not considered a reason for exclusion.

Specimens
ICE Syndrome Corneas. Seven corneas taken from patients with the ICE syndrome at the time of penetrating keratoplasty were divided into quarters. Portions were assigned randomly to scanning or transmission electron microscopy and light or electron microscopic immunocytochemistry and were processed immediately. Correlation between specular photomicroscopy and ultrastructural examination was not attempted.

The ultrastructural appearances of all the corneas were examined by scanning and transmission electron microscopy. Electron microscopic immunocytochemistry was performed on all the corneas on tissue embedded in Lowicryl K4M resin (Agar Scientific, Stansted, UK). Light microscopic immunocytochemistry was performed on all the corneas on tissue embedded in paraffin wax and on one cornea on unfixed frozen tissue.

Normal Corneas. Three normal human corneas
from adult donors (ages 41, 52, and 59 years) were obtained from an eye bank. The time between enucleation and processing did not exceed 18 hours.

The ultrastructural appearances of the corneas were examined by scanning and transmission electron microscopy. Light microscopic immunocytochemistry was performed on portions of the corneas that had been either embedded in paraffin wax or frozen without fixation. Electron microscopic immunocytochemistry was not performed on normal corneas. The methods used to obtain human tissue complied with the tenets of the Declaration of Helsinki.

Transmission and Scanning Electron Microscopy
Specimens were prepared for transmission electron microscopy by fixation in 3% glutaraldehyde, postfixation in 2% osmium tetroxide, dehydration, and embedding in Spurr's resin. Ultrathin sections were stained with alcoholic uranyl acetate and Reynold's lead citrate.

Specimens were prepared for scanning electron microscopy by fixation in 3% glutaraldehyde, dehydration, critical point drying, and gold sputter coating.

Primary Antibodies
Antigens were examined with commercial monoclonal antibodies raised in mice (Table 2). For electron microscopic immunocytochemistry, antibodies to broad-spectrum CKs, CKs 8/18, CK 19, vimentin, and epithelial membrane antigen (EMA) were applied to Lowicryl K4M-embedded tissue. The antibodies to CK 3 and CKs 5/8 were not suitable for use with Lowicryl K4M.

For light microscopic immunocytochemistry, antibodies to broad-spectrum CKs, CKs 5/8, CKs 8/18, CK 19, vimentin, and EMA were applied to paraffin wax-embedded tissue. Antibody to CK 3 was applied to unfixed frozen tissue because it was unsuitable for use with paraffin wax-embedded tissue.

Electron Microscopic Immunocytochemistry
Specimens were fixed in 4% paraformaldehyde in 0.1 M phosphate buffer, pH 7.2, for 4 hours at 4°C and then processed into Lowicryl K4M resin as previously described. Ultrathin sections containing the endothelium

![FIGURE 1. Cornea number 1. Electron micrograph of routinely processed tissue to show desmosomes, tonofilaments, and microvilli in ICE-cells. Magnification, x17,000.](http://iovs.arvojournals.org/pdfaccess.ashx?url=data/journals/iovs/933408/)
Characteristics of the ICE-Cell

FIGURE 2. Cornea number 2. Scanning electron micrograph showing the subtotal-ICE pattern. ICE-cells (left) are coated by microvilli. The surface of the normal endothelial cells (right) is smooth and bears a round elevation from the nucleus. Magnification, ×2,800.

and immediately adjacent stroma were collected on uncoated 700-mesh nickel grids. The immunogold technique was carried out by immersing the grids in drops of the following solutions at room temperature: 1% ovalbumin in modified phosphate-buffered saline (PBS) for 25 minutes, primary antibody in PBS for 2 hours, washes in 10 drops of PBS over 10 minutes, gold-conjugated secondary antibody in PBS for 1 hour, washes in 5 drops of PBS over 10 minutes, and 2.5% glutaraldehyde in nonmodified PBS for 3 minutes. Grids were then jet-washed in distilled water and stained in saturated uranyl acetate in 50% ethanol for 20 minutes, followed by Reynold’s lead citrate for 3 minutes. (The modified PBS contained 0.1% bovine serum albumin, 0.02 M sodium azide, and 0.05% Tween 20). The immunogold technique was carried out on three ultrathin sections for each of the antigens examined.

The secondary antibody was goat anti-mouse IgG and IgM (EM. GAF 10; Biocell Research Laboratories, Cardiff, UK).

Light Microscopic Immunocytochemistry

Portions of cornea were either fixed in neutral buffered formalin and processed in paraffin wax or frozen without fixation in liquid nitrogen. Light microscopic immunocytochemistry on thick sections was carried out with the avidin–biotin–complex technique (Vector, Peterborough, UK).

Controls

The controls used for light and electron microscopic immunocytochemistry were: omission of the primary antibody; substitution of the primary antibody with monoclonal antibody to amyloid A component (M759; Dako, High Wycombe, UK) (amyloid was shown by congo red staining to be absent from ICE syndrome and normal corneas); similarly processed human tissue known to contain the antigen was used as a positive control (Table 2).

