Letter to the Editor

Stem cell-derived Müller glia have potential to enrich *in vitro* models of the blood-retinal barrier

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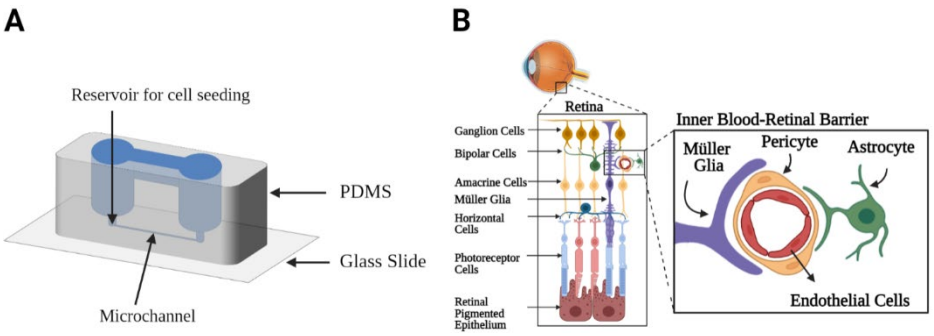
We have read with great interest the article by Ragelle et al. entitled "Organ-on-a-chip technologies for advanced blood-retinal barrier models." The authors highlighted the advancements of in vitro technologies and organ-on-a-chip modeling for the blood-retinal barrier (BRB). However, we write to stress the need and advantages of incorporating induced pluripotent stem cells (iPSC)-derived Müller glia (MG) for more appropriate BRB models to advance regenerative therapies.

As highlighted in the article, significant advancement needed for in vitro BRB studies are the application of human induced pluripotent stem cells (hiPSCs), rather than primary cultures or immortalized cell lines. hiPSCs reduce ethical concerns of animal modeling as well as provide superior physiological relevance and smoother translation to human clinical needs. hiPSCs have been recently used to model retinal neurons, and endothelial cells (EC) of the inner blood-retinal barrier (iBRB)[1], suggesting that hiPSC differentiation into other retinal cell lineages will improve cellular models of the iBRB. Moreover, the combination of microfluidics with hiPSC-based technology holds great promise for the development of comprehensive BRB models, because the system microscale facilitates cell study at physiological spacing and scale . Contemporary microfluidic devices and lab-on-a-chip technology have produced controlled systems to examine neurodegenerative diseases and the study of multiple cell types in an integrated system[1]. Our own laboratory has recently developed a glial line (gLL) microfluidic system (Fig.1B) on the retinal scale to examine changes in hypertrophy, adhesion, and migration of Muller glia (MG) that are hallmarks of gliosis[2] and significant to iBRB integrity. The gLL is fabricated with commercial polydimethylsiloxane (PDMS) and bonded to a microscope slide. It provides a controlled microenvironment where iPSC-derived MG and EC can be seeded for co-culture to examine collective cell behaviors and responses to extracellular stimuli (e.g. hypoxia, glucose).

The iBRB is most commonly modeled with a focus on EC, although this neurovascular barrier tissue is also intricately regulated by MG that span retinal laminae to maintain homeostasis and initite repair (Figure 1A). While EC are vital for the transport of oxygen and nutrients from blood flow across

the iBRB, MG are equally essential to vision via regulation of neurotransmitters and redox signaling that meet the extreme metabolic demands of phototransduction[3]. Retinal degenerative diseases, such as diabetic retinopathy (DR), are largely characterized by iBRB dysfunction. DR, one of the most prevalent diseases affecting eye health, impairs patient vision, as elevated and fluctuating blood glucose levels are associated with leakage via tight junctions of the EC that form the iBRB[4]. The altered tight junctions allow blood-borne elements to penetrate the retina, which can stimulate gliosis, where MG release growth factors and cytokines as neuroprotective responses. Over time, this creates a destructive inflammatory environment for the retina that can result in glial scarring and ultimately vision loss. Because of the overprotective response of MG and their potential to further damage retinal function, MG are essential when studying diseases and for developing therapies that do not elicit prolonged gliotic activity[3]. Despite the significance of MG response to retinal degeneration, few biomedical projects have incorporated the behaviors of MG into studies of the BRB. The combination of microfluidics with hiPSC-based MG hold great promise for the development of comprehensive BRB models to examine the progression of diabetic retinopathy and target MG native responses for the development of treatments against retinal disease.

FIG 1: (A) Schematic of the inner blood-retinal barrier depicting the connection between the retinal capillaries and the retinal network via the Müller glia processes. (B) Schematic of the glia-line microfluidic system developed by our group to examine gliotic behaviors of Müller glia in retinopathies[4].



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