OPEN ACCESS Freely available online

Journal of Clinical and Experimental Ophthalmology

Commentary

A Short Commentary on Understanding Inflammation Associated Ophthalmic Pathologies: A Novel 3D Co-Culture Model of Monocyte-Myofibroblast Immunomodulation

Avi Petroff*

Department of Ophthalmology, Tel Aviv University, Tel Aviv, Israel

ABSTRACT

The article titled "Understanding Inflammation-Associated Ophthalmic Pathologies: A Novel 3D Co-culture Model of Monocyte-Myofibroblast Immunomodulation" describes a simple 3D co-culture system that was used to model a human eye following glaucoma filtration surgery. Various specifications were implemented to the model to allow for a focused assessment on monocyte and myofibroblast immunomodulation of inflammatory cytokine signaling. However, the utility of such a model extends beyond the scope of the original paper, into areas of discovery such as pharmaceutical therapies and tissue-dependent models of inflammation and fibrosis. The original paper highlighted the importance of 3D and co-culture models for obtaining more comprehensive assessments of cellular responses to inflammatory stimuli, and thus the stress on these parameters should be maintained while other parameters may be modified for myriad scientific objectives.

Keywords: 3D; Co-culture; Model; Inflammation; Fibrosis; Monocytes; Fibroblasts

DESCRIPTION

Analysis of system utility

The article titled "Understanding Inflammation-Associated Ophthalmic Pathologies: A Novel 3D Co-culture Model of Monocyte-Myofibroblast Immunomodulation" describes a simple 3D co-culture system designed to facilitate an understanding of ocular myofibroblast interactions with circulating cells of the innate immune system, specifically monocytes [1]. The goal of this model was to facilitate increasingly physiologically-relevant in vitro models of inflammation-associated ophthalmic pathologies.

Of the various inflammation-associated ophthalmic pathologies outlined in the paper, we chose to specifically discuss scarring following glaucoma filtration surgery because of the clinical importance of surgical failure, repeated need for surgery, and the need for improved therapeutic modulation of wound healing [1]. With this in mind, we incorporated components to the system that allowed for a more physiologically-relevant assessment of cellular responses to inflammatory cytokine stimuli. Specifically, we incorporated primary Human Tenon's capsule fibroblasts (HTCFs) suspended in polymerizing Fibroblast-Populated Collagen Lattices (FPCLs) [2] to induce myofibroblast formation in a 3D culture substrate mimicking tenon's capsular tissue.

As well, we attempted to mimic an inflammatory environment constituted by cytokines present in physiological aqueous humor. This was done by pre-treating a subset of cultured HTCFs with Inflammatory Cytomix (IC) (0.75 μg/mL each of TGFβ-1, TNF, IFNγ, and IL1β) for 24 hours prior to co-culture with THP-1 monocytes. This way, we could assess if the responses of THP-1 monocytes, a simplistic but widely used in vitro cell model of inflammatory infiltrate [3], to a cytokine-enriched inflammatory microenvironment were altered by the presence of a biomimetic of tenon's capsule tissue, consisting of myofibroblasts in a 3D collagen matrix, in co-culture [1].

As mentioned above, the use of similar 3D co-culture systems can facilitate discovery of novel compounds that could be viable for therapeutic and pharmaceutical exploration. By assessing changes in gene expression profiles under various glaucomatous conditions, novel therapies can be assessed that appropriately

Correspondence to: Avi Petroff, Department of Ophthalmology, Tel Aviv University, Tel Aviv, Israel, E-mail: avipetroff@mail.tau.ac.il

Received: 01-Jul-2022, Manuscript No. JCEO-22-16759; **Editor assigned:** 04-Jul-2022, PreQC No. JCEO-22-16759 (PQ); **Reviewed:** 18-Jul-2022, QC No. JCEO-22-16759; **Revised:** 25-Jul-2022, Manuscript No. JCEO-22-16759 (R); **Published:** 02-Aug-2022, DOI: 10.35248/2155-9570.22.13.923

Citation: Petroff A (2022) A Commentary on Understanding Inflammation Associated Ophthalmic Pathologies: A Novel 3D Co-Culture Model of Monocyte-Myofibroblast Immunomodulation. J Clin Exp Ophthalmol. 13:923.

attenuate the inflammatory phase and drive inflammatory resolution, leading to normal and healthy wound healing. In the context of glaucoma filtration surgery, such novel therapies could enable the long-term efficacy of the filtration bleb and lasting reduction in IOP for improved clinical outcomes [4]. For example, application of novel immuno-resolving agents to a modified version of our system to stimulate lipid class switching and the production of pro-resolving lipid mediators could theoretically lead to appropriate inflammatory resolution and subsequent healthy wound healing [5].

