Possibility of Cytoplasmic Transportation Between Donor–Host Cell Following Photoreceptor Transplantation

With great interest, we read the article "Stem Cell-Derived Photoreceptor Transplants Differentially Integrate Into Mouse Models of Cone-Rod Dystrophy" by Santos-Ferreira et al.,[1] recently published in *Investigative Ophthalmology and Visual Science*. It's exciting to see that retinal degeneration can be rescued by photoreceptor transplantation in this study. Indeed, as the development of techniques to generate retinal tissue from embryonic stem cell (ES) and induced pluripotent stem cells (iPS), many peers have successfully transplanted photoreceptor to animal model and observed that donor cell could replace diseased cell and integrate into the host tissue. However, we suggest in here that we need to be cautious to interpret these results.

Cell–cell fusion is a highly regulated cell communication event in development, homeostasis, cancer development, and tissue repair by stem cells.[2] Rocca et al.[3] reported that systemically transplanted hematopoietic stem and progenitor cells (HSPCs) could rescue cysteine crystals aggregation in cornea by transferring lysosomes to diseased corneal cells. And this cell-communication event also happened in retina and ciliary margin. Hematopoietic stem and progenitor cells restoring diseased cells by cell–cell fusion was also recorded in lung, liver, and kidney.[4–6] Based on these findings, there is a high possibility that donor photoreceptor precursor can fuse with host photoreceptor. Indeed, similar viewpoint of cell fusion between photoreceptor precursor and host photoreceptor cell was reported on in a 2016 ARVO conference by Singh et al. (*IOVS* 2016;57:ARVO E-Abstract 5320).

In the present article, it is difficult to exclude the possibility of cell fusion. The cell with green fluorescence detected in the outer nuclear layer might be the host cell received fluorescence material (such as green fluorescence protein) from the donor cell, rather than the latter replaced the former. Furthermore, there was probably no real cell replacement and integration. This may be the reason why very few replacement and integration happened in Cpfl 1/Rho$^{-/-}$ mice (more severe photoreceptor degeneration) compared with either wild-type or Prom 1$^{-/-}$ mice, for barely photoreceptor left to fuse with in Cpfl 1/Rho$^{-/-}$ mice. In Figures 3 and 4 of the present article, structures that very similar to tunneling nanotube can be found, which might be the transport bridge between cells as Rustom et al.[7] reported. In addition, in order to distinguish cell fusion and cell replacement methodologically, we recommend that label host retinal cell and donor photoreceptor precursor cell with different fluorescence and to see if fluorescence overlap after transplantation, or use different sex cells between donor and host and to check what kind of genetic change would happen in host cell.

In the end we strongly suggest that this "camouflage phenomena" should be excluded on the road of photoreceptor replacement-therapy study.

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