Stem Cell Therapy May Someday Replace Corneal Transplants

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Stromal (mesenchymal) stem cells from patients' own eyes may replace corneal transplants, suggests a study published in the December 10 issue of Science Translational Medicine.

Sayan Basu, MD, from L. V. Prasad Eye Institute in Hyderabad, India, and colleagues have been working with mesenchymal/stromal corneal stem cells for a decade. The cells, from the limbus area, can regenerate wounded corneas in mice more deeply than can other populations of limbal stem cells that have already been through clinical trials.

Complex Cellular Landscape of the Cornea

The limbus, a thin transitional zone between the clear cornea and the opaque sclera, keeps blood vessels and conjunctiva from growing onto the cornea. It includes a basal fibroblast layer, several types of epithelium, and stem cells.

"The cornea is more complex than most people realize. The outer surface is a layer of self-renewing epithelium. A resident population of stem cells supplies epithelium as they move towards the center and slough off, like the epithelium of skin. Most papers and work on the cornea, when they mention stem cells, are talking about these resident epithelial stem cells," James L. Funderburgh, PhD, a professor of ophthalmology, cell biology, and physiology and associate director, Fox Center for Vision Restoration, at the University of Pittsburgh School of Medicine in Pennsylvania, told Medscape Medical News. He is corresponding author of the new study.

The limbal stem cells described in the new report are different in that they regenerate the stroma of the cornea, which is connective tissue. "Epithelial corneal limbal stem cells regenerate the surface of the cornea, but they do not repair deeper scarring. The way to fix that is a corneal transplant," according to Jeffrey Stern, MD, an ophthalmologist and director of translational research at the Neural Stem Cell Institute in Rensselaer, New York.

From Resurfacing to Regenerating

Epithelial limbal stem cells can repair corneas and restore vision in people with limbal stem cell deficiency, which is uncommon. Causes include rare genetic

conditions, an inflammatory response such as graft versus host disease, infection, adverse effects of cancer treatments, chemical or thermal burns, or pterygium ("surfer's eye").

"Once there's deeper scarring, those limbal cells aren't useful. The new work broadens the potential ability to repair wounded corneas," Dr Stern said. He described the effect of epithelial stem cells as resurfacing, rather than regenerating. Cases of damage extending down to the connective tissue outnumber epithelial cases 100 to 1, Dr Funderburgh said.

The researchers observed the stromal stem cells regenerate corneal tissue in a dish and replicated the findings in mice. But is there a market for autologous deep cornea repair when transplants are readily available? Annually in the United States, 40,000 people receive corneal transplants, but that is not true elsewhere.

"Dr Virender Sangwan, head of the Hyderabad Eye Research Foundation in India, came up to me at a meeting and said, 'a million people in India with corneal scarring can't get transplants,' " Dr Funderburgh said. The groups in the United States and India had been unknowingly zeroing in on the same population of stem cells that regenerate stroma, rather than epithelium.

"Dr Sangwan wanted to work with one of our folks to develop and grow these peoples' own stem cells and give them back to them," Dr Funderburgh explained. In addition to India's lack of an effective tissue donation system, he added, untreated bacterial infections cause many cases of corneal scarring there.

Nurturing and Applying Stromal Stem Cells

The researchers obtained limbal cells from four people undergoing conventional corneal transplants and used specific proteases to isolate stromal cells, which they then expanded in culture. The stem cells persisted, as stem cells do. Initial in vitro studies demonstrated that the cells expressed pluripotency markers, formed spheres in the absence of substrate, and aligned with secreted extracellular matrix along a nanofiber substrate, resembling healthy three-dimensional corneal stroma.

The researchers applied 50,000 stem cells to debrided eyes of mice. Four weeks later, the eyes showed no evidence of inflammation or rejection. They were producing components of normal transparent stromal extracellular matrix (human keratocan and type 1 collagen), and not the proteins that cause the light-scattering characteristic of vision-impairing scars.

Photographs confirmed the absence of scars in the treated eyes, optical coherence tomography indicated lack of light scatter, and transmission electron micrography revealed the highly ordered extracellular matrix that enables light to enter and become focused. "Fibril order is important because it equates roughly to clarity," said Dr Stern.

Straightforward Clinical Procedure

Autologous cornea regeneration will take two stages, said Dr Funderburgh. "A patient comes in and has a biopsy taken from the limbal region, a 2 mm by 2 mm snip of tissue not in the light pathway. It heals quickly, without a lot of discomfort. Then it takes 2 to 3 weeks to grow stem cells out from the biopsy."

The patient returns for a simple outpatient procedure. "The surface of the eye is scraped to remove the epithelial cells, then stem cells are dripped on in a fibrin gel, which holds it onto the surface, and then a contact lens bandage is put on," Dr Funderburgh said.

Clinical trials could begin in the United States within 3 years, Dr Funderburgh hopes, perhaps skipping a large animal study because a phase 1 clinical trial is ongoing in India. "There seems to be very low risk of rejection because the cells are from the patient and grown in the patient's serum," Dr Funderburgh said. Nor is stem cell treatment as invasive as a full-thickness transplant.

"There's an enormous number of patients with corneal stromal scarring in the deeper layer, and the only current treatment is corneal transplant or artificial cornea prosthetic. The hope is that these cells put in the stroma can repair the scars," Dr. Stern concluded.

Limitations of the investigation include not assessing the relationship between the number of stem cells delivered to the wound and speed or degree of healing, whether the cells can replace old scars, and the mechanism of regeneration.

The researchers and Dr Stern have disclosed no relevant financial relationships.

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