RESULTS

Transmission and Scanning Electron Microscopy

ICE-cells were present on all the specimens on the portions processed for routine ultrastructural examination (Figs. 1, 2). They were larger than normal endothelial cells. Their surfaces bore numerous microvilli and sometimes blister-like blebs. Intercellular

FIGURE 3. Cornea number 6. Normal endothelial cells on iridocorneal–endothelial syndrome corneas are devoid of microvilli, desmosomes, and tonofilaments and resemble the endothelial cells of normal corneas. Electron micrograph of routinely processed tissue. Magnification, ×18,000.
TABLE 3. Electron Microscopic Immunocytochemistry on ICE Syndrome Corneal Endothelium

<table>
<thead>
<tr>
<th>Cornea Number</th>
<th>Cell Type</th>
<th>Antibody</th>
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<tr>
<td></td>
<td></td>
<td>CK-BS</td>
</tr>
<tr>
<td>1</td>
<td>Normal</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>ICE cell</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>Normal</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>ICE cell</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>ICE cell</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>Normal</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>ICE cell</td>
<td>+</td>
</tr>
</tbody>
</table>

CK-BS = broad spectrum cytokeratins.

junctions consisted of numerous desmosomes. Internally, there were conspicuous tonofilaments and intermediate filaments, and the heterochromatin of the nucleus was dispersed. ICE-cells were either monolayered or else formed multilayers of up to five cells.

Normal cells were present on three specimens (numbers 2, 4, and 6) on the portions processed for routine ultrastructural examination (Figs. 2, 3). They formed a monolayer. Their surfaces were devoid of microvilli, and scanning electron microscopy showed a round elevation, presumably from the underlying nucleus. Internally there were no tonofilaments and fewer intermediate filaments than in ICE-cells, and the nuclear heterochromatin tended to be marginated.

FIGURE 4. Cornea number 5. Low-magnification electron micrograph of ICE-cells demonstrating intracellular reactivity with antibody to broad-spectrum cytokeratins (arrow shows desmosome). Lowicryl K4M-embedded tissue. Magnification, ×53,000.
Characteristics of the ICE-Cell

Intercellular junctions consisted of apically located tight junctions but no desmosomes. These cells resembled the endothelial cells of the normal corneas used as controls although departures from normal morphology sometimes were seen, e.g., the presence of large intracellular vacuoles.

The stroma and epithelium of the ICE syndrome corneas were unremarkable except for appearances suggestive of scarring and edema.

The morphology of the normal corneas used for comparison was similar to that in a previous report.

Electron Microscopic Immunocytochemistry on ICE Syndrome Corneal Endothelium

ICE-cells readily were distinguished from normal cells at the ultrastructural level by the presence of epithelial features such as desmosomes, tonofilaments, and microvilli, and it was therefore possible to identify which differentiation markers were expressed by the two cell types (Table 3).

In two of the specimens, the appearances were of subtotal-ICE (ICE-cells and normal cells were present). Ultra thin sections cut from these specimens included both cell types, permitting direct comparison of their profile of differentiation markers.

ICE-cells were present in four specimens. They expressed broad-spectrum CKs (Figs. 4, 5), CK 19 (Fig. 6), and EMA (Fig. 7). Antibody to EMA specifically labeled the apical cell surface, including microvilli, while the signal for CKs was localized to intracytoplasmic intermediate filaments. CKs 8/18 and vimentin were absent.

Normal cells were present in five specimens. They expressed vimentin, which was localized to intracytoplasmic intermediate filaments (Fig. 8), but not CKs or EMA.

Light Microscopic Immunocytochemistry on ICE Syndrome Corneas

It was not possible to distinguish ICE-cells from normal cells at the light microscopic level on the basis of their morphology. Staining of serial sections from seven specimens showed four that were positive for broad-spectrum CKs and CKs 5/8 (Fig. 9) and three that were negative for both (Table 4). Serial sections from one specimen were positive for broad-spectrum CKs and negative for CK 3 (Table 4). Results for the stroma and epithelium were similar to those for normal corneas.

Light Microscopic Immunocytochemistry on Normal Corneas

The same staining pattern was observed in all three normal corneas (Table 5). Results for the distribution of vimentin and CKs were consistent with previous reports. EMA was absent except from limbal epithelium, where a weak signal was observed predominantly in superficial cell layers (Fig. 10).

Controls for Electron and Light Microscopic Immunocytochemistry

Immunostaining in negative controls was almost absent. Conversely, the positive controls demonstrated...
strong and specific signal localized to appropriate regions of the tissue.

DISCUSSION

Electron microscopic immunocytochemistry demonstrates that ICE-cells express EMA, broad-spectrum CKs, and CK 19 but not CKs 8/18 or vimentin. Additional findings from light microscopic immunocytochemistry are that these cells express CK 5 but not CK 3; even though their characteristic morphology is not resolved at the light microscopic level, staining of serial sections shows that ICE-cells, which react with the antibody to broad-spectrum CKs, are positive for CK 5 and negative for CK 3. The antibody to CK 5 also reacts with CK 8, but ICE-cells are shown to be negative for CK 8 by electron microscopic immunocytochemistry. ICE-cells were absent from corneas 1, 3, and 6 in the sections used for both electron and light microscopic immunocytochemistry, perhaps because, in these subtotal-ICE specimens, ICE-cells were not present in the regions processed for immunocytochemistry.

