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Generation of retinal pigment epithelial cells from small molecules and OCT4 reprogrammed human induced pluripotent stem cells.

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Abstract

Autologous retinal pigment epithelium (RPE) grafts derived from induced pluripotent stem cells (iPSCs) may be used to cure blinding diseases in which RPE dysfunction results in photoreceptor degeneration. Four-, two-, and one-factor-derived iPSCs (4F-, 2F-, and 1F-iPSCs, respectively) were differentiated into fully functional cuboidal pigmented cells in polarized monolayers that express RPE-specific markers. 1F-iPSCs-RPE (1F-iPS-RPE) strongly resembles primary human fetal RPE (hfRPE) based on proteomic and untargeted metabolomic analyses, and using novel in vivo imaging technology coupled with electroretinography, we demonstrated that 1F-iPS-RPE mediate anatomical and functional rescue of photoreceptors after transplantation in an animal model of RPE-mediated retinal degeneration. 1F-iPS0RPE cells were injected subretinally as a suspension and formed a monolayer dispersed between host RPE cells. Furthermore, 1F-iPS-RPE do not simply provide trophic support to rescue photoreceptors as previously speculated but actually phagocytose photoreceptor outer segments in vivo and maintain visual cycling. Thus, 1f-iPS-RPE grafts may be superior to conventional iPS-RPE for clinical use because 1F-IPS-RPE closely resemble hfRPE, mediate anatomical and functional photoreceptor rescue in vivo, and are generated using a reduced number of potentially oncogenic reprogramming factors.

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