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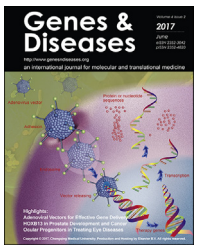

RESEARCH WATCH

iPSC-based treatment of age-related macular degeneration (AMD): The path to success requires more than blind faith

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Abstract Induced pluripotent stem cells (iPSCs) hold great promise for the treatment of human diseases. Two recent first-of-its-kind clinical case reports on the iPSC-based treatment of age-related macular degeneration (AMD) highlight the hopes and challenges associated with the clinical application of iPSCs.

Age-related macular degeneration (AMD) is a leading cause of blindness among the elderly. The hallmark of AMD is the gradual death of photosensory cells due to the degeneration of the adjoining retinal pigment epithelium (RPE), which serves as a nutritional feeder. The treatments currently available for AMD, such as surgical ablation or anti-vascular injection, only slow down the disease progression. An effective treatment that can repair or regenerate the lost RPE is not available. In this respect, the proliferation and differentiation potential of stem cells make them an ideal source of material for the development of next-generation therapies aimed at various tissue degenerative diseases, including AMD.

Relevant to the recent clinical trials of stem cell-based AMD therapy are two case reports with opposite outcomes that appeared simultaneously in the March 16th issue of the *New England Journal of Medicine*. In the first report, a group of Japanese investigators developed an induced pluripotent stem cell line (iPSC) using skin cells from one elderly AMD patient.[1] Differentiated autologous RPE cells generated from the patient's iPSC line were methodically

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screened to confirm the functional identities of the RPE and the integrity of genomes to safeguard against the potential tumorigenic risk, which is a major concern after iPSC transformation. These well-characterized autologous RPE cells were later transplanted into the patient's retina with a very encouraging outcome. The investigators observed long-term survival of the RPE graft (>1 year), suggesting a functional integration of the injected RPE cells. There were no serious complications related to the treated retina, and the visual deterioration has been halted since the transplant. In addition, there was no undesirable (i.e., malignant or fibrotic) proliferation of the engrafted RPE cells. Although the report is noteworthy because it provides the first evidence of a successful human trial using autologous iPSC-RPE, the results are based on only one patient, and an attempt to treat a second patient was aborted due to the detection of gene mutations in the RPE cells differentiated from the autologous iPSC lines. In view of the limited sample number, the safety and efficacy of iPSC-based therapy in the case of AMD have yet to be determined through rigorous statistical means. Of particular concern is the observed genomic aberration of the iPSC product from the second patient, which highlights the well-known issue of genomic instability of iPSC lines and their derivatives. This problem, if unsolved, may emerge as a major economic obstacle for commercial scale-up down the road, considering the time and cost required to develop iPSC sources.[2]

In contrast to the aforementioned outcome, the authors of the second report describe three elderly AMD patients seeking help shortly after they had received unapproved treatment with their own fat tissue-derived "stem cells" in third party clinics.[3] All three patients were treated in both eyes, and all experienced acute vision loss due to serious retinal complications, such as bleeding, retinal detachment, and proliferative vitreoretinopathy, suggesting a fibrotic proliferation of the ill-defined "stem cells". These types of "stem cells" have been extensively studied in the preclinical stage, and were found to contain progenitors of mesenchymal origin, which give rise to lineages of bone, muscle, fibroblast (scar tissue), and cartilage. Although there are a few published reports indicating their potential to differentiate into retinal lineage in culture, the *in vivo* differentiation toward the RPE fate has never been ascertained in animal transplantation studies.[4]

Taken together, these two contrasting reports provide valuable lessons indicating that, without the detailed and accurate knowledge about how these stem cells can be properly differentiated into the desired cell types, the path forward in search of a stem cell-based cure will require more than blind faith. It will require prudence based on solid preclinical evidence; sound government oversight; and, first and foremost, the spirit of "***primum non nocere***".

Conflict of interest

The authors declare that they have no conflicts of interest.

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