Transplanted erythropoietin-expressing mesenchymal stem cells promote pro-survival gene expression and protect photoreceptors from sodium iodate-induced cytotoxicity in a retinal degeneration model

ABSTRACT

Mesenchymal stem cells (MSC) are highly regarded as a potential treatment for retinal degenerative disorders like retinitis pigmentosa and age-related macular degeneration. However, donor cell heterogeneity and inconsistent protocols for transplantation have led to varied outcomes in clinical trials. We previously showed that genetically-modifying MSCs to express erythropoietin (MSCEPO) improved its regenerative capabilities in vitro. Hence, in this study, we sought to prove its potential in vivo by transplanting MSCsEPO in a rat retinal degeneration model and analyzing its retinal transcriptome using RNA-Seq. Firstly, MSCsEPO were cultured and expanded before being intravitreally transplanted into the sodium iodate-induced model. After the procedure, electroretinography (ERG) was performed bi-weekly for 30 days. Histological analyses were performed after the ERG assessment. The retina was then harvested for RNA extraction. After mRNA-enrichment and library preparation, paired-end RNA-Seq was performed. Salmon and DESeq2 were used to process the output files. The generated dataset was then analyzed using over-representation (ORA), functional enrichment (GSEA), and pathway topology analysis tools (SPIA) to identify enrichment of key pathways in the experimental groups. The results showed that the MSCEPO-treated group had detectable ERG waves ($P < 0.05$), which were indicative of successful phototransduction. The stem cells were also successfully detected by immunohistochemistry 30 days after intravitreal transplantation. An initial over-representation analysis revealed a snapshot of immune-related pathways in all the groups but was mainly overexpressed in the MSC group. A subsequent GSEA and SPIA analysis later revealed enrichment in a large number of biological processes including phototransduction, regeneration, and cell death ($Padj < 0.05$). Based on these pathways, a set of pro-survival gene expressions were extracted and tabulated. This study provided an in-depth transcriptomic analysis on the MSCEPO-treated retinal degeneration model as well as a profile of pro-survival genes that can be used as candidates for further genetic enhancement studies on stem cells.

Keyword: Mesenchymal stem cells; Erythropoietin; Sodium iodate; Transcriptome; photoreceptors; Pro-survival genes