ICE cells are morphologically similar to epithelial cells and express the same profile of differentiation markers as do normal limbal epithelial cells. These findings are compatible with two explanations for the origin of ICE-cells. One is that they arise from a heterotopia, i.e., an embryonic ectopia, of ocular surface epithelium. Alternatively, they may result from a metaplasia of normal corneal endothelial cells to an epithelial phenotype in response to a noxious stimulus.

Metaplasia is consistent with the typical age of onset of the ICE syndrome, which is a disease of adulthood. However, although various stimuli may be followed by a metaplastic change of corneal endothelial cells to fibroblasts, there are no known causes of metaplasia of these cells to an epithelial phenotype. In particular, neither glaucoma nor uveitis induces this change. Nonetheless, reports in which DNA sequences specific for herpes simplex virus type 1 were identified in ICE syndrome corneas or in which elevated levels of antibodies to Epstein–Barr virus were
Characteristics of the ICE-Cell

TABLE 4. Light Microscopic Immunocytochemistry on ICE Syndrome Corneal Endothelium

<table>
<thead>
<tr>
<th>Cornea Number</th>
<th>CK-BS (Paraffin Tissue)</th>
<th>CKs 5/8 (Paraffin Tissue)</th>
<th>CK-BS (Frozen Tissue)</th>
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CK-BS = broad spectrum cytokeratins.

shown in patients with the ICE syndrome, raise the possibility that ICE-cells represent a metaplastic response of endothelial cells to viral infection.

It seems possible that heterotopia could result from the complex events of ocular anterior segment morphogenesis because these include the infolding of surface ectoderm to form the lens and a period during which corneal epithelia and endothelia are in direct contact with each other. There are precedents for this type of pathology because dermoid cysts of the iris sometimes develop. Heterotopia might be expected to manifest itself earlier than at the typical age of onset of the ICE syndrome; however, a prolonged period between initial insult and the onset of clinical disease could result from there being a small number of ectopic cells or from a low mitotic rate of these cells. Alternatively, a trigger—perhaps some other ocular pathology, such as a viral infection—might be required to begin proliferation. This would offer an alternative explanation for the reports of herpes simplex and Epstein–Barr viruses.

Other explanations for the origin of ICE-cells seem unlikely. There is no normal cell population in the ocular interior with a similar phenotype from which neoplasia, hyperplasia, or a hamartomatous malformation might originate. They cannot result from displacement of ocular surface epithelium caused by drainage surgery because they are observed by specular photomicroscopy at the onset of clinical disease. Microvilli and blebs are manifestations of corneal endothelial cell division and migration, raising the possibility that the ICE-cell phenotype results from these aspects of endothelial cell behavior. However, this explanation is not in keeping with other ICE-cell characteristics, such as abundant desmosomes and intermediate filaments, or with their epithelial profile of differentiation markers.

Extracorneal disease in the ICE syndrome probably results from the spread of ICE-cells onto the iris and trabecular meshwork. An abnormal layer of ICE-cells covering these tissues has been demonstrated in a report on the ultrastructure of the ICE syndrome. Involvement of tissues contiguous with the endothelium may result from the epithelial nature of ICE-cells because epithelial cells may be "programmed" to movement and proliferation when present in the interior of the eye; this behavior is evidenced by epithelial ingrowth after surgery. However, our finding that ICE-cells express CK 19 offers another explanation for their spread. In normal eyes, CK 19 is expressed strongly by limbal epithelium and is largely absent from corneal epithelium; CK 19 may be a marker for corneal epithelial stem cells situated within the limbus rather than in the basal cell layer of the

TABLE 5. Light Microscopic Immunocytochemistry on Normal Corneas

<table>
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<th>Antibody</th>
<th>Corneal Endothelium</th>
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CK-BS = broad spectrum cytokeratins.

* This region included immediately adjacent conjunctival epithelium.
corneal epithelium itself. Expression of CK 19 may indicate that ICE-cells are intrinsically similar to limbal stem cells in that they and/or their progeny possess the capacity to undergo mitosis and movement.

The morphology and the differentiation marker profile of the normal cells of ICE syndrome corneal endothelium are similar to those of the endothelial cells of normal corneas—both express vimentin but not EMA or CKs. These cells are, therefore, different from ICE-cells and may indeed be normal corneal endothelial cells. In previous studies of this disease, cells that are abnormal but do not have epithelial features are described. Some of the cells classified as normal in our specimens have abnormal features such as intracellular vacuoles; these may be equivalent to the abnormal cells described in earlier reports.

In summary, the characteristics of ICE-cells suggest that this abnormal cell population, which may be of central importance in the pathology of the ICE syndrome, derives from either heterotopic or metaplastic processes. Further research on this condition should seek to increase our knowledge of these cells.

Key Words
corneal endothelium, electron microscopic immunocytochemistry, ICE-cell, intermediate filaments, iridocorneal–endothelial syndrome

Acknowledgments
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