Human stem cell-derived retinal cells for macular diseases

In The Lancet, Steven Schwartz and colleagues report the mid-term and long-term outcomes of the use of human embryonic stem-cell (hESC)-derived retinal pigment epithelial cells for the treatment of dry atrophic age-related macular degeneration and Stargardt’s macular dystrophy, the leading causes of adult and juvenile blindness in the developed world. Both eye diseases involve a disruption of the retinal pigment epithelium, a layer of cells behind the retina that helps to maintain photoreceptors and preserve the blood–retina barrier. In the studies, hESC were differentiated into retinal pigment epithelium cells, and these cells were injected into the subretinal space in the eye with the worst vision in 18 patients—nine with atrophic age-related macular degeneration and nine with Stargardt’s macular dystrophy. The median follow-up was 22 months. Visual acuity improved in ten eyes, remained the same or improved in seven eyes, and decreased by more than ten letters in one eye. The untreated fellow eyes did not show similar improvement. The safety and visual acuity outcomes in the 18 patients further validate the earlier findings reported for the first patient in two studies in 2012.

Fetal retinal pigment epithelium transplantation for patients was attempted in the 1990s. Other clinical experiences followed, but the results were mixed, and the challenges of using reliable cell sources persisted. The use of a well characterised stem cell line that can be readily expanded, easily stored, and retrieved when needed for therapy would be advantageous. The studies by Schwartz and colleagues show that the use of stem cell lines is a viable strategy. Because of its small size, the retina, which typically measures 40 mm and is 0.5 mm thick, with central macula of about 6 mm, is an ideal initial target for therapy, because the number of cells needed for delivery is small. This is important because the risk of teratoma formation for hESC-derived stem cells increases as the number of cells injected increases. In the studies by Schwartz and colleagues, three dose cohorts were used for each eye disorder, with three patients in each group given doses of 50,000, 100,000, or 150,000 cells per eye. Although there was an apparent dose trend noted in patients with atrophic age-related macular degeneration, where the patients given the highest dose showed better visual acuity, this was not noted in the patients with Stargardt’s macular dystrophy. Overall, the numbers were too small to reach a conclusion about dose efficacy. The next phase of clinical trials should help to establish the best dose, and the accompanying studies should provide useful information given that there were no safety concerns.

Portions of the eye that are protected by the retinal–blood barrier might be immunoprivileged, and the results of previous clinical trials showed that transplanted fetal retina and retinal pigment epithelium sheets can survive in patients without immunosuppression. In the studies by Schwartz and colleagues, oral systemic immunosuppression was administered for 1 week before the procedure and continued for 12 weeks thereafter. The investigators report that signs of rejection were not evident in any treated eye for the duration of the studies.

The work by Schwartz and colleagues is a major accomplishment, but the path to get to this point has not been smooth. Since the discovery of hESC in 1998, much has transpired, including political, ethical, and scientific debates, with an overall push to achieve the promise of human therapies. Now, we have follow-up that extends to longer than 3 years in patients treated with hESC-derived stem cells, showing both safety and apparent efficacy. The discovery of human induced pluripotent stem cells in 2007, whereby adult cells could...
be reprogrammed genetically to an hESC-like state, brought further advantages to the specialty, because the use of cells from the same patients with the potential to avoid rejection became theoretically possible.

The patients’ experience in Schwartz and colleagues’ studies has already played a major part in the specialty of stem cell therapy, and has been instrumental in facilitating other trials. Just a few weeks ago, the RIKEN Center for Developmental Biology in Kobe, Japan, announced the treatment of the very first patient with induced pluripotent stem cells—the indication was macular degeneration.10 Much work remains to be done before hESC and induced pluripotent stem cell therapies go beyond regulatory trials, but the path is now set in motion.

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I declare no competing interests.