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Article

Injectable Corneal Endothelial Cells

The potential transformation of the management of endothelial cell failure

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A common theme runs through all the recent advances in endothelial keratoplasty (EK), be it Descemet's stripping automated endothelial keratoplasty (DSAEK), Descemet's membrane endothelial keratoplasty (DMEK), or nanothin DSAEK (NT-DSAEK). The less tissue transplanted, the faster the recovery, the less risk of rejection, and the better the postoperative visual recovery. (See "Background," below.) However, when less tissue is used to carry the corneal endothelial cells (CEC), the more technically challenging the procedure becomes, resulting in the slower adoption of superior methods. The good news: The development of injected cultured CECs may be the ideal endothelial cell transplant to replace primary CEC failure.

Here, we explain the benefits, technique, mechanism, safety and efficacy of injected cultured CECs.

Benefits

Injected cultured CECs remove the need for a carrier when reestablishing a healthy endothelial cell count, and restore a high CEC density without altering the normal corneal curvature. This allows for optimal postop visual outcomes.

Additionally, the lack of a CEC carrier eliminates the risk of graft detachment and decreases the risk of rejection. Further, this therapy is not technically challenging, which lowers the barrier for widespread adoption. In early clinical studies, injected CECs have been used to replenish endothelial cells in Fuchs' endothelial corneal dystrophy, pseudophakic bullous keratopathy, pseudoexfoliation syndrome keratopathy and corneal graft failure.[6]

Technique

Donor cell preparation consists of isolating CECs with multiple steps of cultivation to ensure high-quality cell characteristics. In brief, the CECs are isolated by stripping Descemet's membrane, followed by enzyme treatment to remove the collagen matrix. These cells undergo analysis to confirm their biological characteristics and to verify criteria for surgical use.

The cells are stored in media that maintain the cells' biochemical characteristics. Prior to injection, the cell suspension is supplemented with a Rho-associated protein kinase (ROCK) inhibitor.

The recipient eye is prepared by mechanically removing abnormal extracellular material and degenerated CECs on Descemet's membrane in the central 8 mm diameter area of the cornea. This is performed with a silicone cannula through a 1.6 mm incision at the corneal limbus under local anesthesia. A total of $1x10^6$ CECs are injected with a syringe into the anterior chamber. The patient is then required to lay face-down for three hours to encourage CECs to settle on the inner cornea, and allow for cell adhesion. Postoperative care includes topical steroids and prophylactic antibiotics.[6]

