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Seeing is believing: Stem cells to treat blindness

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Abstract The majority of clinical blindness is caused by a loss of transparency of the lens and cornea, largely due to cataracts and corneal injuries. The most common treatment used to restore the transparency is surgical removal of the damaged tissues, followed by transplantation of donated corneal tissue or an artificial lens. However, these therapies are not without limitations or untoward effects. Unraveling the intricate regulatory signals required for cornea and lens development has made it possible to harness the lineage growth potential of stem cells for cornea repair and lens regeneration, as showcased in two recent studies published in the March 17th issue of *Nature*.

Cataracts and corneal injuries are the leading causes of clinical blindness worldwide due to the resulting loss of the transparency of the lens and cornea. The most common treatment intended to restore the transparency is surgical removal of the damaged tissues, which is followed by transplantation of donated corneal tissue or an artificial lens. However, these therapies are not without limitations and untoward effects. There has been a continuous hunt for alternative cell/tissue sources to transform the treatment. A major driving force behind the recent advances in the treatment of blindness is the explosive progress made in the field of stem cell biology, particularly with regard to somatic pluripotency, self-renewal, and directed tissue-specific differentiation. The unraveling of the intricate regulatory signals of corneal and lens stem cells has made it possible to harness the lineage growth potential of stem cells to provide better cornea repair and lens regeneration. This was showcased in two recent studies published in the March 17th issue of *Nature*.

In one report by Hayashi, et al, cornea epithelial constructs grown and differentiated from human induced pluripotent stem cells (iPSCs) were put to the test in a rabbit model of corneal injury.[1] A rapid repair of the corneal epithelium was observed within the first two weeks post-transplantation compared to the surgical control. Although the long-term engraftment and well-being of the repaired cornea has not been tested in this rabbit model, these early findings demonstrated the potential of iPS cells as an alternative source for clinical cornea repair. Their use may supplant that of somatic limbal epithelial stem cells (LESC), which have been extensively studied as a preferred source for therapeutic ends.[2] Whether these iPSC-based corneal derivatives are functionally superior to those grown from LESC remains unclear. In contrast to LESC, two major challenges remain before the clinical benefit of iPS cells can be realized. One of these challenges is the lengthy time, and thus the prohibitive cost, required to develop patient-specific iPSCs and their derivative corneal constructs. Another challenge is to ascertain the long-term safety of iPSC-derived cells since induced pluripotency requires the ectopic activation of multiple pluripotency genes, which are also associated with cancerous growth.

To avoid these obstacles, the SEAM culture model used by Hayashi, et al to differentiate iPSCs into various lineages of eye tissues may serve as a petri dish platform to dissect the molecular signals required during embryonic eye

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development. The knowledge gained will have a fundamental impact on the manipulation of the eye stem cell environment, making it possible to achieve *de novo* regeneration with minimal molecular and cellular intervention.

The proof of this "organic" approach has just arrived in a second study appeared in the same issue of *Nature* by Lin, et al who searched for ways to regenerate damaged lens tissues.[3] In this study, Lin and colleagues were able to identify the anatomical location of lens epithelial stem/progenitor cells (LEC) in both animal and human tissues. These cells are known to have a role in lens homeostasis and regeneration. Through injury modeling, they confirmed the proliferative response of the endogenous LEC cells based on the expression of several marker genes. Using the knowledge gained in these studies, a less invasive surgery protocol was devised to remove the cataract tissue. This new protocol employed a small peripheral incision on the lens capsule that maximally preserved the residing LEC pool in the capsule. Using this method, the authors were able to coax the regeneration of a functional lens in the experimental animals. Their success was duplicated in their ensuing clinical trial where they treated infants with congenital cataracts.

Although these paradigm-shifting findings seemed to work well in infant patients, it may be difficult to reproduce them during the treatment of adult cataracts due to the different characteristics of age-related cataracts and the diminished LEC pool present in older patients. Further studies are therefore needed, but these preliminary studies provide a ray of hope for better treatments.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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