Treatment of Inherited Eye Defects by Systemic Hematopoietic Stem Cell Transplantation

Victor L. Perez
Departments of Ophthalmology, Microbiology & Immunology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida, United States; vperez4@med.miami.edu

The use of hematopoietic stem cell transplantation (HSCT) to treat leukemic disorders is well established in the treatment of systemic diseases. Similarly, the use of HSCT to treat genetic diseases, caused by the lack or abnormal expression of a gene, such as in sickle cell anemia, is another clinical indication for this form of cell-based therapy. In fact, the use of HSCT to treat this inherited disease is associated with a better rate of engraftment, survival, and decreased complications. Therefore, the use of HSCT to treat genetic inherited diseases has a great potential. The work reported by Cherqui et al.1 demonstrated that the use of HSCT to treat the ophthalmic manifestations is promising and, moreover, shows that the eye can be used to monitor success of engraftment in monitoring clinical response and to dissect mechanisms of action. Cystinosis is caused by a deficiency in the lysosomal cystine transporter, cystinosin (CTNS gene), resulting in cystine crystal accumulation in tissues that include the kidney and the eye. In the eye, crystals accumulate in the cornea causing photophobia, changes in vision, and eventually blindness. Mice in which the CTNS gene has been genetically deleted (CTNS−/−) have a similar phenotype to human disease. In their article, the authors clearly show that the single administration of wild-type, red fluorescently-labeled bone marrow cells (DsRed mice) into CTNS−/− mice is sufficient to reconstitute the population of donor cells into recipient animals. Impressively, their results demonstrated that the restoration of the corneal phenotype was achieved by showing, in vivo, that the reduction of crystals in the cornea occurs, and this correlates with the ex vivo decrease measurement of cysteine accumulation. Moreover, the authors show that donor DsRed HSCT-derived progeny are present in the cornea, which differentiated into macrophages, as displayed by tunneling of nanotubes capable of transferring cystinosin-bearing lysosomes to diseased cells in the eye. This is the first demonstration that HSCT can rescue hereditary corneal defects, and this is directly associated with the recruitment of normally-functioning donor cells into the site of disease to re-establish good organ function. This work strongly supports the potential use of cell-based novel therapies to treat abnormal gene-associated diseases of the eye.

Reference


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