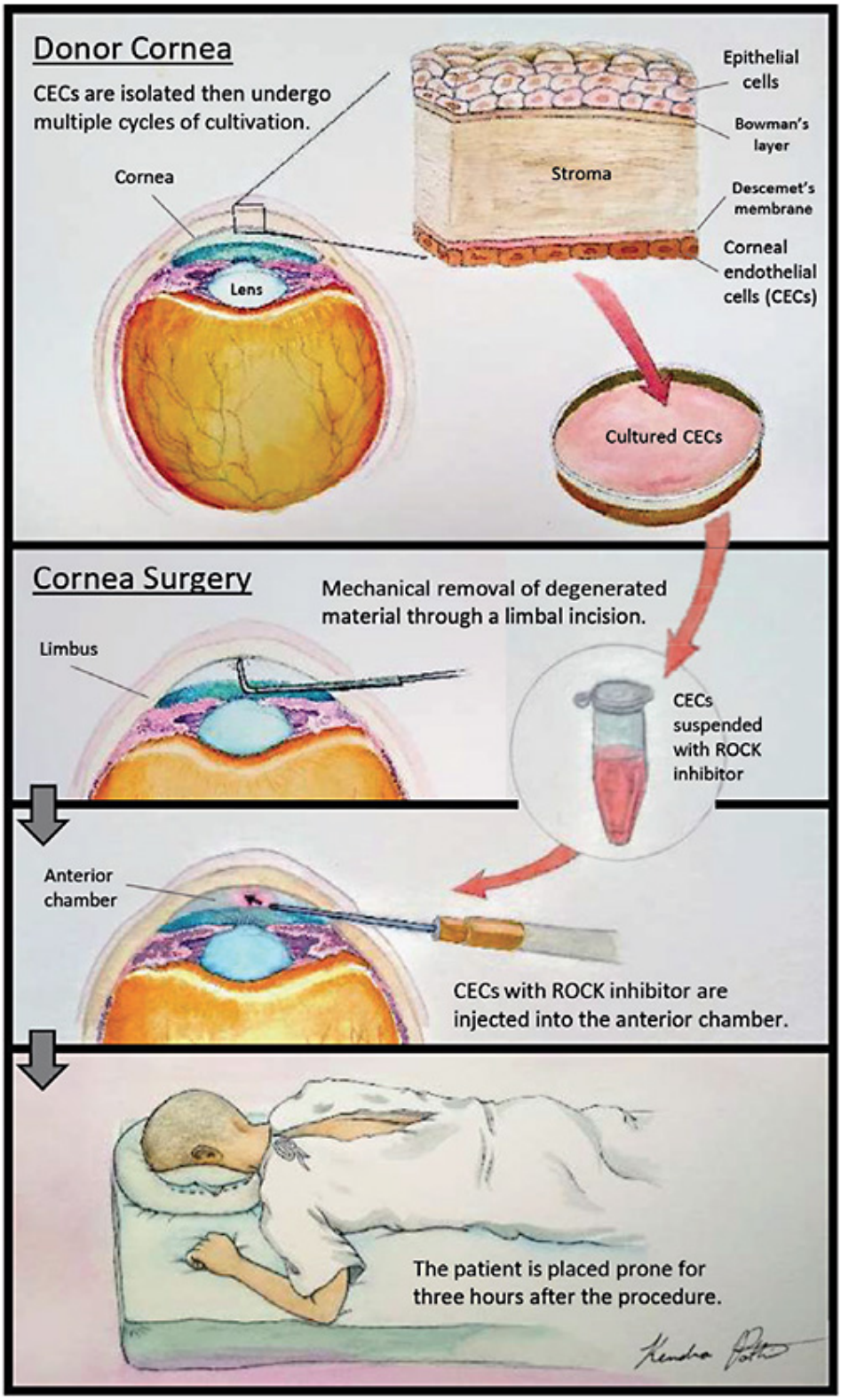
Mechanism

Face-down positioning promotes the migration of CECs toward the inner corneal surface. Adhesion of the CECs is promoted by ROCK inhibition through the suppression of the Rho/ROCK/MLC (myosin light chain)-signaling cascade. Without the ROCK inhibitor, the dissociated cells contract due to actin cytoskeleton activation, which leads to a significant decrease in the cell surface area. Further, when actin contracts, this leads to a decrease in focal adhesion complexes that are necessary for cell adhesion. Therefore, ROCK inhibition promotes cell adhesion with a dual approach of preventing cell contraction by relaxing actin and by increasing focal adhesion complexes that promote CEC adhesion to the inner corneal surface.[7]

BACKGROUND

The past two decades have seen significant improvements in EK in the search for the ideal treatment for CEC failure. The ideal treatment would restore proper corneal function and visual acuity, while having a low failure and rejection risk. Prior to 2000, nearly all CEC failure was treated with PK.[1] The early pioneers of EK worked to create thinner grafts, as these were shown to provide a faster recovery, less rejection risk and better visual recovery.

With the introduction of Descemet's membrane endothelial keratoplasty (DSEK) in 2004 and then DMEK in 2006, the number of EKs performed in the U.S. surpassed PKs by 2011.[2-5] This was followed with the introduction of ultra-thin DSAEK (i.e. UT-DSAEK) and then by NT-DSAEK.



Face-down positioning promotes the migration of CECs toward the inner corneal surface.

Safety

In 2018, Kinoshita et al. published the first clinical study on the safety of cultured CECs. The researchers evaluated the potential for injected CECs to cause IOP elevation secondary to cells migrating through the trabecular meshwork. They reported no perioperative IOP elevation or any abnormal collection of CECs, with the exception of one patient at 8 months follow-up. This elevation was attributed to steroid-induced glaucoma, due to the timing of the increased pressure and no trabecular meshwork abnormalities.

In the 5-year follow-up period, no other IOP elevations were observed. Additionally, this long-term observational follow-up showed no allogenic immune reaction or anterior uveitis development in any of the eyes undergoing CEC injection therapy.[8]

Questions regarding the potential for CECs to pass through the trabecular meshwork into systemic circulation through the episcleral venous drainage was investigated. This was addressed with early animal studies that tracked CECs by fluorescein-labeled tracing and polymerase chain reaction, which did not find evidence of spread to the multiple organ systems evaluated.[7] Since 40% to 50% of injected CECs adhere to the cornea, it is thought the remaining cells are removed by the host immune system or through autophagy.

Efficacy

Recently, long-term observational data have been published that provide support to the efficacy of injected cultured CECs. In the initial clinical cohort, the inclusion criteria required no CECs on specular microscopy, a central corneal thickness (CCT) greater than 630 µm, the presence of epithelial edema and a best-corrected visual acuity (BCVA) worse than 20/40 (Snellen).[6]

In 2020, Numa et al. reported that at 5 years, 90.9% (10/11) of eyes maintained a CEC count of more than 500 cells/mm^2. Of these, 80% (8/10) had a CEC count of greater than 1000 cells/mm^2. An improvement in the CEC hexagonality and a decrease in cell variability was observed over time, which indicates the cells continued to stabilize over the 5-year period. In these same patients, the CCT was less than 590 µm in 90.9% (10/11) of eyes. The 5-year vision outcomes were a BCVA of 20/40 maintained in 90.9% (10/11) of eyes. Of these, 80% (8/10) had a BCVA of 20/25 or better, with 60% (6/10) better than 20/20. These initial results are equivalent with previously reported outcomes for DSAEK and DMEK.[8]

A Promising Solution

The latest long-term data is promising, showing that injected cultivated CECs have comparable clinical outcomes to traditional EK. Another advantage of cultured CECs is that a single donor cornea can provide enough high-quality CECs for multiple recipients. Early clinical studies show the injection of cultivated CECs holds promise to be the ideal treatment for endothelial failure that can restore proper corneal function, has low complications and is easy to implement. It is currently undergoing further FDA clinic trials. **CP**

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