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Microneedles as a potential tool for live cell delivery in retinal diseases: a case study of Top2b-edited RPCs with matched biomaterials

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Top2b editing, retinal cell, electroporation, microneedles

Retinal diseases have received widespread attention in recent years. Retinal degenerative diseases, including age-related macular degeneration (AMD) and retinal pigment epithelium (RPE) degeneration, are among the causes of vision loss, with AMD being particularly prevalent among the elderly [1]. The elderly population has a high prevalence of visual impairment, and the risk is most pronounced in individuals aged 80 and above. Generally, degeneration of the RPE, photoreceptors, and retinal ganglion cells (RGCs) leads to the occurrence of retinal diseases. Current clinical treatment strategies include the regeneration of photoreceptors and RGCs, and transplantation of the RPE [2].

A previous study [3] has shown that Topoisomerase II beta (Top2b) plays an important role in the transcriptional regulation of genes required for retinal development. Recently, in Explor BioMat-X, Dabrowski et al. evaluated how Top2b gene-edited retinal progenitor cells (RPCs) interact with transplantable biomaterials, providing a gene-material synergy strategy for retinal repair [4]. Dabrowski et al. investigated how genetic alterations in Top2b affect the development and migration of RPCs, as well as the adhesion and migration properties of these genetically edited cells on biomaterial substrates intended for transplantation. The main results are threefold. First, RPCs whose Top2b was inhibited by the drug ICRF-193 exhibited impaired developmental capacity, specifically manifested as fewer RGCs, disorganized arrangement, and decreased cadherin content. Second, Top2b affects the migration and adhesion capabilities of RPCs; specifically, Top2b-knockdown (Top2b-KD) RPCs generally showed weakened

migration ability, while those with Top2b overexpression (Top2b-OE) did not exhibit stronger migration ability than normal cells. Third, the editing of Top2b needs to be matched with the specific transplantation material used, as RPCs with different Top2b expression levels exhibited varying adhesion and morphological change capabilities on different materials.

Given the established role of Top2b in regulating RPCs development and migration, the authors designed two sets of experiments to specifically evaluate how manipulating Top2b expression impacts these critical processes both in vivo during development and in vitro upon biomaterials relevant for transplantation.

The first set of experiments used specific pathogen-free (SPF) fertilized chicken eggs for cultivation. In the experiment, researchers established a control group and a Top2b inhibition group using ICRF-193 to inhibit Top2b on embryonic day 4 (E4). It was found that the Top2b inhibition group (ICRF-193) showed significantly downregulated cadherin expression. The ganglion cell layer (GCL) thickness in the suppression group decreased by approximately 30% at the E6 stage compared to the control group, but showed no significant difference at the E12 stage, indicating that Top2b primarily affects cell migration in the early developmental stages. During E6–E10, the Top2b inhibition group showed an approximately 50% decrease in Cdh2 and Cdh7 expression, confirming impaired intercellular adhesion. This demonstrates that Top2b can directly affect the development of RPCs.

The second set of experiments compared three types of cells: Top2b-KD cells, Top2b-OE cells, and untreated wild-type cells (Top2b-WT). Results showed a 2.5-fold increase in CXCR4 expression in Top2b-OE cells, while both CXCR4 and FGFR1 were downregulated in Top2b-KD cells. Transwell migration assays indicated that Top2b-KD cells almost lost migration ability and Top2b-OE migration ability was lower than WT. It was also found that Top2b-WT cells had the largest surface area on laminin (LM), knockdown cells were more elongated on poly-L-lysine, and overexpression cells showed the fastest morphological changes on LM. Thus, Top2b expression influences cell migration, adhesion, and substrate-dependent morphological responses.

Based on the conclusions of this study, the selection of biomaterials for in vivo ocular delivery of living cells should be guided by their gene-expression profiles, providing a reference for formulation development. However, current traditional delivery methods, such as eye drops, ointments, gels, and ocular inserts, are often limited by the ocular physiological structure, such as the blood-retinal barrier (BRB) and tear drainage, and have disadvantages like short drug retention time and low bioavailability [5]. Therefore, effective treatment of retinal diseases necessitates not only the use of suitable biomaterials but also the circumvention of BRB.

Microneedles (MNs), typically measuring hundreds of micrometers in length, have been proven to achieve precise drug delivery to posterior ocular tissues through minimally invasive scleral penetration, effectively circumventing the BRB for high-concentration administration in retinal regions, enabling controlled drug release while increasing bioavailability and reducing systemic adverse effects [6]. In recent years, owing to these features, numerous researchers have investigated MN-based ocular administration for treating ocular diseases, demonstrating rapid dissolution kinetics and excellent biocompatibility [7, 8]. MNs show great potential for clinical translation for cell delivery [9]. For instance, Thakur et al. successfully demonstrated that dissolving microneedles (DMNs) could effectively penetrate the sclera, significantly enhancing the permeability of the macromolecular model drug fluorescein glucan and overcoming the bottleneck in ocular drug delivery [5]. MNs enable precise control over the distribution of therapeutic cells to target tissues while minimizing tissue damage. They also reduce damage to the architecture of living cells, enhance their viability, ultimately improve therapeutic efficacy [10]. Building upon the advantages of MNs and the findings, we believe that future efforts can focus on fabricating MNs from diverse biomaterials. These MNs could deliver Top2b-genetically-edited RPCs that best match individual compatibility. Given Top2b-OE's more pronounced morphological changes and adhesion behavior on LM, future research could develop ophthalmic MNs using LM as the primary substrate for Top2b-OE RPCs. By leveraging LM's specific supportive properties for these cells, the approach could enhance their survival rate during transplantation,

improve directional migration capabilities, and ultimately optimize functional integration. This provides a novel strategy for achieving precise and efficient retinal regeneration therapy. Such an approach could circumvent the limitations of drug delivery to the retina via electroporation and enable more precise treatment of these retinal diseases. While this strategy holds great promise, two critical challenges remain in its clinical translation. The foremost challenge involves developing MNs that can encapsulate fragile living RPCs without causing damage while preserving their viability and functionality. Additionally, rigorous validation of long-term safety post-implantation is essential. Only by proactively addressing these issues can we create clinically viable and safe therapies.

In summary, using the Top2b gene-edited RPCs and corresponding transplantable biomaterial substrates to treat adult visual impairment holds broad application prospects and significant importance.

Abbreviations

AMD: age-related macular degeneration

BRB: blood-retinal barrier

Cdh2: Cadherin 2

Cdh7: Cadherin 7

CXCR4: CXC chemokine receptor 4

DMNs: dissolving microneedles

E12: embryonic day 12

E4: embryonic day 4

E6: embryonic day 6

FGFR1: fibroblast growth factor receptor 1

GCL: ganglion cell layer

LM: laminin

MNs: microneedles

RGCs: retinal ganglion cells

RPCs: retinal progenitor cells

RPE: retinal pigment epithelium

SPF: specific pathogen-free

Top2b: Topoisomerase II beta

Top2b-KD: Top2b-knockdown

Top2b-OE: Top2b overexpression

Top2b-WT: Top2b wild-type

Declarations

Author contributions

KY: Writing—original draft, Conceptualization. SP: Writing—review & editing. XP: Writing—review & editing, Supervision. ZH: Writing—review & editing, Supervision. WW: Writing—review & editing. All authors have read and approved the manuscript.

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The authors declare that they have no conflicts of interest.

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