In a continuation of this concept, an Alamar Blue (AB) assay could be performed to find optimal concentrations of immune-resolving agents while assessing how such agents modulate monocyte-myofibroblast signaling. For example, the Hutnik lab (one of the two labs involved in assessment of this 3D co-culture system) considered assessing the dose-response of HTCFs in 3D cultures with COX-2-acetylating molecule treatment with Alamar Blue, following the manufacturer's protocol [6]. Had this experiment been conducted, absorbance readings could be collected using a fluorescence plate reader at excitation/emission 560/590 nm after 4,24,48 and 96 hours to evaluate metabolic activity and cellular health status (relative fluorescence) vs. drug concentration.

By considering the usefulness of this 3D co-culture model in various contexts, it's intriguing that such a model serves as a scaffold for future experimentation using 3D co-culture models that incorporate fibroblasts embedded in collagen matrices and immune cell signaling. For example, modified systems could analyze signaling of other immune cell types, such as neutrophils and macrophages. The utility of the current 3D co-culture model includes downstream classical or alternative activation of macrophages from monocytes [7]. However, a similar model using HTCFs and macrophages instead of THP-1 monocytes would likely elicit an even stronger immunomodulatory effect due to the increased cytokine secretory capabilities of macrophages. Such a model could also use either classically or alternatively activated macrophages in place of THP-1 monocytes, assessing the effects of each cell type on inflammatory signaling with HTCFs.

Further, modified models could also use monocytes and fibroblasts from various human tissues to compare fibrotic signaling in a tissue context-dependent manner. Though the process of wound healing and fibrosis is quite ubiquitous in many human tissues, the mechanism of onset and signaling cascades likely differ based on tissue type. This is to say, though we assessed THP-1 monocytes and primary HTCFs for modelling the human eye following glaucoma filtration surgery, the parameters of this 3D co-culture model can be modified for myriad translational research projects.

CONCLUSION

One of the key takeaways from the original paper is that there exists the potential to obtain misleading or even incomplete information from mono-culture systems that omit other cell types that may modulate their responses to cytokine stimulation. Further, 2D models omit many of the biomechanical characteristics that influence cells physiologically. Maintaining the 3D and co-culture concepts of this model, the model may be modified through parameters such as immune cell types and inclusion of novel immune-resolving agents. Together, such modifications of this model can enable further exploration into inflammation, inflammatory resolution, fibrosis, and cellular immunomodulation in various physiological contexts.

ACKNOWLEDGEMENT

I acknowledge the students and staff of the O'Gorman and Hutnik laboratories for their support, communication, and mentorship for the duration of the project from the original paper. The discussions regarding this project facilitated many of the ideas expressed in this short commentary.

CONFLICT OF INTEREST

The authors report no conflict of interest.

REFERENCES

1. Petroff A, Pena Diaz A, Armstrong JJ, Gonga-Cavé BC, Hutnik C, O'Gorman DB. Understanding inflammation-associated ophthalmic pathologies: A novel 3D co-culture model of monocyte-myofibroblast immunomodulation. Ocul Immunol Inflamm. 2021; 3:1-12.
2. Bell E, Ivarsson B, Merrill C. Production of a tissue-like structure by contraction of collagen lattices by human fibroblasts of different proliferative potential in vitro. Proc Natl Acad Sci. 1979;76(3): 1274-1278.
3. Chanput W, Mes JJ, Wichers HJ. THP-1 cell line: An in vitro cell model for immune modulation approach. Int Immunopharmacol. 2014;23(1):37-45.
4. Zada M, Pattamatta U, White A. Modulation of fibroblasts in conjunctival wound healing. Ophthalmol. 2018;125(2):179-192.
5. Buckley CD, Gilroy DW, Serhan CN. Proresolving lipid mediators and mechanisms in the resolution of acute inflammation. Immunity. 2014;40(3):315-327.
6. Eilenberger C, Kratz SR, Rothbauer M, Ehmoser EK, Ertl P, Küpcü S. Optimized alamarBlue assay protocol for drug dose-response determination of 3D tumor spheroids. MethodsX. 2018;5:781-787.
7. Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S, et al. Macrophage activation and polarization: Nomenclature and experimental guidelines. Immunity. 2014;41(1):14-20.